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Seven decades of Anti-Psychotic Drugs: A Review

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Abstract *— Since the discovery of the first effective antipsychotic medication (APM) in the mid 1950s, efforts to enhance their efficacy have been limited, despite improvements in tolerability. This stagnation is evident in effectiveness trials conducting in Europe and the United States. Several factors contribute to the failure to develop more effective APMs, including the absence of appropriate assessment tools for core symptoms domains in schizophrenia, reliance on the dopamenergic hypothesis, and the prolifration of "me too" drugs. The classification of APMs is also convoluted, grouping together second-generation, partial agonists, and multimodel APMs despite significant differences in their mechanism of action. Chllenges such as inadequate sample sizes, lack of statistical measures correlating with clinical significanse, and the high cost of newer APMs further hinder drug development. Additionally, there is lack of early predictors of antipsychotic response and tools to optimize APM efficacy. Suboptimal APM use by mental health providers, including excessive maintenance doses and irrational polypharmacy, exacerbates effectivness and medication adherence issues. Despite these challenges,there have been advancaments in APM tolerability and the development of long-acting injectables to address medication nonadherence. This critical review examines 70 years of antipsychotic development, identifies reasons for the failure to develop more effective APMs , and suggestes future directions in this field.*

Keywords *— **Antipsychotic Medication (APM), Efficacy Enhancement Efforts, Dopaminergic Hypothesis, Drug Classification, Medication Adherence Issues***

I. INTRODUCTION

- **Shift in Pharmacotherapy Focus:**
  - Movement from monoamine hypothesis to glutamatergic and GABAergic
  - Mechanisms in depression treatment.
  - Challenge in transitioning antipsychotic paradigm beyond dopaminergic hypothesis in schizophrenia
- **Challenges in Antipsychotic Medication Development:**
  - Difficulty in developing non-dopaminergic antipsychotic medications.
  - Limited efficacy and lack of significant differences in mechanisms of action among current antipsychotics.
    - Antipsychotic response

defined by 20% reduction in PANSS scores.

- **Diagnostic Limitations:**
  - Syndromic diagnosis of major psychiatric disorders.
  - Reliance on theoretical diagnostic tools like DSM and ICD.
  - Inadequate sample sizes hindering subgroup analyses and hypothesis generation.
  - Restrictions on federal funding to RdoC, which lacked scientific rigor.

- **Research Gaps:**
  - Lack of early predictors or intermediate phenotypes for antipsychotic response.
  - Absence of research on maintenance dose and length of antipsychotic therapy.
  - Limited use of measures like therapeutic drug monitoring and pharmacogenetic testing.
  - Overuse of high antipsychotic doses, especially in severe cases, leading to compromised tolerability and adherence.
- **Ownership of APM Development:**
  - Pharmaceutical industry primarily responsible due to lack of clinical trial funding by NIMH.
  - Post-marketing and repurposing trials as less biased alternatives.
  - Limitations of preclinical trial results in generalizability to the population.
- **Cost and Access Issues:**
  - Newly approved APMs often expensive and not covered by Medicaid.
  - Statistical limitations of clinical trials, including reliance on $p<0.05$ and increasing placebo responses.
  - Strategies proposed to reduce placebo response but none foolproof.
- **Current Progress and Considerations:**
  - Despite obstacles, some progress in tolerability observed with second –generation APMs and LAIs.
  - Higher dosing threshold for adverse effects.
  - Impact of LAIs on long –term clinical and functional outcomes.
  - Overview of antipsychotic medication classes over the past 70 years.
    - **Scope Limitation:**
  - Focus on schizophrenia and other psychotic disorders; not covering bipolar disorder management.

Older Antipsychotic Medication Overview:

1. **Classification:**

- Older or conventional APMs are categorized into high potency and low potency.
- Low –potency APMs have a broader range of actions, affecting muscarinic, histaminic and alpha-1 adrenergic receptors, leading to various adverse effects.
- High-potency APMs primarily target dopamine-2 (D2) receptors, resulting in adverse effects mainly related to D2 blockade.

Adverse Effects of Older Antipsychotic Medication:

1. **Low –potency APMs:**

- Adverse effects including dry mouth,

blurred vision, urinary retention, constipation, tachycardia, confusion, and worsening of cognitive function.

- Additional effects such as sedation, short-term weight gain and postural hypotension are also observed.

2. High –Potency APMs:

- Adverse effects primarily stem from D2 receptor blockade, leading to extra pyramidal symptoms (EPS), hyperolactinemia and exacerbation of negative symptoms.

Specific Adverse Effects of Individual Medications:

1. **Haloperidol:**
   - Dose- related mild adverse effects.
2. **Clozapine:**
   - Mild adverse effects, not dose-related.
3. **Risperidone:**
   - Dose-related adverse effects, generally mild.
4. **Olanzapine:**
   - Generally mild adverse effects at lower dose.
5. **Quetiapine:**
   - Adverse effects are absent.
6. **Ziprasidone:**
   - Adverse effects are dose related.
7. **Paliperidone:**
   - Dose-related mild adverse effects.
8. **Aripiprazole:**
   - Adverse effects are almost absent except for akathisia.
9. **Iloperidone:**
   - Generally mild adverse effects at all doses.
10. **Asenapine:**
    - Dose –related adverse effects, generally mild except for akathisia.
11. **Lurasidone:**
    - Generally mild adverse effects except for dose-related akathisia.
12. **Cariprazine:**
    - Adverse effects are almost absent except for akathisia.
13. **Brexpiprazole:**
    - Adverse effects are almost absent except for akathisia.
14. **Lumateperone:**
    - Dose-related, generally low adverse effects.

Clinically Significant Adverse Effects:

- Low –potency APMs pose a risk of QTc prolongation, leading to sudden cardiac death.
- High-potency APMs may cause tardive dyskinsia and neuroleptic malignant syndrome with long-term use.

Benefits of Some Adverse Effects:

- Adverse effects like sedation and weight gain with histamine-1 receptor blockade, reduction in hypertension with alpha-1 receptor blockade, and protection from EPS with anticholinergic effects may be beneficial in some patients.

.**Special Mention:**

- Loxapine is effective in schizophrenia and major depressive disorder due to its metabolite amoxapine, which has antidepressant properties.
- Molindone has moderate D2 receptor affinity, potentially benefiting patients not responding to other APMs.
- Pimozide is FDA-approved for

Tourette's syndrome treatment.

Advances in Antipsychotic Treatments:

- Long-acting injectablea (LAI) with high-potency APMs have improved adherence and maintenance of antipsychotic response, reducing psychotic relapse and rehospitalizations.

Summary:

- Serotonin and dopamine antagonism (SDA) with SGAPMs may mitigate dose- related adverse effects but with limited efficacy, except for clozapine, which remains the gold standard for managing treatment-refractory schizophrenia.

Hyperprolactinemia with Antipsychotic Medications:

- Haloperidol and risperidone show persistent elevation of prolactin levels.
- Clozapine exhibits transient elevation, if any.
- Olanzapine typically shows transient elevation.
- Quetiapine does not cause hyperprolactinemia.
- Ziprasidone's elevation in prolactin levels is transient.
- Paliperidone has a dose-related increase in prolactin similar to risperidone.
- Aripirazole does not cause hyperprolactinemia.
- Iloperidone shows persistent elevation.
- Asenapine's effect on prolactin levels is generally insignificant.
- Lurasidone exhibits a dose-related increases in prolactin.
- Cariprazine and brexpiprazole do not cause hyperprolactinemia.
- Lumateperone shows a generally low dose-related increase in prolactin.

Special Mentioned Antipsychotic Medications:

- Loxapine is effective in both schizophrenia and major depressive disorder due to its metabolite amoxapine, which possesses antidepressant properties.
- Molindone, with a moderate affinity for D2 receptors, may benefit patients unresponsive to other antipsychotics.
- Pimozide is the only FDA-approved treatment for Tourette's syndrome.

Advancements in Antipsychotic Treatments:

- Long-acting injectables (LAI) have been developed with high-potency APMs like haloperidol and fluphenazine, followed by newer APMs such as risperidone, paliperidone, and aripiprazole.
- LAIs improve medication adherence, maintenance of antipsychotic response, and prevent psychotic relapse and rehospitalizations.

Second-Generation Antipsychotic Medications (SGAMs):

- This class includes all APMs developed after conventional APMs, despite significant differences in mechanisms of action.
- There may be confusion and misperception due to the diversity within this class.

Summary on Second-Generation Antipsychotic Medications:

- While SGAPMs offer some relief from dose-related adverse effects due to serotonin and dopamine antagonism, their efficacy benefits are not significantly different from conventional APMs.
- Clozapine stands out as the gold standard for managing treatment-refractory

schizophrenia, although it hasn't been extensively compared with other SGAPMs in post-marketing trials.

Key Points in Antipsychotic Medications and Classification:

1. **Clozapine's Classification:**

   Clozapine, despite being labeled as a newer antipsychotic medication (APM), was approved for clinical use in 1971, preceding some older or first-generation APMs. Its FDA approval came in 1989, possibly delayed due to concerns regarding bone marrow toxicity.

2. **Complexity of APM Classification:**

   The classification of antipsychotic medications into older and newer categories is not straight forward .For example, loxapine, considered as older APM, exhibits stronger D2 receptor blockade to 5HT2A, a characteristic more typical of older APMs.

3. **Atypical Properties of Risperidone:**

   Risperidone, an early atypical APM introduced after clozapine, presents a challenge as it loses its atypical characteristics at higher doses, resembling high-potency APMs like haloperidol in terms of prolactin levels.

4. **Unique Efficacy of Clozapine:**

   Clozapine stands out for its efficacy in treatment-refractory schizophrenia (TRS) and its anti-suicidal effects. If not for its bone marrow toxicity, it could be considered as the first- line treatment option for TRS, improving clinical outcomes and prognosis during the onsetof first-break psychosis.

5. **Challenges in Clozapine Utilization:**

   Despite its efficacy, clozapine is underutilized in the United States and other developed countries due to provider hesitancy. Concerns about clozapine-induced agranulocytosis necessitate strict monitoring under Risk Evaluation and Mitigation Strategy (REMS), which contributes to patient reluctance, particularly related to needle-associated fears.

6. **European Approaches to Clozapine Monitoring:**

   Some European countries, such as the UK, have adopted less stringent monitoring intervals for clozpine treatment, reflecting a nuanced approach to balancing safety and accessibility while addressing concerns about late-onset agranulocytosis.

   These points highlight the complexity of classifying antipsychotic medications and the challenges associated with the utilization of clozapine despite its proven efficacy in specific patient populations.

Clozapine: Unique Characteristics and Considerations

- **Adverse Effects:** Clozapine is associated with various adverse effects, including myocarditis, megacolon, and lowering of the seizure threshold. Notably, clozapine-induced drooling (sialorrhea) can significantly impact oral hygiene and quality of life if left untreated. However, extrapyramidal symptoms (EPS) and hyperprolactinemia are relatively rare with clozpine due to its unique receptor binding profile.
- **Efficacy in Treatment –Resistant Schizophrenia (TRS):** Clozapine remains the only effective APM for TRS. However, not all treatment-refractory patients respond to clozapine. Utilizing laboratory tools like therapeutic drug monitoring (TDM) can optimize clozpine response in some patients.
- **Metabolic Pathways and Genetic Polymorphism:** Clozapine undergoes metabolism via cytochrome P450 (CYP) enzymes, particularly CYP1A2, CYP2D6, and CYP3A4. Genetic polymorphism in these enzymes can influence clozapine's efficacy and tolerability.
- **Therapeutic Drug Monitoring (TDM):** The ratio between clozapine and its primary metabolite, norclozapine (Clz/Nclz), can predict the activity of CYP1A2 and provide insights into clozapine's

efficacy and safety .**Optimal** therapeutic level range between 350 ng/ml and 600ng/ml, with levels above 1000 ng/ml considered toxic.

- **Augmentation Strategies:** In cases where clozapine response is **inadequate**, augmentation strategies like low-dose lamotrigine and aripiprazole may be effective.

Comparison with Other Second-Generation Antipsychotic Medications(SGAPMs):

1. **Olanzapine:** While olanzapine shares some adverse effects profiles with clozapine, it does not demonstrate the same efficacy, despite structural similarities.Olanzapine is commonly prescribed, but its long-acting formulation is underutilized due to post- injection delirium sedation syndrome.
2. **Quetiapine:** Quetiapine exhibits low and transient binding affinities for D2 receptors, leading to lower prolactin levels. However, its efficacy at the recommended daily doses may be more effective, especially in managing secondary psychosis in conditions like Parkinson's disease and dementia.
3. **Pimavanserin:** A newly approved medication, pimavanserin, offers a relatively benign option for managing secondary psychosis, particularly in Parkinson's disease and dementias, where transient dopamine blockade is desirable.

Weight Gain Profiles of Antipsychotic Medications:

- **Haloperidol:** Associated with mild weight gain (<0.5 kg in 6-16 weeks).
- **Clozapine:** Leads to significant weight gain (4 kg in 10 weeks).
- **Risperidone:** Results in moderate weight gain (2 kg in 10 weeks).
- **Olanzapine:** Causes significant weight gain (4 kg in 10 weeks).
- **Quetiapine:** Induces moderate weight gain (2 kg in 10weeks).
- **Ziprasidone:** Considered weight – neutral, with potential benefits for reducing low- density lipids and triglycerides.
- **Paliperidone:** Exhibits similar weight gain profile to risperidone.
- **Aripiprazole:** Generally associated with mild weight gain (0.6 kg in 6 weeks).
- **Iloperione:** Leads to moderate weight gain (2 kg in 4 weeks).
- **Asenapine:** Causes mild weight gain (1 kg in 52 weeks).
- **Lurasidone:** Results in mild weight gain (1 kg in 6 weeks).
- **Cariprazine:** Associated with mild weight gain (0.4 kg to 1 kg in 3-8 weeks).
- **Brexpiprazole:** Induces mild weight gain (1.3 kg in 6 weeks).
- **Lumateperone:** Considered Wight neutral.

Ziprasidone: Unique Pharmacological and Clinical Characteristics

- Metabolic **Profile:** Ziprasidone is the first antipsychotic to report near weight- neutral effects and may even reduce low-density lipids and triglycerides compared to other SGAPMs.
- Clinical **Utility:** Ziprasidone is often used as a first-line treatment for agitation and aggression due to its rapid onset of antipsychotic effects without sedation.
- **Receptor Action Profile:** The chimerical structure of ziprasidone

results in diverse receptor actions, including 5HT2A inverse agonism, D2 receptor antagonism, 5HT1A receptor agonism and moderate serotonin and norepinephrin pump blockade.

- Efficacy **for Depressive and Negative Symptoms:** Ziprasidone demonstrates efficacy for depressive and negative symptoms in schizophrenia and schizoaffective disorders with fewer adverse effects, particularly EPS, hyperprolactinemia and metabolic effects.
- Metabolism **and Drug Interactions:** Ziprasidone is primarily metabolized in the liver with a half-life of about 7 hours at recommended doses. It poses a low risk of pharmacokinetic drug interactions.

QTc Prolongation Risk of Antipsychotic Medications

1. **Haloperidol:** Generally low risk if given orally.
2. **Clozapine:** Exhibits low to mild risk (<10msec above baseline).
3. **Risperidone:** Presents mild risk (12 msec above baseline).
4. **Olanzapine:** Demonstrates low risk (<7 msec above baseline).
5. **Quetiapine:** Shows moderate risk (16 msec above baseline).
6. **Ziprasidone:** Displays moderate risk (12-20 msec above baseline).
7. **Paliperidone:** Similar to risperidone.
8. **Aripiprazole:** Poses low risk.
9. **Iloperidone:** Carries moderate risk (>10 msec above baseline).
10. **Asenapine:** Indicates no to low risk (2 to 5 msec above baseline).
11. **Lurasidone, Cariprazine, Brexpiprazole, Lumateperone:** Shows no risk

Paliperidone: Unique Pharmacological Characteristics and Clinical Utility

1. **Metabolism and Receptor Affinity:** Paliperidone, a metabolite of risperidone, exhibits stronger binding affinity for D2 receptors but does not significantly increase prolactin elevation or EPS compared to risperidone.
2. **Half-Life and Administration:** Paliperidone has a longer half-life than risperidone, allowing for once-daily oral administration. Its status as a metabolite may make it a safer option in patients with liver dysfunction or polypharmacy.
3. **Longer –acting Injectable Formulations:** Paliperidone's long-acting injectables (LAI) formulations provide flexibility in dosing intervals (monthly, quarterly, and biannually), reducing the frequency of clinic visits and potentially enhancing cost-effectiveness.

Iloperidone: Pharmacological Characteristics and Clinical Considerations

1. **Noradrenergic α Receptor Blockade:** Iloperione exhibits potent blockade of noradrenergic α receptors, contributing to potential postural hypotension and dizziness. Slow titration is necessary to mitigate these adverse effects.
2. **Akathisia Risk:** Despite its potent noradrenergic α receptor antagonism, ilopeidone may have one of the lowest risks for akathisia compared to other

EPS, potentially due to its impact on noradrenergic neurotransmission.

3. **Management of Comorbid Conditions:** Iloperidone may be beneficial in managing comorbid hypertension in psychotic or posttraumatic patients due to it are α receptor antagonism.
4. **Weight Gain and QTc Prolongation:** Weight gain with iloperidone falls in the moderate range, comparable to risperidone. However, it carries some risk for QTc prolongation.

Asenapine: Sublingual Administration and Pharmacological Profile

1. **Administration:** Asenapine is available as a sublingual preparation and recently, as a transdermal treatment in the United States. Sublingual administration results in rapid onset of antipsychotic effects and higher bioavailability due to bypassing first-pass metabolism.
2. **Dosing Consideration:** Unlike some SGAPMs asenapinedoes not require dose titration to avoid adverse effects. The starting dose can be effective, and once- daily dosing is feasible.
3. **Weight Gain and Receptor Affinity:** Asenapine demonstrates lower weight gain compared to olanzapine and risperidone. Its antagonism of 5HT7 and adrenergic α2 receptors may potentially augment antidepressant response and offer cognitivebenefits.

Lurasidone: Pharmacokinetics and Receptor Affinity

1. **Absorption and Food Interaction:** Lurasidone's absorption is affected by food but to a lesser extent than ziprasidone. Food increases lurasidone exposure and maximum concentration, albeit modesty.
2. **Receptor Affinity:** Lurasidone exhibits strong affinity for serotonin 5HT7 receptors, potentially impacting cognition. It also acts as a partial agonist at 5- HT1A receptors, contributing to procognitive and potential antidepressant effects.
3. **Safety Profile:** Unlike some SGAPMs, lurasidone has minimal affinity for alpha-1 noradrenergic receptors, reducing the risk for orthostatic hypotension. Its negligible affinity for 5HT2C and histamine H1 receptors predicts a low potency for weight gain and sedation, respectively.

Partial Agonist of Dopamine-2 (D2) Receptors

1. **Concept of Partial Agonism:** Partial agonists of D2 receptors, such as aripiprazole, offer a novel approach by stabilizing dopamine activity depending on baseline neurotransmitter levels. This mechanism differs from full D2 receptor antagonists and may have implications for symptom management in schizophrenia.
2. **Adverse Effect Profile:** Partial agonists may offer a more favorable tolerability profile for adverse effects related to D2 receptor blockade, such as EPS and hyperprolactinemia, compared to full antagonists. Dose-related adverse effects are relatively minimal except for akathisia.

Aripiprazole: Partial Agonist with Unique Pharmacological Properties

1. **D2 Receptor Affinity:** Aripiperazole, approved in 2002, exhibits potent affinity for D2 receptors but acts as a partial agonist rather than a full antagonist, supporting the concept

of system stabilization.

2. **Adverse Effect Profile:** Aripiperazole's partial agonism results in a favorable adverse effect profile, including minimal prolactin elevation and reduces risk of EPS except for akathisia, which is not dose-dependent. Lower incidence of weight gain and metabolic syndrome is observed.
3. **Clinical Applications:** Its partial agonism at D2 and 5HT1A receptors contributes to efficacy across various psychiatric disorders. Aripiperazole is available as a long-acting injectable (LAI), offering sustained plasma levels and reduced hospitalization rates in schizophrenia patients.

Cariprazine: Novel Antipsychotic with Distinct Pharmacodynamic Profile

1. **Indications:** Cariprazine is indicated for schizophrenia and acute manic or mixed episodes associated with bipolar disorder as a monotherapy, distinguishing it from other antipsychotics.
2. **Pharmacodynamics:** Cariprazine exhibits partial agonist activity at D2, D3 and 5HT1A receptors, with a higher affinity for D3 than D2 receptors. Moderate histamine antagonism, low alpha-1 antagonism, and negligible muscarinic cholinergic receptor affinity contribute to its unique profile.
3. **Metabolic Effects and Akathisia:** Cariprazine treatment shows comparable weight gain and metabolic parameters to placebo, with mild to moderate akathisia reported. Higher doses (>3 mg per/day) may increase the risk of akathisia, highlighting dose-dependent effects.
4. **Biologically Active Metabolites:** Cariprazine has two active metabolites, desmethyl and didesmethyl cariprazine, responsible for long-term efficacy and tolerability. Its pharmacokinetic properties contribute to its clinical utility and safetyprofile.

These antipsychotic medications offer distinct pharmacological profiles and clinical applications, providing clinicians with options for tailored treatment approaches in psychiatric disorders.

Brexpiperazole: Latest D2 Receptor Partial Agonist

1. **Indications:** Approved for schizophrenia treatment and adjunctive use in MDD patients with inadequate response to standard antidepressant therapy.
2. **Pharmacodynamics:** Acts as a partial agonist at D2 and 5HT1A receptors and an antagonist at serotonin 5HT2A receptors, with less intrinsic activity at D2 receptors compared to aripiprazole
3. **Clinical Efficacy:** Demonstrates significant improvements in schizophrenia symptomatology and psychosocial functioning compared to placebo, with reduced time to relapse in long term trials.
4. **Safety Profile:** Generally well/tolerated with a lower incidence of activating sedating adverse effects, minimal change as per changes in QT interval and metabolic parameters, and moderate weight gain.

Lumateperone: Multimodal Antipsychotic Medication

1. **Novel Mechanism of Action:** Acts differently from earlier APMs by modulating dopamine serotonin antagonism and exhibiting partial agonism at presynaptic D2 receptors and antagonism at postsynaptic D2 receptors.
2. **Antipsychotic Efficacy:** Lower D2 receptor blockade results in a much lower risk of D2 receptor/mediated adverse effects, such as EPF and hyperprolactinemia.
3. **Potential for Affective Disorders:** Shows efficacy in affective disorders, possibly due to its unique mechanism glutamatergic effects.

Future Directions in Schizophrenia Treatment

1. **Long-Term RCTs:** Conducting large/sample randomized controlled trials to determine optimal treatment duration and maintenance doses, addressing the heterogeneity in schizophrenia and treatment resistance.
2. **Shift in Hypotheses:** Transitioning from dopaminergic to glutamatergic and GABAergic hypotheses to address negative and cognitive symptom domains not adequately managed by current APMs.
3. **Collaborative Efforts:** Multicenter collaborations, partnerships with industry and government and academic consortia are essential for conducting extensive trials and generating new hypotheses for future investigations.

Advanced Schizophrenia Treatment: A Multifaceted Approach

- **Translational Neuroscience:** Utilizing neuroimaging, pharmacogenomics, proteomics, metabolomics and epigenomics to develop novel drug targets, predict drug response and minimize adverse effects for personalized medicine.
- **Improved Medication Adherence:** Personalized antipsychotic treatments that are more efficacious and tolerable can enhance medication adherence, especially through the promotion of long-acting injectables.

II. CONCLUSION

Despite the progress made in schizophrenia treatment, there are still significant unmet needs. Long-term, large-sample randomized controlled trials are crucial to determine optimal treatment duration and maintenance doses, addressing the heterogeneity in schizophrenia and treatment resistance. Furthermore, there is a necessity for a paradigm shift from the dopaminergic to glutamatergic and GABAergic hypothesis to manage negative and cognitive symptoms better. Collaborative efforts involving multicenter collaborations, partnerships with industry and government and academic consortia are essential for conducting extensive trials and generating new hypotheses for future investigations.

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