

Long-acting benzodiazepines among the top predictors of Potentially Inappropriate Psychotropic (PIP) Medication

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Abstract

Background: There is limited information available on the use of PIP medication in older adults having psychiatric illness. **Objective:** To determine the prevalence of PIP medications, and assess its predictors in older adults with psychiatric illness. **Methods:** A cross-sectional study was carried out at a tertiary care hospital on 456 patients of either sex, with a median age of 65 years attending the psychiatry outpatient department. Evaluation of PIP medication was done using Beers criteria 2019 and STOPP criteria 2015. Bivariate logistic regression was used to find out the predictors of PIP prescribing. **Results:** Results of the study reflect that a staggering number of older adults, (more than 91% and 73%) out of total of 456 patients were prescribed with at least one PIP medication identified by Beers criteria and STOPP criteria, respectively. Long-acting benzodiazepine (LABZD) like clonazepam was identified as one of the most commonly prescribed PIP medications by both set of criteria. Further analysis revealed that older adults from rural background (Odds Ratio (OR) 2.60, 95% Confidence Interval (CI) 1.20-5.65; P=0.015), TCA (OR 0.30, 95% CI 0.12- 0.75; P= 0.010), LABZD (OR 33.72, 95% CI 11.27-100.85; P=<0.001), atypical antipsychotics (OR 22.35, 95% CI 5.31- 93.99; P= <0.001) use were most common predictors for PIP medication prescribing. **Conclusion:** The use of PIP medication is highly prevalent among older adults according to Beers criteria and STOPP criteria. The study reflects a more comprehensive and sturdy nature of Beer criteria as it significantly detects more PIP medication than STOPP criteria.

Long-acting benzodiazepines among the top predictors of Potentially Inappropriate Psychotropic (PIP) Medication

Running title: Top predictors of PIP medication use

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Conclusion: The use of PIP medication is highly prevalent among older adults according to Beers criteria and STOPP criteria. The study reflects a more comprehensive and sturdy nature of Beer criteria as it significantly detects more PIP medication than STOPP criteria.

Keywords: older adults, psychiatric illness, predictors, potentially inappropriate psychotropic medication

what is already known about this subject?

Older adult patients with psychiatric illness are at significant risk of receiving potentially inappropriate medication and have a significant drug burden.

what does this study contribute to the literature?

- Increased prescribing of Potentially Inappropriate Medication among older adults with psychiatric illness is a serious health issue that warrants immediate medical attention.
- The high prevalence of medications that should be avoided or their dosage reduced according to the kidney function of the older adults shows the need of medication management while prescribing in older adults.
- Hyperpolypharmacy is associated with the use of PIM in the older adults.

Introduction

A number of psychiatric disorders follow the geriatric population without any invitation, hence psychotropic medications are most frequently used in older adults to treat various mental health conditions.^{1,2} Still, the use of these agents has been associated with a deleterious outcome such as increased sedation, increased risk of stroke, and an increased chance of injuries and falls.^{3,4} Older adults are more prone to adverse events attributable to pharmacodynamic and pharmacokinetic age-related alterations.⁵ Psychotropic medication whose adverse risk exceeds its health benefits, especially when safer or equally effective treatment available, is considered as potentially inappropriate medication (PIMs).⁶ It is imperative to use psychotropic medication judiciously to avoid the adverse effects of these medications in older adults. Various implicit and explicit measures have been developed to determine PIMs in the elderly population.^{7,8} Psychotropic medication covers a higher proportion of PIMs in Beers criteria and STOPP criteria. Beers et al gave the first set of explicit criteria for determining PIMs use by the older adults in 1991.⁹ however, the American Geriatric Society gave official patronage to Beers criteria in 2012 and is now responsible for regularly updating the criteria at a steward cycle of 3 years.^{10,11} Recently, Beers criteria 2019 recommends several psychotropic medications that should be avoided in older adults or limiting their dosage beyond the mentioned dose. It also recommends avoiding psychotropic medicines in older adults with a particular disease as well as the use of three or more Central Nervous System medications in conjunction with each other.¹²

Similarly, the British Geriatric Society recommends the use of STOPP criteria to identify PIMs use in older adults.¹³ Very few studies have examined the PIP medication use in the elderly population using Beers criteria 2003, 2012, 2015, and STOPP criteria (version 1& 2) reported PIP medication prevalence between 7% to 80%.¹⁴⁻¹⁶ No analysis using the Beers criteria 2019 and STOPP criteria 2015 has been carried out to determine the prevalence and predictors of PIP medication in older adults. Hence the present study

was carried out to determine the prevalence and predictors of PIP medication in older adults attending the outpatient psychiatry department based on Beers criteria 2019 and STOPP criteria 2015.

Methods

Setting and Sample

A cross-sectional study was carried out at the psychiatry department/deaddiction center of tertiary care postgraduate teaching hospital on 456 patients of either sex, with a median age of 65 years attending the psychiatry outpatient department. All patients aged [?]65 years attending the outpatient psychiatry department and were prescribed at least one medication and who had given consent to participate in the study were included. Exclusion criteria were as follows: a) Without any psychotropic medication b) incomplete data c) did not provide consent for participation in the study.

Ethical Approval

The protocol for the present study was approved by the Institutional Ethics Committee vide letter No. ERB/UCER/2018/9/3 dated 17/09/2018. The study was carried out in compliance with the ethical standards for biomedical research on human participants.

Data Collection

Prevalidated data collection form was used to collect data on patients' sociodemographic and clinical characteristics such as gender, age, urban/rural living background, educational qualification, smoking or alcohol addiction, number of visits to psychiatry outpatient department, prescribed psychotropic drugs along with their dosage and course of treatment. The authors used validated standardized scales to identify the differential diagnosis. The existence of mild, moderate, severe, very severe depression was assessed by the use of the Hamilton Depression Rating Scale (HAM-D).^{17,18} Cognitive impairment is one of the most significant changes observed in older adults as the aging process is associated with a decline in cognitive function. Cognitive impairment is most commonly caused by delirium and dementia in patients. Updated edition-98 of the Delirium Rating Scale was used to assess delirium.¹⁹ The Mini-Mental State Assessment was used to assess cognitive dysfunction and screen for dementia.²⁰ Authors used the Up & Go test and One-Leg Stand-test to assess Walking difficulty and fall risk.^{21,22}

Evaluation of PIMs

American Geriatric Society Beers criteria 2019 and British Geriatric Society STOPP criteria 2015 (version 2) were used to identify the prevalence of PIP medication in older adults. Two physicians and one pharmacist performed the assessment of PIMs use.

Statistical Analysis

Statistical analysis was carried out by using CorIP. IBM Statistical Package for Social Science Statistics for Windows, Ver. 24.0 and STATA.²³ The Kolmogorov-Smirnov test was used to determine the normality distribution of data. The frequency with percentage is used to express categorical variables. A continuous variable is either defined as mean and standard deviation or median and minimum-maximum values as appropriate. Bivariate logistic regression was performed to identify the predictors for PIP medication prescribing in older adults. The results obtained are expressed in the form of an odds ratio (OR) with a 95% confidence interval (CI). A P- value $of < 0.05$ was considered statistically significant.

Results

In the study, table 1 describes the sociodemographic, clinical characteristic parameters for selecting predictors for PIP medication use in older adult patients (n=456). The demographic data reflects that the median age of 456 patients was found to be 65 years.

The most widely used psychotropic drugs in older adults are listed in Figure 1. LABZDs such as clonazepam, chlorthalidopexide were the most commonly used psychotropic medications (n= 290), followed by atypical

antipsychotics (n= 229), and selective serotonin reuptake inhibitor (SSRI) such as escitalopram, paroxetine, fluoxetine used in 212 patients. The median number of psychotropic medications prescribed was 3 drugs (1-7 drugs). Out of 456 patients, a staggering number more than 73% (n= 336) were prescribed with three or more PIMs, and about one-fourth proportion of the patients (24.2%, n= 110) were prescribed with two drugs. The median number of visits was 5 times (1- 48 times).

In our study, Beers criteria 2019 yielded higher PIP medication use than the STOPP criteria 2015. According to Beers criteria 2019, the overall prevalence of PIP medication use was 91.2% (416/456). The median number of PIP medications prescribed in 416 older adult patients was 2 (1-5). The most frequently prescribed Psychotropic PIMs were found to be clonazepam, quetiapine, risperidone, Lorazepam, etc. whereas according to STOPP criteria 2015, the overall prevalence of PIP medication use was 73.3% (336/456). The median number of PIP medication prescribed in 336 older adult patients was 1 (1- 2). Clonazepam, Chlordiazepoxide, dothiepin, mirtazapine was the most frequently prescribed PIP medication identified by STOPP criteria. Table 2 describes the PIP medications use identified using Beers criteria and STOPP criteria.

Odds ratio reflects the association of exposure of patients to the outcome of a particular parameter and can suggest PIP medication predictors in a study. In the present study, Bivariate analysis, of data shows that the participants from rural background (OR 2.60, 95% CI 1.20-5.65; P=0.015), [?]4 medications (OR 12.25, 95% CI 1.78-84.0; P=0.011), TCA use (OR 0.30, 95% CI 0.120-0.75; P= 0.010), SNRI use (OR 0.20, 95% CI 0.06-0.63; P= 0.006), LABZD use (OR 33.72, 95% CI 11.27-100.85; P=<0.001), short-acting benzodiazepine use (OR 4.71, 95% CI 1.97-11.24; P= <0.001), Atypical Antipsychotic use (OR 22.35, 95% CI 5.31- 93.99; P= <0.001) were found to be important predictors for the PIP medication use as identified by Beers criteria.

Whereas Alcohol addiction (OR 13.13, 95% CI 1.77-97.14; P=0.012), rural background of participants (OR 1.64, 95% CI 1.07-2.53; P= 0.023), TCA use (OR 33, 95% CI 7.80-139.59; P= <0.001), SSRI use (OR 3.51, 95% CI 2.19-5.63; P= <0.001), LABZD use (OR 160.87, 95% CI 53.67-482.19; P= <0.001), Atypical Antipsychotic use (OR 0.43, 95% CI 0.28-0.67; P= <0.001) were found to be important predictors for the PIMs use as identified by STOPP criteria.

Out of a total of 456 patients, the Antianxiety agents were prescribed in nearly 82% (n=378) of the older adults. Out of 378 patients, potentially inappropriate antianxiety agents were prescribed in 97.3% (n=362) and 74.6% (n= 282) older adults as per Beers criteria and STOPP criteria. Our study also found that antidepressants were the second most frequently prescribed psychotropic drug, almost 68.8% of the older adults were prescribed with at least one antidepressant either TCA, SSRI, SNRI. Atypical Antipsychotics were the third most prescribed psychotropic drug in older adults. Beers criteria have given the list of conventional and atypical antipsychotic list, irrespective of diagnosis/conditions that should be avoided in older adults. Among Atypical antipsychotics medication class quetiapine, olanzapine, risperidone is the most common PIP medication prescribed in older adults.

Discussion

To our interpretation, this is the first analysis to determine the prevalence of PIP medication in older adults attending the outpatient psychiatry department using Beers criteria 2019 and STOPP criteria 2015. According to Beers criteria 2019, 91.2% (416 out of 456) of older adults have prescribed at least one PIP medication. Whereas STOPP criteria 2015 identifies 73.3% (336 out of 456) older adults prescribed with at least one PIP medication. Results show that recommendations of Beers criteria have relatively more trespassed for PIMs than STOPP criteria. In other words, Beer criteria seem to have more comprehensive and sturdy recommendations for use of psychotropic drugs as compared to STOPP criteria.

The prevalence of PIP medication reported in our study by using both sets of criteria is significantly higher than the findings of another research conducted based on older Beer and STOPP guidelines.^{24,25} The difference might be due to differences in data collection of sample population or difference in criteria used as this study uses the updated and latest version of both the criteria.

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adults. Out of 378 patients, potentially inappropriate antianxiety agents were prescribed in 97.3% (n=362) and 74.6% (n= 282) older adults as per Beers criteria and STOPP criteria. Beers criteria include a higher proportion of potentially inappropriate antianxiety agents as compared to STOPP criteria. Beers criteria 2019 mention to avoid short/intermediate/long-acting benzodiazepines in all older adults, whereas the STOPP criteria mention only LABZD, but the literature shows that all the benzodiazepines including short/intermediate/Long-acting can cause harmful adverse events (e.g. falls, fractures, cognitive impairment) if use in older adults.^{26,27} Beers criteria and STOPP criteria identify clonazepam as the most common PIP medication irrespective of any condition. Whereas LABZDs are used in older adults with dementia, cognitive impairment, history of fall, and delirium are considered potentially inappropriate.¹² The potential risks of using long-acting agents must be considered while choosing pharmacotherapy for anxiety in older people.

The present study also examined the predictors of PIP medication prescribing with bivariate analysis. The most important predictors of PIP medication prescribing were the rural background of living, [?]4 psychotropic medication prescribed, TCA use, SNRI use, LABZD use, short-acting benzodiazepine use, atypical antipsychotic use according to Beers criteria 2019. On the other hand, alcohol addiction, rural region of living, TCA use, SSRI use, long-acting benzodiazepine, and atypical antipsychotic use came out to be the predictor for PIP medication use according to STOPP criteria 2015.

Our study found that antidepressants were the second most frequently prescribed psychotropic drug as almost 68.8% of the older adults were prescribed with at least one antidepressant either TCA, SSRI, SNRI. Previous studies have reported the same findings on community-dwelling older adults.²⁵ Although SSRIs are preferred agents to treat depression in older adults, TCA is still prescribed in older adults and is considered potentially inappropriate psychotropic medication according to STOPP criteria.²⁸ The use of TCA and SNRI has been associated with substantial anticholinergic effects, sedation effects. Moreover, SNRI users are more prone to cerebrovascular events as compared to SSRI users.⁴ Beers criteria recommend all TCA, SSRI, and SNRI in older adults with syncope, and only TCA should be avoided in older adults with a history of falls or fractures due to its associated strong anticholinergic adverse effects such as confusion, dry mouth, sedation, and orthostatic hypotension. However, STOPP criteria only mention TCA that it should not be used as a first-line treatment in older adults with depression.

Atypical Antipsychotics were the third most prescribed psychotropic drug in older adults. Beers criteria have given the list of conventional and atypical antipsychotic list, irrespective of diagnosis/conditions that should be avoided in older adults. Among Atypical antipsychotics medication class quetiapine, olanzapine, risperidone is the most common PIP medication prescribed in older adults. Beers criteria recommend avoiding antipsychotics in older adults with dementia, cognitive impairment, history of falls or fractures, delirium due to its strong anticholinergic effects, and extrapyramidal side effects. Whereas STOPP criteria only recommend avoiding antipsychotics in older adults with dementia, delirium. In our study, 132 older adults out of 456 patients were prescribed with at least three or more CNS active drug combinations that are considered potentially clinically important drug-drug interactions as mentions in Beers criteria 2019. Thirty-four clinically important drug-drug interactions were identified in older adults by using Beers criteria. In contrast, STOPP criteria don't recommend any guidelines on clinically important drug-drug interaction.

It was observed that most of the countries have developed their own criteria or guidelines to identify PIM in the geriatric population. However, there is a major number of developed as well as developing countries where no guideline/criteria have been chalked out. Healthcare professionals from all over the world use Beers criteria or STOPP criteria to identify PIM in older adults, but there has always been a state of confusion in most countries for uniform use of these guidelines. Hence there is a need that all geriatric societies of the world should come together to make a unified guideline for identifying PIM in the geriatric population.

The present study highlight that the prevalence of PIP medication as determined by the use of Beers criteria and STOPP criteria in older adults is very high that demands immediate attention. The study also reflects a more comprehensive and sturdy nature of AGS Beer criteria as the Beers criteria detect significantly more PIMs than STOPP criteria due to the inclusion of clinically important drug-drug interaction and

more conditions in drug-disease interaction. TCA, long-acting benzodiazepine, and atypical antipsychotic use were some of the risk factors for potentially inappropriate psychotropic medication use in older adults. Although this study gives a greater understanding of PIP medication prescribing in older adults attending the psychiatry outpatient department, there are some drawbacks in the present study that need to be recognized. The study's findings are focused on older adults attending the outpatient psychiatry department, so extrapolation of results to inpatients older adults will not be feasible. Finally, the study did not evaluate the Adverse drug reactions/outcomes resulting from the use of PIP medication detected by Beers criteria and STOPP criteria.

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Author Contributions

Authors' role in study concept and design, acquisition of subjects and/or data, analysis and interpretation of data, and preparation of manuscript.

Study Concept: Dr Malika Arora, Dr Parveen Bansal, Mr Rishabh Sharma, Dr Arvind Sharma, Dr Rakesh Kumar, Mr Manik Chhabra

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Declaration of Conflicting Interests

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Figure 1: Incidence of use of various classes of psychotropic medications in older adult patients (n=456)

SSRI (Selective Serotonin Reuptake Inhibitor); SNRI (Serotonin Norepinephrine Reuptake Inhibitor); Z drugs (Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics);

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Tables.pdf available at <https://authorea.com/users/407474/articles/518132-long-acting-benzodiazepines-among-the-top-predictors-of-potentially-inappropriate-psychotropic-pip-medication>

