Tamoxifen as an effective treatment for refractory mania: a case report

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ABSTRACT
Tamoxifen is a medication that acts as a selective estrogen receptor modulator (SERM) by inhibiting protein kinase C (PKC). It has various effects on different tissues in the body, depending on whether the tissue expresses estrogen receptors. For instance, it can reduce inflammation and neuronal excitability. Several studies have shown that tamoxifen could be effective in treating refractory mania, a type of mania that has shown resistance to mood stabilizers and other treatments. The rationale for its use could be explained by the fact that PKC is an enzyme that seemingly plays a significant role in the genesis of mania. We present the case of a 43-year-old female patient with bipolar disorder, who has had 43 previous hospitalizations and has undergone multiple treatments. Management with tamoxifen was initiated to control the manic episode.

Keywords: bipolar disorder, mania, tamoxifen, Protein Kinase C (PKC), case report.

1 INTRODUCTION
Bipolar disorders constitute chronic and recurring conditions that impact over 1% of the global population. The manic phase stands out as one of the most distinctive stages and regrettably, as a major source of disability, stigmatization, and cognitive impairment for those who undergo it. Manic episodes lead to abrupt and significant disruptions in an individual's everyday behavior, resulting in hindrances to their social and occupational functioning, and at times, even necessitating hospitalization. (Yatham et al., 2018)
The diagnosis of a "manic episode" is established when at least three (or four, in case the mood is predominantly irritable) of the following symptoms are present: heightened self-esteem or feelings of grandiosity, markedly decreased need for sleep, increased verbosity or pressured speech, experiencing a rapid stream of thoughts or a subjective perception that thoughts are constantly accelerating, difficulty maintaining attention, a significant increase in goal-directed activity or psychomotor agitation, and excessive engagement in activities with high potential for adverse consequences. (American Psychiatric Association, 2013; Vieta et al., 2018a) To confirm the diagnosis, it's essential to emphasize that the mood disturbance must result in substantial impairment in overall functioning, potentially requiring hospitalization or being accompanied by psychotic symptoms for diagnosis confirmation. (Amrollahi et al., 2011; Vieta et al., 2018b; Yatham et al., 2018)

Tamoxifen is an oral medication proposed as a potential treatment for bipolar disorder (Dal-Pont et al., 2019; Palacios et al., 2019; Valvassori et al., 2017). Tamoxifen, a non-steroidal synthetic antiestrogen, is widely used in hormone-sensitive breast cancer treatment due to its antagonistic effects on estrogen receptors in breast tissue (Wolf & Jordan, 1994). Research into tamoxifen's potential efficacy in bipolar disorder emerged because, at adequate doses, it inhibits protein kinase C (PKC) (Abrial et al., 2013; Hong et al., 2022; Kishi et al., 2022; Thanvi, 2022; Yildiz et al., 2008)

The observation that lithium, one of the most effective drugs for treating manic episodes, moderates excessive excitatory neurotransmission through its effects on the adenylate cyclase pathway, phosphoinositide pathway, and PKC, along with preliminary data suggesting tamoxifen's (a PKC inhibitor) efficacy in reducing manic symptoms of bipolar disorder, implies that this agent may be a potential treatment in managing this psychiatric disorder. (Abrial et al., 2013; Dal-Pont et al., 2019; Fallah et al., 2016)

A case report was described where tamoxifen was used in acute mania. It is positioned as a third-line treatment option for acute mania, recommended for patients intolerant to conventional psychiatric medications and for cases of treatment-resistant mania or in the event of shortages of first-line medications. (Aldana-López & Medina-Dávalos, 2016)

In summary, tamoxifen inhibits the intracellular action of protein kinase C, like well-established treatments such as lithium and valproate, demonstrating its potential as an antimanic agent in clinical and preclinical studies. A connection has been found between this therapeutic action and PKC inhibition. Below, we describe the case of a patient diagnosed with bipolar disorder where this medication was utilized. In this context, tamoxifen was incorporated into the antimanic treatment. We delve into the mechanism of action of tamoxifen in reducing manic symptoms and establish a comparison between the obtained results, experienced adverse effects, and the patient's progression, in relation to findings present in the available scientific literature.
2 CASE PRESENTATION

A 43-year-old female patient, who experienced an unspecified traumatic brain injury at the age of 7, was diagnosed with bipolar affective disorder in 2007 and has faced a history of at least 47 prior hospitalizations due to manic episodes accompanied by psychotic symptoms. Additionally, she has experienced severe depressive episodes and made multiple suicide attempts. No other significant medical illnesses are recorded. During previous hospitalizations, mood stabilizer therapy was utilized, including schemes with 1.2 g/day lithium carbonate, up to 1.5 g/day valproic acid or semisodium valproate, or up to 1.6 g/day magnesium valproate. Laboratory analyses consistently confirmed therapeutic levels and avoided toxicity.

Given the severity of her symptoms, hospitalization was decided due to her current diagnosis of bipolar disorder with manic episode and psychotic symptoms. The patient has a history of treatment non-adherence and lacks proper family support. During this hospitalization, her treatment was adjusted, including the addition of 40 mg/day tamoxifen. However, the patient exhibited resistance to cooperation, displayed hypersexual behavior, and tended toward agitation, necessitating the application of therapeutic restraints and postponing interviews.

Upon admission, during the mental examination, a woman of apparent age like her chronological age was observed. She had a mesomorphic build and average stature. She was dressed in hospital attire with acceptable hygiene and grooming. She was found walking with difficulty and increasing psychomotor activity in the hallway. Her attitude was inappropriate and uncooperative, and she presented with a hypermimic facial expression. While she was oriented to place and person, her orientation to time and circumstance was impaired. Her comprehension was reduced, and her external environment projection was limited, with difficulty maintaining eye contact with the interviewer.

Her spoken language was poorly articulated, and she had non-evaluative tonal inflections with reduced response latency. Her speech was verbose but lacked a coherent thread, with flights of ideas. The content of her speech was incongruent and expressed sudden occurrences, such as "We're going to dance now... We can do whatever you want! Ah!" There were no observed alterations in the primary order of thought or in sensory perception. Her judgment was detached from reality, and her affect was inappropriate, displaying both euphoric and dysphoric mood. While a comprehensive assessment of cognitive functions was not conducted, they seemed generally impaired. The patient lacked awareness of her illness and projected a disorderly future.

On the second day of hospitalization, there was no improvement, leading to an increase in antipsychotic and benzodiazepine doses, as shown in Table 1. The patient's aggressiveness and agitation continued to escalate, resulting in the need for multiple therapeutic restraints, and this pattern continued unchanged until the eighth day.
Table 1. Treatments used during your admission

<table>
<thead>
<tr>
<th>Date</th>
<th>Day of hospital stay</th>
<th>Indicated treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>November 16, 2022</td>
<td>0</td>
<td>Magnesium Valproate 1200 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Olanzapine 20 mg/day via IM.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clonazepam 1.5 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lithium carbonate 300 mg/day.</td>
</tr>
<tr>
<td>November 17, 2022</td>
<td>1</td>
<td>Olanzapine 30 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Magnesium Valproate 1600 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clonazepam 5 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lithium carbonate 900 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tamoxifen 40 mg/day.</td>
</tr>
<tr>
<td>November 25, 2022</td>
<td>9</td>
<td>Magnesium valproate at 1600 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lithium carbonate at 900 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Olanzapine 30 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clonazepam at 5 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tamoxifen at 40 mg/day.</td>
</tr>
<tr>
<td>November 30, 2022</td>
<td>14</td>
<td>Magnesium valproate 1600 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Olanzapine 30 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lithium carbonate 900 mg/day.</td>
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<td></td>
<td></td>
<td>Clonazepam 5 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tamoxifen 40 mg/day.</td>
</tr>
<tr>
<td>December 5, 2022</td>
<td>19</td>
<td>Magnesium valproate 1600 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Olanzapine 30 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lithium carbonate 900 mg/day.</td>
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<tr>
<td></td>
<td></td>
<td>Clonazepam 5 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tamoxifen 40 mg/day.</td>
</tr>
<tr>
<td>December 12, 2022</td>
<td>26</td>
<td>Olanzapine 10 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clonazepam at 2 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Magnesium valproate 1600 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lithium carbonate 900 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tamoxifen 40 mg/day.</td>
</tr>
<tr>
<td>December 14, 2022</td>
<td>28</td>
<td>Aripiprazole 15 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clonazepam 2 mg/day.</td>
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<td></td>
<td></td>
<td>Lithium carbonate 900 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Magnesium valproate 1600 mg/day.</td>
</tr>
<tr>
<td></td>
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<td>Tamoxifen 40 mg/day.</td>
</tr>
</tbody>
</table>

Source: the clinical evolution of the patient

On the ninth day of hospitalization, a mild improvement in her behavior was noted. She appeared more cooperative, although judgment and inappropriate behavior persisted. Despite reduced agitation, therapeutic restraints were still required on multiple occasions. Laboratory analyses yielded normal results, including complete blood count and lithium levels at 0.7 mmol/L.

By the twelfth day, a more pronounced improvement was observed. The patient was less confused, globally oriented, and delusional ideas of mystical-religious nature decreased, although an expansive mood and hyperfamiliar behavior with medical and nursing staff persisted. Psychomotor agitation also improved.

By the fourteenth day, the patient displayed a hypomanic state with improved behavior and a significant remission of psychotic symptoms. She demonstrated respect for established norms and limits. Her interaction with peers and staff improved, and sexual and hyperfamiliar behaviors decreased. New blood tests were requested to assess treatment adherence and the effects of pharmacological therapy used.
On the sixteenth day of hospitalization, her improvement continued, with a significant reduction in psychotic symptomatology and the absence of grandiose or religious ideas. Interview cooperation increased, and both sexual and hyperfamiliar behaviors diminished.

On the twenty-sixth day of hospitalization, a new evaluation was conducted using the Young Mania Rating Scale, yielding a score of 15 (compared to the initial score of 54), indicating a state of hypomania. In response, olanzapine was reduced to 10 mg/day, and clonazepam to 2 mg/day. Treatment continued with 1600 mg/day magnesium valproate, 900 mg/day lithium carbonate, and 40 mg/day tamoxifen.

At the fourth week of hospitalization, discharge was decided under the diagnosis of bipolar disorder with manic episode and psychotic symptoms in partial remission (F 31.2), with a history of treatment non-adherence (Z 91.1), and lack of adequate family support (Z 63.2). The patient displayed a tendency toward euthymia, cooperation, and improved interaction with peers and staff. She reported no physical discomfort and was referred for outpatient consultation.

For outpatient treatment, olanzapine was replaced with aripiprazole at a dose of 15 mg/day due to sedation experienced with olanzapine. Treatment also included 2 mg/day clonazepam, 900 mg/day lithium carbonate, 1600 mg/day magnesium valproate, and 40 mg/day tamoxifen.

At the time of discharge, the patient appeared her age and maintained proper hygiene and personal appearance. Her facial expression lacked notable features. Her gait and psychomotor activity were unaffected, and no abnormal movements were observed. She responded to calls to attend appointments and displayed a cooperative attitude. She was globally oriented and established appropriate eye contact with the interviewer, maintaining it for appropriate durations.

Regarding her affect, she had a euthymic mood, and her facial expression matched it. Her attention span was appropriate, with preserved comprehension. The patient's verbal language was clear and articulate, adjusting volume and speed to the situation and employing appropriate inflections that reflected the relationship between ideas and emotions. During the interview, her speech followed a coherent line of thought and reached its goals effortlessly, being spontaneous and adapted to the situation. Latency in her responses during the interview was suitable.

Both the patient's thinking and language exhibited coherence, although there were instances of somewhat loose associations between ideas. The content of her thoughts and language aligned with her surrounding reality. The patient denied having thoughts of death, suicidal thoughts, self-harming, or homicidal tendencies during a proactive and repetitive interrogation.

The patient did not report alterations in sensory perception, and her affect leaned toward euthymia, consistent with her emotional state. Her judgment was framed within reality.
A general cognitive decline in cognitive functions was noted, likely due to the natural progression of the illness. The patient had a limited understanding of her mental illness and expressed her plans, stating, "I know where to go to sell myself to get more money; I also want to go back to my church."

3 DISCUSSION

The clinical case highlights the use of tamoxifen as part of the patient's treatment and its positive effect on improving manic symptoms as an available option for managing bipolar disorder. While tamoxifen is commonly used in breast cancer treatment, its application in mood disorders, including bipolar disorder, has been explored.

Several pharmacological strategies have been investigated for manic episodes. (Kishi et al., 2022) The first consideration in acute mania treatment requires a long-term perspective that encompasses not only short-term efficacy and tolerability but also its effectiveness in preventing mania or depression, its long-term safety/tolerability profile, and the risk of treatment-emergent side effects. Other considerations include patients' characteristics during mania, clinical presentation of the manic episode, disease course, and treatment adherence. (Hong et al., 2022) While lithium remains a traditional treatment option, most patients do not respond to lithium monotherapy, leading to the introduction of other drugs like valproic acid, carbamazepine, lamotrigine, etc., each with their limitations. (Abé et al., 2023; Kishi et al., 2022; Vieta et al., 2018b)

In some clinical trials, doses of tamoxifen citrate ranging from 20 to 80 mg per day were used, like established doses of 20 to 40 mg administered in metastatic breast cancer cases, or 20 mg for breast cancer preventive and adjuvant therapy. Nonetheless, tamoxifen is well tolerated even at elevated doses of up to 200 mg per day. (Ledezma-Acevedo et al., 2020; Palacios et al., 2019)

Regarding the mentioned adverse effects, secondary endometrial cancer is a concern, particularly for postmenopausal tamoxifen users, as up to 90% of patients exhibit an endometrial response. (Buijs et al., 2009) While tamoxifen seems associated with various benign endometrial conditions, evidence suggests it doesn't increase endometrial carcinoma risk. (Amrollahi et al., 2011; Chalas et al., 2005)

Studies investigating tamoxifen's efficacy have shown potential anti-manic effects through its ability to inhibit protein kinase C (PKC). (Yildiz et al., 2008; Zarate et al., 2007)

Tamoxifen has been shown to help reduce manic symptoms associated with bipolar disorder, as evidenced by improvements in Young Mania Rating Scale scores. Though it's not yet clear exactly how it works in the central nervous system, studies suggest PKC inhibition might be the key to understanding this effect, like how other medications like lithium operate. (Amrollahi et al., 2011)

It's important to note that tamoxifen is not a first-line treatment for bipolar disorder, and its use in this context can be considered off-label, meaning it's used outside officially approved indications.
However, some preliminary studies have suggested potential benefits of tamoxifen in bipolar disorder patients, especially those with manic symptoms. (Hong et al., 2022; Kishi et al., 2022; Palacios et al., 2019) In another case report, successful use of tamoxifen was described in a patient with recurrent mania refractory to other treatments. (Ledezma-Acevedo et al., 2020) The patient experienced significant improvement in mania symptoms, reduced energy and activity, eliminated delusions, and improved mood without significant adverse effects. (Aldana-López & Medina-Dávalos, 2016)

The obtained results suggest that tamoxifen can be considered a safe and effective option for treating refractory mania in patients not responding to other treatments. (Hong et al., 2022) However, more rigorous studies are needed to confirm these findings and determine the appropriate dosage and optimal treatment duration. The decision to use this medication in our case was made in collaboration with the family and the medical team, carefully considering the balance between risks and benefits. Considering the patient's profile – bipolar disorder with prominent manic symptoms – we chose a 40 mg/day TMX dosage throughout her hospital stay, maintaining her pre-admission medication. While some anti-manic effect was observed, especially regarding behavior and energy reduction, grandiose delusions persisted until discharge. The patient exhibited a significant decrease in the Young Mania Rating Scale (Graph 1) and given her constant therapeutic lithium levels and ongoing manic symptoms, the therapeutic maneuver of introducing tamoxifen was decided upon.

It's crucial to remember that each patient is unique and may respond differently to treatments. In this specific patient's case, using tamoxifen could have been a valid and effective therapeutic option. However, further research and controlled studies are needed to fully understand tamoxifen's role in bipolar disorder treatment.
In conclusion, our experience with using TMX in cases of acute mania successfully replicated its anti-manic effect. We observed a low-profile side effect profile, which contributed to improved adherence likelihood in our patient, as she could tolerate the treatment favorably in terms of side effects and costs. It has been established as a third-line option in acute mania treatment, especially recommended in cases of intolerance to conventional psychiatric medications and in treatment-resistant mania situations. More research is required for a better understanding of how to use tamoxifen in bipolar disorder treatment. When considering any prescription decision, it's important to consider potential long-term side effects. Nonetheless, for those patients who don't respond well to other treatments or experience severe adverse reactions to other medications or due to supply issues, tamoxifen could offer a viable alternative.
REFERENCES


