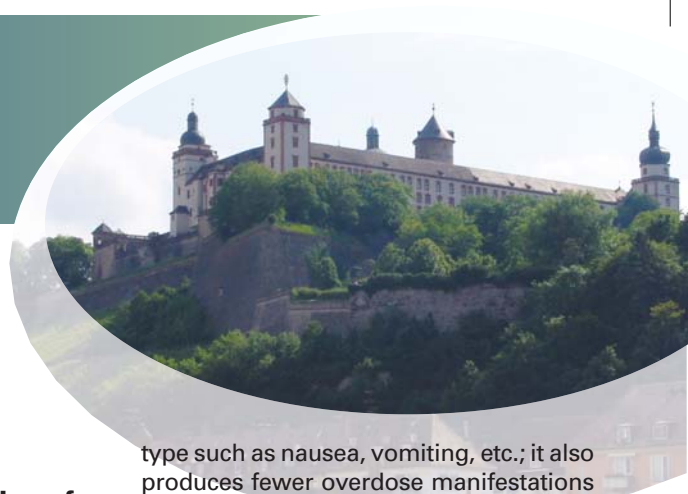


# Parkinson's Disease and Restless Legs



Highly effective in double-blind clinical trials

## Lisuride patch effective and available in a near future

Dopamine agonists have greatly expanded the treatment options for Parkinson's Disease and, in the meantime, have also become the first choice therapy for Restless Legs Syndrome (RLS). With the lisuride patch (Axxonis Pharma AG), which works over a period of two days, a highly effective representative of this substance class will be available in the future in the form of well-tolerated patch. Decades of experience with this proven dopamine agonist and current targeted studies show definitively that this ergot derivative – in contrast to cabergoline and pergolide – is not associated with any increased risk of heart valve fibrosis, as reported by experts at the 39th International Danube Symposium in Wuerzburg.

Dopaminergic therapies have almost normalized the life expectancy of Parkinson's patients in the last 40-50 years, but not their quality of life, as portrayed in the symposium chaired by the university professor and doctor of chemistry Peter Riederer, Wuerzburg. In later disease stages, patients' lives are especially impaired by functional disabilities and complications associated with L-dopa such as dyskinesia and fluctuations in efficacy. Since many transmitter systems are damaged, a drug therapy that acts at several levels could be advantageous or even necessary, according to Dr. Reinhard Horowski, Berlin.

### The pioneering substance lisuride

Lisuride, developed in 1959, is a partially synthetic ergoline derivative, which interacts with a multitude of monoamine receptors. The strong, agonistic effects on D<sub>2</sub> and D<sub>3</sub> receptors are the basis of its efficacy in Parkinson's Disease and RLS. Its action as an agonist to 5-HT<sub>1A</sub> receptors and an antagonist to α<sub>2</sub> receptors seems to have a positive influence on the effect profile. Lisuride may also have neuroprotective effects in humans. In cell cultures, it protects from free radicals and glutamate excitotoxicity (see also the interview on page 4). Lisuride, which has been used in tablet form to treat Parkinson's disease since 1989, is not

known to have any active metabolites and interacts only to a limited extent with the CYP-450 liver enzymes.

### "Kinetics matters"

Its half-life of 2-3 hours and its physicochemical properties make lisuride "an excellent candidate" for controlled delivery, according to Horowski. The innovative patch form achieves a steady release of the active agent over a period of 48 hours. In particular, the pharmacokinetic advantages consist of the avoidance of the first-pass effect and a sustained, high bioavailability with steady plasma levels that have a positive effect on both the night and on morning "off" times. Transdermal application also produces few initial side effects of the dopaminergic

type such as nausea, vomiting, etc.; it also produces fewer overdose manifestations (e.g. dyskinesia) than oral application. Adverse events, as a rule disappear quickly after patch removal.

### Important: no valve fibrosis

In Wuerzburg it was emphasized that, also after evaluation of all available sources, not a single case of fibrotic heart valve changes has ever been reported for lisuride. The scientists attribute this to different receptor profiles of the ergot derivatives; in contrast to cabergoline and pergolide, which stimulate the apparently pathogenetically involved 5-HT<sub>2B</sub> receptor of the heart, lisuride is not an agonist, but a strong antagonist at this serotonin receptor subtype. This has been demonstrated in experimental studies (Fig. 1). Additional details are explained in a poster (see pages 2/3).

### High degree of efficacy confirmed

Lisuride is an established treatment of Parkinson's Disease for decades now. Already in earlier clinical trials, oral lisuride or lisuride administered by subcutaneous minipump had resulted in a dose reduction of L-dopa as well as reduced or delayed the occurrence of motor fluctuations, end-of-dose akinesia and dyskinesia or had improved these complications and reduced patients' "off" times. In a prospective 10-year study of 90 newly diagnosed Parkinson's patients (U.K. Rinne, *Nervenarzt Suppl.*, 1999), the lisuride combination also resulted in a lower mortality rate in comparison to L-dopa alone (13/30 vs. 13/55 patients), but the difference was not statistically significant.

### CDS-compliant therapy

The intermittent oral administration of substances with a short half-life such as L-dopa lead to fluctuating plasma levels and a pulsatile stimulation of the dopamine receptors in the striatum,

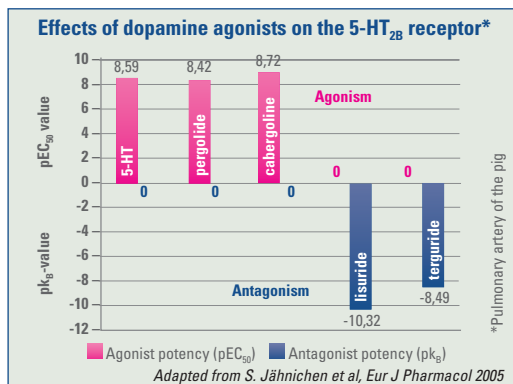


Fig. 1: In contrast to the agonistic effect of cabergoline and pergolide, lisuride is a pure antagonist to the 5-HT<sub>2B</sub> receptor.

### New lisuride patch for RLS

# Superior to an oral dopamine agonist in clinical endpoints

**Because of low awareness in the general public (and in the medical profession as well), many RLS patients currently remain without adequate therapy. It has now been shown in a double-blind comparative study that the lisuride patch, successfully tested in Parkinson's patients, is highly effective also for RLS patients – and that it is superior to an oral, non-ergoline dopamine agonist in a number of relevant clinical parameters.**

Current RLS medications, approved on the basis of randomized studies, include L-dopa and the oral non-ergoline dopamine agonists pramipexole and ropinirole. Whilst the ergot derivatives pergolide and cabergoline are no longer under development, approval will be sought next year or the year after next for the two dopamine agonists lisuride and rotigotine in patch form, according to *Prof. Ralf Kohnen*, Nuremberg. Non-evidence-based treatment options include agents such as gabapentine, opioids and benzodiazepines.

L-dopa is used primarily for less frequent or lighter symptoms (IRLS scale  $\leq 15$ ) "as-needed" at doses of up to 200 mg/day since the danger of augmentation is obviously lower at lower doses. For moderate to severe RLS (IRLS  $> 15$ ) or in cases of augmentation under L-dopa, dopamine agonists now are the therapy of first choice.

### Patch versus tablets

The comparison of various RLS therapy studies showed, according to Kohnen, that ropinirole and pramipexole were more effective than placebo in reducing total IRLS scores (by -3.0 and by -4.7), but that both patch preparations achieved "significantly greater effects" (-8.8 for lisuride; -8.3 for rotigotine). *Kohnen* has now presented "brand new data" from a first-time three-arm RLS study: in TULIR-03, a double-blind, flexible-dose study (*Beneš et al., publication in preparation*), after 2:1:1 randomization patients received lisuride as a patch with a surface area of 10, 20 or 30 cm<sup>2</sup> (0.1, 0.2 or 0.3 mg release per 24 hours), which was changed every other morning, oral ropinirole in a dosage range of 0.5-3.0 mg/day, or placebo (using a "double dummy" procedure), all over a twelve week period. In the end, 300 patients were evaluable.

### Improvement after eight days

Following an eight-week titration period, which was necessary due to ropinirole application guidelines, the total IRLS score showed a significant improvement in symptoms after just eight days in both verum groups. Additional score decreases revealed the greatest reduction in RLS symptoms ( $p < 0.001$ ) on Day 85 in the group with the lisuride patch ( $n = 148$ ) with -14.6 points as compared to baseline, while scores were reduced by only 11.6 points ( $p = 0.003$ ) with ropinirole (placebo: -6.9). In this endpoint, the difference between lisuride and ropinirole was just short of significance, but yielded a trend ( $p = 0.076$ ).

### More responders with lisuride

The lisuride group fared even more favorably, however, in the analysis of the



*Professor Ralf Kohnen, Director of IMEREM and leading RLS expert, explains RLS and its treatment.*

'responder' patients with a more significant difference (IRLS reduction  $> 50\%$  vs. baseline). While 41.3% responded to ropinirole, the responder rate for the lisuride patch was 56.1% ( $p = 0.047$ ). The percentage of responding patients in comparison to baseline was significant for lisuride, but not for ropinirole ( $p < 0.001$  vs.  $p < 0.059$ ); 26.0% of the patients responded to placebo.

Adverse events such as nausea (19.7 vs. 35.9%), fatigue (11.2 vs. 17.9%) and headache (6.6 vs. 14.1%) were less frequent with the lisuride patch than with ropinirole. Local skin reactions were more frequent in the lisuride group (24 vs. 5.1%) and also the most frequent reason for treatment discontinuation due to side effects in the verum patch group (13.2 vs. 1.3%).

No cases of augmentation have been recorded up to now with the lisuride patch. Transdermal preparations such as the lisuride patch due to their continuous release of the active agent could prove to be a promising option also in patients with augmentation, said *Kohnen* in Wuerzburg.

## Etiopathogenesis of fibrotic valve changes: no influence of lisuride

**With the appearance of valvulopathies under dopamine agonists, which has caused the current downgrading of cabergoline and pergolide to second-line medications for Parkinson's therapy, we are probably not seeing a class effect of the ergot derivatives. The reason for the absence of this serious side effect under lisuride apparently is its antagonistic activity with regard to 5-HT<sub>2B</sub> receptors. Details on the current understanding of the induction of fibrosis by different medications were explained by Dr. Klaus Peter Latté, Berlin, at the International Danube Symposium.**

In the poster\* presented, the risks resulting from the activity of the different ergoline dopamine agonists on the trophic serotonin 5-HT<sub>2B</sub> receptor were investigated using the available data. Both of the 8 $\beta$ -substituted ergoline derivatives cabergoline and pergolide were proven to be potent agonists to the 5-HT<sub>2B</sub> receptor in assays involving both cloned cells and tissues. In contrast, there was no agonistic activity for the 8 $\alpha$ -substituted ergoline derivative lisuride. Rather, it was shown in experiments on both the

fundus of the stomach of rats and the pulmonary arteries of pigs (*see Jähnichen et al., Eur J Pharmacol, 2005; see Fig. 7, page 1*) to be a pure and potent antagonist to this receptor subtype. It actually appears that 8 $\alpha$ - or 8 $\beta$ -substitution is a structural determinant as to whether an active agent has an antagonistic or agonistic effect here.

*R. Schade et al. (NEJM, 2007)*, who investigated bromocriptine, cabergoline, pergolide, lisuride, pramipexole and ropinirole in a population-

which favors the development of motor fluctuations and dyskinesia. According to the concept of continuous dopaminergic stimulation (CDS), the delay or even prevention of these complications is achieved by a more consistent availability of the agent in the brain and a physiological, "tonic" receptor stimulation. Therefore, dopamine agonists are the preferred initially recommendation for the early stages of Parkinson's Disease. The guidelines of the German Society of Neurology (Deutsche Gesellschaft für Neurologie [DGN]) recommend them as an initial monotherapy for all patients under 70 years of age who have no significant comorbidity. In addition to the continuous subcutaneous infusion of lisuride through a mini-pump, which can be a good option for severely disabled patients and is currently being investigated in the CALIPSO study, the patch, with its stable plasma levels, complies with the CDS principle.

## Results of the TULIP IIb study

Current studies provide impressive confirmation of the therapeutic benefit of the lisuride patch. In Wuerzburg, Horowski presented the results of the double-blind TULIP IIb study (Poewe *et al.*, publication in preparation) over 14

based study (n = 11,457), found that among these dopamine agonists, only pergolide and cabergoline show an elevated incidence of diseases of the mitral, tricuspid and aortic valves (7.1 and 4.9 resp.). This increase in risk also is in line with the results of earlier echocardiogram studies on Parkinson's patients (e.g. R. Zanetti, *NEJM*, 2007).

The search of a database representing an experience base of 360,000 patient years revealed in the last 30 years no cases of heart valve disease associated with lisuride treatment (C. Hofmann *et al.*, *Clin Neuropharmacol*, 2006). These authors also point out the antagonism of lisuride to the 5-HT<sub>2B</sub> receptor. Bryan L. Roth recently attributed a key role to 5-HT<sub>2B</sub> activation in the induction of fibrosis in an editorial (*NEJM*, 2007).

\* K.P. Latte, B. Schurad, R. Horowski: Lisuride, a dopamine agonist, is a potent serotonin receptor antagonist and is not connected to valvular heart disease. Poster presentation on June 3, 2007 in Wuerzburg

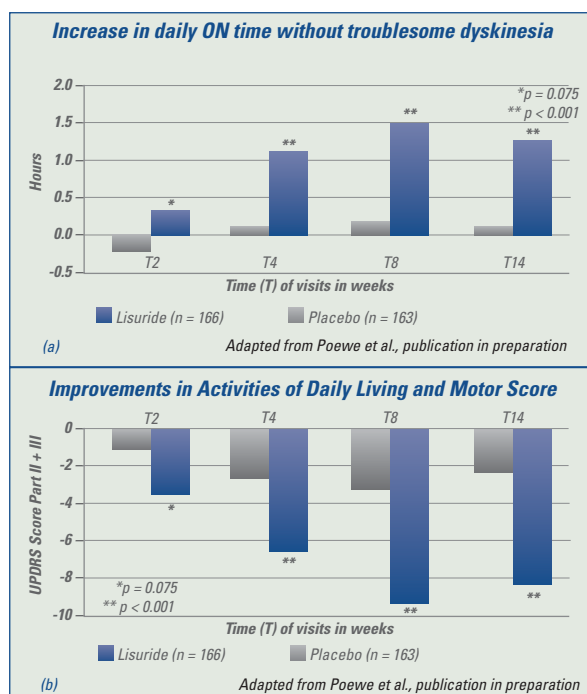


Fig. 2a/2b: The lisuride patch (2 x 20 cm<sup>2</sup> every other evening) significantly improves the daily ON time (a) as well as the Activities of Daily Living (Part II) and Motor Score (Part III).

weeks. The 333 patients in advanced stages of Parkinson's Disease suffered from pronounced "off" times of at least 2 hours daily or 6 hours over 3 days and the majority also suffered from dyskinesia despite optimised oral therapy with L-dopa (plus COMT and/or MAO-B inhibitors in individual cases). They received one or two lisuride patches (20 cm<sup>2</sup>) or a placebo patch every 48 hours.

## Very rapid onset of effect

In these everely ill patients, the result in the lisuride patch group (n = 166) versus placebo (n = 163), in the primary end point, was a reduction in the daily "off" time compared to the baseline with a significant therapeutic effect after just two weeks ( $p < 0.016$ ) that further increased with ongoing treatment. After 14 weeks, the daily "off" time reduction in comparison to the baseline was more than 1.5 hours. In comparison to the placebo, it was more than 1.2 hours ( $p < 0.001$ ). At the same time, the "on time without troublesome dyskinesia" increased significantly ( $p < 0.001$ ) (Fig. 2a). The UPDRS scores for Part II (Activities of Daily Living) and Part III (Motor Score) as well as both scores combined also signifi-

cantly improved with the lisuride patch at the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, and last test point in comparison to the placebo (Fig. 2b). At the end of the study, the patients' quality of life was also significantly higher according to EQ-5D VAS scores in comparison to the placebo ( $p < 0.001$ ).

## Lisuride is well tolerated

Dopaminergic side effects such as nausea, vomiting and orthostatic reactions were even less frequent numerically in the lisuride group than in the placebo group (4.2 vs. 5.4%). A mild somnolence was reported in 3.0 vs. 1.8% of patients, and hallucinations were reported in 5.4 vs. 1.8% of patients. Local skin erythema was the most frequent side effect with lisuride and occurred in 28% of patients (placebo: 4.2%). These improved without treatment and were of the non-allergic type; and some of them showed only a minimal amount of pruritus, for example, according to Horowski. Severe adverse events requiring hospitalization were, again, more frequent with the placebo, with 5 vs. 11 cases. For another side effect of dopamine agonists that has recently been the subject of intense discussion, Horowski was also able to report something positive – pathological gambling has not yet been reported with lisuride.

## Conclusion: a patch with a future

With lisuride, a well-tolerated dopamine agonist, proven over years of use and now available in the form of a patient-friendly, CDS-compliant patch will now be submitted for approval for the treatment of Parkinson's Disease and RLS. In both indications, lisuride, which might also be neuroprotective, is highly effective for reducing symptoms. Heart valve fibrosis and other new or serious side effects are not to be expected. The lisuride patch is expected to become available in 2009. ■

You can find additional information on lisuride, the concept of "continuous dopaminergic stimulation" and current studies on the internet at [www.lisurid-cds.de](http://www.lisurid-cds.de).



University professor and doctor of chemistry Peter Riederer, Würzburg, is one of the pioneers in neuroprotection research.

## Advances in Parkinson's treatment

# "We need multifunctional substances and must treat PD earlier"

An interview with university professor and doctor of chemistry **Peter Riederer**

**The actual cause of the idiopathic Parkinson's syndrome is still unknown. What factors contribute to the dying off of the dopaminergic neurons and therefore to the progression of the disease?**

There are different approaches to this issue: both the genetic approach, which is a hot topic at this moment, as well as pathogenesis through environmental toxins such as lead, manganese, etc. . These forms, however, which make up a maximum of only 1% of the total, affect only a tiny minority of Parkinson's cases. For the remaining sporadic forms, we currently assume one of the causes to be endogenous disorders of the mitochondrial respiratory chain with loss of the energy carrier ATP. Defects in the breakdown of proteins, i.e. in the proteasome function, have also been demonstrated. Both possible explanations can be combined in the very attractive "oxidative stress-proteasome hypothesis".

**What causes the oxidative stress and what processes are responsible for the damage?**

The lack of energy means that the endogenous hydrogen superoxide does not break down into water, but instead interacts with free iron, for example, leading to the formation of radicals, i.e. reactive oxygen species that contribute to degeneration through lipid peroxidation and oxidation of membrane proteins. This is one of the most important mechanisms currently being discussed. The vulnerability of Parkinson's patients to oxidative stress could be due to reduced activity of enzymes that detoxify oxygen radicals.

**How do you evaluate the possibilities of neuroprotective interventions?**

Here we must differentiate. Preclinical neuroprotection and neurorestoration by different substances has been demonstrated very clearly. However, clinical implementation is very difficult. Since even in the earliest clinical phases of the illness an "end stage" with a multi-transmitter disorder is already present, we are always very late with our clinical neuroprotection stu-

dies. But since the first retrospective study of Birkmayer on selegiline in the years 1983-85, the design of clinical neuroprotection studies has improved by considerably.

From a therapeutic viewpoint, we are now going back to the so-called multifunctional substances. These substances, rejected earlier as "dirty drugs", should work not only against disorders of the dopaminergic system, but also those of the "co-degenerating" cholinergic and glutamergic systems that are responsible for many psychic, autonomic and other non-motor problems of patients and which contribute to the deterioration of their quality of life. We need these multifunctional substances – and we must start treatment earlier.

**You and Walther Birkmayer have made significant contributions to the development of lisuride. With which aspects were you especially involved?**

In the years 1976/77 – apomorphine was not yet being used as a therapy at this time – we have been the first to use successfully lisuride intravenously, e.g. for the resolution of akinetic crises, on-off fluctuations and in "burned out" cases. And clinically, we had very good, positive experiences; we were greatly encouraged by the patients' rapid response. Lisuride was actually the first parenterally administered substance used in these situations; the subcutaneous pump was the next logical development. Now comes the patch.

**What advantages are offered by the patch application with its continuous release of active agent?**

First of all, use of the patch once a day or every second day is simpler for the patient. A critical advantage is that a continuous stimulation can be built up and that the first-pass effect in the liver is avoided, i.e. more unmetabolized active agent reaches the circulation. The transdermal application is an advantage for the maintenance of mobility during the night as well, and therefore for a reduced problem of waking up.

Furthermore, it is possible to quickly react to any side effects by removing the patch, in contrast to oral dopamine agonists with half-lives which often last several hours or even a few days.

**In the meantime, the dopamine agonists are the first treatment option for many Parkinson's patients and for (moderately to severe) RLS. What does the receptor profile of lisuride look like, and how do you evaluate the significance of the transdermal preparation for these indications?**

Lisuride has a different effect profile from the other ergoline dopamine agonists and the non-ergoline dopamine agonists rotigotine, ropinirole and pramipexole as well. Lisuride is one of the substances with the greatest affinity for the D<sub>2</sub> receptor in the human striatum and also has a D<sub>1</sub> agonist effect. It also has an activating effect on the D<sub>3</sub> receptor with possible positive results, e.g. on emotional regulation.

Lisuride also has the advantage of being a 5-HT<sub>2B</sub> antagonist. This represents a favorable receptor profile, in contrast to the much discussed fibrosis problem observed among some ergot derivatives, which must be taken into consideration in RLS patients as well. The application has considerable advantages in the treatment of both RLS and Parkinson's syndrome. In the final analysis, the patch is the simpler and better application method.

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