Rasagiline, sleep quality and well-being in Parkinson’s disease: a pilot study

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Abstract
Sleep disorders and excessive daytime sleepiness are among the commonest nonmotor symptoms in Parkinson disease (PD) and can contribute to significantly lower quality of life in affected patients. Various antiparkinson drugs exert a relevant influence on sleep quality, daily vigilance and well-being. In the latest years, administration of monoamine oxidase type B inhibitor (iMAO-B) medications in PD, especially rasagiline, has gained importance due to the hypothesized neuroprotective effect of these agents. Whereas the ‘wakepromoting’ effect of selegine, due to its activating amphetamine-like compounds, has been already described, less is known regarding the effect of rasagiline, a world-wide used iMAO-B drug. A pilot study was carried out to analyze the effects of rasagiline on sleep and health-related quality of life in a small cohort of PD patients. According to our results, PD patients treated with rasagiline referred better sleep quality, required less frequently hypnotic medication, complained of lower daytime sleepiness and presented higher scores in social functioning, perceived energy levels and emotional well-being. Albeit limited by the small sample size, our study suggests an intriguing role of rasagiline in improving sleep and quality of life in PD patients. Further studies are necessary to confirm our preliminary observations.

Keywords i-MAO-B · Antiparkinson medications · Parkinson’s disease · Sleep quality · Health · Quality of life

Introduction
Sleep disturbances are among the toughest challenges in the Parkinson’s disease (PD) management, affecting up to 70% of patients and commonly being refractory to conventional pharmacological approaches [1].

PD can be worsened by either chronic insomnia, circadian rhythm disruption, hypersomnolence, non-refreshing sleep, obstructive sleep apnea, restless leg syndrome and/or REM parasomnia, especially REM behavior disorder (RBD) [2]. Most PD patients complain for a lower sleep quality compared to age-matched healthy controls and, concurrently, elderly people suffering from sleep fragmentation have a higher risk to develop dopaminergic neural loss, in a reciprocal way [3]. Sleep problems may precede the development of typical motor manifestation in PD [4] and contribute to significantly reduce quality of life [5]. In the PD management, the most important goal for the neurologist is to improve motor and non-motor symptoms, in order to preserve a high quality of life.

However, it is well-known that various anti-parkinsonian medications may concur to worsen sleep-related issues: dopamine agonists sometimes induce excessive daytime sleepiness or sleep attacks [6], while l-dopa had been associated with both RBD exacerbation [7] and/or sleep fragmentation [8].

In the latest years, the potential ‘disease-modifying’ effect of various commonly used anti-parkinson drugs has been largely explored. Encouraging results had been reached by pre-clinical investigation on inhibitors of type B monoamine oxidase (i-MAO-B) (especially selegiline and rasagiline), exhibiting a potent neuroprotective function [9].

Currently i-MAO-B drugs are prescribed especially in the youngest PD patients with milder motor manifestations, either...
in monotherapy or, more frequently, as add-on to dopaminergic medications [10]. Therefore, as PD progresses and symptoms become more severe, virtually, all patients will require L-dopa. The choice of adding an i-MAO-B medication is rarely driven by considerations on its impact on sleep/wake regulation.

If the i-MAO-B selegiline is degraded to L-amphetamine, and thus can reasonably worsen sleep quality, conversely, rasagiline has no amphetamine-like properties and therefore lacks impact on sleep. Accordingly, recent studies reveal benefits of rasagiline on PD-associated sleep issues [11, 12]: in particular, the drug can improve excessive daytime sleepiness and consolidate sleep continuity.

In a single-center pilot case-control study, we explored the effects of rasagiline as add-on therapy on sleep and quality of life in a small cohort of PD patients under chronic treatment with the dopamine agonist ropinirole. Our first outcome was to compare sleep quality in patients in monotherapy with the dopamine agonists (controls) versus patients treated with ropinirole combined with rasagiline (cases). We also collected information on daytime sleepiness and health-related quality of life in the two cohorts, using validated questionnaire.

Material and methods

In July and August 2021, we consecutively enrolled patients with early PD (Hoehn & Yahr stage ≤ 2) regularly followed at the University Hospital in Parma, Italy, who were either under chronic monotherapy with ropinirole (controls) or in therapy with ropinirole combined with rasagiline (cases). PD diagnosis was made by a neurologist expert in the field (AN) according to clinical diagnostic criteria from the United Kingdom Parkinson’s Disease (UKPD) Society Brain Bank criteria [13].

Patients affected by pre-existent sleep disturbances or regularly assuming hypnotics or other sleep-promoting medications were excluded.

Patients were recruited during follow-up neurological visits and, as the study was conducted during the acute phase of the Sars-Cov2 pandemia, all the clinical information were collected through the administration of the chosen questionnaires during phone calls. To ensure replicability, data were collected by the same trained investigator (RBS).

Sleep quality was assessed with Pittsburgh Sleep Quality Index (PSQI) [14], a validated test composed of 19 items and generating 7 ‘subcomponent’ scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. The cut-off of 5 in the PSQI differentiates ‘good’ sleepers (<= 5) from ‘bad’ sleepers (>5). Daytime sleepiness was measured using Epworth Sleepiness Scale (ESS) [15], a tool of 8 items assessing the propensity for sleep in common situations. Values > 10 were considered significant for excessive daytime sleepiness (EDS). Quality of life was tested using 36-Items Short Form Healthy Survey (SF-36) [16], which analyzes 8 subitems: physical functioning, role of limitations due to physical health, role of limitation due to emotional problems, level of energy/fatigue, emotional well-being, social functioning, pain and general health.

Statistical analysis

Descriptive statistics were generated for all clinical characteristics and outcome measures as appropriate (for continuous variables: sample size (N), mean, standard deviation (SD); for categorical variables: frequency, percentage). Wilcoxon’s test was adopted to compare differences between groups with respect to our outcomes.

Spearman’s correlation test was used to evaluate relationship between PSQI and SF36 results.

A perfect Spearman correlation (e.g. +1 or −1) is reached when each variable is a perfect monotone function of the other. Both Spearman’s rho coefficient, uncorrect and correct p value, using Holm’s method, are provided.

Results

Detailed descriptive results are summarized in Tables 1, 2, 3, 4 and 5. The final sample included 17 patients (70.5% male, 29.5% female), divided in 9 controls (monotherapy with dopamine agonist) and 8 cases (therapy with ropinirole combined with rasagiline), with a mean age 65.94 (± 8.41) and a mean disease duration of 3.7 years (± 2.49). The daily dosages of dopaminergic agonist were similar between cases and controls (respectively 9 mg ± 2.62 and 7.7 mg ± 3.23). All cases were taking 1 mg of rasagiline and the mean therapy duration with the iMAO-B medication was 12.62 months (± 4.44).

|   | Controls (n= 9) | Cases (n= 8) | p value |
|---|----------------|-------------|---------|
| Age | Mean | SD | Mean | SD |
| Illness duration | 4 | 3.31 | 3.3 | 1.18 | 0.608 |
| Gender (M/F) | 6/3 | 6/2 |
Sleep quality

With respect to our first outcome (sleep quality), cases presented significantly lower scores at PSQI compared to controls (respectively 4.8 ± 2.64 versus 7.6 ± 2.78, p value = 0.026). As detailed in Table 3, exploring subitems, the major difference derived from need for utilization of hypnotic medications (occasional use), which was higher in the control group compared to cases (p value = 0.047). The differences between the scores of the two groups of patients, with respect to sleep quality, are summarized in Fig. 1.

Daytime sleepiness

Cases presented significantly lower values at ESS compared to controls (respectively 7.4 ± 4.8 versus 9.7 ± 3.11, p value = 0.045). The differences between the scores of the two groups of patients, with respect to daytime sleepiness, are summarized in Fig. 2.

Health-related quality of life

Cases and controls presented similar mean scores at SF-36 questionnaire (respectively 72.5 ± 21.28 versus 56.8 ± 18.31, p value = 0.138). However, when exploring subitems, cases presented significantly higher scores in the following categories: social functioning (87.5 ± 16.36 versus 62.5 ± 25, p value = 0.016), energy/fatigue (67.5 ± 23.75 versus 48.8 ± 19.32, p value = 0.045), perceived emotional well-being (78 ± 24.8 versus 60.89 ± 12.1, p value = 0.023), perception of general health (61.8 ± 19.80 versus 45 ± 23.31, p value = 0.045). See Table 4 for details and Fig. 3.

Correlation analysis

We applied Spearman’s correlation analysis with Holm correction to assess relationship between PSQI and SF36 questionnaire results. Main findings are summarized in Table 5.

In the ‘control group’, there was a negative correlation between PSQI score and all the subitems of the SF36 questionnaire, with the exception of item 8, for which the correlation was considered negligible (ρ <0.2) None of these survived after Holm’s correction.

In the ‘case group’, there was a negative correlation between PSQI score and 4 subitems of the SF36, namely, the ones exploring the role of limitation due to emotional problems, emotional well-being, pain and general health. However, none of these survived after Holm’s correction.

Table 2 Questionnaires’ results related to the two groups of patients are presented as mean and standard deviation, together with the associated p value Wilcoxon’s test.

|                      | Controls (n= 9) | Cases (n= 8) | p value |
|----------------------|----------------|--------------|---------|
|                      | Mean  | SD       | Mean  | SD       |         |
| ESS                  | 9.7   | 3.11     | 7.4   | 4.80     | 0.045   |
| PSQI                 | 7.6   | 2.78     | 4.8   | 2.64     | 0.026   |
| SF-36                | 56.8  | 18.31    | 72.5  | 21.28    | 0.138   |

Significant results are highlighted in bold

*The statistical test used to calculate the p value is the non-parametric Wilcoxon test.

Table 3 Pittsburgh Sleep Quality Index scores. Pittsburgh Sleep Quality Index (PSQI) results related to the two groups of patients are presented as mean and standard deviation, together with the associated p value Wilcoxon’s test.

|                        | Controls (n= 9) | Cases (n= 8) | p value |
|------------------------|----------------|--------------|---------|
|                        | Mean  | SD       | Mean  | SD       |         |
| Subjective sleep quality | 1.5   | 1.01     | 0.8   | 0.64     | 0.116   |
| Sleep latency          | 1.1   | 1.05     | 0.7   | 1.03     | 0.443   |
| Sleep duration         | 1.5   | 0.52     | 0.8   | 0.99     | 0.146   |
| Habitual sleep efficiency | 0.5   | 0.72     | 0.5   | 0.92     | 0.691   |
| Sleep disturbances     | 1.2   | 0.44     | 1.2   | 0.46     | 0.947   |
| Use of sleeping medications | 0.5   | 0.88     | 0    | 0       | 0.047   |
| Daytime disfunction    | 1.1   | 0.60     | 0.6   | 0.91     | 0.181   |
| Total                  | 7.6   | 2.78     | 4.8   | 2.64     | 0.026   |

Significant results are highlighted in bold

Table 4 SF-36 scores. 36-Items Short Form Healthy Survey (SF-36) results related to the two groups of patients are presented as mean and standard deviation, together with the associated p value Wilcoxon’s test.

|                            | Controls (n= 9) | Cases (n= 8) | p value |
|----------------------------|----------------|--------------|---------|
|                            | Mean  | SD       | Mean  | SD       |         |
| Physical functioning        | 72.7  | 29.16    | 82.3  | 17.09    | 0.626   |
| Role limitations due physical health | 50    | 37.5     | 59.3  | 46.17    | 0.652   |
| Role limitations due to emotional problems | 44.4 | 33.33    | 70.8  | 33.03    | 0.121   |
| Energy / Fatigue            | 48.8  | 19.32    | 67.5  | 23.75    | 0.045   |
| Emotional well being        | 60.8  | 12.12    | 78    | 24.84    | 0.023   |
| Social functioning          | 62.5  | 25       | 87.5  | 16.36    | 0.016   |
| Pain                       | 70.5  | 22.93    | 73.1  | 24.52    | 0.845   |
| General health              | 45    | 23.31    | 61.8  | 19.80    | 0.045   |
| Total                      | 56.8  | 18.31    | 72.5  | 21.28    | 0.138   |

Significant results are highlighted in bold
Discussion

In the present pilot study, we compared sleep quality, daytime sleepiness and health-related quality of life in patients with PD taking the dopamine agonist ropinirole (controls) versus patients on therapy with ropinirole combined with rasagiline (cases) by means of validated questionnaires.

The choice to focus on an add-on framework (cases) instead of selecting patients taking i-MAO-B as monotherapy was driven by the preference of a real-life scenario as these drugs are commonly used together with other dopaminergic medications in the every-day clinical setting.

Compared to controls, cases presented a better sleep quality and required less frequently administration of hypnotic medications. They also suffered from lower levels of subjective daytime sleepiness. Finally, cases presented higher scores in the social functioning sub-scale of the SF-36 questionnaire, with higher values of energy and a better perceived emotional well-being.

Albeit limited by the small-sample, we believe that our study confirms some interesting points on latent benefits on sleep associated with rasagiline in the pharmacological management of PD.

It has been recently demonstrated that hypnotics (specifically benzodiazepine and antidepressants) can foster functional
decline in various neurodegenerative disorders [17]. Furthermore, sedative-hypnotic molecules demonstrate low efficacy in the management of PD-related insomnia and are often associated with harmful side effects including drowsiness and increased risk of fall [18]. Hence, the possibility to reduce the need for hypnotics in a PD cohort, while ameliorating sleep quality, is a crucial result that needs to be confirmed in wider samples.

EDS in PD patients may lead to abrupt sleep attacks, increasing the risk for car accidents, falls, trauma and lowering the quality of life [19]. In our pilot study, encouraging results came from the use of rasagiline, which significantly improved the level of sleepiness during the day.

The HRQoL tool documented that cases presented significantly better results with respect to social functioning. It is known that PD patients can suffer from emotional and communicative changes due to impoverished emotional facial expressions (the so-called facial masking) [20] and/or difficulties in speaking and verbally expressing themselves, which can cause major disruptions to social functioning. These disturbances may lead to isolation, stigma and loneliness, negatively affecting health-related outcomes [21].

The topic of social functioning is particularly relevant in the current era, when we are still dealing with the tragic consequences of the Sars-Cov2 outbreak, which can exacerbate biosocial relations especially among the more vulnerable categories, including patients with neurodegenerative diseases [22].

Furthermore, recent evidence highlighted the strong bidirectional interaction between sleep and social functioning, with sleep influencing the way people react to stressors, individuals’ empathy and tendency for conflict in close relationship [23]. Hence, the possibility to ameliorate social functioning impacting on sleep quality is a potentially advantageous option.

To assess whether there was a relationship between HRQoL and sleep quality in cases and controls, we performed a correlation analysis between PSQI and SF36 subitems. According to our data, none of the subitems of the SF36 was significantly correlated to PSQI test in either cases or controls. Albeit limited by the small sample size, our findings could suggest that rasagiline independently improve both quality of life and sleep quality in treated patients.

Our results are in line with previous data demonstrating the positive impact of rasagiline on sleep quality in PD patients. Schettino et al. (2016) [11] compared sleep quality and continuity in PD patients assuming levodopa with or without rasagiline and found that the i-MAO-B medication lead to improvement in sleep latency, number of awakening and total sleep time after 12 weeks. Similarly, Schrempf et al. (2018) [12] revealed differences in sleep features when rasagiline was used as an add-on medication in a PD cohort. According to their results, rasagiline enhances sleep continuity and reduces wake-after sleep onset, arousal-index and percentage of light sleep (stage N1).

Finally, previous studies indicated that PD patients taking selegiline may benefit from a switch towards rasagiline in terms of sleep quality and other non-motor symptoms [24], confirming our preliminary impressions.

The study presents a number of limitations. First, our sample was composed of a limited number of patients, also due to restrictive inclusion criteria. This point probably represents the main drawback of our research: we decided to perform a first exploratory pilot study, to test rasagiline effects on PD patients, and, given the encouraging results, we plan to confirm our hypothesis in wider samples. Moreover, sleep features were evaluated only with self-reported questionnaire and, partly due to concerns coming from the Sars-Cov2 outbreak, we were not able to perform any instrumental recording (e.g. video-polysomnography). Finally, it is known that the disease progression could impact on sleep quality in PD patients; hence, we could not exclude that cases took advantage from i-MAO-B medications in terms of motor control and, therefore, indirectly, ameliorate their sleep patterns. To overcome this potential bias, we selected a homogeneous group of early-stage PD patients and we tried to explore our outcome of interest (sleep quality) using complementary questionnaires (ESS, PSQI, SF-36).

Regardless the listed limitations, statistical significance was reached for several items, although larger studies are deemed necessary to confirm and extend clinical inferences.

**Conclusion**

Sleep issues are extremely common and critical in the PD evolution. Some antiparkinson medications can concur to disrupt sleep or may exacerbate daytime sleepiness.
sleep disturbances severely impact on PD patient’s quality of life and daytime functioning. In the present pilot study, we explored the effect of rasagiline, a widely used i-MAO-B medication, on self-reported sleep quality, daytime sleepiness and health-related quality of life. In our sample, rasagline significantly improved sleep quality, reduced the need for hypnotic medications, ameliorated social functioning, increased the level of subjective daily energy and augmented the perceived emotional well-being. Considering the relevance of sleep disturbances in the PD management, wider studies are needed to consolidate these promising results.

Declarations

Ethical approval  The study was approved by the Local Ethical Committee with protocol number 414/2021/OSS/AOUPR.

Informed consent  Informed consent was requested and collected for all participants.

Conflict of interest  The authors declare no competing interests.

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