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Clinical assessment of antipsychotic-induced extrapyramidal symptoms in nursing home residents with schizophrenia

Kliniczna ocena polekowych objawów pozapiramidowych u pensjonariuszy domów pomocy społecznej z rozpoznaniem psychoz schizofrenicznych

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Abstract

This study assessed the incidence and potential risk factors for extrapyramidal symptoms in a population of nursing home residents with schizophrenia receiving antipsychotic medication. A study sample consisted of 261subjects, recruited in nursing homes in Poland. Extrapyramidal symptoms were evaluated using the Simpson–Angus Scale and each extrapyramidal symptoms domain was determined using the appropriate standard scale. The results of the study indicate that approximately 60–70% of patients did not develop extrapyramidal symptoms following prolonged antipsychotic treatment. The risk of extrapyramidal symptoms increased with age, dose of antipsychotic and the number of antipsychotic drugs used concomitantly, and decreased with the duration of the disease. There was no direct effect of gender or common substances of abuse, such as alcohol or nicotine, on the incidence of extrapyramidal symptoms. Among concomitant diseases, hypertension and epilepsy played the most significant role in modulating the incidence and severity of extrapyramidal adverse events. Patients with high blood pressure were less likely to develop extrapyramidal symptoms. Epilepsy significantly increased the risk of some extrapyramidal antipsychotic-induced motor symptoms, such as akathisia and dystonia. Combined treatment with antipsychotic and antidepressant drugs produced slightly higher risk of parkinsonian syndrome. In conclusion, our data indicate that an incidence, type and severity of drug-induced extrapyramidal adverse effects may strongly depend on individual patient characteristics, such as age, gender or comorbid medical conditions and medication, and thus these factors should be taken into account in the therapeutic process.

Key words: extrapyramidal symptoms, antipsychotics, schizophrenia, nursing home residents

Streszczenie

W prezentowanym badaniu oceniano czynniki ryzyka oraz częstość występowania objawów pozapiramidowych u pensjonariuszy domów pomocy społecznej z rozpoznaniem psychoz schizofrenicznych, leczonych długotrwale lekami przeciwpsychotycznymi. Badaną populację stanowiło 261 pacjentów domów pomocy społecznej regionu łódzkiego. Nasilenie objawów pozapiramidowych było oceniane za pomocą ogólnej skali Simpsona–Angusa, a poszczególne domeny objawów pozapiramidowych analizowano za pomocą odpowiednich standardowych skal. U większości badanych pacjentów (około 60–70%) nie stwierdzono objawów pozapiramidowych. Ryzyko wystąpienia objawów pozapiramidowych wzrastało wraz z wiekiem, dawką leku oraz liczbą leków przeciwpsychotycznych przyjmowanych jednocześnie, a zmniejszało się wraz z czasem trwania choroby. Częstość występowania objawów pozapiramidowych nie zależała natomiast od płci czy stosowania przez pacjentów popularnych używek, takich jak alkohol czy nikotyna. Wśród współistniejących chorób największy wpływ na wystąpienie i nasilenie objawów pozapiramidowych wykazywały nadciśnienie tętnicze oraz padaczka. Pacjenci z nadciśnieniem tętniczym byli w mniejszym stopniu narażeni na wystąpienie objawów pozapiramidowych, podczas gdy u chorych na padaczkę stwierdzono podwyższone ryzyko wystąpienia niektórych pozapiramidowych objawów ruchowych, takich jak akatyzja i dystonia. Łączne przyjmowanie leków przeciwpsychotycznych i przeciwdepresyjnych zwiększało ryzyko wystąpienia zespołu parkinsonowskiego. Otrzymane wyniki wskazują, że indywidualne cechy pacjenta, takie jak wiek, płeć, współistniejące schorzenia oraz przyjmowane leki, w znaczący sposób mogą wpływać na częstość występowania, rodzaj i nasilenie polekowych objawów pozapiramidowych, a zatem czynniki te powinny być brane pod uwagę w procesie terapeutycznym.

Słowa kluczowe: objawy pozapiramidowe, leki przeciwpsychotyczne, schizofrenia, pensjonariusze domów pomocy społecznej

INTRODUCTION

Extrapyramidal symptoms (EPS) are the most common adverse events related to antipsychotic treatment. EPS negatively affect the quality of life of schizophrenic patients (Browne *et al.*, 1996) and may contribute to nonadherence to antipsychotic medication treatment (Marder, 1998; Perkins, 2002). Identification of risk factors, biological substrate and treatment options for EPS is necessary to improve the outcomes and safety of antipsychotic therapy.

The four types of drug-induced EPS are akathisia, dystonia, parkinsonism and dyskinesia. They can be classified as "early" or "late" symptoms, depending on the time since initiation or discontinuation of treatment. Early symptoms, including akathisia and dystonia, occur within the first days or months of treatment, while late symptoms, such as tardive dyskinesia, may appear after a few years of antipsychotic therapy (Divac *et al.*, 2014).

Antipsychotic drugs are commonly used in older adults with various conditions, including schizophrenia, psychosis, dementia, mania, depressive disorders and mood disorders (Alexopoulos *et al.*, 2004; Targum, 2001; Wastesson *et al.*, 2015). According to an international survey, the use of antipsychotics among residents of nursing care facilities in different countries is particularly high, with findings of 24% in the USA (Kamble *et al.*, 2009), 25% in Australia (Snowdon *et al.*, 2005), 33% in Belgium (Azermai *et al.*, 2011) and 46% in Austria (Mann *et al.*, 2009). However, few studies have focused on clinical variables that might modify the risk of treatment-related EPS selectively in this group of patients (Avorn *et al.*, 1994). The purpose of this study was to assess the incidence of EPS and to identify potential risk factors for EPS in a population of nursing home residents with schizophrenia receiving antipsychotic treatment.

MATERIAL AND METHODS

A sample composed of 261 nursing home residents from Poland (Lodz region), who were diagnosed with schizophrenia and under continuous treatment with antipsychotics, were enrolled in the study. The inclusion criteria were: age over 18 years, clinical diagnosis of schizophrenia (ICD-10 code F20), and antipsychotic treatment. Exclusion criteria were: no written informed patient consent and Parkinson's disease, essential tremor, Huntington's disease, tics and muscle dystonias diagnosed before antipsychotic treatment. Patients signed a written consent form. The management of each nursing home approved the study. The authors obtained the ethical approval (No. RNN/92/07/KB) for this study from the Ethics Committee at Medical University of Lodz.

The following baseline data were obtained from a retrospective review of the patients' medical records: gender, age, length of stay in the nursing home, treatment duration, antipsychotic doses, other medications, comorbid diagnosis such as diabetes, hypertension, respiratory and heart diseases, neurological diseases and alcohol and nicotine abuse.

The study included one visit in which psychiatric and neurologic evaluations were performed. Psychiatric status and diagnoses were assessed with a Brief Psychiatric Rating Scale (BPRS).

To assess EPS, the Simpson–Angus Scale (SAS) was used. Akathisia was evaluated using the Barnes Akathisia Rating Scale (BARS), pseudoparkinsonian symptoms were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS), the presence of dystonia was determined using the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) and dyskinesia was measured with the Abnormal Involuntary Movement Scale (AIMS) (Suzuki, 2011). Tests were given and evaluated by experienced raters.

To compare the dosage of various antipsychotic drugs received by patients, the doses were expressed as chlorpromazine equivalents, according to suggestions of other authors (Atkins *et al.*, 1997; Bazire, 2010; Rzewuska, 2003; Woods, 2003).

Statistical analysis

Data are presented as means or percentages. Descriptive analysis was performed to depict patient characteristics using the chi-square test, the Mann–Whitney *U*-test and the Kruskal–Wallis ANOVA, as appropriate. To investigate the relationship between EPS and factors such as age, hypertension, epilepsy, duration of disease, use of antipsychotics as mono- or polytherapy and other drugs, univariate logistic regression analysis was performed (one per each symptom/factor combination). The significance was set at $p < 0.05$.

RESULTS

Description of the study population

Baseline demographic and clinical characteristics of the study population are summarized in Tab. 1. The total study sample included 261 residents. The mean age of the included participants was 57.84 ± 11.59 years, of whom 118 (45%) were female. Schizophrenia was diagnosed in 110 (93.22%) women and 133 (93.01%) men ($p < 0.05$; ns). The mean duration of residence in a nursing home was 137.17 ± 108.85 months for all patients, while women had resided significantly longer than men (160.04 ± 112.83 and 118.30 ± 102.04 months, respectively) ($p < 0.001$). The mean duration of disease was 29.56 ± 11.28 years. The mean duration of disease was significantly longer in women than in men (32.24 ± 10.95 and 27.34 ± 11.10 years, respectively) ($p < 0.001$).

Description of diseases, treatments and addictive substance use

The vast majority of the study population was diagnosed with schizophrenia, ranging from 84.62% in the youngest age group (<50 years) to 100% in residents older than 70 years.

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	Gender	
	Female ***n*** **= 118**	**Male** ***n*** **= 143**
Age [years]	61.9 ± 11.02	54.48 ± 10.99
Statistical analysis	Homogeneity of variance (Levene's test) $L = 0.14$, $p > 0.05$	
ICD-10 Schizophrenia Other psychotic disorders Schizophrenia and mild mental retardation	 93.22 (110) 2.54 (3) 4.24 (5)	 93.01 (133) 3.5 (5) 3.5 (5)
Statistical analysis	Chi^2 test = 0.28, $p > 0.05$	
Duration of the disease [years]	32.24 ± 10.95	27.34 ± 11.10
Statistical analysis	Mann–Whitney's *U*-test = 3.31, $p < 0.001$	
Smoking	55.08 (65/118)	82.52 (118/143)
Statistical analysis	Chi^2 test = 23.45, $p < 0.001$	
Alcohol use	8.47 (10)	41.96 (60)
Statistical analysis	Chi^2 test = 40.51, $p < 0.001$	
Hypertension	35.59 (42)	23.78 (34)
Statistical analysis	Chi^2 test = 4.36, $p < 0.05$	
Epilepsy	10.17 (12)	6.29 (9)
Statistical analysis	Chi^2 test = 1.31, $p > 0.05$	
Antiepileptic drugs	35.44 (43)	34.27 (49)
Statistical analysis	Chi^2 test = 0.13, $p > 0.05$	
Antidepressant drugs	10.17 (12)	4.9 (7)
Statistical analysis	Chi^2 test = 2.66, $p > 0.05$	
Anticholinergic drugs	39.83 (47)	33.57 (48)
Statistical analysis	Chi^2 test = 1.09, $p > 0.05$	
BPRS	60.71 ± 13.75	56.98 ± 13.78
Statistical analysis	Mann-Whitney's *U*-test = 2.22, $p < 0.05$	

Values are expressed as mean ± *SD* or % (*n*).
BPRS – Brief Psychiatric Rating Scale; ***SD*** – standard deviation.

Tab. 1. Patient demographics and baseline characteristics

The prevalence of other illnesses, such as hypertension and coronary heart disease, was lowest in the age group <50 years (10.71% and 1.54%, respectively) and systematically increased with age. The highest incidence was observed in the age group >70 years (55% patients with hypertension and 45% with coronary heart disease). Statistical analysis showed significant differences in the prevalence of these diseases between the age groups ($p < 0.001$ and $p < 0.05$). Hypertension and coronary heart disease were significantly more prevalent in women (35.59% and 24.58%, respectively) than in men (23.78% and 13.29%, respectively) ($p < 0.05$).
Polytherapy was mostly used in the youngest age group of patients (<50 years) (93.85%), while 52.5% of residents >70 years old received monotherapy. The differences between age groups were statistically significant ($p < 0.001$). Polytherapy was more frequently used in both men and women.
Antiepileptic drugs were mostly prescribed in residents aged <50 years (46.15%) and significantly less frequently in the older group of patients (>70 years) (17.5%). The opposite trend occurred in the use of anticholinergic drugs, which was the least frequently prescribed medication in the group <50 years (24.62%) and the most common in the age group >60 years (50% and 47.5%, respectively). The differences in the use of both drugs between age groups were statistically significant ($p < 0.05$ and $p < 0.01$, respectively). The overall use of antidepressants in the study population was low, ranging from 5% in residents <60 and >70 years to about 10% in other age groups ($p > 0.05$; ns). No significant differences were found in the use of these drugs when comparing males and females.
Smoking and alcohol use was significantly higher in the age group <50 years (92.31% and 43.08%, respectively). The percentage of smokers and alcohol users decreased with age. In the group of patients >70 years, only 25% were smokers and 5% consumed alcohol. Statistical analysis showed significant differences in smoking and alcohol use between age groups ($p < 0.001$). The prevalence of smoking and alcohol use significantly differed between female and male residents ($p < 0.001$). Smoking was reported by 55.08% women and 82.52% men, while alcohol use was reported by 8.47% women and 41.96% men.

Description of antipsychotic drug utilization

An overall average chlorpromazine-equivalent dose per day in the study population was 568.17 ± 312.82 per patient. The highest chlorpromazine-equivalent dose was observed in the age group >50 years (711.72 ± 291.15). The average chlorpromazine-equivalent dose used in this population in the past was 336.95 ± 143.18.
The overall duration of antipsychotic drug use in the past (prior to the study) was 131.24 ± 82.20 months.
The mean BPRS score in the overall population, irrespective of age, was 58.67 ± 13.8. Women displayed significantly higher BPRS scores than men (means of 60.71 ± 13.75 and 56.98 ± 13.78, respectively) ($p < 0.05$).

Analysis of potential clinical factors contributing to EPS

The incidence of EPS by gender and age groups is shown in Tab. 2. Of the total population of study participants, 63.56% of women and 64.34% of men did not have EPS as determined with the general SAS. There were no differences in the incidence of EPS between men and women ($Chi^2 = 0.02$; $p > 0.05$). Among EPS domains studied, only dystonia measured with the BFMDRS scale was significantly more frequent in women (71.19%) than in men (59.44%) ($Chi^2 = 3.94$; $p < 0.05$).
The incidence of EPS was highest in the oldest age group (>70 years) (42.50%) and in the age group 51–60 years (40.0%), and the least frequent in the age group 61–70 years (26.79%). The most common EPS domains were dyskinesia and dystonia, detected in 90% of the study participants from the oldest age group, while parkinsonism and akathisia were diagnosed with a frequency similar to the general population treated with antipsychotics. Statistically significant differences between the age groups were detected with respect to parkinsonism and dyskinesia.

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	SAS	BARS	BFMDRS	UPDRS	AIMS
Gender					
Female	36.44 (43/118)	22.03 (26/118)	**71.19 (84/118)**	24.58 (29/118)	66.95 (79/118)
Male	35.66 (51/143)	26.57 (38/143)	**59.44 (85/143)**	21.68 (31/143)	67.13 (96/143)
Chi^2	0.02	0.73	**3.94**	0.31	0.01
p	>0.05	>0.05	**<0.05**	>0.05	>0.05
Age					
<50	33.85 (22/65)	18.46 (12/65)	**41.54 (27/65)**	**12.31 (8/65)**	**50.77 (33/56)**
51–60	40 (40/100)	23 (23/100)	**66 (66/100)**	**23 (23/100)**	**64 (64/100)**
61–70	26.79 (15/56)	23.21 (12/56)	**71.43 (40/56)**	**25 (14/56)**	**75 (42/56)**
>70	42.5 (17/40)	40 (16/40)	**90 (36/40)**	**37.5 (15/40)**	**90 (36/40)**
Chi^2	3.69	6.69	**29.31**	**9.18**	**21.09**
p	>0.05	>0.05	**<0.05**	**<0.05**	**<0.001**

Incidence is expressed as % (*n*/total *n*).
SAS – Simpson-Agnus Scale; **BARS** – Barnes Akathisia Rating Scale; **BFMDRS** – Burke–Fahn–Marsden Dystonia Rating Scale; **UPDRS** – Unified Parkinson's Disease Rating Scale; **AIMS** – Abnormal Involuntary Movement Scale.
Values highlighted in bold are $p < 0.05$.
[a] Incidence was calculated as the number of EPS divided by the total number of patients in the group and expressed as a percentage.

Tab. 2. Incidence of EPS by gender and age[a]

The statistical analysis of potential factors contributing to EPS is presented in Tabs. 3–7. Similar scores of all EPS domains were observed in men and women. Factors associated with increased risk of EPS include age, epilepsy, antiepileptic drugs and the number of antipsychotics used in the course of the disease (mono- or polytherapy). Factors associated with reduced risk of EPS include hypertension and duration of disease.
Age slightly, but significantly, increased the risk of EPS. An increase was observed across all age groups in the scores of all EPS domains. Epilepsy increased the risk almost six fold of general EPS, including akathisia and dystonia. Polytherapy (more than one antipsychotic used in the course of therapy) increased the risk of all EPS domains except for dyskinesia. Antidepressants slightly increased the risk of parkinsonism, while antiepileptic drugs doubled its risk. Hypertension reduced the scores of all EPS domains, including dystonia and parkinsonism. The risk of EPS decreased over the duration of the disease (SAS).

DISCUSSION

The first aim of this study was to determine the incidence of extrapyramidal adverse events in nursing home residents with schizophrenia treated with antipsychotics. We found that upon prolonged antipsychotic treatment, approximately 60–70% of subjects did not develop EPS. This result is in line with previous observational studies in which no EPS were reported in about 60% of antipsychotic-treated patients (Avorn *et al.*, 1994; Novick *et al.*, 2010). The most commonly recorded side effects following antipsychotic treatment in the current study were dyskinesia (67%) and dystonia (64.75%). Less common symptoms included parkinsonism (22.99%) and akathisia (24.52%). Data from available research indicate that prevalence of various types of EPS in subjects treated with antipsychotic drugs may vary, depending on diagnostic criteria, dose and type of drugs and sociodemographic and clinical characteristics of patients. For example, akathisia has been considered the most frequent EPS, affecting 25–75% of the antipsychotic-treated population (Miller *et al.*, 1997). Yet, van Harten *et al.* (1997) reported that the most frequent antipsychotic-related side effects were tardive dyskinesia and parkinsonism. Moreover, the study demonstrated that one psychiatric patient may exhibit a combination of different EPS, while the most common combination includes various forms of hyperkinetic or hypokinetic movement disorders.

Scale	Gender		Mann–Whitney *U*-test	
	Female	Male		
	Mean (± *SD*)	Mean (± *SD*)	*U*	*p*
SAS	9.45 ± 5.74	9.28 ± 6.18	0.45	>0.05
BARS	1.80 ± 2.22	2.20 ± 2.15	1.66	>0.05
BFMDRS	8.79 ± 7.71	7.38 ± 7.34	1.43	>0.05
UPDRS	31.99 ± 18.53	28.63 ± 19.07	1.63	>0.05
AIMS	7.24 ± 6.35	6.86 ± 5.82	0.08	>0.05

SAS – Simpson-Agnus Scale; **BARS** – Barnes Akathisia Rating Scale; **BFMDRS** – Burke–Fahn–Marsden Dystonia Rating Scale; **UPDRS** – Unified Parkinson's Disease Rating Scale; **AIMS** – Abnormal Involuntary Movement Scale; ***SD*** – standard deviation.
Values highlighted in bold are $p < 0.05$.

Tab. 3. Statistical analysis of EPS by gender

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Scale	Age [years]				Kruskal–Wallis ANOVA	
	<50	51–60	61–70	>70		
	Mean (± *SD*)	Mean (± *SD*)	Mean (± *SD*)	Mean (± *SD*)	*H*	*p*
SAS	8.45 ± 6.84	9.76 ± 6.03	9.71 ± 5.92	9.33 ± 4.18	3.92	>0.05
BARS	1.89 ± 2.22	2.01 ± 2.16	1.84 ± 2.13	2.54 ± 2.23	3.69	>0.05
BFMDRS	4.88 ± 7.43	7.82 ± 7.13	8.77 ± 7.12	11.90 ± 6.71	**32.22**	**<0.001**
UPDRS	24.43 ± 16.86	29.51 ± 19.97	31.70 ± 18.44	38.88 ± 16.65	**19.00**	**<0.001**
AIMS	5.22 ± 6.51	6.71 ± 5.66	7.93 ± 5.77	9.35 ± 5.47	**16.63**	**<0.001**

SAS – Simpson-Agnus Scale; **BARS** – Barnes Akathisia Rating Scale; **BFMDRS** – Burke–Fahn–Marsden Dystonia Rating Scale; **UPDRS** – Unified Parkinson's Disease Rating Scale; **AIMS** – Abnormal Involuntary Movement Scale, ***SD*** – standard deviation.
Values highlighted in bold are $p < 0.05$.

Tab. 4. Statistical analysis of EPS by age

In this study, we also investigated clinically important potential risk factors of antipsychotic-induced EPS, such as gender, age, antipsychotic doses, duration of psychiatric illness, substance abuse and concomitant diseases and medications.

As expected, the risk of EPS increased with age and antipsychotic dose. Both factors have been previously described as clinical predictors of extrapyramidal side effects associated with antipsychotic therapy (Divac *et al.*, 2014; Kaiser *et al.*, 2002). Elderly patients are particularly vulnerable to adverse drug effects (Barzilai *et al.*, 2012). In elderly patients, a slower rate of pharmacokinetic processes alters drug metabolism and elimination, leading to significant drug accumulation in the body and an increased risk of adverse reactions (Mangoni and Jackson, 2004). Furthermore, aging is associated with alterations in monoamine levels and receptor dysfunction in the brain (Darbin, 2012), thus, drugs acting on the monoaminergic system are more likely to cause adverse events related to treatment. However, despite an increased risk of adverse events in older adults, the use of antipsychotic agents is relatively high in this group of patients (Gareri *et al.*, 2014).

The use of polytherapy with antipsychotics increased the risk of all EPS (except for dyskinesia), probably because of higher cumulative doses. It is important observation, because such drugs are frequently combined, especially for people with schizophrenia.

There were no marked gender differences in the rates of drug-induced EPS, except for dystonia. Women manifested higher incidence of dystonia and greater severity of other EPS domains than men, although the latter effect was not statistically significant. Other studies have reached conflicting conclusions. For example, tardive dyskinesia has been found to be more prevalent in men (Xiang *et al.*, 2011), whereas drug-induced pseudoparkinsonism has been diagnosed more frequently in women (Thanvi and Treadwell, 2009), although other authors have not been able to establish the same correlation (Aichhorn *et al.*, 2006; Kaiser *et al.*, 2002). The discrepancies between results obtained in these studies may result from different research methodology or differences in population characteristics, e.g. ethnic origin (Ormerod *et al.*, 2008).

The risk of EPS was reduced with longer duration of disease. There was no direct effect of common substance abuse, such as alcohol or nicotine, on the incidence of extrapyramidal side effects. However, it was found that alcohol potentiated psychiatric symptoms (measured with the BPRS), while smoking evoked the opposite effect. This potentially adverse association may further implicate the need for dosage adjustments of antipsychotic drugs in alcohol or nicotine users. Many authors consider alcohol a risk factor of drug-induced movement disorders in patients with schizophrenia. It has been shown, for example, that alcohol worsens EPS, such as pseudoparkinsonism, akathisia (Zhornitsky *et al.*, 2010) and tardive dyskinesia (Dixon *et al.*, 1992). The apparent discrepancy between the results obtained in this study and other reports may result from differences in the amount of alcohol consumed by patients.

Among concomitant diseases, hypertension and epilepsy played the most significant roles in modulating the

Scale	Chlorpromazine-equivalent dose/day		Mann–Whitney *U*-test	
	EPS absent	EPS present		
	Mean (± *SD*)	Mean (± *SD*)	*U*	*p*
SAS	516.38 ± 296.63	660.18 ± 321.16	**−3.78**	**<0.001**
BARS	565.74 ± 319.39	575.67 ± 293.96	−0.52	>0.05
BFMDRS	557.37 ± 293.48	574.05 ± 323.56	−0.22	>0.05
UPDRS	557.04 ± 306.02	605.47 ± 334.56	−1.06	>0.05
AIMS	582.88 ± 336.12	560.94 ± 301.45	−0.19	>0.05

SAS – Simpson-Agnus Scale; **BARS** – Barnes Akathisia Rating Scale; **BFMDRS** – Burke–Fahn–Marsden Dystonia Rating Scale; **UPDRS** – Unified Parkinson's Disease Rating Scale; **AIMS** – Abnormal Involuntary Movement Scale; ***SD*** – standard deviation.
Values highlighted in bold are $p < 0.05$.

Tab. 5. Statistical analysis of EPS by chlorpromazine-equivalent dose

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Scale	Duration of disease [years]		Mann–Whitney *U*-test	
	EPS absent	EPS present		
	Mean (± *SD*)	Mean (± *SD*)	*U*	*p*
SAS	29.66 ± 11.36	29.36 ± 11.20	0.51	>0.05
BARS	28.54 ± 11.04	32.67 ± 11.53	**–2.27**	**<0.05**
BFMDRS	24.79 ± 10.18	32.15 ± 11.03	**–4.89**	**<0.001**
UPDRS	28.90 ± 11.06	31.75 ± 11.83	–1.28	>0.05
AIMS	25.88 ± 11.34	31.36 ± 10.84	**–3.73**	**<0.001**

Values are expressed as mean ± *SD*.
SAS – Simpson-Agnus Scale; **BARS** – Barnes Akathisia Rating Scale; **BFMDRS** – Burke–Fahn–Marsden Dystonia Rating Scale; **UPDRS** – Unified Parkinson's Disease Rating Scale; **AIMS** – Abnormal Involuntary Movement Scale; ***SD*** – standard deviation.
Values highlighted in bold are $p < 0.05$.

Tab. 6. Statistical analysis of EPS by duration of illness

incidence and severity of extrapyramidal adverse events. Patients with high blood pressure were less likely to experience EPS caused by long-term use of antipsychotics. Notably, the study conducted by Scigliano *et al.* (2006) in 178 patients with idiopathic Parkinson's disease showed that elevated blood pressure is associated with a reduced risk of Parkinson's disease. This potentially beneficial effect may be associated with pharmacotherapy used in hypertension. For example, the antihypertensive drug propranolol is a first line treatment option for antipsychotic-induced akathisia (Dumon *et al.*, 1992; Fischel *et al.*, 2001; Holloman and Marder, 1997; Lipinski *et al.*, 1988) and its beneficial effect has been linked to beta-2-adrenergic receptors blockade in the brain (Adler *et al.*, 1985). Other groups of drugs used in the treatment of hypertension, such as calcium channel blockers, have also been found to exert potentially therapeutic effects in drug-induced tardive dyskinesia, although the effects have not been confirmed in randomized clinical trials (Essali *et al.*, 2011).

Another potential mechanism may be related to sympathetic and parasympathetic autonomic nervous system dysfunction observed in hypertension and extrapyramidal movement disorders (Brooks, 1997; Ziemssen and Reichmann, 2011). One can assume that increased sympathetic neural activity associated with hypertension (Brooks, 1997) can reduce some EPS.

Finally, direct involvement of specific neurotransmitter pathways within the brain structures that control both motor function and blood pressure, such as dopamine, cannot be ruled out. The brain's dopamine system, particularly the nigrostriatal pathway, plays a direct role in the regulation of both blood pressure and the development of hypertension.

	OR	95% CI	*p*
EPS (SAS)			
Age	1.09	1.04–1.13	**<0.001**
Hypertension	0.49	0.25–0.98	**<0.05**
Epilepsy	5.62	1.70–18.58	**<0.01**
Duration of disease	0.97	0.93–1.01	>0.05
Number of antipsychotics (mono-/polytherapy)	2.45	1.69–3.50	**<0.001**
Akathisia (BARS)			
Age	1.04	1.01–1.07	**<0.01**
Hypertension	1.46	0.76–2.83	>0.05
Epilepsy	4.78	1.43–9.42	**<0.01**
Number of antipsychotics	1.95	?	**<0.05**
Antiepileptic drugs	0.53	?	>0.05
Dystonia (BFMDRS)			
Age	1.01	1.06–1.12	**<0.001**
Epilepsy	6.39	1.39–29.28	**<0.05**
Number of antipsychotics	2.14	1.05–4.38	**<0.05**
Parkinsonism (UPDRS)			
Age	1.09	1.05–1.13	**<0.001**
Hypertension	0.42	0.19–0.91	**<0.05**
Number of antipsychotics	1.76	1.22–2.54	**<0.01**
Antiepileptic drugs	2.14	1.09–4.20	**<0.05**
Antidepressants	1.04	0.31–3.52	>0.05
Dyskinesia (AIMS)			
Age	1.07	1.04–1.10	**<0.001**
Number of antipsychotics	1.94	0.97–3.89	>0.05

SAS – Simpson-Agnus Scale; **BARS** – Barnes Akathisia Rating Scale; **BFMDRS** – Burke–Fahn–Marsden Dystonia Rating Scale; **UPDRS** – Unified Parkinson's Disease Rating Scale; **AIMS** – Abnormal Involuntary Movement Scale; **95% CI** – 95% confidence interval; **OR** – odds ratio.
Values highlighted in bold are $p < 0.05$.

Tab. 7. Potential factors contributing to EPS by univariate logistic regression analysis

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Experimental studies using the spontaneous hypertensive rat model (SHR) revealed a number of changes in the dopaminergic system, such as an increased level of DOPAC, increased expression of dopamine transporter and D1 and D2 receptors in the striatum (Cho *et al.*, 2014; Watanabe *et al.*, 1989) and increased sensitivity of dopamine D2 receptors in the mesolimbic circuit (Russell *et al.*, 1995). Moreover, loss of brain dopamine evoked by lesions of substantia nigra prevents the development of hypertension in SHR rats (de Jong *et al.*, 1995). These data suggest that high blood pressure is associated with hyperactivity of nigrostriatal dopamine. Therefore, it can be assumed that dopamine overactivity in the nigrostriatal system resulting from high blood pressure can compensate functional deficits of dopaminergic transmission in this brain region caused by prolonged antipsychotic medication use. This hypothetical mechanism may explain the reduced incidence of EPS in patients with hypertension observed in the present study.

Epilepsy significantly increased the risk of some extrapyramidal antipsychotic-induced motor symptoms, especially akathisia and dystonia. There are several explanations for this association. Both epilepsy and extrapyramidal side effects are related to abnormalities in the brain's GABAergic system (Boecker *et al.*, 2010; Lasoń *et al.*, 2013). Certain motor complications, such as symptoms of dystonia, may also occur in the course of epilepsy (Newton *et al.*, 1992). Further, patients with epilepsy treated with valproic acid have an increased risk of parkinsonism (Zadikoff *et al.*, 2007). Finally, seizures are associated with overproduction of free radicals in mitochondria (Puttachary *et al.*, 2015). Schizophrenic patients with extrapyramidal signs manifest deficits in antioxidant enzymes (Zhang *et al.*, 2007) which likely explains a greater vulnerability to EPS in patients who suffer from both epilepsy and schizophrenia.

Patients receiving combined treatment with antipsychotics and antidepressant drugs exhibit a slightly higher risk of parkinsonian syndrome. Similar observations have been reported in animal studies (Tatara *et al.*, 2012). This effect may result from adverse drug interactions, as some commonly used tricyclic antidepressants or serotonin reuptake inhibitors block the activity of certain forms of cytochrome P450 responsible for the metabolism of antipsychotics. For example, fluoxetine and paroxetine are potent inhibitors of CYP2D6, involved in risperidone and haloperidol breakdown (Probst-Schendzielorz *et al.*, 2015). In the case of combined use of these drugs, inhibition of CYP2D6 activity by antidepressants may interfere with antipsychotic elimination, increasing its blood concentration and thus potentiating side effects associated with antipsychotic treatment. Spina *et al.* (2002) demonstrated that administration of fluoxetine (20 mg/day) to patients treated with risperidone may cause a four- to ten-fold increase in risperidone plasma levels. Furthermore, approximately 30% of patients receiving combined treatment with fluoxetine and risperidone experienced worsening of akathisia and parkinsonian symptoms. Additionally, pharmacodynamic interactions cannot be ruled out, as both tricyclic antidepressants and serotonin reuptake inhibitors may induce extrapyramidal movement disorders (Gill *et al.*, 1997; Govoni *et al.*, 2001). In clinical practice, a combination of antipsychotics and antidepressants is frequently used in cases of coexisting psychotic and depressive symptoms, which may often be beneficial for patients (Mao and Zhang, 2015). Our findings, in line with data provided by other authors, indicate that this combination can also be associated with adverse interactions, implicating the need for dosage adjustment and antipsychotic level control during therapy.

In conclusion, our data indicate that the type and incidence of drug-induced extrapyramidal adverse effects may strongly depend on individual patient characteristics, such as age, gender or comorbid medical conditions. Further clinical studies involving side effects of antipsychotic treatment in nursing home residents may be required to improve safety and quality of life, as antipsychotic drugs are widely used in this group of patients.

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Conflict of interest

None of the authors declared any conflict of interest.

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