Movement disorders 1

P 2042

Effect of endocannabinoids on \[^{3}\text{H}\]-gaba uptake in rat globus pallidus – relevance to Parkinson’s disease

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Globus pallidus is one of the major constituent nuclei of the basal ganglia. Within the globus pallidus, there is a high density of CB\(_1\) cannabinoid receptors and high levels of endocannabinoids. To date, three endocannabinoids have been identified: anandamide 2-arachidonyl glycerol (2-AG), and noladin ether. In the globus pallidus, CB\(_1\) receptors are localized presynaptically on GABAergic neurons. Activation of CB\(_1\) receptors is believed to result in inhibition of GABA release. We focused on the influence of endocannabinoids on GABA uptake in freshly isolated rat globus pallidus slices. Following incubation with 2-AG (1 microM and 3 microM), we observed a 40%, and 30% increase respectively in \[^{3}\text{H}\]-GABA uptake (p<0.05, one-way ANOVA and Turkey’s post test). When incubated with noladin ether (1 microM), an increase of 57% was observed (p<0.001). The effects of 2-AG were reversed by the CB\(_1\) receptor antagonist AM 251 (1 microM), showing this mechanism is likely to be CB\(_1\) receptor-mediated (p<0.05). In contrast, neither anandamide (0.1–10 microM) nor the synthetic CB\(_1\) receptor agonist WIN 55,212-2 (1–100 microM) had significant effect on GABA uptake compared to the vehicle. Experiments in animal models of Parkinson’s disease suggest that the cannabinergic system plays a role in the pathophysiology of Parkinson’s disease, our results might help to explain the mechanism.

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P 2043

Sumanirole does not increase the incidence of somnolence as measured by the ESS


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Introduction Sumanirole is a new dopamine agonist specific for the D2 receptor. Dopamine agonists are known to cause somnolence with rates ranging from 20% to 40% in clinical trials. The Epworth Sleepiness Scale (ESS) was more precise than adverse event (AE) reporting and was used to assess somnolence with sumanirole.

Methods Somnolence was evaluated in 2 double-blind, randomised, placebo-controlled studies. Both studies had 7-week escalation and 4-week maintenance phases. Early disease patients (Hoehn & Yahr I–III, no levodopa, sumanirole n=78, placebo n=68) were titrated to a fixed dose (0, 2, 8, 24, or 48

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mg/day). Advanced disease patients (Hoehn & Yahr II–IV, on levodopa, sumanirole n=125, placebo n=132) were titrated to their optimum dose (1, 2, 4, 8, 16, 24, 32, 48 mg/day, flexible dose study).

**Results** In early disease, the percentage of patients whose ESS scores were ≥15 (marked drowsiness) at the optimum dose (8 mg/day) were comparable to placebo (8% sumanirole vs 1.5% placebo). The frequency of somnolence reported as an AE was 9.8% at 8 mg/day vs 8.2% in the placebo group. In advanced disease, the percentage of ESS scores ≥15 were comparable to placebo (4.0% sumanirole vs 4.5% placebo). The frequency of patient-reported somnolence as an AE was 5% vs 1.4% with placebo.

**Conclusions** The incidence of somnolence with sumanirole as measured by the ESS was comparable to placebo. Patient-reported AE rates were much lower than those for other dopamine agonists, suggesting that somnolence is not a major side effect of sumanirole therapy.

**P 2044**

**Sumanirole: a highly D2 selective dopamine receptor agonist with efficacy in animal models of Parkinson's disease**

R. B. McCall, N. Nichols, K. Svensson, R. Huff

**Introduction** Dopamine (DA) agonists used to treat Parkinson’s disease (PD) bind non-selectively at the D2, D3 and D4 receptors. D3 and D4 receptors may contribute to the psychiatric disturbances which accompany DA agonist and L-DOPA therapeutics. Eliminating D3 and D4 activating properties of DA agonists could reduce the psychiatric and neurological side effects in treating PD.

**Methods** Human D2, D3 or D4 receptors were expressed in CHO cells and utilized in radioligand binding studies and cell based intrinsic efficacy assays. In rats, 6-OH-dopamine (6-OHDA) solution was injected unilaterally into the substantia nigra and tested 2-weeks post lesion. Three cynomolgus monkeys were treated with MPTP IV at different dosages until variable, but stable, Parkinsonian features appeared.

**Results** The affinity of sumanirole for the D2 receptor is 9.0±1.0 nM. Unlike other dopamine agonists, the affinity of sumanirole at D3, D4 and D1 receptors is at least 200-fold lower than at D2 receptors. Sumanirole was a potent full agonist at the D2 receptor but had no activity at D3 and D4 receptors. In 6-OHDA lesioned rats, sumanirole produced a significant dose-related increase in turning. Maximum efficacy of sumanirole was 2.5–5 fold greater than ropinirole, pramipexole, bromocriptine or pergolide. Sumanirole reduced the disability score in MPTP monkeys.

**Conclusions** Sumanirole is the first highly selective D2-receptor agonist developed for the treatment of PD. Clinical studies to date suggest that the enhanced selectivity of sumanirole will result in an improved side effect profile in Parkinson’s patients.

**P 2045**

**The D2 Pharmacology of Sumanirole**

R. B. McCall, M. Piercey, K. Svensson, V. Sethy

**Introduction** Sumanirole is a highly D2 selective receptor agonist currently under development for the treatment of Parkinson’s disease (PD). Unlike other dopamine (DA) agonists, sumanirole binds selectively to the D2 receptor, exhibiting at least 200-fold selectivity for the D2 receptor versus the D1, D3 and D4 receptors. It is hypothesized that enhanced selectivity of sumanirole will reduce the psychiatric and neurological side effects seen with non-selective agonists in treating PD. The objective of this study is to detail the D2 agonist pharmacology of sumanirole.

**Methods** The effects of sumanirole on substantia nigra DA neuron firing were evaluated in anaesthetised rats. Sumanirole’s effects on DA metabolism of rat substantia nigra and tuberoinfundibular DA neurons were evaluated. The effects of sumanirole on rat striatal acetylcholine levels were determined. Locomotor and behavioural effects of sumanirole were also studied in rats.

**Results** Sumanirole inhibited the firing of DA neurons in substantia nigra pars compacta with an ED50 of 0.54 mg/kg, i.v. and decreased DA synthesis and turnover. These effects were blocked by haloperidol. Sumanirole dose-dependently increased striatal acetylcholine levels. Like other DA agonists, sumanirole suppressed exploratory behaviour and induced yawning in the rat at low doses. Sumanirole produced profound locomotor stimulation in habituated and reserpine-pretreated rats compared to other DA agonists and was blocked by haloperidol.

**Conclusions** The D2 agonist properties of sumanirole are supported by the electrophysiological, biochemical and behavioural effects of the drug. Sumanirole differentiated itself from other agonists on the basis of its profound locomotor stimulatory effects.

**P 2046**

**Neuroprotective effects of Sumanirole**

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**Introduction** Sumanirole is a highly D2 selective receptor agonist currently under development for the treatment of Parkinson’s disease (PD). PD is characterized by a progressive neurodegeneration of nigrostriatal dopamine neurons, in part caused by oxidative stress. Pramipexole, a dopamine agonist used in PD, has been shown to have neuroprotective properties. Therefore, the objective of the present study was to determine if sumanirole has neuroprotective properties in an animal model of neurotoxicity.

**Methods** 3-acetylpyridine (3-AP), a nicotinamide antagonist, is a potent rat neurotoxin. Sumanirole (1–20 mg/kg, PO) was given either pre- or post 3-AP treatment and animals were sacrificed 96 hours later. Neuronal cell counts were performed in the inferior olive and cGMP; ATP and rotordor performance were used as surrogate toxicity markers.

**Results** 3-AP treatment produced significant decreases in cerebellar cGMP and ATP, decrements in rotordor performance and a significant decrease in inferior olive neurons. Sumanirole, given either before or after 3-AP, significantly attenuated 3-AP induced reductions in cGMP; ATP and rotordor performance in a dose-related manner. Sumanirole also significantly reduced the inferior olive neuronal cell loss produced by 3-AP. Pre-treatment with raclopride did not block the neuroprotective effects of sumanirole.

**Conclusion** Sumanirole has in vivo neuroprotective properties that do not appear to be related to the compound’s D2 agonist properties.
**P 2047**

Non-compartmental pharmacokinetic (PK) analysis of Sumanirole in Parkinson’s disease (PD) patients

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**Introduction** Sumanirole is a potent dopamine D2 selective receptor agonist in development for treatment of PD. Because of its receptor selectivity, sumanirole is predicted to have fewer side effects than other dopaminergic agents. A double-blind, placebo-controlled Phase II study was conducted to characterize safety, efficacy and PK of sumanirole in patients with early PD without levodopa.

**Methods** Following dose titration and a 4-week dose-maintenance period with twice daily extended release oral doses of 2, 8, 24 and 48 mg/day sumanirole, 6–9 blood samples/patient were collected from 60 patients at extended-stay visits at the end of dose escalation and dose maintenance (Weeks 8 and 11). Sumanirole plasma concentrations were measured using a validated HPLC method. Data were analysed using Kinetica® and non-compartmental analysis (NCA).

**Results** Trough concentrations and maximum concentrations (Cmax) increased dose proportionally across the daily dose range of 2–48 mg. Time to Cmax was variable, ranging from 1–8 h. Mean AUC 1–12 h values of 49, 194, 539 and 1036 ng.h/mL at 2, 8, 24 and 48 mg/day showed dose proportional increases with interindividual variability of 35–64%. No change in PK parameters was seen at weeks 8 and 11, indicating no time-dependent effect. AUC estimates using NCA were very similar (less than 11% difference in means) to estimates made using a populated PK approach.

**Conclusion** Sumanirole pharmacokinetics in early PD patients were dose proportional over a daily dose range of 2–48 mg and no time-dependent changes were observed.

**P 2049**

Long-term outcomes of thalamic deep brain stimulation for parkinsonian and essential tremor

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Deep Brain Stimulation [DBS] of the thalamic Nucleus ventralis intermedius [VIM] is a treatment for medically intractable tremor. Little data is available about long-term outcomes. Over the past 7 years, 18 patients with tremor dominant Parkinson’s disease [PD] and 15 patients with essential Tremor [ET] obtained DBS-implants. 19 Patients were followed over 5 years. Functional disability was evaluated through the score “Activities of Daily Living”, from the “Clinical Rating Scale for Tremor”. DBS efficacy on tremor was classified “no tremor”, “tremor reduction”, or “no effect”. Functional disability improved in PD from 14+/−6 presurgery to 9+/−4 one year postsurgery, to 9+/−6 five years postsurgery; in ET from 19+/−7 presurgery to 8+/−6 one year postsurgery, to 13+/−5 five years postsurgery. One year postsurgery 72% of tPD and 47% of ET had no tremor, 27% of tPT and 52% of ET had tremor reduction. Five years postsurgery 63% of IPD and 20% of ET had no tremor, 18% of tPD and 60% of ET had tremor reduction. DBS had no effect in 18% of tPD and 20% of ET five years postsurgery. Patients with good outcomes had moderate tremor, normal neuroimaging, and <500mg levodopa/day presurgery.

VIM-DBS had good effects over the first year. This declined, especially in ET. It is unclear if other DBS targets lead to better long-term outcomes in ET. tPD patients requiring low doses of levodopa had good outcomes and may be considered for VIM-DBS. Otherwise, DBS of the subthalamic nucleus is recommended as it improves most motor symptoms of PD.

**P 2050**

Pergolide can induce spontaneous penile erections and hypersexuality in patients treated for advanced, fluctuating Parkinson’s disease

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Pergolide has been repeatedly shown to be effective and safe treatment in the advanced stage of Parkinson’s disease (PD). The complex sexual dysfunction is usually one of the most disabling problems of males suffering from this stage of disease. The effect of dopamine replacement or dopaminergic stimulation on sexual dysfunction in parkinsonian males has already been examined and described in patients treated by L-DOPA or apomorphine, but not by peroral dopamine agonists. The pergolide mesylate (Permax®) was introduced in 32 male patients suffering from advanced, fluctuating PD, who reported also sexual dysfunction. Seven of them (22%) reported important changes of their sexual functions within several weeks of treatment (mean 8, range 6–12) with pergolide. All these seven patients reported substantial improvement in their motor status, together with relatively sudden onset of hypersexuality. They all were hyperlibidinous, and they were hyperactive in the sexual field asking for sexual intercourse daily. They also reported extraordinarily frequent spontaneous
penile erections, which were present every hour, and lasted almost 30 minutes. The treatment in all patients was manipulated to maintain the motor improvement, and to change the hyposexual behaviour and suppress the spontaneous erections. It seems that pergolide can impressively improve sexual functions in patients with PD. In such cases, the introduction of pergolide might be better choice than the treatment with Sildenafil in younger male patients, who are particularly interested in sexual activities also during the course of Parkinson’s disease.

P 2051
Clinical impact of diagnostic SPECT investigations with a dopamine reuptake ligand
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The diagnosis of Parkinson’s disease is based on clinical features with pathological verification. However, autopsy has been found to confirm a specialist diagnosis in only about 75% of cases. Especially early in the course of the disease, the clinical diagnosis can be difficult.

Imaging of dopamine presynaptic transporters (DAT receptors) has provided a possible diagnostic probe in the evaluation of Parkinson’s disease. The cocaine analogue 123-I-ß-CIT is one of several radioligands that have been developed for Single Photon Emission Tomography (SPECT).

The purpose of this study has been to evaluate the impact of 123-I-ß-CIT SPECT on the management and diagnosis of patients with parkinsonism.

We have made a retrospective evaluation of the clinical records of 90 consecutive patients referred to 123-I-ß-CIT SPECT from the neurological department, Bispebjerg Hospital. In 58 subjects the scans revealed altered tracer uptake consistent with Parkinson’s disease, PSP and MSA. A significant change in the management or treatment because of the scan was found in 25 patients (28%). The sensitivity of the examination was 97% and the specificity 83%.

Conclusion A significant clinical impact of DAT receptor imaging was found. DAT receptor imaging is a useful diagnostic probe in patients with a possible diagnosis of parkinsonism.

P 2052
Hypothesis: Developmental form of parkinsonian syndrome
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Despite intensive research, the aetiology of “idiopathic” Parkinson’s disease remains unresolved. It has been suggested that certain apparently innocuous viral infections may elicit in the medium to longer-term neurological deficits; conversely, parkinsonism is among the neurological consequences which can follow viral or bacterial encephalitis. It is especially interesting that many viruses associated with encephalitis exhibit a predilection for the extrapyramidal system. Further, the perinatal period is recognized as critical in the normal development of specific brain regions; exposure to viral infection or other environmental stressors during this period is associated with abnormalities at both the structural and biochemical levels. Specific consequences of such exposure reflect interactions between individual genetic susceptibility, relative vulnerabilities of particular brain regions and the developmental stage at which exposure occurred. Behavioural syndromes reported in children exhibiting early life post-infection neurological damage are generally characterized by relative hyperactivity. Children exhibiting reduced motor activity, however, might not attract the same attention, as their behaviour would not be regarded as problematic from a pedagogic point of view; Huffmann (1968) described, for instance, a “defect syndrome” in postencephalitic children characterized by “generally friendly, cooperative, attentive individuals, who fitted well into their home environment.” Further, Widhalm (1985) reported a hypokinetic/parkinsonoid syndrome in children who had experienced overt problems in utero. We propose that such a syndrome in individuals less than twenty years of age may represent a developmental form of parkinsonism attributable to environmental and genetic factors, and that its incidence is underestimated due to greater community concern with overactive children.

P 2053
Expression of glutathione-S-transferases in blood of Parkinson’s disease patients
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Despite extensive research, the aetiology of Parkinson’s disease (PD) remains unknown and pathogenesis poorly understood. The key pathologic characteristic of PD is a degeneration of the nigrostriatal tract. Among many factors believed to be responsible for the development of PD, there are the oxidative stress and environmental toxins. Glutathione-S-transferases (GST, EC 2.5.1.18) are the most important detoxification enzymes that inactivate a large variety of compounds including organic peroxides. The aim of the present work was to examine the expression of GST isofoms in PD. Studies were conducted on serum and peripheral blood mononuclear cells (PBMC) obtained from blood of PD patients treated with levodopa and dopamine agonists and of healthy blood donors (controls).

Results There was no significant difference in serum GST activity between the group of PD patients (n=40) and the age-matched healthy blood donors (n=30). Western blot analysis revealed increased levels of GST mu and alpha in serum of PD patients but decreased level of the main isoform, GST pi, in both serum and PBMC. RT-PCR demonstrated higher expression of GST mu (4 and 5), alpha and pi in PBMC when compared to controls. The results were statistically significant.

Conclusion Overexpression of GST mu and alpha may be a physiological response to toxic compounds, including radical oxygen species, formed in Parkinson’s disease. The increased expression of GST pi mRNA, not accompanied by the rise of the protein level, may be explained by altered protein translation or increased protein turnover.
P 2054
Peripheral markers of apoptosis in Parkinson’s disease: the effect of dopaminergic drugs.
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Apoptosis may play a central role in the neurodegenerative process of Parkinson’s disease (PD). Experimental studies have suggested that L-DOPA, still the first choice therapy for the disease, may have pro-apoptotic effects, as a result of its oxidant properties. Conversely, dopamine agonists – which are now currently used for PD treatment, mainly as adjunct therapy – have shown neuroprotective effects. In this study, we investigated pro- and anti-apoptotic proteins in peripheral blood lymphocytes of PD patients under therapy with L-DOPA – alone or in association with dopamine agonists – and age-matched controls. We measured activity of caspase-3 (activator of the apoptotic cascade), levels of anti-apoptotic protein Bcl-2 and expression of the peripheral benzodiazepine receptor (PBR), which is thought to represent the intra-cellular binding site for Bcl-2; we also measured lymphocyte levels of anti-oxidant enzyme superoxide dismutase (Cu/Zn SOD). PD patients showed higher caspase-3 activity and lower levels of Bcl-2, compared to controls. Significant differences were observed between the two groups of PD patients, with patients under treatment with L-DOPA plus dopamine agonists showing lower levels of caspase-3 activity and Bcl-2 than patients taking L-DOPA alone. PD patients showed increased PBR expression, compared to controls, with the patients under treatment with dopamine agonists showing the highest values. In addition, patients treated with L-DOPA alone showed marked increase in Cu/Zn SOD levels. In conclusion, PD patients showed increased expression of peripheral pro-apoptotic markers, compared to healthy subjects. This condition was partially counteracted by the presence of dopamine agonists in the therapeutic regimen.

P 2055
FP-CIT (DaTSCAN) SPECT in the differential diagnosis of parkinsonism, a study of 25 cases
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Introduction Separating parkinsonian syndromes, using clinical criteria alone, can be difficult. In other way, discrimination of parkinsonian syndromes is important in view of differences in prognosis and therapy, but structural imaging (CT, MRI) is of limited value for differentiating parkinsonian syndromes. We report 1-FP-CIT (DaT SCAN) SPECT studies of the presynaptic nigrostriatal dopaminergic neurons, in patients with parkinsonism of different aetiology.

Patients and method 25 parkinsonian patients were selected on the basis of bradykinesia, rigidity or tremor.

Results A – Tremor was the principal symptom of 10 patients. The study was normal in 6 patients and the diagnosis was essential tremor (ET). 4 patients had abnormal scans and treatment with levodopa was initiated with good response. B – Multiple system atrophy was the clinical diagnosis in 5 cases. DaTSCAN was normal in 3 of them and pathological in 2 cases, these 2 patients improved with levodopa. C – 6 patients showed parkinsonism and vascular lesions in the TAC, DaTSCAN was normal in 4 patients (vascular parkinsonism) and pathological in 2 (Parkinson’s disease and vascular lesions). D – Depression had been the clinical diagnosis in 4 patients. Abnormal and asymmetrical DaTSCAN SPECT imaging changed the diagnosis to early Parkinson’s disease.

Discussion 1-FP-CIT SPECT imaging has utility in the diagnosis in patients with parkinsonism and differentiating them from ET. In Multiple System atrophy is not clear whether it is possible to make a distinction in individual cases on the basis of the results of imaging studies of the nigrostriatal pathway alone. DaTSCAN in vascular parkinsonism revealed conflicting results.

P 2056
DaTSCAN in differential diagnosis of parkinsonian syndromes
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Parkinson’s disease (PD) is characterised by the loss of dopaminergic neurons in the substantia nigra and decreased dopamine in the striatum. Usually, the diagnosis of PD can be based on the presence of cardinal clinical signs and the response to dopaminergic treatment. In cases presenting with unusual combinations of signs or unclear treatment response, dopamine system can be visualised by DaTSCAN, a SPECT method based on specific binding of FP-CIT, a cocaine analogue labelled by 123I, to presynaptic dopaminergic transporters. We investigated 21 patients (13 men, 8 women, mean age 53, range 36–79). After intravenous administration of FP-CIT, the distribution of radioactivity in the brain was measured using gamma camera with subsequent visual and semiquantitative evaluation. Based on the results, the patients could be divided into following subgroups:

1) Patients without clear response to L-DOPA, showing on DaTSCAN
a) unilateral deficit of radioactivity accumulation in the striatum (9 subjects) – confirming the diagnosis of PD;
b) bilateral reduction of striatal binding (6 subjects) – reflecting advanced PD or wider involvement of basal ganglia in other neurodegenerative disorders;
c) bilaterally normal accumulation of radioactivity (2 subjects) – excluding PD, e.g. in patients with essential tremor;
2) Patients with good clinical response to L-DOPA therapy showing bilateral deficit of radioactivity in the striatum (4 subjects), confirming the diagnosis of PD.

In conclusion, DaTSCAN is a functional assessment of presynaptic dopaminergic system improving the diagnostic accuracy of PD, especially in cases with uncertain response to dopaminergic therapy or with atypical clinical features.

P 2057
Clinical effects of increasing the daily Pergolide dose in pre-treated patients with idiopathic Parkinson’s disease (PD)
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Introduction Many PD patients are treated with suboptimal doses of pergolide ranging from 0.75 to 1.25 mg/day. The present study evaluates the efficacy and safety of a 0.5 mg pergolide dose increase in PD patients.

Methods In this open label multicenter trial patients with a diagnosis of PD were pre-treated with stable doses of levodopa and pergolide (range 0.75–2mg/day). UPDRS Part III motor score was at least 18. The daily pergolide dose was increased by 0.5 mg/day in two 0.25 mg steps over a 4-week period, daily levodopa dose was kept stable. Primary efficacy measure was the change in the UPDRS Part III score from baseline to endpoint after a total of 4 weeks. Other efficacy measures included the UPDRS total score, CGI, and PGI.

Results Mean patient age was 64.5 years (females N=33, males N=78). 96 patients completed the protocol. Mean pergolide dose at baseline was 1.21±0.53 mg/day. The UPDRS total score (baseline: 49.4±18.7; endpoint 37.1±19.6, p<0.01) and UPDRS Part III score (baseline: 33.0±12.5; endpoint: 24.2±13.1, p<0.01) significantly improved. Adverse events included dizziness, nausea, sweating, asthenia, and diarrhoea. No serious adverse events were reported.

Conclusions Increasing the daily pergolide dose by 0.5 mg in PD patients pre-treated with levodopa and low daily doses of pergolide leads to significant improvements in PD symptoms as measured by the UPDRS total score and UPDRS Part III motor score. The dose increase appeared to be safe and well tolerated.

P 2059
Estimation of attentional resources in Parkinson’s disease
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Parkinson’s disease (PD) involves cognitive changes from its early stages, which involve executive functions, and may include specific attentional impairments. We tested the attentional capabilities of 26 early PD patients and 21 age-matched controls with a new computer based visual-motor-attention test (VMAT). Testing included a baseline condition of tracking a 1cm circular target that moved along a sinusoidal or a circular path on a computer screen, by moving a cursor, using an unseen manipulandum. The baseline condition was followed by several experimental conditions in which various numbers of distractor targets and/or distractor cursors interacted with the real target and cursor. The cost of having to cope with distraction was computed by subtracting performance in the baseline condition from that in the experimental conditions. Baseline performance of the patients was significantly inferior to controls. A significant decline in performance was found with increasing distraction in both patients and controls. However, distraction had a significantly greater effect on the controls. Still, in the distracted conditions performance of the patients was significantly worse than the controls. In fact, performance of the controls under distraction was still better than the baseline performance of the patients. These results suggest that PD patients have low attentional resources, which limits their baseline performance and therefore imposes a bottom effect on their performance.

P 2060
Rivastigmine is effective and well tolerated in the treatment of Parkinsonian psychosis of geriatric patients
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The treatment of Parkinson’s disease (PD) with L-dopa has revealed unfavourable effects 5–10 years after the beginning of the therapy. This has led to the present criteria for treatment of de novo patients with PD which mainly rely on the age, and aim to delay the use of L-dopa as long as possible. In a retrospective study data of 155 patients with PD were analysed with the goal of finding a clinical marker for the critical time point when the administration of L-dopa turns to be necessary. We presumed that this marker could be the clinical stage of PD. The clinical stage was assessed using the Hoehn & Yahr (H&Y) scale and the severity of the symptoms using the UPDRS. We found no relationship between the age and the kind of the therapy (dopaminagonists vs. L-dopa) with regard to the clinical outcome. However, a significant interaction was found between the clinical stage and the UPDRS score on the one hand and the therapy on the other. In the H&Y stages 1 to 2.5 the UPDRS scores in patients treated only with dopaminagonists was lower than in patients treated with L-dopa while in the H&Y stage and up the UPDRS scores were lower in the patients treated only with L-dopa. The results show that the clinical stage might be a better criterion than the age to appraise the time point when L-dopa needs to be administrated in de novo patients with PD.

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Conclusions The cholinergic agent rivastigmine reduces neuropsychiatric symptoms when given to elder PD-patients without deteriorating motor function and is well tolerated. This provides a new approach, but does not substitute the need of atypical neuroleptics. More PD-patients should be treated to find out who benefits more from cholinergic than from atypical neuroleptic medication or needs both.

P 2061 Population pharmacokinetics (PPK) of Sumanirole in Parkinson’s disease (PD) patients
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Introduction Sumanirole is a dopamine D2 selective receptor agonist in development for treatment of PD. Because of receptor selectivity, sumanirole is predicted to have increased efficacy and fewer side effects than other dopaminergic agents. Two double-blind, placebo-controlled Phase II studies were conducted to characterize the safety, efficacy and PPK of extended release sumanirole (2–48 mg/day, BID) in patients with early PD or with advanced PD with levodopa.

Methods A PPK model was developed using NONMEM® to characterize sumanirole PPK and the relationship of subject demographics and baseline covariates on PPK variability. Phase I data from healthy volunteers was incorporated for model development.

Results PPK data included 378 patients with normal to severely impaired renal function and 20 healthy volunteers. Sumanirole PPK were described by a one-compartment model with first-order absorption. Volume of distribution (V/F) was fixed to a constant 300 L due to correlation with the absorption rate constant. Apparent clearance (CL/F) estimates were not sensitive to fixed V/F. CL/F was significantly related to creatinine clearance (CcrCL, p<0.001). A gender effect accounted for a difference of <15% on CL/F. At a CcrCL of 75.8 mL/min, sumanirole CL/F was 23.1 L/hr (males) and 20.1 L/hr (females). With CcrCL and gender in the model, age, race, weight, patient status (healthy volunteer vs PD patient) and levodopa were not significant predictors of CL/F.

Conclusions Sumanirole disposition in PD patients was primarily influenced by renal function (CcrCL), only slightly by gender and not by other covariates (age, weight, race, patient status, levodopa therapy).

P 2062 Evaluation of Sumanirole pharmacokinetics in non-clinical species, human volunteers and patients with Parkinson’s disease: Evidence of linear pharmacokinetics across species
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Objective To describe the pharmacokinetics (PK) and disposition of sumanirole in non-clinical species and human subjects.

Background Sumanirole is a potent D2 selective agonist at the dopamine receptor (Kd=9 nM) currently in clinical trials for the treatment of Parkinson’s disease (PD).

Design/Methods Sumanirole PK and disposition of [14C]sumanirole were evaluated in non-clinical species in separate studies of similar design, and also following administration of an immediate-release (IR) formulation to healthy volunteers and PD patients.

Results Sumanirole was generally well absorbed with an absolute oral bioavailability of >65% in mice, rabbits, and monkeys, and 34% in rats. Absorption-rate limited kinetics were observed after oral dosing in preclinical species. The volume of distribution of sumanirole was consistent with extensive tissue distribution. Binding to plasma proteins was minimal (<20% across species). Following single and multiple oral dosing, all species displayed dose-proportional increases in plasma concentrations, and exposure to parent compound accounted for 50%–70% of total drug-related radioactivity. The half-life of total radioactivity in human plasma (4.4±0.74 h) was similar to that of parent compound (4.1±0.72 h). Urinary excretion was the primary route of elimination of drug-related radioactivity (79%–92% of dose). PK characteristics in patients with moderate to advanced PD receiving an IR formulation were similar to those in healthy volunteers.

Conclusions Sumanirole is well absorbed, widely distributed, and displays linear PK across non-clinical species and humans. Parent compound was the major drug-related material in plasma following administration to non-clinical species, healthy volunteers, and PD patients.

P 2063 In vivo and in vitro investigation(s) of Sumanirole clearance in humans: Sumanirole exhibits low drug-drug interaction potential
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Objective To investigate sumanirole’s mechanisms of clearance and potential for drug-drug interactions (DDI).

Background Potency and selectivity of agonists at the D2 dopamine receptor are important in the development of clinically useful agents for the treatment of Parkinson’s disease (PD). In addition, ideal agents should possess desirable ADME characteristics, low potential for DDI, and not be subject to pharmacogenetic differences in drug disposition.

Methods The metabolism and disposition of [14C]sumanirole were evaluated in healthy volunteers. In vitro techniques using individual and pooled human liver microsomes, cloned cytochrome P-450s (CYPs), and human hepatocytes were used to investigate the enzymes responsible for sumanirole metabolism. A comparison of in-vitro and in-vivo metabolite profiles of sumanirole was also conducted.

Results Approximately 50% of sumanirole was eliminated unchanged in the urine after administration of [14C]sumanirole. Multiple metabolites accounted for the remainder of drug clearance. There was favourable agreement in the rank-order abundance of metabolites formed in vivo with those produced via in vitro systems. In particular, multiple CYPs were involved with sumanirole metabolism and sumanirole was not found to be an inhibitor of CYPs. Moreover, all CYP pathways have an apparent Kfm of 300–5000 nM.

Conclusions Sumanirole undergoes multiple metabolic pathways of drug clearance as well as renal excretion. Since PD patients are subject to polypharmacy, the ability to predict DDI using an in vitro approach is helpful. Sumanirole has a low
potential to inhibit CYPs and is not subject to pharmacogenetic differences of drug metabolising enzymes; ideal properties for a dopaminergic agonist.

P 2064

Sumanirole, a new dopamine agonist for the treatment of Parkinson’s disease
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Introduction
Sumanirole is a unique dopamine agonist that has selectivity for the D2-receptor subtype. The pharmacodynamic treatment effect and side effect profile were evaluated in patients with Parkinson’s disease (PD).

Methods
We studied the tolerability, pharmacodynamics, and pharmacokinetics (PK) of different doses of sumanirole (0, 2, 8 and 24 mg/day; immediate-release oral formulation, 4 times daily for 35 days) in 29 moderate to advanced PD patients receiving levodopa.

Results
In spite of the small number of patients and patient variability, results indicated that for several endpoints, one or more of the sumanirole treatment groups had change from baseline values that were superior to the changes from baseline values for placebo. These included UPDRS II (mean change –4% in the 24-mg/day group), reduction in levodopa dose (by 76% and 53% in the 2-mg/day and 24-mg/day groups, respectively), foot tapping test, and step-seconds test. Sumanirole was rapidly absorbed with mean peak concentrations within 1.5 hours following drug administration. Sumanirole Cmax and AUC0.5h values increased dose proportionally and mean half-life ranged from 3.9 to 4.6 hours. No dose-response relationship was evident for the number or types of adverse events that occurred. Sumanirole did not appear to increase the incidence of oropharyngeal hypotension, nor did it demonstrate any clinically relevant or meaningful cardiac effects or changes in electrocardiogram parameters.

Conclusions
Sumanirole was well tolerated and had dose proportional PK. The pharmacodynamic test battery showed evidence of a pharmacodynamic treatment effect for several of the endpoints measured, particularly levodopa dose reduction.

P 2065

Pergolide pharmacokinetics in patients with Parkinson’s disease
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Introduction
Pergolide is widely used in the treatment of Parkinson’s disease, but its pharmacokinetics (PK) is not fully known, as the initial bioanalytical assay was not sufficiently sensitive. A more sensitive assay is now available (lower limit of quantification 10 pg/ml). Understanding pergolide PK is important, especially regarding the recent interest in a “continuous dopamine stimulation” to explain the genesis of L-dopa-induced long-term motor complications (Olanow et al, TiNS 2000).

Methods
We performed a 2-month open label, randomised, multiple oral dose escalating and descending study (up to 3 mg/d on a t.i.d. regimen) conducted in 14 Parkinson’s disease patients (mean age: 62 yrs). Pergolide was analysed using HPLC with mass spectroscopic detection. Non-compartmental PK analysis was used. Parkinson’s disease symptoms were assessed using the UPDRS.

Results
At steady state pergolide was absorbed moderately fast (Tmax=2 to 3 hours post dose) and was eliminated with a terminal half-life of approximately 21 hours (range 6 to 64 hours). Cmax and AUC increased in a proportional manner with the dose over the range of 0.5 to 3 mg, with large intersubject variability (approximately 50%). Pergolide was well tolerated and no serious adverse events were reported. The mean UPDRS III scores were decreased by up to 8 points while on pergolide.

Conclusions
The mean pergolide elimination half-life is approximately 21 hours. This finding supports the potential interest for such a drug regarding the hypothesis of central continuous dopamine stimulation in the management of Parkinson’s disease.

P 2066

The dopamine agonist lisuride provides protection against the deleterious effects of glutamate on dopaminergic neurons
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Introduction
Glutamate excitotoxicity is discussed as a contributing factor to Parkinson’s disease. We recently showed the protective effects of the high affinity D2 receptor agonist lisuride on dopaminergic neurons. We investigated if lisuride was able to protect against glutamate toxicity.

Methods
Dopaminergic neurons in primary culture were pretreated with lisuride (0.001–10 microM) on the 8th day in vitro (DIV) for 24 h. On the 9th DIV glutamate (0.5 mM) was added for 10 min and the survival rate of dopaminergic neurons was determined following a 2-day period of recovery. Alternatively, lisuride was added directly after glutamate treatment during the 2 days of recovery. The D2 antagonist sulpiride was co-administered with lisuride on the 8th DIV. Antioxidative properties of lisuride were tested by preventing the autoxidation of 200 microM L-DOPA.

Results
Glutamate reduced the number of dopaminergic neurons by 69%, while lisuride reduced cell loss by 51% at 0.1 microM when added 24 h before glutamate. Simultaneous addition of sulpiride prevented the effect of lisuride. Even when added after glutamate treatment, lisuride reduced cell loss by 54% at 0.1 microM. Lisuride suppressed autoxidation of L-DOPA by 80% at 1 mM being even more potent than vitamin C (53% reduction).

Conclusion
These data imply that lisuride exerts neuroprotective effects on dopaminergic neurons in primary culture against glutamate excitotoxicity. Stimulation of the D2 receptor seems to play a role, since sulpiride abolished the protective effects. The inhibitory effect of lisuride on L-DOPA autoxidation indicates direct antioxidative properties of the agonist.
Ginsenosides Rb1 and Rg1 as an important and active principle of ginseng extract (Panax ginseng C.A. Meyer, Araliaceae) appear to exert protection against ischaemic and anoxic damage, suggesting an antioxidant and cytoprotective role. This present study was carried out to test the beneficial actions of these two ginsenosides on the survival and neurite outgrowth of dopaminergic cells affected with the excitotoxicant glutamate. Dopaminergic cultures were prepared from embryonic mouse mesencephala cultured first in DMEM (Dulbecco’s Modified Eagle’s Medium) containing 10% fetal calf serum and switched at DIV (day in vitro) 6 to serum free condition. Cultures were grown at 37°C with an atmosphere of 5% CO2 for 11 days. Cultured cells were treated according to the following protocols: i) untreated control. ii) glutamate group: cells were exposed to 0.5 mM glutamate for 15 minutes at day 9. iii) ginsenoside groups: 10 mM of either ginsenosides were added to the medium from day 6 and with glutamate at day 9. Exposure of cultures to excess glutamate (0.5 mM) caused extensive death of dopaminergic cells by 68–76% compared to control. Ginsenoside Rb1 (not Rg1) significantly enhanced the cell number of mesencephalic dopaminergic cells by 18.09% compared to control. Both ginsenosides Rb1 and Rg1 increased the length of neurites by 10–13% compared to cells exposed to glutamate. Thus, we conclude that ginsenosides Rb1 and Rg1 have a potential for neurotrophic and neuroprotective effects on mesencephalic dopaminergic cells.

Autonomic dysfunction in early stages of Parkinson’s disease (P.D.)

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Introduction Although early severe autonomic involvement should alert the clinician for diagnosis other than P.D., autonomic dysfunction does occur most commonly in late stages. The purpose of this study is to investigate the prevalence of autonomic disturbances in early stages of P.D.

Methods Thirty seven patients (19M and 18F) mean age 60 years clinically diagnosed with P.D., Hoehn-Yahr scale score <2 and mean disease duration 3.6 years were studied for autonomic dysfunction in the early stages of their disease. Exclusion criteria were those that Parkinson’s Disease Society Brain Bank guidelines include among the elements necessary to reach correct diagnosis.

Results A significant percentage of patients studied, 70% (26 patients) complained with at least one Autonomic nervous system symptom. Among them, 50% (13 patients) complained for seborrhea, 77% (20 patients) for Gastrointestinal (G.I.) dysfunction, 42% (8 patients) for Erectile dysfunction, 30.7% (8 patients) for Urinary urgency (but not frank incontinence) and 7.7% (2 patients) for Orthostatic Hypotension (O.H.). Furthermore, among patients who reported G.I. dysfunction, 50% (13 patients) had constipation, 23% (6 patients) swallowing difficulties but not severe dysphagia and 23% (6 patients) increased salivation. However, elderly patients are expected to develop relatively earlier genitourinary dysfunction than do younger onset patients due to concurrent urological problems.

Conclusion Autonomic involvement is a relatively late feature of P.D. However, some “autonomic” problems such as constipation, seborrhea, erectile difficulties and less frequently impaired swallowing and salivation seem to be present at the early stages of the disease where others (i.e. O.H., severe dysphagia and incontinence) are uncommon.

Effect of cannabis on Parkinson’s disease symptoms: questionnaire-based study

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Following the information presented in the media we realised some of our patients use cannabis to alleviate their Parkinson’s disease (PD) symptoms. To evaluate their possible experience, all patients with PD registered at the Movement Disorder Centre (MDC) were asked to anonymously complete a questionnaire. Out of 630 questionnaires sent, 339 (53.8%) were returned. The responders’ mean age was 65.7 years (range: 36–92 years) and the average PD duration 8.6 years (range: <1–46). 85 patients (25.1%) reported to have an experience with cannabis, mostly...
using fresh or dried cannabis leaves orally. In this group, 39 patients (45.9%) described mild or substantial alleviation of their PD symptoms in general, 26 (30.6%) improvement of rests tremor, 38 (44.7%) alleviation of bradykinesia, 32 (37.6%) alleviation of muscle rigidity and 12 (14.1%) improvement of levodopa-induced dyskinesias. According to the information obtained from the patients, this alleviation in average occurred 1.7 months (range: 1 hour–6 months) after their first cannabis use. There was a correlation between the duration of cannabis use and feeling of improvement in general PD symptoms (p<0.001, χ² test), rest tremor (p<0.01), bradykinesia (p<0.01) and muscle rigidity (p<0.01). In case of dyskinesias, the beneficial effect did not correlate with the length of cannabis use, but the patients using cannabis with higher frequency reported alleviation of dyskinesias more often (p<0.05). It seems some of the cannabinoids or compounds targeting the cannabinergic system might be useful in the treatment of PD symptoms or drug-induced dyskinesias.

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P 2071
Symptom focused questionnaire in Parkinson’s disease
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How can we improve the management of Parkinson’s disease of patients attending clinic?

The study aimed at improving the quality of care of the Parkinson’s disease patient by using a symptom focused questionnaire (SFQ). The questionnaire developed is a modified form of the Unified Parkinson’s Disease Rating Scale.

Fifty consecutive patients with Parkinson’s disease were sent a questionnaire (SFQ) prior to their outpatient appointment. Patients attended a Movement Disorder Clinic run by a Consultant Neurologist and a Neurology Nurse Clinician. During the consultation the SFQ was then used to augment the consultation process. Following the consultation all patients completed a “General Satisfaction” questionnaire together with a “SFQ Satisfaction” questionnaire.

A comparison group of fifty patients with Parkinson’s disease were not sent the SFQ. An assessment of the quality of their appointment was made by completing the General Satisfaction questionnaire only.

Although a minority reported an unnecessary number of enquiries being made during the appointment, all patients reported satisfaction with the consultation. A third of Parkinson’s disease patients stated that the SFQ permitted time to reflect upon their symptoms of Parkinson’s disease and the totality of symptoms. Thus effectively identifying major causes of concern. The Symptom Focused Questionnaire offers a useful clinical tool in enhancing the outpatient consultation. Patients report that time spent reflecting upon their symptoms, prior to their clinic appointment, effectively assists in identifying their individual needs.

P 2072
Mental disorders in Parkinson’s disease: treatment with quetiapine
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Mental Disorders (MDs) are disabling complications of Parkinson’s disease (PD). We set out to demonstrate the efficacy of quetiapine, in controlling MDs without worsening the parkinsonism, and to ascertain whether quetiapine can facilitate the pharmacological management of advanced stages of PD when MDs appear. The effect of quetiapine on specific psychiatric features was also investigated.

Thirty-five PD patients with disabling MDs were enrolled in this open-label study. Evaluation of motor function, of MDs and of cognitive state were completed before starting quetiapine and after 3 months of stable treatment. Dopaminergic drug variations were monitored throughout the study. MDs significantly improved after 3 months of quetiapine treatment at a mean daily dose of 140 mg, without producing significant changes in motor or cognitive function. Our population displayed three distinct MDs: hallucinations alone, which responded best to quetiapine; delirium, which responded to higher doses of quetiapine, and confusional state which showed only a slight response to the drug. Quetiapine was effective for the treatment of MDs in PD, particularly hallucinations and delirium. Quetiapine did not worsen motor functions and allowed the dopaminergic regimen in PD patients affected by MDs to be managed safely.

P 2073
The analysis of parkinsonian tremor using double axis accelerometer
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Introduction Tremor is a common symptom of many neurological disorders, including also Parkinson’s disease. Objective assessment of tremor indicators – amplitude, frequency, “harmonicity”– is a useful method, which allows discriminating different types of tremor.

Objective The aim of the study was development the method supporting the diagnosis in patients with Parkinson Disease (PD) by application spectral analysis of tremor recorded from palm, using accelerometer sensor.

Material 17 subjects (11 men and 6 women, age 42–81 years, mean 61.1) with clinically confirmed PD and 10 control subjects participated.

Method Recordings were performed with the use of double axis accelerometer and computer interface. Sensor was mounted at the dorsal of palm or fingers. Spectral analysis was done in Matlab of line. Analysis focused on determination shape of spectrum, the frequency of peak, central frequency, and harmonic index (HI).

Results In all subjects with clinically confirmed PD the characteristic sharp peak in spectrum was present at frequencies 5.1 to 7.8 Hz. In subsequent epochs the shape of spectrum significantly differs and HI varies from 0.8 to 0.95. In control group the spectrum was wide and consists of many peaks at frequencies from 3 to 8 Hz. The HI was 0.6 to 0.8.

Conclusion At the present state of our investigation the spectral analysis of acceleration signal recorded from palm seemed to be promising tool for supporting the diagnosis of Parkinsonian tremor.

P 2074
Swallowing disorders in Parkinson’s disease
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Introduction Impairment of swallowing is a common symptom in advanced stages of Parkinson’s disease, which may cause serious complications. The aim of the study was to compare
oral, pharyngeal and oesophageal phase of swallowing of PD patients with healthy controls.

**Material and methods** Swallowing in 11 PD patients and 9 controls was studied by EMG and oesophageal scintigraphy. 8 patients were aware of swallowing difficulties, while 3 did not complain of any.

**Results** PD patients had delayed triggering of swallowing reflex (543±84 ms vs. 230±66 ms in controls, p<0.05), longer time of laryngeal movement (1880±140 ms vs. 1349±154 ms, p<0.05), longer oesophageal phase of swallowing (12.4±2.4 s vs. 6.4±1.2, p<0.001), and much smaller dysphagia limit (the maximum amount of water, which could be swallowed at once – in normal subjects it is >20 ml) – 4.5±0.9 ml. Dysphagia, as assessed by these methods, was present in all cases studied, even in those who did not complained of swallowing problems.

**P 2075**

**Urodynamic abnormalities in patients with Parkinson disease**

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**Introduction** Patients with Parkinson disease (PD) often experience voiding dysfunction. In male patients it could be caused by PD itself or by bladder outlet obstruction, while in female patients causes may be complex and not congruent with symptoms.

**Subjects and methods** In our pilot-study urodynamic testing was performed in 15 patients with PD (9 males) and International Prostate Symptom (IPS) score. This score reflects voiding dysfunction, not only prostatic symptoms, thus it can be used in male and female patients. Data on disease severity was obtained using UPDRS and Hoehn and Yahr Scale. Disease duration, age, sex and treatment with antiparkinsonian drugs were also recorded.

**Results** Urodynamic testing showed detrusor hyperreflexia in 10 patients, hyporeflexia or areflexia in 2, hyperreflexia with impaired contractile function in 2 and hyperreflexia with detrusor-sphincter dysynergia in 1 patient. Severity of voiding disturbances increased with disease severity, with post-void residual urine volume as the parameter showing the best correlation. IPS scores increased with disease severity. Irritative index score correlated with maximum cystometric capacity and obstructive symptom score with post-void residual urine volume. We found no significant differences regarding age, but obstructive symptoms were prevalent in male patients. Influence of antiparkinsonian drugs was not certain.

**Conclusions** Voiding dysfunction in patients with Parkinson disease progressively worsens with advancing of disability (Hoehn and Yahr Scale>3). Dysfunction of the striated urethral sphincter and pelvic musculature is often seen in PD, and delayed relaxation at the time of initiation of voluntary voiding is the main symptom.

**P 2076**

**Excessive daytime somnolence: a follow-up study in de novo Parkinson’s disease**


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**Introduction** Pathophysiology of excessive daytime somnolence (EDS) in Parkinson’s disease (PD) is still debated. Factors related to the disease or to the treatment may be both equally important. We have previously shown that “de novo” PD patients are not different from healthy sex and age matched controls in measures of EDS. We therefore followed up these patients after the introduction of antiparkinsonian drugs.

**Methods and patients** EDS was assessed by means of the Epworth Sleepiness Scale (ESS) in 25 PD patients (mean age 64.7 years, mean symptoms duration 2.6 years) either at baseline, when untreated, and after 1 year of treatment with different antiparkinsonian medications. Motor disability was measured by means of subset III of the UPDRS scale.

**Results** After 1 year of treatment with antiparkinsonian drugs ESS score significantly increased (p=0.01) from baseline, while motor disability remained stable or improved in most patients as a result of treatment.

**Conclusion** The increase in ESS score and consequently of EDS in this group of patients seems to be related mainly to a direct effect of the treatment.

**P 2077**

**Dopamine and depression in patients with Parkinson’s disease**

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**Introduction** ~40–60% patients with PD experience a Major Depressive Episode (DE) requiring treatment. The pathogenesis may be reduced dopaminergic activity, inadequate serotonin secretion, or psychological reactions. It has been observed that depression in PD patients is related to “off” periods of response to levodopa. Since the dopaminergic system has a role in the formation of emotional state, and low levels of dopamine metabolites (HVA) are found in depressive patients, dopamine may participate in the pathogenesis of affective disorder and that there is a potential role for dopamine agonists (DAs) in depression.

**Methods** Thirty-eight patients with PD were diagnosed with Depressive Disorder (DD) (DSM-IV) with DE. Twenty-two had a history of DD. All patients had received inadequate combination treatment for depression (daily doses of nortriptyline and fluoxetine (40 mg)) for 7 weeks while receiving levodopa for PD in 4 daily doses. Pramipexole (PPX) was added the treatment regime of these patients.

**Results** During the first 3 weeks, HAM-D scores (17 items) were reduced by 18%; at 6 weeks, 48%; at 18 weeks, 53%; at 24 weeks, mean reduction of total score reached 61% in 34 patients (N=38). Two of the patients dropped out due to adverse events.

**Discussion** The antidepressive effect of PPX was evident after the first month of treatment, with a distinct improvement in psychomotor state. Further studies are needed to clarify the role of PPX and the dopaminergic system in the pathogenesis of DD and to determine the patient group that responds to treatment with DAs.

**P 2078**

**Excessive daytime sleepiness and “sleep attacks” induced by entacapone- three case reports**

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**Introduction** “Sleep attacks” are events of overwhelming sleepiness that occur without warning, or that occur with a prodrome that is so short or so overpowering that it prevents the
patient from taking appropriate protective measures. New observations imply that inappropriate daytime sleep episodes are not exclusive to dopamine agonists.

**Methods, patients** Three Parkinson’s disease patients reported excessive daytime sleepiness with sudden sleep attacks while receiving entacapone.

**Discussion** In our patients Nos. 1 and 3, there is a strong indication, regarding the time and the diminishment of the sleep attacks after the discontinuation of the entacapone administration, that the cause of the induced daytime sleepiness might be the increased bioavailability of L-DOPA, induced by entacapone. This theory is compromised by previous treatment with tolcapone (patient No.2) without any sleep problems. A possible explanation for the differing action of COMT inhibitors could be explained in terms of central affinity or in terms of different pharmacokinetics. The clinical observation of delayed sleep attacks latency after the entacapone introduction, and about of two weeks of waning after entacapone suspension could be the argument for another explanation. Whether this could mean that the sleep attacks might be induced by entacapone itself remain unknown.

**Conclusion** Our conclusion does not exclude the possible role of PD itself rather than merely the medications in this problem. In any case, our experience strongly suggests that the occurrence of sleep attacks is not exclusively limited to patients treated by dopamine agonists.

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**P 2079**

**Is depression a cofactor for dependence and disability in Parkinson's disease?**

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Twenty percent of patients with Parkinson’s disease (PD) suffer from depression (DP). Several symptoms of PD like bradykinesia and lack of facial expression mimic depressiveness so that DP in these patients is often overlooked and under-treated. However it can be assumed that it diminishes further the already reduced quality of life (QoL) and that it leads to a greater degree of disability and dependence, but the magnitude of this effect is not well studied. 164 patients, 77 male and 87 female, aged 69.8±11.5 with PD were investigated with the help of a semi-structured interview with the aim to compare the degree of dependence upon orthopaedic devices, caregivers and social institutions in PD patients with and without depression. The 27.5% of patients that were found to be depressed (Center of epidemiological studies depression scale >23) showed more cognitive impairment (Matis Dementia Rating scale: 33.9 vs. 129.5, p<0.05) but similar age and gender distribution when compared to non-depressed PD patients. The degree of dependence however was not found to be differing significantly between the groups suggesting that the impact of DP on social status and disability might be smaller than anticipated.
Movement disorders 2

P 3130
Clinical analysis of spinocerebellar ataxia type 2 in Serbian population
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The spinocerebellar ataxia type 2 (SCA2) is dominantly inherited neurodegenerative disease that is characterized with slowly progressive cerebellar ataxia, slow saccades and decreased tendon reflexes. The affected individuals show expanded CAG triplet repeats in ataxin-2 gene, and there is still some controversy about variability of phenotype. The 52 families with autosomal dominant ataxia (ADCA) and 70 isolated cases with idiopathic late-onset cerebellar ataxia from Serbia were analysed for this mutation. Eight affected individuals and one presymptomatic female from 5 families, heterozygous for CAG repeat expansion in the SCA2 gene containing 42–48 repeats, whereas the normal alleles carried 22–23 repeats. We observed a statistically significant inverse correlation between the age of disease onset and the number of CAG repeat units in the expanded alleles (Spearman’s correlation coefficient, p<0.05). All patients showed gait and limb ataxia, 75% had slowed saccades, 87.5% showed decreased or absent tendon reflexes while only one patient had hyperreflexia. Frequencies of slow eye movement correlated significantly with duration of the disease (r=0.855, p<0.01). Nerve conduction studies were performed in seven patients, and six of them had sensory dominant axonal polyneuropathy with reduced sensory action potentials. MRI was performed in eight patients. In Serbian population SCA2 mutation accounted for 9.6% of the known Serbian families with ADCA. Our results suggest that the clinical and genetic characteristics of the Serbian families with SCA2 are similar to descriptions of this disease in other populations.

P 3131
DYT1 mutation in primary torsion dystonia in a Serbian population
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Introduction Primary torsion dystonia (PTD) is a clinically and genetically heterogeneous movement disorder. A GAG deletion at position 946 in the DYT1 gene is responsible for most cases of autosomal dominant early-onset PTD.

Methods We analysed the DYT1 mutation in 52 patients from a Serbian population, selected according to the proposed guidelines for diagnostic testing: (a) 39 patients with PTD onset <26 years, and (b) 13 patients with the disease onset >26 years, but with at least one affected family member with early-onset dystonia.

Results and Discussion Five (10%) apparently sporadic patients were positive for the GAG deletion in the DYT1 gene: two with typical, generalized dystonia, one with long-lasting, non-progressive segmental dystonia, one with multifocal, and one with late-onset, jerky axial dystonia. Molecular analysis of relatives in 2 families revealed that the lack of family history was due to reduced penetrance.

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Bilateral changes in somatotopy of sensorimotor interactions in focal hand dystonia

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Introduction The aim was to detect abnormalities of sensorimotor interactions and their topographic distribution in dystonic patients.

Methods We investigated the effect of digital electrical stimulation on the amplitude of motor evoked potentials (MEPs) to transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES) in hand muscles on the affected and unaffected sides of 8 focal hand dystonia patients and 10 age-matched controls. Non-painful digital stimulation was applied to a contiguous finger (CF) and to a non-contiguous finger (NCF), and preceded TMS or TES at intervals from 10 to 100 msec.

Results In normal subjects, a somatotopic inhibitory effect was detected, i.e. CF stimulation provoked a significantly higher MEP inhibition at intervals of 20–50 msec. In dystonic patients, at the same intervals, the digital conditioning resulted in the absence (80% of muscles examined) or inversion (20% of muscles) of somatotopy. These abnormalities were present on both the affected and unaffected hands. TES conditioning provoked MEP inhibition only at ISIs < 40 msec.

Conclusion MEP suppression in response to digital stimulation is preserved in dystonia, but the somatotopic distribution of the sensorimotor interactions is lost or even reversed in dystonic patients. These abnormalities are present at both the spinal and cortical levels. These alterations are similar to the changes in the arrangement of sensory maps, documented in dystonic patients, suggesting a link between sensory abnormalities and the genesis of motor symptoms. Abnormal spatial distribution of surrounding inhibition may account for the altered topography of sensorimotor interactions in dystonic patients.

Minocycline as neuroprotection in Huntington’s disease

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Objective Huntington’s disease (HD) is a relentlessly progressive, incurable autosomal dominant neurodegenerative disorder. Minocycline delayed disease progression in the transgenic mouse model of HD, inhibited caspase-1 and caspase-3 mRNA upregulation, and decreased inducible nitric oxide synthetase activity in the R6/2 model. Survival was extended by 14%.

Methods In an open label study, minocycline was administrated to 18 patients with genetically confirmed HD. The patients were evaluated at baseline, after 2 weeks, and after 6 months of treatment using the motor scale of Unified HD Rating Scale (UHDRS-I).

Results The 14 compliant patients improved in most parts of the UHDRS, including fine motor tasks, whereas four noncompliant patients deteriorated as expected. In all, UHDRS did not change in the first 2 weeks of treatment but improved thereafter to a significant degree in the compliant group. No adverse effects were reported by the patients spontaneously or were observed directly by the investigators.

Discussion This is the first study of minocycline in HD. Whereas prior studies with other potential neuroprotective agents did not show ameliorative effect, we could demonstrate considerable clinical amelioration of symptoms in HD as seen in the animal model. A possible placebo effect is unlikely due to the unchanged motor functions after 14 days. However, our results should be taken with caution due to the open label design but may lead to some hope in this untreatable neuropsychiatric disease.

Conclusion A double-blind, placebo-controlled trial appears highly warranted to definitively establish the value of minocycline in HD.

Minocycline as neuroprotection in Huntington’s disease in Argentina

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Introduction Huntington’s disease (HD) is a worldwide neurodegenerative disorder. In South America, large kindreds have been identified in Maracaibo, Venezuela and in Cali, Peru. To our knowledge no previous studies, have been reported from Argentinean populations.

Objective to describe the clinical and allelic characteristics in 36 Argentinean individuals.

Methods Since 1999, 21 patients with HD, and 15 persons at risk from 18 putative HD families were evaluated at the Buenos Aires University Hospital. Clinical findings, age at onset, paternal inheritance and ethnic origin were investigated. They were tested for CAG expanded trinucleotide.

Results Twenty-one women and 15 men were included. Initial symptoms were motor in 45% and psychiatric in 45%, while seizures was the symptom of presentation in 10% of cases. Juvenile onset occurred in 13%. Inheritance was maternal in 50%, paternal in 40% of cases, while in 10% it could not be determined. Expanded alleles varied from 40 to 85 CAG units in affected individuals while normal alleles varied from 11 to 33 CAGs. In 10/15 persons at risk, CAG expansion was positive in 3 and negative in 7 individuals. Paternal inheritance was linked to greater increases in repeat size. Ethnic distribution included 18 families; 6 European – Latinos, 5 Saxons, 3 Hispanics (Bolivia, Paraguay and Argentina), and 1 from Syria, in three cases data were not available.

Conclusion Comparing European and Argentinean HD populations of European descent could be of interest to disclose the role of environmental factors in the phenotype expression of HD.
to assess this impact on daily life, however. The objective was to develop and validate an RLS-specific quality of life (QoL) questionnaire (RLSQoL).

**Methods** The 18-item RLSQoL was developed from clinician- and patient-centred item generation to assess the impact of RLS on daily life, concentration, sex life and work life. The RLSQoL was administered twice over a 2-week period to 85 adults with primary RLS. Using a patient-reported version of the RLS Rating Scale (RLSRS-PV), patients rated the severity of their symptoms and whether these symptoms changed over the 2-week period. Analyses were performed to assess reliability, validity and preliminary responsiveness.

**Results** The RLSQoL yielded a summary score with a range of 0–100; higher scores indicated better QoL or less life impact. This summary score demonstrated good internal consistency reliability (alpha >=0.93), test-retest reliability (intra-class correlation coefficient >=0.84) and item-convergent validity (itemscale correlations >=0.40). The RLSQoL distinguished between groups with differing RLSRS-PV symptom severity (F=50.55, p<0.0001) and was sensitive to even rather small changes in RLS status over a 2-week period using patient reports of symptom change.

**Conclusions** The RLSQoL is a valid and reliable measure of the impact of RLS on patient QoL and is sensitive to short-term changes in RLS severity.

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**P 3136**

**The Impact of Restless Legs Syndrome (RLS) on Quality of Life (QoL)**

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**Introduction** There is support for the view that RLS is a CNS dysfunction involving dopaminergic pathways. Sufferers experience sleep loss, extreme discomfort and disruption of normal activities. Assessment of the burden of RLS is critical for evaluating its clinical significance and treatment benefits but its impact on QoL is currently unknown. This study assesses that impact compared with a normative population (norms).

**Methods** The Short Form 36 (SF-36) was administered to 85 patients with primary RLS referred to a specialist clinic. Scores from this group were compared with published norms for SF-36 scales.

**Results** The majority (64.5%) of patients were women; the mean (±SD) age was 62.4 (±14.0) years; 67.1% of patients reported experiencing RLS symptoms almost daily. Significant deficits (10–40 points on 100-point scales) in physical functioning, bodily pain, role functioning, mental health, general health and vitality were noted for the RLS group compared with norms, even when examining results by gender and age. Only those RLS patients over 75 years of age had better scores than age-matched peers (who were experiencing one or more other conditions). In general, scores for RLS patients were equivalent to or worse than scores for norms with depression, arthritis, hypertension or cardiac problems.

**Conclusion** These results suggest a significant impact of RLS on QoL that matches or exceeds that for other major medical disorders. This should be considered when evaluating treatment needs for RLS. Research using larger sample sizes over longer periods of time will examine further the impact on QoL.

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**P 3137**

**Cabergoline in RLS – a double-blind, placebo-controlled, multicentre dose-finding trial**

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**Introduction** Cabergoline is a dopamine agonist (DA) with a long elimination half life (>65 hours) that has shown efficacy in preliminary studies in RLS patients. DAs may possess therapeutic properties superior to levodopa in RLS. This study assessed the efficacy and minimum effective dose of cabergoline in RLS patients in a randomised, double-blind, placebo-controlled multicentre dose-finding parallel group study.

**Methods** 86 Patients with moderate to severe RLS were stratified into 4 treatment groups receiving a target dose of 0mg (placebo), 0.5mg, 1mg and 2mg cabergoline once in the evening. Primary endpoint was the reduction of RLS severity at night between baseline and week 5 (scale 0 to 10).

**Results** All 3 cabergoline treatment groups showed a clinical improvement of (1) the RLS severity at night compared with baseline in contrast to placebo; statistical comparison showed highly significant differences for all 3 cabergoline doses versus placebo. Similar results have been found for (2) the RLS severity before bedtime, (3) RLS severity at day, (4) overall RLS severity in the IRLSSG rating scale, and (5) satisfaction with sleep. The number of adverse events (AEs) with possible relationship to the study drug were placebo: 54.5%, 0.5mg: 66.7%, 1mg: 55%, and 2mg: 59.1%. No serious AEs occurred.

**Conclusions** Cabergoline is a highly efficacious drug for RLS patients. All tested doses (0.5mg, 1mg, and 2mg) were effective compared to placebo. The higher dose provided better effects on daytime symptoms than lower doses of drug compared to placebo.

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**P 3138**

**Augmentation of the restless legs syndrome in relation to long-term treatment with pramipexole and cabergoline**

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**Introduction** RLS patients treated with dopamine agonists can develop augmentation. In a recent study with pramipexole, augmentation occurred in only 5 of 60 RLS patients treated for ≥6 months. In this study, 118 RLS patients treated with pramipexole or cabergoline showed these agents can successfully reduce or eliminate augmentation.

**Methods** Open-label study in RLS patients administered pramipexole or cabergoline for ≥6 months. Pramipexole: 102 patients (mean age = 56 yrs; mean RLS duration = 26 yrs; primary form =78; secondary =24); doses: 0.25, 0.5, 1.0 mg (in 68, 16 patients, respectively). Cabergoline: 16 patients (mean age =58y; mean RLS duration = 18 yrs; primary form =16); doses: 0.5, 1, and 2 mg (in 3, 12, and 1 patient(s), respectively). All received a single dose 2h before bedtime. Seventy-two patients previously received clonazepam (39), gabapentin (23), levodopa (1), pergolide (17), or other (33). RLS diagnosis was made according to ICSD criteria; nocturnal PSGs showed PLMS in all patients.

**Results** Pramipexole-RLS augmentation observed in 9 patients (doses = 0.25, 0.5, 1.0 mg in 6, 2, and 1 patient(s), respectively) after 4, 8, 12, and 15 weeks (in 2, 4, 2, and 1 patient(s), respectively). Previously drugs: clonazepam (4), pergolide (2), pramipexole (1), or opioids (1). Cabergoline- No patients presented augmentation.
Conclusion Hemifacial spasm produced no augmentation. With pramipexole, RLS augmentation occurrence was low (8.3%), unrelated to dose, occurred within 4 months of treatment, and more frequent in secondary than idiopathic RLS (p = .03, Fisher test). Pramipexole and cabergoline may be used to reduce or eliminate augmentation in patients with RLS.

P 3139
Hemifacial spasm: a clinical and epidemiological study in 52 patients
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Objective Hemifacial spasm (HFS) is a peripheral focal myoclonus characterized by unilateral and intermittent spasms in the muscles innervated by the facial nerve. Several reports suggest that primary HFS and arterial hypertension may coexist. We conducted a case–control study to determine whether hypertension occurs more frequently among HFS patients than normal controls.

Materials and methods Cases were selected during a 6-year period among consecutive patients attending one neurological institution. Information was obtained by a standardized questionnaire administered by a trained medical interviewer. Collected data included age, sex, HFS duration, time range between the first symptoms and the correct diagnosis of HFS, education, cigarette smoking, and history of hypertension. We corrected for a bias in case selection by designing a single-centre investigation, recruiting all the consecutive patients who met the eligibility criteria during the study period and using normal controls from the general population of the same area.

Results Primary HFS was diagnosed in 52 subjects (22 men and 30 women, age 63.1±12.5 years) according to published criteria. Mean disease duration was 6.7±11.6 years. HFS was left sided in 30 case patients and right sided in 22. CT or MRI of the brain excluded secondary causes in all patients. The association between exposure variables and case–control status was examined in univariate and multivariate conditional regression models. Hypertension was observed in 22 case subjects and 29 controls (OR=0.55, IC 95% 0.23–1.35).

Discussion Our case-control study does not suggest an association between hypertension and HFS. Further studies are needed to better elucidate this relationship.

P 3140
International database of Tourette syndrome: pilot project in the Czech Republic
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Tourette syndrome (TS) is a neuropsychiatric disorder characterized by multiple motor and vocal tics and accompanied with behavioural disorders. The international database of TS involves 3500 patients from 22 countries (1). Since 2001, the Movement Disorders Centre of General Faculty Hospital, Prague participates in the project. Czech translation of the original form is used. The patients are diagnosed according to the criteria of Tourette Syndrome Study Group. Until April 2002, 50 individuals (36 male and 14 female) have been included. Their average age was 21.9 years (from 9 to 76). Average age at tic onset was 7.7 years (2–19). The age at diagnosis of TS amounted to 16.2 years (5–50), the delay in diagnosis was 8.5 years (0–40). Positive family history was present in 21 cases (42% of patients). Abrupt onset or upsurge after infection was reported by 5 patients (12%). 15 patients (30%) had prenatal or perinatal problems. 41 patients (82%) used medication for tics. 8 patients (16%) did not suffer from other symptoms than tics (“TS only”). Attention deficit hyperactivity disorder occurred in 17 patients (34%), obsessive-compulsive disorder in 11 (22%) and self-injurious behaviour in 8 (16%). Our findings do not substantially differ from the original survey. The drawn data provide valuable information on the clinical characteristics of TS and can serve as a source for further genetic, clinical or pharmacological studies.

References

P 3141
Apolipoprotein E genotypes and phenotypic expression in Wilson’s disease
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Wilson’s disease (WD) is a disorder of biliary copper excretion that may result in severe neurological symptoms and advanced liver disease. The wide variation of phenotypic disease expression cannot be fully explained by the different mutation of the Wilson disease gene. The apolipoprotein E (APOE) is associated with onset of Alzheimer’s disease, and possibly other neurodegenerative disorders. Moreover, in a recent report it was hypothesized that APOE genotype ubiquitously determines the efficiency of neuronal maintenance and repair in these diseases. The aim of the present study was to determine if APOE genotypes are associated with onset age of WD. We studied 59 unrelated patients with WD. An investigation profile was established in which the patients were grouped according to the clinical symptoms at presentation and APOE status. The distribution of APOE genotypes in our patients did not deviate from known distributions in healthy European subjects. The average age at which neurological features appear is significantly later (p=0.019) than the average age of onset of hepatic WD manifestation (25.4±7.8 vs. 21.4±8.2 years, respectively). Within the group of patients with predominantly neurological form of WD, the onset of symptoms was significantly delayed (p=0.045) in patients with ε3ε3 genotype (27.0±7.8 years) in comparison to patients with the ε3ε4/ε4ε4 genotype (21.8±7.1 years). In conclusion, our data suggest that APOE is associated with age at onset of neurological form of WD.

P 3142
Coenzyme Q10 shows neuroprotective effects in mice dopaminergic culture systems
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In Parkinson’s disease (PD), the death of dopaminergic mesencephalic neurons is discussed as the consequence of excessive formation of free oxygen radicals due to mitochondrial dysfunction. While Coenzyme Q10 is known as of beneficial value in a
variety of diseases associated with increased oxidative stress, we investigated the protective effects of CoQ10 in primary cultures of mouse mesencephala and organotypic striatal cultures. Non-crystalline nanoparticles containing CoQ10 as a supercooled melt (guttaQuinon TM) were administered to cultured neurons of both culture systems with or without 1-methyl-4-phenylpyridinium (MPP+, 10 microM) treatment. CoQ10 (0.1 nM – 100 microM) increased the survival rate of MPP+-damaged dopaminergic neurons by 75% (0.001 microM). With higher concentrations of CoQ10 the survival effect showed a plateau of 50%.

In organotypic striatal cultures an enhanced production of lactate could be measured in the supernatant after administration of MPP+ (10 microM and 1 nM) if compared to control cultures (25% and 55%). Simultaneous treatment with CoQ10 prevented this additional formation of lactate significantly (100% with 10 microM MPP+ and 35% with 1μM MPP+). Additionally, in the striatal cultures, CoQ10 showed beneficial effects concerning various enzymes of the energy metabolism that were damaged by MPP+, and also increased the activity of both, the hexokinase and the tyrosine hydroxylase, respectively.

CoQ10 has the capacity to protect dopaminergic neurons in vitro, and is neuroprotective to cultured neurons that were damaged by MPP+, a substance often used in models of PD. Neuroprotective potential of the drugs of interest was assessed by measuring the malonate-induced lesion volume, as expressed by the absence of cytochrome oxidase (COX) activity. The neuroprotective potential of the drugs of interest was assessed by measuring the COX staining. Administration of increasing doses of the D2-specific agonist quinpirole, resulted in increased protection against malonate toxicity, as measured by a decrease in the lesion volume. Conversely, the D1-specific agonist, SKF-38393, as well as the mixed D1/D2 agonist apomorphine, conferred higher neuroprotection at lower than at higher drug concentration. Our data suggest that malonate-induced striatal toxicity can be attenuated by systemic administration of dopamine agonists, with D1 and D2 agonists showing different profiles of efficacy.

### P 3143

**Dopamine receptor agonists mediate neuroprotection in malonate-induced striatal lesion**

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Mitochondrial bioenergetic defects are involved in neurological disorders associated with neuronal damage in the striatum, such as Huntington’s disease or cerebral ischemia. The striatal release of neurotransmitters, in particular dopamine, may contribute to the development of the neuronal damage. Recent studies have shown that dopamine agonists may exert neuroprotective effects via multiple mechanisms, including modulation of dopamine release from nigrostriatonic dopaminergic terminals.

In rats, intrastratal injection of malonate, a reversible inhibitor of the mitochondrial enzyme succinate dehydrogenase, induces a lesion similar to that observed following focal ischemia or in Huntington’s disease. In this study, male Sprague-Dawley rats were injected systemically with increasing concentrations of D1, D2, or mixed D1/D2 dopamine agonists prior to malonate intrastriatal insult. Rats were sacrificed after three days; brain sections containing the striatum were stained, histochemically, for cytochrome oxidase (COX) activity. The protective potential of the drugs of interest was assessed by measuring the malonate-induced lesion volume, as expressed by the absence of COX staining. Administration of increasing doses of the D2-specific agonist quinpirole, resulted in increased protection against malonate toxicity, as measured by a decrease in the lesion volume. Conversely, the D1-specific agonist, SKF-38393, as well as the mixed D1/D2 agonist apomorphine, conferred higher neuroprotection at lower than at higher drug concentration. Our data suggest that malonate-induced striatal toxicity can be attenuated by systemic administration of dopamine agonists, with D1 and D2 agonists showing different profiles of efficacy.

### P 3144

**Ibuprofen has a protective effect in neurodegeneration caused by intoxication with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mouse.**

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Non-steroid anti-inflammatory agents are suggested to have a positive effect in neurodegeneration. In this study we investigated the effect of ibuprofen (IBF) on neuronal survival after intoxication with MPTP. MPTP is a toxin that damages dopaminergic cells of the substantia nigra (SN) and causes a decrease of the dopamine content in striatum.

**Methods** C57Bl male mice, 5 months old, were intoxicated with MPTP (60mg/kg) and prior to intoxication they received IBF (Sigma) in the doses of 10 and 30 mg/kg i.p. Next they received IBF every day to the 7th day of observation. In order to assess nigrostriatal degeneration the dopamine content in striatum were measured by high-pressure liquid chromatography (HPLC) on the 3rd and 7th day following intoxication.

**Results** MPTP alone diminished dopamine content in striatum by about 90% on the 3rd and 7th day as compared to control (p<0.002). Administration of IBF + MPTP caused statistically lower decrease of dopamine as compared to animals that received only MPTP: by 84% on the 3rd day in both doses of IBF (p<0.003) and by 75% (p<0.01) and 68% (p<0.006) on the 7th day in doses of 10mg/kg and 30mg/kg respectively. IBF alone did not change dopamine level.

**Conclusion** Our data indicate that IBF have a neuroprotective effect to neurons injured by MPTP intoxication. This effect was greater if the treatment was prolonged to the 7th day and was dose dependent. The mechanism of IBF action however is unclear and may consist of both anti-inflammatory and direct neuroprotective effect.

### P 3145

**Pro- and anti-inflammatory cytokine mRNA expression in the striatum of C57B1 male mice following intraperitoneal administration of 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP)**

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The inflammatory reaction have been linked with Parkinson’s disease (PD). The neuroinfammation is regulated by numerous signal molecules, including cytokines. The increased density of pro-inflammatory cytokine-producing glial cells in the substantia nigra of patients with PD was documented. This may have several implications for the pathophysiology of this disease. Although the possibility that this cytokines have a neuroprotective effect in this conditions cannot be excluded.

With this context, mRNA levels of IL1beta, IL6, TNFalpha, IFNgamma, IL10 were measured by semi-quantitative RT-PCR in the striatum of mice after 6h, 1, 3, 7 and 14 days post MPTP intoxication. MPTP damages the nigrostriatal dopaminergic neurons.
In the present study we examined inducible mRNA for the cytokines assayed were minimal. IL1beta, IFNgamma, TNFalpha expression was rapidly increased, already at 6h after MPTP injection and peaking at 6h to 24 h. The expression of TNFalfa and IFNgamma mRNA appeared to be biphasic. The second increase of IFNgamma and TNFalpha mRNA was detected at the 7th day after intoxication. IL10 mRNA showed also phasic expression pattern. Two day of IL10 mRNA were seen, immediately (6h) and at the 3rd day post MPTP injection. The moderate increase in the level of IL6 mRNA was observed within 1–3 days following MPTP intoxication. The level of mRNA for IL6 peaked at 7th day time point. Many of cytokines are expressed post MPTP intoxication. These findings suggest that the cytokine network should be studied in detail. The pharmacological modification of the cytokines synthesis may represent a therapeutic intervention that could reduce the neurodegeneration.

P 3146
Nitric oxide synthase mRNA expression and neurotransmitters levels in the striatum of C57Bl/6 mice following toxic degeneration caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropiridine (MPTP).
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Nitric oxide (NO) is involved in important physiological functions of the CNS, including neurotransmission, memory and synaptic plasticity. Under conditions of excessive NO formation, it can act as a neurotoxin and may have a role in the pathogenesis of neurodegenerative disorders such as Parkinson’s disease (PD).

Methods and results In the present study we examined inducible iNOS and neuronal nNOS mRNA expression in the striatum of C57Bl/6 male mice post MPTP intoxication. MPTP is a toxin, which selectively damages dopaminergic neurons. The animals were sacrificed at 6 h and on the 1st, 3rd, 7th, 14th day after MPTP intoxication. The levels of mRNA for iNOS and nNOS were assayed by RT-PCR method. In the control baseline levels of mRNA for iNOS were minimal. Its expression rapidly increased from the 6h after MPTP injection, lasting to the 14th day. Neuronal NOS mRNA showed increase after 24 h and peaked within 3–14 days following MPTP intoxication. Using HPLC we examined neurotransmitters levels. The significant decrease in the level of DA was observed within 1–14 days following MPTP injection, achieving minimal level within days 3–7. The levels of DOPAC and HVA were minimal at the 3rd day post intoxication. The moderate increases in the level of SHT and 5HIAA were seen 6h after MPTP injection.

In conclusion – NO may be a key mediator of nigral degeneration playing a significant role in MPTP inducing PD model. Therefore, pharmacological regulation of NO synthesis offers an important strategy for treatment of neurodegenerative diseases.
P 3149
Iron and oxidative stress in neurodegeneration
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Neurodegenerative diseases are progressive disorders that affect selected neuronal populations of the central nervous system, the exact pathogenesis of this mechanism being unknown. Oxidative damage may contribute to neurodegeneration and oxidation reactions are influenced by the regional concentrations of transition metals such as iron. Hallervorden-Spati disease (HSD) is a rare disorder characterized by an over accumulation of iron in the globus pallidus. Progressive Supranuclear Palsy (PSP) is another neurodegenerative disorder where increased levels of iron have been reported in basal ganglia and mesencephalus.

Methods We report ten patients clinically diagnosed as HSD and fifteen patients with a diagnosis of Probable PSP. The activity of antioxidant enzymes glutathione peroxidase (GLPX) and superoxide dismutase (SOD) was assessed in red blood cells of patients, by a spectrophotometric assay, and compared with healthy controls.

Results A significant increase of SOD activity was observed in HSD patients: 539+/-174.4 U/g Hb and 379.94+/-50.65 U/g Hb for controls. Simultaneous a decrease in GLPX activity was found in both HSD and PSP patients. The GLPX activity was: 9.6+/-2.5 U/g Hb for HSD patients and 12.23+/-1.6 U/g Hb for controls and 6.1+/-2.6 U/g Hb in PSP patients and 9.6+/-2.3 U/g Hb for controls.

Conclusion In the presence of an increase in iron concentration proved to occur in both of this disorders, hydroxyl radical (OH-) is formed according to the Fenton-reaction. Under these conditions oxidative stress is strongly suggested to occur leading to neuronal injury.

P 3150
The role of dopamine agonists in the pharmacotherapy of bipolar depression
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Introduction Reduced dopaminergic activity is associated with idiopathic and bipolar depression, as well as depression in Parkinson’s disease (PD). Results with several antidepressants are controversial or poor, with the exception of nortriptyline and bupropion. Attention should be paid to DAs such as pramipexole (PPX), a selective dopamine agonist with selectivity for the D3 receptor, in the treatment of these conditions.

Methods 32 patients were referred with a history of Type I BAD (current episode of Major Depression according to DSM-IV). All patients had received combined anti-depressive treatment for 7 weeks: daily nortriptyline and fluoxetine, with either Li-thium, carbamazepine, or sodium valproate. Patients were treated with pramipexole (PPX) 3.125 mg daily for 12 weeks. The HAMD-17 Scale was used for the assessment of depressive symptoms.

Results During the first 3 weeks, there was an 18% reduction in HAMD-17 scores; after 9 weeks, 27%. The mean reduction was 34% in 30 of 32 patients. Of the 30 patients who completed the study, no one had any adverse event. Drop-outs (2) for inefficacy and adverse events (insomnia, dry mouth, hypotension, and vomiting) occurred.

Conclusion The high affinity of PPX for D3 receptors may account for its efficacy in bipolar depression and conditions with psychomotor retardation. The great affinity of pramipexole for D3 receptors is possibly the reason for its efficacy in improving the mood of patients with bipolar depression, as well as conditions with psychomotor retardation such as PD, negative symptoms of schizophrenia, and unipolar depression.

P 3151
Long-term Prognosis of vascular hemiballism
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Background and purpose The information concerning the long-term prognosis of vascular hemiballism (HB) are very limited, although it was formerly thought to have a poor prognosis with inexorable progression to death within weeks or months. The aim of this study was to prospectively evaluate the long-term prognosis of HB due to first-ever ischemic strokes.

Methods A cohort of 27 patients with HB due to first-ever ischemic strokes (mean age, 68 years) was followed for a mean period of 30 months (range: 5 days to 150 months), with 2 patients lost to follow-up. Death and stroke recurrence rates were evaluated by Kaplan-Meier analysis.

Results During the follow-up period there were 11 deaths (44%). The survival rate was 85% (95%CI, 71% to 99%) at 6 months, 81% (95%CI, 65% to 97%) at 15 months, 51% (95%CI, 24% to 78%) at 36 months, and only 32% (95%CI, 4% to 60%) at 150 months. The survival rate free from recurrent stroke was 96% (95%CI, 87% to 100%) at 6 months, 91% (95%CI, 79% to 100%) at 12 months, 80% (95%CI, 61% to 99%) at 24 months, and 27% (95%CI, 0% to 71%) at 150 months.

Conclusions The long-term prognosis of patients with HB due to first-ever ischemic stroke is not specifically determined by the very nature of the clinical manifestation of this rare type of involuntary movements. Instead, their long-term prognosis is similar to that of other stroke patients, i.e. follows the etiological pattern of HB.

P 3152
Olanzapine improves tardive dyskinesia in patients with schizophrenia
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Introduction We report preliminary findings of the effects of olanzapine (OLZ) treatment upon tardive dyskinesia TD.

Methods Eligible schizophrenic subjects met restricted Research Diagnosis Tardive Dyskinesia criteria (restricted RD-TD) that specified for abnormal involuntary movements to be of at least moderate severity. Subjects received OLZ, 5–20 mg/day for 8 months within a double-blind design that included up to 2 medication reduction (75%) periods of 2 weeks duration. TD was assessed with the Abnormal Involuntary Movement Scale (AIMS) and psychopathology with the Positive and Negative Syndrome Scale (PANSS).

Results A significant reduction in mean AIMS Total score was demonstrated (N=95; BL=11.9; EP=7.5; p<.001; LOCF). Nearly 70% of subjects no longer met the restricted RD-TD criteria after up to 8 months of treatment, with greater than 50% improving as early as 8 weeks. No statistically significant
rebound worsening of TD was found during the blinded drug reduction periods. A significant improvement in the PANSS occurred (BL=68.2; EP=59.7; p<.001, LOCF).

Conclusions These data, suggesting an ameliorative, rather than masking effect, and the concurrent further improvement in clinical status suggests that OLZ may offer a potential treatment alternative for managing the schizophrenic patient with pre-existing TD.

P 3153
Friedreich’s ataxia associated with agenesis of the corpus callosum: case report of three sisters
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Friedreich’s ataxia (FRDA) is an autosomal recessive disorder that usually begins before the age of 20 years and associated with an unstable expansion of a GAA trinucleotide repeat in the first intron of the FRDA gene on chromosome 9q13. Beside classical FRDA, DNA testing confirmed the existence of atypical variance of FRDA amongst which is late onset FRDA with disease onset after the age of 25 years with frequently retained reflexes and less pronounced extra neuronal complications. Agenesis of the corpus callosum is common malformation with the symptoms that may be unrecognised or minimal, or there may be deficit in the interhemispheric transfer of perceptual information for verbal expression. We report three sisters with PCR testing confirmed FRDA and different age of onset. One of the sisters with age of onset before 25 had typical clinical features (ataxia of gait and limbs, loss of vibration sense, muscle weakness and atrophy, loss of deep tendon reflexes, scoliosis and diabetes mellitus) associated with agenesis of the corpus callosum on brain MRI with consecutive displacement and dilatation of the lateral ventricle. The other two sisters had an atypical beginning at the age of 26 and 37 years with similar clinical features but without extra neuronal complications and brain malformation. Despite of different age of onset they had similar number of GAA triplets. We are presenting this family because the probability of inheriting FRDA in three siblings is very low and there is an unusual association with agenesis of corpus callosum.

P 3154
Is Olanzapine the treatment of choice in Huntington’s disease?
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Objective The therapy of motor symptoms, especially chorea, in Huntington’s disease (HD) is rather difficult. Typical neuroleptics decrease chorea, but care is needed not to increase to doses that impair the individual’s functional level.

Methods In our study, olanzapine was administrated to nine patients with genetically confirmed HD in increasing doses until satisfactory clinical effect or the appearance of side effects. The patients were evaluated at baseline and after 14 days of treatment using the motor scale of Unified HD Rating Scale (UHDRS).

Results The patients improved significantly in 5 of 7 subscores of the UHDRS, including oculomotor function, orolingual function, fine motor tasks, chorea, and statics and gait. No adverse effects were reported by the patients spontaneously or were observed directly by the investigator, although some patients needed rather high dose (30mg per day).

Discussion This study could clearly demonstrate that prior studies used the wrong dose. It is worthwhile mentioning the amelioration in those sensitive fields, which’s impairment was so far said to be the unavoidable drawback of all neuroleptic medication: oculomotor function, orolingual function, and fine motor tasks. The investigators saw a significant improvement in those motor categories – despite the high doses of olanzapine.

Conclusion High-dose olanzapine seems to be useful in choreatic HD patients. A double-blind, placebo-controlled trial appears highly warranted to definitively establish the symptomatic value of olanzapine in HD.

P 3155
Bone mineral density in Huntington’s disease
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Background HD is an autosomal dominantly inherited neurodegenerative disorder due to an increase of CAG repeats in chromosome 4. It is characterised by movement disorder like chorea or gait disability, psychiatric symptoms (depression or psychosis) and dementia. HD patients have an increased risk for falling and perhaps for bone fractures due to their movement impairment.

Design/Methods 15 HD patients (31–73 years) and 100 age and sex-matched controls underwent BMD measurements at the lumbar spine and femoral neck by dual-energy X-ray absorptiometry (DXA, Hologic 4000 plus). Biochemical markers of bone metabolism osteocalcin (OC), c-terminal linked telopeptides of type I collagen (CTX), 25-(OH)-vitamin D, prolactine (PRL) and routine laboratory parameters were assessed.

Results Patients and controls were comparable for anthropometric data and lifestyle factors. Past medical history was evaluated using patients’ neuropsychiatric documentation. HD patients had a significantly decreased BMD at the spine as compared to controls (p=0.03). Furthermore, OC and CTX were significantly elevated in HD patients (p=0.001 and p=0.02, respectively). PRL levels had no statistical effect on BMD so far.

Conclusions HD patients had a significantly decreased BMD and significantly increased bone turnover. This is the first time to describe disturbed bone metabolism and BMD in these patients. Possible causes for these findings may be either an influence of molecular changes due to HD in bone metabolism or the effect of neuroleptic medications in these patients. Our findings indicate that investigation of BMD and bone metabolism is relevant in HD patients due to their high risk for falling.
estimate the clinico-morphological correlation between clinical presentation and CNS lesions.

**Patients** On the basis of performed imaging, there were proved symptoms-correlated lesions in fifty-seven patients with different types of dystonia, according to time of their appearance.

**Results** Our study included 57 patients with dystonia, which appeared as a consequence of focal or multifocal lesions, out of which 7 patients had generalized dystonia, 18 hemidystonia, 6 segmental dystonia, 7 torticollis, 6 blepharospasm, 7 hand dystonia, 3 spasmodic dysphonia and 3 had oromandibular dystonia. Viewed from a highly statistical incidence, stroke was the most frequent cause of structural lesions (33/57 or 57.9%). Relevant pathomorphological changes were present in 50/57 (88%) patients, where 25 (50%) of the patients had lesion in the lenticular nucleus (including individual damage of the putamen and globus pallidus), 12/50 (24%) exhibited thalamus damage and 6/50 (12%) had the damage of the brainstem.

**Conclusion** Generalized dystonia was most frequently associated with bilateral lesion of the putamen, hemidystonia with lesion of contralateral putamen, torticollis with the damage of the caudate nucleus, hand dystonia with lesion of the thalamus and blepharospasm with lesion of the upper brainstem.

**P 3157**

**Huntington’s disease: relation between clinical, genetic and morphometric parameters**

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We analysed clinical data in 80 genetically verified patients with Huntington’s disease (HD) and measured the severity of the caudate nucleus atrophy in all patients using computed tomography (CT) planimetric assessment. We compared the results with values obtained in 43 age matched healthy subjects. The mean values of caudate nucleus between HD patients and healthy controls were significantly different (p<0.001). We found statistically significant inverse correlation between the amount of CAG triplet repeats and the age at the onset of HD (a<0.001). We also observed significant inverse correlation between the duration of HD and the progression of the atrophy of the caudate nucleus (a<0.01). The natural atrophy of caudate nucleus in healthy controls is also present but without the overlapping of the values obtained in HD patients (a<0.01). The amount of CAG triplet repeats in not connected with the character of the first clinical symptoms (motor or psychiatric). Furthermore, the age of the onset of HD is not dependent on the character of the initial symptoms. We observed no relationship between the presence of maternal or paternal heredity and the amount of CAG triplet repeats in HD patients. Moreover, the character of heredity does not influence the age of the onset of HD in our patients. The planimetric measurement of caudate nucleus appeared to be a sensitive tool for the diagnosis of HD.

The aetiology of the selective neuronal death that occurs in Huntington’s disease (HD) is still unknown despite the identification of a gene with expanded CAG repeats but unknown function. Similar to other neurodegenerative diseases an impairment of oxidative phosphorylation enzyme activities restricted to the basal ganglia in HD brain was found. Especially complex II/III and complex IV were found decreased. Recently decreased aconitase activities were observed in basal ganglia whereas enzyme activities in other brain regions and fibroblasts remain unchanged. Decreased aconitase activity was connected with increased oxidative stress whereby NO and ONOO- levels may act as specific inhibitors of this iron-sulphur cluster containing enzyme.

We have studied aconitase activity in platelets from 35 genetically proven HD patients and sex and age matched normal controls. Here we report a highly significant decrease of aconitase activity independent of medication and sex. We propose that oxidative stress may play a major role in the pathogenesis of HD and is not only reflected in brain but also in other sensitive tissues.

**P 3158**

**Decreased aconitase activity in Huntington’s platelet**

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P 3160
Pramipexole in the treatment of restless legs syndrome: a follow up study
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Objective To study the long-term efficacy and safety of prami-
peexole, a new dopamine D2 -D3 receptor agonist in the treat-
ment of restless legs syndrome.
Methods 16 patients aged 33–75 who participated in a previous
open label study were followed for a mean of 6.8 months.
Treatment was started at a dosage of 0.125 mg in every patient
administered one our prior to bedtime and progressively in-
creased until the optimal therapeutic effect was obtained. All
patients filled out evening and morning questionnaires enqui-
ring about restlessness during the daytime and evening (evening
questionnaire) and at bedtime and upon awakenings during the
night (morning questionnaire). The questionnaires were filled
out one week before, at baseline, one month after treatment and
after a mean of 6.8 months of treatment with pramipexole. In
these questionnaires, leg restlessness was rated as follows:
absence of restlessness =0, mild =1, moderate =2, severe =3.
Results The optimal dosage in this follow up study was 0.125
mg for 8 patients, 0.25 for 3 patients, 0.375 for 2 patients, 0.5
for 2 patients and 0.750 mg for 1 patient. The main side effects
(nausea for 2 patients, day time sleepi-
ness without sleep attacks for 1 patient and hypotension for
3 patients) were short lasting and of mild severity. A
significant reduction in leg restlessness was found for
the bedtime and nighttime measures in all patients with prami-
peexole administered at bedtime.
Moreover, pramipexole treatment was not associated with mor-
ing rebound or afternoon augmentation of leg restlessness.
In addition there was no evidence of a decrease in the therapeu-
tic effect of pramipexole in these patients, even 6.8 months after
the initiation of treatment.
Conclusion The study clearly demonstrates that the efficacy of
pramipexole does not decrease after 6.8 months of treatment.

P 3161
Hereditary chin trembling: report of a new family, patho-
genetic hypothesis and treatment with Botulinum toxin
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Hereditary chin trembling is an unusual dominantly inherited
movement disorder characterized by involuntary tremor of the
chin with the absence of any other neurological deficits.
Twenty-seven families from Europe, USA, Canada and Latin
America suffering from this disorder have been described
since 1894.
In this report we present two cases from a new white family,
which gives us the opportunity to discuss the origin of the
abnormal involuntary movement. The clinical and neurophysi-
ological data lead to the suggestion that hereditary chin trembling
is a focal variant of hereditary essential myoclonus localized at
the mentalis muscle. We hypothesize that this involuntary dis-
order may result from hyperexcitability of the lower facial
motoneurons.
We have successfully treated them with Botulinum toxin injec-
tions to the mentalis muscle.

P 3162
Essential tremor in a Czech patient population – a service
based questionnaire study
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Essential tremor (ET) is a chronic condition with a slowly pro-
gressive course where upper limbs and, less commonly, head,
voice and lower limbs exhibit postural and kinetic tremor with-
out other neurological abnormalities.
To analyse the demographic and clinical correlates of ET in
Czech population, a questionnaire was mailed to 320 patients
with previously diagnosed ET. The questionnaire included 15
questions and an Archimedes spiral drawing.
We received 164 completed questionnaires (88 females and
76 males, mean age 62 years). The mean age at disease onset
was 46.6 years (1–83 years). A positive family history was
reported in 46%. Alcohol responsiveness was reported in 33%,
however, 43% chose the “don’t know” possibility. The most
common manifestation was tremor of upper limbs, followed
by head, voice and lower limbs. 17% reported the history of
treatment with levodopa with a total cumulative dose of 18 to
2700g, the mean duration of levodopa use was 37 months (range
1–120 months)
Spiral drawings were scaled using the modified Bain and
Findley Scale (1) that was simplified into 6 grades.
Data obtained in the first questionnaire study concerning ET in
Czech Republic do correspond with the results of previously
published studies. The high occurrence of inadequate treatment
with levodopa shows that ET still may represent a differen-
tial diagnostic puzzle. Archimedes spiral drawing appears as a re-
liable tool for the evaluation of tremor severity and treatment
effect.

References
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P 3163
Spectral analysis of drawing with a digitising tablet for
measuring tremor
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Background Digitising tablet is a new computational method
for quantification of tremor which results are comparable to the
tri-axial accelerometry.

Methods Upper limbs tremor in both hands was assessed in 20
patients with essential tremor and 90 patients with Parkinson’s
disease. The results of Gibson maze test, rating tremor in spirals
and volumetric method were correlated with the results of new
 technique automatically analysing data from hand-written
Archimedes spirals in a virtual triaxial set-up. Tremor intensi-
ty was estimated by means of the signal/noise ratio of dominant
peak of the power spectrum. The frequency of the highest peak
value defined the tremor frequency.


Results Magnitude of tremor based on the speed and accelera-
tion spectrum in the XY axis assessed by digitising tablet cor-
relate with the tremor scores from spiral drawings of both domi-
nant and non-dominant hands, respectively: (Spearman’s corre-
lation R=0.44, p=0.00001; R=0.46, p=0.00001), Gibson maze
test (R=0.24, p=0.03; R=0.22, p=0.05) and volumetric meth-
ods (R=0.24, p=0.0001, R=0.34, p=0.003).
Conclusion A digitising tablet acquisition system is fast, non-invasive, inexpensive and useful as a diagnostic tool. Spiral analysis with digitising tablets could be used as an initial marker of clinical involvement or serve as an objective gauge of change after therapeutic intervention.

P 3164
Clinical assessment of ocular motor disorders in progressive supranuclear palsy, multiple system atrophy and Parkinson’s disease
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Objective To determine significant clinical details of ocular motor disorders in progressive supranuclear palsy (PSP) that could help in diagnostic in early and non-typical cases of the disease. To develop clinical scale for assessment of ocular motor disorders in Parkinsonism.

Background NINDS-SPSP Clinical Research Criteria for PSP has some weak point which causes misdiagnosis of some cases of multiple system atrophy (MSA) and Parkinson’s disease (PD) as PSP.

Design/Methods We have studied 12 patients that met the criteria for possible or probable PSP, 13 patients with possible or probable MSA and 10 patients with idiopathic PD. The Clinical Scale for Ocular Motor Disorders in Parkinsonism (CSOMDP) was developed and prospectively applied.

Results Voluntary saccade slowness was detected in all three groups, though more prominent in PSP patients (p < 0.01). In 25% of PSP patients jerky character of saccades was lost—“smooth saccades”. In 58% there were progressive “wearing off”, festination and hypometria of saccades while MSA and PD patients had just bradykinesia and slight hypo-metria of saccades. MSA and PD patients were able to rise saccades speed to normal or at least increase their speed significantly following to the specially given metronome rhythm (according to CSOMDP). In PSP normalisation or significant increase of saccades speed was noted in 33% for horizontal saccades and 25% of PSP patients jerky character of saccades was lost—“smooth saccades”. In 58% there were progressive “wearing off”, festination and hypometria of saccades while MSA and PD patients had just bradykinesia and slight hypo-metria of saccades. MSA and PD patients were able to rise saccades speed to normal or at least increase their speed significantly following to the specially given metronome rhythm (according to CSOMDP). In PSP normalisation or significant increase of saccades speed was noted in 33% for horizontal saccades and 8% for vertical.

Conclusion For PSP diagnostically useful are alteration of character of saccades and patients inability to increase speed of saccades following to the specially given metronome rhythm, as against MSA and PD.

Results Abnormal MR brain findings were established in 75% of patients. Lesions in brain parenchyma were detected in all untreated, drug-naive patients and in 44% of treated patients. Abnormal signal in globus pallidus, putamen, and caudate nucleus was revealed in 86%, 71% and 71% of treated and in 33%, 33% and 22% of untreated patients, respectively. In 5 out of 8 patients with putaminal pathology (62.5%) and in 4 out of 7 patients with caudate nuclei involvement (57%), only proton density sequence (PDW) exhibited sensitivity to lesion detection, both with T1W and long echo T2W sequences, having being intensive. This superiority of PDW sequence was even more pronounced in the group of untreated patients whereat 80% of putaminal pathology was visible exclusively on this sequence.

Discussion Majority of our neurologically asymptomatic patients with hepatic form of WD had MRI findings, suggesting to different brain lesions. Lower frequency of such lesions in the group of treated patients in comparison to untreated ones, indicated that they might be reversible (chronic chelating therapy). Finally, our results suggest that PDW sequence still plays an important role in correct MR detection of brain lesions in these patients.

P 3166
Spreading of primary dystonia
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P 3167
Electromyographic findings in myasthenia gravis concurrent pathologies
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P 3168
A contribution to the problem of balance preservation in spinal cord injured patients
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P 3165
MRI imaging of the patients with hepatic form of Wilson’s disease
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Objective To detect the sites and frequency of possible lesions applying brain magnetic resonance imaging (MRI) in a group of consecutive, neurologically asymptomatic patients with hepatic form of Wilson’s disease (WD).

Patients and methods Sixteen consecutive, neurologically asymptomatic patients with hepatic form of WD (7 untreated and 9 under treatment) were examined with 1.5 T magnetic resonance imager.

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