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PRIMARY AND SECONDARY FEATURES OF PARKINSON'S DISEASE IMPROVE WITH STRATEGIC EXPOSURE TO BRIGHT LIGHT: A CASE SERIES STUDY

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The antagonism of melatonin in models of Parkinson's disease (PD) can reduce the severity of motor impairment associated with dopamine (DA) degeneration. In consideration of the potent antidepressant effects of bright light therapy (LT), that LT suppresses melatonin secretion, that depression is commonly observed in PD, and that exposure to constant light facilitates recovery from experimental PD, the object of the present study was to strategically administer LT to PD patients and observe the effects on depression, insomnia, and motor performance. Twelve patients diagnosed with PD were exposed to white fluorescent light for 1–1.5 h at an intensity of 1000 to 1500 lux once daily commencing 1 h prior to the usual time of sleep onset, ~22:00 h in most patients. All patients were assessed before LT commenced and at two weeks, five weeks, and regular intervals thereafter. Within two weeks after commencing LT, marked improvement in bradykinaesia and rigidity was observed in most patients. Tremor was not affected by LT treatment; however, agitation, dyskinaesia, and psychiatric side effects were reduced, as verified by decreased requirement for DA replacement therapy. Elevated mood, improved sleep, decreased seborrhea, reduced impotence, and increased appetite were observed after LT. LT permitted the reduction of the dose of L-dopa, bromocriptine, or deprenyl in some patients by up to 50% without loss of symptom control. Factors limiting the efficacy of LT included multiple disease states, treatment compliance, polypharmacy, emotional stress, advanced age, and predominance of positive symptoms. The results of this case series study confirms previous work describing light as efficacious in the treatment of PD and suggest that controlled trials may help to elucidate how LT might be used strategically as an adjunct therapy to improve the morbidity of PD patients.

Keywords Melatonin, Parkinson's disease, Depression, Insomnia, Bright light therapy

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INTRODUCTION

Parkinson's disease (PD) is a neuropsychiatric disorder characterized by the cardinal signs of bradykinaesia, rigidity, and tremor. Secondary features usually include insomnia and depression, with the latter observed in as many as 98% of PD patients, and may be present for two decades prior to clinical diagnosis (Deniker et al., 1975; Fonda, 1985; Girotti et al., 1986; Okun & Watts, 2002; Schnaberth, 1986). While various forms of dopamine (DA) replacement therapy provide some therapeutic benefit, their side effects usually become very severe (Arnulf et al., 2002; Cotzias et al., 1971), with involuntary movement and psychiatric side effects emerging as major complications (Cotzias et al., 1971; Fonda, 1985; Kuzuhara et al., 2001). To make matters worse, the management of the secondary features of PD with antidepressants and hypnotics confound treatment efficacy, thereby aggravating anxiety, sundowning syndrome, and insomnia, as well as compromising the quality of life in these patients (Arnulf et al., 2002). On this basis, strategies that simplify the therapeutic regimen by reducing the total daily dose of DA replacement, decreasing the number of adjuvant drugs, or implementing non-invasive therapies would be advantageous.

In this regard, Artemenko and Levin (1996) employed bright light therapy (LT) to treat the depression associated with PD. This approach was based on evidence demonstrating that strategically applied LT exerts a beneficial effect on seasonal affective disorder (SAD; see Rosenthal et al., 1984, 1988). Not only did LT improve the depression associated with PD, but some aspects of motor function also improved after only a few LT exposures. However, this short-term study (Artemenko & Levin, 1996) provided only limited assessment of the impact of such treatment on motor function and secondary Parkinsonian features, and the authors did not speculate as to the underlying mechanism and if and how melatonin might be involved in the observed therapeutic effect. Elucidating the underlying mechanism is of particular importance, especially in regard to studies suggesting that methods that increase melatonin bioavailability increase the severity of experimental PD, while those that decrease it induce recovery (Willis & Armstrong, 1999; Willis & Kennedy, 2004). Melatonin supplementation of deficient secretion in preclinical forms of PD either has no effect or exacerbates the disease (Burton et al., 1991; Patterson & Vickers, 1984; Willis & Armstrong, 1999), while clinical administration of the hormone is without effect (Papavasiliou et al., 1972; Shaw 1977; Shaw et al., 1973, 1975). Such reports argue against the use of melatonin as a treatment strategy for PD (Antón-Tay, 1974; Antón-Tay et al., 1971).

Recently, preclinical studies employing melatonin injections directly into the cerebral ventricles of animals with experimentally induced PD

showed a worsening of symptoms (Willis & Armstrong, 1999). Conversely, the application of constant light induced a gradual recovery of motor and regulatory function. On this basis, and in collective consideration of reports suggesting the efficacy of LT in the treatment of SAD and non-SAD depression (Benedetti et al., 2003; Martiny, 2004; Rosenthal et al., 1984, 1988), that depression is commonly seen in PD (Deniker et al., 1975; Fonda, 1985; Girotti et al., 1986; Okun & Watts, 2002), and that PD patients have been described as being phase advanced (Bordet et al., 2003; Fertl et al., 1991, 1993), this study sought to assess the effect of LT on the primary and secondary symptoms of this disorder.

MATERIALS AND METHODS

A case series of eight male and four female diurnally active subjects, ranging in age from 46 to 83 (average age 66) yrs and who had been diagnosed with idiosyncratic PD 2–15 yrs earlier, were self-referred from a general practice. They were prescribed LT for the treatment of depression or insomnia on a case-by-case basis. The study was conducted following ethical recommendations (Touitou et al., 2006), and permission to assess motor function was obtained from each subject after informed consent was provided to determine whether LT exerts a detrimental effect on motor performance. While the assessment was open label, care was taken when providing instructions to participants to ensure that the instructions were non-directional, and patients were not alerted to expected outcomes.

LT was administered daily in an intensity of 1000–1500 lux for two to five weeks, unless otherwise indicated, by a light box containing fluorescent tubes without ultra-violet emission. Because melatonin is secreted primarily at night in diurnally active persons (Ralph, 1976; Roth et al., 1962), LT was administered for a duration of 1–1.5 h prior to the usual time of sleep onset, ~22:00 h in most patients. PD subjects have been described as being "phase advanced" (Bordet et al., 2003; Fertl et al., 1991); thus, the time of exposure to LT was selected to correspond to roughly around the assumed peak of melatonin secretion, between 22:00–23:00 h in diurnally active subjects (Bordet et al., 2003).

The motor function of all of the participants was evaluated by three motor tests, which were applied during the light cycle, between 09:00 and 16:00 h. Subjects were assessed on initial presentation prior to receiving LT, at intervals varying from two to five weeks after the commencement of LT, and at regular intervals thereafter for a duration of up to several months. If no therapeutic benefit was achieved after five to eight weeks of LT, it was discontinued. If the subjects were medicated, the time of the last dosing was recorded prior to each assessment.

The first motor test, the latency (time required to complete the task) to ambulate, was assessed when subjects were required to walk a 3 m distance and then return. This test permitted a more or less global assessment of a PD patient's impaired ability to ambulate, taking into account the number of steps (shuffling), cogwheel rigidity, and speed. This test is a derivation of a standardized test reported previously by Feldman (1985).

The second motor test was the fist to elbow latency. The upper arm is extended and held 90° to the plane of the body with the lower arm extended upward 90° to the plane of the upper arm. The top of the clenched fist points toward the ceiling with clenched fingers orientated toward the face. With the opposite hand open, the subject begins by placing the palm of his hand on the top of the clench fist. When told to begin, the subject brings his open hand down, twisting it 180°, and then touching the elbow from underneath. This test measures dexterity, control, coordination, and strength. The latency to perform this task 10 times is recorded. In addition to the amount of time required to perform this task, the quality of performance is also assessed by monitoring the ability of each patient to maintain the arm in an extended position and the ability to completely rotate the hand in a smooth motion from a flat position on the top of the fist to the bottom of the elbow.

In a third motor test, the subject stands placing most of the weight on one foot. The subject then raises the other foot off the floor touching the inside of the knee with the ball of the foot. The foot is then returned to the floor. The latency to perform this task 10 consecutive times is recorded. This test was performed within close proximity of a table to provide support should balance be lost. In addition to the time required to perform this task, the quality of performance is determined by monitoring the ability to flex the foot medially to touch the knee, the ability to raise the foot to the appropriate height, and whether or not the patient needs support when performing the task. For the second and third tests, the subject is asked to count out loud as each of the 10 units is completed. Given that apraxia (the inability to perform complex coordinated movement) is commonly observed in PD and that severely impaired patients find it difficult to count and perform a motor task at the same time, this added task serves as another means of grading the severity of impairment.

To determine if there was a practice effect on any of the motor parameters, 22 non-PD volunteers ranging in age from 42 to 73 (mean age 51) yrs were tested on the latency to walk, fist to elbow, and knee to floor assessments. After the initial test, the participants were again tested two weeks later in the absence of exposure to LT. No practice effect was found when the healthy individuals performed the three motor tests on subsequent occasions.

The clinical assessment of motor performance and psychiatric parameters was made prior to commencing LT, and this served as baseline measurement for each patient. The same parameters were again measured during the course of treatment and at the completion of LT. In addition to assessment of motor function, other monitored signs and symptoms included tremor, bradykinaesia, rigidity, postural tremor, arm swing, kyphosis, handwriting, shuffling/cogwheel gate, masked face, throat clearing, bradylogia, exosialozamia, long- and short-term memory, confusion/disorientation, bradyphraenia, mood swing/irritability, depression, self-confidence, appetite, sleep, and sexual performance. These parameters were evaluated during interview in the presence or absence of caregivers. Side effects of drug administration, including involuntary movement or dyskinaesia, were also assessed. Information on the ability of each participant to perform daily routine tasks was obtained by interview and was based on a variation of the scale of daily living (Larsen et al., 1984). These parameters included dressing, feeding, hygiene, turning in bed, walking, getting out of a chair, climbing stairs, and falling. The clinician rated each patient, and the attending physician independently validated the assessment made by the clinician. If any discrepancies arose, all data for each patient were collectively discussed until consensus was reached. Caregivers for each patient provided additional information, which was taken into account during the evaluation.

All clinical parameters were scored by the attending clinician by means of a Likert-scale (Duvoisin et al., 1987; Likert, 1932) ranging from +++ to − − −, with the level of initial performance rated on an absolute basis. Relative improvements or degradations were scaled in regard to performance during the previous session. Time of the last medication and the on-off status, medication working (on) or not working (off), for each patient was taken into account during each assessment.

RESULTS

As illustrated in Table 1, LT resulted in improved motor function in most subjects. The most remarkable improvement was seen in bradykinaesia and rigidity, which was reflected in the latencies of ambulation, fist to elbow, and toe to knee tests, and/or clinical assessment and performance of daily activities. Ten of the 11 participants who used LT exhibited a 30–50% improvement in motor function on many of these parameters. Those that were compliant and used LT daily generally exhibited a better therapeutic response than those who used it only intermittently (see Table 1; cf. patients 01, 02, 04, 07, and 09, who were inconsistent in the use of LT, versus patients 03, 05, 06, 08, 10, and 11, who were fully compliant to LT). Subjects presenting mainly with tremor showed little change that could be attributed directly to LT. Nevertheless, some indirect

TABLE 1 The Effects of Bright Light Therapy on Parkinson's Disease: Summary of the Effects of Bright Light Therapy (1000–1500 lux) on Motor Performance, Psychiatric State, and Daily Function in Patients Diagnosed 2–15 Years Previously with Parkinson's Disease

Patient	LT Dosage (hrs/ intensity [lux]), duration, compliance	Anti-PD therapy: type, dose/day	Motor Tests: %Δ, Lat walk 3 m, Lat fist-elbow, Lat knee-floor	Clinical/motor/daily living	Psychiat. Change	Drug Δ: dose/day	Sleep: Aspect changed
01F83	1.5 \ 1500, 5 wks, intermittent	Madopar®, 900 mg	=, ↑ 28%, ↑ 43%	CM =, DL =	HAL -, DEL -, PAR -	Madopar®, ↓ 50%	=
02F54	1.0/1000, 4wks +, Intermittent	Zoloft®, 50 mg	↑ 34%, ↑ 50%, ↑ 43%	BAL +, TREM −, DL +	DPR +	Zoloft®, ↓ 100%	++ sleep onset
03M73	1.0/1500, 5 wks +, Compliant	NA	↓ 10%, ↑ 9%, ↑ 14%	=, SBR ++, DL +	DPR +++, SOC ++, CONF +, MEM +	NA	=
04M61	1.5/1500, 1 wk, Intermittent	Prothiadin®, 25 mg; Sinamet®, 500 mg; Eldopril®, 5 mg	↑ 3%, ↑ 26%, ↑ 29%	BR +, RGD +, DL +		Prothiadin®, ↓ 50%	+sleep onset
05F53	1 + 1(morn)/ 1500, 3 wks +, Compliant	Sinamet®, 500 mg	↑ 49%, ↑ 10%, ↑ 28%	BR ++, RGD ++, TREM ++, DL ++	CONF ++, DPR +++, APPT ++	Sinamet®, ↓ 25%	=
06F46	1.0/1500, 5 wks+, Compliant	Sinamet®, 200 mg; Eldopril®, 5 mg	↑ 10%, ↓ 9%, ↑ 13%	RGD ++, BR ++, DYS ++, DL ++	DPR +++	Sinamet®, ↓ 13%; Eldopril ↓ 100%	+++ sleep continuity
07M67	1 + 1(morn)/ 1500, 3 wks, Intermittent	Sinamet®, 500 mg; Parlodel® 5 mg; Eldopril®, 10 mg	↑ 7%, ↑ 14%, ↑ 9%	RGD +, DL =	DPR ++, IPO ++	Parlodel®, ↓ 50%; Eldopril ↓ 100%	=

08M75	1.0/1500, 5 wks+, Compliant	Artane®, 6 mg; Selegiline®, 10 mg; Amantad®, 200 mg; Permax®, 250 mg	↑ 15%, ↑ 13%, ↑ 27%	CM =, DL =	HAL +	Permax®, ↓ 100%; Selegiline, ↓ 50%	++ sleep onset
09M76	1 + 1(morn)/ 1500, 5 wks, Intermittent	Madopar®, 100 mg	↓ 1%, ↑ 14%, ↑ 17%	CM =, DL =		=	+ sleep continuity
10M67	1.0/1500, 5 wks+, Compliant	NA	↑ 33%, ↑ 20%, ↑ 24%	BR ++, RGD ++, SBR +++, DL +++	DPR +++, BPR +++	NA	+++ sleep continuity
11M73	1.0/1500, 5 wks+, compliant*	Sinamet®, 600 mg; Cabaser®, 2 mg	↑ 44%, ↑ 10%, ↑ 25%	BR =, RGD =, DL =	DPR –, CONF –	=	+ sleep continuity

Abbreviations: APPT = appetite; BAL = balance; BR = bradykinaesia; BPR = bradyphrenia; CM = clinical/motor parameters; CONF = self-confidence; Compliant = exposure to bright light therapy as prescribed; DEL = delusional; DL = performance on daily living scale; DPR = depression; DYS = dystonia; ETOH = voluntary alcohol consumption; FAT = fatigue; HAL = hallucinations; hrs = hours; Intermittent = occasional omission of prescribed exposure to bright light therapy; IPO = impotence; Lat fist-elbow = fist to elbow latency (×10); lat knee-floor = knee to floor latency; lat walk 3 m = latency to walk 3 meters; MEL = melatonin self-administration; MEM = memory; morn = morning exposure to bright light therapy; NA = not applicable; Par = paranoia; RGD = rigidity; SBR = seborrhea; Soc = socialization-interaction with others; TREM = tremor; WKS = weeks; Δ = change; (=) = no change; (+) = slight improvement; (++) = moderate improvement; (+++) = significant improvement; (−) = slight deterioration; (− −) = moderate deterioration; (− − −) = significant deterioration; (*) indicates increasing the intensity of light to 3000 lux after several weeks of no response to the 1500 lux intensity, as this patient was blind in one eye.

benefit on tremor was observed. For example, subject (02F54) experienced tremor acutely toward the end of the day, and this made falling asleep difficult. This, in turn, increased the severity of insomnia and anxiety. The application of LT for 1 h prior to this patient's desired bedtime decreased the intensity of tremor and normalized latency of sleep onset.

Additional benefits including reduction in anxiety and agitation were observed soon after LT commenced, and many subjects reported an acute state of relaxation at the onset of each session. Six of the 11 subjects using LT showed noticeable improvement in affect. The antidepressant effect of LT continued for several weeks, and even after it was discontinued. One subject prescribed Zoloft® (sertraline hydrochloride) for depression (02F54) was able to discontinue this medication, as the elevation of mood was greater than that experienced with the full dose of the antidepressant. One of the most noticeable effects of LT that paralleled the observed antidepressant effect was increased socialization (patient 03M73). There was a significant improvement in the drive to experience social interaction, and the number of outings attended increased. This occurred early during the first two weeks of treatment and continued for the duration of LT.

There were also numerous positive effects of LT on regulatory functions and pharmacotherapy. One of the most pronounced effects was on sleep. Prior to commencing LT, eight participants reported significant problems with falling asleep and staying asleep at night. Seven of these eight persons reported improvement in the onset and continuity of sleep after two weeks of LT. This effect was reported in most patients within two or three days of commencing LT and continued for several days following the withdrawal of LT.

In two subjects, hallucinations and delusions resulted from prolonged use of various types of DA replacement therapy. In one participant (01F83) maintained on Madopar® (L-dopa plus the peripheral decarboxylase inhibitor benserazide) for many years, LT had little effect on hallucinations and delusions, even though the dose of Madopar® was reduced by 50%. In another participant (08M75), LT permitted reduction by 50% of the daily dose of Symmetrel® (amantadine hydrochloride), which was taken for several years and during which hallucinations were a common side effect. The later replacement of Symmetrel® and Artane® (benzhexol hydrochloride) with low dose L-dopa completely eliminated hallucinations and delusions. In a third subject (not shown in Table 1) who was self-administering melatonin (1 × 3 mg at 22:00 h), hallucinations were frequent. While this subject was non-compliant with LT, melatonin treatment was withdrawn and hallucinations were no longer reported.

Parlodel® (bromocriptine mesylate) treatment caused sexual impotence in one subject (07M67), and this contributed significantly to relationship problems. Given that this person obtained significant therapeutic

benefit for tremor from this drug, it could not be totally eliminated from the therapeutic strategy. However, the 50% reduction in the daily dose of Parlodel® returned sexual function to normal and improved marital relationship. Decreased appetite after DA replacement therapy was also reversed in two subjects that showed consistent plateauing of body weight loss for several months after commencing DA replacement therapy. In one subject with a 20 yr prior history of anorexia (05F53), before the diagnosis of PD, body weight gain was never experienced. Within two weeks of commencing LT, an increased appetite and body weight gain of 2 kg was observed.

After LT, DA replacement therapy was reduced to a level ranging from 13% to 100% in 5/11 subjects, while antidepressants and soporific drugs were reduced or eliminated in two others. The dose of monoamine oxidase (MAO) inhibitors was also reduced during LT, without deterioration of motor performance or quality of life, and in some cases both were improved. As the gradual reduction of medication was undertaken, an incremental improvement in the response to LT was often observed.

DISCUSSION

The present findings, based on a case series of patients, demonstrate that LT can improve the bradykinaesia and rigidity of PD. The positive symptoms, however, were not as acutely responsive to the intensity and frequency of the LT employed, and few direct effects were seen on tremor during this relatively short-term time span of treatment. Some reduction in the severity of other positive symptoms was experienced as LT permitted the reduction of the daily dose of DA replacement therapy without compromising efficacy. Dyskinaesia and psychiatric side effects, which are commonly seen with DA replacement therapy, were reduced or eliminated. A similar finding was reported previously with an improvement on a computer-assisted motor task in PD patients when LT was employed as antidepressant therapy (Artemenko & Levin, 1996). The amelioration of bradykinaesia that was reported in that study was an incidental observation, as LT was employed to treat the associated depression. No consideration was given to the possible mechanisms of action that may have mediated the antidepressant or anti-Parkinsonian effects. Nevertheless, the improved aspects of motor function seen in that work confirm the observations of the present study, as LT precipitated improvement in motor function plus many aspects of daily living. Attempts to ameliorate depression using REM sleep deprivation has also been reported to reduce the severity of Parkinsonian symptoms, and this may be mediated by an attenuation of melatonin secretion, as the methods employed expose patients to light for at least 24 h (Andrade et al., 1987; Bertolucci et al., 1987; Demet et al., 1999; Reist et al., 1995). The

preference for varying light intensities in patients with neuropsychiatric disease (Gerbaldo et al., 1997) and impaired color perception in PD patients (Sartucci et al., 2003) are also consistent with the present findings, all of which collectively support the contention that the visual system is integrally involved in the etiology and treatment of PD.

Reduced melatonin secretion might be the mechanism by which LT achieves its therapeutic effect, and this is consistent with previous (Willis & Armstrong, 1998, 1999) and ongoing studies (Willis & Kennedy, 2004; Willis & Robertson, 2004, 2005) intimating the involvement of the pineal gland and melatonin in the etiology of PD. It is interesting to note that decreased pineal function associated with advancing age is hypothesized to contribute to the pathological and progressive DA degeneration in PD (Kunz et al., 1998; Mayo et al., 1998; Reiter, 1998; Sandyk, 1990), even though other treatments that have been shown to decrease melatonin secretion provide symptomatic relief. Such treatments include electromagnetic field stimulation (Sandyk, 1992a, 1992b; Welker et al., 1983), electroconvulsive therapy (ECT) (Douyon et al., 1989; Jeanneau, 1993; Krahn et al., 2000), and electrical stimulation of the globus pallidus (Catala et al., 1997). In addition, increased melatonin secretion has also been reported to be associated with prolonged use of DA replacement therapy, at a time consistent with the loss of its therapeutic efficacy (Bordet et al., 2003). Furthermore, the melatonin deficiency hypothesis of PD has been inexorably defended in spite of numerous reports that describe normal melatonin secretion and/or pineal function in old age, in PD, and in severe calcification of the pineal gland (Daramola & Olowu, 1972; Fertl et al., 1991,1993; Hasegawa et al., 1987; Kendall & Cavanagh, 1986; Krstic, 1986; Okudera et al., 1986; Old & Firm, 1974; Wurtman & Axelrod, 1965; Wurtman et al., 1964; Zimmerman & Bilaniuk, 1982). The controversy over this issue thus requires re-evaluation before clinical trials of melatonin to repair oxidative stress are undertaken (Karasek, 1999; Zisapel, 2001).

While the functional state of the pineal gland in Parkinsonism is controversial, there appears to be a consensus of opinion that PD patients are phased advanced (Bordet et al., 2003; Fertl et al., 1991, 1993); that is, the peak plasma concentrations of melatonin secretion occur about 3–4 h earlier in PD patients compared to age-matched controls. In normal subjects, the asymptote of melatonin secretion occurs at ~02:00 h. By prescribing the application of LT 1–1.5 h before retiring to nighttime sleep, the intention was to reduce or eliminate this melatonin peak. As most patients in the present study retired between 21:00 and 22:00 h, LT would be expected to have the effect of inducing a phase delay of the circadian system as well as inhibit peak melatonin secretion, which may be responsible for the observed improvement. While this possibility is currently under investigation (Willis & Robertson, 2005), caution is

recommended in accepting the hypothesis of altered melatonin rhythmicity and concentrations as playing a major role in PD until results of further studies are reported.

LT produced a remarkable antidepressive effect in 50% (6/12) of the subjects. This closely paralleled the improvement in bradykinaesia and rigidity, and this parallel has been observed previously in the treatment of PD (Arieti, 1954). It is interesting to note that many, if not all, anti-PD drugs exert an antidepressant effect at various times (Deniker et al., 1975; Meco et al., 1991; Schnaberth, 1986), but particularly in the early stages of treatment. Such an effect may be unrelated to whether or not such medications act specifically upon nigro-striatal dopamine to produce an antidepressive effect (Price et al., 1995), and this suggestion is consistent with the view that DA may not be the key etiological factor in PD (Willis & Armstrong, 1998).

That the therapeutic effects observed were not due to a practice or placebo effect is supported by four observations derived from the present study. First, a practice effect was not observed when healthy individuals performed the three motor tests on subsequent occasions. Secondly, those who were non-compliant with LT did not benefit as much as those who were complaint and used LT regularly (i.e., subject 12M59). Third, when the spectrum of light was switched from white to red and then back to white (subject 10M67), the condition of the participant changed from remission to relapse and then to remission. Not only does this suggest that LT, per se, is the critical factor, but also that it is the frequency of LT that plays a central role. It may well include those frequencies that most effectively antagonize melatonin secretion (Horne et al., 1991; Lewy et al., 1980; The Parkinson Archive Treasures Pieno Parkinson, 1995; Wright & Lack, 2001; Wright et al., 2001). Finally, the fact that subject 11M73 was totally blind in one eye after removal of a tumor several years earlier and showed little or no improvement despite strict treatment compliance with LT over several weeks is consistent with the conclusion that the observed effects found in the other PD subjects were due to the application and protic detection of the LT.

While there was a high level of consistency in the beneficial effects of LT on motor and psychiatric parameters across patients in this and other studies (Artemenko & Levin, 1996), these results must be interpreted cautiously. Given that the present results were case studies and no design was employed to formally blind the assessors to the treatment or its expected outcome, the clinical evaluation may have been biased. On the other hand, the attending physician had no knowledge about the use of LT in depression or PD, nor of the working hypothesis, and on this basis it might be argued that the bias was minimal, if present at all. This is reinforced by the requirement that the decision to alter medication was made by the attending physician on the basis of his own assessment

and after reaching mutual agreement with the attending clinician. Nevertheless, bias may have influenced the ratings of the more subjective measures by the attending clinicians and this must be taken into account. Equally important to consider is the possible impact of any perceived expectation(s) of the treatment effects and the novelty of the treatment on the patients, the symptoms, and latency tests outcomes. Because care was taken to avoid alerting the patient as to the expected treatment outcomes, and even though the main thrust of the potential bias was aimed at treating depression, the effect of LT on motor function and insomnia might be regarded as unexpected with respect to the patient. Furthermore, the PD patient is generally well educated about his condition, and there is inherent resistance to any suggestion that something as innocuous as light could repair compromised motor function. Generally speaking, their mindset would discount the efficacy of any treatment that did not replace deficient DA, and thus any expectation would be biased against LT rendering a therapeutic effect.

The mechanism by which LT may be rendering a therapeutic effect is not defined in the present study. It is interesting to note, however, that when PD patients experience a recovery of motor function in response to DA replacement, there is often a concomitant elevation of mood in the early stages of treatment (Deniker et al., 1975; Meco et al., 1991; Schnaberth, 1986). There is some suggestion from the present data (see Table 1) that those patients experiencing the most profound therapeutic effect in terms of improved motor function also experience antidepressant and soporific effects. While this must be confirmed in more detail in future controlled studies, the present observations lend support to the suggestion that the pineal gland and its secretion of melatonin may play a more important role in the etiology and treatment of PD than is currently envisaged (Willis, 2005). Whether the therapeutic effect of LT is mediated via pituitary function, by enhancing DA function, or a by a synchronous effect should be the subject of further evaluation.

There were several complicating factors that limited the efficacy of LT, including advanced age, treatment compliance, polypharmacy, the presence of multiple disease states, and the presence of deviant forms of Parkinsonism. In the first instance, the therapeutic effects observed were age-related in that older patients (>75 yrs of age) did not appear to respond as well as those who were 50 to 70 yrs of age. Of course, it is acknowledged that older patients have additional complications, such as arthritis and general frailty, that can restrict motor performance, and this must be taken into consideration during assessment. Younger patients, especially those that were medication naive, responded more readily to LT. Patients that failed to comply with the daily treatment schedule by missing or falling asleep early in the treatment sessions also responded poorly. Routine exposure to LT for 1–1.5 h before falling asleep at the intensity of

1000–1500 lux seemed to produce optimal benefit, but higher light intensities, such as those used in depression, are yet to be trialed. Given that PD is usually accompanied by secondary symptoms, including insomnia (Partinen, 1997), depression (Deniker et al., 1975; Fonda, 1985; Girotti et al., 1986; Okun & Watts, 2002; Schnabeth, 1986), and anxiety (Arnulf et al., 2002), medications dispensed for the purpose of treating these features may have masked the true efficacy of these and other antidepressant treatments, including LT, on the impaired motor function that characterizes this disorder. The prescription of hypnotics is common for the insomnia experienced in PD, and when the prescribed dose becomes ineffective, it is often increased. As a consequence, agitation, anxiety, daytime fatigue, and sundowning syndrome become commonplace, thereby contributing to daytime sleepiness, which is purported to be a component of PD itself (Arnulf et al., 2002). This is complicated further by a decreasing response to DA replacement therapy, resulting in a vicious cycle of escalating PD symptoms, anxiety, excessive DA dosing, and sleep problems. Thus, decreased sleep increases anxiety, and increased anxiety increases PD symptoms, and this often requires an increase in PD medication. This, in turn, enhances the insomnia that requires additional hypnotics. The cycle has to be broken for LT to exert its therapeutic effects and permit reduction of the DA replacement dose to be optimally beneficial. This is how the dose of DA replacement was gradually reduced to a level where optimal therapeutic response was achieved. To ensure that the optimal effect is teased out of the equation, hypnotics and antidepressants should be reduced or eliminated while DA replacement therapy is gradually minimized. This process requires in-depth assessment of patients on a regular basis during the first five weeks of LT.

It is of interest that seborrhoea is commonly reported in PD and is reported to be associated with the increased secretion of melatonin (Maietta et al., 1991; Verschoore & Ortonne, 1993). Clinically effective doses of L-dopa are known to decrease seborrhoea (Burton et al., 1970, 1973), which can also be achieved by exposure to light (Maietta et al., 1991). Given that light exposure reduces melatonin secretion (Brainard et al., 1988), a critical link between the reduction of melatonin and the clinical efficacy of DA replacement therapy is a distinct possibility, lending support to work suggesting that the therapeutic efficacy of DA replacement therapy may be mediated through the pineal (Bruguerolle & Simon, 2002; Willis, 2005).

Although the findings of these case studies are only preliminary, various beneficial effects on the primary and secondary features of PD were noted in most patients comprising our case series, and this warrants controlled trials of LT in PD. If LT proves to be equally effective in such trials, then more efficacious treatment regimes that precipitate fewer side effects may be anticipated. LT as a treatment modality for PD provides a

new perspective from which a better understanding of the etiology of neuropsychiatric disease may be derived.

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After submission of this paper for publication, phototherapy has been reported to improve the symptoms of PD in a double blind, placebo-controlled trial (Pars et al. *Eur. Sleep Res. Soc., Innsbruk*, 443, 2006).

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