Review Article

EXTRAPYRAMIDAL SYMPTOMS AND NOVEL ANTIPSYCHOTIC DRUGS

ABSTRACT

One of the challenges of antipsychotic medication is the occurrence of Extrapyramidal Symptoms. These cannot be easily eliminated considering the pathophysiology of schizophrenia and the established mechanism of action of classical antipsychotics. Theantipsychotics help improve symptoms of schizophrenia by binding to dopamine receptors in the central nervous system and blocking dopamine. This prevents the basal ganglia from getting enough dopamine. Many drugs used in the treatment of mental disorders such as the neuroleptics and antidepressants adversely affect extrapyramidal system function, resulting in symptoms such as tremors and muscle rigidity collectively known as extrapyramidal symptoms. Treatment generally involves lowering the dose or trying a different antipsychotic but drugs may also be used specifically to treat symptoms. This review examines the attempt to eliminate extrapyramidalsymptoms by generations of antipsychotic medications and their comparative efficacy in the treatment of schizophrenia.

Keywords: Antipsychotics, Typical, Atypical, Dopaminergic, Extrapyramidal

1.0 INTRODUCTION

Typical antipsychotics were developed in the early 1950s. And since they first existed before their counterpart, they are also called first-generation antipsychotics (FGAs).Sometimes also referred to as conventional antipsychotics, this class of antipsychotics is effective in the treatment of psychosis and positive symptoms of schizophrenia.A major drawback of these drugs is that they are associated with a wide array of side effects, some of which can be severe. The term “neuroleptic” was used to describe these side effects and therefore was closely associated with typical antipsychotics.These side effects include extrapyramidal symptoms (EPS); which are a group of adverse drug reactions attributable to dysfunction of the extrapyramidal nerve pathway, such as rigidity of the limbs, tremor, and other Parkinson-like signs; dystonia (abnormal facial and body movements); and akathisia (restlessness). These unpleasant effects are observed from patients undergoing treatment for psychosis and related ailments [1].Extrapyramidal symptoms get their name because they are symptoms of disorders in the extrapyramidal system. The extrapyramidal system is a neural network in the brain which regulates posture, skeletal muscle tone and coordination. It includes the cerebellum, which is responsible for balance, and the basal ganglia, which takes the information provided by the cerebellum and vestibular structures; through dopamine receptors and uses this information to modify skeletal muscle movement [2]. Extrapyramidal symptoms are a direct result of the mechanism of action of classical antipsychotics and some other drugs.They are among the most common side effects of the high-potency antipsychotics and have also been reported with use of other drugs e.g., Selective Serotonin Reuptake Inhibitors (SSRIs) [3].When such symptoms are caused by medications or other drugs, they are also known as extrapyramidal side effects (EPSE). The symptoms can be acute (short-term) or chronic (long-term). They include

movement dysfunction such as dystonia (continuous spasms and muscle contractions), akathisia (may manifest as motor restlessness) [4],parkinsonismcharacteristic symptoms such as rigidity, bradykinesia (slowness of movement), tremor, and tardive dyskinesia (irregular, jerky movements) [5].Other causes of extrapyramidal symptoms can include brain damage and meningitis [6]. However, the term "extrapyramidal symptoms" generally refers to medication-induced causes in the field of psychiatry [7]. EPS can occur in both adults and children and may be severeenough to affect daily life by making it hard to move around, communicate with others, or take care of usual tasks.Early symptoms may begin shortly after the starting of a medication and often show up a few hours or days after the first dose. Delayed symptoms can happen after some time of taking the drug depending on the specific side effect.

1.1 PATHOPHYSIOLOGY OF SCHIZOPHRENIA

Schizophrenia is a mental disorder that usually appears in late adolescence or early adulthood. This is characterized by delusions, hallucinations, and the splitting of psychic functions indicated by loosening of association of ideas, detachment from reality and inappropriate emotions and responses often referred to as psychosis [8]. Schizophrenia can also be due to psychotropic medications and isoften a lifelong struggle.Psychotropic drugs are agents that act on the brain cells to change the mental process; such as alcohol or cannabis sativa [9]. Postpartum psychosis can occur after childbirth. For schizophrenic patients, the outside surrounding is often overpowered by an inner nightmare of images and voices. The aetiology of schizophrenia is believed to be related to either a hypersensitivity of the dopamine receptor or that the synthesis or release of dopamine in nerve terminals associated with these receptors is increased. Either of these mechanisms led to excessive stimulation of dopamine receptor sites [4].

1.2 PHARMACOTHERAPY FOR SCHIZOPHRENIA

Antipsychotics, also known as neuroleptics or major tranquilizers, are a class of drugs primarily used to manage the positive symptoms of psychosis including delusions and hallucinations, principally in schizophreniaand bipolar disorder.Numerous antipsychotic drugs are available for clinical use, but with certain exceptions the differences between them are minor. An important distinction is drawn between the main groups, often referred to as classical or typical antipsychotic drugs and atypical antipsychotic drugs is their effect on dopamine receptors.

Blockade of the dopamine receptors in the basal ganglia; results in the extrapyramidal symptoms [6]. These types of antipsychotic drugs that adversely affect the extrapyramidal system function resulting in symptoms such as akathisia, tremors, acute dystonia and Parkinsonism; were called the typical antipsychotic drugs and are typified by chlorpromazine and haloperidol. The unpleasant effect of the extrapyramidal symptoms led to the discovery of atypical antipsychotics like clozapine which has a much lower risk of extrapyramidal symptoms [4]. It was found out that serotonin receptor blockade is a key factor in the antipsychotic effect of atypical antipsychotics like clozapine [4]. Later atypical antipsychotics were broadened to include; efficacy against cognitive and negative symptoms, lack of prolactin elevation and efficacy for treatment resistant patients [10]. Subsequently the world psychiatric association classified the typical antipsychotics as First Generation while the atypical became Second Generation antipsychotics.

1.3 EFFECTS OF ANTIPSYCHOPTIC DRUGS

Effects of antipsychotic drugs differ in normal and psychotic individuals. In normal individuals they produce indifference to surrounding, paucity of thought, psychomotor slowing, emotional

quiet, reduction in initiative and sedation [11]. Spontaneous movements are minimized, but slurring of speech, ataxia or motor incoordination does not occur. This has been referred to as the "neuroleptic syndrome". The effects are appreciated as "neutral" and "unpleasant" by most normal individuals. In psychotic patients they reduce irrational behaviour, agitation and aggressiveness and controls psychotic symptoms. Disturbed thought and behaviour are gradually normalised, anxiety is relieved. Hyperactivity, hallucinations and delusions are suppressed [12]. Extrapyramidal motor disturbances comprise acute dystonia and tardive dyskinesia, but a predominance of lower frequency waves occurs in EEG and arousal response is dampened. However, no consistent effect on sleep architecture has been noted. The disturbed sleep pattern in a psychotic is normalised.Neuroleptics produce hypotension (primarily postural) by a central as well as peripheral action on sympathetic tone, which is more marked after parenteral administration and roughly parallels the α-adrenergic blocking potency [13]. This is not prominent in psychotic patients and is accentuated by hypovolaemia. Partial tolerance develops after chronic use.

Neuroleptics consistently increase prolactin release by blocking the inhibitory action of dopamine on pituitary lactotrophs (cells in the anterior pituitary that produce prolactin in response to hormonal signals including dopamine which is inhibitory and thyrotropin releasing hormone-which is stimulatory) [13]. This may result in galactorrhea and gynecomastia. They reduce gonadotropin secretion but amenorrhea and infertility occur only occasionally. Adrenocorticotropic hormone ACTH release in response to stress is diminished and corticosteroids levels fail to increase under such circumstances. Release of growth hormone (e.g.,GH) is also reduced but this is not sufficient to cause growth retardation in children or to be beneficial in acromegaly. Decreased release of antidiuretic hormone (e.g.,ADH) may result in an increase in urine volume [14]. A direct action on kidney tubules may add to it, but Na+ excretion is not affected.

1.4 ANTIPSYCHOTICS MECHANISM OF ACTION

Though dopamine was identified to play a role in psychosis and antipsychotic medicationthere are many types of dopaminergic receptors.Thetypical antipsychotic drugs are thought to owe their therapeutic effects mainly to blockade of D2receptors [15]. The phenothiazines, thioxanthines and butyrophenones, show preference for D2 over D1 receptors; some newer agents (e.g. remoxipride) are highly selective for D2 receptors, whereas clozapine is relatively non-selective between D1 and D2, but has high affinity for D4 [13].Dopamine, the naturally occurring agonist, interacts with D1 and D2 receptors, and both receptors are found in high density in the corpus striatum and nucleus accumbens.Most striatal neurons have D1 responses and most accumbens neurons have D2 responses.Dopaminergic receptor blockade in the basal ganglia (from the substantia nigra to the striatum -nigrostriatal pathway) appears to cause the extrapyramidal symptoms [13].

2.0 EXTRAPYRAMIDAL SYMPTOMS AND COMPARATIVE EFFICACY OF ANTIPSYCHOTIC DRUGS

Extrapyramidal symptoms are most commonly caused by typical antipsychotic drugs that antagonize dopamine D2 receptors [12]. The most common typical antipsychotics associated with EPS are haloperidol and fluphenazine [10]. Atypical antipsychotics have lower D2 receptor affinity or higher serotonin 5-HT2A receptor affinity which leads to lower rates of EPS [16].

Other anti-dopaminergic drugs, like the antiemetic metoclopramide, can also result in extrapyramidal side effects [17]. Short and long-term use of antidepressants such as selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), and norepinephrine-dopamine reuptake inhibitors (NDRI) have also resulted in EPS[18]. Specifically, duloxetine, sertraline, escitalopram, fluoxetine, and bupropion have been linked to the induction of EPS [18].

The term “Atypical” commonly refers to the diminished tendency of some newer compounds to cause unwanted motor side-effects. Their pharmacological characteristics are different from that of “typical” antipsychotic drugs phenothiazines (chlorpromazine, triflupromazine, thioridazine, trifluoperazine and others), thioxanthines (chlorpothixene, thiothixene, flupenthixoletc.) and butyrophenones (haloperidol, trifluperidol, droperidol and penfluridol and such others). The atypical antipsychotic drugs include clozapine, risperidone, sulpiride, sertindole, seroqueland aripiprazole.The main distinction between “typical” and “atypical” groups rests on the lesser Incidence of extrapyramidal side-effects in the “atypical” group [19], the efficacy in treatment – resistant group of patients [7] and efficacy against negative symptoms like; emotional flattening, withdrawal from social interaction, speech and thought poverty and lost motivation [20].Clozapine is an atypical antipsychotic drug used as a sedative and for treatment-resistant schizophrenia. It is known to have fewer side effects than classical antipsychotics [21]. All phenothiazines, thioxanthines and butyrophenones have the same antipsychotic efficacy, but potency differs in terms of equieffective (equally effective - not comparable) doses. The aliphatic and piperidine side chain phenothiazines (chlorpromazine, triflupromazine, thioridazine) have low potency, produce more sedation and cause greater potentiation of hypnotics, opioids etc. The sedative effect is produced immediately while the antipsychotic effect takes weeks to develop. Moreover, tolerance develops to the sedative but not to the antipsychotic effect.

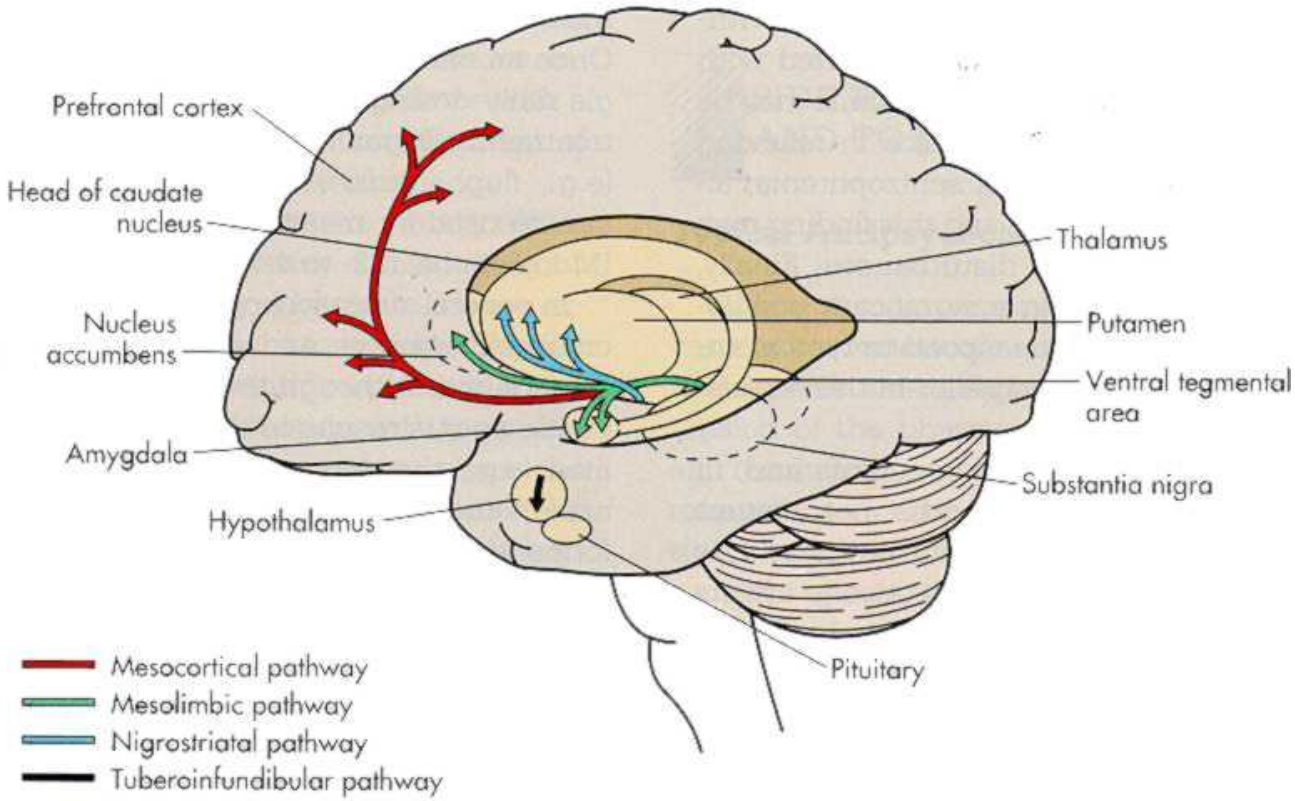

Figure 1: Schematic diagram of the brain.

The firing of dopaminergic neurons and dopamine turnover increases initially; as an adaptive change to blockade of presynaptic dopamine D2 receptors. However, over a period of time this subsides and gives way to diminished activity, especially in the basal ganglia – corresponding to emergence of parkinsonian effect. Catalepsy (a trancelike state with loss of voluntary motion and failure to react to stimuli) arises primarily from acute blockade of postsynaptic D2 receptors.

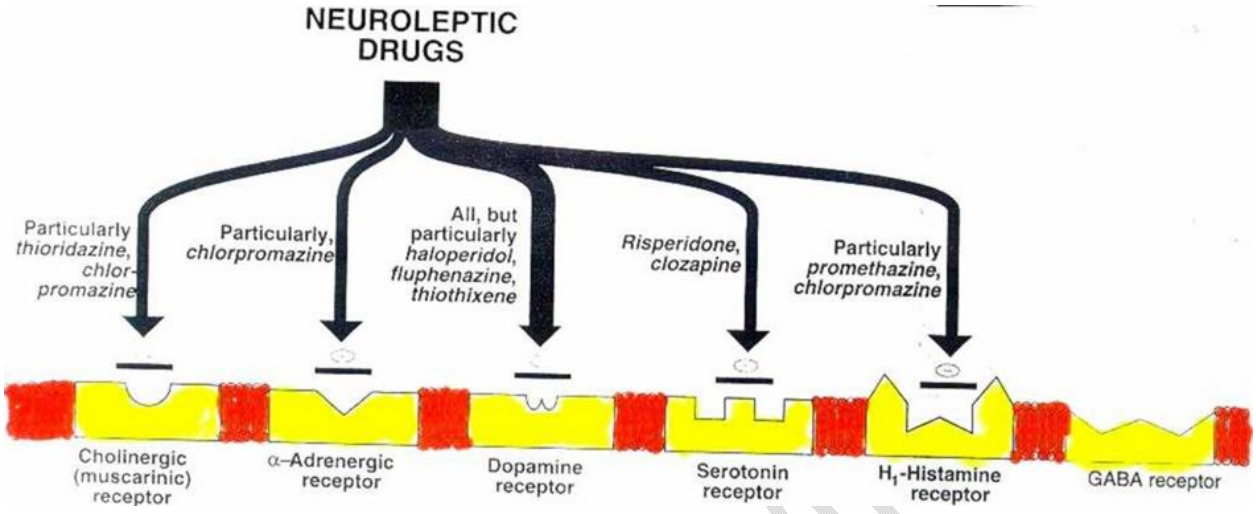

Figure 2: Diagram showing neuroleptic drugs blockade at dopaminergic, serotoninergic, adrenergic, cholinergic and histamine-binding receptors.

3.0 DIAGNOSIS AND TREATMENT OF EXTRAPYRAMIDAL SYMPTOMS

The Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS), the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) and Extrapyramidal Symptom Rating Scale (ESRS) are rating scales are commonly used to assess the severity of movement disorders [22]. These scales provide more information about the symptoms and their severity.

Treatment often helps, but some symptoms may be permanent.In treating EPS, it is important to exclude idiopathic movement disorder as a differential diagnosis [23].Treatment for extrapyramidal symptoms can be difficult. Drugs can have varying side effects, and they affect people differently. Often the only method of treatment is to try different drugs or lower doses to see which provide the most relief with the fewest side effects. Dose reduction or switching agents can be done before attempting to treat EPS with other drugs.Medications are used to reverse the symptoms of extrapyramidal side effects caused by antipsychotics or other drugs, either by directly or indirectly inhibiting dopaminergic neurotransmission. Anticholinergic agents such as procyclidine, benztropine, diphenhydramine, and trihexyphenidyl, and (rarely) dopamine agonists like pramipexoleare a first-line treatment for drug-induced EPS, followed by amantadine.Electroconvulsive therapy (ECT) is one of the most effective treatments for EPS.If the EPS are induced by an antipsychotic, EPS may be reduced by decreasing the dose of the antipsychotic or by switching from a typical antipsychotic to an (or to a different) atypical antipsychotic, such as aripiprazole, ziprasidone, quetiapine, olanzapine, risperidone, or clozapine. These medications possess an additional mode of action that is believed to mitigate their effect on the nigrostriatal pathway, which means they are associated with fewer extrapyramidal side-effects than "conventional" antipsychotics (chlorpromazine, haloperidol, etc.) [24].

Anticholinergic medications are used to reverse acute dystonia. If the symptoms are particularly severe, the anticholinergic medication may be administered by injection into a muscle to rapidly reverse the dystonia [25]. Certain second-generation antipsychotics, such as lurasidone and the

partial D2-agonist aripiprazole, are more likely to cause akathisia compared to other second-generation antipsychotics [26].If akathisia occurs, switching to an antipsychotic with a lower risk of akathisia may improve symptoms [27].Beta blockers (like propranolol) are frequently used to treat akathisia. Other medications that are sometimes used include clonidine, mirtazapine, or even benzodiazepines. Anticholinergic medications are not helpful for treating akathisia [25].Medication interventions are generally reserved for cases in which withdrawing the medication that caused the pseudoparkinsonism is either ineffective or infeasible. Anticholinergic medications are sometimes used to treat pseudoparkinsonism, but they can be difficult to tolerate when given chronically. Amantadine is sometimes used as well. It is rare for dopamine agonists to be used for antipsychotic-induced EPS, as they may exacerbate psychosis[25]. When other measures fail or are not feasible, medications that are used to treat tardive dyskinesia include the vesicular monoamine transporter 2 inhibitors tetrabenazine and deutetrabenazine [25].

4.0 EFFICACY VERSUS SIDE EFFECT

The atypical antipsychotics or second-generation antipsychotics have become the drugs of choice for acute psychoses. They are "atypical" as they are differentiated from "conventional" or first-generation antipsychotics based on their clinical profile. This activity outlines the indications, mechanism of action, safe administration, adverse effects, contraindications, toxicology, and monitoring of atypical antipsychotics in psychosis management. They have fewer side effects regarding extrapyramidal symptoms when compared to typical antipsychotics. Atypical antipsychotics have transformed the treatment of psychoses as they are prescribed for acute psychoses and in the management of schizophrenia, affective disorders (depression and mania), and geriatric agitation [28-30]

Second-generation antipsychotics such as risperidone, ziprasidone, paliperidone, and aripiprazole are all potent antagonists of dopamine D2 receptors, while clozapine and quetiapine are weak D2 antagonists. These antipsychotics also have additional properties such as 5-HT2A antagonism and 5-HT1A agonism. Atypical antipsychotics also have antidepressant properties in combination with other antidepressants and when administered alone. Mechanisms linked to antidepressant actions include serotonin and/or norepinephrine reuptake inhibition. Quetiapine and ziprasidone have weak binding at these sites. Alpha2 antagonism is the mechanism with quetiapine, clozapine, risperidone, and aripiprazole with variable degrees of potency.

Atypical antipsychotics with D2 antagonism and partial agonism combined with 5HT2A antagonism have greater efficacy for mania, and these include aripiprazole, quetiapine, olanzapine, risperidone, and asenapine. Antipsychotics also have histamine, muscarinic (cholinergic), and alpha-adrenergic antagonism. Almost all atypical antipsychotics bind to alpha-adrenergic receptors, but the most potent are clozapine, risperidone, iloperidone, and clozapine. Quetiapine, clozapine, and olanzapine have high anticholinergic properties, whereas other atypical antipsychotics very weakly bind to muscarinic cholinergic receptors[31-33].

5.0 CONCLUSION

Extrapyramidal symptoms can negatively affect quality of life and contribute to frustration and distress. The antipsychotic action of antipsychotics depends on a specific profile of action of the drugs on several neurotransmitter receptors.First-generation antipsychotics commonly cause extrapyramidal symptoms. Atypical antipsychotics have more favourable side effect profiles

which tend to occur at lower rates. These second-generation antipsychotics have less affinity for dopamine receptors and bind loosely and block some serotonin receptors.Stoppage of antipsychotic medication is able to make extrapyramidal symptomsgo away, but this can be also dangerous as one could experience more serious symptoms. In some cases, reactions to antipsychotic medications can be permanent, but treatment often leads to improvement. Due to their superior effectiveness and lesser side effect profile when compared with typical antipsychotics, atypical antipsychotics are a better choice for the treatment of patients with schizophrenia.While at first glance second-generation antipsychoticsmay seem to be preferable to first-generation antipsychotics, the effectiveness of the latter over the former has not been adequately established yet and there is no first-line antipsychotic drug that is suitable for all patients.

Abbreviations

EPS-Extrapyramidal symptoms

EPS-Extrapyramidal syndromeElectroconvulsive therapy (ECT)

EPSE-Extrapyramidal side effects

SSRIs-Selective Serotonin Reuptake Inhibitors

DIEPSS-Drug-Induced Extrapyramidal Symptoms Scale

ESRS-Extrapyramidal Symptoms Rating Scale

APA- American Psychological Association

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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