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Review Article

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Interaction Between anti-Alzheimer's Disease Drugs and Antipsychotic Agents in the Treatment of Behavioral and Psychological Symptoms: Extrapyramidal Side Effects

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Abstract

Alzheimer's disease (AD) is the most common dementia type, accounting on its own for almost 70% of all dementia cases. Behavioral and psychological symptoms of dementia (BPSD) afflict most patients with dementia, especially those with Alzheimer's disease (AD). Treatment options for BPSD include pharmacological and nonpharmacological approaches. However, behavioral symptoms are not always controllable with non-pharmacological intervention, and the psychotropic class of medication more frequently prescribed for behavioral symptoms are atypical antipsychotics. Antipsychotic drugs are often used for the treatment of BPSD. They are prescribed alone or in conjunction with anti-dementia. However, antipsychotic therapy is not free from several, and often serious, adverse events. For instance, it is well known that antipsychotic drugs commonly cause serious extrapyramidal side effects (EPS). It is imperative for clinicians to understand that 5-HT1A receptors or blockade of 5-HT2, 5-HT3 and 5-HT6 receptors can alleviate EPS induction by antipsychotics agent. It is therefore important to understand that appropriate drug choice and combination strategy are important in the treatment of BPSD. I point out that antipsychotic drugs can have extrapyramidal side effects, including parkinsonian symptoms, also when used in AD, and argument drug choice and combination strategies as cholinesterase inhibitors and antipsychotic drugs. Additionally, the advantages and limitation of antipsychotic drugs have been evaluated.

Keywords: Alzheimer's Disease, Behavioral and Psychological Symptoms of Dementia (BPSD), Anti-Alzheimer's Disease Drugs, Antipsychotic Drugs, D2 Receptors, 5-HT Receptors, Extrapyramidal Side Effects (EPS).

Introduction

Alzheimer's disease (AD) is a chronic devastating irreversible neurodegenerative disease, that affects the central nervous system, leading to dementia [1]. Several mechanisms have been proposed to account for the pathology of AD. The most widely accepted disease models are the amyloid cascade hypothesis, the tau hypothesis, the cholinergic hypothesis, and the excitotoxicity hypothesis [2]. The absence of any effective treatment may explain the increase in the worldwide prevalence of AD expected over the next few years [3]. Recent epidemiological data indicate that the number of people with AD worldwide will grow from the current 46.8 million to 131.5 million by 2050 [4]. AD is often seen as fundamentally a disorder of memory and cognition, but there are many important behavioral symptoms associated, each potentially regulated by separate neural networks. Indeed, the main consequences of AD include progressive deterioration of cognitive functions, such as judgment, language, memory, attention, and visuospatial ability, and behavioral and psychological symptoms of dementia (BPSD). Alterations in motor behavior (i.e., wandering), sleep, and nighttime behavior may also be present [5]. According to the definition of the International Psychogeriatric Association, BPSD are "symptoms of disturbed perception, thought content, mood, and behavior frequently occurring in patients with dementia" [6]. A meta-analysis suggests a prevalence of approximately 50% for the most common BPSD symptoms [7]. Cholinesterase inhibitors (ChEI) or anticholinesterase are typically used to improve cognition and, antipsychotic drugs are commonly prescribed to treat BPSD in patients with major neurocognitive disorders [8]. In the present research topic, I review side-effects of AChEIs ad antipsychotic drugs, especially those related to extrapyramidal side effects (EPS), and I provide some new ideas for treating BPSD.

Current Pharmacological Treatment of Cognitive Impairment in Alzheimer's Disease

Inasmuch as its exact mechanism is not known, therapy for AD has still not been found. As known, in the brain, acetylcholine (ACh) is regarded as one of the major neurotransmitters [9]. The loss of cholinergic neurons, results in a profound reduction in the neu-

rotransmitter ACh, which affects learning and memory neuronal circuitry. Currently, there are only these two types of drugs approved for the treatment of AD: cholinesterase inhibitors (ChEIs) and the NMDA-receptor antagonist memantine which are effective only in treating the symptoms of AD, but do not cure or prevent the disease. The deficiency in cholinergic neurotransmission, has led to the development of cholinesterase inhibitors as the first-line treatment for symptoms of this disease. Acetylcholinesterase (AchE), its main activity is the catalysis of ACh hydrolysis, thus yielding choline and acetate ions. Two cholinesterase enzymes are present in the body, acetylcholinesterase (AChE) and butyrylcholinesterase (BchE), and galantamine and donepezil are AChE inhibitors, and rivastigmine inhibits both AChE and butyrylcholinesterase (BchE) [10]. The acetylcholinesterase inhibitors (ChEIs) acts on the nervous system maximizing the availability of endogenous acetylcholine in the brain [11]. The best-known classes, ChEIs as donepezil, rivastigmine and galantamine and the NMDA-receptor antagonist memantine are until now the only specific pharmacological treatments approved for AD, the most common cause of dementia [12]. Donepezil is a reversible non-competitive ChEIs shown to affect cognitive function, as well as improves cerebral blood flow (CBF) [13]. Benefits for the 10 mg dose appear marginally larger than for the 5 mg dose. A higher 23-mg dose form is available, but benefits on 23 mg/day were no greater than on 10 mg/day [14]. Rivastigmine is a brain-selective inhibitor of "pseudo-irreversible" AChE and BuChE that acts by binding to two active sites of AChE (anionic and estearic sites), which results in preventing ACh metabolism [15]. The oral form of rivastigmine, approved for the treatment of mild to moderate AD, is associated with a higher incidence of gastrointestinal side effects. The transdermal form is more tolerable for many patients, although it can cause dermatologic reactions. Galantamine a newly available cholinergic drug that counteracts AD by specifically and reversibly inhibiting AchE, should be considered for treatment of cognitive and functional decline in patients with mild to moderate AD [16-17]. NMDA receptor antagonist, memantine is also used to alleviate the cognitive impairment. Memantine, 20 mg per day should be considered for treatment of cognitive and functional decline in patients with moderate to severe AD [18-19]. Excitatory glutamatergic neurotransmission via N-methyl-d-aspartate receptor (NMDAR) is critical for synaptic plasticity and survival of neurons. Memantine, a low-affinity NMDA receptor antagonist, modulates NMDA receptors to reduce glutamate-induced excitotoxicity and is thought to palliate cognitive decline associated with AD in this way [20]. However, evidence shows that donepezil, rivastigmine, and galantamine yields modest improvements in cognitive and clinical function in patients with mild to moderate AD in the short and long term and have side effects [21]. The N-methyl-D-aspartate (NMDA) receptor antagonist, memantine, which has shown limited beneficial effects in clinical trials [21-22]. Galantamine is effective in treating all aspects of AD and is the first choice for the treatment of AD, however, data is limited [21].

Current Pharmacological Treatment for The Behavioral and Psychological Symptoms of Alzheimer's Disease

BPSD are a group of behavior, mood, perception, or thought disturbances manifesting with anxiety, agitation, delusions, and hallucination [23]. BPSD are non-cognitive symptoms common in the AD, associated with poorer cognitive, functional, and quality of life outcomes, and accelerated progression to severe dementia [24]. In the clinical setting, patients with BPSD most often present with clusters of symptoms commonly co-occur and can, thus, be grouped into behavioral domains that may ultimately be the result of disruptions in overarching neural circuits. Canevelli et al. identified three clusters of symptoms: 1"psychotic" cluster ("delusions" and/or "hallucinations" items); 2"emotional" cluster ("agitation/aggression" and/or "depression/dysphoria" and/or "anxiety" and/or "irritability" items); and 3"behavioral" cluster ("euphoria/elation" and/or "apathy" and/or "disinhibition" and/or "aberrant motor behavior" items) [25]. One major BPSD domain routinely identified across patients with AD is the hyperactivity–impulsivity–irritability–disinhibition–aggression–agitation (HIDA) domain [26]. The global frequency of BPSD increases with the severity of dement, especially agitation and aggression [27]. Anyhow, occurrence of BPSD has been documented in most types of dementias as vascular dementia (VaD), dementia in Parkinson's disease, frontotemporal dementia (FTD), and in mild cognitive impairment [28]. The first-line treatment of BPSD are nonpharmacological treatments including environmental and social techniques; however, the quality of evidence for such interventions is low [29]. Usually, nonpharmacological management is sufficient to control symptoms, but sometimes, the severity of the disorder, makes using drugs, including antipsychotics, necessary to control symptoms [30]. These compounds generally can be classified as "typical" and "atypical" antipsychotics based upon both pattern of clinical effects and mechanism of action. The typical antipsychotic drugs, represented by haloperidol and chlorpromazine, are also called the first-generation antipsychotics (FGA) or neuroleptics. The atypical antipsychotics, including clozapine and risperidone, are considered as the second-generation antipsychotics (SGA). Serotonin 5-HT2A receptor antagonism in combination with D2 receptor antagonism is thought to be the hallmark pharmacology of the SGAs [31]. In the specific case, typical antipsychotics are the classic standard drugs as phenothiazines (chlorpromazine and fluphenazine), butyrophenones (haloperidol), benzamides (sulpiride and tiapride) and frequently cause serious extrapyramidal side effects (EPS), since they bind predominantly to D2 receptors throughout the brain as powerful, long-lasting antagonists, as well as to a broad range of other receptors, including D1, 5-HT2, histamine H1 and α2 adrenergic receptors [32]. On the other hand, atypical drugs (including clozapine, risperidone, olanzapine, aripiprazole, quetiapine, etc.) are favored over typical due to less EPS. They encompass serotonin and dopamine antagonists (SDAs) as risperidone, perospirone, lurasidone; multiple-acting receptor targeted antipsychotics (MARTAs) as clozapine, olanzapine, quetiapine; and dopamine D2 partial agonists aripiprazole [33]. In addition to the antagonistic effect on dopamine D2, they also have a simultaneous antagonist effect on 5-HT receptors, particularly on the 5-HT2A; this results in increased blockage efficacy on the mesolimbic pathways, but not on the nigrostriatal one [32]. Further, atypical antipsychotics into a group with modest affinity for D2, 5-HT2A and other receptors such as H1 and muscarinic receptors M1 (clozapine, olanzapine and quetiapine) and those with potent

antagonist action on D2 and 5-HT2A, high affinity for α1, 5-HT2c and H1 and minimally affinity for M1 receptors (risperidone, paliperidone, lurasidone) [32]. Except for haloperidol and risperidone, none of the antipsychotics are approved for the treatment of BPSD; therefore, these drugs are generally prescribed as off-label [34]. It is known that D2 receptor blockade by antipsychotics in the cortico-limbic regions (e.g., nucleus accumbens) contributes to antipsychotic activities, which alleviates psychosis (e.g., hallucinations and delusions) and behavioral excitation (e.g., agitation, aggression, and hyperactivity) [34]. Second-generation antipsychotics (primarily risperidone, olanzapine, quetiapine, and aripiprazole) are the mainstay of treatment for agitation and aggression, although, in a systematic review of 16 meta-analyses of randomized, controlled trials of these agents, the effect sizes (differences between treatment and placebo) were typically quite small for risperidone, olanzapine, and aripiprazole, ranging between 0.15 to 0.30 in most studies, and quetiapine generally did not differ from placebo [35]. In general, both typical and atypical antipsychotics should be avoided in patients with known cardiac disease due to pro-arrhythmogenic effects (e.g., QT interval prolongation) [36].

Dopamine (DA) And Acetylcholine (ACH) Signaling Systems Must Be in Dynamic Balance In The Striatum For Optimal Movement Control

The basal ganglia (BG) are a group of subcortical nuclei involved in a diversity of functions including motor control. The BG consist of four prominent nuclei, which are interposed between the cerebral cortex and the lower centers of the brain stem and spinal cord. These nuclei include the: striatum (caudate, putamen, ventral striatum including nucleus accumbens), the globus pallidus (internal and external parts), the subthalamic nucleus, and the substantia nigra pars compacta (SNpc) and pars reticulata (SNpr). They form an important center in the complex extrapyramidal motor system, as opposed to the pyramidal motor system represented by the corticobulbar and corticospinal pathways and have been defined anatomically and functionally. Most of the inputs and outputs of the basal ganglia arise from or go to the cortex either directly or indirectly through the thalamus. Pathology within different basal ganglia circuits predictably leads to either hypokinetic or hyperkinetic movement disorders. A detailed discussion of the principal input, intrinsic, and output connections of the mammalian BG is beyond the scope of this review. However, for brevity we will limit this review to striatum, that involved in planning and executing voluntary movements as well as in cognitive processes. The striatum is one of the main components of the basal ganglia which is involved in processes related to voluntary motor control. Here, I attempt to review its participation in a variety of processes, especially, motor functions. The striatum is traditionally subdivided into a dorsal striatum, which includes caudate and putamen, and a ventral striatum, which includes the nucleus accumbens that are separated by the internal capsule, a white matter tract between brain cortex and brainstem. The striatal microstructure comprises two neurochemically defined compartments, the striosome and the matrix. Histopathological studies consistently demonstrate that the striosome occupies 10–15% of the entire striatal volume [37]. Indeed, the striatum is a nonlaminar, highly heterogeneous structure with projection neurons (spiny projection neurons, SPNs, also called medium spiny neurons, MSNs) interspersed among a diverse range of interneuron. Most striatal neurons (~95%) are the GABA-ergic medium spiny neurons (MSNs), also referred to as spiny projection neurons, which are the principal output cell type, and in addition to the MSNs approximately 4% of striatal neurons are GABA-ergic interneurons. The MSNs that express dopamine (DA) D1 receptors project to and inhibit cells in the internal capsule of the globus pallidus as well as the substantia nigra pars reticulata. These projections are referred to as the direct pathway, or the GO pathway, and activation of this class of cells leads to enhanced locomotion. Another MSN population that expresses dopamine (DA) D2 receptors, and these projections inhibit cells in the external capsule of the globus pallidus. This is the indirect, or the NO-GO pathway, and activation of this pathway decreases locomotion [38-39]. Approximately 6% of MSNs in the dorsal striatum express both D1 and D2 receptors. Furthermore, striatal MSNs projecting through the indirect pathway are known to contain the neuropeptide enkephalin, whereas the neuropeptides substance P and dynorphin are expressed in those MSNs projecting directly to the GPi and SNr [39]. In addition to the MSNs, the remaining cells are the large, aspiny cholinergic interneurons (ChIs), constitute only 1%-3% of the total neuronal population in the striatum, but have richly arborizing axons with large terminal fields [40]. The striatum receives inputs from different areas of the cerebral cortex, including association cortical areas far on in the hierarchy of cortical information processing as well as the sensori-motor cortex, and has connections via the globus pallidus and substantia nigra to the thalamus and thence to premotor and prefrontal cortical areas [41]. In essence, the striatum has two main efferent pathways. According direct, and indirect pathway model, cortical inputs enter the striatum and proceed to the output nuclei of internal globus pallidus (GPi) and the substantia nigra pars reticulata (SNr)] via two distinct pathways, on the way to the thalamus which projects back to the cerebral cortex. The direct-pathway (striatonigral) MSNs, that express high levels of both D1dopamine (DA) receptors and M4 muscarinic receptors and project directly to the internal globus pallidus (GPi in primates, GPm in rodents) and SNr, leading to the activation of the thalamus that, in turn, stimulate the cortex. Through these connections, the direct pathway intensifies the motor plan prepared by the cortex. The indirect pathway, that involves relays in the external globus pallidus (GPe) and the subthalamic nucleus (STN), call also striatopallidal MSNs (D2-MSN) highly express D2 dopamine receptors and adenosine A2A receptors and project to the external globus pallidus (GPe in primates, GP in rodents), convert stimulatory corticostriatal glutamatergic input into inhibitory signals to the thalamus [42]. The MSNs of the direct pathway promote the initiation of appropriate movements whereas the MSNs of the indirect pathway provide a no-go signal that suppresses competing movements [43]. Overall, direct, and indirect pathways act in opposition to one another to control movement. Thus, balanced regulation of the direct and indirect pathways is important for motor control. As noted, striatal cholinergic interneurons (ChIs), constitute the largest cells of the striatum that are recognized for their key regulatory roles of striatal and basal ganglia function in normal and diseased state [44].

CHIs provide the striatum with a high cholinergic tone through extensive arborization and tonic firing [45]. Moreover, either MSNs and interneurons of the striatum receive afferents from the ventral midbrain (substantia nigra pars compacta, SNc; ventral tegmental area, VTA), and these projections are mostly dopaminergic [46]. In the striatum, dopamine inhibits CHIs via D2 receptors and loss of striatal dopamine is thought to elevate striatal cholinergic tone [47]. Briefly, the striatum, has intrinsic and extrinsic cholinergic innervation. Intrinsic cholinergic innervation is predominant and consists of cholinergic interneurons that, despite their low number, have been proposed to provide the striatum with one of the highest cholinergic concentrations in the brain; an extrinsic source of acetylcholine is from the pedunculopontine nucleus (PPN) [48]. Of note, ChIs acting via multiple receptor subtypes in postsynaptic and presynaptic targets, exerts a complex modulatory function in the striatum; it contributes to the regulation of the duration, strength, and spatial pattern of MSNs activity and exerts a dual effect on plasticity of the corticostriatal synapse [49]. In conclusion, most striatal neurons are GABAergic medium spiny neurons, which receive excitatory inputs from the cortico-striatal glutamatergic neurons and from cholinergic interneurons within the striatum, and activities of striatal medium spiny neurons and cholinergic interneurons are tonically regulated by dopaminergic neurons derived from the substantia nigra pars compacta (SNc). It is well documented that blockade of dopamine D2 receptor in the striatum and activate the medium spiny neurons and acetylcholinergic interneurons in the striatum, eliciting various EPS symptoms [50]. The clinical benefit of anti-muscarinic cholinergic drugs on symptoms of tremor and rigidity was explained by a model of striatal imbalance between loss of dopamine and hypothesized upregulation of cholinergic neurotransmission, at least in patients with early-stage disease [51-52].

Extrapyramidal Disorders Can Be Caused by Anti-Dementia and Antipsychotic Drugs

ChEIs are typically used to improve cognition and, antipsychotic drugs are commonly prescribed to treat BPSD in patients with major neurocognitive disorders [53]. Recent studies showed that ChEIs, licensed drugs for cognitive impairment due to AD, potentiate extrapyramidal side effects (EPS) induction with antipsychotic treatments [54]. The AChEIs are relatively safe, however, as they are used in vulnerable populations, it is even more important to consider potential side effects. ChEIs are a class of drugs that may disrupt the dopaminergic-cholinergic balance through their effect on cholinergic neurotransmission [55]. Association between cholinesterase inhibitors Pisa syndrome (PS) and cervical dystonia (CD) has been described. PS, a relatively rare truncal dystonia, originally described by Ekbom and co-workers in 1972 (56) and initially it was considered a subtype of dystonia in patients taking antipsychotic agents. It has been suggested that cholinergic-dopaminergic balance in the direction of cholinergic dominance is the main cause of PS [57]. CD, is a painful condition in which neck muscles contract involuntarily, causing head to twist or turn to one side. Evidence for the role of acetylcholine in dystonia includes decreased putaminal cholinergic tracer uptake in single photon emission computed tomography (SPECT) in patients with CD, response to anticholinergic medications, and cases of CD provoked by ChEIs [58]. PS also known as pleurothotonus, is a posture abnormality characterized by lateral flexion of the trunk appearing or worsening while standing or walking and improving with passive mobilization and supine positioning, and the patient resemble the leaning the ancient Pisa tower, which resolves with passive mobilization or supine positioning, and a lateral flexion at least 10°, has been suggested as a diagnostic criterion for PS, although there is no consensus [59]. Among PS, subsequently an association between ChEIs and PS has been described. Considering that cholinergic nuclei are involved in regulating the axial posture tone [60], and disruption of the cholinergic-dopaminergic balance could result in an asymmetric axial muscle tone activation, this is the hypothesized pathogenic mechanism underlying the development of drug-induced PS. The frequency of ChEI-induced EPS remains unclear. To date, there are no randomized clinical trials investigating the long-term adverse reactions of ChEIs. Over the past few decades, there have been several reports of PS and CD in patients taking ACEIs, therefore AChEIs induced PS is limited to case reports and case series. According to post-marketing surveillance, PS has been reported in patients receiving AChEIs (donepezil, rivastigmine and galantamine), though causality is not confirmed [61]. This large pharmacovigilance study reports 52 cases of PS, among them 21 were due to donepezil, 14 were due to rivastigmine and 17 were due to galantamine. This is believed to result from a dopaminergic-cholinergic imbalance. The study by Sobow and Kloszewska showed consequent motor dysfunction termed as extrapyramidal symptoms in 2 patients under the donepezil (5–10 mg/day) group and 3 patients under the rivastigmine (6–12 mg/day) group [62]. There has been a report of three PS cases in an Italian cohort study of 7,395 of AD patients treated with use of the reversible ChEIs commonly prescribed for dementia, including donepezil, rivastigmine, and galantamine, suggesting a pathophysiological role of cholinergic-dopaminergic imbalance in the regulation of axial muscle tone, with an estimated incidence of two per 10,000 patient per year, which is fewer than with antipsychotics [63]. Kwak et al. [64], reported two patients who developed PS after treatment with ChEIs (donepezil and rivastigmine). PS in AD can also be drug-induced (donepezil, rivastigmine, and galantamine) [65-66]. In the case described by Panagiotis et al. [67], patient developed acute a sustained dystonia of the trunk and head to one side after the first dose of donepezil. Rivastigmine-induced dystonia was reported with rivastigmine patch, and dystonia occurred when rivastigmine patch was augmented, but which abated on discontinuation, and reemerged on the same dose patch application [68-69]. PS was reported in a 57-year-old female, after continuous use of rivastigmine (9 mg/d) for nearly 2 years, however, PS disappeared when the drug dose was decreased [70]. From a movement disorder perspective, many cases of trunk dystonia in the form of PS have been reported with the use of AChEIs [71-79]. Within this context, has been accounted a clinical case of PS induced by as witching of a ChEIs treatment from donezepil to galantamine, despite a previous long-term use of donepezil for 5 years without complications [80]. The present case suggests that treatment with galantamine is associated with a higher risk of development of PS than that with other ChEIs. It is interesting that the development of dystonia in a patient using the rivastigmine also supports a rela-

tionship between increased cholinergic transmission and dystonia [81]. Overall, it has been emphasized the importance of the pedunculopontine nucleus (PPN), which is one of the main cholinergic nuclei involved in the regulation of postural tone [60-82]. Therefore, PS manifesting as a side effect of ChEIs may improve after contralateral or ipsilateral stimulation of the PPN [83-84], suggesting a pathophysiological role of cholinergic-dopaminergic imbalance in the regulation of axial muscle tone. Based upon their potency as dopamine D2 receptor antagonists and their actions on serotonin 5-HT2A receptors antipsychotics are commonly classed as either typical or atypical [31]. Clinicians ought to refer to their country's legislation before introducing an antipsychotic drug to treat BPSD. Antipsychotic medication use is frequently associated with unfavorable adverse effects such as EPS. These adverse effects also called drug-induced movement disorders include a wide variety of movement disorders and can be classified into acute and tardive symptoms, such as parkinsonism, dystonia, akathisia, and tardive dyskinesia (TD). The latter movement disorders have been proposed to be caused by a relative cholinergic deficiency secondary to super-sensitivity of dopamine receptors in the striatum. This side effects can cause patients' subjective distress, both of which are disincentives to continue to take medication. Research-based evidence reported that the prevalence of antipsychotic-induced movement disorders among patients on long-term treatment with FGAs was around to be 50 to 75% [85]. Nevertheless, even with these newer agents SGAs, movement disorders are seen in a significant proportion of patients [86]. In a systematic review and meta-analysis aimed at determining the magnitude of antipsychotic-induced EPSEs the prevalence of antipsychotic-induced EPSEs was considerably high. One in five and more than one in ten patients experienced parkinsonism and akathisia, respectively [87].

Appropriate Drug Choice and Therapy-Tailoring: Combination Strategy Is Important in The Treatment of BPSD in AD in Alleviating EPS

A wide range of comorbid diseases is associated with AD and are treated with a variety of comedications not only to address cognitive impairment but also other comorbidities, along with agitation, aggression, or sleep disturbances for which pharmacotherapy may appear like therapeutic effect. On the other that antipsychotics are often used in conjunction with anti-Alzheimer drugs to treat the BPSD. To address comorbidities such as behavioral disorders, 40% on antidepressants and 20% on antipsychotics are estimated [88]. The target symptoms of antipsychotic drugs include inappropriate behaviors, agitation, aggression, and psychosis. Regrettably, the management of BPSD is complicated and challenging. The primary concern regarding the adverse reactions of antipsychotics is induction of EPS. There is a serious difficulty in establishing the best approach to the drug treatment of BPSD, especially regarding the safety profile and the occurrence of EPS. Among the available treatments, different pharmacological approaches, and new options for the treatment of behavioral symptoms have been evaluated. In the framework of an effective pharmacological approach, treatment with a combination of drugs possessing different mechanisms of action may be more beneficial over monotherapy. Therefore, many combination therapies (CT) have been tested in clinical trials [89], focused on mitigating side effects of drugs. Any CT which decreases BPSD, signify a relief for the caregivers as well as providing help in the maintenance of patients' independence and their adhesion to treatment. Indeed, it has been observed that CT with memantine and donepezil leads to a marked decrease, in the deterioration of BPSD compared to patients that were only receiving donepezil [90]. Interestingly, it is well known that many combination therapies have been tested in other clinical trials [91], and the data have revealed that memantine has been demonstrated to ease or improve behavioral and cognitive manifestations of these forms of dementia, various behavioral disturbances (irritability, agitation, aggression, and difficulty eating). In addition, data suggests that memantine may have a favorable safety and tolerability profile compared with AChEIs [92]. The galantamine and memantine combination has also proved to be more effective in AD than the donepezil-memantine combination [93]. The combination of these two pharmacological agents, have proved to be efficacious in the management of AD due to their combined actions on α7nAChR and NMDA receptors [94]. As evidence suggests, galantamine and memantine are well known for their effectiveness in various neuropsychiatric disorders [95]. Patients who were treated with donepezil and choline alphoscerate showed significant improvement in certain BPSD symptoms [96]. Notably, elderly patients, particularly those with dementia, are more sensitive than are younger patients to medication side effects such as EPSs. It should be borne in mind that, on the one hand, aging indicates a reduction in the number of cholinergic and dopaminergic neurons and dopamine D2 receptors [97]. As described previously, I point out that antipsychotic drugs can have EPSs even when used in older adults with dementia. But we should pay more attention to manage the EPSs, discussing drug choice and combination strategies. In addition to the EPS, the antipsychotics also cause agitation, psychosis, aggression, and inappropriate behaviors [98]. It is common knowledge that monoamine 5-hydroxytryptamine (5-HT) or serotonin, is one of the most important neurotransmitters, and is involved in multiple physiological and behavioral processes [99-100]. The pharmacological studies evidenced that the serotonergic system plays a crucial role in regulating various physiological functions including extrapyramidal motor disorders, through multiple serotonin (5-hydroxytryptamine; 5-HT) receptors [101]. Serotonin (5-HT) neurons are in the raphe nuclei and project axons to various brain regions including the cerebral cortex, limbic areas, basal ganglia, diencephalons, and the spinal cord. It is highly possible that the co-clustering of BPSD into domains depends on the circuit- and 5-HTR subunit-specific alterations that occur with AD pathogenesis and further interact with a person's innate neural architecture. Furthermore, several studies also revealed that serotonergic nervous system is closely involved in the pathogenesis and treatment of EPSs and can provide therapeutic benefits. However, before discussing drug choice and combination strategies, we must keep in mind how motor activities are regulated by the serotonergic neurotransmission system [102-103], in other words, understand the physiological mechanism of the serotonergic modulation of antipsychotic-induced EPS. I summarize the evidence for specific serotonergic system alterations across some of the well-defined behavioral and psychological symptoms in AD. 5-HT recep-

tors behaves as both a neurotransmitter and neuromodulator, acting in both central and peripheral systems. It is thereby clearly established that serotonergic neurotransmission is mediated by multiple 5-HT receptors consisting of at least 14 subtypes, and classification and molecular mechanism of the biological activity of serotonin receptors are discussed in [103]. Approaches such as receptor autoradiography, in situ hybridization and immunocytochemistry were used to reveal the distribution of 5-HT receptor binding sites and mRNA expression in the brain [104]. Presynaptic serotonin (5HT) receptors include 5HT1A, 5HT1B/D, and 5HT2B, all of which act as autoreceptors, and their purpose is to regulate the presynaptic serotonin neuron directly, especially its firing and how it releases and stores its own serotonin. There are also numerous postsynaptic serotonin receptors, which regulate other neurotransmitters in downstream circuits. It turns out that 5-HT1A, 5-HT2, 5-HT3 and 5-HT6 receptors play an important role in modulating extrapyramidal motor disorders (103). Advances in research on 5-HT receptors have led to the discovery of various therapeutic agents. The serotonin 5-HT1A receptor is the most extensively studied of the serotonin receptors. New insights indicate that 5-HT1A receptors are predominantly expressed in the limbic areas and the raphe nuclei, and moderate to low concentration of 5-HT1A receptors are also expressed in the cerebral cortex, thalamus, hypothalamus, and striatum [105-107]. Regarding 5-HT2 receptors can be classified into three subtypes, 5-HT2A, 5-HT2B and 5-HT2C receptors, which are cognate in terms of their molecular structure, pharmacology, and signal transduction pathways. 5-HT2A and 5-HT2C receptors are highly expressed in the brain [108]. Especially, 5-HT2C receptors are also widely expressed in the cortex (olfactory nucleus, pyriform, cingulate and retrosplenial), limbic structures (nucleus accumbens, hippocampus, amygdala), and the basal ganglia (caudate nucleus, substantia nigra) [109-110]. The central nervous system distribution of 5-HT2A receptor has been mapped extensively, particularly cortical areas (neocortex, entorhinal and pyriform cortex, claustrum), caudate nucleus, nucleus accumbens, olfactory tubercle and hippocampus, of all species studied [111]. 5HT2A receptors can both promote and inhibit the release of other neurotransmitters. It is well documented that several 5-HT receptor subtypes, including 5-HT1A, 5-HT2, 5-HT3 and 5-HT6 receptors, are involved in regulation of EPS induction associated with antipsychotic treatment [112-113]. 5-HT1A receptors can be found in the brain as presynaptic autoreceptors on serotonergic cell bodies in the raphe nuclei, and postsynaptic heteroreceptors in postsynaptic regions [114], which inhibits neural activities through activating G-protein-gated inwardly rectifying K+ channels. It has become clear that these receptors can be a useful target in the management of various neuropsychiatric disorders. For instance, AD aggression has been associated with reduction in 5-HTR1A in the medial temporal cortex, and within the 5-HTR1 subtype, agonists acting on the 5-HTR1B have more selective anti-aggressive effects in mice than those acting on 5-HTR1A [115]. Further, activation of 5-HT 1A receptors causes reduction of antipsychotic-induced EPS and motor disturbances in animal models [116-117]. Therefore, evidence have revealed that activation of 5-HT1A receptors reduces antipsychotic-induced EPS by inhibiting neural activity in the striatum and motor cortex [103]. As known, in the recent past "biased" 5-HT1A agonists with functional preference for presynaptic autoreceptors in dorsal raphe nucleus versus postsynaptic 5-HT1A heteroreceptors in medial prefrontal cortex have been developed, and it was observed that presynaptic 5-HT1A autoreceptors are also involved to reduce EPS [118-119]. In addition, studies suggest that blockade of 5-HT2A/2C receptors with antagonistic agents attenuates antipsychotic-induced extrapyramidal side effects (EPS) tone down 5-HT2A/2C receptor-mediated inhibition of nigral dopaminergic neuron activity and striatal dopamine release [113]. Namely, blockade of 5-HT2 receptors determines the increase in the release of acetylcholine (ACh) and accelerates the metabolic turnover rate of dopamine, contrary to the responses of striatal neurons to the action of antipsychotic agents that block D2 receptors [120], thus suggesting that the blockage of 5-HT2 receptors may counteract the D2 (and/or D1) blocking activities of antipsychotics in the striatum to reduce EPS. It is well known that relatively high levels of 5-HT3 receptor recognition sites have been located within the caudate nucleus and putamen whereas relatively low levels are detected within cortical regions [121]. As a result, and according with previous studies, some 5 HT3 receptor interactions like blockade of 5 HT3 receptor had been reported to be effective in decreasing EPS [122-124], possibly via acting in the striatum. In fact, blockade of 5-HT3 receptors reduced haloperidol-induced EPS [125-126]. Given that, based on the mechanisms underlying serotonergic modulation of antipsychotic-induced EPS, a series of atypical antipsychotics, been developed. As noted, to reduce EPS new so-called 'atypical', antipsychotics have been recently introduced. Dissimilar the typical antipsychotics, which preferentially block dopamine D2 receptors, the second-generation antipsychotic drugs not only reduce dopamine neurotransmission, but also act on serotonin receptors, especially 5-HT2A receptors and typically as antagonists [127]. The term "atypical" refers to an antipsychotic agent that produces minimal EPS at clinically effective antipsychotic doses [128], and the newer agents are also potent antagonists of serotonin receptors (5-HT2A), this results in increased blockage efficacy on the mesolimbic pathways, but not on the nigrostriatal one [129]. It must be noted, however, that several studies have not demonstrated a clear and significant difference between second- and first-generation antipsychotics, at least for schizophrenia, their better safety profile, particularly for extrapyramidal symptoms (EPS), would grant them some actual advantage [130]. However, atypical antipsychotics mark a wider range of receptors with different affinities. Therapeutically, we should pay more attention to individual pharmacological characteristics of the atypical drug, especially their interactions with 5-HT receptor subtypes. However, based on a different affinity potency these agents divide into a group of drugs with modest affinity for D2, 5-HT 2A and other receptors such as H 1 and M 1 such as clozapine, olanzapine, and quetiapine, and those with potent antagonist action on D2 and 5-HT2A, high affinity for α1, 5-HT2c and H1 and minimally affinity for M1 receptors such as risperidone, paliperidone, lurasidone [131]. It is thereby clearly established the decisive roles of 5-HT receptors, especially 5-HT1A, 5-HT2, 5-HT3, and 5-HT6 receptors, in modulating antipsychotic-induced EPS were revealed. Considering the actions of atypical antipsychotics

with 5-HT receptor subtypes can reduce EPS caused by combined treatment of antipsychotics with anti-Alzheimer's disease drugs, they could be a favorable BPSD treatment in terms of EPS management. We fear in mind that atypical antipsychotics block serotonin 5-HT2 receptors and when the ratio of 5-HT2 to D2 receptor blocking is greater than 1, atypical antipsychotic action such as therapeutic effects on negative symptoms and few EPS are noted [132]. Atypical drug as SDAs, MARTAs, and D2 partial agonists are nowadays the first line drug to treat psychosis and inappropriate behaviors in patients with dementia. Clozapine, which acts on many different receptor types, has been proven to be the clinically most effective drug with the least EPS. Clozapine is the prototype of the new neuroleptics with its high affinity for the 5-HT2 receptor, combined with its low affinity for the dopamine D2 receptor and has a low incidence of Parkinsonism and tardive dyskinesia; due to its favorable receptor profile [131]. Clozapine has served as a template for the development of the next generation of "atypical" antipsychotics. Risperidone was the second atypical antipsychotic developed following clozapine. This antipsychotic drug bocks 5-HT2 receptors with a higher affinity than D2 receptors and has shown good efficacy in treating positive symptoms and increased dopaminergic neurotransmission in the nigrostriatal pathway with reduced EPS [133]. The exact mechanisms by which 5-HT2 blocking improves negative symptoms and induces fewer EPS are unclear. In this regard it is common knowledge that positive symptoms are associated with a hyperdopaminergic state in the limbic lobe, which is rich in dopaminergic innervation. Serotonin inhibits DA release, and in the limbic lobe, with high 5-HT2 and low D2 receptor density, D2 receptor blocking action prevails and positive symptoms are controlled. About the negative symptoms are associated with a hypodopaminergic state in the frontal lobe, which is rich of 5-HT2 and sparse distribution of D2 receptors, therefore serotonin inhibits DA release and the hypodopaminergic state of the frontal lobe becomes normal, thereby improving negative symptoms [132-134]. Olanzapine is chemically like clozapine and shares several aspects of clozapine's in vitro pharmacological profile (stronger affinities for the 5-HT2, muscarinic, and histaminic receptors than for the dopamine D2 receptor). Indeed, Olanzapine antagonizes multiple neuronal receptors including dopamine (D1, D2, D4), serotonin (5HT2A, 5HT2C, 5HT3), histamine (H1) alpha1-adrenergic receptors; acetylcholine at muscarinic M1, M2, M3, and M4 receptors, therefore very important are its high affinities for 5-HT 3 and 5-HT 6 receptors and acts as an antagonist, additionally clozapie like olanzapine, two of the most effective antipsychotics is a potent 5-HT3 receptor antagonist [135]. These pharmacological characteristics translate into clozapine-like clinical benefits, as substantially reduced extrapyramidal side effects, less effect on prolactin, and probably a direct effect on ameliorating negative symptoms. A further improvement in their mechanism of action led to the development of a third generation of antipsychotics. These agents are named dopamine system stabilizers (DSSs) are a potential new class of antipsychotic agents without motor side effects. Aripiprazole may be considered representative of DDSs, with its reduced association with extrapyramidal side effects and its efficacy against both positive and negative symptoms of schizophrenia. Aripiprazole shows a unique pharmacological profile. This antipsychotic agent that contains a carbostyril skeleton and acts as a partial agonist at dopamine D2 receptors [136]. It is well known that aripiprazole is a dopamine D2 agonist, a 5-HT receptor 1A receptor agonist, and a 5-HT2A antagonist, acting as DSSs. This antipsychotic drug possesses moderate 5-HT2 blocking activities, it primarily acts as a dopamine D2 partial agonist and, differs from the other atypical antipsychotics in that it is a partial agonist at D2 as 5-HT1A receptors, and has antagonistic activity at 5-HT2A and 5-HT2C receptors [137]. Aripiprazole can be considered representative of the group third generation of antipsychotics, with its reduced association with extrapyramidal side effects and its efficacy against both positive and negative symptoms of schizophrenia. In the presence of dopamine, aripiprazole decreased dopamine D2 receptor-mediated transmission but did not result in full blockade. In the absence of dopamine, aripiprazole produced small increases in dopamine D2 receptor-mediated transmission consistent with its intrinsic activity [138]. Meta-analytical evidence best supports aripiprazole and risperidone, with substantially less evidence for quetiapine and olanzapine [139]. Moreover, a network meta-analysis, which addressed the treatment of BPSD and not of psychosis specifically, suggested that aripiprazole was the most effective and safe atypical antipsychotic, with olanzapine providing the least benefit overall [133]. However, these atypical antipsychotics target a broader range of receptors with different affinity. It must be noted, the higher affinity for different target receptors justifies the possible different or added desired or adverse effects of the different drugs. We should pay more attention that unlike the typical antipsychotics, which preferentially block dopamine D2 receptors, these antipsychotics also have additional properties such as 5-HT2A antagonism and 5-HT1A agonism. Finally, consistent with these observations, even though atypical antipsychotics have a better safety profile, they may present with several adverse events, as weight gain, lipid disturbance, and glucose dysregulation, thereby contributing to the development of metabolic syndrome [140]. For instance, strong binding to 5-HT2C, α1 and H1 is responsible for the side effects, such as weight gain, sedation, orthostatic hypotension [31].

Conclusions

BPSD represent a group of affective, psychotic, and behavioral symptoms that occur in most patients with dementia, especially those with AD, causing great suffering and increasing the caregivers' burden. Nonetheless, pharmacological treatments with antipsychotics drugs are necessary to treat BPSD. Antipsychotic agents are the first choice to reduce psychosis and behavioral disturbances despite their frequent side effects. Since AD accompanies the loss of ACh neurons ChEIs which can increase the ACh level by inhibiting cholinesterase, are widely used to treat the cognitive impairment. However, these drugs have a propensity to potentiate EPS associated with antipsychotic treatment in a synergistic manner. But we should pay more attention to the interactions between anti-Alzheimer's disease drugs and antipsychotics in induction of EPS. Serotonergic circuitry has been tied to cognitive decline and implicated in several basal and higher brain functions that are perturbed in BPSD. Moreover, serotoninergic system plays crucial roles in modulating EPS associated with antipsychotic treatment. The fundamental role of 5-HT receptors is known, especially of 5-HT1A, 5-HT2, 5-HT3 and 5-HT6 receptors, in

the modulation of EPS induced by antipsychotics. Furthermore, antipsychotics which have 5-HT1A agonistic actions or 5-HT2, 5-HT3, and 5-HT6 antagonistic actions appear to be useful for adjunctive BPSD treatment. Therefore, it is imperative for clinicians to understand how activation of 5-HT1A receptors or blockade of 5-HT2, 5-HT3 and 5-HT6 receptors can relieve EPS induction both by antipsychotics alone and by combined antipsychotic treatments with ChEIs.

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