oped parallel to a progressive cerebral disease. These findings are supported by other recent reports showing that EDS correlates with more advanced PD.[9]

The close correlation between persistent and new EDS and a more advanced PD shows that patients with a more widespread cerebral disease are at increased risk for developing somnolence. The well-known sedation or somnolence that is observed after acute or chronic medication with dopaminergic drugs[10] may therefore be more likely to occur or be especially pronounced in predisposed patients with clinical or preclinical lesions in brain areas that are involved in regulation of the sleep/wake cycle. Therefore, it is especially important to look for somnolence in patients that have a more severe cognitive impairment and disability and to advise them on the hazards (e.g., car driving) that are associated with daytime somnolence.

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Long-term follow up of subthalamic nucleus stimulation in Parkinson's disease

Abstract—Twenty-two patients with PD received bilateral implants for high frequency stimulation of the subthalamic nucleus. The patients were treated for more than 1 year (up to 36 months). At the last visit, the Unified Parkinson Disease Rating Scale (UPDRS) motor score without medication improved by 50.2% ($p < 0.001$) and the UPDRS activities of daily living score improved by 68.4% ($p < 0.001$). The most common long-lasting adverse events were hypophonia and dysarthria; transient events were increased sexuality and mania. The surgical procedure induced transient intraoperative psychosis in seven patients.

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High frequency stimulation (HFS) of the subthalamic nucleus (STN) has been effectively used to treat PD, allowing a reduction in medication requirements,[1] and providing satisfactory control of motor fluctuations and the reduction of dyskinesias.[2] STN HFS has been recently introduced in Europe, but it has not yet been approved in the United States. The clinical course of patients is well established for the first year following the implant,[1-4] but little is known about the efficacy and the safety profile of this procedure beyond the first year.

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Patients and methods. Patients with PD were selected by criteria previously described.[1] Each patient had a brain MRI and was assessed using a standard protocol.

Antiparkinsonian medication was unchanged for at least 1 month before the implant. The levodopa-equivalent daily dose (LEDD) was computed for each antiparkinsonian medication by multiplying the total daily dosage of each drug by its potency relative to a standard levodopa preparation assigned the value of 1. The following conversion factors were used: levodopa controlled-release preparations = 0.77; bromocriptine = 10; apomorphine = 15;

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Table 1 *Demographics and main clinical features of the patients implanted*

Patient no./sex	Age at implant, y	PD duration, y	Implanted pulse generator	Follow up, mo	Weight, kg		LEDD		Sessions*
					Before implant	At last visit	Before implant	At last visit	
1/F	46	10	I	50	43	50	1300	825	8
2/F	60	13	I	48	65	79	3110	900	8
3/F	58	30	I	44	58	63	600	700	7
4/F	62	9	I	36	60	63	785	450	5
5/F	56	22	I	31	52	63	1806	725	5
6/M	60	17	I	30	62	72	3132	168	4
7/M	68	12	I	29	75	74	1225	825	5
8/M	42	15	K	24	78	86	1800	292	5
9/M	51	11	K	21	86	87	900	0	2
10/F	60	19	K	20	46	55	600	153.7	3
11/F	41	9	K	20	54	70	900	461	4
12/F	59	12	K	20	76	60	1135	768	5
13/F	63	28	K	19	43	56	1450	84	2
14/M	56	10	K	18	75	84	850	1250	5
15/M	48	10	K	15	75	87	2080	252	1
16/M	63	16	I	12	62	65	1000	625	3
17/F	56	16	K	12	83	98	1800	400	4
18/F	49	9	K	12	51	62	1200	795	4
19/M	57	14	I	12	55	68	2025	136.6	5
20/M	60	14	K	12	88	73	2253	420	4
21/M	53	11	K	12	76	90	1160	168	4
22/M	71	10	K	12	70	75	2020	420	4
Average (± SD)	56.3 ± 7.7	14.4 ± 5.9	9 I, 13 K	23.1 ± 12.1	65.1 ± 13.9	73.2 ± 14.4	1505.9 ± 722.8	491.7 ± 325.4	4.4 ± 1.7

* Number of reprogramming sessions in each patient.

I = Itrel II; K = Kinetra; LEDD = levodopa-equivalent daily dose.

ropinirole = 20; pramipexole = 60; and pergolide = 100. The total LEDD was then calculated.

Evaluations were performed in the morning, in the practically defined "off" condition[5] and in the best "on" condition under the patients' current drug regimen. The ethical committee of Gemelli Hospital approved the study, and the patients gave their written informed consent. Only the patients with a follow up of at least 1 year were evaluated.

All patients received a bilateral simultaneous STN implant. Unilateral STN implants were performed when necessary for lead reimplantation. Standard stereotactic techniques were used.[1] Test stimulation (pulses of 60 μs at a frequency of 130 Hz) was performed in the operating room before implantation of the leads. A target was accepted when a current of less than 3 V reversed parkinsonian signs on the side contralateral to the implanted hemisphere. All patients were assessed while awake by two neurologists. When transient STN inactivation did not allow clinical efficacy to be evaluated during intraoperative testing, elicitation of adverse events helped to identify the structures stimulated. Adverse events were observed when intraoperative stimulation was gradually increased, and usually consisted of facial hemispasm, paresthesias, tachycardia, hyperpnea, diplopia, or tonic eye deviation.

Chronic stimulation by means of an external device was started on the day following the implant. A 130-Hz (60 μs) current was applied to the lead contact previously identified during intraoperative stimulation. The voltage was gradually increased and other lead contacts stimulated when necessary. The frequency or pulse width was adjusted to keep the voltage as low as possible. The following clinical features were evaluated to set the stimulation settings: tremor (when present), rigidity, bradykinesia, and gait. An MRI scan was always performed before implanting a Medtronic (Minneapolis, MN) Itrel II or Kinetra implantable pulse generator (IPG) in the subclavicular region approximately 1 week after the stereotactic placement. Table 1 lists the type of IPG implanted in each patient.

STN stimulation was continuous for 24 hours per day. The patients were scheduled for evaluation 3, 6, 12, 18, and 24 months after the implant, and once a year thereafter. Each postoperative assessment was performed in the morning, 12 hours after withdrawal of antiparkinsonian medication, and after having turned off the IPG. Four consecutive Unified Parkinson Disease Rating Scale (UPDRS)

Table 2 *Variation of UPDRS activities of daily living and motor scores, of disease staging, of levodopa equivalents administered daily and of energy delivered*

Feature	Baseline	Last follow up	Baseline	18 mo	Baseline	24 mo	Baseline	36 mo
UPDRS	31.6 ± 5.9	10.0 ± 6.3	33.1 ± 6.5	9.9 ± 6.3	33.5 ± 6.4	12.2 ± 7.7	33.3 ± 7.6	13.6 ± 8.1
ADL		−68.4%		−70.1%		−63.3%		−59.2%
		<0.001		<0.001		0.005		0.017
Schwab and	24.5 ± 14.4	80.0 ± 14.1	21.6 ± 12.8	80.0 ± 20.0	24.4 ± 14.2	73.3 ± 19.4	23.3 ± 12.1	72.9 ± 18.0
England*		<0.001		<0.001		0.007		0.017
UPDRS	60.2 ± 9.3	29.9 ± 12.5	60.8 ± 11.1	30.7 ± 15.4	65.0 ± 6.5	33.2 ± 14.5	60.8 ± 15.5	31.0 ± 12.5
motor score		−50.2%		−49.5%		−48.9%		−49.1%
		<0.001		<0.003		0.007		0.017
LEDD	1505.9 ± 722.8	491.7 ± 325.4	1399.5 ± 823.8	554.5 ± 376.8	1579.3 ± 901.0	585.5 ± 313.1	1708.3 ± 1039.4	656.1 ± 259.5
		−69.3%		−60.4%		−62.9%		−69.6%
		<0.001		0.004		0.007		0.024
Hoehn and	4.3 ± 0.8	1.9 ± 0.9	4.3 ± 0.9	2.0 ± 1.0	4.4 ± 1.0	2.5 ± 0.9	4.5 ± 0.8	2.7 ± 0.8
Yahr		−55.9%		−55.8%		−43.2%		−40.0%
Energy, μW		1.53 ± 0.5		1.37 ± 0.4		1.40 ± 0.3		1.25 ± 1.0
Patients	22	22	14	14	10	10	7	7

All values are without medication; with stimulation are compared with baseline values.

* At variance with UPDRS scores, improvement of Schwab and England scores is indicated by increasing values. As this scale measures percent variations in ADL, percent variations of the Schwab and England score have not been measured.

UPDRS = Unified Parkinson Disease Rating Scale; ADL = activities of daily living; LEDD = levodopa-equivalent daily dose.

evaluations were performed: 1) without medication or stimulation; 2) without medication, 30 minutes after switching stimulation on; 3) with medication (according to the daily schedule) at least 60 minutes after switching stimulation off; 4) with medication, 30 minutes after resuming stimulation. The patient, but not the examiner, did not know whether his stimulator was on or off, although some patients succeeded in being aware of stimulation due to transient adverse events produced by switching the IPG on. At the time of each follow-up visit, patients were evaluated for daily living activities by the UPDRS activities of daily living (ADL) score, and for quality of life by the Schwab and England scale. These scales were administered under condition 2 (without medication, 30 minutes after switching stimulation on) and condition 4 (with medication, 30 minutes after resuming stimulation). A global self-assessment scale (considering gross degrees of improvement or worsening on a scale of 0% to 100%) was also administered to each patient. After clinical assessment, medication was reduced as much as possible and the stimulation settings were readjusted, according to the criteria outlined above.

At each visit, changes in scores for ADL and motor performances were compared with the LEDD and the energy delivered by the IPG. The energy delivered by the stimulating electrodes (expressed in watts) was calculated considering the total area under the stimulation pulses, times the number of pulses per second, using the formula $E = (\text{amplitude} \times \text{pulse width} \times \text{frequency rate})^2/\text{impedance}$. For each patient, the total energy delivered on the two sides was calculated. Data analysis was carried out using Wilcoxon's matched pairs test; the limit for significance was $p < 0.05$.

Results. Twenty-two patients (11 males and 11 females) had a follow up exceeding 12 months. Patient 16 (see table 1) died about 13 months after implant because of bowel adenocarcinoma. Postmortem examination confirmed the diagnosis of idiopathic PD. No other patient was lost to follow up. Patient 1 had the longest postimplant observation period of 50 months. Individual clinical features of the patients are listed in table 1.

The drugs taken by the patients at the time of implant were levodopa (22 patients), pergolide (15 patients), bromocriptine (1 patient), apomorphine (subcutaneous infusion in 3 patients), ropinirole (4 patients), and amantadine (4 patients). The LEDD was progressively reduced during the first 6 months after implant. Compared with preimplant values, LEDD reduction was 61.4% ($p < 0.001$) at 6 months and 65.8% ($p < 0.001$) at the last follow up (table 2). The energy delivered was gradually increased during the first quarter after the implant and remained stable thereafter; an average of 1.51 μW was delivered 6 months after the implant and 1.53 μW were delivered at the last follow up. Stimulation amplitude was on average 2.85 ± 0.29 V at 6 months and 2.92 ± 0.35 V at the last follow up. Stimulation settings and the choice of stimulating leads were seldom changed after the first 6 months.

Compared with preimplant measurements, there were no variations of the UPDRS motor score when the patients were evaluated without drugs and with stimulation turned off (52.8 ± 8.7 on the last follow up, compared with 60.2 ± 9.3 at baseline). This nonsignificant reduction in the UPDRS motor score was due to persistence of tremor improvement in some patients (see below). When the patients were evaluated without drugs and with stimulation turned on, the UPDRS motor score improved by 50.2% on the last

Table 3 *Adverse events are listed according to their presumed nature*

Events	Presumed nature (n)
Transient	Increased sexuality (4); manic psychosis (2); seizure (1)
Long-lasting (unresponsive to stimulation withdrawal for few hours)	Hypophonia (4); hypophonia and dysarthria (4); eyelid opening apraxia (4); worsening of depression (2); psychic akinesia (2); limb dystonia (1); bilateral buccinator spasm (1)
Stimulation dependent (improved by stimulation withdrawal for few hours)	Paresthesias (7); ballic-choreic dyskinesias (2); blepharospasm (2); diplopia (1); unilateral buccinator spasm (1)
Events occurring during surgical procedures	Transient intraoperative psychotic reaction (7); lead migration (1); subarachnoid hemorrhage with transient diplopia (1)
Device failures	Unexplained switching-off (3); sudden end of battery life (2)

follow up compared to preimplant values ($p < 0.001$). In the same condition, the UPDRS ADL score improved by 68.4% ($p < 0.001$), and the Schwab & England scale improved from 24.5 ± 14.4 to 80 ± 14.1 ($p < 0.001$; see table 2).

The following items improved remarkably: rigidity, limb akinesia and body bradykinesia, gait and postural impairment (see figure E1, which can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the title link to this article.). Rest tremor disappeared in 11 patients, who were severely tremulous before the implant, and improved significantly in 7 patients. In most patients, turning the stimulation off at the time of clinical assessment caused a rebound of tremor to the preimplant level within the next few minutes. In three patients, when stimulation was turned off, rest tremor recurred but was on average 79.3% milder than baseline tremor. Overall, rest tremor was reduced by 84% ($p < 0.001$) compared with preimplant values.

Motor fluctuations and dyskinesias improved in all patients (see figure E2, which can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the title link to this article.). "Off" period dystonia disappeared in all patients from the 3-month visit and did not recur. Freezing and "on" period dyskinesias disappeared in 20 patients whose clinical condition after surgery was a permanent "on" motor state. Freezing and "on" period dyskinesias did not recur in Patients 4 and 12, but remained significantly improved, providing satisfactory control.

Night sleep and nocturnal hypokinesia were reportedly improved in all patients; insomnia was resolved in all but Patient 6. All patients gained weight after surgery. The patients' weight averaged 65.1 ± 13.9 kg before surgery and increased by 12.4% to 73.2 ± 14.4 kg at the time of last follow up ($p < 0.001$). Weight gain was remarked as unacceptable by Patients 2 and 17.

Transient and long-lasting adverse events are listed in table 3. Four patients presented a transient increase of sexuality that lasted for some months and was accompanied in two of them by manic psychosis. The most common adverse event that did not improve when stimulation was turned off for a short while was hypophonia, which affected eight patients, four of whom were particularly disabled. The most common stimulation-dependent adverse events were paresthesias and dyskinesias. Adverse events related to the surgical procedure or the device are listed in table 3. The most common adverse event related to surgical procedure was a short-lasting psychosis (with hallucinations and delusions), which resolved spontaneously in less than 1 hour and could be handled without interfering with correct lead positioning. Unexplained switch off occurred in three patients using Itrel II stimulators. In one patient, the most likely cause was believed to be use a specific brand of refrigerator. Sudden end of battery life also occurred in two patients bearing Itrel II stimulators. In both instances this required the emergency managing of the patients who resided far from our center.

Discussion. The current series extends and completes earlier observations on the efficacy of STN HFS in PD. In a series of 24 patients implanted bilaterally in the STN, a 60% improvement of the UPDRS motor score and a 50% reduction of the LEDD were reported 1 year after the implant.[3] No detailed information is provided for the 10 patients in the same series, who were followed-up for more than a year. Three reports evaluated patients just 1 year after STN implant.[2,3,6] They deal in total with 64 patients, who had an average UPDRS motor improvement of 62.2% and an average LEDD reduction of 65.3%. The current study provides comparable results for patients evaluated on average 2 years after the implant, indicating that there is no evidence for decay of efficacy of STN HFS during the first 3 years of follow up. In keeping with this, no significant variations of the energy delivered, of the UPDRS motor score, or of the LEDD were observed from 1 to 3 years (see table 2).

The current series is in keeping with previous observations on the efficacy of STN HFS for controlling parkinsonian signs and symptoms.[1] The daily time spent off, "off" period dystonia, and motor fluctuations were abolished after the 3-month visit (see figure E2, which can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the title link to this article.). Complete resolution of early morning dystonia occurred in all patients. Changes of nonmotor symptoms are in part the aftermath of around-the-clock motor improvement. ADL and quality of life indexes improved markedly. "On" period dyskinesias were greatly reduced after STN HFS. This was considered an indirect effect of the efficacy of the procedure brought about by a reduction of antiparkinsonian medication.[2,7] No decay was observed for the im-

provement of motor or nonmotor symptoms throughout the follow-up period.

In keeping with our previous short-term observation, the current series confirmed that limb bradykinesia (defined as the sum of UPDRS items 23, 24, 25, and 26) improved significantly, but less markedly than tremor, gait, postural stability, body bradykinesia, or rigidity.[1] In other studies reporting a more marked improvement of limb bradykinesia, drug reduction was less marked than in the current series.[3,6,8] A recent article compared the patients with STN implants who discontinued medication with those who continued taking medication, observing that patients who discontinued medication scored worse in bradykinesia than patients who continued taking medication.[9] The current data suggest that some medication is required to attain optimal control limb bradykinesia and suggest that the relationship between bradykinesia, drug treatment, and STN HFS needs to be refined further.

Long-term observation of patients is a prerequisite to evaluate the safety profile of STN implants, particularly because it has been observed that more adverse events occurred following implant in the STN than in the globus pallidum internum.[6] Hypophonia and dysarthria have been reported to occur only in patients with STN implants. The current series confirms that these adverse events, which have been observed in a total of eight patients, are a matter of concern. The current study also accounts for a comprehensive listing of adverse events classified according to their presumed nature. The overall picture is that STN implants are well tolerated, particularly considering the impressive benefit given to the patients. Still, special care is required to control unwanted reactions. The list of psychological adverse events is remarkable, encompassing transient events (increased sexuality with manic psychosis), long lasting events (depression, psychic akinesia), and transient intraoperative psychotic reactions. Also notable are sudden device failures; they occurred in three patients who received the implant of a Itrel II IPG, but in none of the patients implanted with Kinetra IPG. Similar episodes have been recently described in two patients who received Itrel II implants.[10] It is conceivable that technical improvements in IPG development will reduce the occurrence of such events.

Finally, no satisfactory explanation can be provided for weight gain that occurred in all patients and persisted throughout the follow-up period. Therefore, although clinical benefits derived from STN implants can be robust, potential adverse events, costs, and inconvenience can also be great. Time is required before data on longer-term follow up (of at least 10 years) of patients bearing STN stimulators will become available. In the meantime, the efficacy and safety profile of this technique support its use in selected patients with PD.

Author's Note: High-frequency stimulation was first approved by the FDA in 1997 for use only in one side of the brain to help control tremors on one side of the body. After acceptance of this paper, on January 14, an expanded use to help control symptoms of advanced PD was also approved. The evidence leading to the widening of clinical indications is mainly derived from STN implants, whereas the first approval was mainly based on Vim thalamic implants aimed to control tremor. The FDA has requested to conduct a 3-year, postapproval study of the system to assess its long-term clinical results. The current data shed new light along this line.

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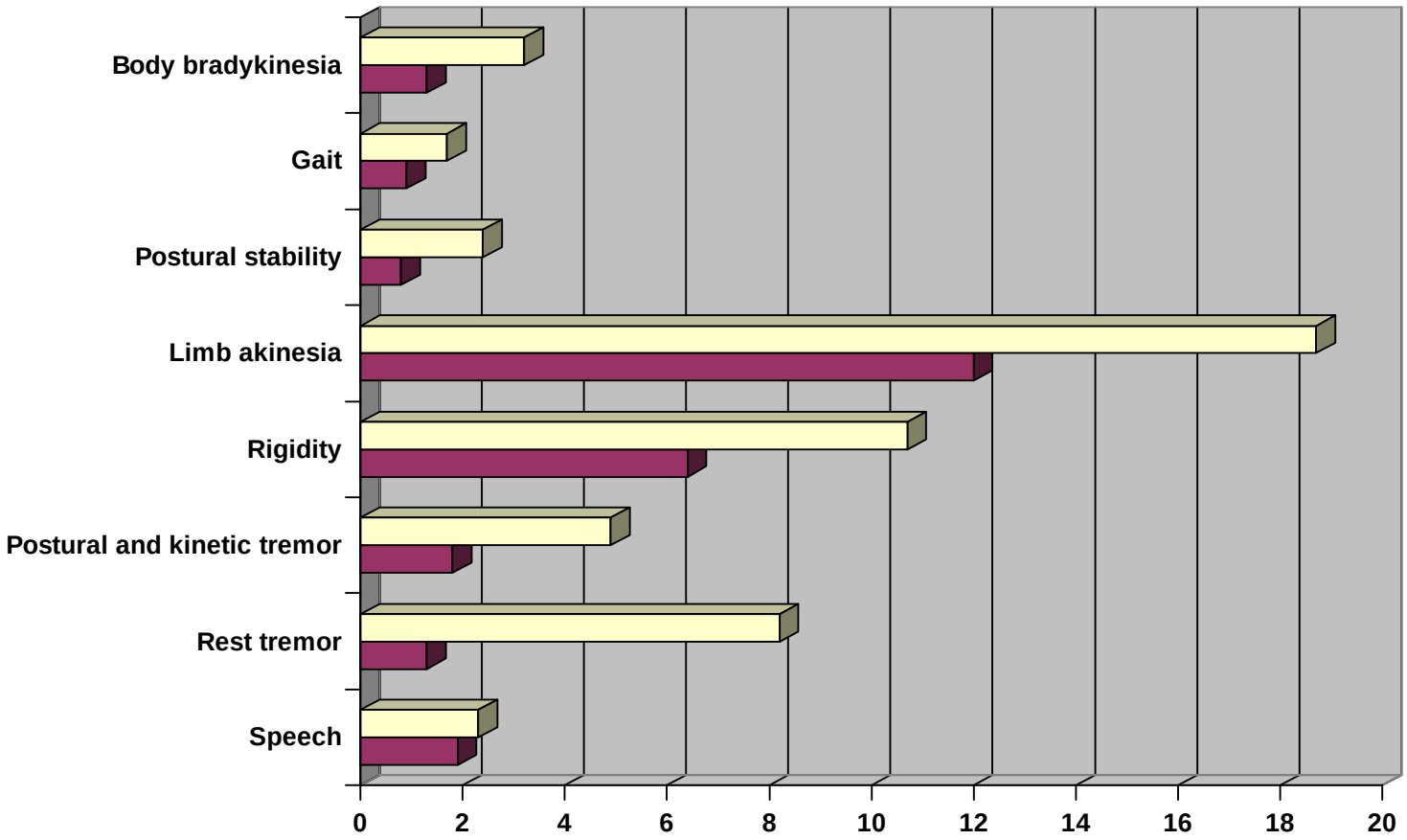

Figure 1. Variations of individual motor signs of the UPDRS score on the last follow up compared to baseline. Limb akinesia is defined as the sum of UPDRS items 23, 24, 25 and 26. Values are without medication. All variances are significant except for speech. Legend: Baseline (yellow bars), last follow up (red bars).

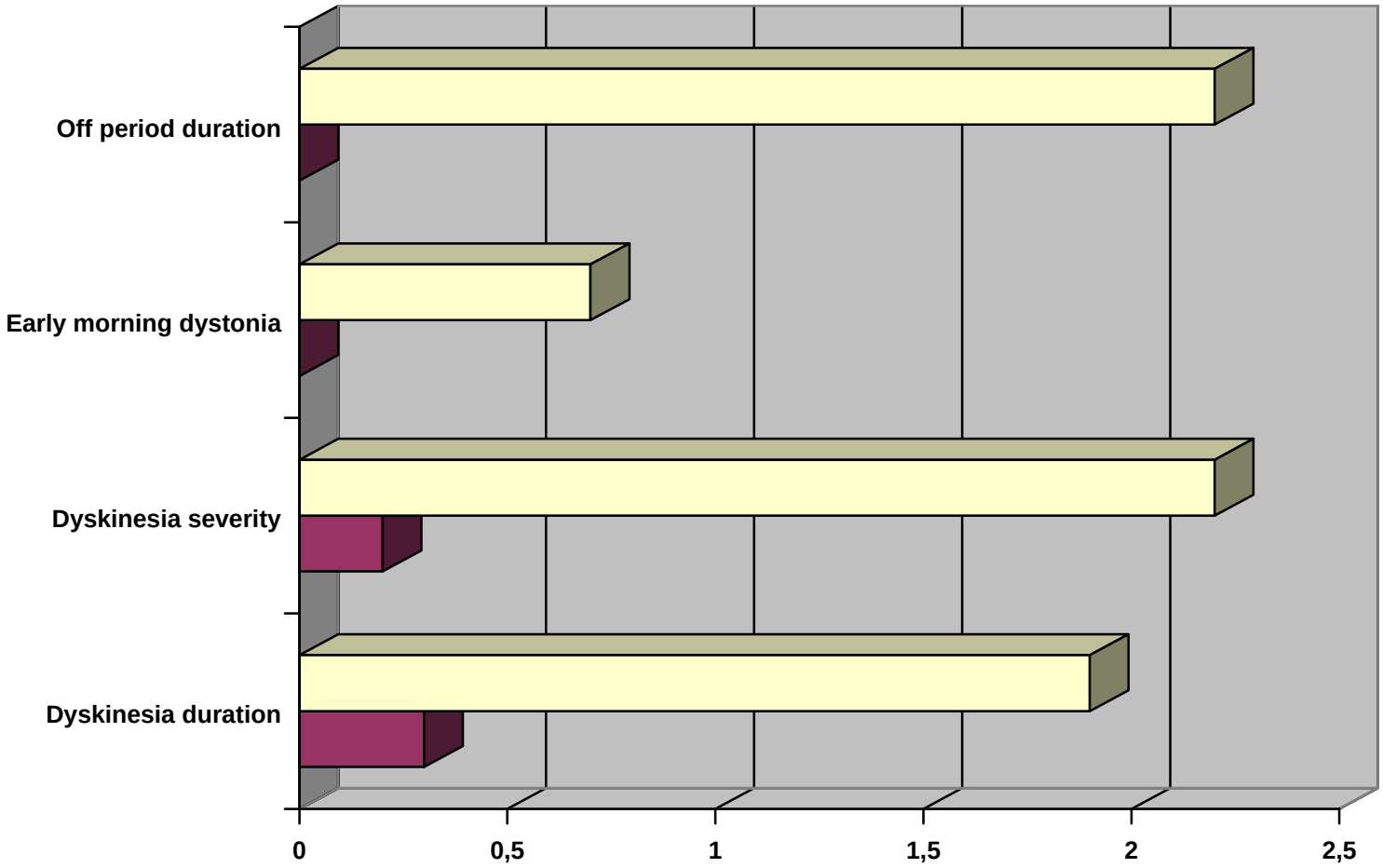

Figure 2. Variation of UPDRS dyskinesia and fluctuation scores on the last follow up compared to baseline evaluation. All variances are significant. Legend: Baseline (yellow bars), last follow up (red bars).