BPSD and Antipsychotics

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Behavioral and psychological symptoms (BPSD) frequently occur during the disease progression; to treat agitation, aggressiveness, delusions and hallucinations, the use of antipsychotic drugs should be limited, due to their safety issues.

Keywords: dementia ; behavioral and psychological symptoms of dementia (BPSD) ; atypical antipsychotics ; typical antipsychotics ; frailty

1. Behavioral and Psychological Symptoms of Dementia (BPSD)

BPSD are among the earliest signs and symptoms of neurocognitive disorders and cognitive decline and, although they fluctuate, their severity exponentially increases over the course of the disease. Neuropsychiatric symptoms are associated with several negative outcomes, such as faster cognitive decline, functional impairment, reduced independence and inability to complete activities of daily living, with progression to more severe stages of dementia and increasing risk for secondary complications such as falls and fractures, causing higher hospitalization rates and eventually early institutionalization [1]. The etiopathogenesis of BPSD is complex as it is probably the result of the interaction of multiple factors, such as biological (brain changes, comorbidities, medications), psychological (personal life history, personality) and social factors (support network, living arrangements) [1]. In their review, Eissa et al. examined the hypothesis that chronic neuroinflammation may be associated with cognitive deficits, and found that central histamine (HA) plays a significant role in the regulation of neuroinflammatory processes of microglia functions in numerous neuropsychiatric diseases such as BPSD [2]. In a meta-analysis by Qing-Fei et al., apathy resulted as the most common neuropsychiatric symptom reported in the Neuropsychiatric Inventory (NPI), followed by depression, aggression, anxiety, sleep disturbances, irritability, change in appetite, motor problems, hallucinations, delusions, disinhibition and euphoria [3]. Psychiatric symptoms like depression, irritability, agitation in cognitively normal subjects may also be predictors of possible more rapid cognitive decline. In their study, Banks et al. assessed the relationship between behavioral symptoms and emergence of mild cognitive impairment or dementia in older adults, over a 4-year period. The results suggested that anxiety and depressed mood moderately increased the risk of developing dementia, primarily Alzheimer's disease, representing precursors to future cognitive decline [4]. The relationship between depressive symptoms and cognitive decline appears to be complex; whether depression is a very early manifestation of Alzheimer's disease or increases susceptibility to it remains to be determined. Nevertheless, a large longitudinal study of people aged 50 to over 90 years showed that depressive symptoms were associated with a slight acceleration in cognitive decline in people aged 60–80 years, but there was no support for the hypothesis that there might be a bidirectional connection between depression and AD [5]. Different BPSDs are often co-present and can be clustered into distinct domains, suggesting that they should be considered as groups of symptoms rather than lonely symptoms, with each group reflecting a different prevalence, timeline, biological and psychosocial correlates. During the last few decades, several studies have been conducted with the aim of identifying possible AD sub-syndromes defined by combinations of different neuropsychiatric symptoms. Most of these studies included only patients with AD, whereas others included patients with various dementia subtypes. In their study, 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) [6]. The study showed no statistically significant impact of different neuropsychiatric sub-syndromes on the rate of cognitive decline, indicating that the cognitive progression of dementia seems to be scarcely affected by the presence of specific clusters of symptoms [6]. Thompson et al. examined the associations between dementia subtypes, severity of dementia and severity of BPSD. They found that severity of BPSD did not differ between AD and vascular dementia, but was higher in those patients with greater severity of dementia [7]. Considering that different behavioral symptoms belonging to different clusters are often co-presenting, the idea that there could be a common underlining neurotransmitters disruption may arise. Monoamine 5-hydroxytryptamine (5-HT), or serotonin, is one of the most important neurotransmitters in the central nervous system (CNS), regulating multiple physiological functions. 5-HT works as both a neurotransmitter and neuromodulator, acting in both central and peripheral systems. Serotonergic circuitry has

been tied to cognitive decline and implicated in a number of basal and higher brain functions that are perturbed in BPSD. It is highly possible that the co-clustering of BPSD into domains depends on different circuits via diverse expression of 5-HT receptor subunits [8]. Dopaminergic system as well is involved in behavioral disturbances genesis and control. Dopamine (DA) is not only fundamental for motor control, due to the activity within the basal ganglia, but is also responsible for the processing of cognitive information, perception and adaptation to the environment [9].

2. Antipsychotic Use in Dementia

Antipsychotics represent the main pharmacological strategy to alleviate BPSD, improving the quality of patients' and caregivers' lives [10]. Despite the warnings issued by the US Food and Drug Administration (FDA), the European Medicines Agency and the UK Medicines and Healthcare Products Regulatory Agency, antipsychotics are often used in individuals with dementia for sustained periods (≥6 months) [11][12], although they are associated with increased risk of death, cerebrovascular adverse events (CVAEs), Parkinsonism, sedation, gait disturbance, cognitive decline and pneumonia [13]. This risk remains elevated for at least 2 years, with an increased number of deaths due to antipsychotics prescription and longer duration of use. A recent meta-analysis including several large retrospective studies showed an increased all-cause mortality associated with antipsychotic use in patients with dementia [14]. Nevertheless, these drugs have been increasingly prescribed over the last several years, even for long-term use. Amongst antipsychotics, only risperidone is indicated for the short-term management of persisting and severe aggression in individuals with AD who have failed non-pharmacological trials [15]. Off-label treatment with antipsychotic medications has grown in the past two decades, with increasing prescription rates, estimated to be between 20% and 50% [16], and is even higher among institutionalized individuals with dementia [17]. Given that, the importance of the careful evaluation of the potential drug–drug interactions between antipsychotics and Ache-I or memantine, especially in a population of older patients often affected by several chronic diseases and undertaking polytherapy, becomes clear [18]. The complex management of BPSD requires a deep knowledge of antipsychotics' mechanism of action, possible pharmacological interactions, symptoms overlapping and spectra, without overlooking the social context, the patient and caregiver counselling and always considering a non-pharmacological therapy as a first approach. The most relevant literature for the possible mechanism of action of antipsychotic drugs derives from studies in schizophrenia and mania; even though it is possible to apply them to a geriatric population from a purely pathophysiological point of view, it is mandatory to fully assess the older and often frail demented patient, in order to minimize adverse events or drug–drug interactions.

Antipsychotics are commonly classed as either typical or atypical based upon their potency as dopamine D2 receptor antagonists and their actions on serotonin 5-HT2A receptors [19]. While several studies, such as the National Institute of Mental Health (NIMH), Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and sub-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 [20].

2.1. Typical Antipsychotics: Mechanisms and Limitations

Based on their chemical structures, they are grouped into several classes: phenothiazines (e.g., chlorpromazine and fluphenazine), butyrophenones (e.g., haloperidol), benzamides (e.g., sulpiride and tiapride), and were developed mainly for the treatment of schizophrenia, with the first agents licensed in the 1950s. Since their discovery, first generation antipsychotics have been the standard for treating psychotic disorders for many decades. These classical neuroleptics or typical antipsychotics display a rather narrow spectrum of therapeutic activity, however, and because of their wide receptor profile, their use is associated with several side effects. 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 [19], they lack the tolerability of newer antipsychotics, inducing, among others, sedation, anticholinergic effects and EPS. Haloperidol is now the most widely prescribed agent from this category, mainly because it is considered a first-line treatment in hypoactive, hyperactive and mixed type delirium, according to NICE guidelines [21]. Haloperidol preferentially binds dopamine receptors (in particular, D2, D3 and D4) and α1 adrenergic receptors, while it has negligible affinity for H1, M1 and 5-HT (in particular, 5-HT 2C) receptors [19]. Although a recent study [22] reported that the number needed to harm (NNH) with haloperidol for the outcome of mortality was similar to risperidone, another more recent study evaluating community dwelling AD patients' mortality documented a higher mortality risk in patients treated with haloperidol compared to quetiapine or risperidone [23]. When a diagnosis of dementia was not required for inclusion, risk of both death and femur fracture in nursing home residents was higher for conventional antipsychotics compared with atypical antipsychotics [24]. Recently, a large retrospective study conducted on a population of patients with newly diagnosed dementia evaluated the impact of antipsychotic medications on acute cerebral and cardiovascular events, hip fracture and venous thromboembolism [25]. The use of antipsychotic drugs appeared to be

associated with increased risk of stroke, thromboembolism and hip fracture, while no increased risk was detected regarding long-term mortality [25]. In addition, a more recent systematic review of 36 Randomized Clinical Trials (RCTs) compared the efficacy of risperidone, haloperidol, SSRI as a class and dextromethorphan/quinidine in treating agitation in people affected by all-types dementias; the results showed that haloperidol was almost the least efficacious among all comparators, dissuading prescription of this medication in this particular case [26]. Lastly, the American Psychiatric Association (APA) recommends that in the absence of delirium, if nonemergency antipsychotic medication treatment is required, then haloperidol should not be used as a first-line agent (Recommendation 1B). Furthermore, the APA recommends that in individuals with dementia and agitation or psychosis a long-acting injectable antipsychotic medication should not be utilized unless it is otherwise indicated for a co-occurring chronic psychotic illness (Recommendation 1B) [27].

2.2. Atypical Antipsychotics: Mechanisms and Advantages/Limitations

Atypical antipsychotics include clozapine, risperidone, olanzapine, quetiapine and aripiprazole. They comprise serotonin and dopamine antagonists (SDAs), multiple-acting receptor targeted antipsychotics (MARTAs) and dopamine D2 partial agonists [28].

It must be noted, however, that these second generation antipsychotics (SGA) target a broader range of receptors with different affinity. In general, they not only exert antagonist effect on dopamine D2, but also have a simultaneous antagonist effect on 5-HT receptors, particularly on the 5-HT_{2A}; this results in increased blockage efficacy on the mesolimbic pathways, but not on the nigrostriatal one [19].

However, different potency of affinity splits them into a group of drugs with modest affinity for D2, 5-HT_{2A} and other receptors such as H_1 and M_1 (clozapine, olanzapine and quetiapine) and those with potent antagonist action on D2 and 5-HT_{2A}, high affinity for α_1, 5-HT_{2c} and H_1 and negligible affinity for M_1 receptors (risperidone, paliperidone, lurasidone) [19]. Clozapine has become the prototype for new neuroleptics, due to its favorable receptor profile and low incidence of Parkinsonism and tardive dyskinesia; however, the increased risk for agranulocytosis, weight gain and metabolic alterations had a negative impact on its use. Risperidone, with higher affinity for 5-HT_{2A} than for D2, has shown good efficacy in treating positive symptoms and increased dopaminergic neurotransmission in the nigrostriatal pathway with reduced EPS [29]. However, the strong binding to 5-HT_{2C}, α_1 and H_1 is responsible for the side effects, such as weight gain, sedation, orthostatic hypotension [19]. The higher affinity for different target receptors justifies the possible different or added desired or adverse effects of the different drugs. In particular, affinity to histamine-1 receptor is higher for olanzapine and quetiapine, to 5HT-5_{1C} for risperidone, clozapine and olanzapine, to adrenergic receptor for clozapine, quetiapine, olanzapine (α1 and α2) and risperidone (α2) [30]. A further improvement in their mechanism of action led to the development of a third generation of antipsychotics. Often referred to as dopamine system stabilizers (DSSs), they act as partial D2, D3 and 5-HT_{1A}-receptor agonists, and antagonists at 5-HT_{2A} receptors. In other words, they can act either as a functional agonist or a functional antagonist, depending on the surrounding levels of dopamine. The antipsychotic action would follow the functional antagonism in the mesocortical pathway, where excess of dopamine causes positive symptoms, while the action as functional agonist in the mesocortical pathway improves the negative symptoms [31]. Reliant on local levels of dopamine, DSSs do not cause motor side effects, preserving dopamine activity in those regions where normal dopamine levels are needed (nigrostriatal pathway) [19]. Aripiprazole may be considered representative of this latter group of neuroleptics, with its reduced association with extrapyramidal side effects and its efficacy against both positive and negative symptoms of schizophrenia. Aripiprazole causes minimal weight gain, sedation and does not produce elevation in serum prolactin levels; most importantly, unlike other neuroleptics, it does not lengthen QTc interval on electrocardiogram [32]. Nonetheless, atypical neuroleptics account for >80% of the neuroleptics prescribed for people with dementia, and the most widely prescribed are risperidone, olanzapine and quetiapine. Several studies compared first generation antipsychotics (FGA) and SGA safety profile. In 2014, the increased risk of cardio and cerebral vascular events (stroke, ventricular arrhythmia, myocardial infarction), as well as hip fractures, has been highlighted [33]. Almost 10% of strokes and hip fractures were more frequent in the group treated with FGAs, whereas the difference in the two groups was lower for myocardial infarction and ventricular arrhythmia. Combining these data, all the adverse events accounted for approximately one sixth of the mortality differences between FGAs and SGAs, even though this difference could be as large as 42% [33]. Recently, a systematic review analyzed a total of 16 meta-analyses evaluating the use of antipsychotics in individuals with dementia; of those, only two were specifically focused on AD, one on LBD and the others more generically on dementia. The authors did not find any evidence in the evaluation of the difference in mortality rates between first and second generation antipsychotics (FGAs and SGAs) in older adults [34]. In particular, 10 meta-analyses evaluated atypical antipsychotics and only two meta-analyses evaluated typical antipsychotic medications. When used in individuals with dementia, including AD, atypical antipsychotic medications, especially quetiapine, showed modest efficacy. Greater responses to atypical antipsychotics were observed in individuals with severe psychosis, aggression and

agitation, whereas smaller effects were noted for subjects with less severe symptoms. Furthermore, in these 10 meta-analyses, antipsychotics use in individuals with dementia was associated with a greater number of adverse effects when compared with individuals treated with placebo, including the risk of CVAEs and death.

In comparative effectiveness studies of second generation antipsychotics, risperidone was superior to quetiapine in the Cohen-Mansfield Agitation Inventory (CMAI) [35]. The effectiveness of quetiapine is considerably weaker than risperidone. Nevertheless, a meta-analysis involving five randomized trials observed a statistically significant effect relative to placebo on neuropsychiatric symptoms, as evaluated with the NPI and overall improvement (Clinical Global Impression (CGI) scores) [36]. Moreover, quetiapine could be the antipsychotic of use to treat BPSD in patients with Parkinsonian features, thanks to the lower induction of extrapyramidal signs [1]. Aripiprazole shows a weaker effectiveness than risperidone as well. Moreover, aripiprazole showed better outcome, compared to placebo, in NPI, Brief Psychiatric Rating Scale (BPRS) and Cohen-Mansfield Agitation Inventory (CMAI), while olanzapine, quetiapine and risperidone did not [35]. Even though atypical antipsychotics have a better safety profile, they may present with several adverse events, such as anticholinergic effects, orthostatic hypotension, seizures, metabolic syndrome, weight gain, extrapyramidal symptoms, sedation and QT-prolongation [1]. Another important finding is the increased risk of stroke and mortality associated with the use of atypical antipsychotics [37].

Notwithstanding the slight advantage of second upon first generation antipsychotics, in the recent network meta-analysis pooling together studies mainly on dementia, but also including mixed and one study comprising LBD, no atypical antipsychotic was consistently associated with better results than the others across all effectiveness and safety outcomes, risk of death included [35].

All these data suggest the importance of being cautious with the prescription of antipsychotics, particularly in frail patients, where the increased risk of hip fracture or cardiovascular events might accelerate or worsen the loss of independence, increase the hospitalization and the global outcome as well as the cognitive impairment. An accurate medical history and global comprehensive medical assessment would reduce the inappropriate prescription of drugs such as olanzapine or risperidone in patients with high cardiovascular risk or cerebral ischemia, as suggested also by the American Psychiatric Association guidelines and STOPP/START criteria.

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