ALZHEIMER'S DISEASE AND TREATMENT
The Use of Antipsychotic Drugs in Patients with Alzheimer’s Disease

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Introduction

Alzheimer’s disease is the most common type of dementia, a progressive neurological disorder that belongs to the primary degenerative dementias. Alzheimer’s disease is the most common cause of dementia (up to 60-80% of cases) in people over 65 years of age, and represents a continuous decline in thinking, behavioral and social skills that affects a person’s ability to function independently [1]. The first and dominant symptom of the disease is a memory disorder, in the form of difficulties in recalling a recent conversation, name or event, followed by apathy and depression. Later, disorders of speech functions, praxis and gnosis appear, which cause the inability to perform daily activities, changes in the patient’s behavior and personality, as well as impairment of cognitive functions [1,2]. In addition to its isolated form, Alzheimer’s disease can manifest simultaneously with other forms of cerebrovascular disease, under the common name of mixed dementia [3].

Abstract

Alzheimer’s disease is the most common type of dementia, a progressive neurological disorder that belongs to the primary degenerative dementias. Alzheimer’s disease is the most common cause of dementia (as many as 60-80% of cases) in people over 65 years of age, and is a continuous decline in thinking, behavioral and social skills that affects a person’s ability to function independently. Bearing in mind that Behavioral and Psychological Symptoms of Dementia (BPSD) are a prominent clinical feature of Alzheimer’s disease, it is clear that the use of antipsychotic drugs is an indispensable therapy. In recent years, many papers have been published on the treatment of behavioral disorders and psychotic disorders in Alzheimer’s disease using antipsychotics, with conflicting conclusions, and the debate in the scientific world is still intense. This book chapter discusses Alzheimer’s disease and treatment, with a particular focus on the use of antipsychotic drugs in patients with Alzheimer’s disease.

Keywords: Antipsychotic drugs; Alzheimer’s disease; Treatment.
affect the development of Alzheimer’s disease, APOE ε2 lowers the risk of the disease, while APOE ε4 not only increases the risk, but also lowers the age threshold for the onset of the first symptoms of the disease [5].

When it comes to environmental factors, an increasing number of studies are seeing the connection between diet, lifestyle and the risk of Alzheimer’s disease. Smoking, overweight, elevated blood cholesterol and hypertension are risk factors, while daily physical activity and a healthy diet are protective factors [6,7]. Traumatic brain injury is another important factor for the onset of Alzheimer’s disease [8]. If a traumatic brain injury (TBI) results in loss of consciousness and post-traumatic amnesia lasting half an hour, it is called a moderate injury, and if the amnesia lasts for more than 24 hours, then it is called a severe injury. According to research, moderate TBI increases the incidence of Alzheimer’s disease by two times, while severe TBI increases the incidence by as much as 4.5 times [9,10].

Pathogenesis of Alzheimer’s disease

In the post-mortem pathological findings in Alzheimer’s patients, there is a pronounced cortical atrophy, especially in the hippocampal area, while the histological findings indicate deposits of extracellular senile plaques and intracellular neurofibrillary fibers. Neuritic senile plaques contain beta-amyloid (Aβ) deposits resulting from proteolytic degradation of Amyloid Precursor Protein (APP). Under normal conditions, APP is degraded by alpha-secretase, and the created beta amyloid contains 40 amino acids and is removed from the brain [11]. However, in Alzheimer’s patients, APP begins to be degraded by beta-secretase and gamma-secretase, and PRS1 and PRS2 also participate in the final degradation. The created Aβ contains 42 amino acids, it accumulates and is not removed from the brain [12,13].

In addition to neuritic plaques, neurofibrillary fibers of phosphorylated tau protein are formed extracellularly and intracellularly. Tau protein enables axonal transport, and its normal functioning requires a balance between phosphorylated and non-phosphorylated forms. With the accumulation of abnormal beta-amyloid extracellularly, calcium ions are increasingly entering the cell causing hyperphosphorylation of tau protein. In addition to changes in the structure and function of proteins, patients with Alzheimer’s disease also experience deterioration of cholinergic neurons, as well as acetylcholine transferase in the hippocampus. The most probable cause is the degeneration of Meynert basal region, as well as the cholinergic septal-hippocampal pathway [14,15,16].

Although Aβ deposits have long been assumed to cause neuronal damage and degeneration in Alzheimer’s disease, recent studies [17,18] show that soluble Aβ oligomers, not Aβ deposits, are the most likely cause. According to new knowledge, soluble Aβ oligomers damage neurons, and consequently senile plaques accumulate in regions of damaged neurons [18]. This is supported by the fact that during the autopsy finding senile plaques in the brain does not have to be correlated with the severity of the patient’s clinical picture during life. In other words, post-mortem autopsy findings can reveal large deposits of Aβ senile plaques without the person having had a clinical picture of mild cognitive impairment (MCI) or Alzheimer’s disease during their lifetime. The reverse is also true, the finding of soluble Aβ oligomers in the areas of the hippocampus and cortical regions responsible for memory correlate with lifelong Alzheimer’s disease, while senile plaques do not have to be present in the brain [18].

Although the exact mechanism of neuronal damage is still unknown, it is assumed that pathological concentrations of Aβ oligomers cause hyper stimulation of N-Methyl-D-Aspartate (NMDA) receptors, either by inhibiting the reuptake of glutamate, or by stimulating glial cells to increase their production. Hyperstimulated NMDA receptors consequently lead to increased entry of calcium ions into the cytoplasm of neurons. An excess of calcium ions not only causes tau protein hyper phosphorylation, but also disruption of mitochondria and cell signaling mechanisms, as well as cell oxidative stress. All these events are a prerequisite for neurotransmitter dysregulation and improper intercellular functioning of neurons [18,19].

Treatment of Alzheimer’s disease

The treatment of Alzheimer’s disease is based on alleviating the symptoms, and since the cause of the disease is still not exactly known, the causal treatment is not possible either. Alzheimer’s disease therapy consists of four cholinimimetics: tacrine, rivastigmine, donepezil, galantamine, and one non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors for glutamate-memantine [20,21]. Atypical antipsychotics (neuroleptics), antidepressants, anxiolytics, etc. are used in the treatment of Behavioral and Psychological Symptoms of Dementia (BPSD). Medicines are introduced gradually to avoid side effects. The effect of drugs weakens with the progression of the disease [22].

Antipsychotics in Alzheimer’s disease

Bearing in mind that Behavioral and Psychological Symptoms of Dementia (BPSD) are a prominent clinical feature of Alzheimer’s disease, it is clear that the use of antipsychotics is an indispensable therapy. The spectrum of action of this group of drugs is really wide, so we find them in use in schizophrenic, manic, borderline personality disorders, acute psychoses and delusions [23]. The development of atypical antipsychotics was an important turning point in the history of psychiatry as it brought effective treatment options with a reduced risk of adverse events. In particular, atypical antipsychotics appear much less likely to cause Extra Pyramidal Symptoms (EPS), a group of movement disorders associated with physical disability and subjective discomfort and agitation, including parkinsonism, akathisia, dystonia, and tardive dyskinesia (a long-term manifestation of EPS). Moreover, the availability of atypical antipsychotics which, unlike typical ones, have fewer side effects and better efficacy, have made this group of drugs one of the most commonly used in psychiatric treatment [24].

Antipsychotics can be divided into three groups.

1) First-generation antipsychotics (typical antipsychotics), such as haloperidol and fluphenazine, which are strong blockers of dopamine D2 receptors and therefore often lead to Extra Pyramidal Side effects (EPS). This group also includes sedative antipsychotics, such as promazine and chlorpromazine.

2) Second-generation antipsychotics (atypical antipsychotics), such as risperidone, olanzapine, quetiapine, clozapine, ziprasidone. The effect of these antipsychotics is achieved through a combination of slightly weaker D2 receptor blockade, but also through numerous effects on other receptors, such as serotonin 5-HT2A and 5-HT2C. These antipsychotics have less EPS, but can lead to weight gain, especially clozapine and olanzapine, to hypotension, especially quetiapine, clozapine, and risperidone, and to hyperprolactinemia, especially risperidone. Some also cause EPS, especially ziprasidone and risperidone at higher doses [25].
3) Third-generation antipsychotics, such as aripiprazole, which is the first partial agonist of the D2 receptor. This antipsychotic has a different profile of side effects, it does not cause an increase in appetite, but it can cause nausea, restlessness and akathisia [26].

Antipsychotics are drugs with a primary action on dopaminergic D2 receptors, whereby atypical and typical differ in additional action on other receptors in favor of atypical antipsychotics [27]. Typical antipsychotics act antagonistically on dopaminergic D2 receptors, blocking the effect of dopamine, therefore extra pyramidal symptoms are expressed with their use [28].

Atypical antipsychotics act not only through dopaminergic, but also through serotonergic and adrenergic receptors, which causes a kind of balance in certain brain regions (nigrostriatal, mesocortical, mesolimbic, and tuberoinfundibular pathway). Namely, in the nigrostriatal pathway, atypical antipsychotics bind to presynaptic 5-HT2A receptors of dopamine neurons, causing the release of dopamine, which prevents or at least reduces the occurrence of EPS because the motor function is preserved. By the same mechanism, atypical antipsychotics act in mesocortical pathways, and olanzapine additionally acts on the release of acetylcholine, which prevents further cognitive decline. From all of the above, it is clear that atypical antipsychotics, by increasing dopamine levels in certain brain regions which is most pronounced in the prefrontal cortex, reduce cognitive decline and motor disturbances, while reducing dopamine levels in other parts of the brain have an antipsychotic function [23].

Adverse effects and dosing of antipsychotic drugs in patients with Alzheimer's disease

Although they are widely used, atypical antipsychotics show significant side effects with a possible fatal outcome in the most severe cases. In 2005, the US Food and Drug Administration (FDA) informed healthcare professionals about the results of 17 randomized controlled trials, reporting a 1.7-fold increased risk of all-cause mortality in dementia patients treated with atypical antipsychotics [29], and in 2008 they also extended this warning to typical antipsychotics, based on reports of a similar or higher risk of mortality in elderly people with dementia taking conventional antipsychotics [30].

Numerous studies have shown a correlation between the use of atypical antipsychotics and the metabolic changes that occur in patients who use them. The increasing number of findings of diabetes, ketoacidosis, hyperglycemia, and lipid dysregulation in patients treated with second-generation (or atypical) antipsychotics raises concern about a possible association between these metabolic effects and treatment with these drugs. Substantial evidence from various human populations, including confirmitory evidence in treated psychiatric patients, indicates that increased adiposity is associated with a variety of adverse physiological effects, including decreased insulin sensitivity and changes in plasma glucose and lipid levels. A comparison of mean weight changes and relative percentages of patients experiencing a specific level of weight gain from randomized controlled clinical trials shows that the liability for weight gain varies significantly among different second-generation antipsychotics. Treatment with clozapine and olanzapine is associated with the highest risk of clinically significant weight gain, while other drugs produce relatively lower levels of risk. Risperidone, quetiapine, amisulpride, and zotepine generally show low to moderate levels of mean weight gain and a modest risk of clinically significant weight gain. Treatment with ziprasidone and aripiprazole is generally associated with minimal mean weight gain and the lowest risk of significant weight gain [31].

Published studies including uncontrolled observations, large retrospective database analyses, and controlled experimental studies, including randomized clinical trials, show that different second-generation antipsychotics are associated with different effects on glucose and lipid metabolism. These studies offer generally consistent evidence that clozapine and olanzapine treatment is associated with an increased risk of diabetes mellitus and dyslipidemia. Inconsistent results and a generally lower effect in studies reporting an effect suggest a limited or increased risk for diabetes mellitus and drug-induced dyslipidemia during risperidone treatment despite a comparable number of published data. A similarly smaller and inconsistent finding suggests a limited or increased risk of diabetes or dyslipidemia during quetiapine treatment, but this is based on less published data than is available for risperidone. The absence of retrospective database studies and little or no relevant published data from clinical trials make it difficult to draw conclusions about the risk of zotepine or amisulpride, although amisulpride appears to have a lower risk of treatment-related dyslipidemia compared with olanzapine. With increasing data from clinical trials, but little or no currently published data from large retrospective database analyses, there is currently no evidence to suggest that ziprasidone and aripiprazole treatment is associated with an increased risk of diabetes, dyslipidemia, or other adverse effects on glucose or lipid metabolism. Limited controlled studies support the hypothesis that clozapine and olanzapine may have a direct effect on glucose regulation independent of adiposity. The results of studies in this area are relevant to primary and secondary prevention efforts aimed at addressing the multiple factors that contribute to the increased prevalence of type 2 diabetes mellitus and cardiovascular disease in populations frequently treated with second-generation antipsychotics [31].

The occurrence of pneumonia in patients suffering from Alzheimer’s disease is most likely favored by anti cholinergic action and blockade of the H1 receptor, which causes difficulty in swallowing, sedation and aspiration of swallowed contents. Both atypical and typical antipsychotic use in elderly patients is associated in a dose-dependent manner with the risk of community-acquired pneumonia [32]. There have also been cases of deep vein thrombosis when taking typical and atypical antipsychotics [23]. A growing number of observational studies indicate an increased risk of venous thromboembolism (VTE) in antipsychotic users. Although the use of certain antipsychotics is associated with VTE, current data cannot conclusively confirm differences in VTE rates between first and second-generation antipsychotics or between individual compounds, nor identify which antipsychotics have the lowest risk of VTE [33]. Hypotension, especially orthostatic, is a frequent phenomenon that occurs with the use of atypical antipsychotics, especially after the use of clozapine (9%), quetiapine (7%), risperidone and olanzapine (5%). Hypotension can lead to dizziness and falls [34]. QTc interval prolongation associated with antipsychotics is a potential risk for the development of life-threatening arrhythmias. The risk is higher when the QTc is greater than 0.45 seconds [35]. Other drug interactions with antipsychotics potentially increase the risk of adverse events, including QTc prolongation [36]. Both the effect and the side effects of antipsychotics derive from their mechanism of action, as well as their receptor profile. Each antipsychotic is unique in its combination of these effects.
The most common adverse effects of antipsychotics are shown in Table 1 [37].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sedation</th>
<th>EPS</th>
<th>Orthostatic hypotension</th>
<th>Anticholinergic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluphenazine</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+++</td>
<td>0</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Note: 0: minimal; +: low; ++: moderate; +++: high; ++++: very high.

People suffering from Alzheimer’s disease are extremely sensitive to the side effects of antipsychotics, much more so than the people for whom antipsychotics were originally intended, namely those suffering from schizophrenia. Namely, schizophrenia appears in young adulthood and the average doses of antipsychotics in the treatment of schizophrenia are intended for this age. Therefore, patients with dementia need significantly lower doses of antipsychotics, which are shown in Table 2 [39].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial dose</th>
<th>Dose titration</th>
<th>Maximum daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>0.25-0.5 mg (1–2 times daily)</td>
<td>0.25 mg for 3–7 days</td>
<td>1 or 2 mg</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5-5 mg (once daily)</td>
<td>2.5–5 mg for 3–7 days</td>
<td>7.5–10 mg</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>25-50 mg (twice daily)</td>
<td>50 mg in 2 doses for 3–7 days</td>
<td>200 mg</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>2-5 mg</td>
<td>2–5 mg for 3–7 days</td>
<td>10 mg</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.25-0.5 mg (1–2 times daily)</td>
<td>0.25 mg for 3–7 days</td>
<td>1 or 2 mg</td>
</tr>
</tbody>
</table>

Most guidelines recommend non-pharmacological measures as first-line therapy for non-cognitive disorders in Alzheimer’s disease. When non-pharmacological measures of dementia therapy do not give results, it is necessary to consider indications for the use of pharmacological agents, and when it comes to psychotic symptoms, atypical antipsychotics are primarily used, primarily risperidone, olanzapine, quetiapine and aripiprazole (Table 2) [39].

Among atypical antipsychotics, risperidone has been the most studied in patients with Alzheimer’s disease, showing moderate efficacy with a generally tolerable side-effect profile at low doses, being relatively inexpensive and widely available, so it is often used in these patients [40]. Available evidence shows that risperidone, olanzapine and aripiprazole show modest benefits in the treatment of aggression and psychosis over 6–12 weeks in people with Alzheimer’s disease [41]. Each antipsychotic has a unique side effect profile affecting individuals differently. It is necessary to bear in mind the warning for the use of atypical antipsychotics that there is a greater risk of a fatal outcome due to serious ventricular arrhythmias and sudden cardiac death, but also stroke, as well as the occurrence of pneumonia, so for these reasons it is very important to weigh the benefits and risks of using these drugs [38,39].

Conclusion

Although the available evidence does not support atypical antipsychotics as a mandatory treatment for behavioral symptoms in Alzheimer’s disease, each case should be carefully considered, especially since there are no effective alternative drugs for treatment [42]. In addition to memory loss, behavioral and psychological symptoms of dementia (BPSD) increase the burden of the disease and further reduce the quality of life of Alzheimer’s patients and their caregivers. Common symptoms of behavioral disorders thought to be targeted by antipsychotics include: impaired problem-solving ability, difficulty maintaining emotional control, agitation, aggression, delusion, apathy, impulsivity, depression, and hallucinations. Mild symptoms of behavioral disorders can be alleviated by non-pharmacological therapy such as psychosocial support, relaxation techniques, reduction of stress in the environment (for example noise), correction of impaired vision and hearing, music therapy and regulation of the daily rhythm. However, in the case of severe restlessness, aggressiveness and delusions, antipsychotic drugs are a powerful therapeutic tool in alleviating these symptoms [43]. At the same time, when introducing antipsychotics, the “start low go slow” principle is extremely important, and the maximum dose should not be higher than 1/3 of the average dose in the treatment of schizophrenia. Unlike schizophrenia, where the use of antipsychotics is continuous, in patients with Alzheimer’s disease they are used for a short period of time, and the therapy is gradually discontinued when the symptoms improve. The largest body of evidence currently exists for risperidone, which is the second oldest atypical antipsychotic widely used off-label for the treatment of Behavioral and Psychological Symptoms of Dementia (BPSD), including agitation, aggression and psychosis [44]. The second antipsychotic according to the amount of evidence is aripiprazole, and olanzapine and quetiapine can also be used [45]. In all people suffering from Alzheimer’s disease who have been treated with an antipsychotic, daily control of blood pressure, pulse rate, state of consciousness, i.e. degree of sedation and possible development of Extra Pyramidal Side effects (EPS) is required. Severity and frequency of symptoms and global functioning and quality of life must always be monitored during treatment. If adverse reactions are observed, it is necessary to immediately lower or stop the therapy. With this method of administration, the probability of severe adverse reactions is much lower. In recent years, many papers have been published on the treatment of behavioral disorders and psychotic disorders in Alzheimer’s disease using antipsychotic drugs, with conflicting conclusions, and the debate in the scientific world is still intense.

References