Analysis of potentially inappropriate medication based on drug-drug interactions in older adults with psychiatric disorders: a retrospective study

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Abstract

Background

Polypharmacy increases the risk of potentially inappropriate medications (PIM) and drug-drug interactions (DDI). This study conducts a retrospective analysis to detect PIMs, DDIs and adverse drug reactions (ADR) among older adults with psychiatric disorders.

Methods

A retrospective analysis was carried out based on medical records of aged inpatient people with psychiatric disorders. Demographic details, hobbies, medical history, medication and laboratory examination were extracted. Three criteria and one online DDIs database were used to detect PIMs and DDIs. The minimally clinically important difference (MCID) was defined as the score change of the Treatment Emergent Symptom Scale (TESS) between admission and discharged. Mean and standard deviation (SD) was used for continuous variables and frequency was calculated for dichotomous variables. Ordinal regression was carried out to detect the independent factors of PIM. Binary logistic regression analysis was implemented to determine the independent factors on the likelihood of ADR or the MCID. ANOVA was used to detect the relationship between the co-administration of drugs and the changes of ALT, AST, urea nitrogen, creatinine, total cholesterol, triglycerides. $P < 0.05$ was considered as statistically significant.

Results

96.8% inpatients had at least 1 PIM and lorazepam was the most frequently prescribed drug (75.0%). Co-administration of three or more central nervous system (CNS) active drugs was the principal DDI (70.45%) and the most frequent DDI which should be avoided was the co-administration of lorazepam and olanzapine (55.5%). The common ADR were constipation (25.6%), hepatotoxicity (14.0%) and extrapyramidal symptoms (13.0%). The co-administration of quetiapine and potassium chloride was an independent risk factor of constipation ($P = 0.011$, $OR = 10.821$, 95%CI [1.738 67.748]) and the score change of TESS scale ($P = 0.024$, $OR = 0.024$, 95%CI [1.274 32.288]).

Conclusions

The rate of PIM in the elderly with psychiatric disorders is high and brought serious adverse consequences. Further studies to prevent medication-related problems and costs such as raising awareness of PIM and DDI among healthcare professionals and patients, regulating deprescription, the pharmacokinetic and pharmacodynamic mechanism of drugs induced DDIs, and the influence of different drug administration routes on DDIs among aged people are needed.

Background

The prevalence of mental illness increases with the population's age for people aged 55 years old and above¹. As a progressive decline in the functional reserve of multiple organs and systems for aged people² and pharmacodynamics and pharmacokinetics of drugs differing from those in younger and middle-aged adults³, somatic multimorbidity and polypharmacy are prevalent in older adults with severe mental illness⁴. Therefore, the issue of safe medication use in older adults with mental illness deserves attention.

As being multimorbidity, polypharmacy is common among older adults. Polypharmacy is used to describe multiple, unnecessary, excessive, or unindicated medication consumption⁵. Although there is no standard threshold of the number of medications, taking 5 or more medications as regular use is widely accepted⁶. The prevalence of polypharmacy ranged between 7–45% among people aged 65 and above⁷ and it was much higher than those of other age groups⁸.

Polypharmacy increases the risk of potentially inappropriate medications (PIM)⁹. PIM is considered to be those drugs which should not be prescribed because the risk of adverse events outweighs the clinical benefit, especially when safer or effective alternatives are available¹⁰. 61.1% of patients aged 65 and above were prescribed 1 PIM, 26.9% with 2 PIMs, and 12.0% 3 or more PIMs¹¹. In addition, as a result of physiological changes and polypharmacy, rates of PIM among elderly patients with mental illness were much higher^{12, 13}.

Furthermore, polypharmacy is a key risk factor for drug-drug interactions (DDI)¹⁴. Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRI) were common medication classes identified as DDI¹⁵. Lexicomp® Drug Interactions provided by Wolters Kluwer is qualified to find out DDIs¹⁶ and are widely used. DDIs are classified according to the potential clinical significance into several categories. As databases are updated, DDIs are constantly updated¹⁷.

PIM and DDI may cause adverse drug reaction (ADR) which would threaten patient safety and public health¹⁸. ADR is defined as an appreciably harmful or unpleasant reaction, resulting from the use of a medication, which affects the follow-up medication plan¹⁹.

Many contemporary 'alert' classifications for DDIs are potentially inappropriate²⁰ if only statistically analyzed without considering clinical significance. Statistical significance which is usually measured by P value and 95% confidence interval is derived from hypothesis testing²¹. Clinical significance refers to a large enough size of difference between groups for patients to consider the difference important²² and is usually measured by a minimally clinically important difference (MCID)²³. The co-administration of some drugs is theoretically associated with an adverse outcome. While, the magnitude of the pharmacokinetic interaction may be below the threshold for clinical significance, such as NSAIDs with diuretics or RAAS-

inhibitors²⁴ and escitalopram or paroxetine with statins²⁵. DDIs with antidepressants are potentially, but rarely clinically significant²⁶.

The aim of this study is to identify PIMs, DDIs and ADRs in older adults with psychiatric disorders. A secondary aim is to find out the DDIs with clinical significance.

Materials And Methods

Study design and setting

This was a retrospective study conducted in the Fourth People's hospital in Lianyungang which is affiliated to Kangda College of Nanjing Medical University. The hospital is a national third level specialized hospital and the only specialized hospital for people with mental illness in Lianyungang city. It is the provincial judicial psychiatric expertise hospital. The study protocol was approved by the Clinical Research Ethics Committee of the Fourth People's hospital of Lianyungang (2021LSYYXLL-P15).

Participants and Eligibility

Medical records for patients hospitalized in geriatric psychiatry department and clinical psychology department from July 2nd 2019 to August 31st 2021 were checked. Medical records were included as patients aged 60 and over. Exclusion criteria were (i) hospital stay less than 3 days; (ii) medication sorts less than 5; (iii) demographic information missing. When the patients admitted to hospital for the same major disease repeatedly, only the latest medical record meeting the requirements was included.

Data extraction and Statistical analysis

Data collected included demographic details (gender, age, education, occupation, marriage, height, weight), hobbies (alcohol and smoking), medical history (course of the disease, number of hospitalizations, length of this hospitalization, major medical diagnosis, total number of medical diagnosis), medication (drug, dosage, length) and liver function laboratory examination (ALT, AST, urea nitrogen, creatinine, total cholesterol, triglycerides). In addition, adverse drug reaction (ADR) was recorded according to Treatment Emergent Symptom Scale (TESS) and the course record which was recorded by doctors. Different dosage forms of the same drug prescribed for the same patient were reported as 1 drug. The data extraction process was conducted by two trained researchers.

PIM was ascertained according to 2019 Beers criteria²⁷, STOPP/START²⁸ and 2017 Chinese criteria of PIM for older adults²⁹. DDIs were checked based on 2019 Beers criteria and Lexi-Interact Online (<https://doctorabad.com/UpToDate/d/di.htm>). The co-administration of drugs which should be avoided was considered severe DDI.

There has been no standardization for clinical significance³⁰. MCID was defined as the score change of the TESS scale between admission and discharged according to the psychiatrist's opinion. As long as the

score changed, it considers clinically significant.

Statistical analysis was conducted using IBM SPSS® Statistics Package version 26.0. Descriptive data were recorded using mean and standard deviation (SD) and frequency. Differences in the distribution of categorical variables were compared using the Pearson's Chi-square (χ^2) test and continuous variables using the independent t test or Spearman regression analysis. Ordinal regression was carried out to detect the influence of demographic characteristics, hobbies, BMI and medical history of the likelihood of PIM. Binary logistic regression analysis was implemented to determine the impact of demographic characteristics, hobbies, BMI and co-administration of medications on the likelihood of ADR or the MCID. ANOVA was used to detect the relationship between the co-administration of drugs and the changes of ALT, AST, urea nitrogen, creatinine, total cholesterol, triglycerides. P value, Odds Ratio (OR) and 95%CI were recorded. $P < 0.05$ was considered as statistically significant.

Results

Baseline Characteristics

A total of 308 patients with psychiatric disorders who were aged 60 years and above were enrolled in this study. The screening process is shown in Figure 1.

Most of the participants were women (71.3%), married (87.3%), with depressive disorder (57.8%). The average age was 69.98 years, the average height was 161.06cm and the average weight was 62.79kg. On average, each patient had 3.91 medical diagnoses, 10.43 drugs and a course of 99.33 months. Each patient was hospitalized 2.50 times and the duration was 25.38 days. The baseline characteristics are summarized in Table 1.

PIM and Associated risk factors

3213 prescriptions were found including 248 sorts of drugs. 96.8% participants received at least 1 PIM.

According to 2019 Beers criteria and 2017 Chinese criteria of PIM for older adults, the most frequently number of PIM for each patient was 2 (30.8%) followed by 3 (26.6%), 1 (13.6%), 4 (13.3%), 5 (8.8%), 6 (2.0%) and 7 (1.6%) in this study. PIM for older adults and PIM due to drug-disease or drug-syndrome interactions are shown in Table 2. Lorazepam (75.0%) was the most frequently prescribed PIM in this study followed by olanzapine (48.4%) and quetiapine (38.0%). Antipsychotics (100%) were the common prescribed PIM for patients with dementia or cognitive impairment.

Based on the STOPP/START version 2, central nervous system and psychotropic drugs were checked. The most obvious PIM was benzodiazepines for 4 weeks and above (16.9%) followed by antipsychotics (other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease (2.3%), first-generation antihistamines (1.0%) and initiation of tricyclic antidepressants (TCAs) as first-line antidepressant treatment (0.6%) in this study.

PIM was correlated to age ($r=-0.180$, $P=0.002$), the number of drugs ($r=0.364$, $P=0.000$), duration of hospitalization ($r=0.187$, $P=0.001$) and education ($P=0.018$). As showed in Table 3, with the increase in education level, the number of drugs and the length of hospitalization, the number of PIM increases. 60-66 years old was an independent risk factor of PIM, while, using 5-11 drugs and 3-17 days of hospitalization were independent protective factors of PIM.

DDIs and Associated risk factors

The prevalence rate of the co-administration of central nervous system (CNS) active drugs such as antidepressants, antipsychotics, antiepileptics, benzodiazepines, nonbenzodiazepines and benzodiazepine receptor agonist hypnotics was 70.5%. The most frequently used combination was lorazepam, olanzapine and escitalopram (16.6%) in this study.

Among 171 patients who had at least 1 co-administration of drugs which should be avoided, 36 combinations were found according to the online database. The co-administration of drugs which should be avoided are listed in Table 4. The co-administration of lorazepam and olanzapine (55.50%) was the most frequently DDI in this study which should be avoided.

The number of diagnoses ($P=0.015$, $OR=0.87$, 95%CI [0.78, 0.97]) was an independent factor for DDI.

ADR and Associated risk factors

More than 10 ADRs were identified. The most frequent one was constipation. All ADRs are listed in Table 5.

When analyzing the independent factors of ADRs, 34 patients who had 2 or 3 combinations of drugs which should be avoided were excluded. As showed in Table 6, duration of hospitalization, number of drugs and the co-administration of quetiapine and potassium chloride was independent risk factors of constipation. Table 7 showed the relationship of extrapyramidal symptoms and administration of drugs. Using 9-11 kinds of drugs was an independent risk factor of extrapyramidal symptoms, while using either quetiapine or escitalopram was a protective factor.

As showed in Table 8, the change of ALT, AST and triglycerides between admission and discharged was associated with the co-administration of olanzapine and clonazepam. While, changes of liver function laboratory examination were all not associated with other co-administrations ($P>0.05$).

MCID and Associated risk factors

Based on Table 9, the number of drugs and administration of either quetiapine or potassium chloride was independent risk factors of MCID. While, the administration of quetiapine or escitalopram was a protective factor of score change.

Discussion

Built on the 3213 prescriptions from the 308 enrolled older adults, 96.8% cases had at least 1 PIM and lorazepam was the most frequently prescribed drug. Co-administration of 3 or more CNS active drugs was the principal DDI and the most frequent DDI which should be avoided was the co-administration of lorazepam and olanzapine. Constipation was the most common ADR. The co-administration of quetiapine and potassium chloride was an independent risk factor of constipation. Moreover, the co-administration of quetiapine and potassium chloride was an independent risk factor of MCID. While the co-administration of quetiapine and escitalopram was a protective factor of MCID.

The prevalence rate of PIM for older adults with mental illness in this study is much higher than that in other studies. For community-dwelling older adults, the PIM rate ranged from 48.3% to 53%^{31, 32}. For aged patients with cancer, the PIM rate ranged from 47.3% to 73%^{33, 34}. Murphy³⁵ found that 55.8% older adults with mild-to-moderate Alzheimer disease were prescribed a PIM with 30.1% being prescribed 2 and more PIMs in nine European countries. For older adults with diabetes, from 56% to 66.2% cases had at least 1 PIM^{36, 37}. Zahwe³⁸ showed that 80.0% of patients with heart failure were taking at least 1 PIM. While, the result showed in this study is a little higher than that (91.04%) in older patients with depressive disorder¹². Differences in the PIM prevalence rates may be related to three reasons. First, three criteria were used as supplements in this study in order to screen all the PIM considering the common drugs used in different countries and the different screening way. Secondly, enrolled patients suffered from diverse diseases so that the drug categories they used were different in different studies. CNS active drugs which have a high proportion based on the three criteria are the primary drugs used for this group patients. Thirdly, study population in studies was in different age ranges and different settings.

Lorazepam was the most commonly prescribed PIM for older adults in this study. It is in line with other studies. Motter¹⁵ found that benzodiazepines and antihistamines were the most common medication classes reported followed by tricyclic antidepressants for older people. Huang³⁹ concluded that benzodiazepines, anticholinergics and antipsychotics were the most frequently prescribed classes. Murphy³⁵ found that benzodiazepines, SSRIs and Proton Pump Inhibitors (PPIs) were the most frequent PIMs. Roux³¹ found that benzodiazepines, PPIs, antipsychotics, antidepressants were the most prevalent PIMs.

Benzodiazepines prescribing to aged people is significantly in excess of what the available evidence suggests is appropriate⁴⁰. Benzodiazepine use was higher in those with psychiatric disorders as people who had a mood disorder were the most vulnerable⁴¹. Psychiatrists had higher rates of benzodiazepine prescription⁴². That may be explained by the need for benzodiazepines, the lack of effective alternative therapies, the attitude of patients and physicians. As many older adults suffer from insomnia and depression, benzodiazepines are the most frequently used to relieve these symptoms⁴³. Nonbenzodiazepine sedatives have similar risks to those of benzodiazepines and are not suitable as alternative drugs to benzodiazepines according to those PIM criteria. Antihistamines, antipsychotics, melatonin, phytotherapeutics, homeopathy and acupuncture are just not recommended for insomnia treatment, and light therapy and exercise have yet to be evaluated⁴⁴.

Co-administration of lorazepam and olanzapine is the most common DDI for older adults. Madhusoodanan⁴⁵ conducted a pilot study and found co-administration of lorazepam and olanzapine caused no adverse consequences. Bergemann⁴⁶ discovered that the co-administration with lorazepam, the dose-corrected olanzapine plasma concentration was no different from the plasma levels under olanzapine monotherapy. While, a case report showed IM olanzapine and IM lorazepam would lower blood pressure and cause dizziness⁴⁷. Lee^{48, 49} revealed that olanzapine and quetiapine inhibited the human ether-a-go-go related gene channels current, and Kowalchuk⁵⁰ found olanzapine inhibited central ATP-sensitive potassium channel.

Constipation, hepatotoxicity and extrapyramidal symptoms are common ADRs in this analysis which are consistent with other literature. Constipation is a common side effect of antipsychotics and it can lead to serious consequences such as paralytic ileus, bowel occlusion and death⁵¹.

Besides, antipsychotics and antidepressants are potential cause of hepatotoxicity, even at therapeutic doses⁵². Drugs which are substrates of CYP450 enzymes have a higher likelihood of causing drug-induced liver injury (DILI) in a dose independent manner, while drugs which are CYP450 inhibitors have a higher likelihood of generating DILI only when they are administered at high daily doses⁵³. Second-generation antipsychotics could lead to extrapyramidal syndrome with risk factors such as the choice of a particular antipsychotics, high doses, history of previous extrapyramidal symptoms, and comorbidity⁵⁴. Moreover, all antipsychotics and antidepressants are commonly responsible for ADRs such as dystonia, akathisia and pseudoparkinsonism⁵⁵. Benzodiazepines and Z-drugs are associated with motor vehicle accidents, falls and fractures, in addition, they may be related to dementia, infections or cancers⁵⁶.

However, three combinations of drugs except for co-administration of quetiapine and potassium chloride which should be avoided according to the database were neither independent risk factors for each ADR nor showing clinically significant. The probable reasons are following. First, it may be due to the pharmacokinetic multiple pathways of drug metabolism and the DDIs are mainly speculated based on the drugs pharmacokinetics features²⁶. Psychiatric patients are at high risk of pharmacokinetic DDIs and the rate of DDI in patients with cytochrome P450 (CYP) inhibitor or inducer are close to 50%⁵⁷.

Psychotropic drugs are usually metabolized by several enzymes which would reduce the risk of DDI²⁶. Second, the route of administration may affect DDIs and ADRs. DDI may be lower in the oral administration of olanzapine and lorazepam according to the database. In this study, antipsychotics, antidepressants and benzodiazepines were all oral administration and lowered the ADRs. Thirdly, each ADR is the result of a combination of multiple factors and other potential risk factors were neglected. For example, QT interval prolongation and/or torsade de Pointes occur only in the presence of multiple risk factors, such as 65 years old or above, pre-existing cardiovascular disease, bradycardia, female, hypokalemia, hypomagnesemia, a supratherapeutic or toxic serum concentration, or the simultaneous administration of other drugs which delay repolarization or interfere with drug metabolism⁵⁸. Fourth, the data is biased. For example, there were no ADRs among all patients who used quetiapine in combination with escitalopram.

PIMs are associated with patients' and doctors' awareness. For patients, they may not be aware if they are taking PIMs³² or want to try non-pharmaceutical methods⁴³. As for physicians, they may lack of the necessary vigilance of PIMs in older adults or lack of skills and training on how to regulate benzodiazepines^{43, 59}. Some doctors worry about the doctor-patient relationship and the stress for an older patient with a limited life expectancy if deprescribing benzodiazepines⁶⁰.

Deprescribing appear to be feasible and safe to solve the problem of PIM⁶¹. Rognstad⁶² conducted an effective educational intervention for general practitioners to reduce the prevalence of PIM.

Deprescribing is suggested to reduce drugs one at a time after careful assessment⁶³. After pharmacist-led deprescribing intervention, patients' symptoms and healthcare expenditures were reduced³⁴.

Furthermore, raising older adults' awareness about PIMs through education is needed³². Future trials should focus on how to improve the understanding of both doctors and patients on PIM and DDI, the pharmacokinetic and pharmacodynamic mechanism of those CNS active drugs, and the influence of different drug administration routes on DDIs.

Strengths and limitations

There are two strengths in this study. First, we discussed DDIs and ADRs from the perspective of statistical significance and clinical significance. Considering clinical medication safety, we analyzed the relationship between co-administration of drugs and ADRs. Second, we attach great importance to a comprehensive investigation of PIM. Considering the differences in commonly used drugs in diverse countries and the focus of different criteria. We used three criteria as supplements to detect PIM as comprehensively as possible.

Our work consists of two limitations. First of all, we focused on elderly patients with a major diagnosis of psychiatric disorders and central nervous system drugs, and ignored PIMs of other systems and the dosage reduced with varying levels of kidney function based on STOPP version 2. Next, we extracted information from the long-term physicians' order and ignored the temporary physician's order.

Conclusion

Above all, the rate of PIM in the elderly with psychiatric disorders is high and DDIs among CNS active drugs need to be concerned. Co-administration of quetiapine and potassium chloride is an independent risk factor of constipation. Further studies to prevent medication-related problems and costs such as raising awareness of PIM and DDI among healthcare professionals and patients, regulating deprescription, the pharmacokinetic and pharmacodynamic mechanism of drugs induced DDIs, and the influence of different drug administration routes on DDIs among aged people are needed.

Abbreviations

PIM

Potentially inappropriate medication
DDI
Drug-drug interaction
SSRI
Selective serotonin reuptake inhibitors
ADR
Adverse drug reaction
MCID
Minimally clinical important difference
NSAID
Non-steroidal anti-inflammatory drugs
RAAS
Renin-angiotensin-aldosterone system
TESS
Treatment Emergent Symptom Scale
SD
Standard deviation
DILI
Drug-induced liver injury
CNS
central nervous system
PPI
Proton Pump Inhibitors
SNRI
Serotonin-norepinephrine reuptake inhibitor

Declarations

Ethics approval and consent to participate

The study was approved by the Clinical Research Ethics Committee of the Fourth People's hospital of Lianyungang (2021LSYYXLL-P15).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YL, MJ, YD, HZ, YC and HW conceived the study and its design. YL, MY and DW included patients and extracted data. MY determined the criterion of clinical significance according to the clinical practice. YL and HW analyzed the data. YL drafted the manuscript. MJ, TZ, YD and YC revised the manuscript. All authors read and approved the final manuscript.

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Table 1. Baseline characteristics (n=308)

Variables	Range/n	SD/%
Age	60-93 years old	7.15
Sex		
Male	89	28.9
Female	219	71.1
Height	143-180 cm	7.48
Weight	32-93 kg	10.15
Course	0.07-612 months	135.08
Drug	5-24	3.70
Duration	3-98 days	14.89
Education level		
Illiteracy	114	37.0
Elementary or junior elementary school	82	26.6
Junior high school	60	19.5
High school or technical secondary school	32	10.4
College or university	20	6.5
Hospitalizations	1-27 times	3.20
Marriage		
Unmarried	4	1.3
Married	269	87.3
Divorced	30	9.7
Widowed	5	1.7
Medical diagnosis	1-10	2.26
Occupation		
Unemployed	192	62.3
Retired	87	28.2
Farming	22	7.1
Others	7	2.4
Smoking		
No	294	95.5
Yes	14	4.5
Alcohol		
No	294	95.5

Yes	14	4.5
Major diagnosis		
Depressive disorder	178	57.8
Organic mental disorder	35	11.4
Schizophrenia	25	8.1
Bipolar disorder	15	4.9
Alzheimer's disease	14	4.5
Dissociative [conversion] disorder	6	1.9
Somatoform disorder	6	1.9
Others	29	9.5

Table 2. PIM for older adults and PIM due to drug-disease or drug-syndrome interactions

Category/Disease or Syndrome	Medication	Frequency (%)
PIM for older adults		
Benzodiazepines	Lorazepam	231 (75.0)
	Clonazepam	22 (7.1)
	Estazolam	10 (3.2)
	Oxazepam	4 (1.3)
	Alprazolam	2 (0.6)
	Clorazepate	2 (0.6)
	Diazepam	1 (0.3)
Antipsychotics, first and second generation	Olanzapine	149 (48.4)
	Quetiapine	117 (38.0)
	Risperidone	14 (4.5)
	Paliperidone	10 (3.2)
	Niergoline	6 (1.9)
	Amisulpride	5 (1.6)
	Perphenazine	5 (1.6)
	Ziprasidone	4 (1.3)
	Aripiprazole	2 (0.6)
	Doxepin	2 (0.6)
	Haloperidol	2 (0.6)
	Sulpiride	2 (0.6)
	Maprotiline	1 (0.3)
Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics	Zolpidem	43 (14.0)
	Eszopiclone	34 (11.0)
Proton-pump inhibitors	Omeprazole	34 (11.0)
	Pantoprazole	2 (0.6)
	Lansoprazole	1 (0.3)
Antiparkinsonian agents	Benhexol	32 (10.4)
Antidepressants	Paroxetine	21 (6.8)
	Fluvoxamine	6 (1.9)
	Fluoxetine	4 (1.3)
	Amitriptyline	1 (0.3)
Antiplatelet drugs	Clopidogrel	8 (2.6)

	Warfarin	5 (1.6)
Potassium-sparing diuretics	Spironolactone	6 (1.9)
Respiratory system medication	Theophylline	5 (1.6)
Sulfonylureas, long acting	Glimepiride	5 (1.6)
	Glyburide	3 (1.0)
Antispasmodics	Atropine (excludes ophthalmic)	1 (0.3)
Anticholinergics	Diphenhydramine (oral)	1 (0.3)
	Promethazine	1 (0.3)
Cardiovascular drugs	Nifedipine, immediate release	1 (0.3)
	Amiodarone	1 (0.3)
Non-cyclooxygenase-selective NSAIDs, oral	Diclofenac	1 (0.3)
PIM due to drug-disease or drug-syndrome interactions		
Central nervous system		
Delirium	Antipsychotics	3 (100.0)
	Benzodiazepines	1 (33.3)
Dementia or cognitive impairment	Antipsychotics, chronic and as-needed use	17 (100.0)
	Benzodiazepines	6 (35.3)
	Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics	3 (17.6)
Parkinson disease	Antipsychotics	11 (84.6)
	Antiemetics	1 (7.7)
Gastrointestinal		
Chronic constipation	Antipsychotics	57 (93.4)
	Antispasmodics	1 (1.6)
History of falls or fractures	Antiepileptics	1 (50.0)
	Antipsychotics	2 (100.0)

Table 3 Correlation of PIM, demographics and drugs

		Estimate	Std.	Wald	df	P	OR	95% CI	
		B	Error					lower	upper
Threshold	0 PIM	-4.137	0.612	45.771	1	0.000	0.016	-5.34	-2.94
	1-2 PIM	-0.451	0.530	0.726	1	0.394	0.637	-1.49	0.59
Location	Illiteracy	0.474	0.532	0.793	1	0.373	1.606	-0.57	1.52
	Elementary or junior elementary school	0.751	0.555	1.830	1	0.176	2.119	-0.34	1.84
	Junior high school	0.783	0.571	1.884	1	0.170	2.188	-0.34	1.90
	High school or technical secondary school	0.606	0.629	0.928	1	0.335	1.833	-0.63	1.84
	College or university	0 ^a	–	–	0	–	–	–	–
	Aged 60-66	0.783	0.306	6.537	1	0.011	2.188	0.18	1.38
	Aged 67-72	-0.035	0.326	0.012	1	0.914	0.966	-0.68	0.60
	Aged 73 and above	0 ^a	–	–	0	–	–	–	–
	5-8 drugs	-1.752	0.325	29.098	1	0.000	0.173	-2.39	-1.12
	9-11 drugs	-0.940	0.315	8.921	1	0.003	0.391	-1.56	-0.32
	12 and above drugs	0 ^a	–	–	0	–	–	–	–
	Duration of 3-17 days	-0.656	0.313	4.395	1	0.036	0.519	-1.27	-0.04
	Duration of 18-28 days	-0.341	0.309	1.218	1	0.270	0.711	-0.95	0.27
	Duration of 29 days and above	0 ^a	–	–	0	–	–	–	–

Table 4 Co-administration of drugs which should be avoided

Co-administration of drugs	Number	Frequency (%)
Lorazepam + olanzapine	116	55.50
Olanzapine + potassium chloride	14	6.70
Quetiapine + potassium chloride	14	6.70
Quetiapine + escitalopram	13	6.22
Olanzapine + clonazepam	8	3.83
Olanzapine + piribedil	3	1.44
Quetiapine + piribedil	3	1.44
Quetiapine + paliperidone	3	1.44
Olanzapine + amisulpride	2	0.96
Olanzapine + fluoxetine	2	0.96
Olanzapine + quetiapine	2	0.96
Olanzapine + paliperidone	2	0.96
Risperidone + ziprasidone	2	0.96
Risperidone + amisulpride	2	0.96
Quetiapine + flupentixol and melitroxine	2	0.96
Escitalopram + ziprasidone	1	0.48
Olanzapine + escitalopram	1	0.48
Olanzapine + estazolam	1	0.48
Olanzapine + oxazepam	1	0.48
Olanzapine + flupentixol and melitroxine	1	0.48
Olanzapine + ziprasidone	1	0.48
Diphenhydramine + potassium chloride	1	0.48
Propranolol + rivastigmine	1	0.48
Paliperidone + amisulpride	1	0.48
Clomipramine + potassium chloride	1	0.48
Metoprolol + rivastigmine	1	0.48
Doxepin + potassium chloride	1	0.48
Duloxetine + fluvoxamine	1	0.48
Risperidone + potassium chloride	1	0.48
Quetiapine + amisulpride	1	0.48
Quetiapine + amiodarone	1	0.48
Quetiapine + fluoxetine	1	0.48

Quetiapine + clozapine	1	0.48
Quetiapine + citalopram	1	0.48
Quetiapine + ipratropium bromide	1	0.48
Lorazepam + potassium chloride	1	0.48

Table 5 Adverse drug reactions

Category	Frequency	%
Constipation	53	25.6
Hepatotoxicity	29	14.0
Extrapyramidal symptoms	27	13.0
Palpitation and fatigue	16	7.7
Abnormal Electrocardiogram	14	6.8
Dizziness and headache	13	6.3
Abnormal sleep	12	5.8
Abnormal blood composition	11	5.3
Gastrointestinal reaction	10	4.8
Others	22	10.6

Table 6 Binary logistic regression of constipation and various factors

	P	OR	95% CI	
			lower	upper
Sex	0.282	1.655	0.66	4.15
Smoking	0.230	0.179	0.01	2.97
Drinking	0.267	3.790	0.36	39.78
BMI	0.418	0.960	0.87	1.06
Age group				
60-66	0.824			
67-72	0.628	1.270	0.48	3.34
≥73	0.905	0.944	0.37	2.43
Duration of hospitalization group				
3-17 days	0.002			
18-28 days	0.003	5.754	1.78	18.60
≥29 days	0.000	7.900	2.52	24.75
Drug number group				
5-8	0.015			
9-11	0.008	4.547	1.50	13.80
≥12	0.007	4.384	1.49	12.90
Co-administration of lorazepam and olanzapine				
Neither	0.141			
Either	0.100	0.435	0.16	1.17
Both	0.066	0.231	0.05	1.10
Co-administration of quetiapine and potassium chloride				
Neither	0.038			
Either	0.158	2.128	0.75	6.07
Both	0.011	10.821	1.74	67.48
Co-administration of quetiapine and escitalopram				
Neither	0.952			
Either	0.754	1.165	0.45	3.02
Both	0.999	0.000	0.00	—
Co-administration of olanzapine and clonazepam				
Neither	0.455			
Either	0.284	1.908	0.59	6.23

Both	0.792	0.719	0.06	8.38
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Table 7 Binary logistic regression of extrapyramidal symptoms and various factors

	P	OR	95% CI	
			lower	upper
Sex	0.555	0.710	0.228	2.213
Smoking	0.391	2.760	0.271	28.137
Drinking	0.835	0.780	0.074	8.160
BMI	0.229	0.917	0.796	1.056
Age group				
60-66	0.585			
67-72	0.307	1.853	0.567	6.056
≥73	0.694	1.300	0.353	4.790
Duration of hospitalization group				
3-17 days	0.483			
18-28 days	0.234	2.118	0.616	7.280
≥29 days	0.389	1.761	0.486	6.381
Drug number group				
5-8	0.057			
9-11	0.017	6.184	1.386	27.585
≥12	0.101	3.629	0.776	16.963
Co-administration of lorazepam and olanzapine				
Neither	0.791			
Either	0.704	1.326	0.310	5.681
Both	0.810	0.754	0.076	7.515
Co-administration of quetiapine and potassium chloride				
Neither	0.893			
Either	0.634	0.723	0.190	2.751
Both	0.999	0.000	0.000	—
Co-administration of quetiapine and escitalopram				
Neither	0.110			
Either	0.036	0.250	0.068	0.911
Both	0.999	0.000	0.000	—
Co-administration of olanzapine and clonazepam				
Neither	0.495			
Either	0.281	0.398	0.075	2.125

Table 8 ANOVA of co-administration of olanzapine and clonazepam on liver function laboratory examination

		Sum of squares	df	Mean square	F	P
dALT	Between groups	4645.593	2	2322.796	5.539	0.005
	Within groups	75066.473	179	419.366		
	Total	79712.066	181			
dAST	Between groups	2061.186	2	1030.593	3.973	0.020
	Within groups	46689.841	180	259.388		
	Total	48751.027	182			
dUrea Nitrogen	Between groups	0.816	2	0.408	0.123	0.885
	Within groups	588.905	177	3.327		
	Total	589.721	179			
dCreatinine	Between groups	309.314	2	154.657	0.719	0.489
	Within groups	38098.080	177	215.243		
	Total	38407.394	179			
dTotal cholesterol	Between groups	4.685	2	2.342	2.622	0.076
	Within groups	155.434	174	0.893		
	Total	160.119	176			
dTriglycerides	Between groups	5.078	2	2.539	4.155	0.017
	Within groups	106.332	174	0.611		
	Total	111.410	176			

Table 9 Binary logistic regression of TESS score change and various factors

	P	OR	95% CI	
			lower	upper
Sex	0.850	0.906	0.324	2.531
Smoking	0.384	3.896	0.182	83.244
Drinking	0.336	0.183	0.006	5.830
BMI	0.252	0.927	0.813	1.056
Age group				
60-66	0.170			
67-72	0.286	0.518	0.155	1.735
≥73	0.356	1.686	0.556	5.117
Duration of hospitalization group				
3-17 days	0.982			
18-28 days	0.900	1.082	0.320	3.655
≥29 days	0.849	1.124	0.337	3.752
Drug number group				
5-8	0.010			
9-11	0.002	10.171	2.268	45.606
≥12	0.018	5.950	1.354	26.152
Co-administration of lorazepam and olanzapine				
Neither	0.693			
Either	0.579	1.476	0.372	5.857
Both	0.870	0.840	0.105	6.718
Co-administration of quetiapine and potassium chloride				
Neither	0.079			
Either	0.024	6.412	1.274	32.288
Both	0.999	0.000	0.000	—
Co-administration of quetiapine and escitalopram				
Neither	0.046			
Either	0.013	0.140	0.030	0.663
Both	0.999	0.000	0.000	—
Co-administration of olanzapine and clonazepam				
Neither	0.895			
Either	0.752	0.780	0.167	3.643

Figures

Figure 1. Flow diagram of enrolled patients

Figure 1

See figure for legend.