ISSN: 2582-4686 SJIF 2021-3.261,SJIF 2022-2.889,
2024-6.875 ResearchBib IF: 9.948 / 2024

THE MULTIDISCIPLINARY JOURNAL OF SCIENCE AND TECHNOLOGY

VOLUME-5, ISSUE-10

CLINICAL PHARMACOLOGICAL APPROACH TO THE USE OF NEUROLEPTIC DRUGS IN DEPRESSIVE SYNDROME

Akhmedov Bahodir Urolovich
Assistant intern of the Department of Pharmacology,
Clinical Pharmacology and Medical Biotechnology, ASMI

Abstract. The clinical use of neuroleptic (antipsychotic) drugs in depressive syndromes represents a complex intersection between psychopharmacology and clinical psychiatry. Traditionally employed in the management of psychotic disorders, certain neuroleptic agents have demonstrated significant efficacy as adjuncts or augmenting agents in depressive disorders, particularly those resistant to conventional antidepressant therapy. Their pharmacological effects extend beyond dopamine receptor antagonism, encompassing modulation of serotonergic, noradrenergic, and glutamatergic neurotransmission. This article examines the pharmacodynamics, pharmacokinetics, clinical applications, and safety considerations of neuroleptic drugs in depressive syndromes, highlighting both their therapeutic potential and the challenges associated with their use.

Keywords: neuroleptics, depressive syndrome, antipsychotics, pharmacology, dopamine antagonists, serotonin modulation.

INTRODUCTION

Depressive syndrome, in its clinical expression, constitutes a heterogeneous group of affective disorders characterized by persistent sadness, anhedonia, psychomotor retardation, cognitive impairment, and vegetative dysfunctions. While antidepressants remain the mainstay of therapy, a substantial proportion of patients — estimated at 20–30% — exhibit incomplete response or treatment resistance. This clinical challenge has prompted the exploration of adjunctive pharmacological strategies, among which neuroleptic drugs have gained considerable attention [1].

Historically, neuroleptic agents were confined to the treatment of schizophrenia and other psychoses due to their ability to block dopamine D_2 receptors and suppress hallucinations and delusions. However, modern psychopharmacology has revealed that certain atypical antipsychotics possess complex receptor activity profiles that influence mood regulation, anxiety, and cognitive processes. These properties have led to their inclusion in treatment algorithms for major depressive disorder (MDD) with psychotic features, bipolar depression, and treatment-resistant depression (TRD). Understanding their clinical pharmacology — particularly their receptor selectivity, dose-response relationship, and interaction with antidepressants — is essential for rational, effective, and safe use in depressive syndromes.

MATERIALS AND METHODS

The classical pharmacological hallmark of neuroleptics is dopamine D_2 receptor blockade in the mesolimbic system, which reduces psychotic symptoms. However, depressive syndromes often involve not only dopaminergic dysregulation but also abnormalities in serotonergic and noradrenergic systems. Atypical or second-generation antipsychotics (SGAs) such as quetiapine, olanzapine, aripiprazole, risperidone, and ziprasidone exhibit complex receptor binding profiles that provide both antidepressant and anxiolytic effects.

For example, quetiapine acts as a moderate D_2 receptor antagonist and potent 5-HT_2A receptor blocker, leading to enhanced serotonin transmission in key brain regions associated with mood.

ISSN: 2582-4686 SJIF 2021-3.261,SJIF 2022-2.889,
2024-6.875 ResearchBib IF: 9.948 / 2024

THE MULTIDISCIPLINARY JOURNAL OF SCIENCE AND TECHNOLOGY

VOLUME-5, ISSUE-10

Additionally, its active metabolite norquetiapine inhibits norepinephrine reuptake, contributing to its intrinsic antidepressant properties. Aripiprazole, a partial agonist at D_2 and 5-HT_1A receptors and an antagonist at 5-HT_2A receptors, stabilizes dopaminergic activity — enhancing it where deficient (such as in depression) and reducing it where excessive (as in psychosis) [2].

These multidimensional receptor actions modulate cortico-limbic circuits implicated in mood regulation, restoring balance in neurotransmission networks that underlie depressive pathology. Therefore, neuroleptics in this context act not merely as antipsychotics but as neurochemical stabilizers capable of influencing both affective and cognitive domains.

RESULTS AND DISCUSSION

Neuroleptic drugs display wide variability in absorption, metabolism, and elimination, which greatly influences their therapeutic profiles. Most atypical antipsychotics are highly lipophilic and exhibit extensive plasma protein binding, allowing for prolonged half-lives and steady-state concentrations with once-daily dosing. They undergo hepatic metabolism predominantly through cytochrome P450 isoenzymes — particularly CYP2D6, CYP3A4, and CYP1A2 — necessitating caution in polypharmacy and in patients with hepatic impairment.

Quetiapine has a half-life of 6–8 hours, requiring multiple daily doses for acute management, while olanzapine and aripiprazole possess longer half-lives exceeding 24 hours, supporting once-daily regimens. Genetic polymorphisms affecting CYP450 enzymes may influence individual responses and the risk of adverse effects, highlighting the emerging importance of pharmacogenomic assessment in personalized psychopharmacology.

The pharmacokinetics of neuroleptics also bear implications for drug interactions with antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), or tricyclic antidepressants. Certain SSRIs (notably fluoxetine and paroxetine) inhibit CYP2D6 metabolism, potentially elevating antipsychotic plasma levels and predisposing to extrapyramidal symptoms or sedation. Hence, careful dose titration and clinical monitoring are imperative in combined regimens.

The use of neuroleptics in depressive syndromes extends across several clinical contexts:

Major Depressive Disorder with Psychotic Features:

In psychotic depression, where delusions or hallucinations accompany severe depressive symptoms, the combination of an antidepressant with a neuroleptic is considered the treatment of choice. Clinical studies have demonstrated that this combination is superior to either agent alone. For instance, the pairing of fluoxetine with olanzapine has shown robust efficacy in reducing both depressive and psychotic symptoms, attributed to synergistic serotonergic and dopaminergic modulation [4].

Treatment-Resistant Depression (TRD): In patients who fail to respond to at least two adequate trials of antidepressants, augmentation with atypical neuroleptics is a well-validated strategy. Aripiprazole, quetiapine XR, and brexpiprazole have been approved for this purpose, as they enhance mood and reduce anhedonia through dopaminergic and serotonergic partial agonism.

Bipolar Depression: Neuroleptics such as quetiapine and lurasidone are first-line treatments for bipolar depression due to their dual efficacy in managing depressive episodes without triggering mania, a risk associated with conventional antidepressants. Their ability to modulate multiple neurotransmitter systems allows mood stabilization and cognitive improvement without significant dopaminergic blockade.

Anxiety and Agitated Depression: In certain subtypes of depression characterized by psychomotor agitation, irritability, or comorbid anxiety, low-dose neuroleptics exert tranquilizing effects by

ISSN: 2582-4686 SJIF 2021-3.261,SJIF 2022-2.889,
2024-6.875 ResearchBib IF: 9.948 / 2024

VOLUME-5, ISSUE-10

antagonizing dopaminergic and adrenergic receptors. This sedative property is particularly useful in the early phase of treatment or in elderly patients intolerant to benzodiazepines.

The therapeutic potential of neuroleptics in depression must be balanced against their side-effect profiles. Extrapyramidal symptoms (EPS) such as rigidity, tremor, and akathisia remain risks, especially with higher doses or in combination with serotonergic agents. Atypical antipsychotics have a lower propensity for EPS due to preferential limbic over striatal D_2 receptor binding, yet subtle motor disturbances may still occur.

Metabolic side effects are among the most concerning, including weight gain, dyslipidemia, insulin resistance, and the development of metabolic syndrome — particularly with olanzapine and clozapine. These changes increase cardiovascular risk and may compromise long-term adherence. Regular monitoring of weight, fasting glucose, and lipid profiles is mandatory.

Sedation and cognitive blunting are common due to histamine H_1 and muscarinic receptor blockade, though the severity varies among agents. Anticholinergic effects such as dry mouth, constipation, urinary retention, and blurred vision are frequent, especially in elderly patients [5].

Combination therapy must be approached with precision, balancing receptor effects and metabolic interactions. Dose titration should follow the principle of "start low, go slow," especially in elderly or medically fragile individuals. The use of therapeutic drug monitoring (TDM) is recommended when clinically feasible to ensure optimal plasma concentrations.

Clinical follow-up should include not only symptom assessment but also metabolic screening, cardiovascular monitoring, and evaluation of extrapyramidal signs. Patient education regarding lifestyle modification, diet, and adherence is integral to maintaining safety and efficacy in long-term treatment.

CONCLUSION

The application of neuroleptic drugs in depressive syndromes exemplifies the evolving sophistication of psychopharmacology — a shift from symptomatic suppression toward neurobiological modulation. Atypical antipsychotics, through their complex receptor activity involving dopaminergic, serotonergic, and adrenergic systems, provide valuable therapeutic options in psychotic, resistant, and bipolar forms of depression. Their use requires a deep understanding of clinical pharmacology, including receptor selectivity, pharmacokinetics, and individual patient physiology.

Yet, the promise of therapeutic benefit must always be weighed against the risk of adverse effects, which can compromise quality of life and adherence. The clinician's task is not merely to prescribe but to manage: to anticipate toxicity, monitor metabolic and neurological outcomes, and tailor therapy dynamically to the evolving clinical picture.

Future developments in neuropsychopharmacology — particularly the integration of pharmacogenomics, receptor imaging, and novel receptor modulators — are expected to refine this therapeutic approach, allowing for greater precision and fewer side effects. Until then, the judicious, evidence-based use of neuroleptic drugs in depressive syndromes remains a cornerstone of advanced psychiatric care — demanding equal measures of scientific knowledge and clinical wisdom.

REFERENCES

1. Stahl, S. M. Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. Cambridge University Press, 2021.
2. Nelson, J. C., & Papakostas, G. I. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis. American Journal of Psychiatry, 2019.

ISSN: 2582-4686 SJIF 2021-3.261,SJIF 2022-2.889,
2024-6.875 ResearchBib IF: 9.948 / 2024

VOLUME-5, ISSUE-10

3. Citrome, L. Adjunctive antipsychotic use in depression: pharmacological rationale and evidence-based review. International Journal of Neuropsychopharmacology, 2017.

4. Kato, M., et al. Pharmacogenomics in the treatment of major depressive disorder: implications for antipsychotic augmentation. Molecular Psychiatry, 2019.

5. Thase, M. E., et al. Quetiapine XR in major depressive disorder: efficacy and safety in randomized clinical trials. Journal of Clinical Psychiatry, 2010.