Mood fluctuations in Parkinson's disease: a pilot study comparing the effects of intravenous and oral levodopa administration

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Objectives: Parkinson's disease (PD) is associated with motor fluctuations that have been shown to improve when stable plasma levodopa levels are achieved with continuous levodopa infusions. Many patients also develop mood fluctuations. In this pilot study, we gathered preliminary information about the relationship between changing mood states and plasma levodopa levels.

Methods: Six patients with idiopathic PD and histories of motor and mood fluctuations participated in a double-blind levodopa infusion study. Subjects received active oral carbidopa/levodopa and a placebo levodopa infusion on one day and placebo oral carbidopa/levodopa and an active levodopa infusion on the other day, in a randomly determined order. Evaluations included serial plasma levodopa levels and assessments of mood and motor states.

Results: Only 4 of the 6 subjects demonstrated mood fluctuations on at least one of the treatment days. All subjects achieved more stable plasma levodopa levels on the active infusion day. Two subjects experienced fewer mood fluctuations on the active infusion day and two experienced fewer on the oral day.

Conclusions: The results of this pilot study suggest that the relationship between mood state and plasma levodopa level may vary among PD patients.

Keywords: Parkinson's disease, mood, fluctuations, levodopa

Introduction

Fluctuations in mood have been reported to occur in up to two-thirds of advanced Parkinson's disease (PD) patients who experience motor fluctuations (Nissenbaum et al 1987). These can be frequent (occurring many times a day), dramatic (patients can shift from very depressed and suicidal to euphoric), and can be more distressing to the patients than the motor fluctuations. Research involving the phenomenology and underlying mechanisms of mood fluctuations in PD has been limited.

Many researchers who have described mood fluctuations indicate that they are linked to the motor fluctuations. The most commonly described pattern is that patients experience lower mood when "off" (immobile, parkinsonian) and elevated mood when "on" (mobile) (Hardie et al 1984; Cantello et al 1986; Friedenberg and Cummings 1989; Lees 1989). However, another study found that some patients feel well when "on" but experience worsening of mood when either "off" or "on with dyskinesias" (Menza et al 1990). These observations led to the hypotheses that mood fluctuations are either: (1) a psychological reaction to motor dysfunction, or (2) manifestations of changing brain dopamine levels.

Investigators who studied intravenous infusions of levodopa in eight PD patients with motor fluctuations demonstrated that both mood states were dose-responsive but that the timing of mood and motor alterations were somewhat discordant, providing

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support for the notion that mood changes are not simply a reaction to motor function (Maricle et al 1995).

In an attempt to better understand mood fluctuations, we asked 17 patients with PD and motor fluctuations to complete hourly diaries for seven days, documenting their mood, anxiety, and motor states using visual analog scales (Richard et al 2001). We were surprised by our finding that although mood fluctuations appeared to be common in this sample, there was no consistent relationship between mood and motor states. We concluded that: (1) mood fluctuations are not merely a psychological reaction to motor state; and (2) mood and motor fluctuations may be, at least in some patients, the result of different underlying patho-physiological mechanisms.

Motor fluctuations in PD have been studied more extensively than mood fluctuations and they are thought to be due to a combination of disease progression and antiparkinsonian medication therapy (Fahn 1999). As dopaminergic neurons degenerate, the neuronal uptake of levodopa and storage and release of dopamine become poorly regulated. There is, in fact, a loss of "motoric homeostasis" and the majority of patients start to experience motor fluctuations within 5 years of beginning levodopa (Poewe 1993). Studies have shown that motor fluctuations can be improved, and even eliminated, if plasma levodopa (and therefore brain dopamine) levels can be maintained constant. This has been effectively done with intraduodenal (Kurlan 1990) and intravenous levodopa infusions (Juncos et al 1990).

The aim of the present study was to gather information about the relationship between mood fluctuations and plasma levodopa levels. We hypothesized that mood fluctuations would be the immediate and direct result of varying brain dopamine levels and that continuous intravenous levodopa infusion, which leads to steady plasma drug levels and is known to ameliorate motor fluctuations, would reduce mood fluctuations.

Materials and methods
Patient selection
Six subjects with idiopathic PD and clinical histories of mood and motor fluctuations provided informed consent for study participation and were admitted to the General Clinical Research Center (GCRC) at the University of Rochester. The University of Rochester Institutional Review Board approved the study. Subjects were recruited from the University of Rochester Movement Disorders Center and

all had been diagnosed with idiopathic PD by neurologists with subspecialty training in movement disorders. The diagnosis was based on careful history and neurologic exam (as well as diagnostic studies as indicated), and all patients demonstrated at least three of the four cardinal signs of PD: rigidity, bradykinesia, rest tremor, and postural instability. Patients all demonstrated a clear-cut response to levodopa therapy, and had no evidence of dementia.

Clinical histories of mood fluctuations were based on the results of questionnaires completed by the subjects. A subject was considered to have mood fluctuations based on an affirmative response to a question regarding their presence. The presence of motor fluctuations was based on response to a similar question and then confirmed by treating physicians who further characterized motor fluctuations as any or all of the following: (1) dyksinesias, (2) wearing off, and (3) "on–off" fluctuations. Subjects were also asked if they had ever been diagnosed with and/or treated for depression and/or anxiety. In preparation for the infusion study, subjects who had clinical histories of motor and mood fluctuations and who consented to participate in the study were asked to complete diaries in which they report mood and motor states on an hourly basis for seven days using visual analog scales.

Levodopa administration
Subjects arrived at the GCRC in the afternoon of day one and underwent physical and neurological exams. A structured clinical interview, the "Structured Clinical Interview for DSM-IV" (SCID) (Spitzer et al 1992) was performed by a trained examiner to yield both lifetime and current DSM-IV psychiatric diagnoses (APA 2000). Subjects received instruction and practiced completing the visual analog scales (see below). There were no dietary restrictions on this day and subjects maintained their usual antiparkinsonian medication regimen until the start of the infusion the next morning.

The subjects then had two treatment days. On one of the days, subjects received active oral carbidopa/levodopa (and active entacapone in the case of subjects who had been taking it with their carbidopa/levodopa) according to their usual dosage regimen and a placebo levodopa infusion (8 am–4 pm) with placebo oral carbidopa (and placebo entacapone if indicated). On the other day, they received placebo oral carbidopa/levodopa and an active levodopa infusion (8 am–4 pm) with active oral carbidopa (and active entacapone if indicated). The treatment assignments were

random and were blinded from all study personnel except the pharmacist. The blind was maintained by using a placebo infusion of normal saline in a covered container and by encasing the subjects' own carbidopa/levodopa (or placebo) and entacapone in opaque capsules. Active or placebo carbidopa was also provided in opaque capsules.

On each of the two treatment days, subjects received a low protein (5 g) breakfast and lunch. Subjects had an intravenous line placed in one arm and a heparin lock (to draw blood samples) placed in the other by 8 am. These lines remained in place until the infusion was stopped at the end of the second treatment day.

Levodopa (or normal saline) was infused intravenously, initially at a rate of 1 mg/kg/h. After the first and second hours of infusion, an independent (not the clinical rater) clinician adjusted the infusion rate to optimize the subjects' motor status. Further adjustments beyond the second hour were not permitted (in an attempt to maintain stable plasma levels). Carbidopa (25 mg) or placebo carbidopa was administered at 7 am, 9 am, 11 am, 1 pm, and 3 pm to prevent nausea.

Subjects had three milliliters of blood drawn from the heparin lock every 30 minutes to assess plasma levodopa levels during both treatment days. Blood draws began just prior to the start of the infusion and continued until it was stopped. Keith Hyland, PhD, performed all plasma assays using high performance liquid chromatography analysis (Baylor Medical College, Houston, TX, USA).

Mood and motor assessments

Visual analog scales (VAS) were completed by the subjects and used to quantify mood state at 30-minute intervals during the infusions (8 am–4 pm) (McCormack et al 1988). Each rating form for mood contained a horizontal 10-cm line with the descriptive anchors "extremely sad" and "extremely happy" at the ends and a 5-cm midpoint labeled "normal" to help guide subjects. Subjects were instructed to make a vertical line through the point on the scale that best represented their mood states for that half-hour. A ruler was used to measure the distance in centimeters from the left-sided anchor to the subject's mark in order to obtain a VAS score. VAS assessing degree of mood changes has been proven to be a valid and reliable method in psychiatric studies and was used by Maricle et al (1995) and Menza et al (1990) in their studies of mood states in PD.

Given the opportunity for direct and objective motor assessment, a single examiner assessed motor function on both treatment days at 60-minute intervals during the infusions (8 am–4 pm) using the motor subset (Part III) of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al 1987). This measure takes about 10 minutes to administer and is appropriate for frequent assessments.

Statistical analysis

Given the small sample size, the analyses are mainly descriptive. However, the mean and variance were calculated for levodopa levels for each treatment day. Wilcoxon signed-rank tests were used to compare the oral and levodopa infusion days in these regards.

Results

There were 5 women and one man with an average age of 65.2 years (range 56–76) and mean Hoehn and Yahr score of 2.7 (range 2–3). Only 4 of the 6 subjects completed the diaries (subjects 1, 2, 4, and 5). Case histories are briefly summarized below and in Table 1 (which also includes information about concomitant medications).

Subject 1 was a 57-year-old woman with a 16-year history of PD (Hoehn and Yahr 1967, stage 3) who suffered from difficult to manage "on–off" fluctuations. She reported a diagnosis of and treatment for depression, confirmed on SCID interview. Her diary revealed motor and mood fluctuations that occurred several times each day and were dramatic (VAS motor scores ranging from 3 to 97 and mood scores ranging from 6 to 93 on a scale of 0–100 mm, with 50 being "normal").

Subject 2 was a 71-year-old woman with a 6-year history of PD (Hoehn and Yahr 1967, stage 2). Her motor fluctuations were characterized mainly by wearing off. She did not experience significant dyskinesias. She denied any psychiatric history, which was confirmed on SCID interview. Her diary revealed mood and motor fluctuations in which she reported low mood during periods of reduced mobility. This was consistent over the 7-day period. She never reported higher than "normal" mood or mobility.

Subject 3 was a 67-year-old woman with a 20-year history of PD (Hoehn and Yahr 1967, stage 3) who suffered from mild motor fluctuations characterized by wearing off and dyskinesias. She reported a diagnosis of and treatment for depression, which was confirmed on SCID interview. She did not complete a diary. During the interview that was conducted as part of the research study, she reported periods of low mood alternating with periods of normal mood.

Table 1 Clinical characteristics of study participants

Patient	Sex	Age	H & Y	SCID diagnoses	Baseline UPDRS	Concomitant medications
1	F	57	3	Mood disorder (depression) due to general medical condition (GMC)	29.5 "On" with dyskinesias	C/L 25/100 7.5 tabs over 8 doses C/L CR 25/100 qd amantadine 100 mg BID pramipexole 0.75 mg TID midodrine 5 mg TID quetiapine 12.5 mg sertraline 100 mg
2	F	71	2	No diagnosis	29.5 Turned "on" during exam	C/L 25/100 × 5 C/L CR 50/200 qd entacapone 200 mg × 5 selegiline 5 mg
3	F	67	3	Major depressive disorder (MDD)	56 "On"	C/L 25/100 × 6 pramipexole 1.5 mg TID amantadine 100 mg BID citalopram 40 mg
4	M	64	3	(1) MDD, threshold, mild, recurrent (2) Generalized Anxiety Disorder (GAD)	53.5 "On"	C/L 25/100 × 6 C/L CR 50/200 × 6 ropinerole 2.0mg × 6
5	F	76	2.5	No diagnosis	33.5 "On" with mild dyskinesias	C/L 25/100 QID C/L CR 50/200 QID pramipexole 1.5 mg TID
6	F	56	3	(1) Mood disorder due to GMC, threshold (2) Psychotic symptoms, threshold (3) Panic disorder, threshold (4) GAD, threshold	49.5 "On" with dyskinesias	C/L 25/100 × 6 pramipexole 1 mgTID lorazepam 1 mg (1/2 qhs)

Abbreviations: C/L, carbidopa/levodopa; BID, twice a day; H & Y, Hoehn and Yahr; qd, every day; qhs, once at bedtime; QID, four times a day; SCID, Structured Clinical Interview for DSM-IV; TID, three times a day; UPDRS, Unified Parkinson's Disease Rating Scale.

Subject 4 was a 64-year-old man with a 12-year history of PD (Hoehn and Yahr 1967, stage 3) who suffered from mild motor fluctuations characterized by wearing off and dyskinesias. He denied a psychiatric history but was noted to have depressive and anxiety diagnoses on SCID interview. He completed a diary which revealed motor and mood fluctuations that were mild and varied in severity from day to day.

Subject 5 was a 76-year-old woman with a 12-year history of PD (Hoehn and Yahr 1967, stage 2.5) who suffered from mild motor fluctuations characterized by wearing off and dyskinesias. She denied a psychiatric history, which was confirmed on SCID interview. She completed a diary which revealed mild motor fluctuations characterized primarily by periods of increased mobility (dyskinesias) and mild mood fluctuations which varied from day to day.

Subject 6 was a 56-year-old woman with a 5-year history of PD (Hoehn and Yahr 1967, stage 3). She suffered from motor fluctuations characterized by wearing off and dyskinesias. She reported a history of anxiety. SCID interview revealed threshold depressive, anxiety, and psychotic symptoms. She did not complete a diary. During

the interview that was conducted as part of the research study, she and her husband reported that she experienced significant mood swings and also had episodes of pain, primarily in her hands. They thought that these "non-motor" episodes may represent wearing off of levodopa effects.

Three participants were given active infusions on day one of treatment, and three were given them on day two. All patients tolerated the infusions well and no adverse events were reported. As a group, there was significantly more variance in levodopa levels during oral levodopa compared with infusion levodopa ($p = 0.03$). The average levodopa level was not, however, statistically different between the two modes of administration ($p = 1$).

Although all subjects had some variation in mood VAS scores throughout the course of each treatment day, only four of the subjects demonstrated prominent mood fluctuations on at least one of the study days. Subjects 1 and 2 (Figure 1) demonstrated both mood and motor fluctuations on the oral levodopa day that were much less prominent on the active infusion day (when plasma levodopa levels were relatively stable). Subjects 4 and 6 (who had very minor motor fluctuations), demonstrated greater mood
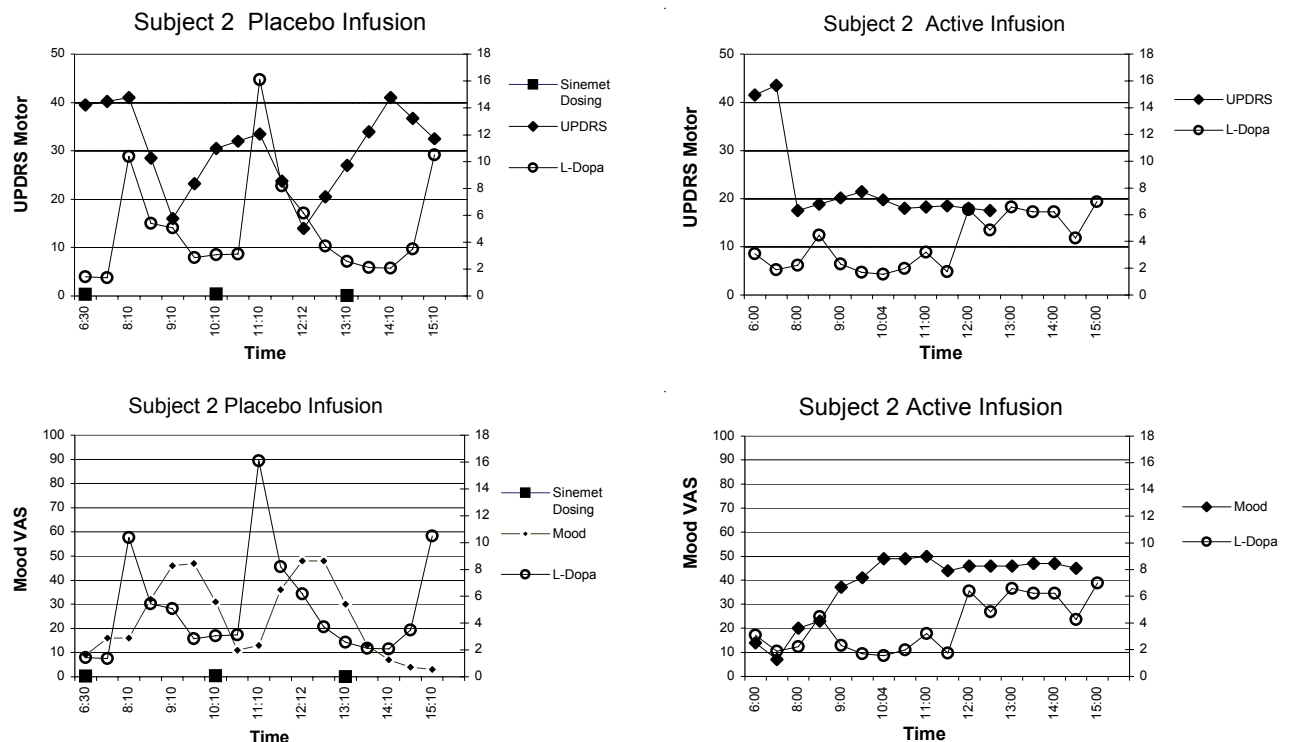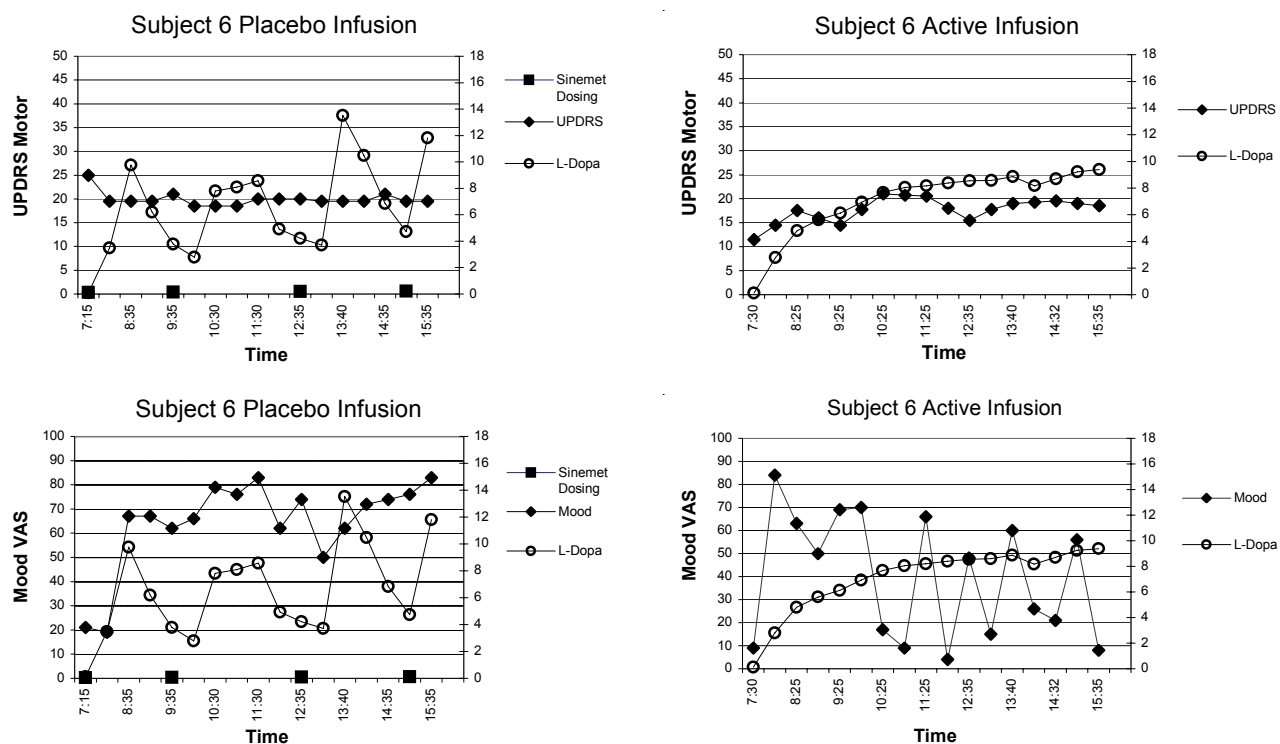
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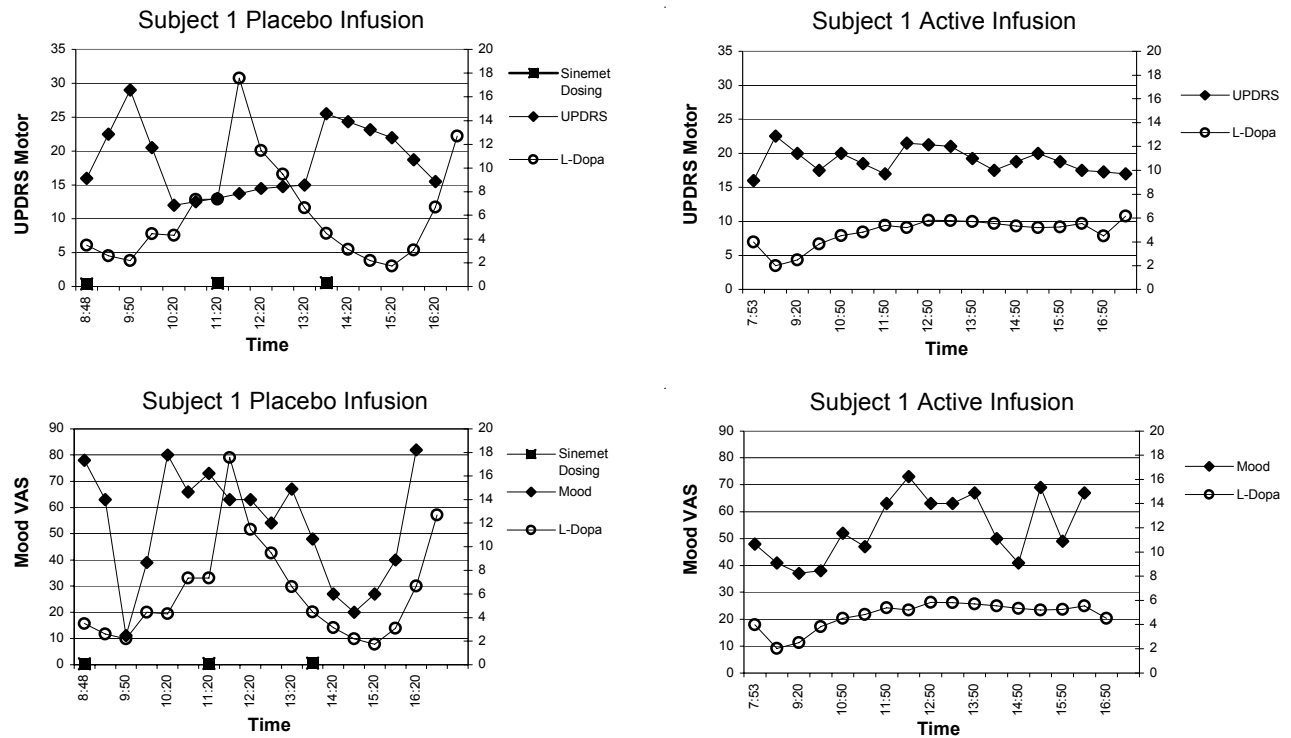
(b)

Figure 1 Oral and infusion levodopa days of subjects who had fewer mood fluctuations on the active levodopa infusion day. These subjects demonstrate the "classic" relationship between mood and motor states (mood is low during periods of decreased mobility). **Abbreviations:** UPDRS, Unified Parkinson's Disease Rating Scale; VAS, visual analog scale.
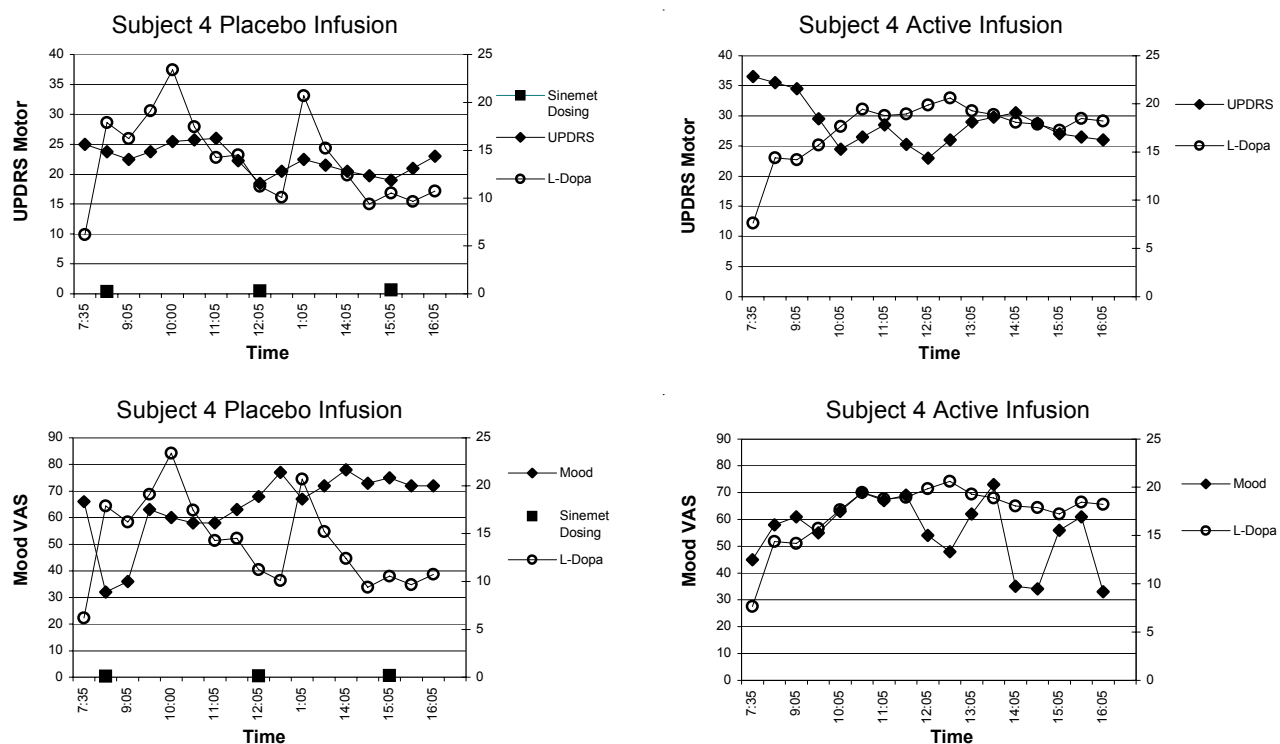
(a)

(b)

Figure 2 Oral and levodopa days of subjects who had more mood fluctuations on the active levodopa infusion day. These subjects had very minor variations in motor states.

fluctuations on the active infusion day (when plasma levodopa levels were relatively stable), as depicted in Figure 2. Subjects 1, 4, and 6 demonstrated "bipolar" mood fluctuations (with VAS mood scores both above and below "normal"), whereas Subject 2's mood fluctuated only between "normal" and low.

Subject 3 had minimal variation in mood on both days and mild motor fluctuations on the oral day that were not present on the infusion day. Subject 5 had minimal variation in mood and motor function on the oral day. On the infusion day, the levodopa infusion rate was too low. The start of the infusion was associated with a sharp decline in levodopa level, followed by a decline in mood and motor function. The levodopa level rose slightly but remained low throughout the day, motor function improved slightly (but remained worse than on oral levodopa) and mood gradually improved and remained "normal".

Discussion

Our pilot study demonstrated that the response of mood to continuous intravenous infusions of levodopa varied among subjects. The study had several strengths. The randomized, double blind, placebo-controlled design served to eliminate bias that is critical in assessing subjective outcomes such as mood. A standard rating scale completed by a trained rater served to provide objective measures of motor state. Ratings of mood and motor function were performed prospectively at frequent intervals. A standard psychiatric interview was utilized to accurately assess current and past psychiatric disorders. Finally, plasma levodopa assays confirmed that, in general, levodopa infusions resulted in steadier plasma levels.

The study also had limitations, including small sample size and observations on only two days, which might influence the interpretation of our results. There are inherent but unavoidable limitations associated with studying emotional states in "artificial" environments. Only 4 of the 6 subjects demonstrated prominent ("classic") mood fluctuations during the period of study.

Two subjects experienced a clear reduction in mood fluctuations during the levodopa infusion. These subjects both had motor fluctuations and demonstrated the most commonly described pattern of mood/motor fluctuations whereby patients are depressed when "off" and euthymic or euphoric when "on". While we cannot rule out the possibility that mood changes were reactive to motor changes, prior research fails to support this mechanism (Maricle et al 1995; Richard et al 2001). A more plausible

theory is that for some patients fluctuations in mood, like fluctuations in motor state, directly reflect changes in plasma levodopa (and presumably brain dopamine) levels. For these patients, therapeutic strategies aimed at achieving steadier levodopa levels, such as controlled-release levodopa, narrowing levodopa dosing intervals, or adding a COMT inhibitor, should be helpful in reducing fluctuations in mood.

Two other subjects (both of whom had very minor motor fluctuations) had mood fluctuations that did not appear to be related to alterations in plasma levodopa levels or motor state. It is possible that for some patients mood is determined by a different neurochemical mechanism. There is ample evidence suggesting a significant role for serotonin and norepinephrine in the occurrence of mood and anxiety disturbances in primary psychiatric populations and in PD (Mayeux et al 1984; Schiffer et al 1988; Paulus and Jellinger 1991; Green et al 1995; Kostic et al 1996; Richard et al 1996; Menza et al 1999; Murai et al 2001). Alternatively, in some patients there may be a more indirect, delayed effect of levodopa (perhaps via other neurotransmitter systems) so that the temporal relationship between plasma levodopa level and mood state is not easily discernable.

Even in patients whose minute-to-minute mood states are not related to plasma levodopa, it is possible that dopaminergic dysregulation somehow "sets the stage" for a loss of affective homeostasis. Evidence for general homeostatic dysfunction in PD includes a wide variety of symptom fluctuations, including motor, mood, anxiety, cognitive, sensory, and autonomic forms, at least some of which develop virtually inevitably after several years of illness and treatment with dopaminergic medications. In support of a dopamine dysregulation role in homeostatic mood dysfunction is the finding that dopaminergic agents can induce "rapid cycling" in patients with previously typical bipolar illness (Ko et al 1981).

Although the small sample size limits our ability to draw definitive conclusions, there were no clear demographic or clinical factors that distinguished the two subjects whose fluctuations improved with infusion from the subject whose did not. For example, although one might hypothesize that an underlying psychiatric disorder or current treatment with an antidepressant medication would have an impact on response to the infusions, we found no evidence for this (see Table 1). Furthermore, direction of mood swings also failed to distinguish those who responded to the levodopa infusion from the ones who did not. One of the two infusion-responders had "bipolar" mood fluctuations (ranging from very elevated to very low mood), whereas the other

fluctuated in a "unipolar" pattern (only between normal and low mood).

Further research is needed to improve our understanding of the phenomenology and neurobiologic mechanisms underlying changes in mood states in patients with PD so that we may provide more rational therapy for this frequent and distressing aspect of the disorder. Studies involving more subjects, with longer observation periods and ensuring optimization of infusion rates may overcome some of the limitations of our study. Functional imaging studies done during different mood states may prove technically challenging in patients with PD-related motor symptoms but they have the potential to help our understanding of the neurobiologic underpinning of mood states. It is also likely that research involving deep brain stimulation-related mood changes will enable us to better clarify the neural circuitry responsible for regulating mood. Given the fact that not all PD patients develop fluctuations in mood, examination of those characteristics that render some patients susceptible to (or protected from) such fluctuations may provide additional insights.

Acknowledgments

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