Bulletin of Pharmaceutical Research 2026;16(2):210
An Official Publication of Association of Pharmacy Professionals
ISSN: 2249-6041 (Print); ISSN: 2249-9245 (Online)
DOI: 10.21276/bpr.2026.16.2.4

RESEARCH PAPER

COMBINATION THERAPY OF IMIPRAMINE AND QUETIAPINE IN AMELIORATION OF COMORBID DEPRESSION AND ANXIETY DISORDERS

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Received: Dec 21, 2025 / Revised: Jun 29, 2026 / Accepted: Jun 30, 2026

Depression and anxiety are considered one of the most prevalent, costly, and burdensome mental health disorders worldwide, with a significant impact on patient's individual and societal well-being. Antidepressants with mood-stabilizing agents are frequently employed in treatment of these debilitating conditions. Besides, treatments of schizophrenia and other complex mental health conditions often possess sedative effects, which induce comorbid or secondary depression, anxiety disorders. Such situations can be challenging due to complexity of the conditions, requiring a combination of psychopharmacological medication to address multiple diseases. Quetiapine is a widely utilized antipsychotic medication, particularly effective in the management of schizophrenia whilst Imipramine is a potent depression inhibitor. The combination of Quetiapine and Imipramine was chosen for this experiment to evaluate the synergy, compatibility, pharmacological advantages, toxicity mitigation and augmentation of effectiveness in patients suffering with secondary depressive symptoms. Mice were fed Quetiapine, Imipramine alone and combination of these drugs separately in groups. Afterwards, Tail Suspension Test (TST) and Forced Swim Test (FST) were conducted on Swiss Albino mice to trigger depression like symptoms followed by behavioral analysis of them. The study revealed that both 0.30 mg Quetiapine and 0.07 mg Imipramine combination as well as 0.60 mg Quetiapine and 0.14 mg Imipramine combination have potential anti-depressant effects. The combination of drugs may be beneficial for comorbid depression and associated mental health disorders. The mood stabilizing characteristics of Imipramine may also be effective in alleviating Quetiapine-induced toxicity. Nevertheless, further extensive research is warranted to confirm the findings, determine the mechanistic pathways involved, optimal dosage and duration of the combination treatment.

Key words: Depression, Anxiety, Atypical antipsychotics, Quetiapine Fumarate, Imipramine.

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INTRODUCTION

Depression and anxiety are common and often co-occurring mental health disorders attributable to work stress, grief, and excessive worry. Depression is marked by persistent low mood, loss of interest and a range of cognitive, emotional and behavioral symptoms. On the other hand, anxiety is characterized by excessive worry, agitation and restlessness, often accompanied by somatic symptoms. Both conditions can have a wide degree of symptom variability among individuals [1]. Comorbidity refers to the simultaneous occurrence of two or more distinct psychiatric disorders in the same individual specifically, the co-occurrence of depression and anxiety disorders, which share overlapping neurobiological substrates and clinical presentations, thereby complicating diagnosis and treatment [1]. In 2011, National Health Interview Survey reported that depressed patients are at higher risks of early death than the other patients [2]. On top of that, one research has made an estimation that about 15% of depressed patients sooner or later die from suicide attempts [3]. Additionally, the COVID-19 pandemic has also drawn attention in rise of depressed patients nationwide. It is estimated that approximately 264 million individuals worldwide are suffering from depression currently [4]. Schizophrenia is another ailment characterized by delusions, hallucinations, unorganized speech and behavior [5]. However, sleeping disorders, depression and anxiety can exist as a comorbid disorder in schizophrenic patients, even due to medication [6]. The co-occurrence of these conditions potentiates a negative impact on the treatment outcomes and quality of life for patients as well. Treatment strategies are becoming necessary for such comorbid mental health conditions and associated core symptoms of the diseases in order to optimize treatment outcomes and maintain overall efficacy of the drug therapy [7,8].

There are many effective treatments available for the management of depression in form of both medication and counseling therapies. The medicines are generally used alone or as a combination of two or more drugs to optimize the complexity and severity of depression [1]. Various classes of antidepressants and anti-psychotic drugs are routinely prescribed to patients with the purpose of achieving synergistic effects and amelioration in symptoms of depression and anxiety disorders. The use of combination therapy has become a popular treatment approach now-a-days for individuals who are experiencing secondary complications such as depression, anxiety, and cognitive impairment [9]. Quetiapine is a widely employed atypical antipsychotic drug which mitigates schizophrenia, bipolar depression, secondary depression, anxiety and sleeping disorders. Its mechanism of action involves the partial activation of the 5-HT1A receptor and the inhibition of the 5-HT2A and D2 receptors [10,11]. However, it elicits severe side effects include severe fatigue, major depressive disorders, daytime drowsiness and mood alteration even when taken in low dose [10-12]. Although Quetiapine is primarily used to treat schizophrenia and bipolar disorder, it has also been found to be effective in secondary depression and anxiety disorders via increasing norepinephrine and serotonin [13]. Imipramine belongs to the class of Tricyclic Antidepressants (TCAs), a broadly ingested medication that attenuates depression, anxiety, acute bipolar depression and other mental health disorders notably [14]. TCAs usually increase the levels of serotonin and norepinephrine in brain by blocking their reuptake, improving mood and anxiety symptoms. Imipramine specifically may also inhibit the activity of enzymes involved in the synthesis of these neurotransmitters, altering mood to a happier, cheerful, calm and enthusiastic state with fewer adverse effects [15].

Depression and anxiety frequently co-occur, often worsened by external stressors like other diseased conditions, significantly increasing the global burden of these disorders. Furthermore, schizophrenia further complicates mental health management, having multiple conditions, including comorbid depression, anxiety, and sleep disturbances. The combination of Quetiapine, an atypical antipsychotic, and Imipramine, a tricyclic antidepressant, presents a potential strategy to enhance therapeutic outcomes by targeting multiple neurotransmitter pathways. While Quetiapine can effectively alleviate schizophrenia and mood disorders, its sedative effects can contribute to secondary depression, which Imipramine may balance out by increasing serotonin and norepinephrine levels. This synergy could improve efficacy and reduce adverse effects, making it a promising intervention for complex psychiatric conditions. However, the interaction between these drugs must be critically

evaluated, as it may introduce unforeseen complications or amplify existing side effects. The long-term impact on neurotransmitter balance and overall brain function remains unclear, necessitating further research to determine safety, optimal dosing, and patient suitability. Individualized treatment approaches, considering patient-specific symptom profiles and medical histories, are essential to ensuring the efficacy and safety of this combination therapy [7-15].

The combination of Quetiapine and Imipramine is postulated to address the secondary symptoms of schizophrenia and other complex conditions. This could potentially lead to more effective treatment options for individuals with other mental disorders who experience similar complex symptoms. Moreover, combining them can be therapeutically beneficial as both of them can increase the levels of serotonin and norepinephrine from different mechanisms. Serotonin and norepinephrine are regarded as important key parameters to achieve anti-depressive effects. The primary objective of this study was to propose a therapeutic regimen for patients with comorbid conditions by investigating the compatibility of Quetiapine and Imipramine, examining their potential synergy, pharmacological effects, and associated toxicities. Additionally, this investigation aimed to determine whether combination therapy could attenuate the pronounced sedative effects of Quetiapine and improve the management of secondary depression, anxiety, and overall mental health.

METHODOLOGY

Drugs and reagents

Commercially available Imipramine Hydrochloride and Quetiapine Fumarate were procured from local pharmacy, manufactured by Incepta Pharmaceuticals Ltd. (Bangladesh). The purchased dose was 100 mg for Quetiapine Fumarate and 25 mg for Imipramine Hydrochloride. To prepare a dosage of medication for mice the required dosage based on body weight of mice was calculated and the water-drug ratio was determined. The tablets were crushed into a fine powders followed by the weighing of an appropriate amount. It was mixed it with distilled water (vehicle).

Animal groups

Healthy 6 weeks old Swiss Albino mice weighed around 25-30 gm was selected to conduct the experiment. A total of six groups were formed, each containing five mice, based on the treatment they received prior to the start of the study. The groups were orally administered: Group 1, Control: distilled H_2O, Group 2: Quetiapine 0.60 mg/kg^{-1}, Group 3: Imipramine hydrochloride 0.14 mg/kg/body weight, Group 4: Quetiapine 0.30 mg/kg/body weight + imipramine hydrochloride 0.07 mg/kg/body weight and Group 5: Quetiapine 0.60 mg/kg/ body weight + imipramine hydrochloride 0.14 mg/kg/body weight. Group 0 received nothing and considered blank. The drugs were ingested 30 minutes prior to the test. 30 min interval was maintained in between each group's oral gavage of the treatment. The standard animal handling and treatment guidelines were followed thoroughly during the experiment.

Tail suspension test

The tail suspension test (TST) is a commonly used behavioral assay to evaluate the antidepressant-like effects of experimental compounds in mice. The TST is based on the observation that animals exposed to uncontrolled and inescapable stress show a decrease in motor activity and an increase in immobility, behaviors that are thought to reflect depression-like states. A reduction in immobility time after treatment with an antidepressant is interpreted as an indication of antidepressant-like activity [16]. Mice were held at 1 cm by the tip of their tail and 50 cm above the ground fifteen minutes later the oral gavage of drugs. They were kept suspended for six minutes and the behavioral parameters were noted down in the last three minutes. If any mice tried to climb via its tail throughout the experiment, it was delicately pulled downwards to resume the experiment [17]. The following behavioral parameters were observed.

Immobility time

The duration in which the mouse remained motionless with no active engagement in movement was noted down as a reduction in immobility time was interpreted as an antidepressant-like response.

Swinging time

The time spent consistently moving its paws while keeping the body straight or swaying side to side was noted down as this behavior is considered an indicator of active struggle against the stressor.

Curling time
The duration of twisting movements involving the entire body was noted down as an indication of attempts to escape or discomfort in response to stress.

Pedaling time
The time spent moving the paws without engaging the rest of the body was noted down as it reflects a distinct locomotor response to stress exposure.

Forced swim test
Forced swim test is another behavioral investigation method to assess the anti-depressant like effects activities of mice when they are forced to swim in a water-filled open glass cylinder (25 × 15 × 25 cm) for six minutes [18]. After the mice were put in the water jar (24 ± 1 °C), the behavioral parameters were noted down carefully for in the last three minutes. After the exposure of experiment, the mice were gently withdrawn from the cylinder jar with the help of a sieve, dried carefully and kept in a warm place until it was completely dried [19]. Following behavioral parameters were observed.

Immobility time
The total duration in which the mouse remained motionless and floated passively in the water without active movements was noted down as a decrease in immobility time after drug administration was considered indicative of an antidepressant-like effect.

Latency to immobility
The time taken for the mouse to first become immobile after being placed in the water was noted down as a longer latency period suggests increased motivation or resistance to a depression-like state.

Climbing time
The duration in which the mouse exhibited vertical movements against the walls of the cylinder in particular attempting to escape was noted down as increased climbing behavior is associated with noradrenergic antidepressant activity.

Swimming time
The total time spent actively swimming around the cylinder without attempting to climb was noted down as enhanced swimming behavior is often linked to serotonergic antidepressant effects.

Statistical significance
Two-way analysis of variance (ANOVA) with Dunnett's t-tests was used to analyze the recorded data using GraphPad Prism 8.0.1 for Windows. Statistical significance was determined based on P values, with values less than 0.05, 0.01, and 0.001 considered statistically significant.

RESULTS
Tail suspension test
In the Tail suspension test, administration of Quetiapine (0.60 mg) resulted in a significant rise in the immobile period compared to control group (141.8s vs. 37.20s, $p < 0.001$, **Figure 1i**), suggesting calming effects. In contrast, treatment with Imipramine (0.14 mg) dramatically reduced the immobility time (2.278s, $p < 0.001$, **Figure 1i**) and simultaneously improved the swinging, curling, and pedaling period compared to the control group ($p < 0.001$, **Figure 1ii-iv**); indicating anti-depressive effects. Similarly, the combination of Quetiapine and imipramine at 0.30 mg + 0.07 mg dose has ameliorated immobility time (19.60s, $p < 0.001$, **Figure 1i**), swinging, pedaling, and curling time compared to the control group ($p < 0.005$-0.001, **Figure 1ii-iv**) which suggests a combination of anti-depressant-like effects and calming effect. Finally, double dose combination of Quetiapine and Imipramine (0.60 mg + 0.14 mg) has shown enhanced the swinging, pedaling, curling time and reduced immobility time the best compared to the control and half-dose treatment groups (11.40s, $p < 0.001$; **Figure 1**), suggesting that the full dose combination has better compatibility in producing anti-depressant and calming effect than other groups.

Forced swim test
Quetiapine (0.60 mg) in the Forced Swim Test (FST) significantly increased immobility time compared control group (90.80s vs. 24.60s, $p < 0.001$; Figure 2 i); indicating a similar calming or sedative effect as TST. On the contrary, treatment with Imipramine (0.14 mg) significantly has drastically improved swimming, climbing time, and latency to become immobile ($p < 0.005$-0.001, **Figures 2ii-iv**), while significantly reducing immobility time compared to the control group (7.80s, $p < 0.001$; **Figure 2i**) which reveals its anti-depressive properties.

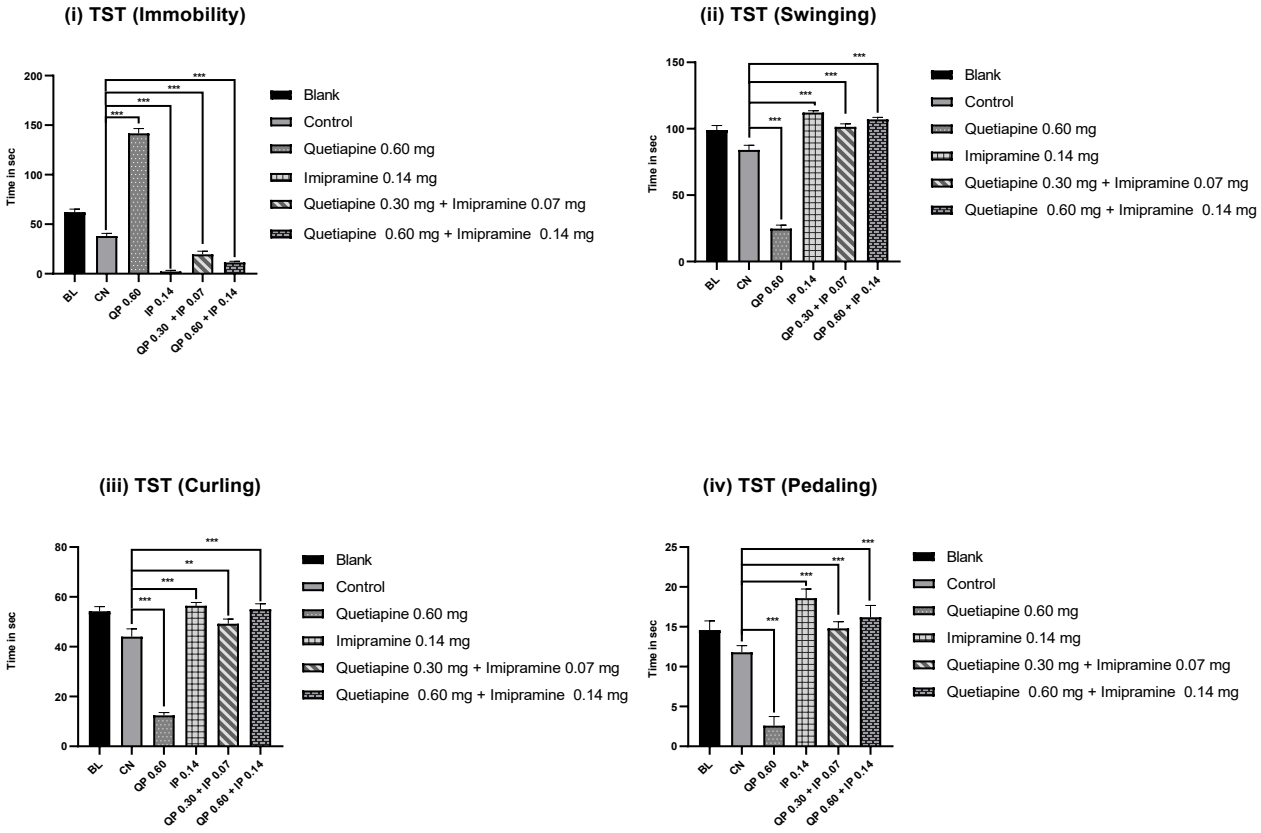


Fig. 1. Effects of Imipramine, Quetiapine, and their combination on Tail Suspension Test (TST) parameters. (i) Duration of immobility, (ii) swinging, (iii) curling, and (iv) pedaling were recorded in seconds across the treatment groups. BL: Blank; CN: Control; QP: Quetiapine; IP: Imipramine; QP 0.60: Quetiapine 0.60 mg; IP 0.14: Imipramine 0.14 mg; QP 0.30 + IP 0.07: combination of Quetiapine 0.30 mg and Imipramine 0.07 mg; QP 0.60 + IP 0.14: combination of Quetiapine 0.60 mg and Imipramine 0.14 mg. Data are presented as mean ± SEM. Statistical significance is indicated as **p < 0.01 and ***p < 0.001 compared with the control group. All groups consisted of n = 5.

Again, the combination of Quetiapine (0.30 mg) and Imipramine (0.07 mg) improved immobility time (18.20s, $p < 0.001$, **Figure 2i**) swimming, climbing, and latency to become immobile ($p > 0.05$-0.001, **Figures 2ii-iv**) compared to control; indicating the calming effect coupled with anti-depressive effect. Finally, the full dose combination of Quetiapine and Imipramine (0.60 mg + 0.14 mg) resulted in the best improvement in latency to become immobile, swimming, climbing activity, and reduction in immobility time compared to the control and half-dose treatment groups (16.20s, $p < 0.001$; **Figure 2**); signifying the better control of full dose combination in producing calming effect as well as anti-depressive effect.

DISCUSSION

Depression is a prevalent and severe mental health disorder, characterized by a deficiency of serotonin. This deficiency has been linked to the onset and severity of depression and is thought to contribute to its pathophysiology [20]. Tryptophan serves as the sole precursor for the biosynthesis of serotonin, both within the peripheral and central nervous systems [21]. In depressed patients, the levels of neurotransmitter 5-HT (5-Hydroxytryptamine) or serotonin is found relatively lower according to the tryptophan paradigm studies [22,23]. The binding of serotonin to its receptors, specifically the 5-hydroxytryptamine 1A (5-HT1A) and 5-hydroxytryptamine 2B (5-HT2B) receptors, has been observed to result in a decrease in serotonin levels. This reduction in serotonin, a neurotransmitter that plays a crucial role in regulating mood, has been implicated in the development of depressive symptoms [24]. In addition, depressed patients who also have anxiety disorders have a strong association with

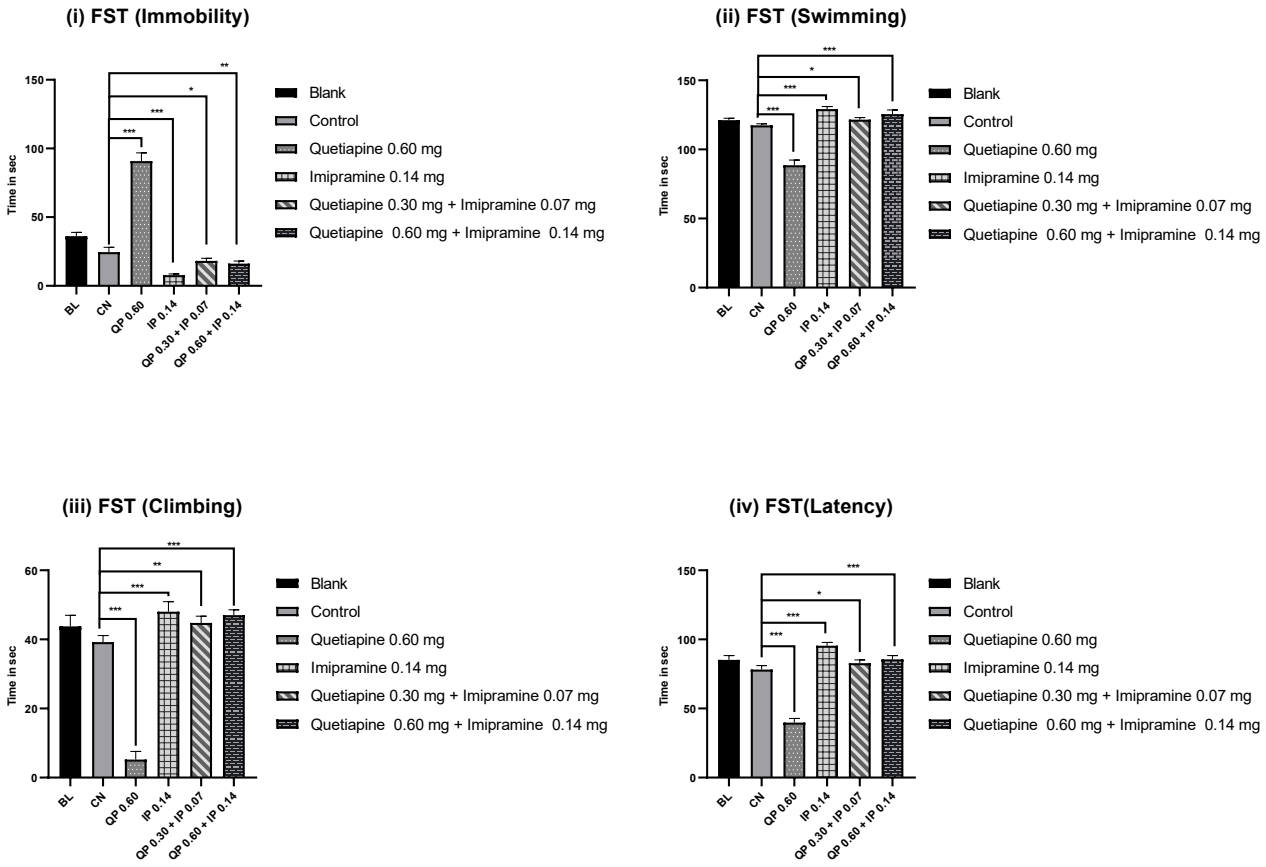


Fig. 2. Effects of Imipramine, Quetiapine, and their combination on Forced Swim Test (FST) parameters. (i) Duration of immobility, (ii) swimming, (iii) climbing, and (iv) latency to become immobile were recorded in seconds across the treatment groups. BL: Blank; CN: Control; QP: Quetiapine; IP: Imipramine; QP 0.60: Quetiapine 0.60 mg; IP 0.14: Imipramine 0.14 mg; QP 0.30 + IP 0.07: combination of Quetiapine 0.30 mg and Imipramine 0.07 mg; QP 0.60 + IP 0.14: combination of Quetiapine 0.60 mg and Imipramine 0.14 mg. Data are presented as mean ± SEM. Statistical significance is indicated as *p < 0.05, **p < 0.01, and ***p < 0.001 compared with the control group. All groups consisted of n=5.

the 5-HT1A receptor which also plays a significant role in anxiety disorders that co-occur with depression [25]. Quetiapine is one of serotonin inducers effective for depression and anxiety [11]. Quetiapine mainly exerts its anti-depressant activity via modulation of multiple neurotransmitters, including dopamine, serotonin, and norepinephrine. It enhances the release of dopamine and serotonin through its inhibitory effects on the 5-HT2A receptor, the alpha-2 adrenoceptor and by increasing the density of the 5-HT1A receptor. Moreover, Quetiapine's primary active metabolite, Norquetiapine, has been found to display antagonistic effects on the 5-HT2C receptor and the norepinephrine transporter, thereby augmenting the levels of norepinephrine in the synaptic cleft, in addition to modulating dopamine and serotonin transmission in the prefrontal cortex. This multifaceted mechanism of action is believed to underlie quetiapine's clinically observed anti-depressant and potential neuroprotective effects. However, the risk profile of quetiapine includes severe drowsiness because it is strong antagonist of H1 receptor [9,27,28].

Imipramine is another serotonin inducer that can reduce stress, anxiety, and depressive behaviors by inhibiting neuroinflammatory signaling through its actions on various receptors such as the D2 receptor, the alpha-1 and alpha-2 adrenergic receptors, and the H1 receptor [13,29-31]. Imipramine possesses its anti-depressive effects by inhibiting the reuptake of norepinephrine and serotonin as well as increasing the amount of dopamine [32]. Since, it can exert positive effects on mood, such as increasing feelings of happiness and

cheerfulness, it may enhance its effectiveness in treating secondary depression in patients with other primary diagnoses, such as schizophrenia. Additionally, imipramine may have a beneficial effect on sleep disorder, producing better sleep reducing day-time drowsiness often associated with other antidepressant medications such as Quetiapine. Regarding the anxiolytic effects observed in the behavioral assays, it is important to consider whether these effects represent a direct pharmacological anxiolytic action or are secondary to the sedative and sleep-promoting properties of the combination. Given that Quetiapine is a potent H1 receptor antagonist with well-documented sedative effects, and Imipramine modulates noradrenergic and serotonergic pathways, the observed reduction in anxiety-related behaviors may be attributable, at least in part, to improved sedation and sleep quality rather than a specific anxiolytic mechanism. Further studies employing anxiety-specific paradigms and mechanistic analyses would be required to conclusively differentiate between direct and indirect anxiolytic effects.

The results of our study indicate that the combination of quetiapine and imipramine has a significant anti-depressant effect compared to depressed mice with minimal drowsy effect. The Quetiapine 0.60mg dose demonstrated a potent sedative effect, suggesting its adverse effects to induce sleep among patients, aligning with previously conducted studies [33,34]. Another study indicated that, norquetiapine (the active metabolite of Quetiapine) produces extreme sedative effect [35]. On the other hand, Imipramine at a dose of 0.14mg was found to exert a significant anti-depressive effect with spontaneous movement. Other studies have also reported similar anti-depressive and anti-anxiety effects with high spontaneous movements [36-40]. Again, the half-dose combination of quetiapine and imipramine (0.30mg + 0.07mg) was found to have robust control in producing an anti-depressant effect while minimizing sedation than the control group. Finally, the full-dose combination of quetiapine and imipramine (0.60mg + 0.14mg) demonstrated the most significant anti-depressant-like effect with better control of sedation than the control group and half-dose combination group, suggesting that it can be a good solution for patients experiencing comorbid condition while taking quetiapine.

Although there is limited literature on the combination therapy of Quetiapine and Imipramine, however previously conducted in vivo studies and clinical trials have supported the efficacy of combining atypical antipsychotics with tricyclic anti-depressants in the treatment of depression in a dose-dependent manner [41]. This suggests that the combination therapy of Quetiapine and Imipramine may be a viable treatment option for individuals suffering from secondary depressive disorders during a complex mental health condition. Additionally, the combination of these two medications may have a synergistic effect in mitigating the sedative side-effects of Quetiapine and augmenting its potential anti-depressive properties.

CONCLUSION

This study aimed to investigate the compatibility of Quetiapine and Imipramine in a comorbid depression and anxiety model, explore their potential synergy, and evaluate whether combination therapy could mitigate the sedative side effects of Quetiapine while improving treatment outcomes for secondary depression and anxiety. Depression and anxiety are major mental health conditions which not only have detrimental effects on the individuals but also create a significant public health crisis that demands attention and action. The combination treatment approach has the potential to promisingly improve outcomes for individuals where behavioral tests can be a useful assaying technique. The tests performed with Quetiapine and Imipramine in this experiment have shown impactful anti-depressive activity. Furthermore, the combination also possessed notable efficacy, not only in the inhibition of depressive symptoms but also in the reduction of drowsiness that can be clinically relevant and useful strategy. However, it is only a preliminary study which can suggest scholars perform advanced experiments for its validation as well as behavioral tests that are insufficient for the complete understanding of the underlying mechanisms involved.

Therefore, it is essential to conduct further studies incorporating techniques such as mechanistic analysis, dosage regimen and duration of action reformulation, compound isolation and characterization through which the combination of Quetiapine and Imipramine may show its anti-depressive effects and comprehend the molecular pathways involved with deeper understanding. Future studies should also incorporate more targeted anxiety-specific

assays to definitively characterize the anxiolytic profile of the combination therapy.

Institutional animal care

All animal studies were conducted (Ref. no. IPSDRLAB/AHCP/01/18) in compliance with the Guide for the Care and Use of Laboratory Animals, 8th edition; The National Academies Collection, as accepted by the institutional guideline for animal care. Institute of Pharmaceutical Skill Development and Research (IPSDR), Bangladesh (project approved on 10/03/2022) authorized the experimental design with an Institutional Ethical Committee Clearance (Ref. No. IPSDRLAB/IECC/11/22).

ACKNOWLEDGEMENTS

We are grateful to Mohammed Mostakim Billah (IPSDR) for his generous co-operation throughout the experiments. The authors would like to extend their appreciation to IPSDR for providing the lab facilities.

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