Searching for new drugs for the treatment of dementia-related psychosis

Poszukiwanie nowych leków w terapii psychozy związanej z otępieniem

Correspondence to/Adres do korespondencji:

Alicja Zakrzewska-Sito
Department of Pharmacology
Institute of Psychiatry and Neurology
9 Sobieskiego St.
02-957 Warsaw, Poland
e-mail: azakrzewska@ipin.edu.pl

Alicja Zakrzewska-Sito [ID], Julita Kuczyńska [ID]

Department of Pharmacology, Institute of Psychiatry and Neurology, Warsaw, Poland

Abstract

Purpose: Along with the aging process, we can observe a deterioration of cognitive functions with the simultaneous occurrence of behavioural and psychological symptoms in the elderly population. Dementia with accompanying psychosis is becoming a growing problem, not only in medical but also in social terms. This article focuses on the issues related to the occurrence of psychosis in dementia, and the need to develop new treatment.

Views: Psychosis in the elderly is different from that occurring with schizophrenia, as it is characterized by a different course and frequent resistance to treatment. In case of elderly patients, psychosis is probably associated with dysregulation of the serotonergic system. Due to the difficulties in using pharmacology in this age group, it is very important to individualize treatment. Antipsychotics are the main treatment used but they have many side effects, so in fact there is a lack of effective and safe solutions. Although pimavanserin is considered to be an effective alternative in the treatment of psychosis, it also carries a higher risk of mortality in this age group.

Conclusions: The search for new, effective and safer drugs in the treatment of dementia-related psychosis works in many directions. New animal models are emerging that allow the screening of various drug "candidates". The available research suggests that the serotoninergic system is a good direction for the search for new therapeutic solutions. As the number of elderly people with dementia increases, there is a great medical need to make it easier for them and their caregivers to function.

Key words: psychosis, BPSD, serotonergic system.

Streszczenie

Cel: Wraz z procesem starzenia u części społeczeństwa można zaobserwować pogorszenie funkcji poznawczych z jednoczesnym występowaniem zaburzeń behawioralnych i psychologicznych. Otępienie i współwystępująca z nim psychoza stają się coraz większym problemem nie tylko medycznym, lecz także społecznym. W artykule omówiono problematykę związaną z występowaniem psychozy w otępieniu oraz wskazano na konieczność poszukiwania nowych leków.

Poglądy: Psychoza występująca u osób starszych różni się od psychozy występującej w przebiegu schizofrenii. Zaburzenia psychotyczne u chorych w wieku podeszłym charakteryzują się innym przebiegiem i częstą opornością na leczenie, a psychoza jest prawdopodobnie związana z dysregulacją układu serotoninergicznego. Ze względu na trudności stosowania farmakologii u osób w wieku podeszłym bardzo ważna jest indywidualizacja leczenia. Podstawowymi lekami są leki przeciwpsychotyczne, ale ich stosowanie wiąże się z wieloma działaniami niepożądanymi. Brakuje skutecznych i bezpiecznych rozwiązań. Jak się okazuje, skuteczną alternatywą w leczeniu psychozy jest pimawanseryna, ale lek ten może również zwiększać ryzyko śmiertelności u osób starszych.

Wnioski: Poszukiwanie nowych, skutecznych i bezpieczniejszych leków w terapii psychozy związanej z otępieniem działa wielokierunkowo. Powstają nowe modele zwierzęce, które pozwalają na badanie kandydatów na leki. Dostępne badania sugerują, że dobrym kierunkiem poszukiwania nowych rozwiązań terapeutycznych jest układ serotoninergiczny. Ze względu na to, że zwiększa się liczba osób starszych z otępieniem, istnieje konieczność poszukiwania nowych leków, by ułatwić im oraz ich opiekunom funkcjonowanie.

Słowa kluczowe: psychoza, BPSD, układ serotoninergiczny.

INTRODUCTION

Increasingly higher life expectancy is one of the most distinctive demographic features of today's population. Elderly people are becoming a growing group of patients in need of special attention. As part of the aging process, a deterioration of cognitive functions is often observed with the simultaneous occurrence of behavioural and psychological disorders, the so-called BPSD (behavioural and psychological symptoms of dementia) [1]. The term was introduced by the International Psychogeriatric Society in 1994 [2]. BPSD consists of symptoms such as psychosis, agitation, irritability, anxiety, confusion, aggression, depression, apathy, sleep problems, and reduced sensitivity to emotional and physical stimuli [3, 4]. Initially, patients display impaired cognitive functions, with the onset of fear and depression, followed by apathy, hyperactivity and anxiety [5]. In the moderate and advanced stages of this process, delusions, hallucinations and aggression might also occur at times [6].

Dementia with psychosis is becoming a particular problem in both medical and social context. This generates a growing medical necessity to meet the needs of elderly people and to improve the quality of life of their caregivers, where they are available. It would be recommendable to develop an optimal therapy that would provide for treatment, even if only of a causal sort, that could stop the progression of the disease and even reverse the symptoms of psychosis in elderly people with dementia.

The aim of this article is to present the concerns related to the occurrence of psychosis in dementia and to disseminate knowledge on the issues related to the search for new drugs in this field.

DEMENTIA-RELATED PSYCHOSIS

The following have a great influence on the appearance of psychosis among the elderly: disorders of the metabolism, perfusion in the parietal, frontal or temporal cortex, genetic factors, medications used, previous brain surgery, coexistence of other diseases, worse general health, age of the patient and possible lack of support in the immediate circles. Studies indicate that the occurrence of delusions in patients with Alzheimer's may be related not only to age, but also to symptoms of depression and aggression [7]. The appearance of hallucinations is probably associated with growing dementia, extrapyramidal symptoms, and movement disorders. Moreover, antihypertensive drugs may contribute to the appearance of delusions, and anti-anxiety drugs to hallucinations [8]. There are also studies that indicate genetic polymorphisms, for example of the apolipoprotein E genotype, the nicotinic receptor, and dopamine and serotonin transporters as possibly being responsible for the psychosis phenotype [9, 10]. The appearance of symptoms of psychosis accelerates the progression of cognitive dysfunction, the appearance of depression, and worsens disability [7]. 41% of patients with dementia/BPSD experience hallucinations, and slightly more (63%) suffer from delusions [4]. Psychosis is more common in vascular dementia than in Alzheimer's disease (54% vs. 36%). There is a correlation between psychotic disorders and the location of vascular changes, e.g. visual hallucinations may appear as a consequence of an occipital lobe stroke [11].

Psychosis in the elderly differs from that in middle-aged or younger people (Table 1). Visual hallucinations, delusions of being robbed, poisoned or abandoned, as well as delusional jealousy are predominant in the elderly. Delusional psychosis constitutes the highest percentage of psychosis in this age group [12], and is more common among women [13]. Psychosis usually appears only in the middle stage of the disease and progresses with worsening cognitive impairment. The most common delusions in dementia include those connected to misidentification, and somewhat less frequently are paranoid delusions [14]. In the case of misidentification, these may be not delusions but misidentification syndromes associated with cognitive disorders [14]. The term of misidentification is related to Capgras syndrome and Fregoli syndrome, which belong to delusional misidentification syndromes that may accompany mental disorders in dementia [15, 16]. Capgras syndrome can occur as a result of damage to the cerebral cortex, which connects the facial recognition center with the limbic system responsible for assigning emotional states to recognized objects. Capgras syndrome can be a consequence of mechanical trauma, stroke and the rupture of aneurysms. The person affected by the disorder described is under the impression that relatives have been changed into doubles, and are strangers with the same appearance and behaviour as the people known to them. There is a lack of trust, and often even aggression, towards the "fraudster" [17, 18]. Another disorder that belongs to the so-called delusional misidentification syndrome is Fregoli syndrome. Patients are convinced that people, objects and places have changed or lost their identity. Such delusions may be a consequence of diabetes and hypothyroidism. Fregoli syndrome also affects people with arterial hypertension, which is often experienced by the elderly. Patients claim that people are in fact the same person who constantly changes their appearance and clothes [19, 20]. Patients may begin to develop delusions of persecution, thinking that someone is eavesdropping or watching them. Delusions in the form of being robbed or poisoned are common in the elderly, increasing their anxiety and aggression. Visual hallucinations are usually more common in Parkinson's disease and in dementia with Lewy bodies. In this case, the affected patients perceive non-existent figures and objects [21]. There are studies in which up to 90% of patients experience visual, and rarely audito-

Table 1. Comparison of psychosis in the course of schizophrenia vs. dementia

Psychosis in the course of schizophrenia	Psychosis in the course of dementia
Auditory hallucinations dominate (commenting voices, orders) (24)	Visual hallucinations dominate (25)
Delusions of reference, grandeur, persecution (26)	Delusions of being robbed, poisoned or abandoned, delusional jealousy (27, 28)
Sensitivity to the effects of antipsychotic drugs (29, 30)	Questionable effectiveness of antipsychotic drugs, dangerous side effects (29, 31)
Hypothetical neurobiological background: dysregulation of the dopaminergic system (32)	Hypothetical neurobiological background: dysregulation of the serotonergic system (33-36)

ry, hallucinations (8-13%) in the course of Parkinson's disease [22]. Among the elderly auditory, olfactory and gustatory hallucinations usually occur as symptoms accompanying visual hallucinations [12]. When visual hallucinations occur, they should be differentiated from Charles-Bonnet syndrome, which is associated with the occurrence of ophthalmic diseases due to cataracts, glaucoma or diabetic retinopathy. The patient then sees non-existent people, animals and objects [23].

Psychotic disorders associated with BPSD are characterized by frequent resistance to treatment. Due to the difficulties in applying pharmacology, it is very important to individualize the treatment process. Non-pharmacological therapy is used as the first-line therapy [37]. In the next stage, drugs are included.

NON-PHARMACOLOGICAL THERAPY

Non-pharmacological therapy is used in patients with BPSD at the initial stage of treatment or as additional support for drug therapy.

Non-pharmacological methods include:
- training of caregivers, aimed at education, providing support, reducing stress, solving problems, teaching them to facilitate tasks and detect the factors causing specific behaviours in patients [37];
- creating a friendly, familiar and safe environment for the patient (environmental therapy);
- consolidating the skills still possessed by the patient, recreating those that have recently been lost (occupational therapy);
- memory training, reality orientation exercises (cognitive therapy);
- evoking memories with the help of stimulating materials, such as photographs or souvenirs (reminiscence therapy) [38];
- physical activity that improves mood, sleep quality, has a relaxing effect (occupational therapy) [39];
- music therapy and aromatherapy to combat depression, agitation and aggression [40-42];
- light therapy, multi-sensory stimulation – improving well-being, sleep problems;
- stimulating appropriate social behaviour, reducing anxiety (validation therapy) [38].

By using non-pharmacological therapy it is possible to alleviate some behavioural disorders in a person with psychosis, occupy their time, prevent confusion, calm them down, and improve cognitive functioning.

PHARMACOLOGICAL THERAPY

Antipsychotic drugs are among the primary medications used in the treatment of BPSD psychosis. Previously, only first-generation antipsychotic drugs, e.g. haloperidol perazine, were used. Currently, when it comes to patients with dementia, the use of these drugs is limited because it is associated with a high probability of side effects, such as muscle stiffness, tremors, depression [43]. Elderly people are more often treated with second-generation antipsychotics, which disrupt the extrapyramidal system to a lesser extent and are more effective [44]. These drugs are designed to reduce the symptoms of psychosis and the associated agitation and aggression. The clinical trials conducted to date reveal that in the treatment of Parkinson's patients with accompanying depressive symptoms, quetiapine, a benzodiazepine derivative may be the preferred choice. In the treatment of psychosis, quetiapine works by blocking the dopaminergic and serotonergic $5\text{-}HT_2$ receptors. Moreover, it exhibits a high degree of affinity with histamine H_1 and α_1-adrenergic receptors, rather high level in relation to α_2-adrenergic receptors, and to a lesser extent to $5\text{-}HT_{1A}$ serotonergic receptors [45]. Risperidone, olanzapine and clozapine have a similar spectrum of action. Treatment with clozapine, which blocks the dopamine D_2 and D_3 receptors, the serotonin $5\text{-}HT_{2A}$ and $5\text{-}HT_{2C}$ receptors, the cholinergic muscarinic receptors, the α_1- and α_2-adrenergic receptors, and the histamine H_1 receptors is used in drug-resistant psychosis. Unfortunately, the use of clozapine carries the risk of agranulocytosis [46]. Antagonism towards $5\text{-}HT_{2A}$ receptors, e.g. in the nigrostriatal region, increases dopaminergic activity and thus reduces the likelihood of extrapyramidal side effects. Blocking the muscarinic receptors may cause disturbances in consciousness, deterioration of cognitive functions, cardiological disorders (arrhythmias, tachycardia), ophthalmic abnormalities (decreased visual acuity), constipation or difficulty urinating [47-49]. With a blockade of the $5\text{-}HT_{2A}$ and $5\text{-}HT_{2C}$ receptors, patients may gain weight due to in-

creased appetite [50]. Weight gain, somnolence and cognitive decline are associated with blocking the histamine H_1 receptors. Studies support some efficacy of risperidone and olanzapine in the treatment of aggression accompanying psychosis. Risperidone shows an advantage over aripiprazole in the treatment of delusions and hallucinations in dementia [51, 52]. Aripiprazole and amisulpride act mainly on dopamine receptors and are therefore moderately effective.

As discussed, the effect of antipsychotics is not ideal because these drugs have a number of side effects and, moreover, can cause death in dementia patients due to possible cardiocerebral incidents [43, 53]. In 2005, the US Food and Drug Administration decided to order manufacturers to include a "black box warning" on the labels of second-generation antipsychotic drugs due to the high risk of mortality in the elderly. Three years later, this order was extended to include second-generation drugs, i.e. clozapine, olanzapine, quetiapine and risperidone, and first-generation drugs, i.e. fluphenazine, haloperidol and chlorpromazine [54].

During the pharmacological treatment of psychosis, the need for proper control of the dosage of procognitive drugs in elderly people with dementia, i.e. cholinesterase inhibitors (rivastigmine, donepezil, galantamine) and memantine, should not be ignored. Apart from antipsychotics, antidepressants/drugs affecting insomnia, and serotonin reuptake inhibitors, i.e. trazodone and citalopram are also used in BPSD patients [55]. Citalopram has been shown to be as effective and even better-tolerated than perphenazine/risperidone in BPSD patients in two published randomized controlled trials. Escitalopram turned out to be even more effective than citalopram in the analysis of two clinical trials [56].

The effect of the available drugs is still insufficient. The lack of an effective alternative to the currently used drugs in BPSD acts as a motor in the search for new pharmacological solutions. The aim is to develop an optimal therapy allowing for treatment, even of the causal kind, that can stop the progression of the disease and even reverse the symptoms of psychosis in the elderly. The priority is to alleviate the symptoms of psychosis, depression, anxiety syndromes or cognitive disorders without disturbing motor functions.

SEARCHING FOR NEW SOLUTIONS IN THE TREATMENT OF PSYCHOSIS IN THE ELDERLY

The search for new, effective and safer drugs for BPSD goes in many directions. A review of clinical trials on the treatment of dementia-related psychosis reveals that the best alternative to clozapine and quetiapine so far is the treatment of patients with pimavanserin, which affects the serotonin receptors [36, 57]. This drug was approved

by the FDA (Food and Drug Administration) in 2016 for the treatment of psychosis in Parkinson's disease. In vitro studies indicated its inverse agonism at the 5-HT$_{2A}$ receptors. Pimavanserin works in the treatment of hallucinations and delusions in the course of psychosis in the elderly. In a multicenter phase III study, its effect in the treatment of Parkinson's disease psychosis was tested. After applying the Scale for the Assessment of Positive Symptoms (SAPS), a 37% improvement in patients' condition was observed [36]. In a 12-week phase II clinical trial in patients with Alzheimer's disease, a significant pimavanserin treatment effect was found compared to placebo (delta –1.84, Cohen *d*-effect size 0.32). The effect was as assessed by using the NPI-NH (Neuropsychiatric Inventory-Nursing Home questionnaire quantifying behavioural changes in dementia). Moreover, this drug did not cause side effects on the extrapyramidal system and cognitive functions [58]. In another study, the use of pimavanserin gave better results in patients with more severe psychosis (delta –4.43, Cohen *d*-effect size 0.73). An over 30% improvement was achieved in 88.9% of patients [59]. In addition, a phase III clinical trial has recently been completed, to assess the efficacy of pimavanserin versus placebo in preventing the recurrence of psychotic symptoms in patients with dementia-related psychosis. The study included patients with various forms of dementia, i.e. dementia with Lewy bodies, dementia in Parkinson's disease, frontotemporal dementia and vascular dementia. The results suggest that pimavanserin reduces the risk of the occurrence of psychosis by 2.8 times compared to placebo in patients with dementia [60]. However, caution should be exercised when using pimavanserin as it may cause QT prolongation and even lead to death (there is a "black box warning" on the label).

A multicenter, randomized, 12-week phase III clinical trial of brexpiprazole in the treatment of agitation in Alzheimer's disease was completed recently. The study involved patients living in institutional or care facilities. This antipsychotic drug has been approved by the FDA for the treatment of schizophrenia. It is active mainly at the 5-HT$_2$ receptors, but is also a partial agonist at the 5-HT$_{1A}$, D_2 and D_3 receptors. The double-blind method with a 30-day observation was used. The efficacy, safety and tolerability of two doses of brexpiprazole (1 mg/day and 2 mg/day) were assessed. An improvement in agitation symptoms was shown compared with patients given the placebo. Brexpiprazole has been shown to be well tolerated. Side effects, such as insomnia, somnolence and residual agitation, have been reported [61]. Similar results were obtained in a 12-week phase III trial conducted in parallel [61].

Another drug that seems interesting in this context is lithium. As is well known, lithium is perfect for the treatment of bipolar disorder and other psychotic disorders involving agitation. In a recent phase II clinical trial, the efficacy of low doses (150-600 mg/day) in the treat-

ment of agitation/aggression with and without psychosis in patients with Alzheimer's disease was investigated. Work is currently underway to submit the results of this study. If lithium proves to have been effective, it will go to the third phase of research [62].

ANIMAL MODELS OF DEMENTIA-RELATED PSYCHOSIS

Animal models play a significant role in the search for new drug "candidates". There are models which reflect changes in the brain of people with Alzheimer's psychosis: transgenic mice overexpressing APP (amyloid precursor protein), 3xTg-AD – a model containing mutations of the APP gene, presenilin 1 M146V and tau P301L protein, and the 5xFAD model – associated with the accumulation of β-amyloid in the brain and a high content of Aβ42 as a result of the use of two human transgenes: the transgene encoding the APP protein with the "Swedish", "London" and "Florida" mutations and the transgene-encoding presenilin-1 with the M156L and L286W mutation [63]). In patients with Alzheimer's disease, an increased density of amyloid plaques, neurofibrillary tangles in the middle frontal cortex, and an increased level of abnormal tau protein in the entorhinal or temporal cortex are found [64]. The presented animal models based on genetic modifications in the future may be used in the search for new drugs acting on the psychotic symptoms of BPSD, i.e. aggression and agitation.

Another animal example that is likely to become a model of dementia-related psychosis is the natural model of spontaneous head twitching (SHT) in elderly rats over 18 months of age [65]. It turns out that with age some rats spontaneously begin to twitch their heads. Specific changes in the behaviour of aging rats resemble the behaviour of young animals following the administration of 5-HT$_{2A}$ agonists, i.e. LSD (D-lysergic acid diethylamide) and DOI (2,5-dimethoxy-4-iodoamphetamine). These psychotomimetic substances induce head twitches in rodents, a behaviour that may resemble the symptoms of psychosis in schizophrenic patients, and these behaviours are undoubtedly based on disturbances in serotonergic transmission [66, 67]. It has been observed that spontaneous head twitches in elderly rats can be inhibited by ketanserin, a 5-HT$_{2A}$ receptor antagonist, and pimavanserin, and enhanced by DOI, a 5-HT$_{2A/2C}$ agonist. No effect at all of amisulpride, an antagonist of D$_2$ and D$_3$ receptors, has been observed. Studies carried out on elderly rats twitching their heads spontaneously suggest that the serotonergic system plays an essential role in the psychosis of elderly people with dementia, and that new compounds should be developed in this direction [65].

THE ROLE OF THE SEROTONERGIC SYSTEM IN PSYCHOSIS IN THE ELDERLY

Based on the available literature, it can be concluded that not only the dopaminergic system is responsible for psychosis in dementia, but also the serotonergic system. This is indicated by the differences between psychosis in the course of dementia and schizophrenia (Table 1). The role of the serotonergic system can be associated with the occurrence of visual and auditory hallucinations in patients with Alzheimer's disease, associated with polymorphisms of the genes encoding serotonin receptors [68]. It is known that 5-HT$_6$ receptors, which are located only in the central nervous system, in particular in the limbic and cortical parts, are responsible for the cognitive sphere and well-being and are associated with the appearance of psychotic symptoms in patients with Alzheimer's dementia [34, 69]. In patients with Alzheimer's disease a lower density of 5-HT$_{2A}$ and 5-HT$_6$ receptors in the prefrontal cortex is observed compared to healthy elderly people [34]. The effect of the serotonin receptors 5-HT$_{1A}$, 5-HT$_2$, 5-HT$_3$, 5-HT$_4$ and 5-HT$_6$ on the change of cognitive functions, mood disorders or psychosis is observed in patients with Parkinson's disease [35]. The effect of 5-HT$_7$ antagonists in models of psychosis is also apparent. In a study by Waters *et al.* (2012) SB-269970, a 5-HT$_7$ antagonist attenuated amphetamine-induced rising on the hind limbs and axial circulation, and phencyclidine-induced hyperlocomotion in rats in an open field study [70]. Similarly, in the case of lurasidone, which is antagonistic to 5-HT$_7$ and shows partial agonism towards the 5-HT$_{1A}$ receptor in relation to the 5-HT$_{1A}$ receptor, it alleviates the deficits caused by the administration of phencyclidine [71].

CONCLUSIONS

To conclude, due to the fact that the elderly with dementia are beginning to constitute an increasing group of patients, it is very important to pay attention to their quality of life. Elderly people often find it difficult to cope. Their life in society can be disturbed, as can that of their caregivers. Psychosis is a very big problem, so finding new pharmacological solutions to treat dementia-related psychosis/BPSD is of great importance. There are no effective and safe drugs for psychotic disorders in this group of patients. The serotoninergic system seems to be a good direction to follow in the search for new drugs. This is indicated by the action of available drugs, the location of receptors, and the natural model of spontaneous head twitching (SHT) in elderly rats.

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