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Actigraphic Evaluation of Motor Fluctuations in Patients with Parkinson's Disease

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ABSTRACT

Background: There is growing interest in developing inexpensive and objective motor fluctuation evaluation methods for Parkinson's disease (PD). **Objectives:** We aim to compare activity level in the off state, on state, and dyskinetic periods as evaluated either by a physician during a levodopa challenge or by a 72-hr on–off diary self-evaluation in the ambulatory setting. Finally, the effect of daily activities on motor activity in PD and healthy controls was further explored. **Methods:** The study was conducted in three consecutive phases. For phase I, in which the on state, off state, and dyskinesia were evaluated using actigraphy, recordings were made during standard acute levodopa challenge in nine dyskinetic PD patients. For phase II, a different set of 16 dyskinetic PD patients was monitored in the ambulatory setting for 72 consecutive hours by actigraphy and a standardized on–off diary. For phase III, 62 PD patients and 14 age- and sex-matched healthy controls wore an actigraph and completed a daily activities diary for 7 days. **Results:** No differences in activity level between on state and off state during the acute levodopa challenge (phase I) or the 72-hr ambulatory period (phase II) were found. Activity during dyskinesia periods was significantly higher than during on state periods without dyskinesia ($p < .01$). During the third phase, dyskinetic PD patients and healthy controls showed higher actigraphy-measured activity as compared to de novo, stable, or fluctuating PD ($p < .0001$), which remained unaltered by daily activities performed during the study period. Tremor UPDRS scores did not correlate with activity level. **Conclusions:** These results confirm the lack of specificity of simple wrist-worn actigraphy and further suggest it may be suitable for dyskinesia assessment but not for on state and off state evaluation.

KEYWORDS: actigraphy, dyskinesia, motor fluctuations, Parkinson's disease

INTRODUCTION

Motor fluctuation assessment in Parkinson's disease (PD) is an important issue for levodopa-treatment optimization. First, wearing-off phenomena and dyskinesia can be evaluated either retrospectively, using part IV of the Unified PD Rating Scale (UPDRS) (Fahn, Elton, & members of the UPDRS committe, 1987) or by an on–off diary, which allows a detailed analysis of total daytime hours spent in a medication-deprived state (off), in good condition (on), or suf-

fering from levodopa-related dyskinesias (Hauser, Deckers, & Lehert, 2004; Hauser et al., 2000). These are subjective tools with poor reliability in general (Brown, MacCarthy, Jahanshahi, & Marsden, 1989). Although reliability can be improved by extensive teaching and concordance testing, need for prolonged hospital stay and/or physician assistance often discourage their application. Direct observation during an acute levodopa challenge is probably the most accurate evaluation method (Merello, Nouzeilles, Arce, & Leiguarda, 2002) but is limited to the observed period and can be influenced by patient's stress or discomfort.

During the transition between on, off, and dyskinetic states, significant changes in body movements can be observed related to changes in tremor, bradykinesia, or dyskinesia. Ambulatory activity monitoring (i.e., actigraphy) can quantify these movements, therefore providing a way to evaluate patients' motor status. Simple inexpensive wrist-worn

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actigraphs were initially developed for this purpose (Katayama, 2001; van Hilten, Hoff, Middelkoop, & Roos, 1994; van Hilten, Hoogland, van der Velde, Middelkoop, et al., 1993; van Hilten, Hoogland, van der Velde, van Dijk, et al., 1993; van Hilten, Kabel, et al., 1993; van Hilten, Middelkoop, Kerkhof, & Roos, 1991; van Hilten, Middelkoop, Kuiper, Kramer, & Roos, 1993) and were later replaced by multichannel devices designed either to more precisely evaluate body postures and movements (Dunnewold et al., 1998). These devices are capable of accurate bradykinesia and hypokinesia (Dunnewold et al., 1998; Dunnewold, Jacobi, & van Hilten, 1997; Keijsers, Horstink, & Gielen, 2006), tremor (Hoff, Wagemans, & van Hilten, 2001; Van Someren et al., 2006), and dyskinesia evaluation (Hoff, van den Plas, Wagemans, & van Hilten, 2001; Keijsers, Horstink, van Hilten, Hoff, & Gielen, 2000; Keijsers, Horstink, & Gielen, 2003a, 2003b2003c). On–off state differentiation by multichannel actigraphy was shown to be feasible by some authors (Keijsers et al., 2006) but not by others (Hoff, van der Meer, & van Hilten, 2004). It is noteworthy that none of these studies employed an acute levodopa challenge as the reference.

Single wrist-worn actigraphic devices were abandoned because they were supposedly not capable of discerning normal movements from PD motor complications (Dunnewold et al., 1998), which has never been proven. As these kind of devices evolved to be more sensitive and remain the cheapest alternative, we considered it worthy to reexplore their utility in PD motor assessment. Therefore, we designed a study comparing activity level in the off, on, and dyskinetic periods as evaluated either by a physician during a levodopa challenge or by a 72-hr on–off diary self-evaluation in the ambulatory setting. Finally, the effect of daily activities on motor activity in PD patients and healthy controls was further explored.

METHODS

Study sample

A consecutive series of PD patients were recruited from a tertiary outpatient clinic. To be included in the study, subjects had to fulfill UKPDSBB (United Kingdom Parkinson's Disease Society Brain Bank) criteria (Hughes, Daniel, Kilford, & Lees, 1992), have a Mini-Mental State Examination (MMSE) score > 24 (Folstein, Folstein, & McHugh, 1975), and not suffer from any condition causing mobility restrictions other than PD. All patients showed positive response to acute levodopa challenge (Merello et al., 2002). Secondary parkinsonism causes were

ruled out through clinical examination, CT scan, and laboratory work-up, including thyroid hormones and urinary copper. A group of age- and sex-matched healthy controls lacking chronic diseases or mobility-restricting conditions were recruited from the general population. The protocol was approved by the local ethics committee and all subjects gave informed consent.

PD evaluation

PD patients were evaluated using the UPDRS and the Hoehn and Yahr Scale (Hoehn & Yahr, 1967). Medication records were used to calculate levodopa-equivalent daily doses (LDED; Razmy, Lang, & Shapiro, 2004). Depending on patient response or lack of previous exposure to levodopa, patients were classified into four categories: (a) levodopa-naïve ("de novo"); (b) levodopa-treated with stable response; (c) levodopa-treated suffering wearing-off but not dyskinesia; and (d) levodopa-treated suffering wearing-off and dyskinesia.

Study procedures

The study was conducted in three consecutive phases. For phase I, a set of dyskinetic PD patients was evaluated after acute levodopa challenge while wearing an actigraph. The activity level during on, off, and dyskinetic states was evaluated actigraphically. Patients remained seated during the whole study. In the second phase, a different set of dyskinetic PD patients were instructed to wear an actigraph and complete a 72-hr on-off diary. Activity level was recorded during the off state, on state, and dyskinetic periods. No attempt to normalize or limit daily activity was undertaken. Finally, in the third phase, healthy controls and PD patients wore an actigraph and completed a daily activity diary for seven consecutive days, thus exploring the effect of daily activities on motor activity.

Motor fluctuation evaluation during phases I and II

During phase I, motor activity during the off state, on state, and dyskinetic periods was evaluated during a standard levodopa challenge (Merello et al., 2002). Levodopa/carbidopa 250/25 mg was administered at 09:00. Motor status and dyskinesia were evaluated using part III of the UPDRS (Fahn et al., 1987) and Dyskinesia Rating Scale for PD (Goetz et al., 1994) at 0, 30, 60, 90, 150, 180, and 240 min after levodopa intake. Actigraphic recording began 20 min before levodopa administration to allow for off state activity evaluation. Patients sat in an armchair with access to reading material or a TV throughout the study and

were not allowed to ambulate except when indicated for the motor status evaluation.

For phase II, a different set of patients was trained to recognize their own motor symptoms and then tested for concordance by a physician. Patients achieving at least 80% concordance were asked to complete a 72-hr standard on–off diary (Hauser et al., 2000, 2004). Daily off state, on state, and dyskinetic periods were evaluated.

Daily activity evaluation

For phase III, healthy controls and PD patients were asked to complete a 24-hr diary, registering voluntary movement while wearing an actigraph for seven consecutive days. Our in-house developed activity diary consisted of a 24-hr period grid divided into 30-min cells. Each cell had to be completed with a number according to the following code: 1, Time spent lying down in bed, performing activities or not; 2, Time spent sitting, performing activities or not; 3, Time spent performing different activities in the upright position, and 4, Time spent performing physical exercises. The design of the diary was based on the Bratteby et al. daily energy expenditure diary (Bratteby, Sandhagen, Fan, Enghardt, & Samuelson, 1998; Bratteby, Sandhagen, Fan, & Samuelson, 1997). Diaries with more than four missing entries were discarded and the subject was reevaluated.

Actigraphy

Subjects wore an actigraphic device (MicroMini-Motionlogger, Ambulatory Monitoring Inc., NY, USA) for each of the three phases previously described, attached to the nondominant wrist, as it has been shown that this location provides the best measure of whole-body movements (McPartland, Kupfer, Foster, Reisler, & Matthews, 1975; van Hilten, Middelkoop, et al., 1993).

The accelerometer is mostly sensitive (>0.003 g) in the radius-to-ulnar axis, but also has sensitivity in the longitudinal and transverse axes due to an off-center-mounted weight at the end of the piezoelectric beam (Jean-Louis, Kripke, Mason, Elliott, & Youngstedt, 2001). Movement in an axis other than the primary axis causes beam torsion, which generates a signal. Accelerations are sampled 10 times per second with an 8-bit A/D converter. The accelerometer generates a voltage during each movement, which is amplified and bandpass-filtered (2–3 Hz). Proportional-integrating mode (PIM) was selected for wrist movement quantification. In PIM, the area under the rectified analog signal is measured for each epoch, and the accumulated counts (range:

0–60,000) are stored. PIM measures movement intensity by adding all deviations from 0 V (i.e., the absolute value of the voltage) every 10th of a second. Counts are stored in the solid memory in 1-min bins. All the devices were calibrated by the supplier.

Statistical analysis

Categorical and numerical variables were analyzed using chi-square and ANOVA respectively. In phases I and II, repeated measures ANOVA was employed to analyze activity level differences between the off state, on state, and dyskinetic periods. In phase III, repeated measures ANOVA was employed to characterize disease states and activity-type effect on activity level. Finally, one-way ANOVA followed by Bonferroni correction was used to compare the percentage of daily time spent performing each activity by the patients and controls. Arcsine-root transformation was employed to render the variable normally distributed. Mean activity was related to patient activity-type or motor status using repeated measures ANOVA. Results were expressed as mean $\pm$ standard error of the mean unless otherwise indicated. Alpha error was set to $p = .05$.

RESULTS

For the first phase of the study 10 dyskinetic PD patients were recruited, 9 of whom completed the evaluation. Mean age was 67 ± 10 years and 60% were males. Mean Hoehn and Yahr score was 3.1 ± 1.0 and mean LDED was 900 ± 400 mg/day. As shown in Figure 1, activity during the off state did not differ from the on state ($p < .5$). On the contrary, activity was more than 30% higher during the dyskinetic periods ($p < .01$ vs. on state without dyskinesia, Figure 1). For the second phase, 16 of 20 recruited dyskinetic PD patients completed a valid 72-hr on–off diary. Mean age was 65 ± 11 years and 55% were males. Mean Hoehn and Yahr score was 3.0 ± 1.0 and mean LDED was 850 ± 300 mg/day. Results from these patients resembled those of phase I in that the off state activity did not differ from the on state ($p < .6$, Figure 2), whereas a significant difference of more than 60% was found between the on state and the dyskinetic period ($p < .01$, Figure 2). For the third phase, 62 PD patients and 14 age- and sex-matched healthy controls were recruited. As expected, major differences in PD characteristics were found between de novo, stable, wearing-off, and dyskinetic PD patients (Table 1).

Healthy controls and PD patients reported spending 15% of their waking hours lying down, 40%
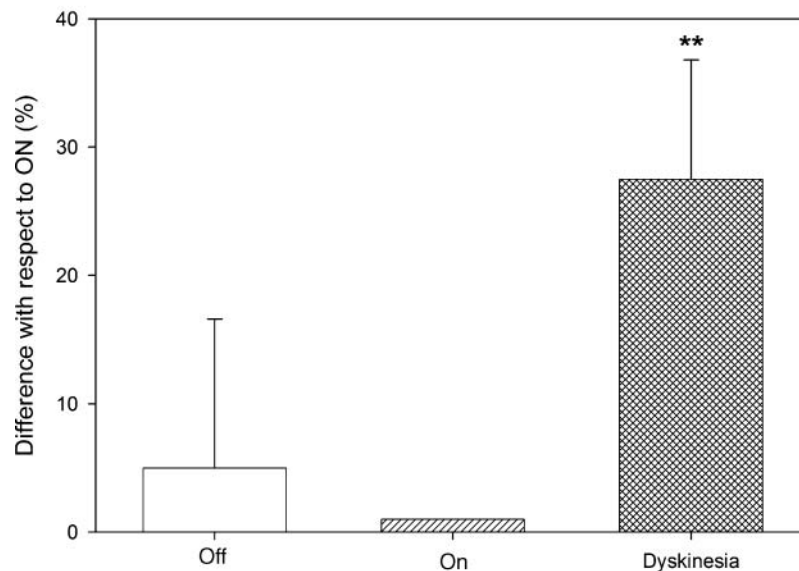
FIGURE 1   Differences in activity with respect to on state (%) during acute levodopa challenge in nine dyskinetic PD patients (phase I). Dyskinesia period showed differences compared to on state (**p < .01, Repeated measures ANOVA). No differences could be found between on state and off state. Shown are mean ± standard error of the mean.

sitting, and 44% in the upright position ($p < .01$, Figure 3). Less than 1% of their time awake was spent performing physical exercise, which was considered insufficient for proper evaluation of results registered while performing this task, and hence not included in the study data analyzed. Dyskinetic patients spent significantly more time lying down and less time in the upright position than healthy controls (respectively, $p < .01$ and $p < .05$, Figure 3).

Actigraphy-measured counts classified according to daily activities in controls and PD patients are shown in Figure 4. ANOVA revealed a significant ef-

fect of the type of daily activities on motor activity. Counts registered while lying down, sitting, and in the upright position were $5,690 \pm 306$, $9,153 \pm 346$, and $12,413 \pm 380$ respectively (mean ± SEM, $F = 73$, $p < .001$, Figure 4). On the other hand, significant differences in the activity of healthy controls, de novo, stable, wearing-off only, and dyskinetic PD patients were identified (respectively, $11,963 \pm 766$, $7,438 \pm 677$, $7,232 \pm 350$, $6,819 \pm 967$, and $9,738 \pm 432$; $F = 12$, $p < .001$, Figure 4). Bonferroni post hoc test of group means indicated that de novo, stable, and wearing-off only PD patients had significantly lower

TABLE 1   Phase III sample characteristics

	Healthy controls	PD patients				
		De novo	Stable	Wearing-off	Dyskinetic	*p*
N	14	12	21	7	22	
Age (years)	64.2 ± 10	71.2 ± 8.6	68.6 ± 7.4	64.1 ± 6.4	69.3 ± 9.9	<.2
Males (%)	5 (35)	6 (50)	13 (62)	5 (70)	12 (54)	<.1
UPDRS II score	–	8.1 ± 5.3	9.0 ± 4.0	14 ± 7.9	12.5 ± 5.8	<.03
UPDRS III score	–	12 ± 8	17.1 ± 8.6	18.5 ± 11.2	20 ± 10.7	<.2
UPDRS IV score	–	0	0	2.2 ± 0.6	5.8 ± 4.1	<.001
Dyskinesia score	–	0	0	0	3.4 ± 2.7	<.001
LDED (mg/day)	–	0	536 ± 333	899 ± 347	879 ± 373	<.001
Disease duration (years)	–	1.9 ± 2.4	5.2 ± 2.8	8.3 ± 3.2	10.9 ± 4.5	<.001
Hoehn and Yahr score	–	1.6 ± 0.4	2.1 ± 0.7	2.5 ± 0.9	2.8 ± 1.0	<.001

Mean ± SEM are shown. Data was analyzed by one-way ANOVA. LDED: levodopa daily equivalent dose.
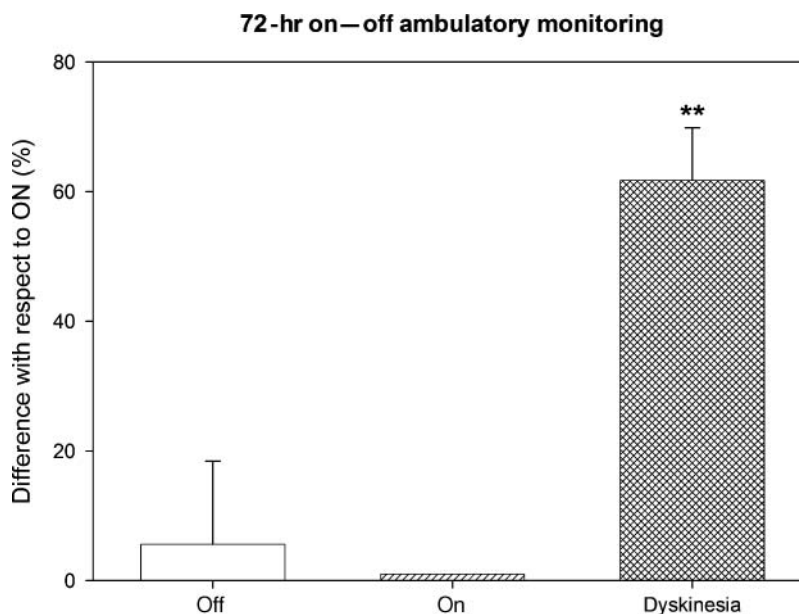
72-hr on—off ambulatory monitoring

FIGURE 2   Differences in activity with respect to on state (%) as evaluated by a 72-hr ambulatory on–off diary in 16 dyskinetic PD patients (phase II). Dyskinesia period showed differences compared to on state ($^{**}p < .01$, Repeated measures ANOVA). No differences could be found between on state and off state. Shown are mean ± standard error of the mean.

activity compared to healthy controls and dyskinetic patients (Figure 4). Tremor scores calculated using part III of the UPDRS for either the dominant or nondominant arm did not correlate with mean activity ($r = 0.1$ $p < .9$ and $r = -0.06$, $p < .9$ respectively). In nondyskinetic patients, mean activity correlated moderately with UPDRS II scores ($r = -0.21$, $p < .05$).
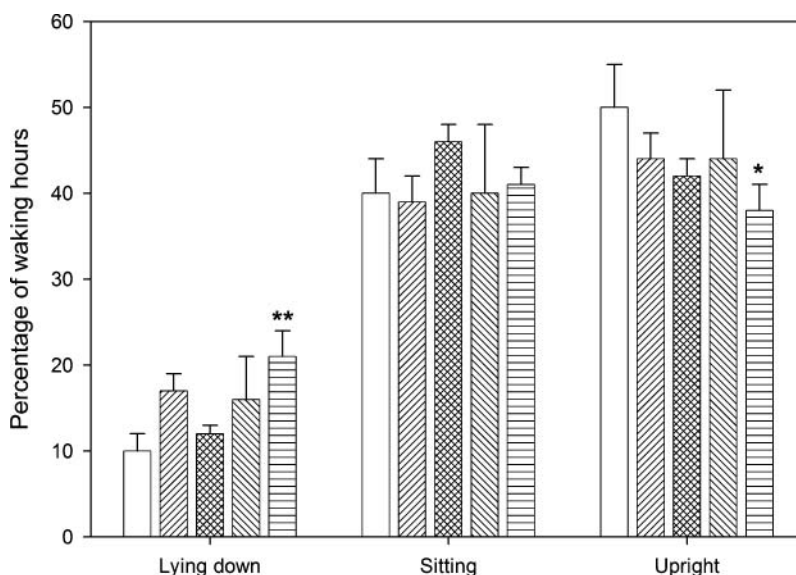
FIGURE 3   Percentage of waking hours reported spent lying down, sitting, or in the upright position in healthy controls (☐) and de novo (▨), stable (▨), wearing-off only (▨), and dyskinetic (☰) PD patients (phase III). Data shown were obtained from daily activities diaries. Repeated measures ANOVA followed by Bonferroni showed that dyskinetic patients spent significantly more time lying down ($^{**}p < .01$) and significantly less time upright ($^*p < .05$) as compared to healthy controls.
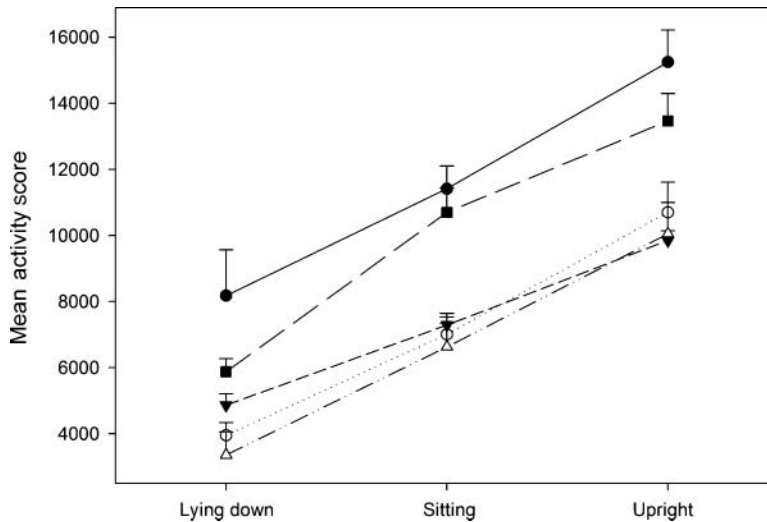
FIGURE 4   Mean activity scores while lying down, sitting, or in the upright position in healthy controls (●) and de novo (○), stable (▼), wearing-off only (△), and dyskinetic (■) PD patients (phase III). One-way ANOVA showed significant effect of activity-type and disease status (respectively, $F = 73$, $p < .001$ and $F = 16$, $p < .001$). Mean $\pm$ standard error of the mean are shown.

DISCUSSION

Although multichannel actigraphic devices can accurately evaluate body posture as well as bradykinesia, hypokinesia, tremor, and dyskinesia, they remain expensive and are not readily available worldwide. Current single wrist-worn actigraphic devices remain inexpensive and are very commonly used. Moreover, they have become more sensitive and, by bandpass-filtering 2–3 Hz range, they can capture regular movement minimizing the confusing effect of tremor, which occurs at the 4–6 Hz movement range. Therefore, we decided to reevaluate this device for PD motor status assessment. The main results indicated that motor activity in the off and on states was indistinguishable. On the contrary, the dyskinetic periods displayed significantly higher activity.

These results resemble previous findings, which showed multichannel actigraphy's inability to differentiate off and on states based on movement acceleration (Hoff et al., 2004; Keijsers et al., 2006). It was argued that actigraphic inability to differentiate on and off states might be related to the device mistakenly labeling low-movement periods as off state periods, or to shortcomings of the off–on diary used as a reference method (Hoff et al., 2004; Keijsers et al., 2006). Our results during an acute levodopa challenge rules out the second possibility and strongly argues against the first one. Another possibility is that the actigraphy model studied herein is still sensitive to tremor despite filtering the 2–3 Hz movement range. Although activity recordings showed no relationship to UPDRS

tremor scores, this possibility cannot be completely ruled out.

We also the explored the possibility of employing daytime activity level for evaluation of overall motor status. Significant differences in motor activity were observed between healthy controls, de novo, stable, wearing-off, and dyskinetic PD patients, which remained unaltered by daily activities performed during the study. De novo, stable, and wearing-off patients showed lower activity compared to healthy or dyskinetic subjects under all activity conditions. As in other experimental situations, the device's lack of specificity limits its usefulness. Nonetheless, the findings that at least in nondyskinetic subjects diurnal activity was related to daily activities performance (UPDRS II) suggest that it may be an indicator of quality of life, but further research is needed. A shortcoming to this part of the study was that the activity diary used was developed specifically for this study based on the daily energy expenditure diary of Bratteby et al. (1997, 1998) and has not been validated prior to this application. Nonetheless, this diary can be a good aid to interpret actigraphy results, but at the expense of needing patients' cooperation and therefore losing one of the advantages of the method.

In summary, in this study, wrist-worn actigraphy found higher activity levels during dyskinetic periods but no differences between on state and off state. Therefore, although not useful for assessing off and on states, simple wrist-worn actigraphic devices can be used for dyskinesia assessment in clinical practice and research. In nondyskinetic patients, daytime

activity level can be an indicator of quality of life, but further research is needed in this area.

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