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Original Research Article

Endoxifen associated Reproductive Endocrine Adverse Effects in Women with Bipolar Affective Disorder: A Retrospective Case Series and Pharmacovigilance Assessment

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Abstract

Background: Endoxifen is the principal active metabolite of tamoxifen and acts as a potent protein kinase C inhibitor. It has gained immense recognition in treatment for acute mania in bipolar disorder. Despite this growing use, its reproductive and endocrine safety in adolescent and reproductive age women remains terra incognita.

Methods: We conducted a retrospective review of five female patients, aged 15 to 28 years, already diagnosed with bipolar affective disorder, who developed menstrual or endocrine abnormalities while on endoxifen. For each case, we examined the clinical timeline, drug exposure history, laboratory reports, pelvic ultrasonography where clinically indicated, dechallenge outcomes and other attributable factors. Causality and severity were assessed using WHO-UMC scale, the Naranjo algorithm, modified Hartwig and Siegel scale and CTCAE (common terminology criteria for adverse events).

Results: The adverse events observed included secondary amenorrhoea, irregular menstrual cycles, hyperprolactinemia, hirsutism, hyperpigmentation and in one patient an ovarian cyst. Serum prolactin levels ranged from 13.07 to 53.4 ng/ml among cohort. Endoxifen was discontinued in every case, following which four patients showed clinical improvement within 6 weeks of discontinuation, while fifth demonstrated a gradual decline in prolactin levels during follow up over 4 months. Causality assessment using WHO-UMC classified four cases as probable and one as possible. Naranjo scores ranging from 5 to 7.

Conclusion: The consistent temporal association between drug exposure and symptom onset, along with positive dechallenge, points to a possible reproductive endocrine safety signal with use of endoxifen. Clinicians should consider incorporating menstrual history and symptoms based endocrine evaluation in routine follow-up of patients on endoxifen therapy. Multicentre prospective studies are needed to determine the exact incidence and risk factors.

Keywords: Endoxifen, Bipolar disorder, Amenorrhoea, Hyperprolactinemia, Menstrual cycle disorders, ovarian cysts, Drug related adverse reactions, Pharmacovigilance.

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Introduction

Bipolar disorder is a recurrent mood disorder which is associated with substantial disability, suicidal risk, relapses and impairment of social and occupational life. Standard guidelines suggest use of mood stabilizers and antipsychotics for bipolar disorders, but long-term use of these drugs for treatment is often constrained due to metabolic, neurologic, renal, thyroid and sexual adverse effects. [1,2]

Bipolar disorder is a substantial global health problem. WHO estimates indicate that approximately 37 million people worldwide (about 0.5% of the global population, or roughly 1 in every 200 persons) were living with bipolar disorder in 2021, while pooled epidemiological reviews place the lifetime prevalence of the full bipolar spectrum in the range of 1-2.5% depending on the diagnostic criteria applied.

In India, the National Mental Health Survey (2015-2016) reported a current prevalence of 0.3% and a lifetime prevalence of 0.5% for bipolar affective

disorder among adults, with higher rates observed in men and in urban metropolitan populations. [3,4] In India, the Central Drugs Standard Control Organization approved endoxifen for the acute treatment of manic episodes, with or without mixed features, in adults with bipolar I disorder in 2019, making it the only country to date where the drug has received regulatory approval for this indication; endoxifen is not yet approved by the US FDA or other major regulators and has not been endorsed as a treatment option by the CANMAT/ISBD or other major international bipolar disorder guidelines. [5,6] Endoxifen (4-hydroxy-N-desmethyltamoxifen) is the major active metabolite of tamoxifen. Administering endoxifen directly prevents CYP2D6-mediated conversion required for activating prodrug tamoxifen. In addition to selective estrogen receptor modulation, endoxifen inhibits protein kinase C (PKC), a signalling pathway implicated in manic states. [5-7]

Guideline-recommended other pharmacotherapy for bipolar disorder comprises mood stabilizers, such as lithium, valproate, carbamazepine and lamotrigine, and second-generation antipsychotics, including olanzapine, quetiapine, risperidone, aripiprazole, asenapine, cariprazine and lurasidone, used alone or in combination for acute mood episodes and maintenance treatment.

Reproductive and endocrinal side effects are more alarming in adolescent and reproductive age group women because amenorrhoea, oligomenorrhoea, galactorrhoea, infertility and hypoestrogenism impairs quality of life, eventually leading to poor compliance and adherence. [8,9]

These adverse effects are mainly due to alteration of "hypothalamic-pituitary-ovarian feedback" is known to increase gonadotropin and estradiol levels eventually stimulating ovarian follicles and functional ovarian cysts in premenopausal females. These effects are reported mostly in premenopausal age groups and are seen to often regress after discontinuation or following conservative management. [10,11] Published studies on endoxifen, mainly emphasizes its antimanic efficacy and short-term tolerability. Reproductive endocrine adverse outcomes related to it are not well acknowledged. A recently published report of ovarian hyperstimulation, amenorrhoea, galactorrhoea, and marked hormonal abnormalities during endoxifen treatment reinforces the need for structured pharmacovigilance in young women. [6,12,13]

The rationale of this retrospective case series is to describe the clinical spectrum, chronology, investigations, management, outcome and pharmacovigilance assessment of reproductive endocrine adverse events observed in female patients diagnosed with bipolar affective disorder receiving endoxifen. Cases were identified from department records if they had a documented bipolar affective disorder diagnosis, had received endoxifen, and developed a new menstrual, reproductive, or endocrine abnormality after exposure, with sufficient records available to establish chronology, investigations, management and outcome; cases with inadequate documentation were excluded. This report was structured and is presented in accordance with the CARE guidelines for case reports. [14]

Results

Five female patients aged 15–28 years were included. The mean age was 23.4 years. All received endoxifen for bipolar affective disorder/ impulsive type of emotionally unstable personality, predominantly 8 mg/day, and developed endocrine manifestations after approximately 4–10 months of exposure. Secondary amenorrhoea and hyperprolactinaemia were the most frequent findings. Endoxifen was discontinued in all the cases on detection of adverse effects. Four patients showed documented clinical improvement after withdrawal, while one remained under follow-up with decreasing prolactin.

Table 1: Cohort Summary

Variable	Finding
Patients	5
Age, mean (range)	23.4 years (15–28)
Female sex	5 (100%)
Endoxifen dose	Predominantly 8 mg/day
Time to adverse event	Approximately 4–10 months
Secondary amenorrhea	3 cases
Hyperprolactinemia / raised prolactin	4 cases
Irregular cycles	2 cases
Ovarian cyst	1 case
Hirsutism / hyperpigmentation	1 case
Improvement after withdrawal	4 cases
Rechallenge	Not performed

Individual Case Narratives

Case 1: A 26-year-old unmarried woman with bipolar affective disorder received endoxifen 8 mg/day. Approximately five months after initiation, she developed secondary amenorrhoea. Serum prolactin was 20.2 ng/mL. Endoxifen was withdrawn and menstrual cycles subsequently resumed, constituting a positive dechallenge as mentioned in table 2.

Case 2: A 15-year-old girl with "impulsive type of emotionally unstable personality" receiving endoxifen 8 mg/day developed secondary amenorrhoea, hirsutism, and hyperpigmentation after approximately four months. Serum prolactin was 25.0 ng/mL. The available record did not establish all Rotterdam criteria or fully exclude mimicking disorders; the presentation was therefore described as a PCOS-like phenotype rather than confirmed PCOS. Menstrual cycles resumed after withdrawal as mentioned in table 2.

Case 3: A 22-year-old woman developed secondary amenorrhoea and irregular cycles after approximately ten months of endoxifen. Serum prolactin was 21.5 ng/mL. Pregnancy, thyroid disease, pituitary pathology, and concomitant medication effects were considered from available records. Endoxifen withdrawal was followed by regularization of cycles as mentioned in table 2.

Case 4: A 28-year-old woman developed irregular cycles and a 6.7 × 5.5 cm ovarian cyst after approximately five months of treatment. Serum prolactin was 13.07 ng/mL.

The cyst resolved after endoxifen was stopped. Because a solitary cyst is not equivalent to polycystic ovarian morphology, it was reported as an ovarian cyst as mentioned in table 2.

Case 5: A 26-year-old woman developed marked hyperprolactinaemia (53.4 ng/mL) after approximately ten months of treatment, with headache and visual symptoms. Endoxifen was withdrawn; prolactin subsequently decreased and follow-up continued, refer table 2.

**Pharmacovigilance and causality assessment was done for all 5 cases using WHO–Uppsala Monitoring Centre system and the Naranjo algorithm. Severity was categorized with the modified Hartwig and Siegel scale, and clinical seriousness was graded using CTCAE version 5.0 where applicable, refer table 3.

Table 2: Individual Clinical Characteristics, Investigations, Management And Outcomes

Case	Age	Dose	Exposure	Adverse event(s)	Prolactin	Ultrasound	Outcome
Case1	26	8 mg/day	~5 mo.	Secondary amenorrhea	20.2 ng/mL	Not documented	Cycles resumed after withdrawal
Case2	15	8 mg/day	~4 mo.	Amenorrhea, hirsutism, hyperpigmentation	25.0 ng/mL	Not documented	Cycles resumed; symptoms improved
Case3	22	8 mg/day	~10 mo.	Amenorrhea and irregular cycles	21.5 ng/mL	Not documented	Cycles regularized after withdrawal
Case4	28	8 mg/day	~5 mo.	Irregular cycles and ovarian cyst	13.07 ng/mL	6.7 × 5.5 cm ovarian cyst	Complete resolution documented
Case5	26	8 mg/day	~10 mo.	Hyperprolactinaemia; headache/visual symptoms	53.4 ng/mL	Not documented	Prolactin decreased; follow-up ongoing

Table 3: Pharmacovigilance Assessment

Case	WHO–UMC	Naranjo	Hartwig	CTCAE 5.0	Principal rationale
1	Probable	**6**	Moderate	Grade 2	Temporal association and positive dechallenge
2	Probable	7	Moderate	Grade 2	Temporal association, phenotype, and dechallenge
3	Possible	5	Moderate	Grade 2	Temporal association; confounding not fully excluded
4	Probable	6	Moderate	Grade 3	Cyst resolved after withdrawal
5	Probable	7	Moderate	Grade 2	Prolactin decreased after withdrawal

Table 4: CARE timeline matrix

Case	Start	Time to event	Key finding	Intervention	Outcome
1	Endoxifen 8 mg/day	~5 mo.	Amenorrhea; PRL 20.2	Stopped	Cycles resumed
2	Endoxifen 8 mg/day	~4 mo.	Amenorrhea; hirsutism; PRL 25	Stopped	Cycles resumed
3	Endoxifen 8 mg/day	~10 mo.	Irregular cycles; PRL 21.5	Stopped	Cycles regularized
4	Endoxifen 8 mg/day	~5 mo.	6.7 × 5.5 cm cyst	Stopped	Cyst resolved
5	Endoxifen 8 mg/day	~10 mo.	PRL 53.4	Stopped	PRL decreased

Discussion

Across all five patients, we saw a fairly consistent pattern of reproductive-endocrine disturbance following endoxifen exposure – amenorrhoea or menstrual irregularity, raised prolactin, androgenic features, and in one patient a reversible ovarian cyst. The temporal link between drug exposure and symptom onset, together with improvement after withdrawal in every case, supports a pharmacovigilance signal, though the absence of rechallenge means a definitive causal claim isn't possible. [15-19]

This is biologically plausible given endoxifen's dual pharmacology: its antimanic effect works mainly through protein kinase C inhibition, while its action as a selective estrogen receptor modulator can disrupt hypothalamic-pituitary-ovarian signalling and, in turn, gonadotropin regulation and ovarian follicular activity. [5,12,20,21]

Tamoxifen offers the closest mechanistic and clinical parallel. In premenopausal women it has been linked to elevated estradiol, ovarian stimulation, and functional cyst formation, and several observational and prospective studies show these cysts resolving spontaneously once tamoxifen is stopped or with conservative management. [10,11]

Hyperprolactinaemia disrupts reproductive function by suppressing pulsatile GnRH release from the hypothalamus, leading to anovulation, menstrual irregularity, amenorrhoea, sexual dysfunction, infertility, and reduced bone mineral density. Concomitant antipsychotics and serotonergic antidepressants are themselves associated with raised prolactin, so they need to be considered as a potential confounder here. [8,9]

We were careful not to label the adolescent patient's hirsutism and hyperpigmentation as PCOS outright, since that diagnosis requires meeting established criteria and ruling out thyroid disease, hyperprolactinaemia, androgen-secreting tumours, and pregnancy – recent guidelines specifically caution against overdiagnosing PCOS in adolescents. [22,23]

One strength of this series is its use of structured timelines alongside multiple causality-assessment tools; even so, these frameworks can support a causal argument but not establish it outright. What we can offer is transparent reporting of chronology, dechallenge, and the alternative explanations we considered, which we think adds clinical value without overstating what five cases can actually tell us. [14-19]

The main limitations are the retrospective design, small sample, incomplete baseline endocrine work-up, and potential confounding from psychiatric illness and co-medications. Because these cases were identified precisely because they had adverse events, this series cannot estimate incidence or comparative risk. Even so, the pattern is clinically relevant – reproductive-endocrine symptoms tend to get overlooked at psychiatric follow-up, and when they are missed, patients' compliance and adherence tend to suffer.

In practice, this means keeping a high index of suspicion for reproductive-endocrine effects whenever endoxifen is prescribed to adolescents or women of reproductive age, evaluating menstrual or endocrine changes early (with imaging where indicated), and reporting suspected adverse reactions through the national pharmacovigilance programme.

Conclusion

Taken together, these five cases suggest that endoxifen therapy in women with bipolar affective disorder may carry a real, if still poorly characterized, reproductive-endocrine safety signal – menstrual dysfunction, hyperprolactinaemia, androgenic changes, and ovarian cyst formation. We cannot establish definite causality from these observations alone, but the consistent timing and improvement after withdrawal are hard to ignore.

Menstrual and reproductive health should be actively monitored during endoxifen therapy, and adverse reactions reported systematically. What is really needed now is a well-designed, prospective, multicentre study to pin down the actual risk, the mechanism, and which patients are most vulnerable**.**

Declarations

Ethics Approval: Institutional Ethics Committee approval with registration no. : IEC/RMC/2026/111 was obtained before starting the study, which was

conducted in accordance with the Declaration of Helsinki.[24]

Consent for publication: Written informed consent and assent for publication was obtained from all the patients/ caregivers. This manuscript follows the CARE guidelines for reporting and anonymized data is provided.

Data availability: De-identified data may be made available by the corresponding author as per the institutional policy.

Author contributions: Dr. Babli Singh: Conceptualization, data curation, investigation, literature review, drafting.

Dr. Varaprasad: Supervision, methodology, clinical validation, critical revision, final approval.

Dr. B.S.B. Mallika: Supervision, critical revision, final approval.

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