(International Print/Online Journal)

SJIF IMPACT FACTOR: 4.617
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume2, Issue 5, Page No: 269-277
September-October 2019

An over view on antipsychotics and their side effects

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Type of Publication: Review Paper
Conflicts of Interest: Nil

ABSTRACT

Antipsychotic drugs play a key role in the treatment of schizophrenia and are increasingly prescribed for other health issues such as bipolar disorder, major depression, dementia and substance abuse. Antipsychotic drugs are of two types typical antipsychotics like haloperidol, fluphenazine, loxapine and atypical antipsychotics clozapine, olanzapine, quetiapine, ziprasidone. In addition, these drugs are also utilized in hospital emergency departments to assist patients presenting with acute psychosis. The use of typical antipsychotics is reduced due to the profound extrapyramidal side effects. The first introduced atypical antipsychotic was clozapine and their use was enhanced due to less incidence of EPS, but atypical antipsychotics are associated with metabolic side effects like weight gain, diabetes mellitus, dyslipidemias. The side effects profile of antipsychotics are observed due to various receptor binding nature of these drugs. Antipsychotics show affinity to various receptors like dopaminergic, histaminergic, cholinergic and other receptors. The side effects like extra pyramidal side effects, metabolic effects can be observed during initial stage of treatment or during the maintenance period of antipsychotic therapy. The side effects like of antipsychotic drugs exhibit greater impact on the patients leading to non compliance of antipsychotic therapy

Keywords: Antipsychotics, weight gain, Extrapyramidal side effects, Dopaminergic receptors.

INTRODUCTION

Antipsychotics are the drugs used in treating psychotic disorders. They emerged as an important class of drugs used in the treatment of Schizophrenia [1]. Antipsychotics in general are classified in to 2 types. First-generation are conventional antipsychotics or typical antipsychotics and the second generation are atypical antipsychotics. The first generation antipsychotics, haloperidol was introduced in 1950s [2].The second generation or atypical antipsychotics were introduced into routine practice from the 1990s. Both the typical and atypical antipsychotics are used in treating acute phase of schizophrenia, related psychosis and also in long term maintenance and prevention of relapse[3]. Antipsychotics are used in the treatment of many disorders like Schizophrenia and Schizoaffective disorders, Major Depressive Disorder with Psychotic features, Delusional Disorder, Severe agitation, Tourette Disorder, Substance-induced psychotic disorder and many other psychotic disorders [4].

CLASSIFICATION OF ANTIPSYCHOTICS:

The first generation antipsychotics also referred as neuroleptics are chemically classified into following types.

1. Phenothiazines
2. Butyrophenones
3. Thioxanthenes

4. Dihydroindolones
5. Dibenzepines
6. Diphenylbutylpiperidines

Phenothiazines include drugs like chlorpromazine, levomepromazine, promazine, triflupromazine which contain aliphatic side chain and mesoridazine, pericyazine, pipotiazine, thioridazine these drugs contain piperidine side chain other drugs like perphenazine; fluphenazine and trifluperazine contain piperazine side chain. Among which the aliphatic and piperidine containing agents are of low to medium potency and piperazine agents show medium to high potency [5]. All typical antipsychotics can be administered orally and parenterally except for thioridazine, pimozide, and molindone. Haloperidol and fluphenazine can be given in long-acting depot parenteral form [4]. Butyrophenones which are of high potency include drugs like benperidol, droperidol and haloperidol. Thioxanthanes group includes flupenthixol, clopenthixol, thiothexane, zuclopenthixol. Dihydroindolones include molindone. Dibenzapines includes clotiapine, loxapine. Diphenylbutylpiperidines includes agents like fluspirilene and pimozide which are of high potency [5].

The second generation or atypical antipsychotics are characterized by relativelyhigh affinities to 5-HT2A serotonin receptors and lower affinities for D2-dopamine receptors [6]. Food and Drug Administration (FDA) has approved 12 atypical antipsychotics as of the year 2016. They are risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine, lurasidone, iloperidone, cariprazine, brexpiprazole, and clozapine [4]. The categorization of atypical antipsychotics based on D2 binding affinity helps in understanding the incidence of EPS differences among these agents

Table: 1 Classification of Atypical antipsychotics based on D2 Binding Affinity [7]

Low affinity	1. Clozapine 2. Quetiapine	• Less D2 potency • Less 5-HT2 potency • Less parkinsonian EPS • Multiple receptor blockade effects • More weight gain
Medium affinity	1. Olanzapine	Causes more weight gain
High affinity	1. Resperidone 2. Ziprasidone 3. Aripiprazole	• More dose-related D2 binding affinity • More parkinsonian EPS • Few other receptor blockade effects • Less weight gain

INDICATIONS OF ANTIPSYCHOTICS:

Antipsychotic agents are used in treating wide range of psychiatric disorders. FDA approved indications of antipsychotics for the various treatments of psychiatric disorders include:

Table: 2 FDA approved typical antipsychotics indications [8]

1.chlorpromazine	• Schizophrenia • BipolarDisorder(mania) • Hyperactivity • Behavioural problems	• Intial:30-75 mg/day,divided q6-12hr • maintenance:200 mg/day
2.Droperidol	Agitation	10 mg IM
3.Fluphenazine	Psychotic disorders	0.5–40 mg

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4.Haloperidol	• Schizophrenia • Hyperactivity • Severechildhood behavioural problems • Tourette syndrome	• Moderate:0.5-2mg q8-12hr initially • Severe:3-5mg q8-12hr initially, not to exceed 30 mg/day • 0.5-2 mg PO q8-12hr initially
5.Loxapine	Schizophrenia	• Initial: 10-25 mg PO q12hr • Maintenance: 60-100 mg/day divided q6-12hr; not to exceed 250 mg/day
6.Perphenazine	Schizophrenia	4-8 mg PO q 8hr
7.Pimozide	Tourette syndrome	• Initial: 1-2 mg PO q Day, not to exceed 10 mg/day • Maintenance: <0.2 mg/kg/day or 10 mg/day
8.Prochlorperazine	• Schizophrenia • Generalized Nonpsychotic anxiety	• 5-10 mg PO q6-8hr, not to exceed 150 mg/day
9.Thiothixene	Schizophrenia	• Mild-Moderate: initial: 2 mg PO q8hr, may increase to 15 mg/day • Severe: initial 5 mg PO q12hr • Maintenance: 20-30 mg/day, not more than 60 mg/day PO divided q8-12hr
10.Thioridazine	Schizophrenia	• Initial: 50-100 mg PO q8hr. • Maintenance: 200-800 mg/day PO divided q6-12hr
11.Trifluoperazine	• Schizophrenia • Generalized Nonpsychotic anxiety	1-2 mg PO q12hr

Atypical Antipsychotics (AAPs) when compared with the conventional antipsychotics were marketed with fewer incidences of adverse side effects such as extrapyramidal symptoms. As a result, AAPs were extensively used not only for the US Food and Drug Administration (FDA)-approved indications but also for other conditions not approved [9]. Atypical antipsychotics are divided into two major pharmacological groups, like multiple receptor antagonists, such as clozapine, olanzapine, quetiapine and more selective 5-HT2/D2 antagonists like risperidone, sertindole, ziprasidone and zotepine.

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Side effects like weight gain, metabolic disorders, dyslipidemia and metabolic syndrome are high with olanzapine, clozapine, olanzapine and quetiapine [10].

Table: 3 INDICATIONS OF ATYPICAL ANTIPSYCHOTICS [11]**:**

1. Aripiprazole:	• Bipolar I disorder, monotherapy • Bipolar I disorder, adjunct therapy • Major Depressive Disorder (MDD) • Schizophrenia	10-30 mg PO OD
2. Asenapine:	• Bipolar I disorder, monotherapy • Bipolar I disorder, adjunct therapy • Schizophrenia	• 10 mg PO q12hr initially, may be decreased to 5 mg PO q12hr • 5 mg PO q12hr • 5 mg SL q12hr initially maintenance: up to 10 mg PO q12hr
3. Clozapine:	• Schizophrenia • Treatment resistant schizophrenia • Schizoaffective disorder	• 12.5 mg PO once dailyMaintenance: 300-450 mg/day by end of 2 weeks
4. Ipoperidone:	Schizophrenia	• 1mg PO everyday increase to an effective dose of 6-12 mg/day not to exceed 24 mg/day
5. Lurasidone:	• Schizophrenia • Bipolar Depression • Adjunctive therapy for Bipolar Depression, with	• 40 mg PO everyday not to exceed 160mg/day • 20 mg PO everyday initially, not to exceed 120 mg/day • 20 mg PO everyday

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	lithium or valproate	
6. Olanzapine:	• Schizophrenia • Bipolar I disorder, Depressive episodes	• 5-10 mg/day initially, Maintenance: 10-20 mg/day • 5 mg PO adjusted to range of 5-12.5 mg/day
7. Paliperidone:	• Schizophrenia, • Schizoaffective disorder	• 6 mg PO Qam, not to exceed 12 mg/day • 6 mg PO qDay
8. Quetiapine:	• Bipolar I disorder, acute treatment of manic episodes • Bipolar I disorder, acute treatment of depressive episodes • Bipolar I disorder, maintenance therapy • Schizophrenia • MDD, adjunct therapy	• 400-800 mg/day, not to exceed 800 mg/day • 50 to 200mg • 400-800 mg/day PO divided q12hr • 150-750 mg/day • 150-300 mg/day
9. Risperidone:	• Schizophrenia • Bipolar mania	• 2-8 mg/day once daily or divided q12hr • 2-3 mg/day
10. ziprasidone:	• Schizophrenia • Bipolar mania	• 20 mg PO q12hr not to exceed 80 mg q12hr • 40-80 mg q12hr

MECHANISM OF ACTION OF ANTIPSYCHOTICS:

Antipsychotics are the drugs which mainly act on the neurotransmitters and regulate the levels of different neurotransmitters like dopamine, serotonin, histamine, norepinephrine and acetylcholine.

The first generation antipsychotics (neuroleptics) are the drugs which mainly acts on the dopamine receptors.These drugs acts on subtype D2 of dopamine receptors. The D2 receptor may exist in two interconvertible (high and low) affinity states for agonist binding. In schizophrenia, the balance between these two states is proposed to be altered [12]. In contrast, only typical antipsychotic drugs increase neurotensin (NT) mRNA expression, tissue concentrations, and its release in the caudate/putamen. The increased neurotensin release in the Nucleus accumbens (NAcc) may mediate some of the therapeutic effects of antipsychotic drug, whereas increased NT release in the CPu is mediated to cause the acute EPS and tardive dyskinesia induced by antipsychotic drugs. The long term administration of typical and atypical antipsychotic drugs additionally decreases NT content in the prefrontal cortex and bed nucleus of the striaterminalis, indicating that these changes may be closely related to the clinical efficacy of antipsychotic drugs [13].

The second generation or atypical antipsychotic drugs acts by exhibiting the high-affinity for the serotonin receptor [14]. The atypical agents are different from first generation antipsychotic agents in their lower affinity for dopamine D2 receptors and

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greater affinities for other neuroreceptors, like serotonin or 5-hydroxytryptamine (1A, 2A, 2C, 3, 6 and 7) and norepinephrine (a1 and a2)[1]. Neuroleptics bind more tightly to the dopamine D2 receptor than the dopamine, with dissociation constants lower than that for dopamine. Whereas, the atypical antipsychotics such as quetiapine, clozapine, olanzapine, sertindole, ziprasidone, and amisulpride bind more loosely than to the dopamine D2 receptor and have dissociation constants higher than that for dopamine[15].

CLASSIFICATION OF SIDE EFFECTS:

The side effects profile of these drugs can be classified as

1. Extrapyramidal side effects
2. Metabolic disorders

Typical antipsychotics were soon recognised to cause extrapyramidal side effects (EPS), including Parkinsonism, acute dystonias, akathisia, and tardive dyskinesia. EPS are observed in nearly 80% patients exposed to these drugs [16]. Other typical antipsychotic like thioridazine, droperidol, pimozide can cause clinically significant QT interval prolongation which may lead to the ventricular arrhythmias, torsade de pointes[3]. Atypical antipsychotics usually cause fewer incidences of EPS but causes metabolic disorders. Agranulocytosis due to clozapine is a fatal condition that requires immediate medical attention [10]. Metabolic side effects like weight gain, diabetes mellitus, hyperlipidemia, QT interval prolongation, myocarditis, sexual side effects and cataract are observed in patients taking atypical antipsychotics [17].

MECHANISM OF NON-EPS SIDE EFFECTS:

The most common and distressing non-EPS side effects of antipsychotics include weight gain, anticholinergic side effects, sedation, sexual dysfunction, and amenorrhea and galactorrhea [18].

ENDOCRINOLOGICAL SIDE EFECTS:

The mechanism responsible for inducing weight gain in antipsychotics like olanzapine and clozapine therapy includes their high affinity for H1and H3 receptors as histamine is involved in regulating and controlling food intake. In general histaminergic neurons are located in the tuberomamillary nucleus of the posterior hypothalamus and project their axons through most of the brain and regulate the food intake along with hypothalamus by depolarising the selected brainstem neurons in the Nucleus Tractus Solitarius (NTS) and Dorsal Motor Nucleus (DMN) of the vagal nerve in the Dorsal Vagal Complex (DVC) [19]. Blockade of histamine at H1 receptor by atypical antipsychotics showed a stronger correlation with weight gain as compared with the blockade of 5HT2- receptors [20]. Antipsychotics also results in Diabetes Mellitus due to weight gain and also by promoting insulin resistance directly. For instance, insulin secretion is regulated by M3 receptors through peripheral and central cholinergic pathways. Therefore, antipsychotics induced DM may be partly due to blockade of central and peripheral M3 receptors leading to an initial disruption of insulin secretion and glucose homeostasis that can progressively lead to insulin resistance and DM during chronic treatment[21]. Metabolic syndrome is a triad of diabetes, hypertension, and hypercholesterolemia associated with abdominal obesity and dyslipidemia. The underlying pathophysiology of the metabolic syndrome is thought to be hyperinsulinemia and insulin resistance [7].

ANTICHOLINERGIC SIDE EFFECTS:

The anticholinergic effects of antipsychotic drugs are hypersalivation, blurred vision, constipation, delirium, dry mouth, paralytic ileus, tachycardia, and urinary retention. In general, the anticholinergic action of antipsychotic drugs is caused by effects on the parasympathetic nervous system via cholinergic postganglionic fibers and postsynaptic muscarinic-type acetylcholine receptors. However, peripheral sympathetic effects of drugs on sweat glands and certain blood vessels could also be mediated through cholinergic transmission [21].

SEXUAL SIDE EFFECTS:

Antipsychotics also cause sexual side effects due to their affinity towards dopamine, alpha-adrenergic and other receptors. Blocking of dopamine secretion leads to hyperprolactinemia which affects sexual function, particularly libido and erection, by increasing gamma-aminobutyric acid (GABA)-ergic activity and opioid levels [23]. The schizophrenic patients on antipsychotic therapy are more commonly affected by sexual dysfunction than those with affective

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disorders and patients with untreated schizophrenia [17]. AAPs can affect sexual function in the following ways [23]:

1. By centrally blocking dopaminergic receptors in the hypothalamus, contributing to hyperprolactinemia, galactorrhea, menstruation, or erection disorders and reduced libido.
2. By peripherally blocking α-adrenergic receptors, responsible for dilation of the arteries in the penis.
3. By an unspecific central sedative effect leading to reduced sexual activity.

EXTRAPYRAMIDAL SIDE EFFECTS:

Extra pyramidal side effects are mostly associated with typical antipsychotics and to a lower extent to atypical antipsychotics. The risk of developing EPS has been shown to increase when D2 receptor occupancy reaches 70 to 80% and also the occupancy of 5-HT2A receptors may alleviate EPS induced by high rates of D2 occupancy [7]. Patients may present with pre existing motor abnormalities, before the initiation of any antipsychotic medications. However, the majority of extra pyramidal symptoms are exhibited after exposure to antipsychotic medication [17]. Generally EPS develop into two phases [24].

1. Early onset Acute EPS
   Acute EPS often develop upon the beginning of treatment with antipsychotics or when the dose is increased.
2. Later-onset EPS
   This usually occurs after prolonged treatment and present as tardive dyskinesia.

The motor manifestations include [24]:

- Akathisia -- Restlessness and pacing
- Acute Dystonia -- Sustained abnormal postures and muscle spasms, especially of the head or neck
- Parkinsonism -- Tremors, Skeletal muscle rigidity and bradykinesia
- Tardive Dyskinesia -- Characterized by involuntary, repetitive facial movements such as grimacing, tongue protruding, oculogyric crisis, lips puckering as well as torso and limb movements.

TYPES OF EPS:

1. Dystonias [25]:
   It is characterized by sustained muscle activity that frequently causes twisting and repetitive movements and abnormal postures or pain. Acute dystonic reactions mostly affect the head and neck area causing oculogyric crisis, laryngeal dystonia, blepharospasm, trismus and torticollis. The postures can be associated with spasms or tremor (a regular oscillation of a body part) and can be painful.

   Treatment: Trihexyphenidyl 2 to 10 mg po tid, Benztropine 3 to 15 mg po once/day Diphenhydramine 50 mg IV or IM q 20 min for 2 doses

2. Chorea and athetosis [26]**:** These are an important hyperkinetic movement disorders in psychiatry which are frequently combined as choreoathetotic movements, in which an abrupt irregular movement called choreatic movements seems to causea writhing or stretching movement called athetosis.

   Treatment: Tetrabenazine up to 100 mg/day

   Amantadine 300–400 mg/day

3. Akathesia:
   Akathesia is referred to an inability to sit. It can be described as a sensation of motor restlessness that is typically present throughout the entire body.

   Treatment: Amantadine 100–150 mg po bid

   Benztropine 1–2 mg po bid

   Biperiden 1–4 mg po bid

   Procyclidine 2.5–10 mg po bid

   Propranolol 10–30 mg po tid

   Trihexyphenidyl: 2–7 mg po bid

4. Parkinsonisism:
   Antipsychotics induced parkinsonism occurs between few days to several months after the initiation of the treatment. Risk factors for this type of Parkinsonism are age (elderly), gender (females), cognitive deficit, and early onset EPS [24].

Treatment: Benztropine 1–2 mg po bid

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Diphenhydramine 25–50 mg po tid

5. Tardive Dyskinesia:
   The risk of TD is highest in the first five years of treatment with typical neuroleptics, and that the incidence of TD decreases after the first five years [7].

MECHANISM OF EXTRAPYRAMIDAL SIDE EFFECTS:

As all neuroleptics acts by antagonising the dopaminergic D2 receptor, psychosis in schizophrenia is due to the increased dopaminergic activity caused by rise in brain dopamine D2 receptors in the mesocortical and mesolimbic pathways. The neuroleptics antagonise dopamine activity in mesocortical, mesolimbic pathway and reduce the symptoms of psychosis whereas the inhibition of dopamine transmission in the nigrostriatal system results in the extra pyramidal side effects [16]. The simultaneous blockade of different types of neurotransmitters may result in the differences in drug induced Parkinsonism risk with neuroleptic drugs. The blockade of D2 and serotonin (5-HT2A) receptors may reduce the risk of drug induced Parkinsonism therefore atypical antipsychotics exhibits less incidence of EPS due to their affinity towards 5-HT receptors. Typical antipsychotics due to strong affinity towards dopamine receptors than dopamine itself accounts for increased risk of extra pyramidal effects [16].

CONCLUSION:

Use of antipsychotics in the treatment of psychotic disorders is very essential. But the monitoring of associated side effects profile of antipsychotics favours in enhancing the patient compliance towards the treatment which results in reducing the relapse of psychotic symptoms and events. Counselling the patients regarding the unwanted effects of antipsychotics helps in addressing the EPS or metabolic effects early and prevents the worsening of the patient condition both with psychotic affects and antipsychotic adverse effects. Clinical pharmacist plays an important role in providing essential patient counselling regarding disease, drug therapy and life style modifications.

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