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# Novel Antipsychotics: Mode of Delivery, Side Effects and Clinical Trials

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**ABSTRACT:** Newer antipsychotics, which have a lower EPS than first-generation antipsychotics, are emerging as the preferred treatment of a wide range of psychological illnesses, including schizophrenia and others(1)(2). Because of their considerable potency, the key objective of medication administration is to reduce dosage frequency while reducing EPS. Several novel medication delivery techniques, such as transdermal and intranasal formulations, have been developed to overcome the constraints of traditional drug administration. Long-acting action is provided by the depot injectable formulation, which decreases dosage frequency and improves patient compliance. Even though they diminish EPS, they have several significant and uncommon adverse effects, including metabolic syndrome, neuroleptic malignant syndrome, and TD (tardive dyskinesia). In India, 318 clinical trials for 118 disorders are currently underway. Around 30 clinical trials on six different conditions were done for psychosis which provide insight into the utilisation of distinctive antipsychotics in the treatment of psychological disorders. The classification, mechanism of action, drug delivery, adverse side effects, clinical trials, contraindications, and patent search for second generation antipsychotics are all addressed in this review article.

**Keywords**: Newer antipsychotics, EPS (extrapyramidal symptoms), TD (tardive dyskinesia)

## I. INTRODUCTION

Antipsychotics are the cornerstone of schizophrenia pharmacology. In 1952, the discovery of the first antipsychotic drug, 'Chlorpromazine,' marked the beginning of a new era in psychopharmacology(3). As a result of this discovery, researchers began to understand synaptic transmission as a chemically mediated mechanism rather than an electrical one(4). Delusions, hallucinations, and paranoia are all symptoms of psychosis that are treated with these medicines. They're mostly used to treat schizophrenia, bipolar depression, and anxiety(3). Neuroleptics are antipsychotics that act on nerves(5).

Antipsychotics are majorly classified as first-generation antipsychotics and second-generation antipsychotics.

Antipsychotics of the first generation (also known as typical antipsychotics) are competitive inhibitors of a number of receptors, but their antipsychotic actions are due to competitive blockage of D2 receptors(6).

Chlorpromazine (100-800mg/day) is the first antipsychotic (low potency). Thioridazine (100-400mg/day) Triflupromazine (50-200mg/day)

Fluphenazine (1-10 mg/day), Haloperidol (5-20 mg/day), Pimozide (2-6 mg/day), and Thiothixene (5-60 mg/day) are examples of first-generation antipsychotics (high potency)(7)(8).

Second-generation antipsychotics (also referred as atypical antipsychotics) are novel antipsychotics that produce fewer EPS (extrapyramidal symptoms) than traditional antipsychotics that target both serotonin and dopamine receptors.

Aripiprazole (10-30 mg/day), Clozapine (100-300 mg/day), Molindone (50-70 mg/day), Olanzapine (2.5-20 mg/day), Quetiapine (50-400 mg/day), Risperidone (2-8 mg/day) are only just few examples.

When it was revealed that clozapine was much more effective than chlorpromazine and had fewer extrapyramidal symptoms, newer antipsychotics were introduced in 1989. Clozapine, Risperidone, Olanzapine, Ziprasidone, Quetiapine, Amisulpride, Sertindole, Lurasidone, Paliperidone,

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Iloperidone, Asenapine, and Aripiprazole are the 12 SGAs approved by the FDA since about 2016 (more recently brexpiprapole, cariprazine, Zotepine).(9)Indications for treating bipolar disorder with many second-generation antipsychotics (SGAs) issued by the Food and Drug Administration in the 2000s provide a chance to investigate aspects that affect the proliferation of an innovative treatment to a new group(10)(11).

Atypical antipsychotics can be classified based upon their pharmacodynamic properties that is affinity to specific receptors.

**Serotonin-dopamine antagonists (SDA)** are the atypical antipsychotics having high affinity for serotonin 5-HT2A receptors and dopamine D2 receptors (also alpha-adrenoreceptors). E.g., iloperidone, Risperidone, Sertindole, Ziprasidone(8)(4).

**Multi-acting receptor-targeted antipsychotics (MARTA)** are the drugs having affinity for 5-HT2A D2 and receptors of other systems (cholinergic, histaminergic, 5-HT1A, 5-HT2C and others). E.g., Clozapine, Olanzapine, Quetiapine(4).

**Combined D2/D3 receptor antagonists** are Drugs that preferentially block D2 and D3 subtypes of the D2-like receptors. E.g., Amisulpride, Remoxipride, Sulpiride(4).

**Partial dopamine receptor agonists**. E.g., Aripiprazole(4).

## II. MECHANISM OF ACTION

Second-generation antipsychotics work in a variety of ways. They have a greater affinity for 5-hydroxytryptamine (5-HT) 2A receptors than D2 receptors and a lesser affinity for D2 receptors than first-generation antipsychotics(12)(13)(5). They disrupt postsynaptic dopamine D2 receptors in two ways:

1. They block the mesolimbic pathway, thereby alleviate positive psychotic symptoms.
2. Block its mesocortical, nigrostriatal, and tuberoinfundibular circuits, minimizing negative consequences(14)(15).

Atypical antipsychotics act by blocking D2 receptors (D2, D3, D4) and don't work by blocking D1 receptors (D1 and D5). Atypical neuroleptics have a greater level of release than conventional antipsychotics. This is considered to as the Fast-off mechanism. Neurotransmitter receptors are fundamental components of metabolic regulations, providing them targets for neuroleptic medication regimen(16).

Theory of L-dopa psychiatric disorder (fasting off D2). When endogenous dopamine is able to displace a non-specific neuroleptic medication, atypical event happens. This finding proves that low concentrations of SGAs are effective in the treatment of neurodegenerative conditions. In the treatment of psychosis, a 10% percent antipsychotic drug indeterminate amount is commonly utilised. Remoxipride is a good SGA medicine because it doesn't cause EPS or hyperprolactinemia, but that doesn't block 5-HT receptor(15)(14).

According to Meltzer et a monoamine's neurotransmitter - Intropin antagonism theory, a higher quantitative association of drug affinity for monoamine neurotransmitter receptors relative to Intropin 2 receptor affinity will predict untypically and can make a case for SGAs' improved effectivity and reduced EPS social accountability. 5 PET findings prove that therapeutic dosages of Risperidone, Olanzapine, and Ziprasidone result in greater than seventieth occupancy of D2 receptors suggest that a certain threshold of D2 receptor antagonism may be required in the manufacture of neuroleptic pharmacological effects(14) .

## III. DRUG DELIVERY FOR SECOND GENERATION ANTIPSYCHOTICS

Second-generation antipsychotic drug delivery should be patient-centered, with the goal of delivering the drug to the brain with minimal adverse effects. Given the potency of most second-generation antipsychotic drugs, the purpose of medical delivery should be to reduce dose frequency as much as possible. The oral and injectable methods of administration are the most common routes of administration for second-generation antipsychotics on the market. Oral formulations include Orodispersible tablets, capsules, oral solutions, and sublingual tablets, and injectables include long-acting depot injections. It is possible to reduce the requirement for frequent dosing by using long-acting depot injections(17). Antipsychotics are administered by transdermal and intranasal routes, which have proven to be effective and creative.

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| Drug | FDA Approval date | Dosage form | Route of administration | Dose ranges | Pharmaceutical company | Brand name |
|---|---|---|---|---|---|---|
| Clozapine | 1990 | Tablet, suspension | Oral | 150–160 | Switzerland | Clozaril ® |
| Risperidone | 1993 | Tablet, injectable | Oral, injection | 2–8 | Johnson & Johnson | Risperdal® Risperdal consta® |
| Olanzapine | 1996 | Capsule, tablet, injectable | Oral, injection | 10–30 | Eli Lilly | ZYPREXA |
| Quetiapine | 1997 | Tablet | Oral | 300–800 | AstraZeneca | Seroquel® |
| Ziprasidone | 2001 | capsule, injectable | Oral, injection | 80–200 | Pfizer | Geodon® |
| Aripiprazole | 2002 | Tablet, injectable | Oral, injection | 10–30 | Otsuka/bristo-myers | Abilify® ABILIFY MAINTENA ® |
| Paliperidone | 2006 | Tablet, injectable | Oral, injection | 3–12 | JANSSEN PHARMACEUTICALS | Invega® INVEGA SUSTENNA® |
| Asenapine | 2009 | Sublingual tablets, patch system | Oral, transdermal | 10–20 | Schering-Plough HISAMITSU PHARMACEUTICAL CO INC | Saphris® SECUADO® |
| Iloperidone | 2009 | Tablet | Oral | 12–24 | Novartis AG | Fanapt® |
| Lurasidone | 2010 | tablet | Oral | 40-160 | Dainippon sumitomo pharma | Latuda® |
| Brexpiprazole | 2015 | Tablet | Oral | 2-4 | OTSUKA PHARMACEUTICAL | Rexulti® |
| Pimavanserin | 2016 | Tablet, capsule | Oral | 17–34 | ACADIA PHARMACEUTICALS | Nuplazid® |

**Table no. 1: Drug delivery for second generation antipsychotics**

## IV. ADVERSE EFFECTS OF ANTIPSYCHOTIC MEDICATIONS

As compared to first-generation antipsychotics, second-generation antipsychotics have fewer adverse medication effects(18). Patients on first-generation antipsychotics have reported akinesia, parkinsonism, dyskinesias, dystonia, and dysphoria(19)(3). Although the dopamine pathway is the primary likely target for all antipsychotics, many therapeutic and ADE (adverse drug effects) of SGAS are dependent on the combination of receptors occupied(20)(21)(22).

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About all SGAs show some common side effects which involves Low blood pressure, feeling dizzy, and/or increased heart rate, especially when standing up fatigue, sedation, dry mouth, agitation, increased appetite, constipation, headache, anxiety, upset stomach, feeling dizzy, drowsy or restless, muscle stiffness or spasms(23). Newer antipsychotics (2nd generation), clozapine & olanzapine, cause's problems related to metabolic syndrome, like obesity of type 2 diabetes mellitus(24)(25).

Second-generation antipsychotics have the following main adverse effects:

**Metabolic syndromes**

Patients with schizophrenia are twice as likely to develop diabetic metabolic syndrome as the general population(26)(19). They also have a two-fold increased risk of cardiovascular disease mortality(5). Olanzapine elevates cholesterol levels more than Aripiprazole, risperidone, and quetiapine, while risperidone raises cholesterol levels more than olanzapine(27)(28)(13).

**Akathisia**

The word "akathisia" comes from the Greek word "akathemi," which means "never sit down." This is a syndrome wherein the patient has muscle twitching and uneasiness(29). Risperidone and quetiapine are the most commonly prescribed SGAs in children, followed by Aripiprazole, Olanzapine, and Ziprasidone. SGAs, in particular akathisia, can cause EPSE (extrapyramidal side effects). Side effects of aripiprazole include agitation, headache, and akathisia. Mirtazapine may be effective in the treatment of akathisia(23).

**Pseudo parkinsonism**

Females and the elderly are the most typically affected. GEEman Tremor, rigidity, and postural irregularities are all symptoms of akinesia, bradykinesia, or reduced motor activity. Except for risperidone, SGAs carry a reduced prevalence of pseudo-parkinsonism. Anticholinergics have been shown to be effective in the treatment of pseudo parkinsonism, however this has not been properly investigated. This disorder is treated with benztropine and ethopropazine.

**Neuroleptic Malignant Syndrome**

Antipsychotic medication use can cause a life-threatening reaction, but this is rare. It can begin as early as the first week of antipsychotic therapy, but it can also progress over time. The neuroleptic malignant syndrome is characterized by labile blood pressure, skin flushing, tachypnoea, tachycardia, and sialorrhea, as well as a pallor (NMS)(30). According to some estimates, the death rate could be as high as 9% of the total population. 20 percent of the 177 NMS instances included patients underneath the age of eighteen. The first-line treatment for NMS includes benzodiazepines, skeletal muscle relaxants, and D2 agonist. In this case, electroconvulsive therapy has been performed(31).

Constipation, urine retention, dry mouth, and impaired vision are all anti-cholinergic symptoms of SGA. Impaired memory, dry mouth, constipation, tachycardia, blurred vision, suppression of ejaculation, and urine retention are all side effects of clozapine and olanzapine. If not addressed early on, these problems may worsen. Antipsychotic dose is lowered, adequate hydration is achieved by increased fluid intake, and oral lubricants are used. Lactose, sorbitol, and laxatives like senna are utilized as osmotic agents.(6)

**Cardiovascular**

ECG abnormalities such as a prolonged QT interval and orthostatic hypotension can develop with any antipsychotic(19). Paliperidone can develop cold or hot temperature sensitivity, and also QTC prolongation(30). QTc prolongation can also be caused by Ziprasidone, Asenapine, and Clozapine(26)(32).

**Tardive Dyskinesia/Syndrome (TD)**

It exhibits unusual involuntary motions in this situation. Buccolingual masticatory (BLM) or orofacial moments are examples. Frequent blinking, eye deviation, lip smacking, and brow arching are all indications. The abnormal involuntary movement scale (AIMS) and the Dyskinesia identification system are used to investigate TD. The DISCUS approach (condensed user scale technique) is used to detect TD in its early stages(23).

**Sexual Dysfunction**

Both FGAs and SGAs have negative consequences such as decreased arousal, decreased frequency of intercourse, and diminished desire. In both men and women, long-term hyperprolactinemia develops gynecomastia (mostly in men). Treatment includes use of prolactin sparing antipsychotics(6).

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## V. CLINICAL TRIALS IN ANTIPSYCHOTICS

In India, clinical trials expand the treatment therapies and development of alternatives for therapeutics for psychotic problems. Clinical trials reveal applications of them not only in the treatment of psychotic problems but also for palliative of disorders like burns, catatonia, cognitive disorders, Huntington disease and nutrition disorders to mitigate trauma and anxiety associated with chronic diseases and poor quality of life(33)(2).

In India, around 318 clinical studies are in process for 151 various disease conditions. For antipsychotics, around 30 clinical trials are completed for 6 different psychotic conditions.

| Sr. no. | Disease condition | Clinical trial phase | Study type | Interventions | Study duration | Allocation | Actual enrollment |
|---|---|---|---|---|---|---|---|
| 1 | Schizophrenia(34) | Phase 3 | Interventional | Drug: Placebo<br>Drug: RO4917838<br>Drug: Antipsychotics (Standard of Care) | 3 years 5 month 15 days | Randomized | 629 |
| 2 | Schizophrenia(35) | Phase 2 | Interventional | Drug: Bacopa monnieri<br>Drug: Nardostachys jatamansi<br>Drug: Olanzapine | 2 years | Randomized | 200 |
| 3 | Schizophrenia(36) | Phase 3 | Interventional | Drug: paliperidone ER<br>Drug: Placebo | 1 year 7 months | Randomized | 201 |
| 4 | Schizoaffective Disorder Psychotic Disorder(37) | Phase 3 | Interventional | Drug: Placebo<br>Drug: Paliperidone ER | 1 year 6 months | Randomized | 307 |
| 5 | Schizophrenia(38) | Phase 3 | Interventional | Drug: RISPERDAL CONSTA<br>Drug: Paliperidone palmitate | 2 years 2 months | Randomized | 1221 |
| 6 | Schizophrenia(39) | Phase 3 | Interventional | Dementia Praecox | 5 years 1 month | Non-randomized | 400 |

Table no.2: Clinical trials on second generation antipsychotics from NCBI

## VI. CONTRAINDICATIONS

Antipsychotic medication is not advised for the treatment of dementia-related psychosis. The FDA has issued a boxed warning regarding the increased risk of stroke in seniors taking second-generation antipsychotics(7). Antipsychotics should

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be avoided during pregnancy, particularly in the first trimester, and should only be used if the benefits outweigh the risks. Breastfeeding is discouraged because antipsychotics are released in breast milk.Second-generation antipsychotics and other medications that prolong the QTc interval should be avoided, according to the guidelines(13).

## VII. PATENT SURVEY FOR NOVEL ANTIPSYCHOTICS

For patent purposes, novel antipsychotics have been studied. Some of the interesting patents are summarized as below.

| Sr. No. | Patent | Formulation dosage form | Composition | Claims |
|---|---|---|---|---|
| 1. | WO2013091334A1 | | Rapamycin + risperidone, olanzapine, quetiapine, and aripipramine | Rapamycin is found in a drug used to treat schizophrenia. |
| 2. | US8173107B2 | Inhalation | loxapine | Inhalation aerosol for loxapine |
| 3. | US20170112801A1 | Inhalation | Cannabinoid + second-generation antipsychotics | An inhalant is included in the delivery method. |
| 4. | WO2007067714A2 | Marketed formulations | second-generation antipsychotics + opioid receptor antagonist. | To address weight gain or pain sensitivity as a side effect |
| 5. | US7932249B2 | sustained release or depot formulations | Olanzapine pamoate dihydrate | Olanzapine pamoate dihydrate is used to treat schizophrenia, acute mixed or manic episodes associated with bipolar I disorder, agitation associated with schizophrenia, agitation associated with bipolar I disorder, agitation associated with dementia, or borderline personality disorder. |
| 6. | WO2010006249A1 | Sustained release formulations | psychoactive drug(olanzapine) and a tyrosine - derived polyarylate. | The formulation comprising claim 1, where quantities are such that the formulation releases the psychoactive for at least 1 to 5 days when tested in vitro under physiological conditions at 37°C. |
| 7. | US20110039806A1 | Modified release | an antipsychotic drug and a tetracycline(minocycline) | A combination therapy consisting of an antipsychotic |

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| | | | | |
|---|---|---|---|---|
| | | | | medication and a tetracycline for the treatment of psychotic diseases, including schizophrenia. |
| 8. | CN103690516A | oral membrane | Aripiprazole | Aripiprazole, pullulan polysaccharide, and additive make up the majority of an Aripiprazole pelliculae pro cavo oris. |
| 9. | WO2013080046A1 | Salt form | lurasidone hydrochloride. | At least one CNS condition, such as bipolar disorder or mixed depression, must be treated. |
| 10. | WO2011143755A1 | | NO donor + second-generation antipsychotics | An organic NO donor, an inorganic NO donor, a NO-releasing medication, a binary NO producing system, a chemical that serves as a physiological precursor of nitric oxide, or a NO mimetic compound are all examples of NO donors. |
| 11. | US7973043 | Marketed formulation | Antipsychotics + antidepressant | Combination of antipsychotics and dopamine system stabilisers, as well as a newer antidepressant |
| 12. | US5453425A | Oral aqueous solution | Risperidone | Water, risperidone, or a pharmaceutically approved acid addition salt are given orally. |
| 13. | EP2854858A1 | Implant | Risperidone or paliperidone | An injectable intramuscular depot composition suitable for forming an in situ solid implant in the body, comprising risperidone and/or paliperidone, or any |

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| | | | | pharmaceutically acceptable salt thereof, in any combination, a biocompatible copolymer based on lactic and glycolic acid with a monomer ratio of lactic to glycolic acid of from 45:55 to 55:45, and DMSO as solvent. |
| 14. | US9532991B2 | sustained release microsphere | Risperidone | Risperidone or 9-hydroxy risperidone or salts thereof are included in the microsphere formulation, as well as a polymer blend that includes a first uncapped lactide-glycolide copolymer and a second uncapped lactide-glycolide copolymer, where the first uncapped lactide-glycolide copolymer has a high intrinsic viscosity and the second uncapped lactide-glycolide cop |
| 15. | EP0697019B1 | | Risperidone pamoate | Aqueous suspension is an injectable dose type. |
| 16. | EP0733367A1 | Polymer coated tablet | olanzapine | Hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methylcellulose, and ethyl cellulose are among the polymer coat options. |

## VIII. CONCLUSION

Newer antipsychotics that operate on both types of receptors have shown clinical acceptability in the treatment of psychotic illnesses; especially for the first line treatment of scizophrenia. This reduces extrapyramidal symptoms and makes them a preferred therapy option for doctors; however, they do have a few unusual negative effects. Clinical investigations in India have revealed the use of newer antipsychotics in a variety of treatments. Novel routes for drug delivery of newer antipsychotics, such as nasal drops or spray,

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transdermal patches, and mouth dissolving films, may also be considered by researchers and scientists.

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