From Diagnosis to Management of Parkinson’s Disease
This report reflects the view and experience of the lecturers who have approved the summaries.

Text: Michael Wainwright and Helena Nordlund, Transgraf, Uppsala

Graphic design, photo and production: Eevalisa Edjäll, Orion Pharma AB

© Orion Pharma AB, Sweden
Parkinson’s disease is characterised by a chronic progressive neurodegeneration that damages the central nervous system pathways. A variety of movement and cognitive functions are affected and patients thus display a broad spectrum of symptoms. Disease progression is highly individual, and so is treatment.

The 9th Scandinavian meeting on Parkinson’s disease, held in Copenhagen, Denmark, attracted about 150 delegates from Sweden, Finland, Norway, Denmark and other European countries. Two intensive days of presentations and lively interactive discussions illustrated the many different facets of Parkinson’s disease as clinicians, researchers, and representatives for patient organisations shared their knowledge and experiences with an eager-to-learn audience. Scandinavian Movement Disorders Society was responsible for the scientific programme while practical arrangements were taken care of by Orion Pharma together with Solvay Pharma.

The ultimate objective of this meeting is to contribute to better treatment and care of patients with Parkinson’s disease. At Orion Pharma, we know that well-planned treatment really makes a difference for these patients, and that interest in learning more about this aspect of the disease is great among all who work with them.

The 10th Scandinavian meeting is scheduled to be held on March 19–20, 2010 in Stockholm. Until then, we are happy to provide you with this report summarising the presentations held at this year’s event. We wish you pleasant reading!

Kaisa Tarkkanen
Head of Region Scandinavia
Orion Pharma, Sweden
From Diagnosis to Management of Parkinson’s Disease

9th Scandinavian Meeting
MARCH 27–28, 2009 • COPENHAGEN, DENMARK

Chairmen Friday, March 27, 2009:
Espen Dietrichs, MD, PhD, Professor. Department of Neurology, National Hospital, Oslo, Norway
Lene Werdelin, MD, PhD. Department of Neurology, Bispebjerg Hospital, Copenhagen, Denmark
Jan Aasly, MD, PhD, Professor. Department of Neurology, Trondheim, Norway
Martin Grabowski, MD. Department of Neurology, Reykjavik, Iceland
Håkan Widner, MD, PhD, Professor. Department of Neurology, Lund, Sweden
Erik Hvid-Danielsen, MD. Department of Neurology, Aarhus, Denmark

Chairmen Saturday, March 28, 2009:
Sven Påhlhagen, MD. Department of Neurology, Karolinska University Hospital, Stockholm, Sweden
Sigurlaug Sveinbjörnsdottir, MD, PhD, Professor. Reykjavik, Iceland
Lene Werdelin, MD, PhD. Department of Neurology, Bispebjerg Hospital, Copenhagen, Denmark
Susanna Lindvall, Swedish Parkinson’s Disease Association, Stockholm, Sweden
Contents

Professor Espen Dietrichs: Neuroprotective treatment in Parkinson’s disease: A current option? .......................................................... 4

Dr. Donald Grosset: Drug compliance and other patient factors in treating Parkinson’s disease.......................................................... 6

Professor Patrik Brundin: Transplantation in Parkinson’s disease: Problems and possibilities ................................................................. 8

Professor Andrew J. Lees: The first medical consultation to discuss the treatment of Parkinson’s disease ........................................ 10

Professor Wolfgang Oertel: When and how to optimise Parkinson’s disease therapy .......................................................... 12

Professor Jan Herzog: Is there a rationale for surgery at an earlier stage? ... 14

Professor Daniela Berg: Transcranial ultrasound as a neuroimaging tool in Parkinson’s disease ........................................ 16

Dr. Jan Linder: Brain MRI for the differential diagnosis of Parkinson’s disease and atypical parkinsonian syndromes ..................... 18

Dr. Per Borghammer: PET and SPECT imaging in movement disorders – diagnostics and pathophysiology ........................................ 20

Professor Kailash P. Bhatia: Diagnosis and differential diagnosis of seldom movement disorders: Best approach ...................... 22

Dr. Sven Pålhagen: Depression in Parkinson’s disease: An update .............. 24

Dr. Valerie Voon: Impulsive and compulsive behaviours in Parkinson’s disease .......................................................... 26

Professor Michael Jöbges: Evidence-based rehabilitation in Parkinson’s disease: State of the art ................................................... 28

Associate professor Lena Hartelius: Speech and voice in Parkinson’s disease .......................................................... 30

Professor Bastiaan Bloem: Organisation of Parkinson care: Ideas from The Netherlands .......................................................... 32
From Diagnosis to Management of Parkinson’s Disease

The topic of neuroprotection in Parkinson’s disease (PD) is generally regarded a difficult one. At the first sign of the idiopathic disease, 60–80% of pigmented nigral cells have already been lost. At the same time, however, our knowledge of PD continues to improve. Its genetic causes are now better understood, for example, and our evidence base related to the exogenous causes of PD is growing all the time. We have recently learned that Lewy-bodies can be found in striatal fetal graft neurons, and much speculation has surrounded the occurrence of such changes in grafted cells. It is thus considered that neuroprotection should be a viable option in PD, although the exact means of achieving this are currently unclear.

Possible strategies for neuroprotection

Several opportunities and potential targets for neuroprotection present themselves and the list of proposed substances that may induce an effect is thus long; adenosine A2A receptor antagonists, AIF inhibitor, caspase inhibitors, Co Q10, COX-2 inhibitors, creatine, estrogens, flavonoids, GABA agonists, ganglioside GM1, GDNF, GLU release inhibitors, lazaroids, melatonin, meloxicame, minocyline, NSAID, quinacrine, reduced glutathione, remacemide, riluzole, etc., etc.

Laboratory results often show promise but the clinical effect is uncertain. It is clear that animal models of PD behave quite differently from human models. In addition, neuroprotective properties have been claimed for virtually every drug currently used for symptomatic treatment.

The problem of measuring effect

A major stumbling block that hinders investigations into possible neuroprotective effects is the difficulty in making realistic measurements. No direct method for quantifying brain stem neurons exists today, which means that we cannot count surviving neurons in the substantia nigra, for example. It is thus unclear whether or not SPECT/PET imaging, UPDRS changes, the need for levodopa, or the occurrence of motor fluctuations actually reflect the number of surviving cells.

In addition, compensatory mechanisms provoked by PD progression may obscure the interpretation of results. All are likely to be influenced by dopaminergic therapy, which makes interpretation even more problematic.

Drug treatment may modify disease progress

It is recognised that drug treatment has beneficial effects but is still unclear whether this is due to neuroprotection or to a positive influence on compensatory mechanisms. It may be a better approach to talk about the ‘disease-modifying effects’ of drugs and to see whether this can be seen in those most commonly used today.

Levodopa

This question was addressed in the ELLDOPA study (Fahn S et al, 2004). This double-blind, randomised study showed that subjects treated with levodopa for 40 weeks had less severe parkinsonism than placebo-treated subjects even after a 2-week washout. Furthermore, the highest dose group showed the greatest benefit. Levodopa may thus actually have neuroprotective value. However, the study did not conclusively demonstrate a slowing of disease progression since the same result could have arisen from a very long-lasting symptomatic benefit of levodopa.

Dopamine agonists

A similar question can be raised with dopamine agonists. Their early use delays motor fluctuations and they are known to protect dopaminergic cells in culture. It has been suggested that they reduce dopamine degradation. This may be related to D3-receptor activation, although this possible neuroprotective effect of pramipexole is not abolished by dopamine receptor blockers. A direct action on the mitochondrial mem-

Neuroprotective treatment in Parkinson’s disease: A current option?

Although several substances show neuroprotective properties in laboratory settings, no drug has so far been shown to halt or slow nigral cell death in Parkinson’s disease patients in clinical use. Nevertheless, certain clinical trial findings have led to neuroprotective actions being suggested for many drugs used for symptomatic treatment. Drug therapy with some of the substances available today does seem to have disease-modifying properties. The question of whether or not they act in a neuroprotective manner was one of the key issues addressed by Professor Dietrichs.
brane action potential with inhibition of apoptosis has been proposed as one possible effect mechanism. It is also known that dopamine agonists have antioxidative properties.

Clinical documentation of a neuroprotective effect is lacking but SPECT-data from the CALM-PD (pramipexole) and PET-data from REAL-PET (ropinirole) studies may be taken to suggest neuroprotective properties. The REAL-PET study, for example, showed a lower loss in fluoro-dopa uptake with ropinirole compared with levodopa, suggesting a greater loss of dopaminergic terminals with the latter treatment, i.e. a protective effect of ropinirole (Fig. 1). A disease-modifying effect can thus be discerned, but again the question of whether or not this represents neuroprotection remains.

**MAO-B inhibitors**

Like dopamine agonists, MAO-B inhibitors can be considered to show some neuroprotective properties in the laboratory. Once again, however, several clinical investigations failed to demonstrate an effect. However, the Norwegian–Danish study assessed the progression of PD in terms of the levodopa dosage required in patients given selegiline or placebo, and found that the selegiline group had a slower increase in levodopa requirement than the placebo. That the mean levodopa curves diverged over the 5-year period of the trial was hard to explain purely by a symptomatic effect of the drug, thereby suggesting a neuroprotective phenomenon (Fig. 2). This effect has also been noted by others. The Norwegian Basal Ganglia Club algorithm of treatment strategies in PD thus suggests selegiline as an initial treatment measure following diagnosis.

It also appears that the MAO-B inhibitor rasagiline can be considered disease-modifying. The ‘delayed-start’ ADAGIO trial looked at a symptomatic versus disease-modifying effect for rasagiline at 1 mg/day and 2 mg/day concentrations. The study comprised 2 phases. Patients were randomly assigned to rasagiline or placebo in the first phase, and both groups received the active drug in the second phase. The shape of the resulting curves (diverging in the first phase and parallel in the second) suggests a disease-modifying effect for the 1 mg/day concentration but not for 2 mg/day (Fig. 3).

The Norwegian algorithm could thus be further developed to include selegiline or rasagiline as an initial disease-modifying treatment measure following diagnosis. When symptomatic treatment is required (especially in younger patients) a dopamine agonist may be considered. This can be combined with levodopa therapy whenever the need arises.
A number of studies have pointed out the importance of Parkinson’s disease (PD) patient concerns and perceptions about their medication, as well as the need to investigate newly-diagnosed PD patients for signs of depression and cognitive impairment. The latter issue may, for example, predict a poorer outcome at 5 years’ disease duration and should perhaps, therefore, influence the baseline therapy choice.

Patients who elect not to start anti-parkinson medication

The PD-LIFE study demonstrated a deterioration in quality of life (QoL) in patients who delayed the start of their medication (Grosset D et al, 2007). At baseline, 198 patients were drug naïve, while by 9 months 39% had chosen therapy, and by 18 months 68% had chosen therapy. At 18 months, the QoL of those remaining drug naïve had deteriorated. Despite worsening symptoms which would benefit from starting treatment, some patients decide to delay starting treatment, as they are fearful of side-effects (both short and longer term).

At the same time, patients who do start treatment don’t necessarily improve enormously. In a typical monotherapy trial comparing agonists with levodopa, patients will on average improve from a typical UPDRS motor scores in the mid-20s. There are residual features, however, with an average score of 10 after titration to optimal response. In general, both dopamine agonist (usually supplemented with levodopa) and levodopa curves appear similar and return the patient back to baseline after approximately 2 or 3 years of treatment.

Probability of dyskinesias

The development of dyskinesias is one of the features that will influence patient perception of PD. A very high incidence of dyskinesia in the very young onset PD patient (under 40 years) has previously been suggested, and while recent data indicate that the actual level may not be quite so high, the current impression gained from a 5-year levodopa/dyskinesia risk study is that risk does decline according to patient age at presentation (Kumar N et al, 2005). Age is thus a factor to consider.

Degree of cognitive impairment

Another relevant patient factor is cognitive ability. Depression at baseline and poorer self-rated cognitive function predict deteriorating QoL (Marra CA et al, 2008). In fact, the baseline QoL score was the greatest predictor of deteriorating QoL, which is somewhat reminiscent of the PD-LIFE study data, where the patients who elected not to start treatment experience worsening QoL, which potentially predicts deterioration in the longer term.

One group who looked at this aspect in newly-diagnosed patients found evidence of mild cognitive impairment in about 36% of patients, and that this predicts a poor outcome at 5 years (Foltynie T et al, 2004). It can thus be argued that patients with baseline poor QoL and mild cognitive dysfunction face a poorer outcome at 5 years and, presumably, at 10 years, and that these factors should therefore be considered when making treatment decisions.

Compliance to prescribed therapy

Therapy compliance or adherence can be measured in many ways: counting tablets, asking the patient to fill out questionnaires, checking blood levels, looking at how much they collect from their pharmacist, and monitoring with electronic pill bottles.

Initial work on the subject suggested that only 10% of patients took medication exactly as prescribed, and that deviating from their prescribed drug regimen is frequently a positive choice that patients make. In PD, the way patients take their medication can influence the clinical response. Poor compliance can result in pulsatile rather than continuous dopaminergic stimulation and thus potentially prime motor fluctuations, for example.

Can we rely on just asking the patient or giving...
them a questionnaire or are electronic pill bottles needed? Glasgow pilot data showed that counting tablets and using pill bottles gave very similar results in patients with good adherence, but not in the subset with poor adherence (Fig. 1). A relation between medicine usage and QoL was also seen, the under-users had significantly worse scores than those with satisfactory adherence.

**European PD multicentre therapy compliance study**

The largest PD therapy adherence study ever performed, comprising 112 patients, found low rates (12.5%) of under-utilisation (took <80% of prescribed doses), and that this was associated with higher motor scores, more OFF-time, more tablets per day, worse mobility, longer disease duration and (once again) young age. In real terms, under-users took only 232 mg levodopa of their prescribed dose of 765 mg, compared to approximately 386 mg of their prescribed 400 mg for those with satisfactory adherence (Fig. 2). Furthermore, OFF-time rather than dyskinesias was a significant factor in this under-use.

What may therefore be happening is that some patients return to the clinic, say that they have deterioration, receive a recommendation to increase their dose, and yet do not take it.

The multicentre study also showed that timing adherence (doses taken at correct time intervals) was only 24.4% (Grosset D et al, 2009).

Studies of patient concerns about medication generally show that PD patients have relatively low concerns relative to other diseases, which should translate into good therapy compliance. Of interest, however, is the finding that 38% of poor therapy compliers report feeling under-treated by their medication (Grosset K, unpublished observations).

**Simplifying drug regimens can help**

Some work suggests that simplifying treatment may help. For example, a study involving the addition of entacapone to levodopa and then switching to levodopa/carbidopa/entacapone (Stalevo) showed improving UPDRS motor scores from 30 at baseline to 22 after the introduction of Stalevo (Fig. 3). Although the total medication adherence only showed a slight tendency to improve, the number of days that patients took the right number of tablets showed a strong increase. Interestingly, the introduction of Stalevo gave an improvement in timing compliance.

---

### References:

Transplantation in Parkinson’s disease: Problems and possibilities

The prospect of cell replacement therapy for Parkinson's disease has generated much excitement. Professor Brundin reviewed progress in neural transplantation research in Parkinson's disease over recent decades and described the main obstacles that hinder the technology from becoming an established treatment. Current attempts to obtain high numbers of dopaminergic neurons from differentiated stem cells were discussed and the main challenges for future clinical grafting highlighted.

Results in the clinical setting

In Lund, 18 patients have received human donor tissue from routine abortions, typically aged 5½ to 7½ weeks after fertilisation, i.e. very small embryos. The tissue is placed stereotactically into the brain. Some patients are operated bilaterally and some unilaterally. In about one third, the result works extremely well, in one third it works moderately well, and in the remaining third it does not work at all, perhaps due to technical reasons.

In the first category of patients, quite dramatic improvements in bradykinesia can be seen (Fig. 1). The time to complete 20 hand turns can, for example, be cut from 28 seconds preoperatively to 8 or 9 seconds after 6 years. However, up to 8 donors per patient (or per side of the brain) are needed and this constitutes a large practical problem. Differentiating stem cells to use as donor tissue instead of aborted embryos would help considerably.

Production of dopaminergic neurons from stem cells

A number of techniques have been used in attempts to get stem cells to differentiate and use as donor tissue, including growing adult brain stem cells in culture dishes and trans-differentiating bone marrow cells.

However, none has met with much success in animal studies so far.

Taking embryonic stem cells derived from the inner cell mass of a blastocyst soon after fertilisation of the egg may, however, be more hopeful. Many laboratories have focused on this technique and protocols that lead to dopamine neurons do exist, albeit rather complex protocols. It may, for example, take 40 days to achieve neuron precursors plus a further 9 days before we see anything resembling a dopamine neuron culture (Fig. 2). Even then, only 15–40% of the cells are dopamine neurons.

These cells can nevertheless be grafted and in rat models of PD, the use of dopamine transporter markers suggests that good survival is achieved. However, staining with the dopamine synthesising enzyme tyrosine hydroxylase shows that only cellular debris artefacts remain – although several other grafted neurons survive and thrive, there are no dopamine neurons left. Translating positive results in a culture


**Generation of dopamine neurons from human ES cells**

<table>
<thead>
<tr>
<th>hESC</th>
<th>Select colonies</th>
<th>Expand Neural precursors</th>
<th>Plate</th>
<th>14 days</th>
<th>GROWN ON FEEDER CELLS</th>
<th>GROWN ON PLASTIC</th>
<th>Replate every 5-7 days</th>
<th>GROWN ON COATED GLASS</th>
<th>Replate</th>
</tr>
</thead>
</table>

Fig. 2. Many stem cells protocols are complex. It may take 30 days before anything resembling a dopamine neuron culture is seen (Morizane A et al, 2009).

Dish into a transplant procedure is thus difficult, and most laboratories have run into similar problems.

More effective differentiation is clearly needed and here the work of Shinya Yamanaka and colleagues may prove significant in the future. His group discovered that fibroblasts from skin can be genetically modified so that one in 10,000 (or even less) become stem cells (Takahashi K, Yamanaka S, 2006). Many later publications confirmed that this is an exciting and rapidly moving field but still one that is not free of problems. For example, dopamine neurons are not easy to make from these stem cells and the risk of tumour formation after grafting needs to be faced.

**Future clinical challenges include graft-induced dyskinesias**

A 2001 paper in the New England Journal of Medicine (Freed CR et al, 2001) showed that 5 out of 33 patients in a double-blind, placebo-controlled trial developed dyskinesias that were coupled to grafts. Other groups, including the team that Professor Brundin is part of, have since then also seen this phenomenon, and even though most of these patients would argue that this is not particularly troublesome for them, it is nevertheless graft-derived dyskinesia and therefore an issue that needs to be addressed.

Professor Brundin’s group have now, together with Professor Angela Cenci in Lund, developed an animal model for investigating this phenomenon where parkinsonian rats are treated with levodopa. Among the key findings that emerged were that these dyskinesias are more likely to appear with very large grafts placed in a certain part of the striatum, and that they disappeared when the graft is removed by immune rejection. Most importantly, the dyskinesias seem to be dependent on prior levodopa-induced abnormal involuntary movements. Many related studies are ongoing, but if this animal model holds true, pre-graft patients who have not developed levodopa-induced dyskinesias may be unlikely to develop graft-induced dyskinesias later. A better understanding of graft-induced dyskinesias is nevertheless needed before initiating ‘stem cell’ therapies in PD.

**Grafted neurons can develop Lewy bodies**

Post-mortem autopsies performed on two patients (each grafted twice) who died 11–16 years after grafting revealed between 14,000 and 29,000 dopamine neurons per tract and axons extending into the brain.

Post-mortem microscopic examination to confirm PD also showed that both patients had Lewy bodies in their substantia nigra. Surprisingly, Lewy bodies were also discovered in the grafts. Furthermore, in the 16-year-old graft, approximately 5–6% of the cells had Lewy bodies, whereas in the 12-year-old graft (same patient, other side of the brain) only 2% had Lewy bodies, suggesting a time-dependent phenomenon. This discovery is contrary to what was expected and thus prompted speculation about the underlying mechanism. Here, the up-regulation or possible modification of $\alpha$-synuclein, perhaps initiated by inflammation or import of misfolded protein into a grafted cell from the surrounding host brain, may play a role (Fig. 3).

**Conclusion**

Although not yet proven in properly controlled trials, it seems clear that grafts can still function beyond a decade, and that the phenomenon of Lewy bodies can reveal much useful information. We also need to learn more about graft-induced dyskinesias. Finally, stem cell-based therapy still awaits ‘the perfect cell’.

**References:**

- Morizane A et al. (submitted 2009).
The first medical consultation to discuss the treatment of Parkinson’s disease

Newly-diagnosed Parkinson’s disease patients are often fearful and uncertain about what lies ahead. The initial medical consultation is thus vital in helping patients to understand their disease. Professor Lees also highlighted the role of treatment consultations, and that of published guidelines in helping to select a suitable initial therapy from the options now available.

Although current Parkinson’s disease (PD) therapies tend to focus on drugs and surgery, a good supportive doctor with a pleasant bedside manner remains an essential part of the art of healing. It should always be remembered that there is a very strong placebo effect in PD. A 20% placebo improvement in motor disability scores is quite frequent in controlled trials, and the effect can last for several months.

The initial consultations

In PD, the first consultation is absolutely critical. The way the diagnosis is discussed and the narrative style adopted is extremely important. Patient associations have highlighted this fact and all physicians need to improve in these aspects. Doctors, even the busiest, must listen to their patients – one US study showed that doctors interrupted their patients every 2 minutes in an average consultation.

We need to let patients tell their story, and the first consultation should thus take at least 45 minutes. Treatment options should really not be discussed at all, although patients need reminding that PD is no longer a death sentence and that very effective treatments do exist. A second consultation just to discuss PD and its natural history may well be needed before starting talk about treatment.

Patient fears need to be discussed frankly, and it may be quite difficult to establish what these are on the first consultation. Many feel that they are going to die prematurely and even more are concerned that they will be in a wheelchair within a few years’ time. The taboo subject of dementia may come up in the early consultation and many patients appear to have been indoctrinated with the fact that the drugs used to treat PD only work for a few years. Many have also heard about drug-induced involuntary movements.

As the goals of therapy in a chronic neuro-degenerative disease are very different from treating acute illnesses or even cancer, it must be made very clear what the goals are. In the absence of a cure, efforts should focus on symptomatic relief for motor disabilities as well as on key quality of life issues. The concepts of neuro-protection and neuro-rescue are really aspirational today, but can nevertheless contribute to helping give patients confidence and allay their fears.

Treatment consultations and choices

The treatment consultation may be the third, fourth, or even later. It is important to set the scene, explain that medical treatment is designed to reduce symptomatic severity, i.e. it’s palliative, and to give optimistic examples of what can be achieved. Remind patients of the many famous or not so famous people who have PD yet who still lead active and productive lives.

To tailor the treatment to the patient, as much information as possible needs to be gathered, not just from the patient but also from the family. Getting family members to sit in is absolutely vital in treatment consultations.

Clinical expertise (i.e. implicit knowledge) has a central position when making treatment decisions for individual patients. This embraces wisdom, know-how, clinical experience and, probably more than anything, intuition. It would be fair to say that it is the ‘art of medicine’ rather than strict evidence-based medicine. Patient preferences and actions are also key issues to consider, as is the clinical state of the patient and comorbidities, the latter of which, e.g. dementia, diabetes or osteoarthrosis, are a very important issue in PD. Research evidence is also part of the picture, and today a number of good sources are available (Fig. 1).

Such sources of evidence are available to all practitioners, but perhaps the evidence-based mantra, although all pervasive, should nevertheless be viewed as a two-edged sword; it could be a utopia (Level 1 evidence with Grade A recommendations!) or it could be a nightmare, particularly if you have fiscally-minded physicians and healthcare managers who are trying to save money.

From Diagnosis to Management of Parkinson’s Disease
Cochrane Systematic Reviews  
www.cochrane.org
Movement Disorders Society Evidence Based review  
www.movementdisorders.org
www.aan.com
National Institute for Health and Clinical Excellence (NICE) Guidelines 2006  
www.nice.org.uk

Fig. 1. Evidence-based research information in Parkinson’s Disease is available via several national and international databases.

Clinical practice guidelines
The clinical practice guidelines that arise from evidence-based medicine represent an attempt to distil a large body of medical knowledge into a convenient, readily usable format. They are useful and used by many, but even though they are essentially based on the same evidence, every country has its own guidelines, and the recommendations of how to begin treating PD vary considerably.

One issue that most guidelines tend to neglect is that of efficacy. When talking to patients about treatment options, we often over-emphasise side effects of drugs and don’t emphasise sufficiently their relative efficacy.

The UK National Institute for Health and Clinical Excellence (NICE) guidelines on early treatment options do try to build in efficacy by showing that levodopa is clearly much more efficacious than MAO-B inhibitors in early treatment (Fig. 2). However, the NICE PD algorithm on general interventions for patients with PD is rather non-committal and it is not possible to identify a universal first choice drug therapy for people with early PD.

Algorithms and guidelines can, of course, be very useful in their attempt to homogenise clinical practice, at least to a reasonable level. One of the paradoxes of clinical trials, however, is that while they are an excellent means of assessing whether an intervention works, they are not always as proficient at predicting who will benefit from it.

For example, a female PD dementia patient with a mini-mental score of 19 who was severely handicapped cognitively with memory, attention and visual spatial problems improved on treatment with rivastigmine such that her mini-mental score increased to 30. This effect would, nevertheless, not be expected based on data from the EXPRESS study (Poewe W et al, 2006).

The presentation ended with an interactive session illustrating several patient examples.

<table>
<thead>
<tr>
<th>Initial therapy for early PD</th>
<th>First-choice option</th>
<th>Symptom control</th>
<th>Risk of side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Motor complication</td>
<td>Other adverse events</td>
</tr>
<tr>
<td>Levodopa</td>
<td>✓</td>
<td>+++</td>
<td>↑</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td>✓</td>
<td>++</td>
<td>↓</td>
</tr>
<tr>
<td>MAO-B inhibitors</td>
<td>✓</td>
<td>+</td>
<td>↑</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>×</td>
<td>Lack of evidence</td>
<td>Lack of evidence</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>×</td>
<td>Lack of evidence</td>
<td>Lack of evidence</td>
</tr>
<tr>
<td>Amantadine</td>
<td>×</td>
<td>Lack of evidence</td>
<td>Lack of evidence</td>
</tr>
</tbody>
</table>

Fig. 2. The NICE clinical guidelines on Parkinson’s disease include medical treatment options in early disease (www.nice.org.uk). +++ = Good degree of symptom control. ++ = Moderate degree of symptom control. + = Limited degree of symptom control. ↑ Evidence of increased motor complications/other adverse events. ↓ Evidence of reduced motor complications/other adverse events.

References:
www.nice.org.uk
When and how to optimise Parkinson’s disease therapy

Parkinson’s disease therapy may comprise pharmacotherapy, functional neurosurgery and non-medical interventions, and choosing an individual strategy depends on the age of disease onset, disease duration, patient age at consultation, multi-morbidity and patient social and care status. Optimising pharmacotherapy in relation to motor symptoms aims to fully relieve the patient of motor symptoms and fluctuations by a combination of drugs, while at the same time avoiding dyskinesias and drug-induced psychosis. Professor Oertel focused on levodopa and dopamine agonist therapy, presenting data from 4 newly released studies.

In the period around 1993, Parkinson’s disease (PD) was considered to be due to dopaminergic degeneration and appropriate medication to deal with this was generally available. Since then genetic and environmental aspects were revealed and the Braak hypothesis and role of Lewy bodies began to predominate the discussion in etiopathogenesis of PD. The situation surrounding PD thus changed. In addition, patients now live longer due to improved general medical care. This longer life-length means that patients get multi-morbidity and that they will reach the age and stage where dementia will manifest. Non-motor symptoms rather than motor complications are thus assuming greater importance in routine clinical practice.

Lewy bodies, dementia and Alzheimer’s disease

Dementia associated with PD is generally recognised as dementia with Lewy bodies (DLB), where dementia occurs before Parkinson syndrome, and PD with dementia (PDD), where dementia will eventually appear in the span of 10–15 years after the age of approximately 65 years. The brain of PD patients with dementia (irrespective of cause) has a marked deficit in the cholinergic system, and the question of what is more important – the cholinergic deficit or the dopaminergic deficit – becomes relevant here.

Furthermore, studies (including Lewy body and amyloid imaging) in normal subjects and PD, PDD, DLB and Alzheimer’s disease patients suggest that PD and Alzheimer’s will meet at a future ‘crossroad’, an occurrence that should prove beneficial as the research and therapy of Alzheimer’s is considered about 5–10 years ahead of that of PD.

Symptomatic therapy guidelines – review of key trials

The general goal of restoring the dopaminergic deficit and maintaining it within the therapeutic window in order to keep the patient mobile can manifest itself quite differently according to patient status and country of location (e.g. dopamine agonists tend to be favoured in Germany, levodopa or dopamine agonists in the United Kingdom and MAO-B inhibitors in some parts of Scandinavia as the initial monotherapy). A number of recent clinical trials may help us understand this situation better, the first two of which are the ADAGIO and CALM-PD trials.

ADAGIO and CALM-PD trials

The ADAGIO trial looked at a symptomatic versus disease-modifying effect for the MAO-B inhibitor rasagiline at 1 mg/day and 2 mg/day concentrations. The study comprised two phases: in the first, patients were randomly assigned to study drug or placebo, in the second, all received the active drug. Study outline and visits are shown in Fig. 1.

Results included the finding that the 2 mg/day early-start group showed significant benefits versus placebo in the placebo-controlled phase, but did not show superiority versus the delayed-start group at the end of the active-treatment phase. However, the 1 mg dose did meet the primary endpoints of the study Olanow CW et al, 2008a.

Fig. 1. The ADAGIO trial design included two phases: Phase I, a 36-week double-blind, placebo-controlled phase, and Phase II, a 36-week double-blind, active-treatment phase in which all patients received active study treatment (Olanow CW et al, 2008b).
The CALM-PD trial investigators set out to compare the long-term outcomes in early PD patients initially treated with the agonist pramipexole (N=151) with those of subjects initially treated with levodopa (N=150) with special regard to motor complications. This is one of two key trials that drive therapeutic guidelines in Germany. The primary outcome variable was the time-weighted average of self-reported disability scores in the ON and OFF-states at final visit (Parkinson Study Group CALM Cohort Investigators, 2009).

After 6 years, 20.4% of patients initially treated with pramipexole had dyskinesias compared with 36.8% in the initial levodopa arm, but interestingly the severity of the dyskinesias was low in both groups (1.1 vs. 1.3 respectively, \( p=0.06 \)) according to the Lang–Fahn ADL dyskinesia scale. Both groups had, therefore, very similar dyskinesia profiles with the only real difference being somnolence. The mean Epworth Sleepiness Scale score was significantly higher (\( p<0.001 \)) in the initial pramipexole group (11.3) than in the initial levodopa group (8.6), i.e. patients with the agonist were more tired than those with levodopa. This may suggest a future shift in German guidelines from agonist to either agonists or levodopa, with money-saving as the main motivation.

**FIRST-STEP trial**

The FIRST-STEP (Favourability of Immediate-Release of carbidopa/levodopa versus STalevo: Short-Term comparison in Early Parkinson’s) trial is a direct improved-symptom-control comparison between Stalevo (levodopa/carbidopa/entacapone [L/C/E]) versus standard levodopa/carbidopa (L/C) in early PD patients requiring levodopa therapy. The duration of treatment was 39 weeks and study medication was taken 3 times daily.

Results showed that patients treated with L/C/E improved more when measuring UPDRS II and III together (\( p=0.045 \)), which was the primary objective of the study (Hauser RA et al, 2009). A key observation was that treatment with L/C/E was associated with a numerically lower incidence of both dyskinesias (5.3% versus 7.4%, respectively) and wearing-off (13.9% versus 20.0%, respectively) compared with L/C treatment. This finding was not statistically significant, but a trend could be discerned (Fig. 2).

**STRIDE-PD trial**

The aim of the STRIDE-PD study (STalevo Reduction In Dyskinesia Evaluation) was to evaluate whether treatment with Stalevo (L/C/E) when used as initial levodopa therapy for PD would be able to delay the time to onset of dyskinesia compared with a standard formulation of L/C, both given 4 times daily. The primary endpoint was the time to onset of dyskinesia.

Results showed that the time to dyskinesia was shorter in L/C/E-treated patients compared with L/C-treated patients, and also that the incidence of dyskinesia during the study period was higher in the L/C/E group. Wearing-off was reported more frequently in L/C-treated patients compared with L/C/E-treated patients. Patients treated with L/C/E had slightly better PD symptom control in comparison to L/C-treated patients during the whole study period. The primary endpoint was thus not met, but it should be recognised that the key question asked in the study had a high level of ambition.

The study did, however, show that L/C/E treatment is well tolerated, effective and may help to increase compliance. Based on the results of the study, it will not be used in levodopa-naïve patients but, as previously, in patients with symptoms of wearing-off.

**References:**

Olanow CW. Ann Neurol 2008a;64(Suppl 12):S68.
Olanow CW et al. Mov Disord 2008b;23:2194-201.
Subthalamic deep brain stimulation (STN-DBS) has been demonstrated to be an effective treatment for ameliorating motor symptoms in Parkinson’s disease (PD) and for improving quality of life (QoL). Reduction in off-phases and dyskinesias of approximately 70% have been observed. Furthermore, a reduction in dopaminergic medication of around 55% has been noted.

A paper (Kleiner-Fisman G et al, 2006) published as a supplement of the Movement Disorder Society Journal reviewing almost 1,000 PD patients, showed that a reduction of the UPDRS motor score in the range of 30 points can be expected. For activities of daily living (ADL), the improvement was in the range of 13 points. Long-term (60 month) follow-up studies have also shown the therapy to be sustainable.

Improvement in QoL measured by PDQ-39

A multicentre randomised study on 180 patients prospectively assigned into two groups reinforced this picture (Deuschl G et al, 2006). One group was assigned to STN-DBS and the other to optimised medical therapy. Follow-up was 6 months. The primary outcome was QoL assessed by the disease-specific quality measurement PDQ-39. Results showed an overall change of the PDQ-39 summary index of about 25%, with an even more pronounced improvement in certain sub-items (mobility, ADL, emotional well-being and stigmatisation). In contrast, 6 months of optimised medical therapy did not produce any change in the PDQ-39 (Fig. 1).

Treatment effect of STN-DBS in younger PD patients

It can thus be concluded that STN-DBS is an effective therapeutic option for improving QoL in PD patients. However, most patients in the above studies had advanced PD. In the randomised QoL study, for example, the overall age was 60, disease duration was on average 13 years, and the Hoehn and Yahr (H&Y) stage was 3.5. With younger patients, the situation is likely to be much different.

PD is increasingly seen as a multi-dimensional disease that involves more recognised motor symptoms as well as considerable psychosocial impairment. We know that younger patients experience a higher degree of psychosocial impairment, usually show an excellent response to dopaminergic medication, and display a higher risk of developing dyskinesias. Additionally, young patients usually have a lower degree of comorbidity and are generally not impaired by cognitive problems. Their risk for surgical complications should also be quite low.

A viable option for the young PD patient?

Whether or not STN–DBS is a viable option for younger PD patients requires careful consideration: Key questions are: will the therapy really improve motor symptoms, is there a surgical risk, will it impact psychosocial impairment, and will it modify the course of the disease?

The body of evidence for such issues is quite small, but one study does shed some light on the situation.
In this, 20 patients with an average age of 48 years and disease duration about 7 years were randomly assigned to either STN-DBS or best medical treatment. Their UPDRS motor scores were quite low and all had an excellent response to dopaminergic medication. Follow-up was 18 months and the outcome parameters were motor score, QoL, cognition and psychiatric mobility (Schüpbach WM et al, 2007).

At follow-up, the STN-DBS group had a motor score reduction of about 80%, i.e. an excellent response to the therapy. In addition, dopaminergic medication could be reduced by approximately 70%. In the best-medical-treatment group, however, no significant changes were seen.

A retrospective surgical risk study found an overall mortality in the range of 0.4%, and also noted that patients of a younger age (less than 60 years) had a much lower incidence of adverse effects than those older than 60 years, probably due to the higher co-morbidities in the latter group (Voges J et al, 2007). STN-DBS thus appears to be a safe therapeutic option for young PD patients.

**Marginal effect on psychosocial burden**

Regarding the psychosocial burden of the younger PD patient, it has been shown that younger patients have a greater feeling of being stigmatised by the disease (Schrag A et al, 2003). For example, the incidence of marital discord is higher, they have a higher impairment of disease-specific QoL, and their professional work suffers, with many seeking early retirement.

How does deep brain stimulation impact on these psychosocial factors? One retrospective study involving 29 patients (82% married, 55% still with a professional activity) aged around 50 years with a disease duration of almost 10 years showed that 18 months of STN-DBS did not improve their situation (Fig. 2).

In fact, 60% of patients reported continuing or new marital problems following treatment. In addition, 44% gave up working after treatment, despite often excellent motor improvement. The risk for suicide, a major concern in all PD patients following STN-DBS, has also been found to be somewhat higher in young males.

**Neuroprotective effect under investigation**

The final issue of a potential neuroprotective effect of STN-DBS is currently unresolved. A neuroprotective effect seen in MPTP monkeys has not yet been reproduced in STN-DBS-treated PD patients. Current studies show disease progression in the range of 10-12%, which is similar to patients not treated by neurostimulation.

Recently initiated trials that are recruiting young-onset PD patients with a course of disease less than 4 years and at H&Y stage 2 may give us a better picture on the neuroprotective perspectives of STN-DBS.

In conclusion, future studies will show whether an early neurostimulation treatment of PD patients might not only improve their motor impairment or prevent them from developing complications, but also reduce the risk of psychosocial impairment. This might provide a better and longer professional life of PD patients (Fig. 3).

**Fig. 2. In PD patients aged around 50 with disease duration of almost 10 years, 18 months of STN-DBS treatment did not markedly improve their social functions (Schüpbach WM et al, 2006).**

**Fig. 3. Ongoing trials may show that giving STN-DBS earlier in disease progression may improve PD patients’ motor functions and slow down the development of severe psychosocial impairments (Jan Herzog 2009).**

**References:**


Transcranial ultrasound is a quick, safe and non-invasive imaging method for diagnosis and differential diagnosis of various intracranial pathologies. In Parkinson’s disease, the evaluation of echogenicity changes in small deep brain structures may possibly prove useful even before motor symptoms have occurred. Professor Berg described the method and pointed out its strengths and weaknesses.

Transcranial ultrasound (TCS) requires a high-end ultrasound machine, a 1.5–4 MHz ultrasound probe, and a sufficient bone window. For the diagnosis and differential diagnosis of Parkinson’s disease (PD), the mesencephalic and the third ventricular scanning planes are used.

Diagnostic challenges

Today, PD cannot be clinically diagnosed until neurodegeneration has progressed far enough to manifest as motor symptoms. By then, about 60% of the neurons in the substantia nigra and 80% of the dopamine-producing cells in the striatum are already lost (Fig. 1). Diagnosis can also be difficult in the clinical phase, even at specialised centres, up to 20% of diagnoses are incorrect up to death.

Individuals with PD typically display increased echogenicity of the substantia nigra, so-called hyperechogenic areas are found in more than 90% of PD patients and these can be well reproduced by different investigators. Nevertheless, TCS can be said to be a subjective method, a shaking patient with a shuffling gait may influence the sonographer’s interpretation of the scan. To exclude this bias, Professor Berg’s group has performed a study in which the sonographer was completely blinded. The patient was hidden under a blanket, the room darkened, and the patient not allowed to be tremor-dominant. Of the 42 patients with clinically diagnosed PD, 36 did indeed display substantia nigra hyperechogenicity. Consequently, 6 patients were false negative, but it must be taken into account that the PD diagnosis was based on clinical observation only. Of the 36 controls, 30 had a normal substantia nigra. Six patients were thus false positive (or the TCS detected a case or cases of what was not yet clinically evident). Altogether, the diagnosis of PD solely based on TCS results had a positive predictive value of 85.7% and a negative predictive value of 82.9%, indicating that TCS is a valuable additional tool when diagnosing PD (Prestel J et al, 2006).

Differential diagnosis

Differentiating between idiopathic, symptomatic and atypical PD is difficult and uncertain, even at specialised centres. As long as the classification is based on clinical findings, a definite diagnosis can only be made post-mortem.

TCS may be one way of improving differential diagnoses. It is possible, for example, to differentiate PD from symptomatic parkinsonism, i.e. hydrocephalus, tumours, or unipolar depression. Essential tremor is more difficult, as quite a few essential tremor patients have hyperechogenicity of the substantia nigra. An important aspect, however, is that patients with essential tremor develop PD up to 4 times more often than the general population, and it is possible that essential tremor patients with hyperechogenicity of the substantia nigra are the ones more prone to developing PD later on.

In patients with atypical parkinsonian syndromes, the area of hyperechogenicity is generally the same as in controls, with only a small area of hyperechogenicity compared to idiopathic PD. Increased echogenicity of the substantia nigra is predictive for idiopathic PD, whereas normal echogenicity of the substantia nigra, particularly when combined with a hyperechogenic lentiform nucleus, suggests an atypical parkinsonian syndrome (Behnke S et al, 2005).
TCS as an early diagnostic marker
Substantia nigra hyperechogenicity can be used in the early diagnosis and even as a marker of predisposition, as it does not seem to change during the course of the disease (Schweitzer KJ et al, 2006).

In a recent prospective, blinded study aiming to determine the diagnostic value of TCS in the early stages of parkinsonian syndromes, 60 patients presenting with the first, still unclear clinical symptoms of parkinsonism were examined. The positive predictive value of substantia nigra hyperechogenicity for idiopathic PD was 92.9% and the classification accuracy was 88.3% (Fig. 2). Thus, the routine use of TCS in the clinic could be most helpful in early diagnosis by excluding a number of secondary or atypical parkinsonian syndromes at very early stages, thus enabling disease-specific therapy to be started earlier.

Investigating the possibility of premotor diagnosis
The prevalence of substantia nigra hyperechogenicity in healthy individuals has first been systematically investigated in a study on 417 healthy subjects. This study showed that in all age groups from the age of 20 up to at least 70 years, approximately 8–10% of individuals display increased echogenicity similar to PD (Berg et al, 1999, Berg et al, 2002). Fortunately, this does not mean that 9% of the general population will develop PD. The observation may nevertheless have some functional relevance, for instance by disclosing a vulnerability factor for dopaminergic stress.

One way of stressing the dopaminergic system is to apply antipsychotic drugs. In a TCS study performed on patients admitted to a psychiatric hospital for the first time for treatment with antipsychotics, patients with larger areas of echogenicity of the substantia nigra were shown to display more severe extrapyramidal signs (Fig. 3).

During the premotor phase of PD, a number of well-known clinical signs occur, e.g. depression, olfactory and autonomic dysfunction, neuropsychological deficits, and REM sleep behaviour disorder. Interestingly, all these symptoms are associated with substantia nigra hyperechogenicity. To investigate if individuals with substantia nigra hyperechogenicity and pre-motor markers are more prone to develop PD later in life, a multicentre study including more than 1,800 individuals over the age of 50 is being carried out. At the moment, this study is not clinically relevant as there is no treatment available, but the results may become important if a truly disease-modulating drug is developed.

TCS is thus potentially a very useful method, but one that does suffer from some as yet unresolved problems. Most important are the differences in bone windows, both regarding contrast and resolution of fine structures and differences in angulation. For example, in approximately 10% of subjects, the substantia nigra simply cannot be seen. Another problem is the difference in resolution between different ultrasound machines, which requires every sonographer to have a control group and his or her own standard and cut-off values, just like electrophysiology. A third problem is the need for experience.

References:
Brain MRI for the differential diagnosis of Parkinson’s disease and atypical parkinsonian syndromes

In Parkinson’s disease, obtaining a correct diagnosis is of great importance for planning treatment and resources, for prognosis, and for the patient’s own coping. Today’s diagnostic criteria are mainly based on patient history and certain clinical examinations. They are not developed for use in a clinical setting and certainly not for use early in the course of the disease. Imaging modalities like brain MRI may be a way of improving diagnosis. Dr. Linder described different MRI techniques, with special focus on structural MRI. He also presented the ongoing Umeå study, a 5-year prospective investigation on a population-based incidence cohort with parkinsonism.

Many reports describe the characteristic changes for the different parkinsonian disorders as seen through a range of imaging techniques, including MRI, pre- and postsynaptic PET and SPECT, FDG-PET, and transcranial ultrasound. MRI has several advantages: it is non-invasive, it involves no radioactive radiation, it is available in most centres, and it is relatively cheap.

**Structural MRI – the most readily available MRI technique**

The usefulness of routine structural MRI for the differential diagnosis of Parkinson’s disease (PD) with atypical parkinsonian syndromes in everyday clinical practice has been investigated in a study by Yekhlef and colleagues. They developed a scoring system with 11 MRI pointers that was reasonably successful in discriminating PD from progressive supranuclear palsy (PSP), multiple system atrophy of the Parkinson type (MSA-P), and normal aging (Yekhlef F et al, 2003).

Another study using this scoring system, including 21 patients with PSP, 23 patients with PD, 25 patients with MSA-P, and 31 age-matched normal subjects, calculated the ratio of the area of the midbrain to the area of pons with mid-sagittal MRI, thereby separating PSP from the other syndromes (Fig. 1).

In a structural MRI study focusing on the superior midbrain profile, Righini and colleagues reviewed MRI studies of patients with PSP and PD by means of 5 parameters: midbrain superior profile on mid-sagittal T1-weighted images, midbrain atrophy, tegmental abnormal T2 hyperintensity, abnormal T2 putaminal hypointensity or hyperintensity on axial proton density-weighted images. Results showed that an abnormal superior profile of the midbrain facilitates the distinction of PSP from PD and may support the clinical differential diagnosis of parkinsonism. The method had a sensitivity of 68% and a specificity of 88.8% (Righini A et al, 2004).

**Other MRI techniques**

Diffusion weighted imaging (DWI) makes it possible to separate MSA-P from PD and PSP by measuring changes in the middle cerebellar peduncle (Nicoletti G et al, 2007).

Segmented Inversion Recovery Ratio Imaging (SIR.RIM) is a completely automated measure of MRI signals in the substantia nigra pars compacta that has been demonstrated to be a highly sensitive method for differentiating PD from controls (Hutchinson M, Raff U, 2008).

Voxel-based morphometry offers non-biased, observer-independent morphometric MRI analysis. This semi-automated whole-brain analysis measurement of volume and atrophy can separate PD from PSP and controls with a sensitivity of 83% and a specificity of 79% (Price S et al, 2004).

Volumetric analysis measures whole brain and regional volumes, thereby distinguishing PSP and MSA-P from each other, from PD, and from healthy controls (Paviour DC et al, 2006).

MR spectroscopy can be used to determine the metabolite pattern in MSA. The significant reduction of the N-acetylaspartate to creatine ratio (NAA/Cr)
in MSA patients in the pontine base and putamen makes it possible to separate MSA from PD even before clinical manifestation of symptoms (Watanabe H et al, 2004).

Pattern analysis is based on automated computer differential classification of tissue composition and deformation features, thereby distinguishing PD from PSP and MSA with 91% accuracy (88% specificity, 93% sensitivity) (Duchesne S et al, 2009).

Another whole–brain analysis has been investigated in drug-naïve patients with de novo PD. Results showed an increase of fractional anisotropy values that was more pronounced in patients with the akinetic-rigid type, probably reflecting diffuse subtle grey matter loss. (Tessa C et al, 2008).

Quite a large number of parkinsonian disorders with characteristic MRI images can thus be found, most of which concern structural abnormalities or imaging sequelae of abnormal iron deposition. The different parkinsonian disorders have their individual characteristics (Fig. 2). However, these imaging findings have in most cases been studied in late-stage patients where the use of established clinical criteria secures the diagnosis. To establish criteria for early differential diagnosis, we need large prospective studies following newly-diagnosed patients, and performing serial investigations. The Umeå study is an attempt to achieve this.

### The Umeå study

The Umeå study is a 5-year prospective study on a population-based incidence cohort with parkinsonism. Clinical examinations and different forms of imaging are performed regularly (Fig. 3).

When the patients have been followed for 60 months, most of them will have fulfilled the diagnostic criteria for their respective parkinsonian disorder.

### References:

PET and SPECT imaging in movement disorders – diagnostics and pathophysiology

Functional neuroimaging in movement disorders has advanced our current understanding of pathophysiology and helped evaluate treatment effects. Dopaminergic tracers have served as the primary neuroimaging biomarker in the differential diagnostic work to date, but alternatives are increasingly being utilised. Dr. Borghammer discussed the roles of the most commonly employed SPECT and PET tracers in differential diagnostics and briefly reviewed recent neuroimaging findings that advance our pathophysiological understanding.

Dopaminergic tracers are the most commonly used PET and SPECT tracers for movement disorders and several agents exist for imaging dopamine transporters. DaTSCAN is well known to all who work in this field and the shift from comma shape to full stop, signaling loss of dopamine, is now a familiar sight.

Relevant patient categories include Parkinson’s disease (PD) patients and those with the atypical diseases multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). A DaTSCAN can thus help differentiate between these disorders and possible movement disorders that have an intact dopamine system, e.g. essential tremor. Dopamine transporter imaging can similarly differentiate between Lewy body dementia (LBD) (dopamine loss) and Alzheimer’s disease (intact dopamine system) (Fig. 1). DaTSCANs can also illustrate progressive loss of striatal pre-synapses over the time course of disease.

Drug interactions important

For a DaTSCAN to work successfully, the patient must pause or fast from a number of drugs. One key category relevant to drug interaction is the antidepressive SSRI class of drug.

Many PD patients take SSRI drugs, and while patients do not need to abstain from this type of medication, SSRIs can lead to a 10% over-estimation of striatal values. Patients will thus look healthier than they are. For this reason, it is important to always inform the nuclear medicine department about the current medication status of the referred patient.

Another commonly used agent is the PET fluorodopa tracer (F-DOPA). An F-DOPA PET scan has better resolution than the DaTSCAN, making it a better choice for many research purposes. However, for clinical use, the accuracy of the two tracers is very similar. In addition, an F-DOPA PET scan is often more expensive and less readily available than the DaTSCAN.

Post-synaptic dopamine receptors

Post-synaptic tracers such as raclopride for PET and IBZM for SPECT imaging both label the D2 dopamine receptors. These agents can be used for differentiating MSA and PSP from idiopathic PD. However, the sensitivity and specificity values are only 60–80% in most studies.

In summary, for routine clinical use, DaTSCANs and F-DOPA scans can equally well identify patients with a presynaptic dopamine loss of the striatum. They cannot, however, differentiate between PD, MSA, PSP, and LBD.

Usefulness of heart imaging with MIBG

Other methods may prove to be more useful. One such technique is the use of the tracer MIBG, which although it does not cross the blood-brain barrier, can nevertheless be used for differentiating brain disorders. Patients suffering from idiopathic PD, LBD and
primary autonomic failure (PAF) are all characterised by cardiac sympathetic denervation. Patients with atypical parkinsonian disorders (MSA, PSP, CBD), on the other hand, have normal or only slightly affected cardiac innervation (Fig. 2).

The MIBG imaging method has been most widely investigated by Japanese workers. Some studies demonstrated sensitivity and specificity values of 90–95% for differentiating idiopathic PD from MSA, although more recent work suggests that these values were probably overly optimistic. Nevertheless, MIBG may be a promising adjunct imaging method for differentiating movement disorders.

**Glucose consumption imaging**

Another imaging modality capable of differentiating PD from atypical disorders is glucose consumption imaging using fluorodeoxyglucose (FDG) PET. Individual brain disorders are characterised by specific perturbations of cerebral glucose metabolism. Thus, distinct patterns of relative cerebral hypo- and hypermetabolism can be identified in each brain disorder. Using advanced statistical analysis, individual movement disorder patients can then be matched against the disease-specific patterns and the most probable diagnosis estimated (Fig. 3).

In general, only larger nuclear medicine departments are in possession of sufficient know-how and the necessary databases of healthy controls and patient scans to make use of this methodology. However, the development of common scanner-independent databases could make the dissemination of this approach very attractive, considering that FDG is the most widely available and affordable PET tracer.

**References:**


Fig. 2. MIBG scans of the heart can differentiate patients with autonomic denervation of the heart (idiopathic PD, DLB, primary autonomic failure) from patients with intact cardiac innervation (MSA, PSP, CBD) (Kashihara K et al, 2006).

Fig. 3. Patterns of cerebral glucose consumption obtained by FDG PET scans can differentiate MSA and PSP patients (diamonds) from healthy controls (circles) and from patients with Parkinson’s disease. Mean and standard deviation are also displayed (Eckert T et al, 2008).
Early diagnoses of parkinsonism tended to divide the disease into true Parkinson’s disease (PD), which meant that the patient had bradykinesia, and pseudo-PD where bradykinesia was not present, as well as several rarer causes. Discussions of atypical PD inevitably centred around progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and cortico-basal degeneration (CBD) and these latter disorders generally represented the ones that were more commonly misdiagnosed.

Even in the hands of experts, misdiagnosis rates could approach 25%. This figure has now been reduced as we have learnt more about how to differentiate these disorders and have even become ‘experts’ in MSA, PSP and CBD. This helps illustrate that as we become better at recognising forms of the disease that we believe are rare, we realise that this is not actually the true situation as more and more cases are found. The advent of genetic studies and of imaging has made a big difference in this respect.

Case 1 – tremor, imbalance, postural giddiness and cognitive problems

A 55-year old man presented with a 5-year history of resting tremor, imbalance and postural giddiness. When his postural giddiness was measured by blood pressure, a drop of more than 25 mm was recorded. His face was seen to be hypermimic. The latter fact, plus the combination of the other symptoms, could suggest MSA (a 5-year history of resting tremor can be regarded as a ’red flag’ for MSA).

However, the man’s wife said that he had cognitive problems, he had recently got lost in familiar surroundings and had difficulty with his banking routines, for example. His cognition is therefore not as good as it used to be, and he is making some suggestive remarks to neighbouring women. Cognitive abnormality does not really fit in with the usual picture of MSA.

Additional information obtained was that the postural instability leads to falls and that the patient has poor reflexes. His eye movements are, however, normal and his family history revealed nothing peculiar. A DaTSCAN was performed, which was normal. This generally excludes MSA as a possible cause as we know that MSA, PD and PSP all have abnormal DaTSCANs.

In contrast, an MRI scan revealed characteristic hyperintensities in the middle cerebella peduncle, a classic indication of the Fragile X 55-repeat premutation. The patient thus has Fragile X syndrome. Fragile X is the commonest cause of inherited mental retardation in men. It can extend to severe cognitive or intellectual disabilities and symptoms also can include distinct physical and behavioural features.

Fragile X is reminiscent of MSA, we see parkinsonism, dysautonomia and intranuclear inclusions. If you have a patient whose symptoms look like MSA, but who has a normal DaTSCAN, or a patient who resembles MSA, but has a lot of cognitive abnormality and is a man, consider Fragile X as a possible diagnosis.

Fragile X is being found more and more frequently. The expansion of 55–200 repeats falls within the premutation range and these individuals present with parkinsonism, dysautonomia and ataxia. Patients with more than 200 repeats present with a classic Fragile X-related mental retardation. Differentiating the Fragile X syndrome diagnosis from that of MSA is important because the prognosis is quite different, the former group live much longer.

Case 2 – IQ 72, first-degree consanguinity, akinetic and dystonic grimace of the face

The patient (male) was aged 39 at examination. When aged 16, he had an acute psychotic event and became hypomanic. He received fenotiazine and lithium, immediately after which he became akinetic rigid. The fenotiazine was suspected and then stopped. Some initial improvement was seen with anticholinergic treatment, but despite withdrawing the lithium as
well, the patient’s condition continued to deteriorate. His cognitive performance also worsened. His IQ fell to 72 and his performance IQ to 86. A cousin was also found to be affected with a similar problem, i.e. there was first-degree consanguinity.

The patient was thus akinetic and had a dystonic grimace of his face. With a history of recessive disorder, this would suggest Wilson’s disease. This was not the case, however. The patient had a lot of spasticity and in Wilson’s disease, we do not see such profound spasticity. When the patient’s eye movements were investigated, it was noted that the horizontal movements were fine, but not the vertical, i.e. the patient could not look up.

We thus see a male aged 39 with an akinetic rigid syndrome (onset age about 17 or 18) that is progressive with a cognitive effect, parametral features and an upgaze supranuclear gaze problem. This was written up as hereditary, juvenile PD with parametral signs of mental retardation. If the patient had been aged 70, PSP would have been a candidate diagnosis, but not in a man yet to reach 40.

We now know that this patient has Kufor-Rakeb disease, a genetic form of PD characterised by autosomal recessive, levodopa-responsive parkinsonism with pyramidal degeneration, supranuclear gaze palsy and dementia. The gene for Kufor-Rakeb disease (known as ATP13A2) has been assigned a locus on chromosome 1p36 that was previously assigned Park 9.

ATP13A2 is considered to be important. It leads to lysosomal dysfunction, but our understanding of what else it does is as yet incomplete. It is also interesting from a genetic point of view because it seems that chromosome 1 is also the location for many other Park genes. Chromosome 1 thus seems to be a hot-spot for several of these more unusual parkinsonian conditions.

References:
Depression in Parkinson’s disease: An update

Depression is a common psychiatric problem associated with Parkinson’s disease, with a negative impact on both functional ability and quality of life. Recognising depressive symptoms at an early stage can help reduce compensatory mechanisms and optimise treatment. However, it is still not clear what therapy should be used, and more studies are warranted to better understand the role of treatment with antidepressants in Parkinson’s disease patients with depression. Dr. Pålhagen reviewed current theoretical approaches to the mechanisms behind depression in Parkinson’s disease and gave some treatment recommendations.

The neuropsychiatric features of Parkinson’s disease (PD) include mood disorders, cognitive dysfunction, and complex behavioural disorders (Fig. 1).

A common problem – but how common?

According to a systematic review of depression rates in PD, the average prevalence of major depressive disorders is approximately 17% and the prevalence of clinically relevant depressive symptoms is approximately 25% (Reijnders et al, 2008). However, estimated prevalence rates of depression in PD vary greatly between different trials, ranging from 2.7% to more than 90%. The main reason for this variance is most likely trial bias. Different assessment tools are used, study designs and patient criteria vary, and most studies do not discriminate between major depression, minor depression and dysthymia.

A NIH-sponsored workshop set up to reduce this bias recommended changes in the Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic criteria for PD. It also recommended an inclusive approach to symptom assessment, i.e. that all symptoms are taken into account, regardless of their overlap with PD or other medical conditions, as well as the inclusion of subsyndromal depression in clinical studies and specification of timing of assessments for PD patients with motor fluctuations (Marsh L, 2006).

Severe implications

In PD patients, depression causes more rapid disease progression, reduced ADL function, impaired cognitive function, increased mortality and reduced quality of life for both patient and caregiver. The profile of depressive symptoms in PD patients is somewhat different from that of depressed patients without PD (Fig. 2).

More frequent

- Dysphoria
- Aggression
- Irritability
- Sadness
- Pessimism
- Suicidal ideation

Less frequent

- Feeling of guilt
- Self blame
- Feeling of failure
- Feeling of punishments
- Delusions
- Hallucinations
- Suicidal acts

Cause or effect?

Depression in PD can be discussed from two different points of view, either as an expression of a common underlying neurodegenerative disease and thereby as an intrinsic part of PD, or as a co-morbid depression, separate from PD. Knowledge of which is correct will make it possible to develop better diagnostic tools and to optimise treatment.

The loss of dopamine-producing cells in the substantia nigra occurs very early in the course of the disease, as does the loss of noradrenaline innervations.
in the limbic system, and this may be one cause of depression and anxiety.

Dopamine undoubtedly has an important role in depression. One compelling piece of evidence for this is that drugs that deplete dopamine and noradrenaline (e.g. reserpine) cause depression, while drugs that increase dopamine and noradrenaline (e.g. some tricyclic antidepressants) improve depression. It has also been demonstrated that D2-receptor antagonists may cause depression.

Reduced dopaminergic activity is associated with psychomotor retardation, mental slowing, reduced attention and concentration, reduced executive function, reduced initiative and motivation, and reduced self-reward.

**Other transmitters influencing depression**

All symptoms of depression, however, cannot be explained solely by alterations in dopaminergic transmission. Some symptoms are explained by alterations in other neurotransmitters, mainly noradrenaline and serotonin. Reduced noradrenergic activity is associated with anhedonia, reduced motivation, reduced emotional memory, loss of energy, and loss of libido – a good picture of the depressive symptomatology in PD. Reduced serotonergic activity is associated with anxiety and panic, reduced impulse control, reduced aggression regulation, sleep disturbances, reduced appetite, and loss of libido.

In mood disorders, many different mechanisms interact. A concept of neurocircuitry models underlying depression has been proposed, involving the prefrontal cortex, amygdala and related parts of the striatum, pallidum and medial thalamus. In PD, major depression could be the result of a more advanced, widespread degenerative disease – a dysfunction between reduced catecholaminergic (dopamine and norepinephrine) and serotonergic systems.

**Therapeutic approaches**

Treatment with levodopa improves most cognitive and behavioural functions in the ON-state, but it does not remedy all depressive symptoms, and concomitant antidepressive treatment is often indicated.

Many open-label studies show positive effects of tricyclic antidepressants and SSRIs, but very few randomised clinical trials. Furthermore, some studies have shown negative results, primarily owing to high placebo response. However, two recently published randomised, placebo-controlled studies have compared the effects of an SSRI and a tricyclic antidepressant.

The study by Menza and colleagues compared the effects of paroxetine CR, nortriptyline and placebo in 52 patients – the largest placebo-controlled trial to date in this patient group. Primary outcomes were change in the Hamilton Depression Rating Scale (HAM-D) and number of responders at 8 weeks. The results showed that nortriptyline was superior to placebo for the change in HAM-D, while paroxetine CR was not (Fig. 3).

In the study by Devros and colleagues, the short-term efficacy of citalopram, desipramine and placebo were compared in 48 patients measured with the Montgomery Asberg Depression Rating Scale (MADRS) score. After 14 days, desipramine showed an improvement compared with citalopram and placebo, and both treatments produced significant improvements after 30 days. The authors concluded that desipramine’s more intense short-term effect was outweighed by its lower tolerability.

Dopamine agonists seem to have a positive effect on depressive symptoms in some PD patients, but published studies on their effects on PD depression are lacking. According to a recently published meta-analysis, pramipexole had a beneficial effect on mood and motivational symptoms in PD patients without a major depressive disorder. The clinical value of pramipexole in the treatment of depressive and apathetic syndromes requires, however, further investigation.

**Recommendations**

OFF-period dysphoria requires optimisation of existing anti-parkinsonian therapy, while primary depression may require additional therapy. In younger patients, second-generation dopamine agonists may be of value. An SSRI or SNRI may be a good choice for some patients, and if there is no effect at 3–4 weeks, a tricyclic antidepressant can be tried. Tricyclic antidepressants may also be used in combination with an SSRI or SNRI. In very serious cases, transcranial magnetic stimulation (TMS) or electroconvulsive therapy (ECT) are possible alternatives.

References:

Impulsive and compulsive behaviours in Parkinson’s disease

Impulsive and compulsive disorders associated with Parkinson’s disease are gaining increased awareness. These disorders are frequently seen in younger patients. Dr. Voon described associated factors and mechanisms behind the development of impulsive and compulsive behaviours and gave management recommendations.

Impulse control disorders (ICDs) associated with Parkinson’s disease (PD) include pathological gambling, shopping, hypersexuality and binge eating. These behaviours tend to be associated with urges and cause distress or have negative consequences. It is quite clear from the literature that they are associated with the use of dopamine agonists.

Another similar behaviour associated with PD is punding: repetitive, aimless, excessive behaviour, ranging from a simple shuffling of bricks or excessive cleaning to complex behaviour like painting or gardening. Whether or not punding is associated to a greater extent with the use of levodopa as compared to dopamine agonists has not yet been established.

Compulsive medication use, or dopamine regulation syndrome, is also a disorder associated with PD. It is characterised by excessive use of medication for motivational or psychological reasons rather than motor reasons, and is associated with dyskinesias and psychiatric side effects. Compulsive medication use has been associated with levodopa use.

A not uncommon problem

The overall prevalence of ICD’s seems to be fairly similar in different studies. In a recent multicentre study from the US based on self-report questionnaires including over 3,000 patients at 46 movement disorder centres, the total prevalence was 13.6% (Weintraub D et al, Mov Disord abstract, 2008).

Dopamine agonists are the most important associated factor

It is quite clear from the literature that ICD’s in the form of pathological gambling, hypersexuality, compulsive shopping and binge eating are associated dopamine agonists. Furthermore, it has been argued that pramipexole, with its higher affinity for D3 than D2-receptors, may be more likely to be associated with ICDs. The majority of data, however, point toward a class effect of dopamine agonists.

ICD’s also occur in other neurological disorders treated with dopamine agonists. For example, in a study conducted in Germany on patients with Restless Legs Syndrome (RLS), 7.4% of patients had an ICD (Voon V et al, in review).

Certain personal characteristics increase the susceptibility for developing an ICD. According to a recently performed multicentre study, factors associated with ICD’s in PD are younger age, higher levodopa use, a family history of gambling problems, current smoking and being single (Weintraub D et al, Mov Disord abstract, 2008). Other studies have reported associations with a personal or family history of alcohol use disorders, experimental drug use, novelty seeking, impulsivity, compulsive behaviours, and depressed mood.

It is possible that PD has a protective role in terms of its neurodegenerative process, with lower novelty seeking and risk taking as a result. Patients susceptible to developing an ICD are thus ‘protected’ until exposed to a dopamine agonist. However, PD may also facilitate the development of ICD’s in terms of cognitive deficits (Fig. 1).

Underlying mechanisms

Sensitisation is believed to play an important role in the development of compulsive medication use. In a
study using pharmacological challenge with levodopa in 8 patients with compulsive medication use and 8 control PD patients, compulsive medication users had greater presynaptic dopamine release in the ventral striatum, but not in the dorsal putamen. The authors’ interpretation was that these individuals are more likely to develop neuronal sensitisation when exposed to pulsatile administration of levodopa (Evans AH et al, 2006).

As neuron sensitisation has been described as a mechanism underlying dyskinesias, the same group also investigated whether or not punding was associated with dyskinesias, and this proved to be the case. The authors suggest that the neural systems mediating the expression of dyskinesias and punding might overlap (Silveira-Moriyama L et al, 2006).

Reward learning is another cognitive mechanism with implications for the development of ICD’s. Phasic dopamine release is believed to act as a teaching signal during learning by coding for prediction error, but may be affected by dopamine agonists. For example, patients with pathological gambling and compulsive shopping on dopamine agonists are better at learning from rewards or gains than from losses. Neuroimaging reveals that these patients have greater striatal activity to prediction errors and predicted outcomes.

These patients have also been shown to be more likely to choose gambles or risky choices over sure choices compared to controls. Neuroimaging shows that pathological gambling patients have striatal hypoactivity when choosing a risky option (Voon V et al, in review).

**Management strategies**

The management of compulsive medication use in the acute phase may require hospitalisation. The goal is to restrict dopaminergic medication gradually in order to manage side effects like mania and psychosis. Management should be multi-disciplinary and, if possible, involve the patient’s family. In the subacute phase, as the dopaminergic dose actually decreases, the risk of withdrawal symptoms must be recognised. The main long-term objective is relapse prevention. Medication should be supervised and management should be multi-disciplinary. Some patients benefit from treatment with continuous administration of levodopa or a longer-acting apomorphine pump, or possibly STN-DBS surgery.

The most important goal for the management of pathological gambling is to decrease or discontinue the dopamine agonist treatment. Switching to another dopamine agonist may also be considered, but whether or not this is actually helpful is a controversial issue. One case report suggests that long-acting rotigotine has also been associated with pathological gambling (Wingo TS et al, 2009). The patient may need treatment for any associated depression, financial and external controls, family intervention and support, and referral to a gambling treatment unit. STN-DBS surgery is a possibility, a multicentre study suggests that this may be helpful as it allows decreases in medication dose (Ardouin C et al, 2006). It is important to bear in mind, however, that patients may get worse during the postoperative phase, with new-onset gambling evident. A greater risk for post-operative suicide attempts may also occur. In a multi-centre study involving 5,025 STN-DBS patients, 0.4 % completed suicide and 0.9% attempted. Suicide attempts were clearly associated with a past history of ICD or compulsive medication use, postoperative depression and being single (Fig. 2).

**Conclusions**

In the development of ICD’s, a range of associated factors interact in terms of neuronal activity, with ventral striatal hypoactivity similar to that of general pathological gamblers. Sensitisation also plays a role, at least in compulsive medication use. Adding a dopamine agonist causes greater striatal activity regarding prediction error, i.e. rewards are seen as better than expected, which is associated with increased risk-taking behaviour (Fig. 3).

**References:**


Evidence-based rehabilitation in Parkinson’s disease: State of the art

The broad variety of clinical symptoms of Parkinson’s disease is only partially treatable by pharmacological intervention, and non-pharmacological approaches are thus highly warranted. Professor Jöbges discussed non-pharmacological treatment alternatives for different symptoms of Parkinson’s disease and presented some general therapeutic guidelines.

According to the Braak staging of Parkinson’s disease (PD), the pathological process spreads well outside of the substantia nigra, affecting several neurotransmitter systems other than dopaminergic ones. Especially in late disease stages, the neuropathological lesions are widespread, explaining the many-fold clinical symptoms. From this point of view, it seems unlikely that the substitution of one single neurotransmitter could treat all manifestations of PD. This also appears to be evident from a clinical perspective, in the later stages of PD, the major causes of the disease are not dopaminergic.

The symptoms of PD most relevant for quality of life are in part resistant to dopaminergic stimulation, and this is the reason why other therapeutic approaches are needed. Good evidence for the effectiveness of rehabilitation programmes exists. For example, in an analysis of 18 published studies on rehabilitation programmes, all but 2 had positive effects. In addition, the effects were sustained for up to 6 months (Horstink M et al, 2006).

For rehabilitation programmes to be truly effective, they must be individually tailored. To accomplish that, we must start by prioritising the symptoms, focussing primarily on the most life-threatening ones, and find techniques to improve them.

Dysphagia – a major cause of death

The prevalence of dysphagia in individuals with PD has been estimated to 80–100%, the severity correlating with disease duration (Coates C, Bakheit AM, 1997). It is one of the most life-threatening symptoms in PD patients and a leading cause of pneumonia. A Swedish community-based study examined a cohort of 170 PD patients and 510 matched controls. Results revealed a shorter survival time for PD patients, with a mortality rate ratio of 1.6 after 9 years. While the primary causes of death in the control population were ischaemic heart disease and cerebrovascular disease, pneumonia was the cause of death in 27 cases (22%) in the PD group (Fall PA et al, 2003).

Even one single swallowing training session can improve swallowing function. In a study including 10 parkinsonian patients, the initiation time of the swallowing reflex (‘premotor time’) was calculated from an electromyogram of the submental muscles. After a training session focused on muscle strength and the Mendelson manoeuvre, premotor time decreased significantly ($p=0.0051$) (Nagaya M et al, 2000).

Another study investigated the effects of Lee Silverman Voice Treatment (LSVT). At baseline, the most prevalent swallowing motility disorders were oral phase problems, including reduced tongue control and strength. In the pharyngeal stage of the swallow, reduced tongue base retraction resulting in residue in the vallecula was the most common disorder. Oral and pharyngeal transit times were prolonged. LSVT resulted in an overall 51% reduction in the number of swallowing motility disorders. Some temporal measures of swallowing were also significantly reduced, as was the approximate amount of oral residue after liquid swallows. In addition, vocal intensity improved (El Sharkawi A et al, 2002).

Postural instability – a common and serious problem

Up to 96% of PD patients experience a decline in postural reactions during the course of the disease (Koller WC et al, 1989).
Parkinsonian patients have problems initiating compensatory steps: their steps are too late, too short and not backwards, so that they cannot find the centre of gravity. A prospective study by Professor Jöbges and colleagues aimed to identify a therapeutic approach for enhancing protective postural responses in PD patients. The 14 participants were aged 41–75 years with PD diagnoses stretching back 9–23 years (Jöbges M et al, 2004).

Postural instability was divided into 2 parts: during standing and during gait, and the respective enlargement of the corrective reactions was identified as treatment goal (Fig. 1). The intervention constituted 2 daily 20 minute-sessions of training compensatory steps.

After the intervention, the length of compensatory steps increased (Fig. 2), and step initiation shortened. Gait analysis showed increased cadence and step length, improved gait velocity, and a shortened period of double support, i.e. the time when both feet are in contact with the ground. All these changes were significant (p<0.05) and stable for 2 months after the end of the training period without additional training. Furthermore, these positive changes resulted in a significant and sustained improvement of the mobility subscore of a quality of life questionnaire (PDQ-39) (Jöbges M et al, 2004).

**Freezing of gait**

Freezing of gait is another common cause of falls. An important first measure is to modify the environment to prevent freezing, e.g. reducing the amount of furniture to make a room less crowded. In addition, several different therapeutic interventions have been investigated.

The Jörg stick, a walking stick with a recumbent step at ground level, can be helpful in overcoming freezing of gait. It is not, however, very good for preventing freezing – taking every step over the Jörg stick may in itself cause falls.

Visual cues are excellent for preventing freezing of gait and increasing stride length, both as a therapeutic approach and at home.

Acoustic cues may be a useful alternative, especially as visual cues cannot be placed everywhere. For acoustic cuing to work, the frequency must be right: too slow may result in no effect and too high, i.e. more than 10% of the individual’s average walking frequency, may lead to even more freezing.

**Other symptoms**

Tremor cannot be cured by a rehabilitation program, but behavioural training has been shown to reduce tremor (Mohr B et al, 1996). The therapeutic principle of tremor reduction is simple: the psychological factors influencing tremor are identified and managed in a behavioural approach manner (Jankovic J et al, 1993).

Good evidence for functional improvement with strength training is available. For example, a study on resistance training and gait function showed that PD patients who underwent resistance training had gains in strength and performance similar to those of normal elderly adults. PD patients also had significant gains in stride length, walking velocity and postural angles compared with pre-treatment values (Scandalis TA et al, 2001).

Some general therapeutic guidelines can be applied to all forms of non-pharmacological therapy aimed at parkinsonian patients (Fig. 3).

**References:**

Speech and voice in Parkinson’s disease

Up to 90% of individuals with Parkinson’s disease develop speech and voice disorders, with deleterious effects on communication, health, psychological well-being, and quality of life. Associate professor Hartelius, a certified speech and language pathologist, described the characteristics of speech and voice disorders in Parkinson’s disease and the current evidence for different types of treatment.

Speech and voice is the product of arguably the most advanced sensori–motor system in the human body (Fig. 1). Nearly 90% of individuals with Parkinson’s disease (PD) develop speech disorders during the course of their illness but only 2–3% receive speech treatment. Speech disorders associated with PD are characterised by reduced voice volume (with a tendency for voice volume to decay over time), poor voice quality, reduced pitch variations, and reduced range of articulatory movements. Many patients also develop a tendency for speech articulation to festinate or rush as well as hesitant and/or dysfluent speech. Furthermore, PD exercises a strong influence on communication even before alterations in intelligibility or motor status become apparent.

Speech analysis
Speech is a complex motor act, and communication between individuals is an even more complex phenomenon. Still, there is an apparent need to measure and quantify the degree and severity of speech and communication disorders.

The two main types of speech assessments are auditory–perceptual analysis and instrumental analysis. An auditory–perceptual analysis is based on recordings and can be done blindly, but the method has questionable reliability. Instrumental analysis, e.g. acoustic analysis, is a more reliable measure and gives more precise measurements. For example, it permits measuring aspects of speech that are not yet audible or measurable in other parts of the body, and has therefore been described as a potential biomarker of early disease progression.

Speech intelligibility can be a major concern
Perceptual and acoustic analyses, however, only measure the impairment aspect of the speech disorder, not its consequences in terms of intelligibility and the listeners’ ability to take part in different life situations. In a study of 125 PD patients and age-matched controls, almost 70% had decreased intelligibility, i.e. they were not very well understood by listeners. The decrease was not dependent on disease severity, duration or motor phenotype, and the patients’ own perceptions of the extent of change did not necessarily reflect objective measures of intelligibility. As many as 47 patients (38%) placed speech changes among their top four concerns regarding their PD (Miller N et al, 2007).

There is also a strong perception of negative impact on communication between ‘before’ and ‘now’. This has been demonstrated in another study by the same group, including 176 people with PD and their carers. The perception of negative impact proved to be irrespective of age and gender, and largely independent of disease severity, duration, and intelligibility (Miller N et al, 2008).
Effects of pharmacological and surgical interventions

Traditionally, speech disorders in PD have been attributed to dopamine deficiency and muscle rigidity. Supporting this assumption is some evidence for improved speech function with levodopa treatment, but with great variability in group results (Ho AK et al, 2008). Other studies suggest alternative etiologies, e.g. deficits in internal cueing, scaling movement force and amplitude, sensori-motor gating, or even self-perception of voice.

The effects of deep brain stimulation of the subthalamic nucleus (STN-DBS) on speech are varied and inconclusive. Dysarthric symptoms frequently appear as side-effects and pre-existing dysarthria can be worsened. Dysarthria is reported as an adverse side effect in as many as 4–17% of patients (Benabid AL et al, 2009).

The variability in reported effects of STN-DBS on speech may be accounted for by a number of factors, including disease-specific variables, type and degree of dysarthria before surgery, and stimulation-related variables such as location of electrodes, amplitude and frequency of stimulation. Recent findings suggest that other stimulation sites may be more promising in terms of speech effects.

In a German study (Klostermann F et al, 2008), the speech and motor functions of 19 PD patients with bilateral STN-DBS were studied in stimulation on and off mode. The results showed a significant worsening of speech performance (Fig. 2).

The effects of repetitive transcranial magnetic stimulation (rTMS) on vocal function have been investigated in a study on 30 patients with PD, using active or sham 15 Hz rTMS of the left dorsolateral prefrontal cortex, and with acoustic and perceptual voice analysis performed by a blind rater. Active treatment was demonstrated to improve voice fundamental frequency (Dias AE et al, 2006). Longitudinal studies are needed to assess long-term therapeutic and side effects of rTMS.

Laryngosurgery is another possible treatment alternative, albeit temporary. One study has demonstrated the use of vocal fold injection of collagen with positive results in 5 of 6 patients. The authors concluded that laryngosurgery is a safe, well tolerated and effective temporary method of subjectively improving voice and speech in selected PD patients (Sewall GK et al, 2006).

Behavioural treatment – proven efficacy

Reasonably strong evidence suggests that treatment of global speech parameters such as loudness, rate, prosody or general instructions such as ‘clear’ speech is effective for PD patients with dysarthria.

The strongest evidence regarding treatment effectiveness is for modification of loudness, specifically the LSVT (Lee Silverman Voice Treatment) LOUD protocol (www.lsvt.org). LSVT is an intensive 4-week programme including 16 individual training sessions. Treatment effects are sustained at follow-up after 1 and 2 years. The technique is simple, basically just teaching the patients to think loud and training them to phonate as intensely as possible. By going beyond their own voice calibration and acting like they do when shouting, patients not only improve audibility, the effects are also generalised to improve intelligibility, articulation, swallowing, communicative gestures, and even neural functioning (Sapir S et al, 2008).

To conclude, there is an urgent need for clinical practice guidelines including speech, language and swallowing assessment and intervention for individuals with PD, and many patients are helped by early referral to a speech and language pathologist.

References:

Parkinson’s disease (PD) is a highly complex disease, and awareness that motor symptoms represent only the tip of the iceberg is gaining ground. What most concerns patients are the non-motor symptoms: pain, depression, sleep disturbances, autonomic failure, cognitive decline, etc. – symptoms that to a large extent determine quality of life and that do not respond very well to medication or stereotactic neurosurgery. Awareness that treatment must be individually tailored to the different subtypes of PD is also increasing.

Like the disease, the care for PD patients is complex, and although the patient should be at the centre of it (Fig. 1), this is not always the case.

Compensation with physiotherapy
Physiotherapy cannot cure PD, but it can help compensate for many of its manifestations, and good scientific evidence now supports this viewpoint. For example, auditory and/or visual cues can significantly improve gait by bypassing defective basal ganglia circuitry. Even just removing furniture from a crowded room can be very helpful.

Many PD patients find clever solutions to their problems, solutions that can also be helpful to others. One example is an engineer who had difficulties walking in his garden. He invented a ‘walking ladder’ with low steps laid out in the grass. A former badminton champion who could not release the shuttle could do this by lifting his hand twice prior to release. A man who had difficulties rising from a chair found he was helped by pushing his right arm forward and then making the rest of the body follow it.

The everyday application of physiotherapy has, however, several weaknesses. One problem is poor communication between health-care professionals. We sometimes do not speak each other’s languages, and we are frequently unaware of whether or not another professional is involved in giving the patient some form of therapy.

Another weakness is that patient referral is inadequate. We see too many false-positive cases, which is a waste of time and resources, as well as too many false-negatives, resulting in people with a real need of physiotherapy not being referred.

A third weakness is the lack of expertise among physiotherapists. They have no specific training regarding PD, there are no established guidelines, and most therapists have too few patients to build-up sufficient experience. Some physiotherapists do, of course, have excellent knowledge and experience, but they can be hard to find.

The Dutch experience
In order to strengthen the health-care chain and improve the care given to PD patients, Parkinson Center Nijmegen (ParC) has built-up a system for periodic referral to a multi-disciplinary team as well as for delivery of adequate care close to the patient (Fig. 2).

The system gives every patient the opportunity to periodically visit an expert for assessment and advice, while regular care is provided within the immediate vicinity of the patient’s home. The ParkinsonWeb is a...
The Dutch experience consists of periodic multidisciplinary assessment in a tertiary referral center (ParC), adequate delivery of care within the immediate vicinity of patient’s home (ParkinsonNet), and optimal communication between different health professionals (ParkinsonWeb) (Bastiaan Bloem, 2009).

A platform comprising several information and communication technologies used to facilitate communication and make the system effective.

Most importantly, the patients are made co-producers of the health-care system and they participate actively on an equal level, rather than being just passive care-consumers. One example of this collaborative care is the use of electronic files that the patients complete at home.

ParC – a service centre

The key word at ParC is service, not only to the patient and the family but also to referring colleagues, a referring neurologist is a client, and as such should be treated well. For this purpose, the specialists at ParC use an electronic agenda by which neurologists at surrounding hospitals can make appointments while the patient is present. This is highly appreciated by both patients and colleagues.

Prior to visiting ParC, patients are asked to complete a detailed questionnaire and to list their major problems. This list dictates the programme for the visit and the specialists that each patient needs to meet. It all takes a great deal of planning, but if done a few weeks in advance it works out quite well.

Multi-disciplinary meetings are held every morning, where each patient scheduled that day is discussed for 10 minutes. This has really been a key to success, yielding lots of information. During these meetings, the different specialties have learnt to speak each other’s languages.

The final consultation with the patient is without a desk, without hierarchy, and the spouse is asked to participate.

After visiting ParC, patients are asked to rate the different specialists they have met during the day by filling in a questionnaire on the ParkinsonWeb. This way of making caregivers purposely vulnerable makes the system highly transparent: if a physiotherapist is rude to a patient, it immediately shows up on the web.

ParkinsonNet – health-care close to the patient

ParkinsonNet consists of a selected group of physiotherapists, occupational therapists and speech therapists who have been specially trained and who work according to guidelines. The selection ensures that in addition to special training, these specialists also get to see sufficient PD patients to maintain, and to extend, their knowledge. This expertise is also made visible, for example, by information brochures for each regional ParkinsonNet network and on the website. This way, patients have a selection of experts in the region from which they can choose.

Quality indicators for the experts are also used. Patients can hand out warnings if a physician or therapist does not live up to their expectations. After 2 warnings, the specialist is excluded from the network.

ParkinsonWeb – facilitates communication

ParkinsonWeb is designed for information, education, communication, and electronic patient files. For health professionals, one practical application is a virtual learning community. A forum where patients can address their questions is also included.

It is a common notion that information and communication technology is only for the young, but older people seem to be especially happy about it. Furthermore, electronic patient files seem to suit PD patients particularly well as they can enter information at their own pace, at home. In addition, it saves a lot of time for the caregivers.

The electronic patient files are also used to implement guidelines. Of course, guidelines are not mandatory and each specialist must be allowed to make decisions based on individual reasons, but if the patient is not helped by the measures taken, the specialist must be able to defend those decisions.

The effects of using electronic guidelines for decision-support and for benchmarking the quality of the network have been investigated in a recently performed, as yet unpublished study including 705 patients allocated to either ParkinsonNet or usual care. Results show that with ParkinsonNet, the number of patients per therapist increases steadily over time and that the health-care professionals’ knowledge of PD increases significantly. Furthermore, costs are reduced, primarily owing to skilled therapists in the community obviating the need for expensive care at rehabilitation centres, thereby bringing about a shift from more expensive in-patient treatment to cheaper community care.
Great potential
Reducing health-care costs simply by organising care in a more opportune way can help manage the tremendous increase in health costs that we are facing. The Dutch Ministry of Health, among others, has shown great interest in the project and recently allotted funding for its further development. The project has won several awards over recent years and obtained Pearl Status in 2009.

Patient examples
Professor Bloem finished his presentation with an interactive video session in phenomenology and instructive cases, thereby truly illustrating the complexity of PD. He also gave examples of common differential diagnoses and their characteristic features.
From Diagnosis to Management of Parkinson’s Disease