Dama International Journal of Researchers (DIJR), ISSN: 2343-6743, ISI Impact Factor: 1.018
Vol 3, Issue 02, February, 2018, Pages 27 - 35, Available @ www.damaacademia.com

Biopharmaceutical Aspect of Drugs Used in Psychosis (Hallucinations and Dellusions) Associated with Parkinson's Disease

Maria Lettisia Meo[1], Didik Hasmono[2]
Department of Clinical Pharmacy, Faculty of Pharmacy,
Airlangga University, Surabaya, Indonesia
E-mail: gwae23@gmail.com

Abstract
Parkinson's disease (PD) is the second most common neurodegenerative disease, exceeded only by Alzheimer's disease (AD). Psychosis can be a major problem in Parkinson's disease. Psychosis is a frequent complication of PD, and it is characterized mainly by visual hallucinations and delusions, which are often paranoid in flavor. Psychotic symptoms are present in up to 50% of patients with Parkinson's disease. These symptoms have detrimental effects on patients' and caregivers' quality of life and may predict mortality. Psychosis (hallucinations and delusions) occurring in the context of Parkinson's disease may be primary, reflecting a progression of the underlying disease process, or secondary to the use of dopaminomimetic drugs. Attempts to reduce dopaminomimetic drugs or the initiation of antipsychotics can exacerbate motor symptoms in Parkinson's disease with psychosis (hallucinations and dellusions). Psychosis in Parkinson's disease (PDP) often responds to low doses of atypical neuroleptics but adverse event but the side effects and safety of each drugs should still be observe. Therefore the selection of appropriate therapy is expected to improve the quality of life of psychosis patients with Parkinson's disease

***Keywords**: Antipsichosis, Parkinson Desease, Psychosis*

I. INTRODUCTION

Parkinson's disease is a synucleinopathy resulting in progressive neuro degeneration marked by motor dysfunction and non-motor symptoms including psychosis (Cummings, *et al*., 2014). In some Parkinson's disease patients, Parkinson's disease with psychosis appears even before motor symptoms occur or before any treatment is given, and is thus a core non-motor feature of their Parkinson's disease (Stahl, 2016). In a retrospective study of 143 patients with PD admitted to a neurology ward in a community hospital in a 6-year period, 37% were admitted for motor complications and 24% for psychosis. Mean duration of hospitalization was 11 days compared with 7 days in age-matched controls without PD (Sarva & Henchcliffe, 2016). Psychosis is a common and distressing group of psychiatric symptoms affecting people with PD, usually manifesting as hallucinations and delusions (Ballard, *et al*., 2015). Psychotic symptoms, particularly visual hallucinations and paranoid delusions, occur in up to 40% of patients with Parkinson's disease (PD) who receive dopamine (DA) replacement therapy. Psychotic symptoms in PD psychosis (PDP) are a significant cause of distress to patients and their caregivers, and are associated with greater functional impairment, caregiver burden, nursing home placement, and increased mortality. As a result, antipsychotic drug treatment is often used to manage persistent and troublesome psychotic symptoms in PD patients (Meltzer, *et al*., 2010). Best-practice treatment guidelines promote initial consideration of comorbidities and reduction of dopaminergic therapy. However, these approaches are often insufficient and few other therapeutic options exist. Typical antipsychotics can cause profound dopamine D2 antagonism and worsen parkinsonism (Cummings, *et al*., 2014). The low doses of risperidone and olanzapine, two atypical antipsychotic drugs with diminished liability to cause EPS, also worsen motor symptoms in PDP, even at the minimal doses needed to treat psychotic symptoms. Quetiapine, another atypical antipsychotic drug, has been reported in a number of open-label studies to reduce psychosis in PD without worsening motor symptoms, but sedative and hypotensive effects also limit its tolerability (Meltzer, *et al*., 2010). Clozapine shown antipsychotic benefit without worsening motor symptoms in several randomized controlled trials. Pimavanserin is a selective serotonin 5-HT2A inverse agonist without dopaminergic, adrenergic, histaminergic, or muscarinic affinity, and is in development as a treatment for Parkinson's disease psychosis (Cummings, et al., 2014).

I. PARKINSON'S DISEASE AND PSYCHOSIS

Parkinson's disease (PD) is the second most commonst neurodegenerative disease, exceeded only by Alzheimer's disease (AD). I n 1817, James Parkinson made the seminal observations on this disorder defining a specific neurodegenerative illness characterized by bradykinesia, resting tremor, cogwheel rigidity, and postural reflex impairment (Apetauerova, 2012). Clinically, PD is characterized by rest tremor, rigidity, bradykinesia, and gait impairment, known as the "cardinal features" of the disease. Additional features can include freezing of gait, postural

instability, speech difficulty, autonomic disturbances, sensory alterations, mood disorders, sleep dysfunction, cognitive impairment, and dementia, all known as nondopaminergic features because they do not fully respond to dopaminergic therapy (Olanow & Schapira, 2013). Psychosis, defined as hallucinations and delusions, is present in up to half of patients with Parkinson's disease, but there is some debates about its cause. In some Parkinson's disease patients, Parkinson's disease with psychosis appears even before motor symptoms occur or before any treatment is given, and is thus a core non-motor feature of their Parkinson's disease (Stahl, 2016). From a pharmacologic perspective, PDP likely represents an imbalance between dopamine and serotonin systems in the brain. Treatment of PDP, consisted of either lowering the doses of dopaminergic antiparkinsonian agents or adding another antipsychotic agents, although the efficacy of antipsychotics for parkinson's disease with psychosis has been poorly documented and is often associated with worsening of motor symptoms of Parkinson's disease (Stahl, 2016).

I. PATHOPHISIOLOGY OF PSYCHOSIS WITH PARKINSON'S DISEASE

The pathophysiology of PDP is not entirely understood but is likely multifactorial. Many PD-related factors are associated with the development of psychotic symptoms, including older age of disease onset, being older than 65 years of age, more advanced disease, fewer years of education, female gender, impaired visual acuity and higher doses of dopamine agonists. Traditionally, the use of dopamine receptor agonists as a therapy for PD was thought to contribute to an increased likelihood of developing PDP (Broadstock, Ballard, & Corbett, 2014). Higher PD medication doses have been implicated, and hypersensitization of dopaminergic receptors in the striatum due to chronic stimulation by medications may cause limbic dysfunction and misattribution of internal stimuli originating from the external world (Ravina, *et al*., 2007; Zahodne and Fernandez, 2008; Sarva & Henchliffe, 2016). While there remains no clear association between dopamine treatment and PDP, other neurotransmitter systems have also been investigated, most notably the cholinergic and the serotonergic systems. Striatal cholinergic neurons become overactive as PD progresses, and this imbalance between dopaminergic and cholinergic systems has been suggested to play a role in the development of PDP, as anticholinergic medication use can also lead to hallucinations (Broadstock, Ballard, & Corbett, 2014). Dysfunction in serotonergic and cholinergic function may contribute to PDP (Sarva & Henchcliffe, 2016). The degeneration of the raphe nuclei altering the inputs to the cortex and caudate–putamen and indirectly affecting cholinergic function (Broadstock, Ballard, & Corbett, 2014). The serotonergic system is known to be affected in PD, with ongoing degeneration of the raphe nuclei altering inputs to the cortex and striatum, and indirectly affecting the cholinergic system. Moreover, stimulation of the 5HT2A receptors on cortical glutaminergic neurons leads to increased dopamine release in the nucleus accumbens (NA) and ventral tegmental area (VTA). This activation of the VTA and NA can lead to hallucinations (Sarva & Henchcliffe, 2016). Local stimulation of 5-HT2A receptors of glutamatergic neurons in the prefrontal cortex leads to subsequent activation of dopaminergic neurons within the ventral tegmental area as well as elevating glutamate levels within the nucleus accumbens (Broadstock, Ballard, & Corbett, 2014).

II. MECHANISM OF ANTIPSYCGOSIS DRUGS OR NEUROLEPTICS

The affinity of neuroleptic drugs for the D2-receptor correlates closely to their antipsychotic potency, and the blockade of D2-receptors in the forebrain is believed to underlie their therapeutic actions. Unfortunately, blockade of D2-receptors in the basal ganglia usually results in movement disorders. Some neuroleptics, in addition to blocking D2-receptors, are also antagonists at 5HT2 receptors, and it is thought by some that this may somehow reduce the movement disorders caused by D2-antagonism, which can be seen in figure 1 (Neal, 2012).

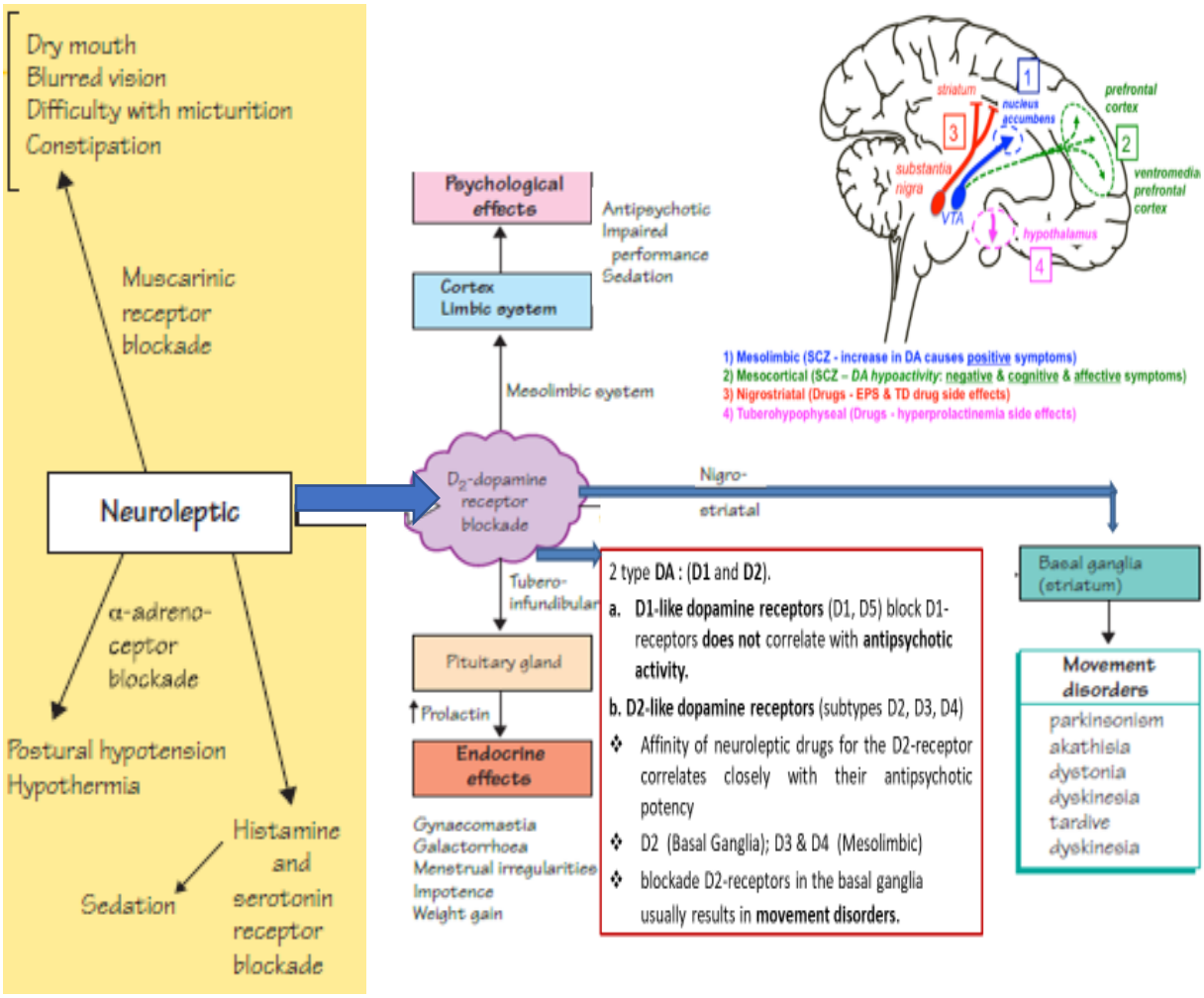
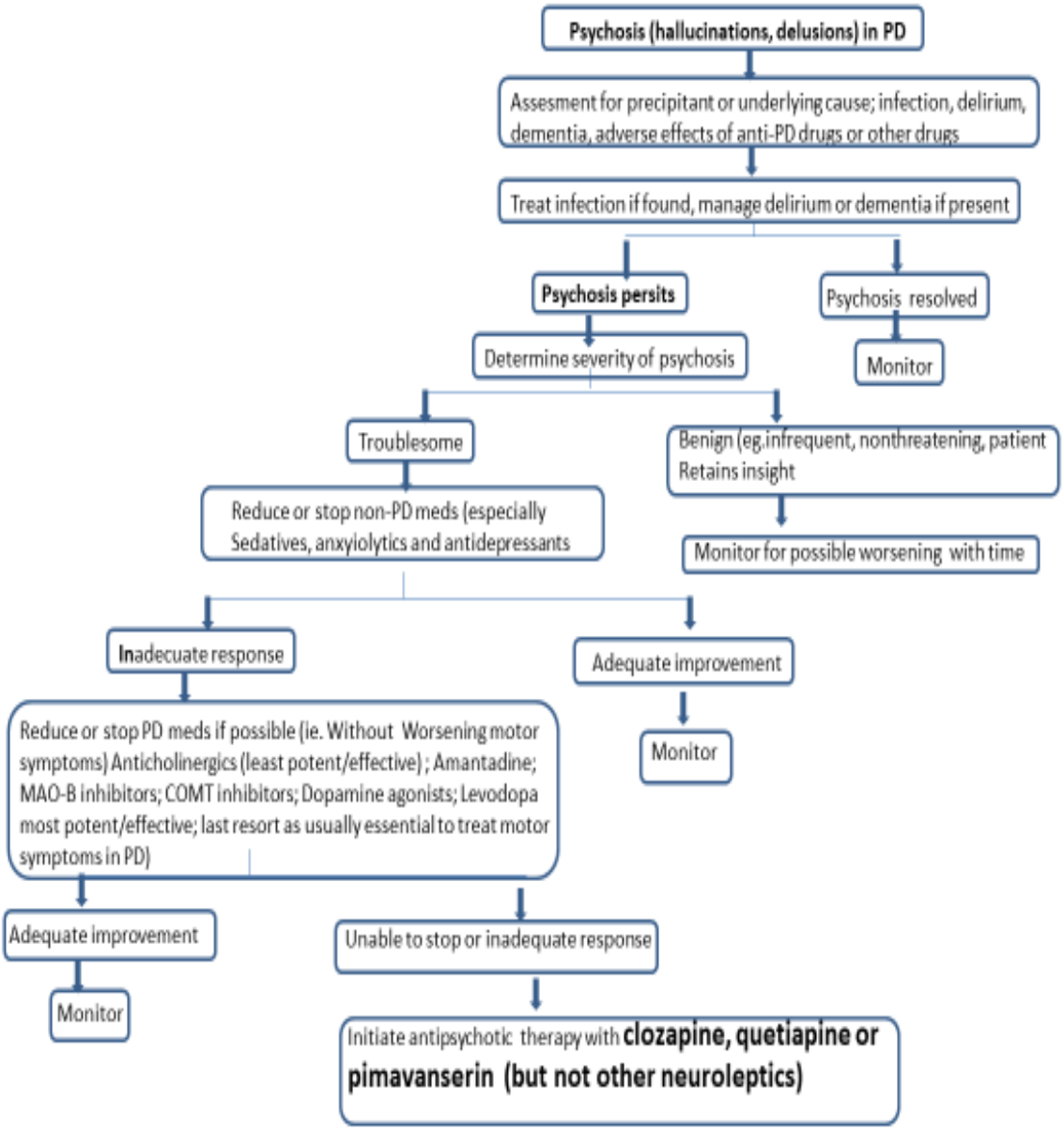


Figure 1. Mechanism and receptor blockade of Neuroleptic (Neal, 2012; Olanow & Schapira, 2013)

III. CURRENT TREATMENT OF PSYCHOSIS WITH PARKINSON'S DISEASE

A review article stated that the anti-Parkinson's diseases medications may need to be reduced. Clearly such a reduction will, at some point, result in worsened motor function (Friedman, 2013). Antiparkinsonian drugs may be reduced or stopped in reverse order of their potency and effectiveness if hallucinations are causing disability; the suggested sequence begins with anticholinergic drugs, followed by amantadine, monoamine oxidase type B (MAO B) inhibitors, catechol-O-methyl transferase (COMT) inhibitors, and dopamine agonists. Carbidopa/levodopa should be the last of a drug combination to be reduced, since it is the most effective antiparkinson agent and least likely to cause psychosis. Management of psychosis in patients with parkinson's diseases can be seen in table 1 (Friedman, 2013; Tarsy, Hurtig & Dashe, 2016).

Table 1. Management of psychosis in patients with parkinson's diseases



Clozapine was the first antipsychotic that was recognized as safe and effective for the treatment of psychotic symptoms in patients with PD (Divac, *et al*., 2016). Many open label reports involving hundreds of patients at multiple centers attested to clozapine's efficacy without impairment of motor function (Friedman, 2013). The efficacy and safety of extremely low doses of clozapine in the treatment of psychosis in PD patients were confirmed in two double-blind, placebo-controlled clinical trials. These doses are approximately tenfold lower than doses indicated in the treatment of schizophrenia. Current practice now is to introduce clozapine to PD patients in doses ranging from 6.25 to 12.5mg/d and not to exceed 50mg/d. These doses dramatically reduce psychotic symptoms without worsening the motor symptoms (Divac, *et al*., 2016). Clozapine is approved in some countries for the treatment of PDP, but not in the United States. The American Academy of Neurology (AAN) task force on PD only suggests that clozapine be "considered," along with quetiapine, despite the evidence of efficacy in the former and failure in the latter (Friedman J. H., 2013).

It has been hypothesized that clozapine, at doses which are effective in PDP (6.25– 75 mg/day), 3–10% of the doses usually used to treat schizophrenia, does not sufficiently block limbic DA D2 receptors to achieve an antipsychotic

effect through DA D2 receptor blockade, and that a more likely basis for its antipsychotic activity in PDP is serotonin (5-HT) 2A receptor blockade. This is consistent with abundant evidence that hallucinations can result from the stimulation of cortical 5-HT2A receptors and can be blocked by 5-HT2A inverse agonists or antagonists and that 5-HT2A antagonism is integral to the antipsychotic properties of multireceptor acting atypical antipsychotic drugs, such as clozapine and quetiapine (Meltzer, *et al*., 2010).

Other concerns regarding to the use of clozapine in PD patients are anticholinergic effects, metabolic disturbances, and the risk of agranulocytosis. There is a strict blood count monitoring required during treatment with clozapine. This means weekly blood draws during the first six months of clozapine administration, every other week for the second six months and after that every four weeks for the duration of the treatment, and also frequent visits to the pharmacy ("no blood, no drug"). It is also reported as the main reason for the discontinuation of clozapine in nursing homes, even in patients with clear therapeutic benefits (Divac, *et al.*, 2016).

Quetiapine, another atypical antipsychotic drug, has been reported in a number of open-label studies to reduce psychosis in PD without worsening motor symptoms, but sedative and hypotensive effects also limit its tolerability (Meltzer, et al., 2010). Furthermore, in three placebo-controlled, double-blind, randomized trials, quetiapine failed to show superiority to placebo on measures of psychosis in PDP (Meltzer, *et al*., 2010). Despite lack of clear evidence for its efficacy, quetiapine is widely prescribed for the treatment of psychosis in patients with PD. Its safety profile probably makes it an attractive alternative to clozapine, especially as quetiapine does not require vigilant blood count monitoring (Divac, *et al*., 2016). Nevertheless, it remains widely used as the initial drug treatment for PDP, at doses from 25 to 300 mg/day, and is the drug of choice for PDP according to the American Academy of Neurology Practice Parameters Task Force on the treatment of PD, clozapine is recommended only after quetiapine fails to manage psychotic symptoms (Meltzer, *et al*., 2010).

Sedation and postural hypotension are the most frequently reported side effects of quetiapine in doses used in PD patients. However, recent findings by Weintraub *et al* showed increased mortality in PD patients treated with quetiapine, with hazard ratio of death compared to nonuse of an antipsychotic of 2. Even higher risks were shown for olanzapine and risperidone, but no results were shown for clozapine (Weintraub, *et al*., 2016; Divac, *et al*., 2016).

In April 2016 the US Food and Drug Administration (FDA) approved pimavanserin for treatment of hallucinations and delusions associated with PD in the United States, thus becoming the first drug registered for treating psychotic symptoms in any of the movement disorders. The efficacy of pimavanserin in the treatment of schizophrenia is currently being investigated (Divac, *et al*., 2016; Sarva & Henchclife, 2016). Prior to that, general treatment guidelines were limited in use of pharmacotherapy, mainly relying on use of quetiapine and clozapine (Zahodne & Fernandez, 2008; Jakel & Stacy, 2014; Sarva & Henchclife, 2016).

Pimavanserin is a nondopaminergic, selective serotonin 5-HT2a inverse agonist, also devoid of affinity for adrenergic, histaminergic, or muscarinic receptors. Due to its unique mechanism of action in the heart's electrical cycle, pimavanserin is a viable treatment option for PD patients with psychosis since it does not worsen motor symptoms and does not cause sedation (Divac, *et al*., 2016). Ventral tegmental area (VTA) dopamine neurons are under excitatory control of the medial prefrontal cortex 5-HT2A receptors. Blocking these receptors may treat psychosis, and it is thought that clozapine's blocking activity at the 5-HT2A receptors likely contributes to its beneficial effects in PDP. Inverse agonists also potentiate the effects of dopamine blocking agents, suggesting a possible interplay between cortical serotonergic inputs and the dopaminergic neurons of the nucleus accumbens (NA) (Sarva & Henchcliffe, 2016).
A systematic review and meta-analysis, quetiapine has not demonstrated statistically significant efficacy or tolerability, but is associated with troublesome side-effects and high drop-out rates. However, important to note these studies were small and that there is anecdotal evidence of efficacy. Quetiapine should therefore be used with caution. A retrospective chart review of a clozapine clinic for patients with Parkinson's disease found a 66% response rate to clozapine. However, there was a 41% retention rate to the service due to the inconvenience associated with frequent blood monitoring. Pimavanserin is novel treatment that warrants further investigation. Further research is needed, including adequately powered RCTs of various antipsychotics using uniform rating scales (Jethwa & Onalaja, 2015).

IV. CONCLUSION

Quetiapine, clozapine and pimavanserin may be used as antipsychotics in patients with Parkinson's disease but should be used with careful monitoring of side-effects and safety as well as further research still remains to be done on pimavanserin.

References

Apetauerova, D. (2012). Parkinson Diseases. In R. H. Jones, A. G. Srinivasan, & R. A. Baker, *Netter's Neurology 2nd Edition* (pp. 287-298). Philadelphia: Elsevier Saunders.

Ballard, C., Isaacson, S., Mills, R., Williams, H., Corbett, A., Coate, B., . . . Burn, D. J. (2015). Impact of Current Antipsychotic Medications on Comparative Mortality and Adverse Events in People With Parkinson Disease Psychosis. *Journal of the American Medical Directors Association - Elsevier*, 1-7.

Broadstock, M., Ballard, C., & Corbett, A. (2014). Novel pharmaceuticals in the treatment of psychosis in Parkinson's disease. *Expert Review of Clinical Pharmacology*, 7(6) 779–786 .

Cummings, J., Isaacson, S., Mills, R., Williams, H., Chi-Burris, K., Corbet, A., Ballard, C. (2014). Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet, 383*(2014), 533-540.

Divac, N., Stojanovic, R., Vujovic, K. S., Medic, B., Damjanovic, A., & Prostran, M. (2016). The Efficacy and Safety of Antipsychotic Medications in the Treatment of Psychosis in Patients with Parkinson's Disease. *Behavioural Neurology*, 1-7.

Friedman, J. (2013). Parkinson disease psychosis: Update. *Behavioural Neurology (27)*, 469-477.

Friedman, J. H. (2013). Pimavanserin for the treatment of Parkinson's disease psychosis. *Informa Healthcare*, (14) 1969-1975.

Jakel, R. J., & Stacy, M. (2014). Parkinson's disease psychosis. *Journal of Parkinsonism and Restless Legs Syndrome*, 41-51 (4).

Jethwa, K. D., & Onalaja, O. A. (2015). Antipsychotics for the Management of Psychosis in Parkinson's Disease: Systematic Review and Meta-Analysis. *British Journal of Psychiatry Open*, 27-33.

Meltzer, H. Y., Mills, R., Revell, S., Williams, H., Johnson, A., Bahr, D., & Friedman, J. H. (2010). Pimavanserin, a Serotonin2A Receptor Inverse Agonist, for the Treatment of Parkinson's Disease Psychosis. *Neuropsychopharmacology*, *35*(2010), 881-892.

Neal, M. J. (2012). *Medical Pharmacology at a Glance Seventh Edition.* Ukraina: Wiley-Blackwell.

Olanow, C., & Schapira, A. (2013). Parkinson's Disease And Other Extrapyramidal Movement Disorders In: Harrison's Neurology in Clinical Medicine, 3rd Edition. In S. Hauser, & S. Josephson, *Parkinson's Disease And Other Extrapyramidal Movement Disorders In: Harrison's Neurology in Clinical Medicine, 3rd Edition* (pp. 333-346). New York: McGraw-Hill Education.

Ravina, B., Marder, K., Fernandez, H., Friedman, J., McDonald, W., & Murphy, D. (2007). Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. *Movement Disorder Society*, 1061–1068.

Sarva, H., & Henchcliffe, C. (2016). Evidence for the use of Pimavanserin in the Treatment of Parkinson's Disease Psychosis. *Therapeutic Advances in Neurological Disorders, 9(6)*(2016), 462–473.

Stahl, S. M. (2016). Mechanism of action of pimavanserin in Parkinson's disease psychosis: targeting serotonin 5HT2A and 5HT2C receptors. *Brainstorms- Clinical Neuroscience Update, 21*(2016), 271-275.

Tarsy, D., Hurtig, H. I., & Dashe, J. F. (2016). Management of nonmotor symptoms in Parkinson disease. *Elsevier-UpToDate*, 1-10.

Weintraub, D., Chiang, C., Kim, H. M., Wilkinson, J., Marras, C., Stanislawski, B., Kales, H. C. (2016). Association of Antipsychotic Use With Mortality Risk in Patients With Parkinson Disease. *Journal of American Medical Association Neurology*, 73(5): 535–541. .

Zahodne, L., & Fernandez, H. (2008). Pathophysiology and treatment of psychosis in Parkinson's disease: a review. *Drugs Aging 25*, 665–682.