Chapter

Drug-Induced Delirium among Older People

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Abstract

Although underdiagnosed, delirium is a common and potentially preventable problem in older patients, being associated with morbimortality. Drugs have been associated with the development of delirium in the geriatric population and may be considered the most easily reversible trigger. Polypharmacy, prescription of deliriogenic, anticholinergic and potentially inappropriate drugs are contributing factors for the occurrence of the disturb. Furthermore, changes in pharmacokinetic and pharmacodynamic parameters, which are intrinsic of the aged process, may contribute for cognitive impairment. Identification and reversal of clinical conditions associated with delirium are the first step to treat the disturbance, as well as mitigation of environmental factors and the exposition to deliriogenic drugs. Current evidence does not support the prescription of antipsychotics and benzodiazepines for the treatment of delirium. However, the judicious use of first- or second-generation antipsychotics can be considered in severe cases. Multi-component non-pharmacological, software-based intervention to identify medications that could contribute to delirium, predictive models, tools, training of health professionals and active actions of pharmacovigilance may contribute to the screening, prevention, and management of delirium in older people. Besides, it is also important to improve the report of drug-induced delirium in medical records, to develop properly risk management plans and avoid cascade iatrogenesis.

Keywords: aged, emergency service, hospital, drug-related side effects and adverse reactions, delirium, pharmacovigilance

1. Introduction

1.1 Definition, diagnosis and treatment

According to the Diagnostic and Statistical Manual of Mental Disorders [1], delirium is defined as a complex syndrome characterized by disturbance in attention (reduced ability to direct, focus, sustain, and shift attention), awareness (reduced orientation to the environment), and an additional disturbance in cognition

(memory deficit, disorientation, language, visuospatial ability, or perception), which are not better explained by another preexisting, established, or evolving neurocognitive disorder. There is evidence that it is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies [1]. The disturbance develops over a short period of time, usually from hours to a few days, and tends to fluctuate during the course of the day, often with worsening in the evening and night when external orienting stimuli decrease [1].

Delirium is considered a serious global public health problem because it can increase the rate of morbidity and mortality [2], prolong hospitalization, promote institutionalization, worsen physical, cognitive and social outcomes [3], besides to increase health costs [4] and loss of independence among people affected by this health condition [5].

Regarding clinical presentation of delirium based on the psychomotor behavior changes, delirium can be classified into: a) hyperactive (the individual has a hyperactive level of psychomotor activity that may be accompanied by mood lability, agitation, and/or refusal to cooperate with medical care); b) hypoactive (the individual has a hypoactive level of psychomotor activity that may be accompanied by sluggishness and lethargy that approaches stupor); c) mixed level of activity (the individual has a normal level of psychomotor activity even though attention and awareness are disturbed. It also includes individuals whose activity level rapidly fluctuates) [1]. Delirium can also be classified in 5 subtypes: i) substance intoxication delirium; ii) substance withdrawal delirium; iii) medication-induced delirium; iv) delirium due to another medical condition; and v) delirium due to multiple etiologies [1].

The diagnosis for medication-induced delirium is applied when disturbance in attention and an additional disturbance in cognition arise as an adverse drug reaction [1]. The codes for diagnoses, according to the 10th revision of the International Classification of Diseases and Related Health Problems (ICD-10), depend on the type of substance related to delirium (**Table 1**).

In June 2018, the World Health Organization (WHO) released a pre-final version of the ICD-11 [6]. Under mental, behavioral or neurodevelopmental disorders, the neurocognitive disorders group (6), includes delirium (6D70), which can also be classified as being due to: a medical condition classified elsewhere (6D70.0), psychoactive substances, including medications (6D70.1); multiple etiological factors (6D70.2), unknown or unspecified etiological factors (6D70.3), delirium, other specified cause (6D70.Y) and; delirium, unspecified or unknown cause (6D70.Z) [6].

Although the pathophysiological mechanisms of delirium remain unclear, several evidences suggest the participation of different neurotransmitters and biomarkers. Among the most investigated mechanisms is cholinergic dysfunction,

Substance	Withdrawal delirium	Intoxication delirium	ADR
Opioids	F11.231	F11.121; F11.221	F11.921
Sedative, hypnotic, or anxiolytic	F13.231	F13.121; F13.221	F13.921
Amphetamine (or other stimulant)	—	F15.121; F15.221	F15.921
Other classes	F19.231	F19.121; F19.221	F19.921

Legend: ADR = adverse drug reaction.
Source: DSM-5 (2013).

Table 1.
ICD-10-clinical modification codes for the [specific substance] related to delirium.

which may contribute to some of the manifestations known to be present in delirium, such as cognitive deficits associated with memory loss [7, 8].

Identification and reversal of clinical conditions associated with delirium are the first step to treat the disturbance, as well as mitigation of environmental factors and the exposure to deliriogenic drugs [9]. Non-pharmacological approaches should be provided in order to prevent and manage the neuropsychiatric symptoms related to delirium, such as: avoid the use of physical restraints, catheters, and bed alarms, ambulate patient, address sensory impairment, encourage exposure to bright light during the day, among others [8].

Current literature does not support the prescription of antipsychotics [10] and benzodiazepines [11] for the treatment of delirium in hospitalized patients. A meta-analysis study found that the prescription of antipsychotics did not control the symptoms of delirium nor reduced the severity and mortality associated with the disorder, when compared to other treatments. In addition, no differences were observed between typical and atypical antipsychotics in patients hospitalized in non-critical wards, regarding symptom resolution of delirium [12]. However, the judicious use of first- and second-generation antipsychotics can be considered for the treatment of severe delirium symptoms, especially in the management of agitation associated with the hyperactive subtype [13], as well as when non-pharmacological interventions have failed and the symptoms put the affected individual at risk and they are distressing for family and caregivers. In these cases, the treatment should start with low doses and be further titrated until the required effect is achieved [8].

Regarding prevention, multi-component non-pharmacological interventions have shown to reduce the incidence of delirium, compared to usual care adopted among non-critical inpatients [14]. However, there is no clear evidence that cholinesterase inhibitors, antipsychotic medication or melatonin is able to reduce its incidence [14]. Nevertheless, the use of technology to help pharmacist to identify medications associated with the occurrence of delirium may contribute to decrease the incidence of the disturbance in older people [15]. This approach allows for drug adjustments aiming to prevent or solve drug-related problems associated with neurological disorders.

2. Epidemiology of delirium

Delirium is the most common psychiatric syndrome in hospitalized patients [16]. The general occurrence of delirium cases in hospitals can be between 29 and 82%. In a systematic literature review, which assessed the occurrence of delirium in inpatients at the admission, the authors related an occurrence rate in Europe between 4% in France to 31% in Sweden [17]. In the community, this occurrence is reduced to 1–2%. This great difference in percentages results from the emergency units being the places where people presenting the signs and symptoms of delirium normally go to. In fact, 17% of the older people in the community and 40% of those who live in nursing homes frequently attend emergency units with this diagnosis. Moreover, during hospitalization there are many contributor factors for the increased risk of delirium occurrence [18, 19]. Therefore, differences in the incidence of delirium are observed among the different inpatient units within a hospital (**Table 2**). The intensive care units (ICU), palliative care, oncology and postoperative are usually the places where delirium events occur the most, around 50–82% [18, 19].

This wide variation in the occurrence of delirium, when comparing different units, can be extrapolated to its prognosis. The main prognoses in patients with delirium are falls, catheter-associated infection, weakness, longer hospital stay and death, with this risk being 2 to 4 times greater in patients admitted to the ICU, and

1.5 times greater in patients admitted to general wards [19]. For this reason, the prevention of delirium is very important in health care. Thus, improved knowledge of the main delirium-related risk factors is essential for all health professionals who assist these patients directly.

Although a single factor may cause delirium, especially in the older people, its occurrence is usually considered multifactorial. In addition, as noted in the incidence of cases, the occurrence of delirium is associated with patient's vulnerability to harmful factors, for example, critically ill patients may begin to experience delirium from the administration of a sedative, in contrast to healthy patients where this syndrome is unlikely to occur due to the involvement of a single stimulus. Consequently, there are individual-associated vulnerability factors, as well as precipitating factors that may potentially increase or not the risk of triggering delirium (**Table 3**) [18, 19].

	Incidence (%)
Surgical	
Cardiac	11–46
Non-cardiac	13–50
Orthopedic	12–51
Medical	
General medical	11–14
Old age medicine	20–29
Intensive care	19–82
Stroke	10–27
Dementia	56
Palliative care, cancer	47
Nursing home or post-acute care	20–22

Table 2.
Incidence of associated delirium in different inpatient units. Adapted from Inouye, 2014 [18].

Vulnerability factors of the individual	**Precipitating factors**
Age (> 70 years)	Polypharmacy (≥ 5 drugs)
Cognitive deficiency	Psychoactive use
Dementia	Infectious disease
Functional impairment	Surgery or trauma
Visual deficiency	Indwelling catheters
Stroke	Physical restrictions
History of alcohol dependence	Coma
Depression	Metabolic disorders (blood urea, abnormal pH values, sodium reduction, glucose reduction)
Multimorbidity	

Table 3.
Vulnerability factors of the individual and precipitating factors associated with the occurrence of delirium. Adapted from setters, 2017 [19].

In relation to the individual's vulnerability factors in the general population, the occurrence of delirium is normally more associated with involvement by other comorbidities, such as stroke and depression. In people admitted to hospitals, other factors are also associated with the occurrence of delirium, such as dementia, cognitive impairment, functional impairment, visual impairment, a history of high alcohol consumption, and advanced age (> 70 years) [18].

Regarding the precipitating factors, the occurrence of delirium in the general population is mostly associated with abnormal laboratory parameters, such as high serum urea. In inpatients, in addition to metabolic disorders resulting from laboratory tests, it is worth mentioning other important factors, such as polypharmacy (≥ 5 drugs), the use of psychoactive drugs, and especially physical restrictions [18].

3. Delirium in older people

Delirium is a common and potentially preventable syndrome in older people hospitalized patients, being associated with high mortality rates ranging from 25–33%, thus resulting in longer hospital stays, high health costs, functional decline, increased falls, hospital readmissions, development of dementia or long-term cognitive impairment, and higher rates of morbidity. Delirium can also cause adverse events after hospitalization, including lasting functional limitations, persistent cognitive decline, and loss of quality of life for the patient and caregivers. The occurrence of new cases of delirium during hospitalization of older people varies from 6–56%; while the prevalence of delirium at the time of admission of older people varies from 14–24%. Furthermore, with the population's advancing age, delirium stands as a public health concern as it tends to increase in the future [20–23].

Although in some cases delirium can be caused by a single drug or underlying disease, in most cases delirium is the result of the combined action of predisposing and precipitating factors. It is, therefore, a multifactorial condition, which involves the interrelation between the patient's vulnerability to delirium at the time of hospital admission (predisposing factors) and precipitating factors that may arise during hospitalization. In this perspective, patients considered vulnerable (for example, those with dementia or a serious underlying disease) may experience delirium due to the use of a single dose of a sedative aimed to sleep. In contrast, patients resistant to the development of delirium may present this condition after a series of combinations, such as general anesthesia, major surgery, sleep deprivation, immobilization and the use of multiple psychoactive drugs [20]. In general, an intervention in one or more of these factors is considered sufficient for the delirium to be resolved [23].

The main predisposing factors for the occurrence of delirium at the time of hospital admission are the severity of the underlying disease, visual deficit, basal cognitive level, and dehydration. On the other hand, there are precipitating factors contributing for the development of delirium during hospitalization, for example: use of physical restrictions, malnutrition, addition of more than three drugs in the previous day, especially psychoactive drugs, use of urinary catheter. It is known that dementia is the most prevalent predisposing factor at the time of hospital admission, since it is able to increase the possibility of developing delirium by two to five times; however, any chronic disease can predispose delirium. Among the precipitating factors, the use of drugs is emphasized, being considered an extremely usual factor during hospitalization, originating up to 40% of cases. Consequently, the occurrence of delirium increases in direct proportion to the number of drugs used, due to the greater chance of adverse events and drug interactions take place [23].

Thus, in order to prevent the development of delirium resulting from the use of drugs, it became necessary to develop risk management plans, which is currently a prerequisite for a good pharmacovigilance service [9].

It is a fact that the prevention of delirium in the older people should stand as the main goal throughout the health care supply provided by health professionals, since the delirium prevention is always preferable to its treatment. However, when delirium occurs, early intervention and adequate management have been shown to improve the results for these patients [21, 22]. Despite the adverse consequences associated with delirium, the performance of health professionals in recognizing, registering, and treating it is still inappropriate. The lack of knowledge of the risk factors related to delirium in hospitalized older people is responsible for failures in the records in medical charts, in the notification and in the communication of the occurrence of delirium. In addition, the existence of knowledge gaps in screening and diagnosis using evidence-based tools are the main barriers to care [22].

Confirming the diagnosis of delirium in older people can be a challenge in complex clinical situations, with multiple demands and even more when the diagnosis is made by non-specialized health centers or unskilled professionals. The clinical manifestations of delirium and the factors associated with this condition can be confused with elements characteristic of aging, as well as being recognized as only cases of dementia or depression [24, 25]. The assessment of delirium superimposed on pre-existing dementia must be part of the differential diagnosis, as it happens in 90% of the cases with hospitalized older people [26]. In addition, hyperactive presentations of delirium can be misdiagnosed as hypomanic episodes [24, 25]. Estimates indicate that the recognition of delirium in the usual care only happens in 12–35% of the occurrences [26].

Considering that the prevention of delirium is essential in health institutions, clinical guidelines and models promoting the prevention, diagnosis and treatment of delirium have been developed and published internationally. However, it appears that they have not been properly implemented in clinical practice, which reinforces the need to initiate patient-centered care approach in the detection, prevention, and treatment of delirium, as well as in discharge planning [27].

The prediction of delirium in health services is extremely relevant to direct resources to prevention programs for patients most likely to have the syndrome. Although different tools have been developed in recent years, there are still no predictive models with adequate performance and recommendations for routine use in health services. Considering the current period of evidence, the insertion of predictive modeling and artificial intelligence in the health sector is a promising field for future research [28]. Moreover, when associated with a patient safety program, it has the potential to significantly improve the quality of care.

To improve this scenario, there are support strategies and tools for the delirium evaluation. Initially, it is extremely important to be aware of the signs and symptoms, as well as in the early observation of their onset (appearance of disorders and mental fluctuations), to avoid undesirable worsening [18, 26]. Therefore, the history of the episode is fundamental, with the record consistency of the steps that resulted in the event and thus it will be possible to carry out a comprehensive assessment of the potential triggering causes [18, 26]. Thus, the notoriety of providing instruction for people is justified because, in addition to the health team, family members and/or caregivers will also be crucial for the collection of this information [18].

Regarding the diagnostic decision support tools, studies in the literature have shown to provide validated instruments for this purpose [29]. Among them, it is worth highlighting the Confusion Assessment Method (CAM) [30], due to the reliability of its psychometric properties (specificity of 89% and sensitivity of 94%)

and because of the amount of evidence supporting the improvements in the evaluation resulting from its use [18, 31].

Acute beginning, confused thinking, lack of concentration, impaired consciousness, disorientation, noticeable disorders, hypoactivity and hyperactivity, detriment of memory and alteration of the sleep–wake cycle are the factors analyzed by CAM, with an application time of 5 minutes [30]. Still on the applicability, this tool has versions adapted to the areas that differ in the levels of health care for the older people (nursing home, emergency and intensive care units) [32, 33]. In order to guarantee the sensitivity and specificity of the CAM, there is an indication for the rater to be trained for the timely administration of the method and, to ensure the hypothesis of delirium, the older people's cognition should be evaluated by some specific test (for example, Short Portable Mental Status Questionnaire [34], Mini-Mental State Examination [35], Montreal Cognitive Assessment [36] or the Mini-Cog [37]).

The Confusion Assessment Method (CAM) Diagnostic Algorithm [30].

- **Feature 1: Acute onset and fluctuating course**

  This feature is usually obtained from a reliable reporter, such as a family member, caregiver, or nurse, and is shown by positive responses to the questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or did it increase or decrease in severity?

- **Feature 2: Inattention**

  This feature is demonstrated by a positive response to the question: Did the patient have difficulty focusing attention, for example, being easily distractible, or have difficulty keeping track of what was being said?

- **Feature 3: Disorganized thinking**

  This feature is shown by a positive response to the question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

- **Feature 4: Altered level of consciousness**

  This feature is demonstrated by any answer other than "alert" to the question: Overall, how would you rate this patient's level of consciousness? (alert [normal], vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable]).

The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4.

However, the implementation of delirium screening, detection, documentation, and notification guidelines present several challenges, being associated with a series of contextual and organizational issues. One of the major issues to be considered by health professionals is the use of a variety of descriptors to document and communicate their delirium assessments, since important and necessary information for the prevention and treatment of delirium may not be efficiently communicated in the medical records [22].

Medical records generally include descriptors, such as disorientation, agitation, altered level of consciousness, fluctuating mental state, confusion, negative behavior and hallucinations, but the term delirium is rarely mentioned [22]. This factor restricts the identification of this type of incident in an active pharmacovigilance system, as well as impairs the proper assessment of the case in the process of passive surveillance of drug-related adverse events. Therefore, it is essential to take into consideration on these evidence-based techniques, given that episodes of delirium are related to geriatric syndromes (incontinence, pressure injuries and falls), and with a long-term prognosis of attenuated survival rate, health conditions that result

in the need for rehabilitation and other adversities that affect cognition, such as dementia [18, 38]. Older people who were affected by delirium can be stratified in a public vulnerable to poor outcomes and this context predicts an alarming epidemic, given the increase in population longevity [38].

The Agency for Healthcare Research and Quality (AHRQ) points out delirium as an indicator of healthcare quality, because it is estimated that up to 40% of cases can be avoided in the general population and preventive interventions must involve the care environment (for example, lighting, availability of calendar, clock and other signages), the culture of team practices (for example, implementation of protocols for screening and continuous assessment of delirium, deprescribing and review of pharmacotherapy), in addition to measures for preliminary identification of risk factors [39]. Preventing, recognizing, and treating delirium has become a public health priority.

Owing to achieve quality and safety attributes at all levels of care for the older people, in addition of taking into account the severity of the complications caused (as poor quality of life, increased hospital stay and risk of death) and the high consecutive costs (from $ 143 to $ 152 billion per year), it is necessary to encourage the training of health professionals enabling them to recognize cases of delirium, as well as risk factors, treatment and prevention [18, 26]. The adequate documentation concerning the occurrence of delirium in health services and the initiative to educate the population about this disorder, can greatly contribute to the improvements in the management of this clinical condition [18, 26].

4. Drug related problems (DRPs) in the context of drug-induced delirium

Older people are a population at high risk for presenting DRPs and unnecessarily suffer from diseases and injuries resulting from excessive or inadequate consumption of drugs. Drug-induced delirium appears as a frequent consequence of these DRPs, which are associated with aspects of necessity, adherence, effectiveness, or safety of pharmacological treatment. In the care of older patients, the regular review of the pharmacotherapy is an essential service, but it is often neglected. Hospital and community pharmacists are in an ideal position to perform this task [40].

The behavior of the health professional team in just renewing previous prescriptions of polymedicated patients, without practicing review of pharmacotherapy, may result in the maintenance of treatments that are no longer necessary. Thereby, it becomes essential to assess the maintenance of each drug in terms of its benefit, when compared to the deliriogenic potential and the anticholinergic burden, with additional caution in drug discontinuation in those patients displaying an increased probability of delirium due to substance withdrawal syndrome [41]. The review should also include over-the-counter or easily accessible medications, herbal medicines and supplements, which are also associated with delirium (e.g. anticholinergics, antihistamines, non steroidal inflammatory drugs, muscle relaxants) [41, 42].

Any drug used to treat delirium, such as antipsychotics and benzodiazepines, will cause psychoactive effects and may further impair the state of consciousness. Therefore, the prescription of such drugs should be discouraged as they consist in a DRP of necessity (unnecessary drug), except in cases with severe symptoms that put the older people at risk, especially in the management of agitation associated with the hyperactive subtype of delirium. If the use of antipsychotics is indeed mandatory, the lowest dose and the shortest treatment period possible should be the chosen option. Benzodiazepines are restricted to the management of delirium due to alcohol and other drugs withdrawal [13, 43].

On the other hand, pharmacological treatment is regularly necessary in the management of factors that can contribute to the alteration of the state of consciousness, such as pain, infections, kidney disease, dehydration, metabolic and hydroelectrolytic disorders, among others [18, 19]. The absence of pharmacological interventions in this regard also constitutes a DRP (necessary drug not prescribed).

Delirium can also be a result of adherence problems (DRP of adherence). Aging brings a series of physical, mental, and social barriers to the adequate follow-up of pharmacotherapy, such as impaired vision, hearing and dexterity, difficulty in understanding and lack of home support. In the pharmacotherapeutic scheme, confusion predisposes to the occurrence of overdoses or even to the abrupt withdrawal of drugs, situations that trigger delirium. The pharmacist can develop strategies to make self-administration easier, aware the patient and reduce the complexity of pharmacotherapy (drug or formulation change, making boxes and guidelines, activation of alarms, etc.), in addition to educational actions for encouraging adherence [40, 44].

Some non-pharmacological factors can also contribute to the development of delirium and, when treated ineffectively (DRP of effectiveness), they may increase the chance of its occurrence. The sharp change in attention, awareness and cognitive functions can be triggered, for example, by uncontrolled infection, dehydration condition not reversed, and inadequate pain management (insufficient doses of opioids) [45].

All subtypes of delirium can be induced by Adverse Drug Reactions (ADR) [46]. When attention and cognition disturbance appear as a side effect of a drug taken as prescribed, this is characterized as a DRP of safety [1].

In older people, especially those diagnosed with dementia [46], most of these deliriogenic drugs have anticholinergic properties and are considered potentially inappropriate for this age group [47–49], with pyrilamine and methscopolamine being recently added to the list of drugs to be avoided [48].

Other drugs previously reported as capable of inducing delirium are opioids, antihypertensives (beta blockers associated with higher delirium rates when compared to calcium channel blockers), diuretics with the potential to cause hyponatremia, and dopaminergics [46, 50–52]. Abrupt withdrawal of benzodiazepines is related to hyperactive delirium, so de-escalation is advised [46].

Although the drugs described above are more often related to the development of delirium, it is essential to consider most drugs as risk factors in older people, due to the delirogenic potential of the aging process, illness or hospitalization [50]. Therefore, deprescribing should be considered when feasible.

In the case of drugs with anticholinergic activity, mainly muscarinic, changes in pharmacokinetic and pharmacodynamic parameters with advancing age increase the susceptibility to induce delirium [53]. After identifying those who potentiate delirium, they should be stopped or replaced by safer medicines [54].

Strategies for identifying, preventing, and solving actual and potential DRP essentially include the review of the pharmacotherapy and pharmacotherapeutic follow-up. These pharmaceutical services contribute to the prevention and resolution of deliriogenic drugs-induced ADR, decrease the incidence of delirium, minimize the occurrence of adverse events in people who are being treated with antipsychotics and allow polypharmacy to be assessed [55, 56].

5. Auxiliary instruments in the active search for DRPs in the context of drug-induced delirium

Most adverse events in the older people, especially those related to delirium, could be prevented by avoiding the prescription of Potentially Inappropriate

Medication (PIM), especially when safer alternatives are available for use. Most deliriogenic drugs have anticholinergic properties and are considered to be PIMs [47–49].

The development of evidence-based PIM lists is a complex task, as the geriatric population is usually excluded from clinical trials. Based on the opinion and consensus of experts, including pharmacists, geriatricians, nurses and other health professionals, several tools have been developed to assess whether drug use in the older people is appropriate [57]. One of the most used is the American Geriatrics Society (AGS) Beers Criteria, which was developed in the United States in 1991 and has further undergone several updates, the most recent one being published in 2019 [48]. The latest version of the AGS Beers Criteria organizes PIMs in five lists: drugs that are potentially inappropriate for the majority of the older people (high risk of adverse events and the existence of safer alternatives); drugs that should be avoided in older adults with specific clinical conditions; drugs to be used with caution; combinations of drugs that can cause harmful interactions; drugs that should be avoided or that require dose adjustment in the older people with impaired kidney function [48].

Another widely used prescription screening tool in the older people is the STOPP/START criteria, created in 2008 in Europe and updated in 2014 [58]. This tool is composed by the topics STOPP (Screening Tool of Older Persons' Prescriptions), which presents a list of PIMs organized by physiological systems, and START (Screening Tool to Alert to Right Treatment), which warns about missing treatments that should be initiated in older adults. This instrument also includes drug–drug interactions and drug-physiological status interactions [58].

Despite the existence of a large number of lists, tools and criteria for PIMs within the scientific literature, other factors should also be considered when reviewing pharmacotherapy, such as the older people's particularities, biological age, other therapeutic options and the specific needs of each patient.

The risk of drug-induced delirium in older adults can be assessed by the Delirium Drug Scale (DDS) [59]. The rank for the deliriogenic burden ranges from 0 to 3, according to the potential of the drug to induce delirium. Considering each drug with a potential delirium risk, the weighted DDS score should be calculated, so the exposure to the drugs that induce delirium is considered low when the scores vary between 0 and 1 excluding the value of 0; and high the score obtaind from DDS is greater than 1 [60]. Low exposure to drugs leading to delirium does not significantly increase the chances of delirium. For this reason, if the benefits of the therapy outweigh the risks, the prescribed doses can be safely tolerated [60].

Regarding the anticholinergic burden, the sum of the scores of anticholinergic activity magnitude for each prescribed drug, ranging from 1 to 3, is performed. The higher magnitude of anticholinergic activity leads to a higher score attributed to the drug [61]. Although there is no consensus in the literature, the average daily anticholinergic load ≥ 2 is considered high [62]. High anticholinergic burden is associated with increased risk of morbidity and mortality, hospital stay length, institutionalization, functional and cognitive decline [61].

6. Strategies for mitigating and preventing drug-induced delirium

6.1 Risk management: active and passive monitoring strategies for drug-related adverse events

Ensuring the safe use of drugs is one of the priorities of health systems worldwide, given that the estimated global cost due to failures in the process of using

these technologies is approximately US $ 42 billion annually. The safety use of drugs is a complex concept comprising multifactorial origins in different stages of the prescription, dispensing and administration processes, and in all these processes there is a risk of drug-related adverse events, meaning, the harms that may arise from the inadequate/inappropriate use of these medicines [63].

The occurrence of drug-related adverse events is distinguished as a relevant cause of morbidity and mortality, by causing suffering and dissatisfaction of patients and rising health care costs [64]. Thus, it is important to use strategies to prevent the incidence of adverse events and to mitigate the resulting social and economic impacts.

Drug-related adverse events are the main cause of preventable harms to the patient, with monitoring strategies occurring through two types of surveillance systems: active and passive. In this context, in order to reduce incidents, including drug-related adverse events, many health systems have implemented passive surveillance systems, which are allusive to spontaneous incident reports, aiming to identify and describe the risks and causes associated with adverse events, harmless incidents and near misses [64]. As they are cost-effective, these voluntary notification systems are responsible for a large part of the reports containing drug-related adverse events, conferring the potential to improve health care through the monitoring, reduction, and prevention of adverse events. However, there are still challenges associated with the data obtained from these systems, as this information is often difficult to interpret and manipulate due to underreporting, as well as their content and variability in the attribution of event categories by notifiers [64, 65].

Therefore, active surveillance systems complement passive systems. Although the active system is more costly, the information is obtained through direct contact, at regular intervals, between the team responsible for the active search and intensive monitoring of adverse events and the sources of information, mainly through the analysis of documents linked to the medical records of the patients, either retrospectively or prospectively [64, 66].

6.2 Patient safety, pharmacovigilance, and delirium

Delirium is an indicator of health quality in older people and, therefore, its prevention is an essential parameter for patient safety. Given the association between delirium and other common geriatric syndromes, its prevention benefits the improvement of the quality and efficiency of health services. The prevalence of delirium, its severity and duration can be significantly reduced when considering the existing risk factors [67].

The current management of delirium emphasizes the importance of its prevention, preferably through a non-pharmacological approach implemented in multiple sectors of health services. In this context, the following actions for patient safety are highlighted as [56, 59, 67]:

- Staff training: health professionals involved in the care of patients should be trained in relation to delirium, its diagnosis, management, and adequate documentation;

- Support from health professionals in providing guidance on the environment: the hospital environment must be adapted to the special needs of patients. The decline in sensory function in older adults can cause additional psychosocial stress, which may be exacerbated by cognitive impairment. In these circumstances, appropriate signs can be placed in the patients' wards, rooms, and bathrooms. Tools for temporal and situational guidance can be made available,

such as charts with personal information, date, and year, as well as clocks visible to patients. In addition, suitable accessories can be made available to prevent falls;

- Hospital admission phase: the health team can implement some non-pharmacological preventive interventions in this phase, for instance the realization of verbal guidelines, written recommendations for patients (posters, leaflets), instructions to the health team on the prescribed drugs and interventions and the appropriate ages;

- Implementation of treatments advised by international guidelines for the prevention of delirium: adaptation of surgeries and anesthesia; use of medications and pain treatment appropriate to the patient's age; pain monitoring; prevention of movement restrictions, such as when using catheters; use of benzodiazepines and anticholinergic drugs should be avoided; prescription of individualized and significant daily activities for the prevention of delirium, for example reorientation, cognitive activation, non-pharmacological promotion of sleep, and reduction of anxiety;

- Patients and their families should be individually advised on the risk and prevention of delirium. Family members can support individualized activities to prevent delirium by providing specific information about the patient, by collaborating with health care and by promoting individualized communication.

It is noteworthy that drug toxicity and polypharmacy are two of the main risk factors associated to delirium, especially in older patients with underlying comorbidities [62]. Anticholinergic, antipsychotic, benzodiazepine, and opioid agents are known to be highly deliriogenic [50]. However, several case reports show that drugs with a low suspicion of being deliriogenic can, in fact, present this particularity [68]. Therefore, the institutionalization of pharmacovigilance protocols for the management of delirium risks associated with the use of medications are of utmost importance.

The pharmacovigilance system is responsible for monitoring the safety of drugs and for adopting measures to reduce the risks and increase the benefits related to the use of drugs, as well as enabling improvements in patient safety and quality of life. Pharmacovigilance activities include: collecting and managing data on drug safety; the analysis of individual case reports to detect new drug-related adverse events; the proactive risk management to minimize any potential risks related to medication use; the communication and information to stakeholders and patients [69].

The suspected cases of delirium associated with the use of drugs identified by health service professionals, users and caregivers are notified to the drug manufacturers and health authorities in order to record these potential adverse events in the pharmacovigilance system. Such conduct makes it possible to screen and investigate the real association between these notified drugs and delirium. Notifications are generally sent voluntarily and reviewed by governmental organizations responsible for the safety of drugs on the market, which, in turn, forward the notifications to the Uppsala Monitoring Center, the World Health Organization collaborating centre for international drug monitoring.

For these reasons, it is highly important to establish a database to assess the safety issues of drugs in the post-marketing stage. This database system will allow to increase public knowledge regarding the drugs capable of inducing delirium, namely by identifying and monitoring the already known deliriogenic drugs, those

potentially deliriogenic, as well as new drugs displaying the potential to cause delirium [68].

Finally, the knowledge regarding the frequency with which these potentially deliriogenic drugs are attributed as the primary cause of delirium has shown to help in the clinical practice and in the possible prevention of the [20]. Therefore, the elaboration of a list of drugs that are notably potentially deliriogenic and have the potential to cause delirium demands a plausibility research to determine a definitive association. This list of drugs associated with delirium can provide valuable information to health professionals, allowing for the prevention of delirium or its timely diagnosis, apart from avoiding other adverse events [68].

The knowledge about this important drug-related adverse event involving the occurrence of delirium can promote concrete actions to improve the quality of care for the older people, with the active participation of the multidisciplinary team, especially with a systematic implementation of institutional protocols for the prevention of delirium. Thus, it is essential to increase the population's knowledge, especially of health professionals, about delirium, its associated risks, and the need to document suspected cases of delirium associated with the use of drugs. Pharmacovigilance is the right tool for this.

7. Conclusions

In sum, delirium may increase morbidity and mortality, prolong the length of hospital stay, promote institutional long-term care, worsen functional, cognitive, and social outcomes, increase health costs, and exacerbate the loss of independence of older people. The most common factors significantly associated with delirium among this population are severity of medical illness, visual impairment, urinary catheterisation, electrolyte disturbance, immobility, frailty, and length of hospital stay. The use of deliriogenic, anticholinergic and potentially inappropriate drugs, as well polypharmacy, are also contributing factors to the occurrence of delirium.

To prevent the harm associated with acute cognitive impairment, pharmacovigilance activities, pharmaceutical care in the geriatric population and predictive models are advised, since they may contribute to the screening, prevention, and management of delirium. Furthermore, it is important to improve competences of healthcare professionals to properly report the occurrence of delirium in medical records and apply patient-centred clinical methods to prevent iatrogenic cascades.

Appendices and Nomenclature

ADR	Adverse Drug Reactions
AGS	American Geriatrics Society
AHRQ	Agency for Healthcare Research and Quality
CAM	Confusion Assessment Method
DDS	Delirium Drug Scale
DRPs	Drug Related Problems
ICD	International Classification of Diseases and Related Health Problems
ICU	intensive care unit
PIM	Potentially Inappropriate Medication
START	Screening Tool to Alert to Right Treatment
STOPP	Screening Tool of Older Persons' Prescriptions
WHO	World Health Organization

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References

[1] APS. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®) 5th Edition;2013.

[2] Dani M, Owen LH, Jackson TA, Rockwood K, Sampson EL, Davis D. Delirium, frailty, and mortality: interactions in a prospective study of hospitalized older people. J Gerontol a Biol Sci Med Sci. 2018;73(3):415-418.

[3] Minden SL, Carbone LA, Barsky A, Borus JF, Fife A, Fricchione GL, Orav EJ. Predictors and outcomes of delirium. Gen Hosp Psychiatry. 2005; 27(3):209-14.

[4] Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Ynouye SK. et al. One-year health care costs associated with delirium in the elderly population. Arch Intern Med 2008;168(1):27-32.

[5] Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in older persons: advances in diagnosis and treatment. JAMA. 2017;318(12):1161-1174.

[6] World Health Organization. International Classification of Diseases for Mortality and Morbidity Statistics-Eleven Revision (11 ICD). Disposable at https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/897917531. Accessed in November 20th, 2020

[7] Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. Am J Geriatr Psychiatry. 2013; 21(12): 1190-1222.

[8] Hshieh TH, Inouye SK, Oh ES Delirium in the Elderly. Clin Geriatr Med 2020; 36(2):183-19.

[9] Kassie GM, Ellett LMK, Nguyen TA, Roughead EE. Use of medicines that may precipitate delirium prior to hospitalisation in older Australians with delirium: An observational study. Australas J Ageing.; 2019; 38(2):124-131.

[10] Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis. J Am Geriatr Soc. 2016;64(4):705-14.

[11] Li Y, Ma J, Jin Y, Li N, Zheng R. et al. Benzodiazepines for treatment of patients with delirium excluding those who are cared for in an intensive care unit. Cochrane Database Syst Rev. 2020; 2(2): CD012670.

[12] Burry L, Mehta S, Perreault MM, Luxenberg JS, Siddiqi N, Hutton B, Fergusson DA, Bell C, Rose L. Antipsychotics for treatment of delirium in hospitalised non- ICU patients (Review). Cochrane Database Syst Rev. 2018 ;6(6):CD005594.

[13] Han JH, Suyama J. Delirium and Dementia. Clinics in Geriatric Medicine; 2018; 34 (3): 327-354.

[14] Siddiqi N, Harrison JK, Clegg A, Teale EA, Young J, Taylor J, Simpkins SA. Interventions for preventing delirium in hospitalised non-ICU patients. Cochrane Database Syst Rev, 2016;3:CD005563.

[15] Woodhouse R, Burton JK, Rana N, Pang YL, Lister JE, Siddiqi N. Interventions for preventing delirium in older people in institutional long-term care. Cochrane Database Syst Rev; 2019;4(4):CD009537.

[16] Thom RP, Levy-Carrick NC, Phil M, Bui M, Silbersweig D. Delirium. Am J Psychiatry. 2019; 176:10. DOI: 10.1176/appi.ajp.2018.18070893.

[17] Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-inpatients: a systematic literature review. Age Ageing. 2006;35: 350-364. DOI: 10.1093/ageing/afl005.

[18] Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014 Mar 8;383(9920):911-22. doi: 10.1016/S0140-6736(13)60688-1

[19] Setters B, Solberg LM. Delirium. Prim Care Clin Office Pract. 2017; 44:541-559. DOI: 10.1016/j.pop.2017.04.010

[20] Inouye SK. Prevention of delirium in hospitalized older patients: Risk factors and targeted intervention strategies. Ann Med. 2000;32: 257-263. DOI:10.3109/07853890009011770

[21] Strijbos MJ, Steunenberg B, van der Mast RC, Inouye SK, Schuurmans MJ. Design and methods of the Hospital Elder Life Program (HELP), a multicomponent targeted intervention to prevent delirium in hospitalized older patients: efficacy and cost-effectiveness in Dutch health care. BMC Geriatr. 2013;13: 78. DOI:10.1186/1471-2318-13-78

[22] Zalon ML, Sandhaus S, Kovaleski M, Roe-Prior P. Hospitalized older adults with established delirium: Recognition, documentation, and reporting. J Gerontol Nurs. 2017;43: 32-40. DOI:10.3928/00989134-20161109-01

[23] Lôbo RR, Silva Filho SRB, Lima NKC, Ferriolli E, Moriguti JC. Delirium. Med (Ribeirao Preto Online). 2010;43: 249. DOI:10.11606/issn.2176-7262.v43i3p249-257

[24] Hall RJ, Meagher DJ, MacLullich AM. Delirium detection and monitoring outside the ICU. Best Pract Res Clin Anaesthesiol. 2012 Sep;26(3):367-83. DOI: 10.1016/j.bpa.2012.07.002

[25] Leonard M, Spiller J, Keen J, MacLullich A, Kamholtz B, Meagher D. Symptoms of depression and delirium assessed serially in palliative-care inpatients. Psychosomatics. 2009 Sep-Oct;50(5):506-14. doi: 10.1176/appi.psy.50.5.506.

[26] American Academy of Nursing. Twenty-Five Things Nurses and Patients Should Question. Choosing Wisely: an initiative of the ABIM Foundtion, 2018. Available from: https://www.choosingwisely.org/societies/american-academy-of-nursing/

[27] Lee-Steere K, Liddle J, Mudge A, Bennett S, McRae P, Barrimore SE. "You've got to keep moving, keep going": Understanding older patients' experiences and perceptions of delirium and nonpharmacological delirium prevention strategies in the acute hospital setting. J Clin Nurs. 2020;29: 2363-2377. DOI:10.1111/jocn.15248

[28] Rieck KM, Pagali S, Miller DM. Delirium in hospitalized older adults. Hospital practice (1995). NLM (Medline); 2020. pp. 3-16. DOI:10.1080/21548331.2019.1709359

[29] Adamis D, Sharma N, Whelan PJ, Macdonald AJ. Delirium scales: A review of current evidence. Aging Ment Health. 2010 Jul;14(5):543-55. doi: 10.1080/13607860903421011.

[30] Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990 Dec 15;113(12):941-8. DOI: 10.7326/0003-4819-113-12-941

[31] Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium?: value of bedside instruments. JAMA. 2010 Aug 18;304(7):779-86. DOI: 10.1001/jama.2010.1182

[32] Han JH, Zimmerman EE, Cutler N, Schnelle J, Morandi A, Dittus RS, et al. Delirium in older emergency department patients: recognition, risk factors, and psychomotor subtypes. Acad Emerg Med. 2009 Mar;16(3):193-200. DOI: 10.1111/j.1553-2712.2008.00339.x

[33] Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med. 2001 Jul;29(7):1370-9. DOI: 10.1097/00003246-200107000-00012

[34] Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. J Am Geriatr Soc. 1975 Oct;23(10):433-41. DOI: 10.1111/j.1532-5415.1975.tb00927.x

[35] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189-98. doi: 10.1016/0022-3956(75)90026-6

[36] Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005 Apr;53(4):695-9. DOI: 10.1111/j.1532-5415.2005.53221.x

[37] Borson S, Scanlan J, Brush M, Vitaliano P, Dokmak A. The mini-cog: a cognitive 'vital signs' measure for dementia screening in multi-lingual elderly. Int J Geriatr Psychiatry. 2000 Nov;15(11):1021-7. DOI: 10.1002/1099-1166(200011)15:11<1021::aid-gps234>3.0.co;2-6

[38] Witlox J, Eurelings LSM, de Jonghe JFM, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in Elderly Patients and the Risk of Postdischarge Mortality, Institutionalization, and Dementia: A Meta-analysis. JAMA. 2010;304(4):443-451. doi:10.1001/jama.2010.1013

[39] Rubin FH, Neal K, Fenlon K, Hassan S, Inouye SK. Sustainability and scalability of the hospital elder life program at a community hospital. J Am Geriatr Soc. 2011;59(2):359-365. doi:10.1111/j.1532-5415.2010.03243.x

[40] Wiffen P, Mitchell M, Snelling M, Stoner N, editors. Oxford Handbook of Clinical Pharmacy. 2. ed. New York: Oxford University Press, 2012. 674 p. DOI: 10.1093/med/9780199603640.001.0001

[41] Scott IA, Hilmer SN, Reeve E, Potter K, Le Couteur D, Rigby D, et al. Reducing inappropriate polypharmacy: The process of deprescribing. JAMA Internal Medicine. 2015; 175(5):827-834. DOI: 10.1001/jamainternmed.2015.0324

[42] Agbabiaka TB, Wider B, Watson LK, Goodman C. Concurrent Use of Prescription Drugs and Herbal Medicinal Products in Older Adults: A Systematic Review. Drugs and Aging. 2017; 34:891-905. DOI: 10.1007/s40266-017-0501-7

[43] Hshieh TT, Inouye SK, Oh ES. Delirium in the Elderly. Psychiatric Clinics of North America. 2018;41(1):1-17. DOI: 10.1016/j.psc.2017.10.001

[44] Sharma M, Loh KP, Nightingale G, Mohile SG, Holmes HM. Polypharmacy and potentially inappropriate medication use in geriatric oncology. Journal of Geriatric Oncology. 2016; 7(5):346-353. DOI: 10.1016/j.jgo.2016.07.010

[45] Morrison RS, Magaziner J, Gilbert M, Koval KJ, McLaughlin MA, Orosz G, Strauss E, Siu AL. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. Journal of Gerontology: MEDICAL SCIENCES. 2003;58(1):76-81. DOI:10.1093/gerona/58.1.m76

[46] Alagiakrishnan K, Wiens CA. An approach to drug induced delirium in the elderly. Postgraduate Medical Journal. 2004;80:388-393. DOI: 10.1136/pgmj.2003.017236

[47] Fosnight S. Delirium in the elderly. In: Richardson MM, Chessman KH, Chant C., editors. Pharmacotherapy Self-Assessment Program. 7th ed. Lenexa: American College of Clinical Pharmacy; 2011. p. 73-96.

[48] AGS. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. Journal of the American Geriatrics Society. 2019;67(4):674-694. DOI: 10.1111/jgs.15767

[49] Salahudeen MS, Duffull SB, Nishtala PS. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: A systematic review. BMC Geriatrics. 2015; 15:31. DOI: 10.1186/s12877-015-0029-9

[50] Catic AG. Identification and management of in-hospital drug-induced delirium in older patients. Drugs Aging. 2011;28(9):737-748. DOI:10.2165/11592240-000000000-00000

[51] Harrison PJ, Luciano S, Colbourne L. Rates of delirium associated with calcium channel blockers compared to diuretics, renin-angiotensin system agents and beta-blockers: An electronic health records network study. Journal of Psychopharmacology. 2020;34(8):848-855. DOI:10.1177/0269881120936501

[52] Zieschang T, Wolf M, Vellappallil T, Uhlmann L, Oster P, Kopf D. The Association of Hyponatremia, Risk of Confusional State, and Mortality. Dtsch Arztebl Int. 2016;113(50):855-862. DOI: 10.3238/arztebl.2016.0855

[53] Meyer S, Meyer O, Kressig RW. [Drug-induced delirium]. Therapeutische Umschau. Revue therapeutique. 2010;67(2):79-83. DOI: 10.1024/0040-5930/a000015

[54] Garpestad E, Devlin JW. Polypharmacy and Delirium in Critically Ill Older Adults: Recognition and Prevention. Clinics in Geriatric Medicine. 2017;33(2):189-203. DOI:10.1016/j.cger.2017.01.002

[55] Clegg A, Siddiqi N, Heaven A, Young J, Holt R. Interventions for preventing delirium in older people in institutional long-term care. Cochrane Database of Systematic Reviews. 2014; 1: CD009537. DOI: 10.1002/14651858.CD009537.pub2

[56] Kassie GM, Ellett LMK, Nguyen TA, Roughead EE. Current practice and opinions of hospital pharmacists regarding their role in the screening, prevention and treatment of delirium. International Journal of Clinical Pharmacy. 2017;39(6):1194-1200. DOI:10.1007/s11096-017-0547-y

[57] Motter FR, Fritzen JS, Hilmer SN, Paniz EV, Paniz VMV. Potentially inappropriate medication in the elderly: a systematic review of validated explicit criteria. European Journal of Clinical Pharmacology. 2018; 74: 679-700. DOI: 10.1007/s00228-018-2446-0

[58] O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: Version 2. Age and Ageing. 2015; 44(2):213-218. DOI: 10.1093/ageing/afu145

[59] Nguyen PVQ, Pelletier L, Payot I, Latour J. Drug Delirium Scale (DDS): A tool to evaluate drugs as a risk fator for delirium. Internacional Journal of Innovative Reasearchin Medical Science. 2016;1(6):232-237. DOI:10.23958/ijirms/vol01-i06/02

[60] Nguyen PVQ, Pelletier L, Payot I, Latour J. The Delirium Drug Scale is associated to delirium incidence in the emergency department. International

Psychogeriatrics. 2018;30(4):503-510. DOI: 10.1017/S1041610217002538

[61] Nery RT, Reis AMM. Development of a Brazilian anticholinergic activity drug scale. einstein (São Paulo). 2019;17(2):eAO4435. DOI:10.31744/einstein_journal/2019AO4435

[62] Hwang S, Jun K, Ah YM, Han E, Chung JE, Lee JY. Impact of anticholinergic burden on emergency department visits among older adults in Korea: A national population cohort study. Archives of Gerontology and Geriatrics. 2019;85:103912. DOI: 10.1016/j.archger.2019.103912

[63] Machen S, Jani Y, Turner S, Marshall M, Fulop NJ. The role of organizational and professional cultures in medication safety: A scoping review of the literature. International Journal for Quality in Health Care. Oxford University Press; 2019. pp. G146–G157. DOI:10.1093/intqhc/mzz111

[64] Capucho HC, Carvalho FD, Cassiani SHDB. Farmacovigilância: Gerenciamento de Riscos da Terapia Medicamentosa para a Segurança do Paciente. 1st ed. São Caetano do Sul: Yendis; 2011

[65] Fong A, Harriott N, Walters DM, Foley H, Morrissey R, Ratwani RR. Integrating natural language processing expertise with patient safety event review committees to improve the analysis of medication events. Int J Med Inform. 2017;104: 120-125. DOI:10.1016/j.ijmedinf.2017.05.005

[66] Monteiro SAMG, Takano OA, Waldman EA. Evaluation of the Brazilian surveillance system for adverse events following vaccination. Rev Bras Epidemiol. 2011;14: 361-371. DOI:10.1590/S1415-790X2011000300002

[67] Sánchez A, Thomas C, Deeken F, Wagner S, Klöppel S, Kentischer F, et al. Patient safety, cost-effectiveness, and quality of life: reduction of delirium risk and postoperative cognitive dysfunction after elective procedures in older adults—study protocol for a stepped-wedge cluster randomized trial (PAWEL Study). Trials. 2019;20: 71. DOI:10.1186/s13063-018-3148-8

[68] Currow DC, Rowett D, Doogue M, To THM, Abernethy AP. An International Initiative To Create a Collaborative for Pharmacovigilance in Hospice and Palliative Care Clinical Practice. J Palliat Med. 2012;15: 282-286. DOI:10.1089/jpm.2012.9605

[69] Fornasier G, Francescon S, Leone R, Baldo P. An historical overview over Pharmacovigilance. Int J Clin Pharm. 2018;40: 744-747. DOI:10.1007/s11096-018-0657-1