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CASE REPORT
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A New Dawn for Geriatric Bipolar Disorder: Promising Impact of Endoxifen – A Case Report

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Abstract

Bipolar disorder (BD) is a complex and debilitating mood disorder that affects a significant portion of the population, including the elderly. This case report briefs the utilization of endoxifen for the treatment of BD in an elderly patient. A 74-year-old male with a history of recurrent manic episodes exhibited symptoms of irritability, over-talkativeness, overspending, and disturbed sleep. After unsuccessful attempts with various medications, including mood stabilizers and antipsychotics, the patient was prescribed endoxifen 4 mg daily, escalating to 8 mg within four days. Over six weeks, a remarkable improvement was observed, evident in a decrease in the Young Mania rating scale (YMRS) score from 32 to 6. Notably, minimal side effects were encountered. This case underscores the potential of endoxifen as a promising therapeutic option for managing bipolar disorder in the elderly. Further research with larger cohorts is warranted to validate these findings and explore their long-term efficacy and safety.

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Introduction

Bipolar disorder (BD) stands as a formidable challenge within the landscape of psychiatric illnesses, characterized by its chronic and recurrent nature, alternating periods of euthymia, mania/hypomania, and depressive episodes, often accompanied by mixed features.[1] Treating manic episodes is intricate, requiring multifaceted strategies for both immediate relief and long-term management, which is often challenging due to the complexity of symptoms and the goal of maintaining stability over time.[2]

Though various pharmacological agents, including mood stabilizers such as lithium, valproic acid, carbamazepine, and second-generation antipsychotics (SGAs: quetiapine, asenapine, olanzapine, ziprasidone, aripiprazole, risperidone, and cariprazine) are available,[3] achieving optimal clinical outcomes among BD patient remains a formidable task. This intricacy is further compounded when catering to the elderly population, where considerations of age-related physiological changes, comorbidities, and polypharmacy introduce unique challenges in treatment selection and tolerability.[4]

The interplay between protein kinase C (PKC) pathways in modulating mood regulation has been well-documented.[5,6] Therefore, endoxifen, an innovative compound with direct PKC inhibiting property,[7] could offer a novel perspective in the management of BD. Moreover, Ahmad and co-authors recently reported the anti-manic activity of endoxifen in their clinical trials.[8,9] Herewith, we present a case study of a 74-year-old man grappling with recurrent manic episodes, which sheds light on the complexities of BD management in the elderly population and introduces a novel avenue of exploration - the potential role of endoxifen.

Clinical Presentation

A 74-year-old retired teacher hailing from Sambalpur, Odisha, sought medical attention accompanied by his daughter at our outpatient department (OPD). The patient presented with a range of distressing symptoms that included rage outbursts, irritability, over-talkativeness, overfamiliarity, overspending, heightened psychomotor activity and disrupted sleep patterns persisting for the past 30 days. Notably, the medical history of the patient revealed a past episode of obsessive doubts 25 years ago, characterized by prolonged engagement in repetitive cleaning rituals and compulsive checking behaviors. During this period, he received treatment with escitalopram (up to 20 mg/day) for three months, leading to significant alleviation of his obsessive-compulsive symptoms. Remarkably, after the resolution of the index episode, no residual obsessive symptoms were reported. We ruled out substance or drug abuse by taking history from the patient and having the daughter corroborate the same. Neurological examination of the patient was within normal limits and imaging was done wherein the NCCT Brain of the patient was normal, effectively ruling out any organicity or past cerebrovascular events.

Further exploration of medical history revealed that he had experienced two more such episodes, with the first occurring three years ago, indicating a new pattern in his condition (Figure 1). During this episode, he exhibited pronounced irritability, anger outbursts, increased psychomotor activity, decreased need for sleep, overfamiliar behavior and excessive spending tendencies. He was prescribed lithium (900 mg/day) and olanzapine (10 mg/day) for a duration of one month, yielding a notable improvement. Nonetheless, adverse effects such as weight gain, tremors, and lower limb swelling emerged, prompting a reduction in lithium dosage to 600 mg/day and a cross-tapering of olanzapine to aripiprazole (5 mg/day) in pursuit of better tolerability. Surprisingly, the patient again encountered a problem of tremors in his hands and increased appetite accompanied by a deranged lipid profile, which prompted lifestyle interventions, including exercise and dietary adjustments in consultation with a nutritionist. Unfortunately, after three months, the patient was asymptomatic with regard to his mood but had concerns about the negative impact on his lipid profile and persistent weight gain; hence he did not hesitate to discontinue the treatment.

Following this phase, the patient again presented six months ago with echoing symptoms of over-talkativeness, overspending, decreased need for sleep and authoritative behavior. Unwilling to endure side

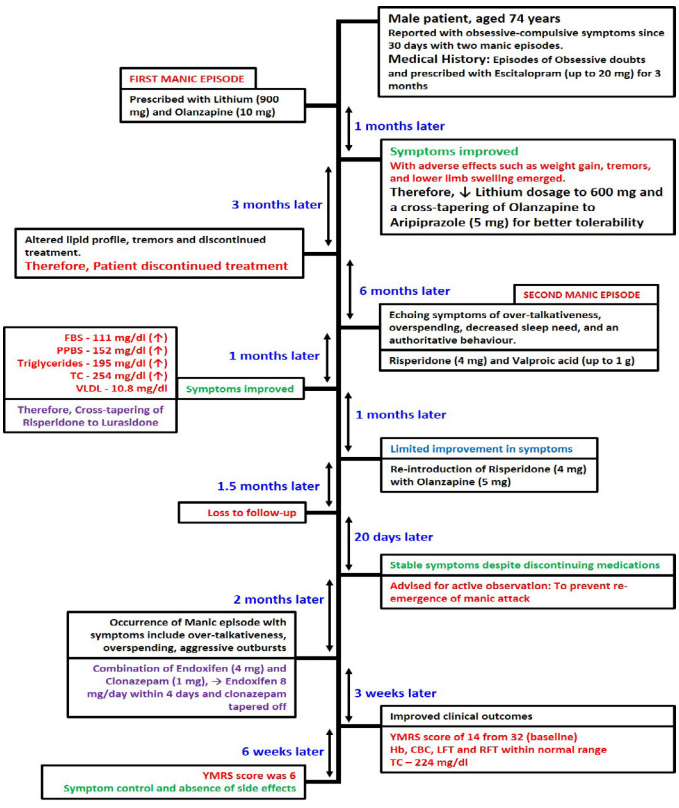

Figure 1: Timelines of interventions and outcomes

effects, he refused to receive lithium, olanzapine or aripiprazole. As an alternative approach, treatment with risperidone (4 mg/day) and valproic acid (up to 1 g/day) was initiated, leading to noticeable symptomatic improvement within a month. However, further investigations revealed marginally elevated blood sugar levels and a deranged biochemical profile (fasting blood sugar: 111 mg/dl; post-prandial blood sugar: 152 mg/dl; triglycerides: 195 mg/dl; total cholesterol: 254 mg/dl; very low-density lipoprotein (VLDL): 10.8 mg/dl) although devoid of prior medical history of diabetes, hypertension, dyslipidemia or any other chronic illness, the metabolic profile of the patient was perturbed, necessitating strategic interventions involving exercise and dietary modifications.

Despite initial progress, the patient once again faced challenges in adherence clearly due to his past experience with psychiatric medications wherein he had experienced a negative effect on his lipid profile and struggled with weight gain, prompting a cross-tapering of risperidone to lurasidone (up to 120 mg/day). The subsequent month he witnessed limited improvement, prompting the re-introduction of risperidone (4 mg/day), this time in combination with olanzapine (5 mg/day). A comprehensive plan encompassing pharmacotherapy, exercise, and dietary consultation was established to ensure metabolic stability. In an intriguing twist, the patient encountered a period of self-sustained stability, only to be lost to follow-up after 1.5 months. His eventual return after 20 days highlighted his ability to maintain stability despite discontinuing medications. Active observation was advised so as to timely intervene in case of re-emergence of manic symptoms.

Two months ago, the patient further displayed a constellation of symptoms, including over-talkativeness, overspending, and aggressive outbursts. Given his tumultuous history with medication, both the patient and his family were apprehensive about treatment. In response, endoxifen (4 mg/day), along with clonazepam, was prescribed. The novelty of endoxifen was explained to allay concerns about past side effects, and clonazepam was introduced to mitigate sleep disturbances which was eventually tapered.

Treatment and Clinical Course

The treatment approach commenced with the administration of endoxifen 4 mg and clonazepam 1-mg/day, with a swift titration of endoxifen to 8 mg/day within a span of four days and clonazepam was eventually tapered off. Over the ensuing three weeks, a marked amelioration in the clinical condition of the patient was observed, demonstrated by a substantial reduction from the baseline Young Mania Rating Scale (YMRS) score of 32 to a notably improved score of 14 (Figure 1). This decrease in the YMRS score indicated a noteworthy alleviation of manic symptoms. Additionally, physical examination of the patient yielded unremarkable findings, except for a hemoglobin level of 10.36 g/dl, and within-range results for complete blood count, liver function tests, and renal function tests. A slightly deranged lipid profile with a total cholesterol value of 224 mg/dl was noted. A CT brain scan was conducted, ruling out any organic pathologies. A neurological examination had previously been done and was within normal limits.

A second follow-up after six weeks unveiled a remarkable reduction in YMRS score to 6 (Figure 2), underscoring the sustained positive trajectory of the clinical course. Encouragingly, the patient exhibited not only symptom control but also an absence of side effects, indicating his commendable compliance and adherence to the treatment. At this stage, endoxifen remained the pivotal element of his treatment regimen, demonstrating an ability to effectively manage symptoms while controlling potential side effects over a period of two months. The patient's written informed consent was taken prior to applying scales, he was explained in detail about the medication's potential side effects and consent was taken for the documentation of this process as well.

Discussion

This case underscores the intricate nature of bipolar disorder treatment in the elderly, highlighting the complexities and challenges of medication management, the importance of tailored interventions, vigilant follow-up to achieve optimal outcomes and patient compliance. The clinical course of the

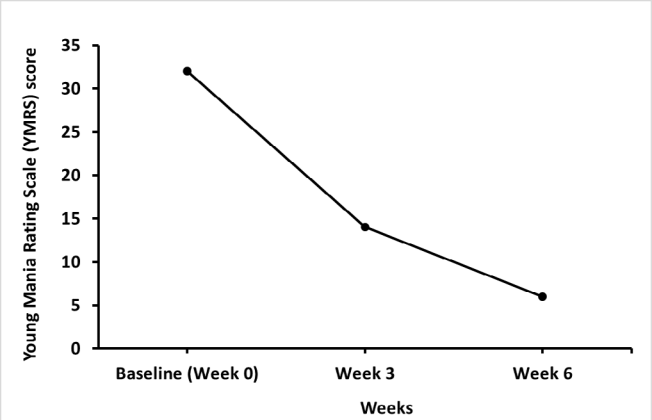

Figure 2: Change in YMRS score over time

patient highlights the need for personalized treatment strategies and novel therapeutic agents, such as endoxifen. The use of conventional mood stabilizers and antipsychotics is often associated with relapses of manic episodes and the emergence of side effects that can lead to poor adherence and discontinuation.[10] In this case, the prior experiences of a patient with side effects, including weight gain, tremors, and deranged lipid profile, led to treatment discontinuation. This further complicated the management, necessitating alternative interventions.

Endoxifen, a direct protein kinase C inhibitor, is a newly approved medication that addresses the challenges posed by conventional medications.[11] The positive response of the described patient to endoxifen, characterized by a significant reduction in YMRS scores and sustained improvement in clinical condition, suggests its potential efficacy in managing manic symptoms is in line with the results of phase II and phase III clinical studies.[8,9] Notably, the absence of substantial side effects played a pivotal role in promoting treatment adherence and overall success. The case also emphasizes the importance of comprehensive assessment and monitoring. Regular follow-ups, assessment of blood parameters, and close observation of the clinical status of the patient were vital in ensuring the effectiveness and safety of the treatment. Additionally, the collaborative approach involving counseling and referral to a dietician exemplifies the holistic care required for elderly patients with bipolar disorder.[12] However, this case report also highlights the need for further research and larger-scale clinical trials to establish the safety and efficacy of endoxifen in elderly patients with bipolar disorder. Long-term effects, potential interactions, and comparative studies with existing treatments remain essential aspects to explore.

Limitation

The limitations of this case report include (1) it is a single patient experience, which limits the generalizability of the findings; (2) the lack of comparative data with established treatments; (3) a relatively short observation period.

Clinical Implications

The favorable profile of endoxifen in terms of efficacy and tolerability makes it a valuable addition to the treatment armamentarium for elderly bipolar patients. Its novel mechanism of action and observed symptom reduction with minimal side effects warrant further investigation through larger clinical trials to establish its role as a viable treatment option in managing bipolar symptoms in this population. Long-term studies should assess its impact on relapse prevention, overall functioning, and quality of life.

Conclusion

This case study highlights the potential of endoxifen as an effective and well-tolerated treatment option for elderly patients with bipolar disorder, emphasizing the importance of tailoring treatments to individual patient needs. Further research is crucial to validate these findings and provide a promising therapeutic avenue for improving the lives of elderly individuals with bipolar disorder.

Consent to Participate

Participants provided a written informed consent form to participate in the study. Consent for publication was obtained from the participant or legally authorized representatives and authors involved in this study.

Conflicts of Interest

The authors declare no conflict of interest to report.

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The authors declare that no funds, grants, or other support have been received from Government or non-government bodies either to conduct this study during or for the preparation of this manuscript.

Data Availability Statement

The datasets generated during the study are available from the corresponding author upon reasonable request.

Author's Contribution/ CRediT Author's Statement

Both authors were part of the study design and involved in the acquisition of data data interpretation. They critically wrote the first draft and, subsequently, revised the manuscript for important intellectual content and approved the final manuscript. Both authors made substantial contributions to this study and agreed to be accountable for all aspects of the work.

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