LETTER TO THE EDITOR

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Patterns and determinants of drug-related neurological problems in older outpatients: An exploratory analysis of a six-year long observational study in North India

Key words: developing country, drug side effects/interactions, motor disorders, neuropharmacology, geriatric medicine

Dear Editor,

Adverse drug reactions (ADRs) and poor compliance to therapy frequently cause hospitalization in older patients (Shah and Hajjar, 2012). So far, bleeding manifestations and metabolic disturbances have been projected as the major drug-related reasons for hospitalization in the elderly (Franceschi *et al.*, 2008; Giardina *et al.*, 2018; Pedrós *et al.*, 2016). Older patients are also prone to drug-related neurological disturbances including sleep disorders, movement disorders, and delirium. However, studies investigating drug-related neurological problems have been scarce in the old. To fill the gap, we conducted a subgroup analysis of a six-year-long prospective study in the geriatric outpatient department of a large referral center in north India (Kaur *et al.*, 2023). The study was conducted from January 2015–September 2021 and patients ≥ 50 years of age developing any drug-related problem (DRP) were enrolled (Pharmaceutical Care Network Europe, 2020). Specifically, for the present analysis, DRPs affecting the nervous system were assessed. Outcomes such as hospitalization and recovery were recorded. Among those with ADRs, patients at risk of drug-induced movement disorders (DIMDs) were identified.

In 10,400 patient registrations, 1031 DRPs (933 ADRs) were observed in 666 patients (Kaur *et al.*, 2023). A total of 187 drug-related neurological issues were reported in 173 patients (1.8%), next only to metabolic disturbances ($n = 206$) (Table 1). Out of 187, 169 were ADRs and 15 problems were related to drug discontinuation. Sedation (47, 27.8%), tremor (24, 14.2%), and vertigo (20, 11.8%) were the three most common neurological ADRs. Altogether, 47 DIMDs were observed in 46 cases (27.8% of neurological ADRs). Calcium channel blockers (CCBs) including valproate, cinnarizine, amlodipine, cilnidipine, trimetazidine, and pregabalin were the commonest class associated with DIMDs ($n = 19$, 40.4% DIMDs) followed by antipsychotics ($n = 10$, 21.3%). Among 187 cases, 36 DRPs in 34 patients (19.3%) needed hospitalization and drug-induced extrapyramidal symptoms (EPS, $n = 12$, 33.3%) were the commonest reason. Non-antipsychotic drugs were involved in eight (66.7%) cases of EPS. Drug discontinuation and supportive therapy were required in 158 neurological ADRs and caused full improvement in 126 (79.7%). Mortality was recorded in one patient suspected of baclofen-associated seizures.

In unadjusted analysis, a significant association of DIMDs was observed with age, presence of dementia, parkinsonism, psychiatric diagnoses, and lung disease ($p < 0.05$). These factors were then included in the regression analysis. After adjusting for co-variates, older adults ≥ 65 years of age, patients with dementia, and patients with lung disease had 3.45, 5.76-, and 3.1 times higher odds of DIMDs, respectively (Supplementary Table 1). No significant interaction was observed between age, presence of dementia, and lung disease.

Drug-induced neurological disturbances were the second most common DRPs in older outpatients. Nearly 20% of drug-related neurological problems required hospitalization with DIMDs being the commonest cause. In few previous studies, neurological problems have been highlighted among the common causes of drug-related hospitalization in the old but with little information on their details and patterns (Giardina *et al.*, 2018; Olivier *et al.*, 2009). In a US-based study of 1999–2000, <5% of adverse drug events were accounted for by neuropsychiatric disturbances with only 0.3% contribution by EPS (Gurwitz *et al.*, 2003). On the other hand, close to 20% of ADRs in the present study were neurological disturbances with 5% of ADRs being DIMDs. Among older adults with ADRs, a 3.5 times higher odds of DIMDs was observed in patients of ≥ 65 years of age. Those with dementia, and underlying lung disease had nearly 6 times and 3 times higher odds of DIMDs, respectively. Patients with dementia are often prescribed valproate and/or antipsychotics for the management of behavioral symptoms. Considering the risk of DIMDs and the subsequent risk of hospitalization, an individualized risk-benefit approach should be considered in such patients. Traditionally, antipsychotics are associated with maximum risk of EPS. On the contrary, CCBs were the commonest class associated with DIMDs including EPS in our study. These disparities might be related to specialty-specific lower prescribing trends of antipsychotics in

Table 1. Types of neurological drug-related issues, individual neurological ADRs, ADRs requiring hospitalization, and drugs involved

NEUROLOGICAL PROBLEM RELATED TO ADR, $N = 169$	NEUROLOGICAL PROBLEM RELATED TO DRUG DISCONTINUATION, $N = 15$	NEUROLOGICAL PROBLEM DUE TO OTHER CAUSES, $N = 3$
Common ADRs[$]	**Resurgence of**	Failure of neuropathic pain medicines (2)
Sedation (47)	Seizures: 3	Others (1)
Pregabalin (11), clonazepam[*] (8), valproate (5), amitriptyline (5)	Neuropathic pain: 4	
	Parkinsonian features: 2	
	Tremor: 3	
	Abnormal behavior: 1	
	Altered sensorium: 1	
	Irritability:1	
New onset tremor (24)		
Amlodipine (5), valproate (2), levosalbutamol (2), levofloxacin (2), levosulpiride (2)		
Vertigo (20)		
Pregabalin (5), metoprolol (2)		
Drug-induced parkinsonism (10)		
Antipsychotic [*] (6), antiemetic [*] (6)		
Dizziness (10)		
Gabapentin (3), ARB[#] (3)		
Drug-induced movement disorders (47)[$$]		
CCB[@*]: 19		
CCB alone: 10		
Antipsychotics: 10 (SGA: 7, FGA: 3)		
Antipsychotics alone: 7		
Levosulpiride: 9		
Levosulpiride alone: 3		
Beta agonists: 7		
Beta agonist alone: 4		
Xanthines: 4		
Requiring hospitalization 32	**Requiring hospitalization 3**	**Requiring hospitalization 1**
Common causes of hospitalization		
1. Drug-induced extrapyramidal disorders (12)	Seizures: 2, Altered sensorium: 1	
Drug-induced parkinsonism (10)		
Antiemetic[*](7): levosulpiride (4), metoclopramide (1), domperidone (2) Antipsychotics[*](4): Olanzapine (1), quetiapine (1), trifluoperazine (1), chlorpromazine (1)		
Anti vertigo[*](1): Cinnarizine (1)		
Cardiac drugs[*] (3): Cilnidipine (1), Trimetazidine (2)		
Neuroleptic malignant syndrome (2)		
Cilnidipine and levosulpiride (1), risperidone (1)		
2. **Altered sensorium (5)** due to		
Hypoglycemia (glimepiride) (1)		
Hepatitis (Anti Tubercular Therapy) (1)		
Renal dysfunction- ramipril (1)		
Hyponatremia -diuretics (2)		
3. **Seizures (3)**: Amitriptyline (1), glimepiride (1), baclofen (1)		
4. **Dyskinesia (2)**: Phenytoin (1), entacapone (1)		
5. **Physiologic tremor (2)**: Inhaled beta agonists and systemic xanthines (2)		
6. **Serotonin syndrome (1)**: Amitriptyline + fluoxetine (1)		
7. **Forgetfulness (1)**: Trihexyphenidyl (1)		
8. **Confusion (1)**: Cinnarizine + dimenhydrinate (1)		
Death: 1[!]	–	–

[$]Only common ADRs mentioned (total does not add up to 169)
[$$]Inclusive of all movement disorders (tremor, parkinsonism etc); this number includes individual ADRs also.
[*]Alone or in combination with other drugs.
[!] In a case of baclofen-associated seizures.
[@]CCBs included valproate, cinnarizine, amlodipine, cilnidipine, trimetazidine, and pregabalin.
ADRs: adverse drug reactions, ARB: Angiotensin receptor blocker ([#]telmisartan, olmesartan and losartan, each was involved in one case of vertigo, hence clubbed as ARB), CCB: calcium channel blocker, FGA: first generation antipsychotic, SGA: second generation antipsychotic

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our center. Interestingly, as per a recent study, CCBs shared a strong association with future idiopathic Parkinson's disease in patients of drug-induced parkinsonism (DIP) (Jeong *et al.*, 2021). Although causality could not be inferred due to our study design, it would be prudent to have additional vigilance for levosulpiride and cardiac calcium channel blockers such as amlodipine, cilnidipine, and trimetazidine. Levosulpiride is an easily available over-the-counter antiemetic and has been implicated in EPS ranging from DIP to the lethal neuroleptic malignant syndrome (Kaur *et al.*, 2022).

The study is one of the first and the longest study on neurological ADRs in older outpatients. However, neurological ADRs occurring during hospitalization and the percentage of hospital admissions occurring due to neurological ADRs were not estimated. ADR rates were not calculated for patients with specific diseases. With multiple bivariate tests performed, the chances of type 1 error may be above 60%. However, this being an exploratory analysis, the same were conducted to find possible associations between independent variables and DIMDs. The regression results need cautious interpretation as the implicated risk factors might be related to prescribing trends. DIMDs were the most common neurological ADRs with CCBs as common culprits. Head-to-head comparisons with dopamine blockers may illustrate the relative risk of EPS. Mechanistic insights into movement disorders by CCBs and their interaction with dopamine blockers should be explored. An individualized approach is warranted when prescribing behavioral modifiers in older patients with dementia. The ethnicity-related differences in the predilection of older patients to neurological ADRs need investigation.

Conflict of interest

None.

Source of funding

None.

Description of authors' roles

UK: Conducted and supervised data collection, performed the data analysis, review of literature and wrote the first draft.

SSC: Supervised the data collection, involved in patients' management, and approved the final draft.

JR: Assisted in data compilation, analysis, presentation, and review of literature.

AS: Supervised the data collection and review of literature.

ISG: Supervised the data collection and was involved in patients' management.

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Supplementary material

For supplementary material accompanying this paper visit https://doi.org/10.1017/S1041610223000807

Data availability

The collected data may be made available upon reasonable request after permission from local regulatory bodies.

Consent

Consent was obtained from the participants to participate in the study as well as for publication of results.

Ethical approval

The study obtained permission from the Institute Ethics Committee (Institute of Medical Sciences) with approval number: Dean/2015-16/EC/411.

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