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Imperative Future To-Do List: We Face Enormous Problems of Delirium - But Do We Really Eliminate the Fundamental Causation?

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Editorial

This editorial on delirium from a synoptic internal medicine/clinical pharmacology view is based on eight years of daily real-life experience, during which I have personally conducted more than 56,200 Individual Pharmacotherapy Management (IPM) assessments [1] in critically ill and multimorbid elderly patients in trauma and surgical intensive care units at Halle University Hospital (UKH).

These are patient groups extraordinary suspectible to delirium because most frequently on polypharmacy from their prescribed outpatient medication already and often suffering from preexisting organ deterioration as chronic kidney disease, cardiac and pulmonary dysfunction, anemia, blood pressure and glucose disorders and concurrently requiring surgical intervention in the acute hospital situation. This itself frequently indicates additional prescription of analgesics as opioids, and probably antibiotics and antifungals.

The adjustment and fine-tuning of each drug according to their degradation in the very patient with his/her individual acute organ capacities to metabolize and/or renally eliminate a medication in synoptic reference to Adverse Drug Reactions (ADRs) and Drug Drug Interactions (DDIs) on pharmacodynamic and pharmacokinetic level seem to be the best guide through a preventative delirium access since we could achieve a tenfold reduction by the IPM designed and accordingly applied in the elderly traumatology patients [1].

IPM means clearly more than only analyzing DDIs through interaction checks or just the implementation of tools such as positive or negative lists of appropriate or inappropriate medications in the elderly. These may be helpful to a certain extent, but they never capture the individual patient with his or her personal organ situation and comorbidities often necessitating an unavoidable polypharmaceutical comedication, that is comprehensively covered by the IPM designed accordingly in this respect. Consistent implementation of IPM was documented to be highly effective in preventing complicating delirium, being associated with a reduced incidence of almost zero (0.5%) in the elderly traumatology patient setting [1].

The main delirium risk may result from any deterioration leading to a reduction in cerebral energy [2]. From a comprehensive view thus we have to attend to a broad and heterogeneous field of potentially causal links whether hypotensive, hypoglycemic, hypoxemic and severely anemic, hypothermic, hyponatremic or hypercalcemic due to e.g., electrolyte disturbances, to water balance disorders as e.g., exsiccosis, all kind of cardiac arrhythmias, respiratory and cardiovascular insufficiency or failure, circulatory dysfunction or failure, hyperviscosity syndrome and rheological perfusion disorders, chronic kidney disease and uremic syndrome, single or multiple organ failure, diseases of the central nervous system e.g., Parkinson's disease, epilepsy, stroke, craniocerebral trauma, intracranial bleeding and subdural hematoma, dementia and meningitis, alcohol or drug withdrawal, intoxicants, abuse and drug addiction, drug overdosage, deficiency in vitamin B12, folic acid or thiamine, liver cirrhosis and hepatic encephalopathy, infectious disease, fever, sepsis, tumors, lactic acidosis or further acid-base balance as well as metabolic disturbances such as hyperlipidemia, hyperglycemia as e.g., also triggered by application of high-caloric intravenous nutrition,

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transient corticosteroids or stress, to diabetes insipidus, and, even Addison's disease, especially in patients on preceding longterm corticosteroids, to hyperaldosteronism, and thyroid dysfunction, in which you should avoid rapid onset of high-dose thyroids as they may induce atrial fibrillation. Each of these issues requires being addressed and treated in its individually targeted manner. Part of these conditions are often amplified or even induced by the patient's medications, and beyond that, mostly the cumulative effects of ADRs resulting from polypharmacy in particular are not appreciated at all.

This, among others, becomes especially relevant in the perioperative situation when the patient is co-administered opioid analgesics in addition to his or her preexisting medications. They, e.g., enhance the blood pressure-lowering effect of all antihypertensives the majority of elderly patients are prescribed and on any preexisting postoperative or periinfectious hypotension. Furtheron, in this context, a major focus must be on serotonergic opioids e.g., phenylpiperidine opioids fentanyl, methadone, pethidine and tramadol, and the morphine analogues oxycodone and codeine, which, in combination with the frequently administered antidepressants of the SSRI group e.g., citalopram, sertraline, or the SSNRIs, e.g., venlafaxine, duloxetine, can cause a serotonergic syndrome [3], in all its varying intensities, resembling delirium. And particularly antibiotics' inherent risk of Antibiotic-Associated Encephalopathy (AAE), with 3 clinical phenotypes from underlying pathophysiologic mechanisms of neurotoxicity [4], or antifungals of which themselves often with ADRs in terms of confusion, constantly require timely fine-tuning of the dosage, especially in elderly and multimorbid patients with chronic kidney disease. In addition, body weight, BMI, and especially serum protein and albumin frequently are extremely low to subnormal in elderly patients [5], thus affecting the bioavailability of strong protein-binding drugs. Renal insufficiency and proteinuria can increase the risk neurotoxic ADRs not only by elevating serum concentrations but also increasing drug bioavailability because of lower serum protein levels, as documented, e.g., for antibiotics [6]. Exaggerating the problem, low serum protein levels themselves also decrease protein glycation and carbamylation known to cause alterations in the integrity of the blood-brain barrier, thus rises the entry of e.g., antibiotics into the CNS [7]. I doubt whether this is considered at any stage of indicating and prescribing drugs. Although it is a common condition, particularly in increasingly elderly and intensive care patients, the clinical consequences in terms of dose adaption still have not been studied sufficiently.

Achieving healthy ageing at all, including the prevention of delirium, requires a lot more consistent application of the much-cited holistic patient perspective so that this terminus does not remain wishful thinking and a blanket of words. Without the enforced promotion of this view, at the very latest by the discipline of geriatrics, which in this context ultimately should perform IPM in every elderly patient and obligatorily should evaluate and score every geriatric assessment result in the very respect to the patient's current medication list, as e.g. psychotropic agents and opioids the elderly patients often are on certainly have an impact not to neglect on the elderly patients' cognition and reactivity being assessed, we will continue to be confronted with delirium in a never-ending and typically ever-triggering prescription cascade that often only modulates the situation like bad make-up. As pointed out, e.g., treating delirium in severely hypotensive or hyperglycemic patients with antipsychotics rather means exacerbating the situation except when the dose finally reaches a level high enough to fully sedate the patient as obviously practiced. The prescribing cascade typically misses eliminating the fundamental causation. Well recognized warnings, according to their citation frequency, emerge throughout decades from literature, in 1997 Rochon and Gurwitz described the risks associated with the prescribing cascade and in this context called for the need to optimize drug treatment in the elderly patients most affected [8].

Unless we focus on any drug-induced delirium, on every metabolic, electrolyte, blood pressure or infection condition and address personal sensitivity disorder and discomfort as e.g., from pain, bladder and other catheters or drainages, and disorientation or isolation we can never capture the exact underlying reason to treat the patient delirium in a targeted manner. Perhaps this is why many patients who suffer from delirium also subsequently experience long-lasting corresponding confusion disorders and cognitive impairments being repeatedly or ongoing on one or more antipsychotics and even additional benzodiazepines just for further sedation in hyperactive delirium, although agitation is a major ADR risk from antipsychotics themselves [9-11].

The effect of pharmacological delirium treatment has been discussed controversially [12,13]. If there still remain clinical indications to treat delirium [14,15] with, e.g., transient and always dose-limited antipsychotics of the butyrophenone class besides e.g., clonidine or more selective α-2 adrenoceptor agonists as dexmedetomidine and mivazerol, these controversely discussed measures may only be applicated strongly time limited and under monitoring to improve patient safety after iatrogenic drug and all other eliminable causes have been ruled out and all kind of nonpharmacological approaches have failed. In this context principle pharmacological aspects in prescribing the antipsychotics most often seem to be neglected: for melperone according to its guiding principle from the SmCP the dose is to keep as low and the duration of treatment as short as possible [9], and we have to contribute to its obviously clinically relevant moderate CYP2D6 inhibition effect on frequently administered drugs as e.g., metoprolol, etc. [16], pipamperone notably being without these pharmacokinetic DDI risks [9], and haloperidol, which to be aware of being increased available in genetically poor CYP2D6 metabolizers, concomitant potent CYP2D6 and CYP3A4 inhibitors [10]. Any antipsychotic bridge with its own inherent ADRs including patient's further psychotic, neurologic and cardiac disorders, and a threefold increased risk of cerebrovascular events, must be de-installed as soon as possible [9-11]. Besides the rather long terminal elimination half-life of haloperidol as a lipophilic substance is 24 hours on average (range of means 15 to 37 hours) plasma levels are increased in the elderly patients [11] and with chronic administration e.g., 4 weeks, half-lives of up to 21 days have been reported. Haloperidol and its ADRs and DDIs can persist in many patients for weeks, and in some patients for months after the last dose [17]. After oral administration, haloperidol accumulates in the brain about 20-fold compared to the blood [18]. After discontinuation of haloperidol medication, brain concentration decreases only slowly. This accounts for the characteristic clinical finding that ADRs of haloperidol are delayed even after discontinuation, the estimated

elimination half-life of haloperidol in brain tissue is 6.8 days [18]. Do we indeed bear this in mind when we prescribe the drug? Or are these facts even totally unknown to the prescriber?

To complete and to reflect on the mostly difficult and critical situation of delirium treatment in this context, something almost curious should be mentioned additionally: Although haloperidol has been approved for more than half a century, and despite it is on the WHO list of essential medicines [19], even on its core list as defined by the WHO "The core list presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment" [19], and although haloperidol been the most widely used typical antipsychotic and is commonly often prescribed even in critically ill patients with organ deterioration, neither the effect of renal dysfunction on the pharmacokinetics of haloperidol nor the effect of hepatic dysfunction on the pharmacokinetics of the drug has ever been studied according to Summary of Product Characteristics (SmPC) [11]. Who is responsible for this decades-long laxity in the approval of a drug? Why do responsible drug regulatory agencies and authorities neither at the national, nor European and other international levels require secondary delivery of this essential drug data for individual patient-adapted dosing mandate an accurate drug degradation record to enable the prescriber in adequate dosing according to the patient organ functions and necessary adjustment according to potential DDIs? In addition, it is important to mention, that after severe and even lethal outcomes post marketing [20], currently, after decades, the maximum haloperidol daily dose for elderly patients has become limited to 5 mg. Similar vague are the corresponding recommendations for melperone stating that in the case of a history of renal, hepatic and circulatory dysfunction, melperone should be dosed cautiously, and the corresponding functions should be checked at regular intervals [9]. In this regard, is it kept in mind that particularly the elderly patients often suffer from impaired renal function when prescribing nonadapted dosages of melperone? Various psychotropic risks may even worsen the delirious condition including agitation etc. as identified and specified in SmPCs of antipsychotics and benzodiazepines themselves, summaries that should be respected more adequately by any prescriber as the SmPCs form the "basis of information for healthcare professionals on how to use the medicine safely and effectively" [21].

In our group-matched retrospective study on 404 patients the effect of the comprehensive IPM adjusting each drug according to its SmPC to the individual patient condition we could find an IPM associated relative reduction of complicating delirium prevalence by 90.2% in the elderly traumatology patients in hospital. This elderly patient group hospitalized for trauma even aged 81.5 ± 6.5 years was on a mean medication number of 10.4 ± 3 that could not be further reduced because of the underlying multimorbidity. The IPM bases on a complete digital patient record to guarantee an "overall view of the patient" in terms of ensuring entire respect to all diagnoses, organ functions via laboratory data, ECG, vital parameters, all kind of diagnostic results and patient complaints. In addition to the association of IPM with reduced complicating delirium, we found numerous drug-associations, thus presumably iatrogenic, for complicating delirium. And despite an unavoidably persistent high number of perioperatively administered drugs in the multimorbid elderly IPM-intervention group, our targeted IPM focus on six frontline aspects with reduction of antipsychotics, anticholinergic burden, benzodiazepines, serotonergic opioids, elimination of pharmacokinetic and pharmacodynamic DDIs, and overdose reduced complicating delirium almost completely by 10-fold. The factors most strongly associated with complicating delirium were cognitive dysfunction, nursing home residency, antipsychotics, muscle relaxants, antiparkinsonian agents, xanthines, transient disorientation documented in the fall risk scale, antibiotic-requiring infections, antifungals, and ICU stay [1]. The identified delirium-associated factors are consistent with those outlined in ICD-classification and several previous studies and may be helpful if integrated into a sophisticated screening scale to identify patients at risk.

Furtheron, besides the risk from pain management with various analgesics, most urologic agents for incontinence therapy are associated with risk of delirium related to their anticholinergic effects.

There are some less frequent, yet notable delirium resembling conditions as from hypercalcemia, sometimes the first indicator of a bone metastasizing progressive tumor or more frequently the result of longterm treatment with hydrochlorothiazides. We also find hypercalcemia with enduring physical inactivity. These entities require specific countermeasures to lower serum calcium and thus a targeted treatment that is effective without adding antipsychotics, which are administered far too frequently and inappropriately in confused patients, therefore possibly even exacerbating the delirium resembling problems. Any cascade of prescriptions must exclude any iatrogenic cause of triggering or worsening of the patient's clinical confusion condition.

Most often the medication-associated risk factors even cumulate from polypharmacy and obviously the increasing number of specialist physicians treating the same patient because of multimorbidity administer their medication without reviewing or even being aware of the concomitant ADRs and resulting DDIs from medications already prescribed by colleagues of other disciplines. This is a fact the patient should be informed about himself in terms of health education and patient empowerment. Patients' own knowledge of important risks of any drug use, although unavoidable, would promote personal responsibility for as long as possible, a topic that is not really being addressed and utilized at present. The IPM outcome research indicates an urgent need to review polypharmacy for drug and patient safety not only in the late and affected stage in elderly hospitalized patients, but earlier already also in older citizens at increasing risk of delirium, cognitive impairment, and even dementia and fall events to accelerate underrepresented promising preventative solutions.

From the multidomain access of delirium prevention there has been no breakthrough power of a single factor so far. Obviously, this is not the case with drug-related association. As the IPM data indicate, a lot can be done here, optimizing the mostly uncontrolled polypharmacy based on the SmPC of each drug with respect to all ADRs, plus the frequently critical risks of DDIs and overdoses. The prescribing cascade for delirium treatment is serious and often the start of a vicious circle: e.g., as depicted patients on low blood

pressure become worsened as antipsychotics aggravate the blood pressure lowering effect of preexisting antihypertensive agents most patients are prescribed, thus intensify often preexisting or even induce delirium or disorientation by aggravating hypotension.

Elderly patients' perceptions of helplessness, insecurity and loneliness in unfamiliar surroundings and background noise, with unfamiliar individuals responsible for partly intensive personal care, any kind of stress and discomfort as from urinary retention and catheters, pain, uncertainty, and disorientation are cumulative risks that are well known and must be addressed. Delirium prophylaxis and non-pharmacological treatment according to geriatric consultants (Stegmann S, Mühlhammer D, 2022, UKH, unpublished) should include an accepted typical multidimensional approach with analogously precise practical advice - "1: Avoidance and treatment of infections, urinary retention, fever, pain, exsiccosis, electrolyte disturbance, delirium-promoting drugs; 2: Providing security (if possible, fixed reference persons, inclusion of family members, avoidance of unnecessary transports/transfers); 3: Stress reduction (empathic tone, low ambient noise level); 4: Orientation (structured daily routine, adapted lighting conditions, promotion of a normal sleep-wake rhythm, calendar, large clock, hearing aids, visual aids); 5: Activation (early mobilization, self-help promotion, activating-therapeutic care, social interactions)."

These measures and early nutrition cover accepted recommendations as e.g., the evidence-based and consensus-based statements regarding prevention and treatment in elderly patients according to the EJA guidelines on postoperative delirium [15].

Thus, the list, to be worked through is extensive and plausible, but according to the impressive results of a very individual and comprehensive medication review in synopsis with the patient-specific clinical condition and organ functions, IPM should 1st. : Be at the top of the priority list and 2nd. : Guaranteed to be performed in order to exclude an incorrect prescription cascade with antipsychotics, which may themselves even contribute to the feared long-term negative cognitive consequences of delirium with institutionalization of a patient who was at home before hospitalized.

Also, for any delirium prophylaxis recommendations and measures as maybe supposed by delirium associations such as the EDA, ADS, ADA or delirium guidelines and any SOPs, the first priority should always be the focus on the medication list and its iatrogenic interferences as a predominant delirium risk from polypharmacy in the elderly, pre-diseased, multimorbid and frail patients. The almost complete reduction of complicating delirium associated with IPM forces to define and minimize the medication-related harms as the main challenge to be addressed by a policy-regulated advocacy for urgent delirium prevention and corresponding adequate treatment.

It is interesting to note in this context that the same IPM measure in the studied patient population was also associated with a significant reduction in in-hospital fall events, reflecting the broad intersection within medication risks that contribute to both feared delirium and fall events. Indeed, their burden on individual patients and their families, as well as on the economic health care system, argues for a policy-based requirement for comprehensive IPM as a strong prevention strategy that has been unrecognized and underregulated, so far.

Given the alarming percentages of delirium incidence, with a range depending upon the patient setting studied as from 30% to 80% among patients in intensive care and from 5.1% to 52.2% among surgical patients, varying with the type of procedure [22] and finding a pooled delirium prevalence of 48.9% as one further defined entity "Delirium Superimposed on Dementia" (DSD) [23] the problem is concerning and increasing considering the rapidly ageing world population. Delirious elderly patients are hospitalized longer, institutionalized, and decease more commonly [23,24] with a mortality rate up to 30%. Institutionalization is likely to imply the absence of a healing environment important for the recovery of patients in delirium, thus triggering a vicious circle that will probably continue the prescription cascade with antipsychotics. In a prospective one-year study in 2020 Fuchs et al. found a prevalence of delirium across all included services by 32% [25]. Alongside the demographic development means an increasing burden to patients and economic health care system worldwide [26]. The severe rise with age coincides with a parallel increase in prevalence of polypharmacy in this very patient group. In nursing home residents and palliative care, typically representing a patient group which mostly is on a wide and critical liberal dispension of combinations with antipsychotics, antidepressants, and opioids simultaneously, the delirium incidence is particularly high.

To improve patient safety WHO's continuous challenges [27-29] are currently aligned with the United Nations Decade for Healthy Ageing (2021-2030) to further progress them; and OECD reports [30] on patient safety deficits reflect the recognized sociopolitical weight and responsibility that needs to be enforced. The consequent and urgent task for the future is to adequately prevent and treat delirium by always implementing the long overdue mandatory comprehensive and holistic medication review of the high-risk uncontrolled polypharmacy and to exclude any medical risk from critical indications or contraindications, overdosage, ADRs, and pharmacodynamic and pharmacokinetic DDIs and thereby simultaneously eliminating all hypotensive, hypoxic, metabolic, electrolyte and iatrogenic, often cumulative confusion disorders, before placing the patient on further medications such as antipsychotics.

To sum up: Besides constant efforts to optimize delirium definitions and elaborate screening tools and prevention strategies, the to-do list must obligatorily always focus on the patient's medication. Eliminating fundamental causation of delirium, as the IPM results indicate, means that pharmacotherapy must be managed at a highly individualized level, adapting each medication to the patient's very specific acute condition and organ functions for capacities of drug degradation, and fully accounting for each medication's ADRs and DDIs. The IPM resultant may even necessarily differ from current disease guidelines, as these still almost never respect the multimorbidity and polypharmacy of our increasingly elderly patients, who necessarily require an individualized, holistic, synoptic view on the medication prescribed. The IPM outcomes research provides important evidence for the urgent need to evaluate polypharmacy for drug and patient safety, not only in older hospitalized patients but also in older citizens at increased risk for delirium, cognitive impairment, and even dementia, to accelerate underrepresented promising prevention strategies against iatrogenic risk from uncontrolled polypharmacy.

Given this background, the introductory question is to be answered: For the imperative future to-do list, the elimination of all iatrogenic delirium risks from polypharmacy and each medication as fundamental causation, identified by the IPM efficacy in the elderly patients, must be mandatory. To sustainably promote patient and drug safety in delirium prevention, not only delirium associations and guideline elaborators, but also patient associations, health policy authorities and health insurance providers must press for this overdue demand and anchor it politically. And a distinct ICD classification that codes medication-induced delirium or presumed iatrogenic medication-induced delirium as a separate disease entity to indicate appropriate targeted medication withdrawal instead of an additional pharmacologic prescription cascade will be an important step forward in making unaware physicians more sensitive to under-recognized iatrogenic medication-induced delirium.

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Conflicts of Interest

UW received honoraria from Bristol Myers Squibb and Pfizer.

References

1. Drewas L, Ghadir H, Neef R, Delank KS, Wolf U. Individual Pharmacotherapy Management (IPM) - I: a group-matched retrospective controlled clinical study on prevention of complicating delirium in the elderly trauma patients and identification of associated factors. BMC Geriatr. 2022; 22: 29.
2. Wilson JE, Mart MF, Cunningham C, Shehabi Y, Girard TD, et al. Delirium. Nat Rev Dis Primers. 2020; 6: 90.
3. Rickli A, Liakoni E, Hoener MC, Liechti ME. Opioid-induced inhibition of the human 5-HT and noradrenaline transporters in vitro: link to clinical reports of serotonin syndrome. Br J Pharmacol. 2018; 175: 532-543.
4. Bhattacharyya S, Darby RR, Raibagkar P, Gonzalez Castro LN, Berkowitz AL. Antibiotic-associated encephalopathy. Neurology. 2016; 86: 963-971.
5. Wolf U, Eckert S, Walter G, Wienke A, Bartel S, Plontke SK et al. Prevalence of oropharyngeal dysphagia in geriatric patients and real-life associations with diseases and drugs. Sci Rep. 2021; 11: 21955.
6. Manian FA, Stone WJ, Alford RH. Adverse antibiotic effects associated with renal insufficiency. Rev Infect Dis. 1990; 12: 236-249.
7. Chow KM, Szeto CC, Hui AC, Li PK. Mechanisms of antibiotic neurotoxicity in renal failure. Int J Antimicrob Agents. 2004; 23: 213-217.
8. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. BMJ. 1997; 315: 1096-1099.
9. Summary of Product Characteristics. Melperone-CT 25 mg / 50 mg / 100 mg film-coated tablets. Melperone-CT 25 mg/5 ml solution. 2022.
10. Summary of Product Characteristics. Pipamperon-neuraxpharm 40 mg tablets. Pipamperon-neuraxpharm 120 mg tablets. 2022.
11. Haldol and associated names. Summary of product characteristic: 10-52. 2022.
12. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014; 383: 911-922.
13. Boncyk CS, Farrin E, Stollings JL, Rumbaugh K, Wilson JE, et al. Pharmacologic Management of Intensive Care Unit Delirium: Clinical Prescribing Practices and Outcomes in More Than 8500 Patient Encounters. Anesth Analg. 2021; 33: 713-722.
14. Maschke M. et al. Delirium and confusion including alcohol withdrawal delirium, S1 guideline. 2020. in: German Society of Neurology (ed.), Guidelines for diagnostics and therapy in neurology. 2022.
15. Aldecoa C, Bettelli G, Bilotta F, Sanders RD, Audisio R, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. Eur J Anaesthesiol. 2017; 34: 192-214.
16. Hefner G, Unterecker S, Ben-Omar N, Wolf M, Falter T, et al. Prevalence and type of potential pharmacokinetic drug-drug interactions in old aged psychiatric patients. Contemp Behav Health Care. 2015; 1.
17. de Leon J, Diaz FJ, Wedlund P, Josiassen RC, Cooper TB, et al. Haloperidol half-life after chronic dosing. J Clin Psychopharmacol. 2004; 24: 656-660.
18. Kornhuber J, Wiltfang J, Riederer P, Bleich S. Neuroleptic drugs in the human brain: clinical impact of persistence and region-specific distribution. Eur Arch Psychiatry Clin Neurosci. 2006; 256: 274-280.
19. World Health Organization. World Health Organization model list of essential medicines: 22nd list. 2021. Geneva: World Health Organization. 2021.
20. Huybrechts KF, Gerhard T, Crystal S, Olfson M, Avorn J, et al. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population-based cohort study. BMJ. 2012; 23: 344: e977.
21. European Medicines Agency. Product-information requirements. The contents of these webpages are © EMA [1995-2022].
22. Zoremba N, Coburn M. Acute confusional states in hospital. Dtsch Arztebl Int. 2019; 116: 101-116.
23. Han QYC, Rodrigues NG, Klainin-Yobas P, Haugan G, Wu XV. Prevalence, Risk Factors, and Impact of Delirium on Hospitalized Older Adults with Dementia: A Systematic Review and Meta-Analysis. J Am Med Dir Assoc. 2022; 23: 23-32.e27.
24. Kukreja D, Günther U, Popp J. Delirium in the elderly: Current problems with increasing geriatric age. Indian J Med Res. 2015; 142: 655-662.
25. Fuchs S, Bode L, Ernst J, Marquetand J, von Känel R, et al. Delirium in elderly patients: Prospective prevalence across hospital services. Gen Hosp Psychiatry. 2020; 67:19-25.
26. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-Year Health Care Costs Associated with Delirium in the Elderly Population. Arch Intern Med. 2008; 168: 27-32.
27. World Health Organization. Quality Assurance and Safety of Medicines Team. The safety of medicines in public health programmes: pharmacovigilance, an essential tool. 2006.
28. World Health Organization. Medication Without Harm - Global Patient Safety Challenge on Medication Safety. Geneva: World Health Organization. 2017. Licence: CC BY-NC-SA 3.0 IGO.
29. World Health Assembly, Decade of healthy ageing: the global strategy and action plan on ageing and health 2016–2020: towards a world in which everyone can live a long and healthy life: report by the Director-General. World Health Organization. 2020.
30. The Health Care Quality Indicators Team Final report. Data and Analysis of Data on Patient Safety within the OECD Health Care Quality Indicators Project (OECD-PS). 2018; 1-294.