

NICERGOLINE IN THE TREATMENT OF DIZZINESS  
IN ELDERLY PATIENTS. A REVIEW

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SUMMARY

In elderly patients, dizziness occurs very frequently with significant effects on the patient's life. Its frequency increases with age, and may arise from a variety of causes. Chronic dysequilibrium in elderly patients is most probably related to disturbances within the central nervous system, due either to altered neuronal functions or to an underlying vascular disease. Nicergoline, a drug used in the treatment of cognitive disturbances in geriatric patients, improves dizziness in elderly demented and non-demented patients. In a double-blind, placebo controlled trial the drug improved (i) the severity of symptoms, measured by the dizziness assessment rating scale (DARS), (ii) the overall clinical conditions revealed by global impression scale, and (iii) the perceived quality of life estimated by the dizziness handicap inventory (DHI). These results indicate a possible positive effect also on posturographic measures. Moreover, the improvement occurred at no expense of the established strategy of postural control suggesting that the effect is mediated by a substitute compensatory mechanism allowing the patient to preserve consolidated postural strategies. The results of previous open clinical studies in about 3000 patients are in agreement with those findings. Overall, severity of symptoms decreased by 68 % (57 % in the control study). Globally, the results indicate a beneficial effect of nicergoline on symptoms related to balance disorders of central origin. Animal studies show that the drug displays a broad spectrum of actions on cellular and molecular mechanisms. Moreover, animal research specifically aimed at vestibular pathophysiology has revealed that nicergoline improves vestibular compensation in models of vestibular lesion. Chronic treatment with nicergoline improved the time-course of behavioral recovery in old rats after hemi-labyrinthectomy and counteracted the regulation of cholinergic receptors observed after lesion in old rats. Nicergoline interacts at several levels by various mechanisms, from the molecular level to cognitive function, probably enhancing spontaneous plasticity phenomena underlying the central vestibular compensation. This effect is not dependent from the interaction with a single-transmitter-identified neural pathway, but from anatomical, functional and neurochemical synergistic adjustments in several brain areas.

Keywords: dizziness in elderly, vestibular compensation, nicergoline treatment

## INTRODUCTION

Dizziness occurs frequently in the general population. It has been estimated in the USA that 3,200 patients out of 100,000 new cases/year visit a primary care physician because of this complaint (Sloane, 1989). About 13-30 % of adults had experienced at least one episode in their lifetime (Hoffman et al., 1999). Moreover, 3.5 % of adults experience a chronic recurrent episode longer than a 1-year duration by the age of 65 years. As a presenting problem in primary care, dizziness increases in frequency with age, so that it is the 4th most common neurological complaint of geriatric patients (Colledge et al., 1996) and also the web-site

<http://www.geriatricsyllabus.com/syllabus/main.jsp?cid=SCC-CER-1#chapter2>

In the old age, dysequilibrium seems to be related to multiple etiology suggesting an altered control of different subunits of the balance system. Vestibular compensation is a complex process (Curthoys and Halmagyi, 1995; Curthoys, 2000), based on substitutive mechanisms bound to reduce the functional redundancy of the balance system as a whole. In elderly patients, small deficits of various subunits occur during the years and force the system to compensate, thus progressively reducing its redundancy. Therefore, requests moderately impeding on the system, as walking in a poorly lighted room, may seriously impair the control procedures of the balance mechanisms. Dysequilibrium is associated with frequent falls or with concern about falling and with an increased prevalence of disability as well (Aggarwal et al., 2000). In elderly people vascular disease may be the most important pathophysiological clinical finding (Colledge et al., 1996) suggesting a more frequent occurrence of a central impairment for dizziness in old age.

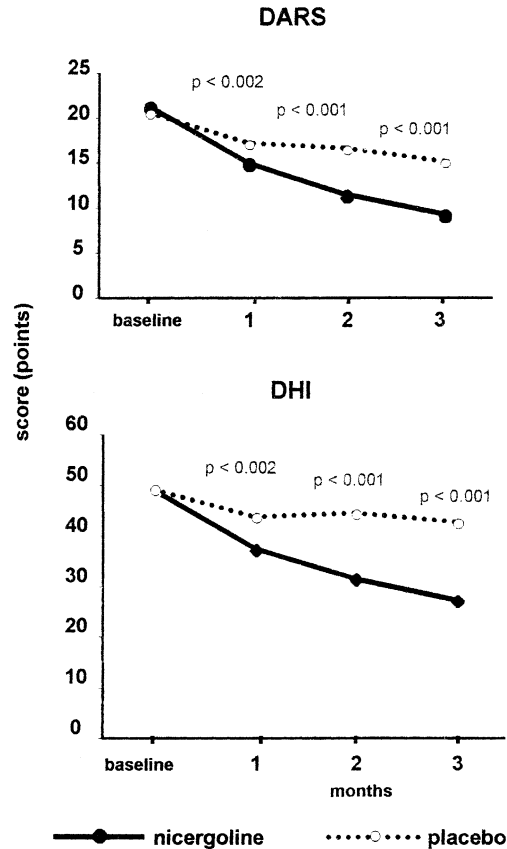
Nicergoline (Sermion®) is a drug widely used in the treatment of dementia. Significant improvement of cognitive symptoms and overall clinical conditions have been observed in a number of placebo-controlled clinical trials in mild to moderately demented patients (Fioravanti and Flicker, 2002). Moreover, the drug was shown to have a consistent positive effect on concurrent symptoms of vertigo and dizziness (Saletu et al., 1995; Herrmann et al., 1997; Nappi et al., 1997). Animal studies indicate that the drug is endowed with a broad spectrum of actions on cellular and molecular mechanisms. Whether these effects are inter-related or represent multiple, unrelated properties, is still unclear. The drug increases the regional cerebral blood flow (rCBF), glucose uptake and utilization, activates protein synthesis, enhances cholinergic and catecholaminergic neurotransmitter functions and improves

age-related cognitive deficits, stimulates phosphoinositide turnover, modulates translocation of protein-kinase C (PKC) and PKC-mediated  $\alpha$ -secretase processing of amyloid-precursor protein. It protects neurons from death induced by oxidative stress or apoptosis, and interacts with endogenous nerve growth factor-mediated processes, providing trophic support to cholinergic neurons (Winblad et al., 2000).

The specific effect of nicergoline in the treatment of vestibular disturbances has been investigated in a number of clinical studies (Pignataro et al., 1990; Felisati et al., 1993, 2002; Mira et al., 1995). They were focused on elderly patients presenting dizziness (unsteadiness, lack of balance, feeling of antero- or latero-pulsion, etc.) as the main symptom. The clinical observations are corroborated by interesting preclinical findings indicating a protective effect of the drug in the mechanisms involved in vestibular compensation (Giardino et al., 1997, 2002; Winblad et al., 2000).

## RESULTS

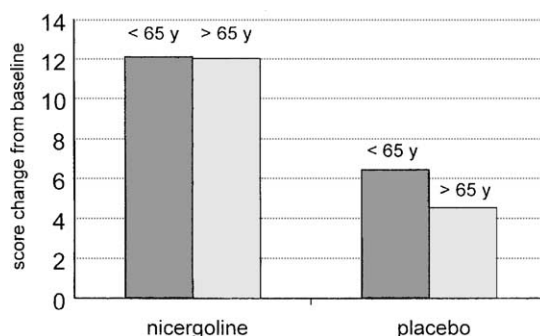
In a prospective, randomized, parallel group, double blind, placebo-controlled trial (Felisati et al., 2002), 86 patients of mean age  $67.1 \pm 7.8$  years, ranging 50-85 years, have been treated with nicergoline (30 mg orally, twice a day) for 3 months or with matching placebo. Inclusion criteria specified presence of equilibrium disorders of central origin on the basis of a complete clinical and instrumental oto-neurological examination. The patients were evaluated at baseline and then monthly by the dizziness assessment rating scale (DARS) (Felisati et al., 1991) and by the dizziness handicap inventory (DHI) (Jacobson et al., 1991). The results of this study showed that nicergoline improved clinical symptoms, as measured by a significant score reduction of DARS and DHI ( $p < 0.001$  vs. baseline and placebo) (Figure 1 and Table I). Response rates were also in favor of nicergoline treatment. Moreover, nicergoline treatment was equally effective in the patients older than 65 years and in younger patients. On the contrary, elderly placebo treated patients exhibited the worst response compared both to younger placebo patients and nicergoline patients in both subgroups (Figure 2). Coherent significant changes from baseline of various posturographic parameters (Guidetti, 1996) were observed only in the nicergoline group. Significant improvement was observed in 3 out of 4 main posturographic variables in nicergoline group and only 1 in placebo patients (Figure 3).



**Figure 1.** DARS and DHI score reduction was significantly greater in nicergoline group already since the first month of treatment and the difference from increased during study. (Felisati et al., 2002) The score changes of DARS and DHI correlated significantly (not shown,  $p < 0.01$ ).

Earlier open studies on vestibular disturbances (Pignataro et al., 1990; Felisati et al., 1993; Mira et al., 1995) included overall more than 3000 patients affected by dizziness of central origin, aged 45-85 years, treated by the same treatment schedule as for the placebo-controlled study. Clinical rating was carried out mostly (2396 patients) by a 4-point empirical scale that was used to assess dizziness severity (0 = none; 1 = mild; 2 = moderate; 3 = severe). The DARS scale was applied to 753 patients. Significant reduction of severity was observed in all studies. The mean reduction of total score ranged from 78 to 57 % with a

mean overall value of 68 %. In all studies, the improvement progressed from the first to last assessment.



**Figure 2.** Changes of DARS score during treatment in patients younger and older than 65 years. The patients treated with nicergoline showed a greater change irrespective of age (Felisati et al., 2002), while the placebo group displayed some age-dependence.

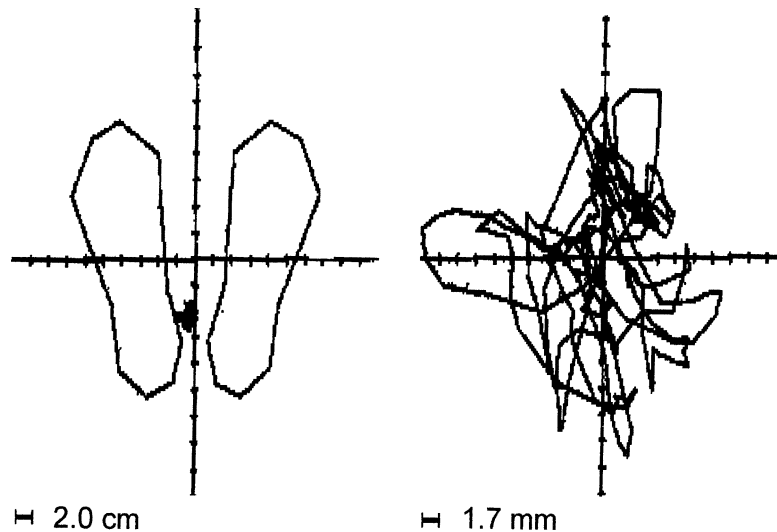
**Table I**

CHANGES IN DARS AND DHI SCORES (mean  $\pm$  SD) (Felisati et al., 2002)

	Nicergoline		Placebo	
	Baseline	Endpoint	Baseline	Endpoint
DARS total	21.5 $\pm$ 6.9	9.2 $\pm$ 6.4	20.7 $\pm$ 7.4	15.1 $\pm$ 8.2
DHI total	49.1 $\pm$ 24.1	27.3 $\pm$ 19.7	49.2 $\pm$ 23.0	42.7 $\pm$ 26.2
functional	17.9 $\pm$ 9.0	10.0 $\pm$ 7.3	18.1 $\pm$ 9.4	15.5 $\pm$ 9.9
emotional	16.5 $\pm$ 10.5	8.7 $\pm$ 7.8	16.9 $\pm$ 10.4	14.5 $\pm$ 10.0
physical	14.8 $\pm$ 6.5	8.3 $\pm$ 5.9	14.3 $\pm$ 5.6	12.7 $\pm$ 7.5

Changes after nicergoline treatment were significantly greater ( $p < 0.001$  vs. placebo) in all rows of this table.

Of the patients, 86 were assessed by objective measurements including rotational vestibular testing (sinusoidal and stop-test), visual-ocular controls (saccadic and pursuit) and static posturography. At the end of treatment, no significant change was observed for rotational-vestibular and visual-ocular test evaluations, however, the accuracy of visual-ocular movements was significantly improved ( $p = 0.03$ ). All static posturographic measurements, i.e., area, length and velocity, improved significantly ( $p < 0.003$ ), except for area measurement with eyes closed, which was reduced. These results indicate altogether a treatment effect on static balance in upright position.



**Figure 3.** Graphic representation of static posturographic tracing. On the left side, the position of virtual feet is indicated related to the position of the center of gravity, which is shown as a darker irregular spot between the feet areas. On the right, the tracing of the center of gravity displacement is magnified. Any point of the line represents the position of the center of gravity at a specific time. The test duration is approximately 40 sec. During this time, the graphics of the displacement of the center of gravity create a "knot". Fundamental parameters for the evaluation of static posturography are the sway area (measure of stability) and trace length (measure of the adjustments the balance system operates to maintain posture).

Overall safety of nicergoline is very satisfactory. Only 4.5 % nicergoline and 4.6 % placebo patients (controlled study) and about 2 % patients in the open studies reported treatment-related adverse events, mainly nausea, of mild severity. Vital signs or of clinical chemistry are generally not affected, except for an occasional, transient and clinically silent serum uric acid increase. Treatment discontinuation is infrequent (about 2 %).

## DISCUSSION

Globally, the results of these studies indicate that nicergoline has a positive effect on symptoms related to balance disorders of central origin. Reduction of severity of symptoms has been observed in all clinical measurements used; the improvement, as measured by the DARS scale, was confirmed by the concomitant reduction of the self perceived handicap as measured by the DHI scale. This concordance indicates that the treatment exerts a positive effect on the life of the patients. Particularly in old age, dizziness is often an elusive

symptom, difficult to be evidenced by objective findings: the oto-neurological examination, except posturography, is often normal or very slightly affected. This fact may help to explain why in these studies the vestibulo-ocular reflex (VOR) tests were not significantly modified by the treatment. Moreover, due to the selection criteria excluding specifically the major peripheral vestibular impairment, the patients predominantly had normal basal VOR, therefore, no changes from baseline of any significance were expected.

The reduction of posturographical alterations after treatment suggests that nicergoline is effective in reducing impaired balance. This hypothesis is supported in particular by the improvement concerning the area of oscillation around the center of gravity (area measurements) and the compensatory effort needed to maintain balance (length measurements). Under physiological conditions, various strategies of control of balance, and specifically of posture, are used. They may preferably rely upon one of the systems involved in the control of balance (visual, vestibular or proprioceptive). The findings from the double blind, placebo-controlled study indicate that the strategy of postural control showed little change in either of the treatment groups. This fact suggests that the drug interacts physiologically with the mechanisms of postural control, allowing and facilitating the system to compensate without altering the strategies the system has already accustomed to.

The positive effect of the treatment is, moreover, accompanied by a very good tolerability, which adds in terms of efficiency, considering how easily treatment-emergent symptoms may be elicited in elderly patients, in particular within the balance system.

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