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Iatrogenesis and neurological manifestations in the elderly **Iatrogénie et manifestations neurologiques chez les personnes âgées**

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Abstract

Older people are often exposed to polypharmacy in a multimorbidity context. Inappropriate polypharmacy is often harmful, increasing the risk of inappropriate prescriptions and therefore adverse drug events (ADEs). Five to 20% of all hospital admissions are related to ADE in older people, among which 40 to 70% could be prevented. However, identifying ADEs and drug-related admissions in the elderly is challenging because ADEs often present as common geriatric problems such as falls, delirium, which might be due to the aging process, underlying diseases, and/or medications. In the pharmacovigilance database of the World Health Organization, drug-related neurological manifestations are the third reported cause of ADEs in the elderly, and neurological drugs are the third leading class of medications involved in ADEs. We must therefore be particularly vigilant, both in our prescriptions but also in our diagnoses to avoid prescribing inappropriate treatments and detect ADEs. Even though multiple pharmacologic changes occur in the elderly (absorption, distribution, drug metabolism and excretion), most of medications are still often prescribed at the same daily dosage as in young adults. When prescribing any drug for old patients, we should remember that daily intake should be adapted to these specificities, keeping in mind the old well-known aphorism “start low, go slow”.

In this review, we describe the main drug-related neurological manifestations (drug-induced movement disorders, falls, seizures, delirium, hypoglycemia, stroke, hyponatremia, peripheral neuropathy and myopathy, and serotonin syndrome) and the main drugs associated with neurological manifestations (dopamine receptor blocking agents, antithrombotics, anticholinergics, beta-lactams, antidepressants, benzodiazepines, mood stabilizers).

Keywords: iatrogenesis, elderly, neurological manifestations, adverse drug events.

Abbreviations

ADE: adverse drug event

AT: antithrombotics

ATC: anatomical therapeutic chemical

CNS: central nervous system

EMA: European Medicines Agency

ICSRs: individual case safety reports

MAOIs: mono amine oxidase inhibitors

MedRA: Medical Dictionary for Regulatory Activities

NSAIDs: non-steroid anti-inflammatory drugs

SOC: system organ class

SSRIs: selective serotonin reuptake inhibitors

SNRI: selective norepinephrine reuptake inhibitors

TCAs: tricyclic antidepressants

WHO: World Health Organization.

Introduction

The number of elderly people is constantly increasing in developed countries, and by 2050, the proportion of people aged 60 years and older is expected to rise to one-third of the population [1]. To be more in touch with reality, the concepts of oldest-old, defined variously as individuals aged above 80 or 85 years or more, and the extreme elderly, defined as those aged above 90 years, have been proposed [2,3]. This population is the fastest growing part of the population worldwide and represents the majority of elderly patients hospitalized, especially in geriatric wards [1,3,4]. The specificity of this aging population is the occurrence of multiple diseases, a condition known as multimorbidity or comorbidity [5]. Polypharmacy is therefore common in older people, around 20% of people above 70 take five or more drugs [6]. Between five to 20% of all hospital admissions are known to be related to adverse drug events (ADEs) in people aged ≥ 65 years, and 40 to 70% of these ADE-related admissions could be prevented [7,8]. On June 24th 2019, 4,224,468 (20.8%) individual case safety reports (ICSRs) and 1,881,037 (9.3 %) ICSRs - concerning respectively >65 years and >75 years - were registered in Vigibase (among 20,305,716 ICSRs), the pharmacovigilance database of the World Health Organization. We must therefore be particularly vigilant, both in our prescriptions but also in our diagnoses to avoid prescribing inappropriate treatments and detect ADEs [9]. In this chapter, we will focus on iatrogenesis and neurological manifestations in the elderly. As shown in Figure 1, the reported ADEs affecting the central nervous system (CNS) were the third most reported cause of adverse reactions in the elderly (17.4%, N = 327,950 ICSRs). Moreover, CNS drugs (according to the anatomical therapeutic chemical (ATC) classification) were involved in 17.9% (third leading cause after cardiovascular drugs and antineoplastic & immunomodulating agents) of total

ICSRs in the elderly population. These drugs were responsible for 14.3 % (fourth leading cause) of the fatal outcomes in the elderly (> 75 years).

1. Pharmacologic changes related to age

Despite the fact that multiple pharmacologic changes occur in the elderly, most medications are still often prescribed at the same daily dosage as in young adults. When prescribing any drug for old patients, one should remember that daily intake should be adapted to these specificities, keeping in mind the old well-known aphorism “start low, go slow”. The absorption, distribution, metabolism, and excretion of medications are affected to various extents by the normal aging process and by diseases commonly associated with increasing age. Pharmacokinetic and pharmacodynamics changes in the elderly are detailed in Table 1 and in appendix 1.

2. Neurological symptoms related to iatrogenesis in the elderly

Table 2 shows the main drug-related neurological manifestations in the elderly.

2.1 Drug-induced movement disorders

Drug-induced movement disorders are frequent. They represented 20% of all movement disorders observed in a population-based study in patients aged from 50 to 89 [10]. For a recent review on drug-induced movement disorders, readers can refer to Factor et al. [11].

- **2.1.1 Parkinsonism**

As these symptoms are potentially avoidable and will have a consequence on the quality of life and functional performances of elderly patients [12] and as antipsychotic use is increasing in elderly patients [11,13], iatrogenesis should always be looked for in the oldest-old with parkinsonism. Overall, drug-induced parkinsonism was the first or second leading

cause of parkinsonism in several population-based studies or in cohorts from tertiary movement disorders clinics, making it an important differential diagnosis [14–18]. Incidence increased with older age and was higher in women, as opposed to all types of parkinsonism in which men predominated [15]. Time trends were towards a decrease in drug-induced parkinsonism incidence over the years, as the use of atypical antipsychotics decreased over time. Cases related to antipsychotic use for treating mood disorders and dementia with agitation increased over time whereas those used for treating schizophrenia decreased.

Drugs involved are dopamine blocking or dopamine-depleting medications for the most. They are mainly the well-known atypical antipsychotics and antiemetics including metoclopramide and promethazine, second and third generation atypical antipsychotics, such as aripiprazole and brexpiprazole, but also more rarely other drugs such as motility agents, selective serotonin reuptake inhibitors (SSRI) antidepressants (i.e. fluoxetine, sertraline, paroxetine), certain calcium-channel blockers (e.g. piperazine derivatives, flunarizine and formerly commercialized cinnarizine, that block dopamine receptors) and non-dopamine-blocking drugs, such as lithium and valproic acid [11,19–25]. Atypical antipsychotics and metoclopramide should not be under-recognized as a cause of drug-induced parkinsonism [11,21] as they often lead to diagnostic failure in the elderly [26]. For a more extensive list of causative agents of drug-induced parkinsonism in the elderly see reviews by Bonnet et al. [27] and by Lopez-Sendon et al. [28].

Clinically, drug-induced parkinsonism is classically described as acute/subacute, bilateral symmetric syndrome in which tremor is infrequent compared to Parkinson's disease. Tremor and asymmetry should not rule out drug-induced parkinsonism [14]. A study by Munhoz et al., compared the effect of drug class on motor phenotypes. Classical neuroleptics induce worse bradykinesia, rigidity, axial, total motor, and disease stage scores, with higher

frequency of rigid-akinetic parkinsonism. Atypical neuroleptics induce less severe but similar forms as typical antipsychotics. With calcium channel blockers, tremor scores are worse [21,28]. Duration of drug exposure to induce parkinsonism seems shorter with classical neuroleptics and parkinsonism seems to last longer with calcium channel blockers [20,21]. Up to 25% of cases have persisting or even progressive parkinsonian signs, suggesting subclinical degenerative pathology uncovered by drug exposure, and needs to be particularly looked for in elderly patients [29].

- **2.1.2 Non-parkinsonian tremors**

Drug-induced enhanced physiologic tremor and rest and action tremors are frequent among elderly patients. Consensus definition criteria have been recently published by the movement disorder society [30]. Though a long list of drugs can induce tremor and can be consulted elsewhere in details [11,16–18,27], the major ones frequently used in the elderly population are thyroid hormone replacement, beta adrenergic agonists, amiodarone, lithium, particularly in case of intoxication but not only, sodium valproate particularly in older women, and other antiepileptic drugs (such as carbamazepine and phenytoin), SSRI and imipraminic antidepressants, typical antipsychotics, antiemetics and anti-cancer drugs. Immunosuppressants, such as cyclosporine and tacrolimus, are also providers of tremor but less commonly used in elderly people [11,16–18,27]. Benzodiazepine, ethanol and opiate withdrawal syndromes should also be kept in mind.

Management should include discontinuation or decreasing the dosage of the drug involved, or adding propranolol in case the drug needs to be maintained.

- **2.1.3 Akathisia**

Acute and subacute akathisia after introduction of a drug, and akathisia after withdrawal of a drug occur mostly with antipsychotics (see specific subsection). Other major causative

agents are all subclasses of antidepressants with a prevalence of 5/1000. Other drugs involved are benzodiazepines, carbamazepine, tetrabenazine, levodopa, lithium and sumatriptan [27].

- **2.1.4 Myoclonus**

Almost all classes of drugs have been linked to myoclonus, see Janssen et al. for a more extensive listing [31]. They are mostly related to drug intoxication leading to encephalopathy, favored in the elderly by underlying renal failure. The five classes of drugs most often reported are opiates, antidepressants, anticonvulsants, antipsychotics and antibiotics [27,31]. The clinical phenotype covers the whole spectrum, from focal to generalized distribution. Drug-induced myoclonus is usually reversible following withdrawal of the offending drug.

- **2.1.5 Chorea**

Manifestations can present as generalized chorea and hemichorea. The most frequent obvious drugs causing chorea are antipsychotics during tardive dyskinesia (see specific subsection) and levodopa during peak-dose dyskinesia. Many other drugs can induce iatrogenic chorea but usually not specifically in patients above the age of 70 [27,32,33]. In elderly patients, other drugs may be anticonvulsants (such as phenytoin, gabapentin, carbamazepine and valproate), anticholinergics, antihistaminic drugs, antidepressants and Lithium. Non-ketotic hyperglycemia and hypoglycemia are possible causes of chorea in elderly patients with poorly controlled diabetes, hence indirectly an adverse effect of anti-diabetic medication, and should be looked for as it can be reversible [34].

- **2.1.6 Cerebellar ataxia**

The cerebellum is particularly sensitive to insults in the elderly thus many drugs can induce cerebellar ataxia among which anticonvulsants (phenytoin, carbamazepine), anti-cancer

drugs, immunosuppressants (cyclosporine, tacrolimus) and lithium [27]. The toxicity of drugs such as phenytoin, carbamazepine and lithium are dose-related [18].

- **2.1.7 Dystonia and dyskinesia**

Dystonia is not very frequent in the elderly population with a prevalence of around 1% [10,35]. Manifestations are mainly related to OFF biphasic levodopa-induced dyskinesia, or dystonia linked to neuroleptic use with tardive dyskinesia (see specific subsection).

- **2.1.8 Drug-induced movement disorder emergencies**

There are three major life-threatening movement disorder emergencies: neuroleptic malignant syndrome (with antipsychotics), serotonin syndrome (with serotonergic agents among which SSRI but not only [36], see specific subsection) and parkinsonian hyperpyrexia syndrome (in case of abrupt withdrawal of antiparkinsonian medications). Mortality ranges from 5% to 15%. Dehydration is an important predisposing factor.

They share core clinical features that are acute onset, hyperthermia, rigidity, autonomic dysfunction and mental status change. Tremor is present in neuroleptic malignant syndrome and parkinsonian withdrawal syndrome. Myoclonus occurs in serotonin syndrome. Higher doses of the medications involved are an important risk factor. Being aware of their existence is very important in particular in the oldest old patients that are often institutionalized, as early recognition of their appearance is important to discontinue or reintroduce the treatments involved as early as possible and improve prognosis.

2.2 Serotonin syndrome

Serotonin syndrome is a drug-induced condition caused by excessive serotonin. It begins within hours to a day after initiating or increasing a serotonin-elevating drug and mostly

happens when associating two or more drugs that increase serotonin. Polypharmacy makes the geriatric population at high risk of developing serotonin syndrome [37].

The main drugs involved are those with serotonergic properties such as most of the antidepressants (i.e. SSRI, mono amine oxidase inhibitors (MAOI), imipraminic antidepressants), tramadol, dextromethorphan, antihistamines, triptans, buspirone, lithium, St John's wort and their association (see Table 3 and drug-drug interactions subsection).

Hunter's criteria are considered as the gold standard for diagnosing serotonin syndrome with 84% sensitivity and 97% specificity.

Clinically, serotonin syndrome is a triad of neuromuscular, autonomic and mental status changes, that occur along a spectrum of severity rated from mild to severe [37].

Neuropsychiatric symptoms range from nervousness and insomnia to impaired consciousness, and hypomanic symptoms. Early neurological symptoms such as ataxia, akathisia, and mydriasis may precede myoclonus, ocular clonus, tremor, and hyperreflexia.

Minor autonomic symptoms are tachycardia, dyspnea, diarrhea, and blood pressure dysregulation, whereas fever and diaphoresis need to be considered as severe symptoms.

Yet, it is common to experience jitteriness, increase in anxiety, and irritability for one to two weeks after starting an antidepressant drug or increasing its dose, without predicting the occurrence of a serotonin syndrome [38].

2.3 Seizures

Seizures will occur either while using drugs that will lower seizure threshold, or due to withdrawal of drugs chronically used, or in the context of drug-drug interactions, lowering, for instance, anticonvulsants concentration.

Many drugs used in the elderly can lower seizure threshold, and for a more comprehensive list, readers can refer to Grosset and Grosset [18]. Clozapine, tricyclic antidepressants, and lithium may particularly precipitate drug-induced seizures. However, many other classes are implicated, including but not only, the frequently used analgesics, antipsychotics, other antidepressants, anticholinergics and antihistamines.

Withdrawal seizures need to be prevented by progressively decreasing chronically prescribed drugs such as benzodiazepine, antiepileptics or any drugs lowering seizure threshold in case of abrupt stopping.

2.4 Delirium

Delirium, defined by either the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) or by the 10th revision of the International Statistical Classification of Diseases and Related Health Problems as an acute confusional state with decline in attention and cognition, is a life-threatening, but potentially preventable clinical syndrome that affects as many as 50% of elderly people in hospitals [39]. Increased age seems to be a predisposing factor for one of the three motor subtypes of delirium: the hypoactive form [40]. Hypoactive delirium, dominated by symptoms of drowsiness and inactivity, can be more difficult to diagnose and is therefore associated with poorer outcome (increased rates of cognitive decline, admission to institutions, and mortality) compared with the two other motor subtypes of delirium: hyperactive and mixed forms [40]. Physicians must be aware of this hypoactive form, especially since available data suggest that 80% of all cases of delirium are hypoactive and/or mixed motor subtypes [40].

Usually delirium is multifactorial in elderly people, and in this vulnerable population with several predisposing factors (including dementia), a seemingly benign insult might be

enough to precipitate delirium [39]. The initial etiological assessment should systematically mention iatrogeny because polypharmacy, the use of psychoactive drugs and physical restraints have been identified as the main precipitating factors of delirium, increasing by four-and-a-half-times the risk of delirium [39]. One of the leading mechanisms postulated to contribute to delirium include imbalance in neurotransmitters (especially cholinergic deficiency or dopamine excess) with a positive correlation with the adverse effects of anticholinergic or dopaminergic drugs [39]. It should be noted that the use of cholinesterase inhibitors to prevent delirium, based on cholinergic deficiency, has not been proven efficient [41,42].

2.5 Falls

Approximately 33% of individuals older than 65 years undergo falls, among which 50% of them fall more than once a year [43,44]. Polypharmacy is a strong risk factor for falling in this population (multiplied by 4 in individuals taking from five to nine medications) [45]. But it is increasingly clear that it is the type of drugs, rather than the number, which predicts falls [45,46]. Moreover, pharmacogenetic factors, in particular polymorphisms of cytochrome enzymes, may play a role in individual sensitivity to fall risk-increasing drugs, listed for further details in Just et al. [47].

Association with the use of anticholinergic and sedative drugs, as reflected in the Disease Burden Index, the anticholinergic cognitive burden scale and Beers criteria, increase the risk of falls and lower quality of life in the elderly [45,46,48,49]. SSRI antidepressants [45,50] but also tricyclic antidepressants, short and long-acting benzodiazepines, antipsychotics, antiepileptics, possibly antiparkinsonian drugs and analgesics (in particular opioids) are commonly reported as associated with a higher risk of falls in the elderly [45,50–52].

Regarding cardiovascular drugs, use of a nonselective β -blocker, contrary to selective β -blockers, is associated with an increased risk of fall in the older population [53]. Loop diuretics also seem to be significantly associated with this risk [54]. A common consequence could be postural hypotension leading to falls. Correction of drug-induced hyponatremia reduces the risk of falls [55].

2.6 Hypoglycemia

When attending an elderly patient with aggravation of cognitive disorders, delirium, repeated traumatic falls and/or other atypical neurological symptoms, physicians should be alert to prolonged hypoglycemia, often nocturnal and or asymptomatic, which is particularly common in the elderly and unrecognized [56–58]. Hypoglycemia, usually defined as blood glucose levels below 70 mg/dL or 3.9 mmol/L is the biggest concern in the treatment of older people with diabetes [56,59]. Variables strongly associated with hypoglycemia are wide glucose variability and lower average blood glucose level (HbA1C) [57]. This is why, almost all expert opinions and guidelines suggest liberal glycemic goals by aiming for higher HbA1C in the elderly population [60]. Therefore, in older adults with few comorbidities and normal cognitive and functional status, HbA1C < 7.5% is recommended. On the other hand, in patients with end-stage chronic diseases, or moderate-to-severe cognitive dysfunction or dependency in more than two activities of daily living, a goal of HbA1C < 8.5% is recommended [57]. For the group of patients with intermediate health (multiple chronic diseases, mild to moderate cognitive dysfunction or dependency in more than two instrumental activities of daily living), HbA1c goals of < 8% are recommended [57].

Reducing the complexity of the insulin regimen, using medication with a lower risk of hypoglycemia, assessing unrecognized hypoglycemia by continuous glucose monitoring , and

offering individualized education sessions are all good strategies to lower the risk of hypoglycemia in this frail population [57,58].

2.7 Stroke

Despite numerous advances over the last 50 years, stroke continues to be a leading cause of death and disability worldwide [61]. Clinical trials have demonstrated the safety and efficacy of antiplatelets for non-cardioembolic stroke prevention, while anticoagulants are more often used for cardioembolic stroke prevention [61,62]. Underuse or overuse of antithrombotics may be responsible for stroke (refer to the corresponding chapter).

2.8 Hyponatremia

Clinical features of hyponatremia are lethargy, muscle cramps, anorexia and headaches while mild hyponatremia can often be asymptomatic in elderly patients [63].

The prevalence of hyponatremia increases significantly with age. Risk factors for hyponatremia in the elderly are female gender, low body mass index, low baseline serum sodium level, concomitant non-psychiatric medication use (diuretics, NSAIDs, proton-pump inhibitors, angiotensin-converting enzyme inhibitors), and presence of heart failure, malignancy, liver disease or adrenal insufficiency [63].

There seems to be no consistent difference in the incidence of hyponatremia in adults 60 years of age or older among different SSRIs, SNRIs and mirtazapine though it appears to be lower with bupropion and tricyclic antidepressants [64]. Anti-epileptic drugs may be at risk of causing hyponatremia in the elderly, carbamazepine and oxcarbazepine being the most common drugs involved [65].

2.9 Peripheral neuropathy

Peripheral neurologic deficits are commonly found during physical examination of older patients, most commonly caused by diabetes and alcohol abuse [66,67]. However, when symptoms of peripheral neuropathy appear, the possibility that they have been induced by drugs should be considered ('drug induced peripheral neuropathy' (DIPN)) [67,68].

There is no geriatric specificity to DIPN. It often presents as a sensory polyneuropathy with paresthesia that might be accompanied by pain with a distal, symmetric sock-and-glove-shaped neuropathy. Motor symptoms and signs are generally minor. DIPN can have an important impact on patients' quality of life and be a cause of falls in the elderly. DIPN can begin weeks to months after initiation of treatment. In most cases, the pain and paresthesia completely resolve after cessation of treatment. However, in some cases, DIPN is only partially reversible and can be permanent [67,68].

Drugs that have been implicated in the iatrogenic development of DIPN include, among others, chemotherapeutic agents (vinca alkaloids, taxanes, platinum, oxaliplatin, bortezomib, thalidomide), immunosuppressants (interferon, leflunomide), antimicrobials (antimycobacterial agents, metronidazole), cardiovascular drugs (statins, amiodarone), levodopa (intestinal infusion), psychotropic and anticonvulsants [67–72]. For reviews on DIPN, the readers can refer to Durrieu et al; Jones et al., and Vilholm et al. [67,68,71].

Most often, no specific treatment is required other than a possible reduction or cessation of the specific agent causing the neuropathy. When the neuropathy is associated with pain, a specific treatment like duloxetine and gabapentin may be required to relieve the pain [67,68].

2.10 Myopathy

Drug-induced myopathy is one of the most common myopathies ranging from mild acute myalgia to chronic weakness and rhabdomyolysis. There are about 150 drugs involved, the most frequent are statin, glucocorticoids and colchicine [73]. Yet, there is no evidence to suggest an increased risk of myopathy in older adults receiving statin therapy [74] and there are no data specific to the elderly population and the other drugs potentially involved. In fact, a hospital-based study [75] found that only 2% of myopathies in patients over the age of 70 were considered toxic, while 50% were inflammatory myopathies, 32% were genetically-determined myopathies, and 16% were myopathies of unspecified cause. Moreover despite age-related sarcopenia, there doesn't seem to be an increase in muscle weakness and serum creatine kinase activity with advanced aged when myopathies occur.

3. Some drugs frequently associated with iatrogenesis in the elderly

3.1 Neuroleptics, dopamine receptor blocking agents

- 3.1.1 Movements disorders

A wide span of movement disorders can be induced by antipsychotics and their use is increasing in the elderly, particularly in nursing homes making it very important to be aware of the full range of movements possibly induced by these drugs in elderly people [11].

These movements can have very different time frames after introduction of the drug. Delayed onset and persistent movements comprise tardive syndromes, characterized by abnormal involuntary movements caused by long-term exposure to dopamine receptor blockers. Several different subtypes of tardive syndromes exist. The most frequent ones, occurring typically in elderly women, are tardive dyskinesia, which typically comprises of complex orofacial dyskinesias and stereotypies, or choreic neck and trunk movements. Tardive dystonia more typically occurs in young men hence will not be detailed here.

As well, movements can have a subacute onset and be chronic reversible disorders: drug-induced parkinsonism and acute or subacute akathisia, which are both frequent in the elderly. Acute onset and reversible disorders are also observed, such as acute onset dystonia, which is seen mainly in young men and children, hence will not be further detailed here; or neuroleptic malignant syndrome which is of importance due to its potential severity (see specific subsection).

Among the above listed movement disorders, chronic parkinsonism and tardive dyskinesia, then akathisia are the most frequently induced in the elderly. Dystonia is uncommon among older patients [27,76]. In a study focusing on the elderly, higher daily doses of neuroleptics at study entry, greater cumulative amounts of prescribed neuroleptics (with a cumulative incidence of 60% of tardive dyskinesia and 23% of severe cases after three years of treatment), and greater severity of negative symptoms were predictive of severe tardive dyskinesia [77,78]. Tardive movements seem less common and parkinsonism milder with atypical rather than first-generation antipsychotics [11,21,79]. Annual incidence of akathisia depends on the subtype of antipsychotic: 4% from quetiapine or olanzapine, 20% with other second-generation antipsychotics and up to 50% with haloperidol.

In case of neuroleptic-induced adverse effects such as tardive syndromes or parkinsonian syndrome, discontinuation of the antipsychotic, if possible, will help. Switching to a drug with a lower affinity for D2 receptors, such as clozapine, is recommended if the neuroleptic treatment has to be pursued, or if a tardive syndrome persists. Prophylaxis with anticholinergics is not recommended, and should be particularly avoided in the elderly. Treatments that can be added are dopamine depleting agents such as (deu)tetrabenazine in case of tardive syndromes, but depression being an adverse effect, it should be used with

caution in the elderly patients more prone to it. Guidelines for the treatment of tardive syndromes are further detailed elsewhere [80].

- 3.1.2 Other risks related to use of antipsychotics

Importantly, antipsychotics can induce other adverse effects. For instance they also show anticholinergic effects (see specific subsection) and have a cardiac and vascular toxicity which need specific monitoring as required by the French Medicines Agency (ANSM) [81].

3.2 Antidepressants

Antidepressants are mainly underused within the geriatric population because of the many atypical forms of late-life depression misleading the diagnostic in favor of either late-onset schizophrenia or anxiety disorders [82]. It is important to be aware of the anticholinergic side effects of all antidepressants. Selective serotonin reuptake inhibitors (SSRIs), except paroxetine, selective norepinephrine reuptake inhibitors (SNRI), bupropion and mirtazapine have lower anticholinergic effects than tricyclic antidepressants which should be avoided in elderly patients [83]. Some side effects are more frequent in elderly patients such as hyponatremia (see specific subsection) and movement disorder.

Tardive dyskinesia triggered by antidepressants would be more frequent in diabetic patients and women, and if associated with anticholinergic treatments but may be rare in patients never previously exposed to antipsychotic drugs [84,85].

3.3 Benzodiazepines

Benzodiazepines are lipophilic drugs that have anxiolytic, hypnotic, anticonvulsant, myorelaxant and anterograde amnesiant effects. Age-associated liver and renal decline and an increased body fat lead to an accumulation of benzodiazepines and their active metabolites, by prolonging their half-life, enhancing the risk of overdose and withholding

certain side effects even at standard doses [86]. It is therefore recommended in the elderly to use short half-life benzodiazepines and those not metabolized by the liver such as lorazepam and oxazepam.

In this population, risk factors of sedation are cognitive impairment, hypoalbuminemia and chronic renal failure [87]. Long-term use may be associated with disinhibition, depression, impaired concentration and memory [86]. Neurological benzodiazepine-related side effects include impaired motor coordination, dizziness, and vertigo with an increased risk of fall, slurred speech and blurry vision [88]. Benzodiazepine use alters long-term memory but respects sensory and short-term memory causing anterograde and not retrograde amnesia. Within explicit memory, episodic memory is impaired while semantic memory is not. While implicit memory impairments coincide with peak plasma levels of benzodiazepines, impairments in explicit memory tend to last longer [88]. Paradoxical reactions to benzodiazepines are characterized by acute excitement, impulsivity, irritability, suicidal behavior and increased risk of seizures in epileptics [89]. Reports related to this reaction in elderly are scarce, but probably underdiagnosed. Risk factors for developing paradoxical reactions are advanced age, male gender, psychiatric disorders and dementia [89]. Preventable risk factors are higher dose of benzodiazepine, parenteral use, short half-life benzodiazepines and co-prescription of anticholinergics drugs [89]. Symptoms of withdrawal typically include anxiety, dysphoria, agitation, delirium, and seizures. Withdrawal syndrome is frequent and under diagnosed in the elderly population because of the misuse of benzodiazepines and the fact that withdrawal symptoms may be milder from those seen among younger patients [90].

3.4 Mood Stabilizer

- 3.4.1 Lithium

As exposed previously, lithium has a low therapeutic index. Moreover serum lithium level is a poor predictor of brain lithium concentrations in older patients and is not correlated with symptoms of neurotoxicity [91]. These symptoms include delirium, fatigue, tremor, myoclonus, gait instability and sometimes seizures [92]. Yet, delirium rates in geriatric lithium users do not differ from valproate-treated patients [93].

- 3.4.2 Anticonvulsant agents

There is a risk of dyskinesia and parkinsonism (see specific subchapter).

3.5 Anticholinergic drugs

Drugs with anticholinergic properties (DAPs), acting on the muscarinic receptors in the central and peripheral nervous systems and inhibiting acetylcholine-mediated responses by competitively binding to these receptors, are a heterogeneous group of medicines including some antihistamines, antidepressants, antipsychotics, antiepileptic drugs, antiarrhythmic, skeletal muscle relaxants, antimuscarinic bronchodilators, and medications for gastrointestinal and bladder disorders [94]. Some studies have estimated that in nursing homes more than 30% of older residents take more than two anticholinergic drugs, and 5% take more than five [94,95]. They are considered as potentially harmful to older people because of their adverse effects peripherally and especially on the nervous system. The most frequent short-term central side effects are dizziness, headache, drowsiness, weakness, nervousness, delirium, dyskinesia, lethargy, syncope, and insomnia [94,96]. Over the past decade, prolonged exposure to anticholinergic drugs has been linked to long-term cognitive decline or dementia among community-living cohorts and nursing home residents [97]. To assist clinicians in minimizing the use of drugs with anticholinergic action in elderly,

especially people with cognitive impairment, various anticholinergic risk scales have been produced [46,48,96].

3.6 Antithrombotics

Antithrombotic (AT) drugs, which include antiplatelet and anticoagulant therapies, are used to prevent and treat many cardiovascular disorders, such as strokes [98]. With the aging of the population, these treatments are increasingly being prescribed all around the world and are the most frequent drug class implicated in serious and fatal adverse drug events, particularly bleeding events [98]. Clinical trials have demonstrated the safety and efficacy of antiplatelets for non-cardioembolic stroke prevention, while anticoagulants are more often used for cardioembolic stroke prevention [62]. Older people are at higher risk of ischemic or hemorrhagic stroke than younger adults [99], therefore prescribing appropriately ATs in the elderly is essential.

Despite this evidence, there is a gap between guidelines and observed medication use. Underuse is particularly frequent in elderly patients after a stroke: less than 50% of patients with known atrial fibrillation are on anticoagulant treatment, 70–85% of patients eligible for antiplatelet agents receive this treatment [100,101]. The ESC 2016 guidelines, considering the risk/benefit of anticoagulants, state that "Falls and dementia are associated with increased mortality in atrial fibrillation patients, without evidence that these conditions markedly increase the risk of intracranial hemorrhage. Hence, anticoagulation should only be withheld from patients with severe uncontrolled falls (e.g. epilepsy or advanced multisystem atrophy with backwards falls), or in selected patients with dementia where compliance and adherence cannot be ensured by a caregiver"[102]. In addition to this underuse, overuse of ATs and their association may be responsible for hemorrhagic events. At least a third of

adults in high-income countries are taking oral antithrombotic drugs at the onset of intracerebral hemorrhage [103]. It is therefore essential to re-evaluate oral AT prescriptions regularly in the elderly to prevent ischemic or hemorrhagic stroke in this at-risk population.

3.7 β -lactam-induced encephalopathy

β -lactam antibiotics are the most frequently prescribed antibiotic class, in both the community and hospital settings, representing almost 60% of antibiotic prescriptions in 2012 in Europe [104]. β -lactam and particularly cephalosporin and penicillin (mainly piperacillin and tazobactam) can produce encephalopathy. Because elderly are generally excluded from studies, it is difficult to explain the mechanisms involved in the drug-induced encephalopathy in elderly [105]. Nevertheless, age appears to be a risk factor principally due to changes in antibiotic pharmacokinetics (advanced renal insufficiency).

Symptom onset occurs within seven days of therapy initiation. The manifestations are impaired consciousness, psychotic symptoms [defined as the presence of delusions or hallucinations], myoclonia and seizures. Electroencephalogram is often abnormal with epileptiform discharges, slowing or triphasic waves [106]. Usually, patients require intensive care, but the outcome is usually favorable without sequelae upon discontinuation or dose reduction of the antibiotic therapy, within 6 h to 15 days [106,107].

In terms of pathophysiology, the mechanism of neurological adverse drug reactions is not very well known. Among the main hypotheses, the ability of β -lactam antibiotics to induce seizures would be principally linked to the β -lactam ring whose enzymatic degradation is thought to prevent the occurrence of seizures [108].

4. Some neurologic and relevant drug-drug interactions in the elderly

In France, 2,162 cases of drug interactions (out of a total 12,494 cases) are reported in the elderly (17.3% of cases) in the national pharmacovigilance database of which 294 concern neurological effects (SOC terms) and 370 involving at least one CNS drug (ATC classification). Some neurologic and relevant drug-drug interactions in the elderly are presented in Table 3.

Perspectives and conclusion

Elderly patients are often exposed to polypharmacy in a multi-morbidity context. Polypharmacy increases the risk of inappropriate prescriptions and the risk of ADEs. However, identifying ADEs in older people is challenging because ADEs often present as common geriatric problems such as falls, delirium, neuropathy, seizures, etc... which may be due to the aging process and underlying diseases.

Therefore, when confronted with any neurological manifestation, physicians must have the iatrogenic hypothesis in mind: any symptom can be iatrogenic until proven otherwise. In this review, the main drug-related neurological manifestations (drug-induced movement disorders, falls, seizures, delirium, hypoglycemia, stroke, hyponatremia, peripheral neuropathy and myopathy, and serotonin syndrome) and the main drugs associated with neurological manifestations (dopamine receptor blocking agents, antithrombotics, anticholinergics, β -lactams, antidepressants, benzodiazepines, mood stabilizers) in the elderly have been described.

The emergence of new therapies that prolong the survival of patients, particularly in infectious diseases (i.e. human immunodeficiency virus, etc.) or in cancer (i.e. immune checkpoint inhibitors, CAR-T cells, etc.) and the extension of indications to the elderly will expose them to multiple adverse drug reactions and to a potential risk of drug-drug interactions. Indeed cancer is primarily a disease of elderly people, around 50% of all new

cancer cases each year are diagnosed in people over 70, with mortality increasing with age [109].

In addition, these new therapies (sometimes combined) have many “novel” adverse effects (such as auto-immune diseases induced by immune checkpoint inhibitors, etc.) whose incidence and severity will determine their benefit/risk ratio, especially in so-called at-risk populations (e.g. geriatrics) [110–113]. Unfortunately, for elderly patients few data are available in the literature about safety/efficacy of targeted-therapies and immunotherapy [111].

Since 2011, the European Medicines Agency (EMA) has proposed specific guidelines for drug development across the complete span of drug lifecycle as well as information meant for older patients. Regarding pharmacovigilance, the EMA considers that benefit-risk assessment, medication errors and monitoring of specific side effects occurring in older patients should be included in the risk management plan or as post-authorization measures [114].

Conflict of interest:

None of the authors has any relevant conflict of interest to declare.

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Figure legends:

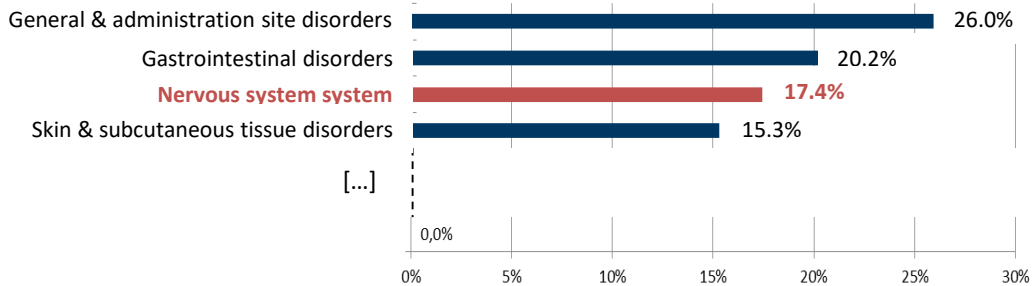
Table 1: Pharmacologic changes in the elderly

Table 2. Main drug-related neurological manifestations in the elderly

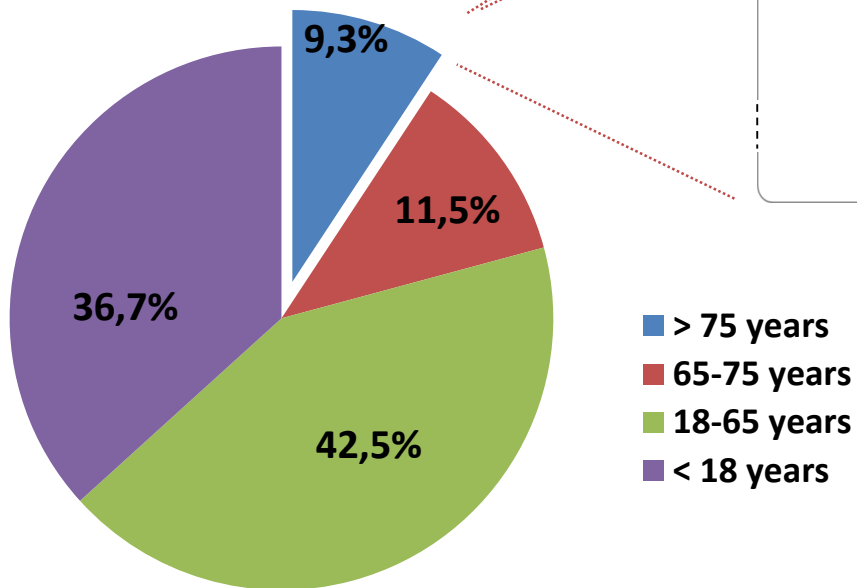
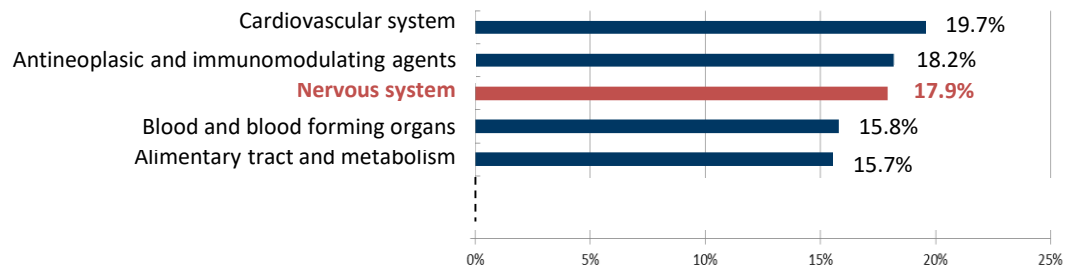
Table 3: Main drug-drug interactions relevant for clinical practice in the elderly

Figure 1: Proportion of reported Adverse Drug Events in Vigibase by age with (a) the repartition of main suspected drugs (according to ATC classification), and (b) the proportion of reported Adverse Drug Events affecting the central nervous system.

Reaction (MedDRA)



Drug (WHODrug)



Proportion of reported Adverse Drug Reactions in Vigibase

Table 1: Pharmacologic changes in the elderly

Pharmacokinetics changes		
Absorption	<ul style="list-style-type: none"> - Delayed (but not significantly affected for passively absorbed drugs) - ↑ for high clearance drugs, ↓ for drugs derived from prodrugs 	<ul style="list-style-type: none"> ↑ gastric pH (↓ gastric acid secretion) ↓ intestinal and splanchnic blood flow ↓ gut motility ↓ gastric emptying ↓ presystemic first-pass metabolism ↓ hepatic blood flow ↑ bioavailability
Distribution	<ul style="list-style-type: none"> distribution volume and diffusion either ↓ or ↑: - lipid-soluble drugs: ↓ drug concentration, ↑ half-life - hydrophilic drugs: ↑ drug concentration, ↓ half-life 	<ul style="list-style-type: none"> ↓ organ perfusion blood flow malnutrition leading to ↓ protein fixation (not significant) modifications of body composition (↓ lean body mass, ↑ percentage of fat) ↑ permeability of blood-brain barrier
Renal excretion	<ul style="list-style-type: none"> Progressive linear decrease ↑ half-lives of drugs 	<ul style="list-style-type: none"> Larger inter-individual variability Plasma creatinine concentration not reliable
Metabolism	<ul style="list-style-type: none"> ↓ hepatic excretion for drugs with high hepatic extraction ratio 	<ul style="list-style-type: none"> ↓ hepatic blood flow
Pharmacodynamics changes		
	<ul style="list-style-type: none"> increased pharmacodynamics or defective homeostatic systems Underlying preclinical neurodegenerative disease 	<ul style="list-style-type: none"> ↑ synergic effect of drugs (including adverse effects) Favored by polypharmacy and drug interactions

Table 2. Main drug-related neurological manifestations in the elderly

Symptoms	Main Drugs	Comments
Drug-induced movement disorders		Frequent
Parkinsonism	- dopamine blocking or dopamine-depleting medications (antipsychotics and antiemetics, SSRI, Ca ²⁺ -channel blockers) - lithium, valproate	- worse with classical antipsychotics - possible persistence if underlying Parkinson's disease
Non-parkinsonian tremors	- thyroid hormone replacement, beta adrenergic agonists, amiodarone, lithium, antiepileptics (valproate, carbamazepine, phenytoin), SSRI and imipraminic antidepressants, typical antipsychotics and antiemetics and anti-cancer - withdrawal syndromes to benzodiazepines, ethanol, opiates	- discontinuation of drug if possible - propranolol otherwise
Akathisia	- antipsychotics and antidepressants	
Myoclonus	- opiates, antidepressants, anticonvulsants, antipsychotics and antibiotics	- focal or generalized; reversible
Chorea	- antipsychotics and levodopa (peak-dose) - anticonvulsants, anticholinergics, antihistaminic, antidepressants, lithium	- generalized and hemichorea - specific attention if diabetics (non-ketotic hyperglycemia and hypoglycemia, potentially treatable and reversible)

Cerebellar ataxia	- anticonvulsants, anti-cancer, lithium	
Dystonia and dyskinesia	- antipsychotics and levodopa (OFF low-dose)	- other dystonia rare in elderly
Drug-induced movement disorder emergencies	- antipsychotics, serotonergic agents, abrupt withdrawal from antiparkinsonian agents	- vigilance in dehydrated or institutionalized elderly patient
Serotonin syndrome	antidepressants (SSRIs < SNRIs) MAOIs (antidepressants, Parkinson's treatment, and antibiotics) triptans, buspirone, lithium	-polypharmacy (drug-drug interaction) -range of severity from mild to severe
Seizures	- drug-induced: Clozapine, tricyclic antidepressants, and lithium. also analgesics, antipsychotics, other antidepressants, anticholinergics and antihistamines, or any drugs lowering seizure threshold - withdrawal seizures: abrupt stop of benzodiazepine, antiepileptics	
Encephalopathy induced by beta-lactams	Cephalosporins and penicillins (mainly piperacillin and tazobactam)	- in case of renal failure notably - outcome usually favorable after discontinuation or dose reduction
Delirium	- polypharmacy +++ (drug-drug interaction) - anticholinergic drugs - dopaminergic drugs - morphine agonists	- predisposing factor for hypoactive form - multifactorial

Falls	- anticholinergic and sedative drugs - nonselective β -blockers, loop diuretics	very frequent ++ often causing orthostatic hypotension
Hypoglycemia	- hypoglycemic drugs (oral or insulin)	- prolonged hypoglycemia, often nocturnal and / or asymptomatic - liberal glycemic goals by aiming for higher HbA1C in the elderly population
Hyponatremia	antidepressants, antiepileptics diuretics, NSAIDs, proton-pump inhibitors, angiotensin-converting enzyme inhibitors	frequent multifactorial asymptomatic if mild
Peripheral neuropathy	chemotherapeutic agents (vinca alkaloids, taxanes, platinum, oxaliplatin, bortezomib, thalidomide), immunosuppressants (interferon, leflunomide), antimicrobials (antimycobacterial agents, metronidazole), cardiovascular drugs (statins, amiodarone), levodopa (intestinal infusion), psychotropic and anticonvulsants	
Myopathy	statin, glucocorticoids and colchicine (and many other drugs)	
Stroke	- antiplatelets - anticoagulants	- underuse of antithrombotic and risk of ischemic stroke - overuse of antithrombotic and risk of hemorrhagic stroke

Abbreviations: MAOIs: Monoamine Oxidase Inhibitors; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; PD: Parkinson's Disease; SNRIs: Serotonin and Norepinephrine Reuptake Inhibitors; SSRIs: Selective Serotonin Reuptake Inhibitors.

Table 3: Main drug-drug interactions relevant for clinical practice in the elderly

Drugs	Associated drugs	Potential effects	Strain level of the interaction
Pharmacodynamic interactions			
Morphine and opioids	- Opioids - Atropinic drugs (<i>i.e.</i> tricyclic antidepressant, most atropinic H1 antihistamines, atropinic anti-Parkinson drugs, atropinic antispasmodic drugs, disopyramide, phenothiazine antipsychotics and clozapine)	↑ constipation or colonic akinesia	Precaution for use /to consider
	- Opioids - Benzodiazepines - Barbituric	↑ respiratory depression	To consider
Tramadol	- Other substances with serotonin properties such as linezolid, most of antidepressant drugs (MAOi, tricyclic, SSRIs, SNRIs), Lithium, ...	↑ serotonin syndrome	Precaution for use Contraindicated with irreversible and non-specific MAOi (<i>e.g.</i> iproniazid) and selective MAO-A inhibitors (<i>e.g.</i> moclobemide)
Selective serotonin reuptake inhibitors	- Anticoagulants (<i>e.g.</i> direct oral anticoagulants, vitamin K antagonists, heparins) - Platelet antiagregant (<i>i.e.</i> NSAIDs, clopidogrel, ticagrelor, prasugrel, ...)	↑ bleeding (by decreasing adhesive capacity of platelets by hyperstimulation of 5-HT _{2R})	Precaution for use
Pharmacokinetics interactions			
Lithium	Acetazolamide	↓ plasma concentration of lithium (risk of inefficacy)	Precaution for use

	ACEi/sartan/NSAIDs/diuretics (loop diuretics, thiazides, ...)	↑ plasma concentration of lithium (risk of overdose and toxicity)	Not recommended
AEs (phenytoin, carbamazepine and phenobarbital)*	Anticoagulant drugs (e.g. direct oral anticoagulants and vitamin K antagonists)	↓ plasma concentration of anticoagulants (risk of inefficacy with resulting thrombosis)	Not recommended (direct oral anticoagulants) + Precaution of use (vitamin K antagonists)

Abbreviations: 5-HT_{2R} : serotonergic receptors; ACEi: angiotensin-converting enzyme inhibitor; AEs: Antiepileptic drugs; MAOi: MonoAmine Oxydase inhibitor; NSAIDs: nonsteroidal anti-inflammatory drugs; SSRIs: selective serotonin reuptake inhibitor; SNRIs: serotonin and norepinephrine reuptake inhibitor

* strong enzymatic inductors in particular of CYP3A4