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The Influence of Piracetam on Actual Driving Behaviour of Elderly Subjects

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A group of 38 elderly (60–80 year) deficient drivers were examined with regard to their driving ability. Their lane-tracking performance during highway driving was measured in real traffic. Their postural stability was also measured. They were given a daily dose of 4·8 g piracetam or placebo over two separate four-week periods in a double-blind, placebo-controlled, cross-over study. Overall, driving performance did not change under the influence of piracetam, although there was a trend towards improvement after 4 weeks of treatment. Postural stability improved during piracetam treatment. A longer treatment period might provide more insight into the hypothesized performance enhancing effects of piracetam. Given the scrutiny with which deficient performers on the driving tests were selected, the results were considered disappointing. © 1998 John Wiley & Sons, Ltd.

KEY WORDS — nootropics; ageing; driving performance; balance; piracetam

INTRODUCTION

It has been claimed that piracetam (2-oxy-1-pyrrolidinone acetamide) can enhance memory and learning in normal subjects and that it is able to reverse mild age-related cognitive decline (Fioravanti *et al*., 1991). The mechanisms of action of piracetam are largely unknown. No direct effect (agonistic or antagonistic) on any known CNS-receptor has been demonstrated. Instead, it has been hypothesized that piracetam potentiates already present neurotransmission. Piracetam's effects are strongly dependent on the presence of normal steroid neuromodulation (Mondadori *et al*., 1989). Animal experiments have suggested that piracetam can protect or restore neurone membrane stability and also that it might affect second messengers such as cyclic AMP, thereby improving neurotransmitter efficiency. Another possible mode of action is by enhancing microcirculation in the brain (Gouliaev and Senning, 1994; Mondadori, 1994; Vernon and Sorkin, 1991).

The objective of the present study was to investigate whether piracetam can exert a beneficial effect on the actual driving performance of non-demented elderly subjects. Accident statistics show that per km driven, older drivers become increasingly involved in traffic accidents (Barr, 1991; Van Wolffelaar, 1988; Waller, 1992). One double-blind study has provided some evidence that piracetam can improve driving in the elderly (Schmidt *et al*., 1991). The initial performance of 101 motorists over the age of 60 during real traffic conditions was compared with their performance after 6 weeks of treatment with either placebo or piracetam. The percentage of correctly solved sign-observance items, which reflects orientation and perception in real traffic conditions, significantly increased more in the piracetam-treated group than in the placebo-treated group. However, driving performance in this study was established by means of subjective ratings of an observer.

The present study was designed to examine the effect of piracetam with an objective measure of driving performance. Subjects between 60 and 80 years of age, who were judged to be deficient drivers in a prior screening test, were admitted to

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the study. It was hypothesized that 4 weeks of treatment with piracetam could reverse the mild deficiency in driving performance, whereas 4 weeks of placebo treatment would have no effect on our driving tests.

A secondary objective of this study was to measure the effect of piracetam on static body balance in the elderly. The measurement of postural instability is recognized as a very sensitive indicator of aging (Stelmach *et al*., 1990), as well as of the impairment induced by many psychoactive drugs (McClelland, 1989). Furthermore, it has been shown that piracetam can improve both dynamic and static postural stability in patients with chronic balance disorders (Deberdt and Boucher, 1992). Disturbed equilibrium is a very common problem in the aged, and even though our subjects were not specially selected or screened for balance disorders, a poorer static body control in comparison with younger people can be expected (Maki *et al*., 1990). Therefore, piracetam could have a beneficial effect on the objective assessment of body balance in our sample.

METHOD

Subjects

Subjects were recruited by means of announcements in several local newspapers. Elderly drivers, aged between 60 and 80, were requested to apply to participate in a study assessing the effects of a drug on driving behaviour. The subjects were paid for their participation. The protocol of this study was approved by the Medical Ethics Committee of the University Hospital Maastricht. The study was conducted in accordance with the Declaration of Helsinki as modified in Tokyo (1975), Venice (1983) and Hong Kong (1989).

Screening and selection procedure

Medical exclusion criteria were: (1) any sign of pathological cardiac conduction abnormalities in ECG recordings, (2) body weight 15% outside of population norms, (3) alcohol or drug abuse or the Medical Supervisor's suspicion of the same, (4) present psychiatric disorders requiring outpatient or regular inpatient therapy, (5) overt severe cardiovascular, cerebrovascular, respiratory, renal or hepatic disorders or history of such, (6) epilepsy or any other severe neurological disorder, (7) diabetes or any other endocrine/metabolic disorder, (8) severe sleep disorders, (9) articular disease, and (10) use of CNS-active medication (e.g. benzodiazepines, nootropics, antidepressants and opioids). Screening of these criteria was based on information from medical history and a physical examination (including a 12-lead ECG). Moreover, subjects had to possess a valid driver's license, have a total driving experience of at least 20 years, and a recent driving experience of 3000 km during the last year.

The purpose of the screening which followed was to identify 'deficient drivers'. Only subjects who were classified as such, according to two separate criteria, entered the study. The first criterion was the performance of a subject during a standard city driving test. The test involved driving a car over a preselected urban circuit in the presence of a licensed driving instructor. Approximately 30 min were required to complete the test. The subjects were requested to drive according to the instructions given by the instructor and commonly accepted safety standards. The performance of a subject was scored by the instructor using a 111-item checklist (the Advanced Driver's Examination), developed by the Royal Dutch Organization of Drivers (ANWB). These items were scored as either 'sufficient', 'moderate' or 'insufficient'. The criterion for discriminating acceptable, or safe, driving from deficient, or unsafe, driving, was exceeded when less than 80% of 22 items pertaining to visual perception or anticipation of traffic events were scored sufficient; i.e. >4 items rated insufficient or >8 items rated moderate (De Gier, 1980).

The second criterion of deficient driving was derived from the standard highway driving test which is described below (O'Hanlon, 1984). In short, this test gives a measure of road-tracking error, obtained from the standard deviation of lateral position (SDLP) of the vehicle within the traffic lane. Extensive experience with this measure has indicated that the mean SDLP for young and middle-aged drivers for a 100 km driving test is about 21 cm. No normative data for elderly drivers were yet available. However, a study with a 60 km version of the standard test showed that older people had a higher SDLP on average than younger people (Van Wolffelaar *et al*., 1987). A mean difference in SDLP of about 20% was found. In the present study, a candidate was classified as 'deficient' if his/her SDLP equalled or exceeded 24 cm.

Drug treatment

Piracetam and placebo were orally administered in the form of identically appearing tablets. Two tablets of 1·2 g were ingested twice a day (i.e. a total dose of 4·8 g/day) for 4 weeks. The daily doses of medication were self-administered at approximately 8·00 and 20·00 h. Urine samples were obtained during the visits at the institute on day 7 and day 28 in both periods. The purpose was to ensure that for each subject the proper medication was dispensed and to check for compliance. Samples were stored frozen until the conclusion of the data collection period. All samples were assayed for the presence of piracetam.

Study design

Drug treatments were administered in separate 4-week periods according to a double-blind, cross-over design. The order of treatment was balanced across subjects and assigned to the subjects using a randomization list. Baseline assessments were carried out on the day before treatment started, whereas the double-blinded assessments were carried out after 14 days of treatment and after 28 days of treatment in both periods. A washout period of at least 4 weeks and usually 5 weeks, interspersed between the successive treatment periods for a given subject.

Testing procedure

Subjects came to the institute on a weekly basis for five successive weeks in both treatment periods. At day 0, 14 and 28 of each treatment period, the driving test and body-sway measurement took place. Medication started on the evening of day 0 (i.e. after the baseline test) and ended in the morning of day 28. On test days, visits were always scheduled at the same time of the day for a particular subject. The subjects were not allowed to drink beverages containing caffeine before or during the tests.

The driving test

Each subject was informed beforehand of his/her legal responsibility to drive safely at all times. The subjects were informed of the possibility that some of the treatments might impair their ability to do so. They were encouraged to tell the driving instructor immediately if they ever doubted their ability to continue driving in a safe manner. The driving test was conducted over a 95-km circuit on a primary highway. The highway consisted of two traffic lanes (3·75 m wide) in each direction. The subjects were instructed to maintain a constant speed (95 km/h) and a steady lateral position within the right traffic lane, preferably in the middle. They were allowed to deviate from these instructions in order to pass a slower vehicle. The test vehicle was an extensively modified station wagon. An electro-optical device ('Lane-Tracker') was installed for measuring the lateral position of the vehicle relative to the painted stripe at the side of the road. The analog signals from the lateral position sensor was A/D converted and sampled on-line at 4 Hz by an inboard 80286 microcomputer. These measures yielded mean values and standard deviations over time of the lateral position. This method was standardized and has been repeatedly applied for measuring the effects of drugs on driving (O'Hanlon *et al*., 1986).

Body sway

Postural instability, or body sway, was measured using the stabilometry method (Kapteyn *et al*., 1983). It involved the use of a balance platform that measured the location of the vector of force which extends vertically downward from the body's centre of gravity, and its movement over time. Analog output of force transducers within the platform were digitized and analyzed to yield simultaneous measures of lateral and sagittal motion. Subjects were instructed to maintain a static, erect posture while standing over the centre of the balance platform with their feet together (at a comfortable, but small distance). Two 30-s recordings followed. The first with the subject's eyes open, the second with eyes closed. While standing with the eyes open, the subject was required to fixate on a target mounted on the wall from a distance of 2·0 m. Measures obtained from the electroposturograph were: lateral–lateral sway velocity, anterior–posterior sway velocity, quadratic velocity (a composite score of both velocities), curve length (path length of vector) and curve surface (the area circumscribed by the path). Analysis of the body sway parameters were performed separately for measurements with eyes open, eyes closed and for the ratio eyes closed/eyes open. This latter variable is known as the Romberg Quotient and indicates the decrease of postural stability due to the elimination of visual compensation. A quotient close to 1 means that

stability can be maintained in spite of the absence of visual input. The higher the quotient, the more one relies on the visual system for postural control.

Data analysis

MANOVA for repeated measurements was used to test the influence of the treatment on the dependent variables measured in the driving and postural stability tests. Two within subject factors were specified: treatment (2 levels: piracetam or placebo) and day of treatment (2 levels: day 14 and day 28). The baseline scores were used as covariates, when necessary; i.e. variables whose baseline values were not the same. Analyses were performed with and without an additional between subjects factor, namely order of treatment (2 levels: piracetam first or placebo first). Additionally, individual piracetam–placebo comparisons for the assessments at day 14 and day 28 were made irrespective of the outcome of the multivariate test, using one-tailed paired *t*-tests.

RESULTS

None of the drug treated subjects had to be excluded from the analysis because of failure to find the drug in the urine.

Comparison between selected and rejected subjects

A total of 134 candidates were screened for participation in the study. Ninety-three of these were rejected because of a SDLP below the criterion of 24 cm. Forty-one subjects passed the initial screening, three of which dropped out later for reasons unrelated to the treatment. Because the last 2 drop-outs were not replaced, 19 subjects received the treatments in the order piracetam–placebo, whereas 19 subjects received the treatments in the order placebo–piracetam.

The mean (±standard error) SDLP upon screening, of the selected subjects was 27·5 (±0·5) cm as compared to 19·3 (±0·3) cm for the subjects not selected.

There were no demographic differences between selected and rejected subjects. The mean age and sex distribution of the two groups are shown in Table 1, along with the variable 'km driven during previous year'. On none of these variables there were significant differences between the rejected and selected subjects.

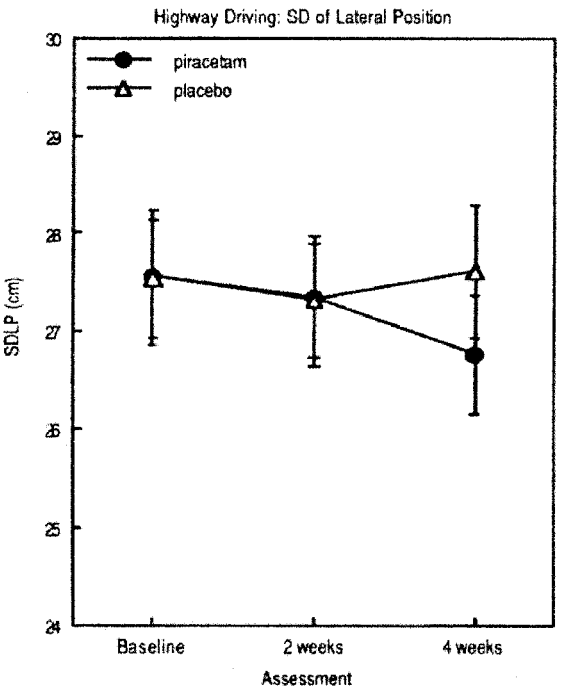

Figure 1. The effect of 4 weeks of treatment with piracetam and placebo on the standard deviation of lateral position in the highway driving test, taken at baseline, and after 2 and 4 weeks of treatment. Left: mean and SE of SDLP of the whole group ($n = 38$). Right: mean and SE of SDLP as a function of order of treatment ($n = 19$ for both treatment orders)

Standard Deviation of Lateral Position (SDLP)

The mean values obtained during the different conditions are shown in Figure 1. The treatment effect on the difference scores was not significant ($F_{1,37} = 0{\cdot}6$; n.s.). There was neither a significant effect for day of treatment ($F_{1,37} = 0{\cdot}08$; n.s.) nor for the treatment by day interaction ($F_{1,37} = 1{\cdot}32$; n.s.). Individual drug–placebo comparisons

Table 1. Demographic variables and driving experience for selected and rejected subjects

	Selected subjects ($n = 38$)	Rejected subjects ($n = 93$)	Total ($n = 131$)
Mean age ± SEM	66·9 ± 0·8	65·6 ± 0·5	66·0 ± 0·4
(Range)	(60–79)	(60–80)	(60–80)
Proportion male : female	32 : 6	79 : 14	111 : 20
Mean km driven in previous year (±SEM)	13200 (1135)	13600 (518)	13500 (524)

employing one-tailed *t*-tests revealed that there was no difference after 14 days of treatment ($t_{37} = 0{\cdot}04$; n.s.), but that SDLP was somewhat lower (i.e. better) after 28 days of piracetam relative to placebo ($t_{37} = 1{\cdot}80$; $p < 0{\cdot}05$).

Body sway

Anterior–Posterior Velocity (A–PV). Curves for the Romberg Quotient appear in Figure 2. As can be seen, in the piracetam condition, the quotient decreases from baseline to treatment period. The treatment effect was significant ($F_{1,37} = 5{\cdot}59$, $p < 0{\cdot}05$). This seems to have been due to an increased stability in the eyes-closed condition, where there was also a significant difference between the treatments for A–PV ($F_{1,37} = 4{\cdot}8$, $p < 0{\cdot}05$). Stability with eyes open did not improve as a result of piracetam treatment.

Lateral–Lateral Velocity (L–LV). The lateral sway proved to be a less sensitive indicator for the treatment effect than the anterior-posterior sway. No significant treatment differences were obtained for the Romberg Quotient or for separate measurement with eyes open or eyes closed.

Quadratic Velocity (V2). The Romberg Quotient for the composite score of sway in both directions (V2) was significantly different between treatments ($F_{1,37} = 4{\cdot}35$, $p < 0{\cdot}05$). Neither the two separate eyes open or eyes closed measurements differed significantly between conditions.

Curve Length (CL). For curve length (Figure 2), the treatment effect on the Romberg Quotient was significant ($F_{1,37} = 4{\cdot}68$, $p < 0{\cdot}05$). Neither of the two separate measures (eyes open or closed) were significantly different in the two treatment conditions.

Curve Surface (CS). No significant differences between treatments emerged for the Romberg Quotient or for the separate eyes open, eyes closed measures.

DISCUSSION

The primary objective of the present study was to test the hypothesis that actual driving performance after piracetam treatment would be different than after placebo treatment in a group of healthy elderly people who were judged to be deficient

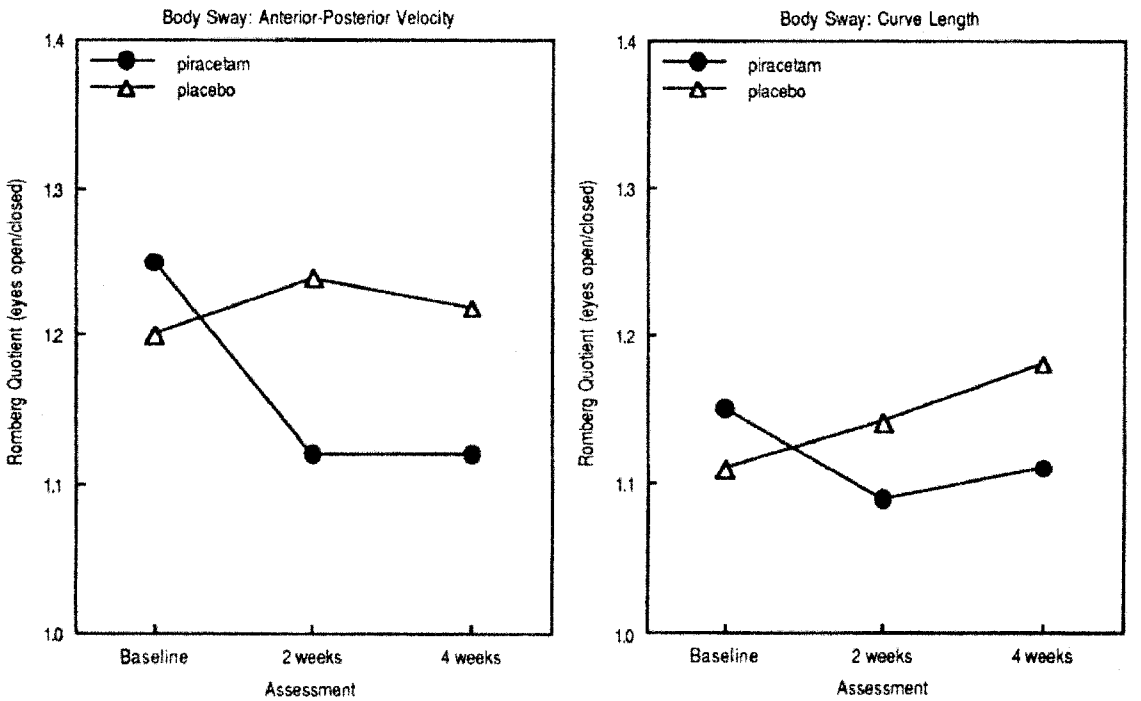

Figure 2. The effect of 4 weeks of treatment with piracetam and placebo on measures of body sway, taken at baseline, after 2 and 4 weeks of treatment. Left: Romberg Quotient of Anterior–Posterior Velocity. Right: Romberg Quotient of curve length

drivers according to two different criteria. It was hypothesized that performance on the driving test would improve more after 2 and 4 weeks of treatment with piracetam than it would after 2 and 4 weeks of treatment with placebo. Overall, the hypothesis could not be confirmed. Overall, the decrease in SDLP during piracetam condition did not differ significantly from that in the placebo condition. However, we found a very slight indication of improvement after 4 weeks of treatment with piracetam. The absolute magnitude of this effect was negligible, particularly when viewed in the context of the high SDLP scores of the treatment group as a whole. Therefore, this 'effect' could serve as a typical example of a marginal statistical significant, but clinically irrelevant one. However, it must be noted that in comparison with the recent state-of-the-art in clinical trials investigating the effect of similar substances in similar populations, i.e. cognition enhancers in age-related cognitive decline, the duration of our study was short. Usually, a minimum of 12 weeks is recommended as the minimum duration of the treatment period. So, it could very well be that the above described 'marginal piracetam effect' was signifying the beginning of its developing into a clinical significant effect, which would take another 8 weeks to develop.

The clinical response to piracetam, i.e. the incidence of subjects responding positively to the treatment, has been estimated to lie in the 10–30% range (Mondadori, 1994). Thus, piracetam might not lead to an improvement of road tracking performance in all subjects, but it might do so for some. This was reported in previous findings (Schmidt *et al*., 1991). For the one parameter for which a significant piracetam effect was found (orientation towards and observation of traffic signs), the results were more pronounced for the subjects who had the worst scores on the baseline test. If it can be conclusively demonstrated that piracetam can have a beneficial effect on driving performance of even a small proportion of elderly drivers, this would have major implications. Accident statistics show that older drivers (from age 60 onward) are at greater risk of getting involved in traffic accidents when the distance travelled is taken into account. Moreover, the total number of older drivers increases rapidly, and they will also be travelling larger distances per person (Waller, 1991). At present no drug is known to improve driving performance of elderly people. If piracetam would be able to do so for a proportion of elderly drivers, especially for the most deficient drivers, this would be very promising. However, our method of selecting the subjects apparently did have no beneficial effect on increasing the clinical response rate. In general, if no predictor of this 'clinical response' to piracetam can be found and successfully applied, research into piracetam's effect on behaviour will only be of academic interest and hence will have no future in treatment of age-related cognitive decline.

An important finding of the present study was that piracetam improved postural stability of elderly subjects as indicated by the Romberg Quotient for anterior–posterior velocity, velocity of sway in both directions and total sway-curve surface. The Romberg Quotient indicates the degree to which stability can be maintained after the elimination of visual compensation. With piracetam, the deterioration in stability with eyes closed was significantly less than with placebo. If drugs improve postural stability, there is evidence that the central availability of cognitive processing resources is suppleted (Stelmach *et al*., 1990; Teasdale *et al*., 1993), and hence psychomotor and cognition enhancement could be the result. Such a hypothesis seems prominent in the case of the piracetam-like drugs and could very simply be tested by having the subjects' cognitive performance tested in standing position while simultaneously measuring their postural stability. Yet, this has, to our current knowledge, never been done.

REFERENCES

Barr, R. A. (1991). Recent changes in driving among older adults. Special Issue: Safety and mobility of elderly drivers: Part I. *Human Factors*, **33**, 597–600.

De Gier, J. J. (1980). *Geneesmiddelen en Verkeersveiligheid*. Elinkwijk, Utrecht.

Deberdt, W. and Boucher, A. (1992). *Piracetam in Vertigo: A Pharmacological Overview*. UCB.

Fioravanti, M., Bergamasco, B., Bocola, V., Martucci, N., Nappi, G., Neri, G., Fabbrini, G. and Agnoli, A. (1991). A multicentre, double-blind, controlled study of piracetam vs placebo in geriatric patients with nonvascular mild-moderate impairment in cognition. *New Trends in Clinical Neuropharmacology*, **V**, 27–34.

Gouliaev, A. H. and Senning, A. (1994). Piracetam and other structurally related nootropics. *Brain Res. Brain Res. Rev*., **19**, 180–222.

Kapteyn, T. S., Bles, W., Njiokiktjein, C. J., Rodde, L., Massen, C. H. and Mol, J. M. F. (1983). Standardization in platform stabilometry being part of posturography. *Agressologie*, **24**, 321–326.

Maki, B. E., Holliday, P. J. and Fernie, G. R. (1990). Aging and postural control. A comparison of spontaneous- and induced-sway balance tests. *J. Am. Geriatr. Soc.*, **38**, 1–9.

McClelland, G. R. (1989). Body sway and the effects of psychoactive drugs: A review. *Hum. Psychopharmacol.*, **4**, 3–14.

Mondadori, C. (1994). In search of the mechanism of action of the nootropics: new insights and potential clinical implications. *Life Sci.*, **55**, 2171–2178.

Mondadori, C., Ducret, T. and Petschke, F. (1989). Blockade of the nootropic action of piracetam-like nootropics by adrenalectomy: an effect of dosage? *Behav. Brain Res.*, **34**, 155–158.

O'Hanlon, J. F. (1984). Driving performance under the influence of drugs: rationale for, and application of, a new test. *Br. J. Clin. Pharmacol.*, **18**, 121–129S.

O'Hanlon, J. F., Brookhuis, K. A., Louwerens, J. W. and Volkerts, E. R. (1986). Performance testing as part of drug registration. In *Drugs & Driving*, O'Hanlon, J. F. and De Gier, J. J. (Eds), Taylor & Francis, London, pp. 311–330.

Schmidt, U., Brendemuhl, D., Engels, K., Schenk, N. and Ludemann, E. (1991). Piracetam in elderly motorists. *Pharmacopsychiatry*, **24**, 121–126.

Stelmach, G. E., Zelaznik, H. N. and Lowe, D. (1990). The influence of aging and attentional demands on recovery from postural instability. *Aging*, **2**, 155–161.

Teasdale, N., Bard, C., LaRue, J. and Fleury, M. (1993). On the cognitive penetrability of posture control. *Exp. Aging Res.*, **19**, 1–13.

Van Wolffelaar, P. C. (1988). *Oudere Verkeersdeelnemers: Verkeersproblemen en Educatiedoelstellingen*. University Press, Groningen.

Van Wolffelaar, P. C., Brouwer, W. H. and Rothengatter, T. (1987). Compensation Strategies of Elderly Car Drivers. In *Contemporary Ergonomics*, Megaw, E. D. (Ed.), Taylor & Francis, London.

Vernon, M. W. and Sorkin, E. M. (1991). Piracetam. An overview of its pharmacological properties and a review of its therapeutic use in senile cognitive disorders. *Drugs Aging*, **1**, 17–35.

Waller, J. A. (1992). Research and other issues concerning effects of medical conditions on elderly drivers. Special Issue: Safety and mobility of elderly drivers: Part II. *Human Factors*, **34**, 3–15.

Waller, P. F. (1991). The older driver. Special Issue: Safety and mobility of elderly drivers: Part I. *Human Factors*, **33**, 499–505.

