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ORIGINAL COMMUNICATION

Driving in Parkinson's disease – a health hazard?

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Abstract *Background* The driving safety of Parkinson's disease (PD) patients has lately been questioned after several authors reported road accidents caused by sleep attacks in PD patients on dopaminergic medication. *Objectives* To determine 1) whether PD patients in general and those on dopaminergic medication in particular are especially prone to cause severe road accidents and 2) whether there are PD symptoms or dopaminergic side effects with the potential to compromise driving safety. *Data source* Relevant articles were identified by electronic search of biomedical databases (1966–2002: MEDLINE, EMBASE, PASCAL, PUBMED), the Cochrane Controlled Trials Register, and reference lists of located articles. *Results* Despite frequent occurrence of potentially hazardous dopaminergic side effects (2–57 %) and disabling parkinsonian non-motor and motor disabilities (16–63 %), the two existing studies on accident rates suggest that PD patients are not more prone to cause road accidents than the rest of the population. Five further reports including 1346 patients and focusing on dopaminergically induced sleep attacks provided comparably low accident figures (yearly incidence: 0 %–2 %). Because of low figures meta-analysis was intended but finally deemed inappropriate as the methodology of included studies varied greatly and was frequently flawed. *Conclusion* Further prospective community-based well designed studies on accident risk in PD patients are needed to provide evidence based driving recommendations.

Key words driving · car accidents · Parkinson's disease · sleep attacks

Introduction

In the past 40 years, tremendous effort has gone into developing safe dopaminergic agents to keep Parkinson's disease (PD) patients mobile, working and driving for as long as possible. This effort has suffered a major setback with recent reports that these medications may cause sudden irresistible sleep attacks during driving and other activities of daily living [10, 20, 27]. In response to these incidents, the U. S. Food and Drug Administration and Health Canada appended a black-box warning to the package inserts of two dopamine agonists, cautioning patients not to drive when on medication. In Europe and many countries throughout the world, driving of patients treated with these agents has also been re-

stricted, often with major socio-economic impacts [20]. These measures, which are more restrictive than found for any other sedative medication, are based upon an assumption that PD patients taking dopaminergic substances carry a higher risk for motor vehicle accidents. This opinion, however, is not shared by important opinion leaders in the field of movement disorders [27] who argue that such drastic intrusions into the personal rights of PD patients, with all their social and medico-legal implications [17, 27], should be based on sound evidence which has yet to be provided.

We reviewed the current literature in an attempt to answer the following questions: 1) Are there symptoms in PD that are potentially hazardous for safe driving? 2) Are the side effects of dopaminergic medication potentially hazardous for safe driving? 3) Are PD patients particularly prone to cause severe road accidents? and 4) Are patients on dopaminergic medication particularly prone to cause severe road accidents? Answers to these questions were intended to be used to create a possible foundation for evidence based driving recommendations with particular focus on suggestions whether 5) PD patients should be banned from driving or not.

Data sources

Relevant publications were identified by 1) electronic search of four general biomedical databases for articles published between 1966 and December 2002 (MEDLINE, EMBASE, PASCAL, PUBMED); 2) the Cochrane Controlled Trials Register and 3) reference lists of located articles. Key words of the search process for the primary objective (accident proneness of PD patients) consisted of: a) "Parkinson" or "Parkinson's disease" or "parkinsonism"; b) "driving" or "accident"; c) "dopamine agonist" or "levodopa" or "dopaminergic"; d) "sleep attack" or "sleep episode" or "sleep"; and e) a combination of a and b, b and c, a and d, and b and d. For this task full length published articles of all languages were screened. Articles not containing specific information on accident rates were excluded.

With the perspective of combining data of the different identified articles and in an attempt to draw conclusions relevant to the general PD population these articles had to be analysed in regard to methodological comparability and validity. We checked whether study eligibility criteria were clearly defined and particularly whether diagnostic criteria relevant for inclusion (PD) or exclusion (dementia, severe motor-dysfunction) were stated. Further important aspects that were thought to prevent data amalgamation, were differences in or uncertainty about study design, data acquisition, and the definition of study endpoints ("sleep attack", "accident"). For the study it was also of relevance whether the cause of reported accidents was provided or not and in particular whether it was stated that the patient was responsible for the accident. Another important issue was the mentioning of accident outcome regarding both bodily harm and damage to property. With the aim of performing a combined risk factor analysis studies were screened for complete provision of demographics (age, gender), disease related data (disease duration, disease severity measures), and time-relationship between occurrence of accidents and data acquisition (particularly concerning disease related data). An analysis of the sample from which the data was obtained and of a possibly included control group was thought to provide information on possible extrapolation of results.

Eligible data were abstracted on the basis of predefined evaluation criteria by two authors (CH and BH) independently, checked for accuracy and amalgamated. Evaluation criteria consisted of the categories: adequate (A), not stated (B), inadequate (C), and not applicable (n. a.). Disagreements about inclusion into an evaluation category were solved by discussion.

Concerning the secondary objective (potentially hazardous dopaminergic side effects) only reports in English of randomized controlled trials were included. Key words of the search process consisted of a combination of: a) "Parkinson" or "Parkinson's disease" or "parkinsonism"; b) "controlled clinical trial" and c) "dopamine agonist" or "bromocriptine" or "cabergoline" or "pergolide" or "pramipexole" or "lisuride" or "ropinirole".

Are there PD symptoms with the potential to compromise driving safety?

Driving a car is a highly complicated activity carried out in a constantly changing environment [14]. It consists of cognitive and psychomotor functions that are thought to be impaired in PD [9, 14, 25], such as perception [14], information processing [15], decision making [7, 41] and maintaining of attention [7]. Particularly troublesome for patients while driving are difficulties in carrying out tasks simultaneously [41] which tax their impaired short-term and non-verbal precognitive memory [15], as well as their impaired visual, visuospatial [7] and visuoperceptual [14] functions.

The patients' most commonly self-perceived problems while driving include motor fluctuations, dyskinesias, difficulties with managing pedals, and assessing distance proportions [11]. On the other hand patients often claim that tremor and dyskinesias reduce in intensity when they focus their attention on driving, thus making driving less difficult and safer (Table 1) [35].

Table 1 Non-motor side effects of dopaminergic medication effecting driving safety

non-motor side effects	incidence rate
sleep episodes and sleep attacks	2–30.1 %
daytime somnolence	3.7–57 %*
insomnia	14.6–28 %*
delusions	1–15 %*
psychosis	11.2–14 %*

* incidence rates as reported in controlled clinical trials

Do dopaminergic medications potentially compromise driving safety?

Effects of dopaminergic agents on non-motor function

Several undesired effects of dopaminergic agents have recently been blamed for reducing the driving safety of PD patients treated with these medications (Table 1). The foremost concern is that of a reduced state of vigilance. Sudden irresistible onsets of sleep with or without a prodrome of sleepiness (termed "sleep episodes" or "sleep attacks", respectively) have been described with levodopa and all dopaminergic agents [27]. Whether these two are the spectrum of but one entity or whether sleep attacks exist as a distinct phenomenon has already been discussed in detail in other publications [19, 20]. In short it can be stated that initially several authors had opposed the concept of sleep attacks and suggested that falling asleep was invariably preceded by warning signs [27]. The most recent literature however, particularly the descriptions of two direct clinical observations [21] and the report of one polysomnography recording [40], seem to provide evidence that sleep attacks without preceding warning signs really do exist [19, 20]. The combined prevalence rates of these two sleep disturbances is thought to be between 2 and 30.2 % [20] and sleep episodes can be assumed to be five times as common as sleep attacks [13].

Daytime somnolence, another common side effect potentially hazardous to PD drivers, has also been found in all dopaminergics with prevalence rates of 9.5 %–15.1 % for pergolide [1], 3.7 %–57 % for pramipexole [29], 22.3 % for ropinirole [33], and 27.2 % for bromocriptine [33]. The prevalence of insomnia was 14.6 % with ropinirole [33], 27 % with cabergoline [22], and 28 % with levodopa [29]. Delusional states and florid psychosis are a frequent finding in PD patients under dopaminergic treatment ranging from 1 to 14 % and 5 to 11.2 % respectively [1, 22, 29, 33]. These episodes can occur both during the day, affecting driving directly, and during the night (often also experienced as nightmares disturbing patients' sleep), and thus indirectly influencing daytime vigilance.

However, several positive effects of specific dopaminergic medications, resulting in better sleep and thus causing better alertness during the day, have also been described. Slow-release dopa preparations have been found to reduce sleep fragmentation [36]. Levodopa reduces pharyngeal obstruction and thereby respiratory arousals [36]. Long-acting agonists and slow-release preparations were found to suppress night time tremor, early-morning dystonias and restless legs syndrome or periodic limb movements in sleep [3], thus reducing still other forms of unwanted sleep interruptions. Depression, a common comorbidity in PD, was found to be positively influenced by potent antidepressive effects of pramipexole [6]. Difficulties of sleep initiation or of maintaining uninterrupted sleep, which are key symptoms of depression, are therefore expected to subside together with altered mood when patients are put on pramipexole [3].

Whether dopaminergic medication impairs cognitive function to an extent that it would affect safe driving has been controversial [2, 8, 12, 24]. Recent studies have tried to explain previously found discrepancies by linking differing effects in patient groups to differing degree of brain pathology [24]. Several studies [2, 8, 12, 24] suggest that in untreated patients with early PD chronic dopaminergic replacement might even be associated with significant cognitive improvement. Tests assessing learning and long-term verbal and visual memory, visuospatial abilities, and various executive tests indicative of frontal lobe functioning revealed better scores after treatment compared with baseline in this patient group. Stable patients with moderate disease stage, however, were found to show little or no changes [23], and advanced and fluctuating patients might even deteriorate during acute levodopa challenge [23].

Effects of dopaminergic agents on motor function

Disabling motor fluctuations as long-term side effects were shown to occur in 47–63 % of patients after several years of treatment with levodopa [31] or other dopaminergic medications [30, 38] (Table 2). Together with dyskinesias, which occur in about the same percentage (16–54 %) [26, 30, 32, 34, 38] in a comparable time period, they are thought to be caused by non-physiological (pulsatile) stimulation of dopamine receptors [4]. Nonetheless, levodopa, like all other dopaminergic agents, significantly improves bradykinesia, rigidity and tremor, thus making patients more fit for safe driving. New long-acting dopaminergic agonists, when used as initial therapy, were found to significantly delay the onset of motor complications [5]. In patients with advanced disease, continuous apomorphine administration was found to reverse motor fluctuations and dyskinesias [4]. Thus dopaminergic medications have been shown to have various effects on both motor and

Table 2 Motor complications with dopaminergic drugs effecting driving safety

	Pramipexole	Ropinirole	Cabergolide	Pergolide	L-dopa	general
source	[30]	[32]	[34]	[26]	[26, 32]	[38]
n	301	268	419	294	n. a.	129
study period	4 yrs	5 yrs	5 yrs	3 yrs	3–5 yrs	n. a.
rescue-levodopa	yes	yes	yes	no	n. a.	n. a.
adverse events						
Dyskinesias	25%	20%	22%	16%	46–54%	4–53%
Fluctuations	47%	–	–	–	33–63%	8–63%

non-motor function in PD which may potentially affect driving safety, but when used selectively the overall positive effects seem to outweigh the negative ones.

Are patients with Parkinson's disease particularly prone to cause severe road accidents or severe traffic violations?

Literature providing figures on incidence rates of accidents caused by PD patients is scarce (Table 3), and where available, information on accident outcome is lacking in most cases. A total of seven studies [9, 10, 13, 16, 35, 37, 39] including five on accidents in connection with sleep attacks [10, 13, 16, 37, 39] were included. Of the excluded sleep attack studies one did not provide specific information on accidents [28] and one that was not a full length study reported cases of accidents without providing a denominator [17].

The two studies [9, 35] performed before the concept of sleep attacks became known provide valuable information on general accident risk in PD patients regardless of the underlying cause. Ritter and Steinberg [35] found PD patients to cause fewer accidents and traffic violations when compared with overall national rates. In this study, of 156 drivers in a cohort of 359 German PD patients, only 7.7 % were registered with the state traffic commission for traffic offences or accidents. This figure was significantly lower than the 25 % found for the general population in Germany, and consisted of one minor accident (with minimal bodily harm), seven minor violations and two major offences. In three cases the driver's license was withdrawn. Unlike other drivers, PD patients had no repeated offences and no offences in connection with drunk driving.

Dubinsky [9] found that PD patients did not have more lifetime accidents with bodily harm than controls. However, with increased disability there were significantly more accidents occurring per million vehicle miles of travel (PD: Hoehn and Yahr stage III: 80 vs. normal controls: 14.3 accidents per million vehicle miles; $p < 0.001$).

Table 3 Key characteristics of studies covering accidents in patients with Parkinson's disease

Reference	c	l	design*	cts	recruitment	POM	Elig.	n	male sex**	age**	duration**	H&Y**
Ritter and Steinberg 79 [35]	G	G	retrosp.	1	MDC	acc.	PD	359	– (85%)***	–	– (10)	n. a.
Dubinsky et al. 91 [9]	USA	E	retrosp.	1	MDC + PS	acc.	PD	150	– (–)	– (67.8)	– (–)	– (2.8)
Frucht et al. 1999 [10]	USA	E	?	3	MDC	SA	PD + Pxl	400	100% (–)	65.1 (–)	6.5 (–)	2 (–)
Hauser et al. 00 [13]	USA	E	retrosp.	1	MDC	SA	PD + Pxl	37	100% (55%)	71.5 (61.0)	2.5 (3.4)	– (–)
Hobson et al. 02 [16]	Can	E	retrosp.	18	MDC	SA	PD – D – F	638	– (–)	– (65.7)	– (8.1)	– (2.2)
Tan et al. 02 [39]	Sp	E	retrosp.	2	MDC	SA	PD – D	201	n. a. (62%)	63.7 (n. a.)	n. a. (4.1)	n. a. (2.5)
Schlesinger and Ravin 03 [37]	USA	E	retrosp.	1	MDC	SA	PD + DA	70	66% (80%)	69 (63.2)	7 (8.9)	2 (3)
Total				27				1855				

* Type of study design reflecting the occurrence of the outcome measure (i. e. if the outcome measure occurred prior to study onset the study was classified as being retrospective and prospective otherwise)

** Scores of PD patients involved in accidents and of the total number of study patients (in brackets)

*** Provided for drivers only

c Countries where studies were performed included Canada (Can), Germany (G), Singapore (Sp), and the United States (USA)

l article languages (l): English (E) or German (G)

cts, n Number of recruited centers (cts) was 27, and that of recruited patients (n) 1855

POM Primary outcome measure (POM): sleep attacks (SA) or accidents (acc)

MDC, PS Recruitment: movement disorders center (MDC) or self help group of the Parkinson society (PS)

Elig., PD Eligibility criteria (Elig.) included the diagnosis of Parkinson's disease (PD), PD patients on dopamine agonist (PD + DA), PD patients on pramipexole (PD + Pxl) and PD patients excluding dementia (PD – D) or excluding severe functional deficit (PD – F)

Are patients on dopaminergic medication particularly prone to cause severe road accidents?

Because of the recently heightened awareness of accidents caused by sleep attacks induced by dopaminergic medications, five studies are available on this topic (Table 3).

Descriptions of accident severity, however, were provided for only four patients. In his retrospective study on 400 PD patients treated with pramipexole Frucht [10] reported a 2 % annual incidence rate of accidents caused by sleep attacks. In a recent study on 638 consecutive PD patients Hobson [16] stated that only one minor accident occurred. Hauser et al. in their study of 37 pramipexole treated patients [13] reported on two accidents without injuries. Schlesinger and Revin found that three [37] out of 70 consecutive patients on DAs caused an accident. No accidents were reported by Tan [39] in their cohort of 201 consecutive PD patients.

When comparing all studies sudden onset of irresistible sleep while driving occurred in 3.3 % to 28 % of PD patients, but only 0–0.24 % of active drivers had an accident (Table 4). The annual incidence rate of car crashes caused by sleep attacks was between 0 % and 2 %. In most individual studies the total number of patients involved in an accident was too low and data too inconsistent to allow for a comparison between different PD medications or other potential risk factors.

When analysing the methodological quality of data presented in the before mentioned studies by applying stringent evaluation criteria we obtained the following results (Table 5): Only one study [9] identified inclusion criteria in a way that would allow reproducibility. In six studies no diagnostic criteria for PD and in one no definition for exclusion criteria "dementia" were provided [16, 39]. Where inclusion criteria were stated they varied greatly and consisted of "PD patients of previously performed pramipexole studies" [13] or "PD patients on DAs" [37] or "PD patients excluding those with dementia" [16, 39] and "severe functional disability" [16]. Control groups were lacking in all but two studies [9, 39]. In one of them healthy controls were recruited through announcements in local newspapers, a mode of selection that might not have provided a representative sample [9]. In all but one study that enrolled PD patients from self help groups [9], patients were recruited exclusively from movement disorders outpatients departments. All but three [10, 16, 39] were single center studies and only one sleep attack study and one general study were performed outside the North American continent [35, 39].

A definition of the study endpoint "sleep attack" was provided in four studies [10, 37] and that of "accident" in one only [9]. Even in articles where study periods were well defined [9, 13, 16, 35, 39] and disease-related data provided there was a big time difference between the occurrence of the accident and the time of the examination. Thus – and this limitation the authors mention themselves [9, 16] – values of correlations between accident risk and disease severity scores (Hoehn and Yahr scale, Epworth Sleepiness score), evaluated up to several years after the event, remain questionable.

Patient data concerning demographics, disease specific data, and treatment were insufficient in several studies so that a combined post hoc analysis of risk factors was rendered impossible. The reason for this incompleteness of data can be explained to a large extent by the fact that accidents were but rarely the primary outcome measure and therefore not sufficient accident specific data were included in the various papers.

Should patients with Parkinson's disease be banned from driving?

Several factors intrinsic to PD and several effects of dopaminergic medication have the potential to influence negatively a patient's ability to drive. However, general accident rates in PD are low, and despite a substantial frequency of sleep attacks occurring in PD patients on dopaminergic medication, severe accidents in association with sleep attacks are rare. Unfortunately most of

Table 4 Frequency of accidents and sudden irresistible onset of sleep (SIOS)

source	n	driver n (%)	SIOS n (%)	SIOS/D n (%)	acc. n (%)	acc./D (%)	acc. inc. (%)
Frucht et al. 99 [10]	400	? (–)	? (–)	? (–)	8 (2 %)	?	2 %
Hauser et al. 00 [13]	37	? (–)	9 (24 %)	7 (–)	2 (5.4 %)	?	1.6 %
Hobson 02 [16]	638	420 (65 %)	? (–)	14 (3.3 %)	1 (0.2 %)	0.24 %	–
Tan et al. 02 [39]	201	32 (16 %)	28 (14 %)	9 (28 %)	0 (0 %)	0 %	0 %
Schlesinger and Ravin 03 [37]	67	? (–)	24 (35 %)	19 (–)	3 (4.5 %)	?	–

n total number of recruited patients
SIOS sudden irresistible onset of sleep, consisting of both sleep attacks and sleep events
SIOS/D sleep attacks while driving
acc. (n) indicates the number and
acc. inc. the annual incidence of accidents caused by sleep attacks

Table 5 Methodological quality of included studies regarding accident related data*

study	eligibility criteria**	demographics	disease data	R_x	study period	study design	data acquis.	definition of SA	definition of accident	cause of accident (liability)	outcome*** of accident	time-relationship****	control group
Ritter and Steinberg [35]	B	B	B(A)	B	A	A	A	n. a.	B	C	A/B	C	C
Dubinsky et al. [9]	A	B	B (A)	B	A	A	A	n. a.	A	C	C/B	C	A
Frucht et al. [10]	B	A (B)	A (B)	A (B)	A	B	A	C	B	A	A/B	B	C
Hauser et al. [13]	B	A (C)	A(C)	A	A	A	A	A	B	A	A/B	C	C
Hobson et al. [16]	B	B (A)	B (A)	B	A	A	A	A	B	A	A/B	C	C
Tan and Ravin [39]	B	n. a. (A)	n. a. (A)	n. a. (A)	B	A	A	A	B	n. a.	n. a.	C	A
Schlesinger [37]	B	A (A)	A (A)	C (A)	B	A	A	A	B	B	B/B	C	C

* Number of accidents not being the primary outcome measure of most studies the amount and quality of data provided for accidents is limited. The applied quality criteria regarding completeness of reported data include the categories: "A" (adequate), "B" (not reported), "C" (inadequate), and "n. a." (not applicable). Categories in brackets refer to the total patient population, those without to patients included in accidents

** eligibility criteria were only graded as adequate (A) when containing clearly defined inclusion and exclusion criteria; meaning either a reference to diagnostic criteria (like U. K. Brain Bank criteria for PD or DSM IV for dementia) or a clear descriptive definition.

*** first number relates to bodily harm and second to damage of property

**** Time-relationship between accident and acquisition of patient data particularly disease related data

the existing studies are methodologically flawed and the presented data so incoherent that no combined analysis or generalized conclusions regarding driving recommendations seemed feasible.

As this topic is of great importance to PD patients and general public alike and insufficient relevant data are available so far a well designed prospective, population based, and multi-center designed study is urgently needed. Because driving habits are subject to great regional variations [18] centers should be chosen from multiple sites and possibly various countries. Such a future survey has to include a large number of PD patients in order to cover enough accidents (which seem to be very rare in PD) and to provide sample sizes for each treatment group that are large enough to allow for a group comparison between different PD-medications. A comparison with accidents in age and sex-matched healthy controls and possibly a second control group consisting of patients with progressive disability that also reduces a lifetime of driving is necessary. To allow inferences to be made about the general population subjects should obviously not be selected from newspaper announcements or super-specialist centers but rather in a representative fashion. Inclusion criteria should be well defined as should be the endpoints. Driving ability should not be judged only upon accident severity. Instead of including all PD patients irrespective of covered mileage into the analysis, accident rates should rather be calculated on basis of PD patients with the "intention to drive" versus the "time" these patients spend driving. Structured prospective evaluation of possible predictors and screening tools like the Epworth Sleepiness Scale or the Inappropriate Sleep Composite Score will hopefully provide much needed information about risk factors. From a study design like this we could hope to obtain solid data for evidence based driving recommendations that would ensure a high degree of safety for PD patients and the general public.

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