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Dream Phenomena Induced by Chronic Levodopa Therapy

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Summary

Twenty-seven of eighty-eight (30.7 %) Parkinsonian patients on chronic levodopa or levodopa/carbidopa therapy developed drug related dream phenomena. The patients reported three separate types of new dreams which we have classified as vivid dreams, night terrors and nightmares. These dreams are correlated to the duration of levodopa therapy although the mechanism of their production is unclear.

Introduction

We have recently completed a study designed to examine the prevalence, both cross-sectionally and retrospectively, of three types of psychiatric side effects of antiparkinsonian drug therapy; vivid dreams, hallucinatory/illusionary experiences, and psychotic thought disorders. In contrast to many previous such studies (*Moskovitz et al.*, in press), this study was designed to control systematically for such factors as individual predisposition to psychiatric pathology evidenced by a past history of psychosis, significant dementia, and the etiology of the parkinsonian state (*Goodwin*, 1971). In this paper, we will discuss the nature and possible basis of levodopa-induced dreams. The possible mechanism involved in the production of hallucinatory/

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illusionary experiences and psychiatric thought disorders has been reported previously (*Moskovitz et al.*, in press).

Methods

Eighty-eight patients, 49 males and 39 females, with a diagnosis of idiopathic Parkinson's disease were selected at random from our clinic population. Individuals with evidence of severe dementia and those with a previous history of functional psychosis were systematically excluded from our sample: those patients with mild to moderate dementia were included. Patients with a past history of nonpsychotic psychiatric disorders or a family history of psychotic mental illness were not eliminated.

Past medical records were reviewed, and patient and family interviews were conducted to determine the prevalence and qualitative nature of adverse psychiatric side effects and their relationship to long-term levodopa therapy. All 88 patients had been on levodopa for at least six months.

The mean age of the patients was 69.4 years (range 32—84 years), while the mean duration of known parkinsonism was 8.3 years (range 2 to 20 years). All patients had been in Stage III (72 points) or Stage IV (12 points) prior to the initiation of therapy with levodopa or levodopa/carbidopa. The average dosage of levodopa was 3.4 grams per day: the average dosage of combined levodopa/carbidopa was 950 mg/95 mg per day. The usual dosage of amantadine in patients on these agents was 200 mg per day, while all anticholinergic agents were used sparingly in dosages considered to be in the low therapeutic range.

Results

The overall cross-sectional prevalence of patients exhibiting one or more of the side effects within the past year of antiparkinsonian therapy was 48.8 % (43 of 88 patients): the individual prevalence of the different psychiatric manifestations are shown in Table 1. Twenty-seven of the 88 patients (30.7 %) developed drug-related dream experiences, 26 of 88 (29.5 %) developed hallucinations, 5 of 88 (5.7 %) demonstrated illusions, 8 of 88 (9.1 %) manifested psychotic delusional symptoms, and 3 of 88 (3.4 %) showed confusional psychoses.

Three types of new dream experiences were reported by the 27 above-mentioned patients and/or their spouses (Table 2). All the dreams reported here were new events, different in nature from the normal dreams which occurred prior to antiparkinson therapy. The variety of dream phenomena were classified as follows:

1. Vivid dreams—These levodopa-related dreams, which have not been heretofore described in the literature, were qualitatively vivid,

Table 1. *Annual prevalence of psychiatric side effects during chronic levodopa or levodopa/carbidopa therapy*

Psychiatric Side Effects	Number	Percentage
Dreams	22/88	30.7
Hallucinations	26/88	29.5
Illusions	5/88	5.7
Psychotic Delusional Symptoms (Nonconfusional)	8/88	9.1
Confusional Psychoses	3/88	3.4

This data represent 69 side effects in 43 patients—22 exhibiting one side effect, 16 exhibiting two side effects, and five exhibiting three side effects.

Table 2. *Prevalence of dreams in parkinsonian patients on chronic levodopa or levodopa/carbidopa therapy*

Type of Dream	Number	Prevalence/88 patients
Vivid dreams	20	22.7 %
Night terrors	6	6.8 %
Night mares	5	5.7 %
One or more of the above	27	100.0 %

seemingly real, temporally condensed, internally organized and coherent, often affectively neutral, with a frequent theme of persons and events from the dreamer's remote past. Dreams of this type were reported by 20 of the 88 patients (22.7 %).

2. Night terrors—These were all reported by the families as the patients were always amnesic for these experiences. Typically, the patients were noted to scream, call out, and thrash about in their sleep, or to awaken screaming but to remain amnesic for both the screaming and awakening. This phenomenon occurred in six of the 88 patients (6.8 %).

3. Nightmares—These consisted of classic, frightening, often paranoid, nightmares and, like the vivid dreams, were felt by the patients to differ from previous dreams. Dreams of this nature were present in five of the 88 patients (5.7 %).

Of the 27 patients who manifested one or more kinds of dream phenomena, 23 had only one type (17 vivid dreams, four nightmares, and two night terrors) and four had two types. Of these four patients, three had vivid dreams and night terrors and one had nightmares and night terrors.

Fifty-four of the 88 patients (61.4 %) had previously been on anticholinergic agents alone or in combination with amantadine for at

least six months, but they reported no dream alterations. Two others who had received these drugs did report medication-related dream experiences which became more marked during subsequent levodopa therapy. The prevalence of drug-related dreams in parkinson patients not on levodopa was thus only 3.7 % compared to 30.7 % on levodopa.

All patients in the study were on chronic (*i.e.*, greater than six months) treatment with either levodopa or levodopa in combination with carbidopa. As can be seen in Table 3, both the incidence of the first occurrence and the prevalence of these dreams is related to the duration of levodopa therapy. Eleven of the 88 patients (12.5 %) on levodopa for one year reported the first occurrence of these dreams, while 12.7 % (7/55) noted them initially during the second year of therapy, 9.3 % (4/43) during the third year, and 10.7 % (3/28) after more than three years on levodopa. The prevalence increased from 13/88 (14.8 %) during the first year to 16/55 (29.1 %) during the second year, to 18/43 (41.9 %) during the third year, to 13/28 (46.4 %) during the fourth year.

No difference was found between patients with these new dreams and those without for the following parameters: age, stage of disease, disability, concurrent medications or family history of psychosis (one patient in each group).

Table 3. *Relationship of vivid dreals, night terrors and night mares to duration of anti-parkinson therapy*

	N	Incidence	Prevalence
Prior to ang therapy:	88	0	0
On anti-cholinergic and/or amantadine	54	22 (3.7 %)	2 (3.7 %)
During first year of levodopa or levodopa/carbidopa	88	11 (12.5 %)	13 (14.7 %)
During second year	55	7 (12.7 %)	16 (29.1 %)
During third year	43	4 (9.3 %)	18 (41.9 %)
After more than 3 years	28	3 (10.7 %)	13 (46.4 %)

Discussion

In this patient population, the prevalence of particular differentiable psychiatric side effects related to antiparkinsonian drug therapy, including vivid dreams, hallucinations, illusions, nonconfusional paranoid psychoses, and toxic confusional psychoses, was found to be much higher than determined in most previous studies (*Goodwin*,

1971; *Barbeau,* 1969; *Klawans* and *Garvin,* 1969; *McDowell et al.,* 1971), but comparable to the findings of *Celesia* and *Barr* (1970) and *Sweet et al.* (1976). In contrast to the latter two studies, our patients were screened to eliminate those who were postencephalitic, severely demented, or who had histories of psychotic pathology—all factors predisposing to psychiatric side effects. In light of this study design, our findings suggest that levodopa can generate, as well as reactivate, hallucinatory and psychotic events.

The data presented here demonstrate that chronic levodopa therapy, by itself or in conjunction with carbidopa, is associated with the occurrence of new dream phenomena and is related to the duration of such therapy but not to the age of the patient, duration of disease, disability, or concurrent therapy. The mechanism whereby chronic levodopa therapy can elicit such dreams is unclear.

Holman et al. (1975) have summarized the current neurotransmitter theories of sleep as follows: catecholaminergic and cholinergic mechanisms have been shown to be most integrally involved in the regulation of waking or arousal. Serotonergic neurons play a role in the induction of non-REM sleep, as well as in triggering the initiation of REM sleep, with evidence suggesting differential serotonergic systems involved in the different functions. The maintenance of the REM episode is most likely norepinephrine-mediated, while phasic and tonic events within the REM episode are regulated by serotonergic and cholinergic neurons.

Focusing particularly on the REM stage of sleep in humans, catecholamine concentrations have been found inversely correlated, and serotonin concentrations directly correlated, to REM sleep (*Wyatt,* 1972). In a patient on long-term levodopa therapy with concomitant decrease in brain serotonin activity (*Goodwin et al.,* 1971), as well as increased catecholamine turnover, one would find a double stimulus for suppression of REM sleep (*Wyatt,* 1970; *Post et al.,* 1972; *Spitzer et al.,* 1972). Although some evidence contradictory to the above expectations exists, with *Kales et al.* (1971) reporting no consistent effect of chronic levodopa on sleep patterns in parkinsonian patients, and *Schmidt* and *Knopp* (1972) and *Puca et al.* (1973) demonstrating an actual increase of REM sleep in parkinsonian patients as a result of levodopa therapy, more recent studies (*Castaldo et al.,* 1973; *Bergonzi et al.,* 1974) have suggested that the paradoxical findings may be reconcilable as dose-related phenomena. That is, while low doses of levodopa may enhance REM sleep, higher clinical doses may suppress it.

In conjunction with these data, the exact descriptions of the dream states take on added significance. It is known that mental activity

which is visual and hallucinatory has been reported from non-REM as well as from classically dream-associated REM sleep (*Foulkes*, 1962). Nearly all our subjects who experienced medication-related vivid dreams reported that these dreams were clearly distinguishable from the "normal" dreams they had experienced all their lives. This would lead one to speculate that the dreams being reported are either phenomena occurring outside the REM period or in a somehow altered REM period. Classically, reports of non-REM experiences have tended to be qualitatively less dream-like (*i.e.*, less elaborate, bizarre, implausible, vivid, and emotional) and more thought-like than REM reports (*Foulkes*, 1962; *Rechtschaffen et al.*, 1963; *Fisher et al.*, 1974) resulting in less copious recall overall (*Rechtschaffen et al.*, 1962). The dream reports encountered in our study certainly do not fit this description, although more recent evidence has shown some reported non-REM dream content to be indistinguishable from the content of REM awakenings (*Fisher et al.*, 1974).

Investigation of the hypnagogic hallucinations seen in narcolepsy is one of the distinct areas in sleep and dreaming research where qualitative dream reports seem to parallel those received from our levodopa patients. These hallucinations are characterized by their striking vividness and their marked dissociation from any sense of having been asleep (*Dement et al.*, 1966)—the same attributes as the vivid dreams of chronic levodopa therapy. *Dement et al.* (1966) explain the vividness and seeming reality of the narcoleptic's dreams as a result of the distinctive occurrence of the REM period at the immediate onset of sleep. Where in normal subjects the non-REM period that intervenes between wakefulness and REM sleep produces a marked discontinuity in waking and dreaming mentation, in the narcoleptic there is, in effect, no break at all. The dream phenomena are therefore strikingly remembered and integrated into the individual's waking gestalt. By analogy, the explanation of sleep-onset REM periods can be hypothesized to account for the particular qualitative nature of levodopa-induced dream experiences as well: only formal EEG study during sleep could support or discount its validity.

The non-REM sleep-onset hypnagogic activity of normal subjects may, however, provide a more likely analogy. The hypnagogic experiences of sleep-onset (descending stages 1 and 2) closely resemble the vivid dreams in our study: they, too, are primarily visual (with rare secondary auditory and tactile imagery), dramatic, affectively neutral, brief and temporally condensed to produce a snapshot-like quality, most often internally coherent, frequently as symbol-laden and promary process as REM dreams, and often actually believed to

occur in the "real world" (*Foulkes* and *Vogel,* 1965). Further questioning of our subjects would be necessary to determine if the levodopa-induced dreams are indeed sleep-onset phenomena, while only EEG studies could verify these as non-REM dreams.

The subgroup of our patient population in whom families reported nighttime outbursts of vocalization, motoric agitation, and seeming fearfulness, none of which was remembered by the subjects, brings to mind the *pavor nocturnus* of children termed "incubus" in adults. Individuals with this sleep disorder suddenly exhibit, during stage 3 of 4 sleep, "an 'impaired arousal response' characterized by a waking alpha EEG pattern, extreme motility, somnambulism and vocalization in the form of piercing screams, moans or gasps" (*Kales* and *Kales,* 1974). Heart and respiratory rates increase as does the amplitude of respirations. Physiologic changes last approximately a minute or two. Subjectively, there are feelings of anxiety and respiratory oppresssion as well as a sense of doom. In true night terrors, there is either amnesia for the incident or recall limited to a single frightening image (*Broughton,* 1968; *Gastaut* and *Broughton,* 1965; *Kales* and *Kales,* 1974; *Fisher et al.,* 1973 a; *Fisher et al.,* 1973 b). *Flemenbaum* (1976) reports *pavor nocturnus* as a complication of single nighttime tricyclic or neuroleptic dosage schedules, proposing the mechanism to be enhancement of non-REM sleep (particularly stage 4; *Jus et al.,* 1975), perhaps at the expense of a depletion of REM time (*Kales et al.,* 1970). Analogously, it may be speculated that chronic levodopa stimulation may (via catecholaminergic and/or secondary serotonergic controls on various aspects of the sleep cycle) suppress REM sleep and enhance non-REM stage 4 sleep, resulting in night terrors.

Overall, no specific conclusions about the etiology or pathophysiology of vivid dreams associated with chronic levodopa therapy can be made. Nevertheless, evidence suggests a pharmacologically-based REM cycle alteration resulting in either distorted REM phenomena, REM experiences temporally displaced into non-REM sleep or waking activity, or distinct non-REM dreams. Analogies to previously observed phenomena in the field of sleep and dreaming are provocative, although the final proof will lie with EEG documentation.

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