CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com *Review Article*

ANTIPSYCHOTICS- CLASSIFICATION, USES, AND ADVERSE EFFECTS

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Abstract:

Introduction: *Antipsychotic agents are categorized usually as either "typical antipsychotics" or "atypical antipsychotics". Typical antipsychotic pharmacological agents, which are also called first-generation antipsychotics or traditional antipsychotics, include chlorpromazine and haloperidol. On the other hand, atypical antipsychotic pharmacological agents, which are also called second generation antipsychotics, include risperidone, quetiapine, and olanzapine. Both typical and atypical antipsychotics work in similar mechanisms by inhibiting the activation of specific receptors in the dopamine pathway.**Aim of work:** In this review, we will discuss the antipsychotics- classification, uses, and adverse effects, **Methodology:** We did a systematic search for antipsychotics- classification, uses, and adverse effects using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.**Conclusions:** The prescription of atypical antipsychotic agents, like quetiapine and olanzapine, has been significantly increasing and in many conditions, they are sometimes prescribed "off-label" – which is a worrying trend due to their possible risk of developing harmful adverse events. Therefore, atypical antipsychotic agents must only be used in their specific indications and with caution, especially among older patients and young adults. Atypical antipsychotic agents can be indicated for schizophrenia treatment and other associated conditions and in some cases to treat the behavioral and psychological manifestations related to dementia (risperidone only). Antipsychotics are not first-line treatments for patients with anxiety and are not generally recommended for the use in patients with posttraumatic stress disorder or insomnia.*

Key words: *antipsychotics, classification, uses, and adverse effects.*

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Please cite this article in press Mohammed Abdulhakim Hamad Al Hattab et al., ***Antipsychotics- Classification, Uses, and Adverse Effects.,*** *Indo Am. J. P. Sci, 2018; 05(12).*

INTRODUCTION:

Antipsychotic agents are categorized usually as either "typical antipsychotics" or "atypical antipsychotics". Typical antipsychotic pharmacological agents, which are also called first-generation antipsychotics or traditional antipsychotics, include chlorpromazine and haloperidol. On the other hand, atypical antipsychotic pharmacological agents, which are also called second generation antipsychotics, include risperidone, quetiapine, and olanzapine. Both typical and atypical antipsychotics work in similar mechanisms by inhibiting the activation of specific receptors in the dopamine pathway. However, atypical agents are less often associated with extrapyramidal adverse events, which are strongly correlated with the use of old typical agents. On the other hand, atypical agents, along with typical agents, are linked with serious adverse events, indulging diabetes mellitus, cerebrovascular events and cardiovascular mortality [1]. In this paper, we will review the recent advances on antipsychotics-grouping, uses, and adverse events.

Antipsychotic agents are generally used in providing therapy for patients with schizophrenia and associated conditions and in some other cases to manage behavioral and psychological manifestations related to dementia (specifically risperidone). Global experience indicates that antipsychotic agents are being increasingly indicated for use in off-label cases like anxiety and insomnia [2]. The use of atypical antipsychotic agents has been increasing in many parts of the world and it is probably that off-label use is an important factor in this wide increase. Special Authorities usually put restrictions on prescribing antipsychotics but these have been removed recently on olanzapine prescription. Risperidone (both depot injection and tablets) and quetiapine antipsychotics have also been available for use without restriction since the year 2008.

Classically, primary care physicians are responsible for writing prescriptions for patients, once an antipsychotic agent has been started by a psychiatrist after making a diagnosis of a case like schizophrenia. If a primary care physician wants to start treatment, then it is best to only prescribe the drug in the presence of classical recognized manifestations and to discuss the therapy with a psychiatrist prior to prescribing. It is also important for physicians to be highly cautious when prescribing these agents for elderly patients, young individuals and those at higher risk of cardiovascular disease, mainly due to increase weight, diabetes mellitus or elevated cholesterol.

METHODOLOGY:

We did a systematic search for antipsychotics-classification, uses, and adverse effects using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: antipsychotics, classification, uses, and adverse effects.

Adverse effects of atypical antipsychotics

Most adverse events are common with the use of all antipsychotic agents, including both typical antipsychotics and atypical antipsychotics, but can occur in different degrees for each pharmacological agent. Common dose-dependent adverse events usually include:

- Sedation:
  Mainly seen with olanzapine, clozapine, and quetiapine.
- Anticholinergic effects:
  These include constipation, dry mouth, and blurred vision, and are mainly seen with olanzapine and clozapine.
- Dizziness and postural hypotension:
  Mainly seen with risperidone, clozapine, and quetiapine.

With the significantly increasing use of these pharmacological agents, many adverse events related to the use of atypical antipsychotic agents have been reported, like diabetes mellitus, metabolic syndrome, obesity, higher risk of cerebrovascular events (especially in older patients), higher risk of cardiovascular mortality, seizures and tardive dyskinesia.[3] These adverse events have also been reported with the use of typical antipsychotic agents.

Metabolic adverse events:

Metabolic adverse events, which are linked to the use of antipsychotic agents, are of special concern due to the increasing cardiovascular morbidity and mortality. Olanzapine and clozapine have been specifically linked to significant increase in weight, dyslipidaemia and hyperglycaemia. Patients using these agents usually report a continuous hunger sensation. Weight gain can be very high and up to a gain of two kilograms in a period of 2 weeks, which needs a review of the medication use. All patients who have been prescribed an antipsychotic must be educated on diet and lifestyle interventions and observed for the development of diabetes.[4]

Extrapyramidal effects

Atypical antipsychotic agents are usually thought to lead to the development of less extrapyramidal adverse events when compared to typical antipsychotic agents. A previous meta-analysis concluded that olanzapine, clozapine, and risperidone are significantly less likely to cause extrapyramidal manifestations when compared to low potency typical antipsychotic agents (like chlorpromazine).[5] Most of studies have concluded that there are no significant differences between members of the atypical group regarding extrapyramidal effects [3].

Monitoring requirements for clozapine

Patients who are using clozapine need close observation as clozapine can lead to the development of neutropenia, which may progress to a potentially serious agranulocytosis. Blood investigations (including WBCs count and absolute neutrophil count) are important [6]:

- 10 days before initiating therapy.
- Every week for eighteen weeks of therapy
- Every 4 weeks after that an until the end of therapy.
- 4 weeks following discontinuation of the drug.
- Following discontinuation of the drug due to abnormal results, until levels return to normal

Patients who develop any evidence of infection, like sore throat, fever or flu-like manifestations will need urgent CBD. Patients must also be educated to report any such manifestations.

Other adverse events include constipation which is usually linked to the use of clozapine and can sometimes be serious and potentially fatal. The co-prescription of a laxative agent among patients who are receiving clozapine is routinely recommended. Other adverse events of clozapine use can be similar to adverse events of other antipsychotic agents, but antimuscarinic side effects (like dry mouth, blurred vision, and urinary retention), sedation and increased weight can usually be more obvious. The concomitant use of some medicines may significantly increase the rate of adverse events due to:

- The potential risk for developing bone marrow suppression, especially with the use of drugs like trimethoprim, nitrofurantoin, co-trimoxazole, sulphonamides, and carbamazepine.
- The elevation of plasma concentrations of clozapine, especially with the use of drugs like erythromycin and ciprofloxacin.

Tardive dyskinesia

Incidence of new-onset tardive dyskinesia following the use of antipsychotics has been found to be about three percent with the use of risperidone and one or two percent with the use of other atypical antipsychotic agents. Generally, tardive dyskinesia can potentially develop in about twenty percent of patients who are receiving therapy with typical antipsychotic agents [7]. Tardive dyskinesia is considered to be of special concern because it might not be clear immediately, is usually not sensitive to treatment, might be permanent and might progress even if treatment stops.

Atypical antipsychotics for the treatment of schizophrenia and related disorders:

Patients who are diagnosed with schizophrenia must usually be treated by a multidisciplinary team of physicians, which should include both primary care and secondary care. The early diagnosis and prompt management of a first schizophrenia episode is crucial as this could significantly benefit prognosis and potentially even the progression of the disease [8].

Typical antipsychotic agents and atypical antipsychotic agents are usually used for the management and treatment of schizophrenia. Both types of antipsychotic agents have been linked to the development of adverse events with the presence of a significant variation in each patient's response to therapy. Therefore, the same pharmacological agent cannot be administrated for each patient. Generally, an antipsychotic agent is initiated at a relatively low dose and then carefully increased to prevent or decrease the rate of adverse events.

Some guidelines recommend the administration of an atypical antipsychotic agent as the first treatment choice in patient with schizophrenia due to their relatively low risk of developing extrapyramidal adverse events when compared to the administration of typical antipsychotic agents. On the other hand, this recommendation has been assessed recently following the increasing concerns of developing metabolic adverse events with the use of atypical antipsychotic agents, which could be more serious on chronic use [9].

Clozapine is generally recommended in patients who have treatment resistance, after the patient has already attempted at least 2 other antipsychotic agents. This pharmacological agent cannot be prescribed in primary care settings, but primary care providers can have an important role in the

monitoring for the development of adverse events. Pharmacological therapies for patients with schizophrenia must always be used in accordance to comprehensive psychosocial interventions.

Atypical antipsychotics for the treatment of behavioural and psychological symptoms of Dementia

Behavioral and psychological manifestations of dementia include; aggressiveness, disturbance in activities and psychotic malfunctions. Non-pharmacological therapy is advised as a first-line, but in severe cases pharmacological treatment can be used to treat dementia. Risperidone is considered to be the only atypical antipsychotic agent that is approved for the administration in patients with dementia. Antipsychotic agents usually achieve relatively few benefits for patients with dementia and in some cases; they can have higher potential of developing serious adverse events. A recent study estimated that for every one hundred patients who have dementia and are using an antipsychotic, only twenty will show benefits but there will be one death and one cerebrovascular event [10].

Atypical antipsychotic agents must be used with great caution in the elderly, because of the higher incidence and prevalence of developing adverse events and should only be used in cases with severe clinical manifestations. The decision to administrate an antipsychotic agent must be discussed with the patient, the family and the caregivers. Initial doses of the agent must be decreased to at least half the usual dose or even less, with considering other factors like the weight of the patient, the presence of additional comorbidities, and the concomitant use of other pharmacological agents. Treatment must also be regularly monitored and reviewed. Antipsychotic therapy is not considered to be effective for the treatment of symptoms like wandering, social withdrawal, irritability, pacing, touching, cognitive dysfunction and incontinence. Patients who have any of these symptoms might respond to other interventions like environment improvements.[11]

Off-label uses of atypical antipsychotics:

In a recent study that was conducted in Canterbury, more than ninety-six percent of psychiatrists were found to prescribe antipsychotic agents for different off-label uses. Quetiapine was found to be the most commonly prescribed antipsychotic in these cases. The 3 most common causes for off-label administration of quetiapine were: anxiety (in up to 89 percent of cases), sedation (in about 79 of cases) and posttraumatic stress disorder (in about 57 of cases). Overall, it is thought that between forty percent and seventy percent of atypical antipsychotic agents are prescribed for off-label uses. It is commonly accepted that there is few evidence present to support antipsychotics prescription for off-label uses, but this practice is becoming more widespread and there no sufficient guidance as to whether it needs to be decreased, or if patients are really getting benefits from using these pharmacological agents in addressing these indications [12].

Marketing done by drug companies has a significant role in the elevation of rates of use of antipsychotic agent within the last years. In the US, 2 drug companies settled out of court, after getting a charge for illegally advertising for the off-label use of olanzapine and quetiapine [13], 18 Off-label use of antipsychotics is considered to be legal in many countries, making the prescription of atypical antipsychotic agents possible in patients with indications like anxiety. However, the physician who prescribe such pharmacological agents must be careful in weighing up potential harms and benefits and must also consider other appropriate pharmacological agents (or even non-pharmacological interventions) prior to prescribing an antipsychotic. The decision to use an antipsychotic must be thoroughly discussed with the patient and their family members and with careful documentation of all the details in the patient's notes.

When dealing with patients who have anxiety, the use of a selective serotonin re-uptake inhibitor is considered to be the step in the treatment. Psychological therapy, like cognitive behavioral therapy, is equally beneficial. Patients must be treated for twelve weeks prior to the assessment of benefit of SSRIs. Therapy might require to be continued for other six to twelve months following the resolution of anxiety manifestations [14].

There are few evidences suggesting that quetiapine antipsychotic might be beneficial as an intervention in cases of generalized anxiety disorder. However, because of potentially serious adverse events that are associated with the use of quetiapine, it must be only administrated for short-term anxiety therapies and only of if other appropriate pharmacological therapies or psychological interventions had been attempted and failed.

Post-traumatic stress disorder (PTSD)

PTSD is a psychiatric condition in which the patient will develop manifestations following the exposure to

traumatic events. Three clusters of manifestations are classically found: re-experiencing the unpleasant event, avoidance and hyperarousal. Interventions in patients with PTSD include a combination of psychological interventions, administration of pharmacological agents and providing sufficient social support. The first choice of pharmacological agents is generally an antidepressant, usually an SSRI. There is not enough evidence to recommend the use of quetiapine antipsychotic (or any other antipsychotic agent) for PTSD treatment [15].

Insomnia often occurs secondary to an underlying etiology like another disease or poor sleep hygeine. Management and treatment of the underlying etiology will most likely improve insomnia. The first and best management is improving "sleep hygiene". This is achieved by educating the patients to avoid excess alcohol, nicotine and caffeine use, avoid any stimuli at night, avoid staying in bed when not trying to sleep and learning relaxation techniques. If these interventions do not resolve the insomnia, pharmacological interventions can be considered only for short-term use. Zopiclone or shorter-acting benzodiazepines can be good choices. This is recommended with using the lowest possible dose and for the shortest duration [16]. Antidepressants are not generally recommended for patients with insomnia unless there is associated depression or anxiety.Quetiapine antipsychotic is not generally recommended for insomnia treatment unless there is another psychiatric condition like schizophrenia. Quetiapine has been found to improve total sleep duration and sleep efficiency but adverse events like abnormal leg movements and restlessness are considered to be significant limitations for its use [17].

CONCLUSIONS:

The prescription of atypical antipsychotic agents, like quetiapine and olanzapine, has been significantly increasing and in many conditions, they are sometimes prescribed "off-label" – which is a worrying trend due to their possible risk of developing harmful adverse events. Therefore, atypical antipsychotic agents must only be used in their specific indications and with caution, especially among older patients and young adults. Atypical antipsychotic agents can be indicated for schizophrenia treatment and other associated conditions and in some cases to treat the behavioral and psychological manifestations related to dementia (risperidone only). Antipsychotics are not first-line treatments for patients with anxiety and are not generally recommended for the use in patients with posttraumatic stress disorder or insomnia.

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