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Retrospective post-authorisation safety study investigating the relationship of first-generation antihistamines with sedative effect and the risk of falls in older patients

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For patients at the age of 65 years or older an increased risk of falls in association with the intake of first-generation antihistamines with sedative effect is discussed. Currently, there are no valid data that can either confirm or disprove this risk. In this retrospective non-interventional safety study, the primary objective was to investigate a possible causal relationship between falls in patients ≥ 65 years of age and the intake of first-generation antihistamines. Secondary objectives were to investigate a possible causal relationship of falls after taking first-generation antihistamines for the subgroups < 65 years, 65-84 years and ≥ 85 years; to determine the fall rate of patients ≥ 65 years of age and of the subgroups < 65 years, 65-84 years and ≥ 85 years; and to identify causes of falls in patients ≥ 65 years. Out of the 13,866 physicians who were invited to participate in the study, 524 (3.8%) opened the link to the survey. The evaluation included verified data sets of 169 physicians who were either general practitioners or resident neurologists who had in total treated 313,046 patients within the previous six months. 9,922 patients had fallen at least once (total fall rate 3.2%). The rate of falls increased with age (< 65 years 1.1%; 65-84 years 3.9%; ≥ 85 years 9.9%). The fall rate of patients aged 65 years and older was 5.4%. Only a small proportion (2.9%, 8,942 patients) of the altogether 313,046 patients recorded had taken a first-generation antihistamine at any time within the previous six months. In the records of 9.5% (940 patients) of the 9,922 patients who had fallen the intake of first-generation antihistamines was documented. Detailed information was available for 379 of these patients with a total of 505 falls. The analysis of these cases indicates that in almost three quarters of falls (72.5%, 366 falls) there is no causal link between the intake of first-generation antihistamines and the fall. In almost 95% of the remaining 123 falls, the physicians suggested between one and seven possible alternative causes of falls (mainly underlying and concomitant diseases). This suggests that first-generation antihistamines do not play a relevant role in the fall incidents.

1. Introduction

Approximately 28-35% of people aged 65 and older experience an incident of falling each year (WHO 2007; Blake et al. 1988; Prudham and Evans 1981; Campbell et al 1981). This percentage increases to 32-42% for those over 70 years of age (WHO 2007; Tinetti et al. 1988; Downton and Andrews 1991; Stalenhoef et al. 2002). The frequency of falls increases with age and frailty level (WHO 2007). Falls occur as a result of a complex interaction of risk factors. The main risk factors reflect the multitude of health determinants that directly or indirectly affect well-being (WHO 2007).

Factors for which an association with an increased risk of falling has been identified include female gender, age 80 years and older, cognitive impairment, falls within the previous six months, impaired vision, rheumatic diseases, frailty, multimorbidity, vitamin D status, polypharmacy and household hazards (Smith et al. 2017; Pfortmueller et al. 2014; Moylan and Binder 2007). Fall-risk-increasing drugs (FRIDs) include central nervous system-acting agents, cough preparations, nonsteroidal anti-inflammatory drugs, anti-Alzheimer's agents, antiplatelet agents, calcium antagonists, diuretics, α-blockers, digoxin, hypoglycaemic drugs, neurotoxic chemotherapeutic agents, nasal preparations, and anti-glaucoma ophthalmic preparations (Chen et al. 2014).

The use of first-generation antihistamines is also being discussed as a risk factor for an increased fall risk (Alvarez et al 2015; Cho et al. 2018; Lee et al. 2016). First-generation antihistamines approved in Germany for the short-term treatment of sleeping disorders include doxylamine and diphenhydramine. Both act by blocking the histamine type 1 (H1) receptors and are sedating due to their effects in the central nervous system (Bethesda 2012, updated 2017).

Data on a possible association between first-generation antihistamines and an increased risk of falls is limited. In a meta-analysis performed in year 2016 (Cho et al. 2018) five studies (Chang et al. 2011; Lee et al. 2016; Lee 2011; Choi et al. 2012; Alvarez et al. 2015) were identified and evaluated. The studies included three case controls, one case-crossover and one cohort study. The analysis showed an increased risk of falling (odds ratio 2.03; 95% confidence interval 1.49-2.76) when taking first-generation antihistamines. However, three of the five studies did not differentiate between antihistamines of different generations, which differ in their indications and thus also in the duration of use, frequency of intake and dosage. Correspondingly, first-generation antihistamines are used as long-term treatment for allergies, while for sleeping disorders they are used as short-term therapy. For this reason and due to the small number of studies and unadjusted results, a clear interpretation of the analyses is limited. In 2019, an extensive database search was conducted in PUBMED, BIOSIS, BIOTECHNO, CABA, EMBASE, ESBIOBASE, and SCISEARCH to identify studies on the risk of falls under doxylamine. No further studies could be identified that provide robust data on the risk of falls under doxylamine.

In Germany, there are currently discussions about making first-generation antihistamines with sedative effect available only on prescription to patients over 65 years of age. The PRISCUS list of potentially inadequate medication for the elderly, for example, contains warnings against taking doxylamine because of the increased risk of falling (Holt et al. 2011). However, the data analysis of the adverse reaction reports based on the information provided by pharmaceutical companies did not provide strong evidence of an increased risk in the elderly with regard to fall-associated adverse reactions. The data available to postulate an increased risk of falls among the elderly are limited, both in the area of spontaneous adverse reaction reporting and based on studies. No final conclusion can be drawn about an increased risk of falls among older people when doxylamine is used correctly. At present, the German Federal Institute for Drugs and Medical Devices (BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte) does not consider this to be sufficient to make the use of doxylamine in older patients subject to prescription. (Bundesinstitut für Arzneimittel und Medizinprodukte, Sachverständigen-Ausschuss für Verschreibungspflicht, 18.02.2020)

The aim of this retrospective survey was to collect data on the incidence and causes of falls in older patients, with a special focus on first-generation antihistamines as a possible cause. This data should help to answer the question whether older patients have an increased risk of falling after taking first-generation antihistamines. This safety study was not limited to a specific product, but considered all first-generation antihistamines with sedative effect.

2. Investigations and results

2.1. Study design and legal framework

The study was a non-interventional post-authorisation safety study, which was carried out as retrospective cross-sectional medical chart review in accordance with German Medicines Law (§ 63f) and GVP Module VIII (EMA/813938/2011 Rev 3: Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies, 9 October 2017). The study was registered in the European Union electronic Register of Post-Authorisation Studies (EU PAS Register) with the number EUPAS31817 and was notified to the German Federal Institute for Drugs and Medical Devices (BfArM).

Primary study objective: Investigation of a possible causal relationship between falls in patients ≥ 65 years of age with the intake of first-generation antihistamines with sedative effect during the last 6 months. Secondary objectives: Investigation of a possible causal relationship of falls after taking first-generation antihistamines with sedative effect for the subgroups < 65 years, 65-84 years and ≥ 85 years; determination of the fall rate of patients ≥ 65 years and for the subgroups < 65 years, 65-84 years and ≥ 85 years; identification of causes of falls in patients ≥ 65 years.

The participating physicians were requested to check their patient records for specific information based on a defined list of questions. They were asked to determine the number of affected patients and, in the case of falls after the intake of first-generation antihistamines, to provide relevant case data from patients and their fall(s).

2.2. Participating physicians

A total of 13,866 general practitioners and resident neurologists in Germany were invited to take part in the online survey. 524 physicians (3.8%) opened the link to the survey, 96.2% (13,342 physicians) ignored the invitation despite numerous reminders and contact attempts. Of the 524 physicians who opened the link to the survey, data sets from 169 physicians were validated and included in the evaluation. Of these, 162 (95.9%) were general practitioners and seven (4.1%) neurologists.

2.3. Patient characteristics

The 169 physicians whose data was included in the evaluation had treated a total of 313,046 patients (patient base) within the previous six months. 48.5% of these (151,927 patients) were 65 years old or older.

A total of 379 validated patient records were included in the evaluation. Each of these patient records included at least one fall after the intake of a first-generation antihistamine. A total of 505 falls were documented for these 379 patients.

In more than 90% of the 379 patients, at least one and up to eight underlying and concomitant diseases were listed. The most frequently reported diseases were vascular disorders (46.4%), cardiac disorders (37.7%), metabolism and nutrition disorders (36.9%), nervous system disorders (25.1%) and musculoskeletal and connective tissue disorders (17.9%). A comparable distribution was found among patients aged 65 years and older.

Underlying and concomitant diseases of the patient documentations according to primary system organ class (MedDRA pSOC) are shown in Table 1.

Table 1: Underlying and concomitant diseases of the 379 validated patients according to primary system organ classes (MedDRA pSOC) sorted by frequency

Underlying and concomitant diseases MedDRA pSOC	Number of patients	Percentage of patients
Vascular disorders	176	46.4%
Cardiac disorders	143	37.7%
Metabolism and nutrition disorders	140	36.9%
Nervous system disorders	95	25.1%
Musculoskeletal and connective tissue disorders	68	17.9%
Psychiatric disorders	30	7.9%
Respiratory, thoracic and mediastinal disorders	27	7.1%
Eye disorders	12	3.2%
General disorders and administration site conditions	11	2.9%
Renal and urinary disorders	11	2.9%
Ear and labyrinth disorders	10	2.6%
Gastrointestinal disorders	9	2.4%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9	2.4%
Endocrine disorders	8	2.1%
Injury, poisoning and procedural complications	7	1.8%
Skin and subcutaneous tissue disorders	5	1.3%
Surgical and medical procedures	5	1.3%
Hepatobiliary disorders	3	0.8%
Immune system disorders	3	0.8%
Reproductive system and breast disorders	3	0.8%
Infections and infestations	2	0.5%
Social circumstances	1	0.3%
None / not specified	37	9.8%
Total number of patients	**379**	**100%**

2.4. Fall rates and causes

In total, the physicians reported that 9,922 of 313,046 patients had fallen. The largest number of affected patients were between 65 and 84 years old (44.4%), followed by the over 85-year-olds (38.3%) and the under 65-year-olds (17.3%). The calculated fall rate for all patients was 3.2%; the fall rate for patients aged 65 years and older was 5.4%. As expected, the fall rate increased with

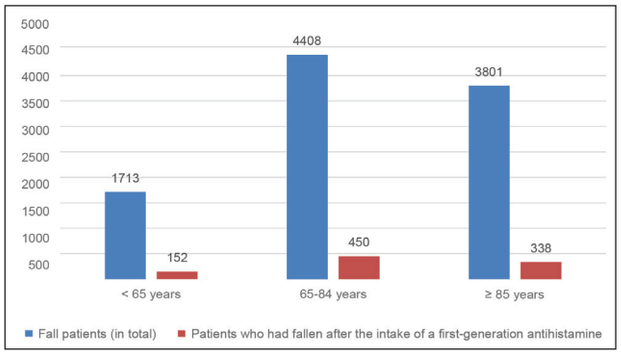

Fig. 1: Total number of patients who had fallen (blue) and number of patients who had fallen after the intake of a first-generation antihistamine (red) within the previous six months for the different age groups..

age: At the age of under 65 years, it was 1.1%, at the age between 65 and 84 years 3.9%, and at the age of 85 years and older 9.9%.
From the total of 313,046 patients, 8,942 (2.9%) had taken first-generation antihistamines at some point within the previous six months. Of these patients, 40.1% were 65 to 84 years and 26.1% aged 85 years and older. More than half of the physicians (59.8%) reported no incident of falling among their patients treated with first-generation antihistamines.
Less than 10% of the 9,922 patients who had fallen (940 patients, 9.5%) had taken a first-generation antihistamine. The proportions were similar for the different age groups (see Fig. 1): Among the under 65-year-olds, 8.9% of the patients affected had taken a first-generation antihistamine; among the 65- to 84-year-olds, it was 10.2 %; and among the patients aged 85 years and older 8.9%. However, the documented intake of a first-generation antihistamine at any time within the previous six months does not necessarily mean that there is actually a correlation between the intake and the fall. In order to assess whether a possible causal relationship exists, the individual cases were analysed.

A secondary study objective was to identify what caused patients 65 years and older to fall. All physicians who had reported at least one affected patient ≥ 65 years of age (n=165) were asked to identify the factors that they considered to be the main cause(s) of falls in patients aged 65 years and older; multiple answers were possible. The possible causes of falls in patients aged 65 years and older reported by the physicians are listed in Table 2.

2.5. *Analysis of reported falls*

940 of the 9,922 fall patients had taken a first-generation antihistamine. Detailed information on 505 falls, which occurred in 379 patients who had taken a first-generation antihistamine, was available. For structured analysis of these 505 falls the following categories were defined:

– *No causal relationship*: The physician assessed the causal relationship between the first-generation antihistamine's intake and the fall as "no relationship".
– *Causal relationship unlikely*: The physician assessed the causal relationship between the first-generation antihistamine's intake and the fall as "unlikely".
– *Invalid – Date of fall before the start of antihistamine intake*: The physician assessed the causal relationship between the first-generation antihistamine's intake and the fall as "possible" or "probable", although the first-generation antihistamine had only been taken after the fall.
– *Invalid – Date of fall more than three days after end of antihistamine intake*: The physician assessed the causal relationship between the first-generation antihistamine's intake and the fall as "possible" or "probable", although the first-generation antihistamine was the last time taken more than three days before the fall. Taking into account the (fivefold) half-lives, a causal relationship in these cases can be assessed as unlikely. The half-life of doxylamine is given as 10.1 to 13.11 hours, or 12.5 to 15.5 hours for geriatric patients. For diphenhydramine, the half-life is between 4 and 8 hours and up to 13.5 hours for older patients (IBM Micromedex® DRUGDEX® 2020).

Table 2: Possible causes of falls in patients aged 65 years and older who had fallen within the previous six months (765 answers from 165 physicians)

Causes of falls in patients ≥ 65 years of age (multiple answers possible)	Absolute frequency	Relative frequency
Neurological disorders e.g. stroke, parkinsonism, gait disorders, vestibular disorders, dementia, delirium	146	88.5%
Musculoskeletal disorders e.g. osteoarthritis, joint deformities, kyphosis, age-related muscle weakness, podiatric conditions	128	77.6%
Sensory abnormalities e.g. visual impairment, hearing impairment, peripheral neuropathy	123	74.5%
Cardiovascular diseases e.g. orthostatic dysregulation, arrhythmias, syncope	118	71.5%
Polypharmacy no conclusive link to an individual medicinal product	80	48.5%
Other chronic medical conditions e.g. anaemia, diabetes mellitus, lung diseases, depression	59	35.8%
Sleeping disorders not treated or insufficiently treated	49	29.7%
Unknown causes	34	20.6%
Certain medicinal products In order of frequency: sedatives (5x), antihypertensive drugs (3x), benzodiazepines (3x), hypnotics (3x), sleep-inducing drugs (3x), psychotropic drugs (2x), alpha-1 adrenergic antagonists, analgesics, antidepressants, antihistamines, diazepines, morphine, tamsulosin, Z-drugs, zolpidem	18	10.9%
Other causes In order of frequency: alcohol (2x), dizziness (2x), stumbling (2x), gait disorder/malposition, injury, lack of drinking, mess/tripping hazards/ladders, overdoses of medication	10	6.1%

– *Not assessable*: The physician assessed the causal relationship between the first-generation antihistamine's intake and the fall as "possible" or "probable", although a temporal relationship between the intake of the first-generation antihistamine and the fall could not be evaluated due to missing or unknown information. For falls with intake of doxylamine tablets or orodispersible tablets further details for case evaluation were requested but were not known to the physicians.
– *Relevant falls*: The physician assessed the causal relationship between the first-generation antihistamine's intake and the fall as "possible" or "probable", and the cases have not been classified as "invalid" or "not assessable". Consequently, relevant falls are defined as those falls for which first-generation antihistamines may come into question as the cause of the fall but it is not a statement about the severity or seriousness of the fall.

The 505 falls were evaluated based on the categories above (Table 3).

Table 3: Analysis of the reported falls with regard to a possible causal relationship to the intake of first-generation antihistamines

Category	Number of falls (absolute)	Number of falls (relative)
No causal relationship	131	25.9%
Causal relationship unlikely	194	38.4%
Invalid - Date of fall before the start of antihistamine intake	15	3.0%
Invalid - Date of fall more than three days after end of antihistamine intake	26	5.1%
Not assessable (due to missing or unknown information)	16	3.2%
Relevant falls (antihistamine intake may come into question as fall cause)	123	24.4%
Total	**505**	**100%**

In almost three quarters of falls (72.5%, 366 falls), a causal relationship between the intake of first-generation antihistamines and the fall is not to be assumed. For 325 falls the physicians assessed the causality as "not related" (25.9%, 131 falls) or "unlikely related" (38.4%, 194 falls); and 41 falls were categorised as invalid as they occurred either before taking the antihistamine (3.0%, 15 falls) or more than three days afterwards (5.1%, 26 falls).

For 16 cases (3.2%), the causal relationship could not be assessed due to missing information. For the remaining 123 falls (24.4%), a causal relationship is possible according to this evaluation ("relevant") why they were further analysed. Of these 123 falls, 69.1% (85 falls) were recorded for patients between 65 and 84 years, 22.8% (28 falls) in the 85+ age group and 8.1% (10 falls) in the under-65s.

The seriousness of the falls was assessed by the physicians according to the German Medicines Law (§ 4(13)): "Serious adverse reactions are adverse reactions that are fatal or life-threatening, require hospitalisation or the prolongation of existing hospitalisation, or lead to persistent or significant disability, incapacity, congenital anomalies or birth defects". The physicians categorized 12.1% (61 falls) of all 505 documented falls and 14.6% (18 falls) of the 123 relevant falls as serious. Hospitalisation was the most frequently mentioned criterion leading to the classification "serious". Thus, more than 85% of the falls were not serious and occurred without medically significant consequences for the patients.

For each documented fall, the physicians were asked whether they considered other causes of falls beyond the potential involvement of first-generation antihistamines possible. The alternative causes of falls listed by the physicians for the 123 relevant falls are shown in Fig. 2.

The listed alternative causes show a similar distribution in the subgroups of relevant falls (for which first-generation antihistamines may come into question as a possible cause of the fall) and all reported falls: cardiovascular diseases (relevant 39.0% / total 34.3%), neurological disorders (relevant 38.2% / total 28.3%), musculoskeletal disorders (relevant 29.3% / total 24.6%) and sensory abnormalities (relevant 26.0% / total 19.2%). In contrast, untreated or inadequately treated sleeping disorders are listed more frequently for the relevant falls with 30.9% than for all falls with 16.4%.

The possible alternative causes mentioned by the physicians are comparable for all patients and patients over 65 years of age. In about 95% of the cases, both in the relevant falls of all patients and in the subgroup of patients over 65 years of age, physicians named at least one, and up to seven alternative causes.

In only seven relevant falls, representing 1.4% of the total number of 505 falls, the reporting physicians did not identify a possible alternative cause for the fall. However, the details given in the case narratives, the concomitant medication and the underlying and concomitant diseases show that for all seven falls, alternative causes are present or at least possible.

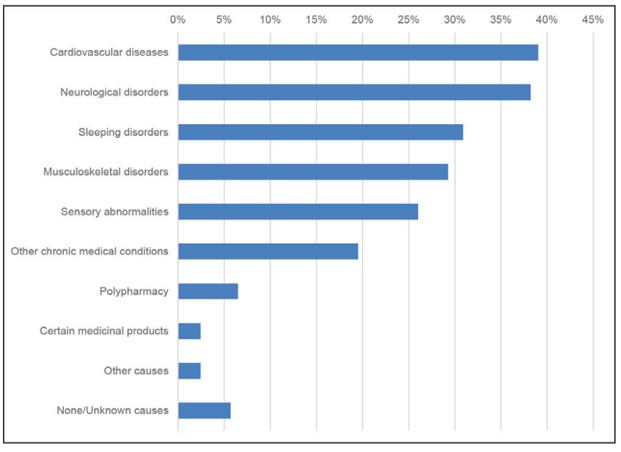

Fig. 2: Alternative causes of falls (n=246, in %) mentioned by the physicians for all 123 relevant falls (multiple answers possible).

3. Discussion

More than 13,500 physicians were invited to participate in the study. Although only a small percentage responded to the invitation, the 169 participating physicians contributed to a large patient collective of more than 313,000 patients treated within the previous six months. The low response rate from physicians could possibly be due to the fact that the topic "first-generation antihistamines as a possible cause of falls" is not perceived as a relevant topic in the medical community. It is known that falls result from a complex interaction of risk factors, and increased exposure to risk factors increases the risk of falling (WHO 2007). In this study, the four most frequently cited alternative causes of falls in patients over 65 years taking first-generation antihistamines are

the same as the causes of falls in patients over 65 years of age in general. Thus, the following underlying and concomitant diseases were suspected by the physicians to be the main causes of falls for patients over 65 years of age (in alphabetical order): cardiovascular diseases, musculoskeletal disorders, neurological disorders and sensory abnormalities. In this study, too, the underlying and concomitant diseases were suspected by the physicians as causes of falls in patients aged 65 years and older. Sleeping disorders were assessed as a possible cause of the fall by 29.7% of the physicians in the present study. There is a correlation between poor sleep and increased morbidity in the elderly and it has been shown that shortening the sleep period is associated with a reduction in health-related quality of life (Lubetkin and Jia 2018).

As expected, the fall rate increases with age (< 65 years 1.1%; 65-84 years 3.9%; ≥ 85 years 9.9%). Among the 9,922 patients who experienced a fall, less than 10% (940 patients, 9.5%) had taken a first-generation antihistamine. Thus, more than 90% of falls occurred without the potential involvement of a first-generation antihistamine. More than half of the physicians (59.8%) reported no incident of falling among their patients treated with first-generation antihistamines.

The analysis of the 505 falls documented in detail suggests that the proportion of falls in which the first-generation antihistamine may be at least partly responsible is even lower: in almost three quarters of falls (72.5%), no causal link can be assumed: First-generation antihistamines were suspected as a possible cause in 41 falls, even though they had been taken after the fall (15 falls) or the last intake was more than three days before the fall (26 falls). In addition, in almost two thirds of falls (64.4%) the reporting physicians assessed the causality as negative or unlikely. However, it should also be taken into account that the data is based on the information available to physicians in their patient records. It can be assumed that the participating physicians are not always fully aware of the use of over-the-counter (OTC) products by their patients on the one hand and of all fall events on the other.

In the study, only a small proportion of the fall patients had taken a first-generation antihistamine within the previous six months. Only for a quarter of the more precisely analysed fall events with documented intake of a first-generation antihistamine is the intake even considered a possible cause of the fall. This suggests that first generation antihistamines do not play a relevant role in the incident "fall". Almost one third of the physicians considered sleep disorders to be a possible cause. Low-threshold access to adequate treatment for sleep disorders is therefore very important.

4. Experimental

4.1. Survey description

An online survey by DocCheck Community GmbH was chosen for conducting the study. The survey was developed in consultation with an expert review and through a pre-test phase. A total of 13,866 physicians of the DocCheck Panel, including all 10,995 general practitioners and 2,871 resident neurologists, were invited to participate in the survey.

The pre-test phase took place from October 22 to 28, 2019, with the main survey starting on October 29. Data collection was completed on December 12, 2019. The evaluation and preparation of the final report took place in January and February 2020 (final report dated March 05, 2020).

The following variables were asked: Part 1 (basic survey): Personal data of the physician: First name, last name, practice address, lifelong physician number; sociodemographic data of the physician: specialty and field of activity, gender, age and federal state; size of the patient population (patients treated within the previous six months); incidence of falls (including the main causes in patients ≥ 65 years); number of patients with sleeping disorders; number of patients taking first-generation antihistamines due to sleeping disorders or other reasons; number of falls while taking first-generation antihistamines (within the previous six months).

Part 2 (Patient documentation): Case data on falls related to first-generation antihistamines: demographic patient data: age, gender, concomitant diseases and -medications, previous falls and frequency of falls; fall-related information: specific antihistamine including dose, use and period of use, causality, seriousness, outcome, causes and description of the fall.

4.2. Statistical analysis

The evaluation of the data was done by descriptive statistics. The data was analysed by summation as well as by calculation of absolute and relative proportions and incidence rates. The data was collected and evaluated according to the following age groups: < 65 years; 65-84 years; ≥ 85 years.

4.3. Ethical considerations

This safety study was a retrospective data collection in which no patients were prospectively recruited. A risk for patients could thus be completely excluded. Therefore, no advice or opinion from an independent ethics committee was obtained.

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Conflicts of interest: The authors declare that they are employees of STADA Arzneimittel AG.

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