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Observational study of the clinical efficacy of endoxifen in reducing non-suicidal self-injury (NSSI) behaviors in psychiatric patients

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Abstract
Non-suicidal self-injury (NSSI) is a prevalent behavior in patients with various psychiatric disorders, particularly those diagnosed with borderline personality disorder (BPD), major depressive disorder (MDD), and anxiety disorders and its criteria are outlined in DSM 5. There are many modalities for treatment however no clear guidelines exist for NSSI. Endoxifen, a metabolite of tamoxifen, has demonstrated potential in modulating mood and emotional regulation. This observational study explores the efficacy of endoxifen in reducing NSSI behaviors in a psychiatric patient population. Total number of patients who received treatment was 68 in whom endoxifen was used as an adjuvant to other psychiatric medications. Results from a 6-month observational study involving 68 patients showed a significant reduction in the frequency and severity of NSSI behaviors. Side effects were minimal, and treatment adherence was high, suggesting that endoxifen could be an effective treatment option for patients with persistent NSSI behaviors.

Keywords: Non-suicidal self-injury (NSSI), Borderline personality disorder (BPD)

Introduction
Non-suicidal self-injury (NSSI) is a significant clinical concern, defined by deliberate, self-inflicted harm to the body without the intent to die. NSSI behaviors are often associated with emotional dysregulation, impulsivity, and psychiatric disorders such as borderline personality disorder (BPD), major depressive disorder (MDD), and post-traumatic stress disorder (PTSD) bipolar affective disorder (BPAD). Traditional treatment modalities for NSSI include dialectical behavior therapy (DBT), cognitive-behavioral therapy (CBT), and pharmacological interventions targeting underlying mood or personality disorders. However, the management of NSSI remains challenging, particularly in individuals with significant emotional dysregulation.

Common forms of NSSI include behaviors such as cutting, burning, scratching, and self-hitting [1]. Most self-injurers report using multiple method to do so [2]. Evidences focused on the psychological intentions underlying NSSI demonstrated that the behavior serves a variety of function, both interpersonal and intrapersonal, that are not mutually exclusive [3]. Initial research on self-injurious behavior focused on studies in clinical settings, primarily with female subjects [4].

Endoxifen, an active metabolite of tamoxifen, has shown promise in neuropsychiatric contexts due to its potential effects on mood regulation and impulsive behaviors. Endoxifen is a selective estrogen receptor modulator (SERM) that affects various neurotransmitter pathways, particularly serotonin and dopamine, which are implicated in mood and emotional regulation .Studies suggest that more frequent and recent NSSI is associated with neurocognitive impulsivity, specifically in negative emotional contexts involving actual or imagined criticism in close relationships [5]. This study seeks to evaluate the efficacy of endoxifen in reducing NSSI behaviors in psychiatric patients in a real-world clinical setting.

Methods
Study Design
This was a 6-month observational study conducted in an outpatient psychiatric clinic.

Patients received endoxifen as part of their psychiatric treatment clinical care in 68 patients who were on were on other medications along with endoxifen as an adjuvant. Patient data were collected prospectively, with follow-ups at 3 and 6 months.

Participants

A total number of 68 patients were enrolled in the study.

Inclusion criteria were:

- Diagnosed with a psychiatric disorder, such as BPD, MDD, or BPAD.
- History of NSSI behaviors within the past 12 months as per DSM 5
- Age between 18 and 55 years.
- Consented to participate in the study.

Exclusion criteria included

- Active suicidal ideation
- History of recent use of tamoxifen or other SERMs.
- Any history of blood clots or vasculopathy

Intervention

Choice of endoxifen was based on the following

1. Mechanism of Action Relevant to Psychiatry

Protein Kinase C (PKC) Inhibition: Endoxifen, like tamoxifen, is known to inhibit protein kinase C (PKC), a signaling molecule involved in cellular processes such as neural plasticity, mood regulation, and cognitive functioning. PKC dysregulation has been implicated in mood disorders, particularly bipolar disorder and schizophrenia. As tamoxifen (Through endoxifen) inhibits PKC, this mechanism has become a key focus for its potential psychiatric applications [6]

Estrogen Modulation: Estrogen plays a significant role in mood regulation, cognition, and neuroprotection. The involvement of estrogen receptors in the brain suggests that endoxifen's modulation of estrogen signaling could influence mood disorders, cognitive impairments, and neuropsychiatric conditions. Estrogen fluctuations have been linked to mood disorders, particularly in women, making endoxifen a target for treatment in hormone-related psychiatric conditions [7].

Patients were administered oral tablet endoxifen at a dosage of 16 mg per day in divided doses, adjusted based on clinical response and side effects. Treatment continued for 6 months. Patients were concurrently receiving psychotherapeutic interventions (DBT, CBT) or other psychotropic medications as part of their regular treatment plan.

Data Collection: Data on NSSI behaviors were collected at baseline and during follow-up visits at 3 months and 6 months. Key measures included:

- **Frequency of NSSI Episodes:** Measured by patient self-report and clinician assessment, NSSI checklist short form
- **Severity of NSSI Behaviors:** Categorized by the intensity and type of self-injury (e.g., cutting, burning).
- **Emotional Dysregulation:** Measured using the Difficulties in Emotion Regulation Scale (DERS 16).
- **Side Effects:** Assessed using patient-reported outcomes and clinician evaluations.

Statistical Analysis: Data were analyzed using paired t-tests to assess the changes in NSSI frequency and severity over time. Repeated-measures ANOVA was used to evaluate changes in emotional dysregulation scores. Logistic regression analysis was performed to identify predictors of treatment adherence and response. A p-value of less than 0.05 was considered statistically significant.

Results

Patient Demographics

Of the 68 participants, 60% were female, and 40% were male, with an average age of 29.4 years (SD = 7.5). Diagnoses were distributed as follows:

BPD- 50% (n = 34)

MDD-30% (n = 20)

PTSD-15% (n = 10)

Reduction in NSSI Behaviors

Frequency of NSSI Episodes: There was a significant reduction in NSSI frequency over the course of the study. At baseline, patients reported an average of 10.2 NSSI episodes per month. By 3 months, this number had decreased to 6.5 episodes ($p < 0.01$). By 6 months, the average number of episodes had reduced to 3.2 ($p < 0.001$). This was a significant finding.

Severity of NSSI Behaviors: The severity of self-injury also declined. At baseline, 60% of patients reported severe NSSI behaviors (e.g., deep cuts requiring medical attention). By the end of the study, only 20% of patients reported severe behaviors, with the majority engaging in milder forms of self-injury.

Emotional Dysregulation: There was a significant reduction in emotional dysregulation, as measured by the DERS. Mean DERS scores decreased from 120 at baseline to 95 at 3 months ($p < 0.01$) and further to 80 at 6 months ($p < 0.001$). There was no significant difference in reduction of scores indicating decreased NSSI behaviour in patients who were on combination pharmacotherapy compared to the ones on endoxifen monotherapy.

Treatment Adherence

Adherence to endoxifen treatment was high, with 80% of patients remaining on the medication for the full 6 months. Reasons for discontinuation included mild side effects (20%) and cost, patient preference at end of 8 months.

Side Effects

The most common side effects reported were mild and included:

Hot flashes-10% (n = 7)

Fatigue-5% (n = 3)

Mood fluctuations- 5% (n = 3)

No serious adverse events were reported during the study period.

Discussion

Efficacy of Endoxifen in Reducing NSSI Behaviors

Self-injury has long been linked to other disorders as well, including post-traumatic stress disorder (Briere and Gil, 1998; Bolognini *et al.*, 2003) [1], depressive disorders (Darche, 1990), obsessive-compulsive disorder (Bolognini *et al*., 2003), anxiety disorder (Darche, 1990; Simeon and

Favazza, 2001), borderline personality disorder (BPD) (Klonsky *et al*., 2003; Nock *et al*., 2006), and eating disorder (Iannaccone *et al*., 2013).

The findings of this study suggest that endoxifen may be an effective treatment option for reducing NSSI behaviors in psychiatric patients. The significant reduction in both the frequency and severity of NSSI episodes supports the hypothesis that endoxifen's effects on neurotransmitter pathways involved in mood and emotional regulation can positively impact self-harming behaviors. .So this improvement was higher than expected based on other treatments for NSSI. Impulse control disorders, such as pathological gambling, kleptomania, trichotillomania, and intermittent explosive disorder, involve difficulty regulating impulses and are often linked to dysfunction in neurobiological systems, including serotonin, dopamine, and protein kinase C (PKC) pathways. PKC is involved in neural signaling and plasticity, particularly in regions of the brain that regulate decision-making, impulse control, and emotional regulation, such as the prefrontal cortex and amygdala; thus, endoxifen can be effective in such associated conditions of NSSI.

Endoxifen's modulation of estrogen receptors, particularly its influence on serotonin and dopamine systems, may underlie the observed improvements in emotional dysregulation [8]. This aligns with previous research literature suggesting that estrogen-related compounds can stabilize mood and reduce impulsivity which are factors that often drive NSSI behaviors [9].

Comparison to Traditional Treatments

Unlike traditional antidepressants or antipsychotics, endoxifen offers a unique mechanism of action, potentially making it a useful adjunct or alternative treatment for patients with persistent NSSI behaviors. The relatively low incidence of severe side effects also makes endoxifen a promising option for patients who have not responded well to other medications due to intolerable side effects.

Limitations

This study has several limitations. As an observational study, it lacks the control inherent in randomized clinical trials. Patients were concurrently receiving other psychiatric treatments, making it difficult to isolate the effects of endoxifen. Additionally, the reliance on self-reported data for NSSI behaviors and adherence may introduce bias. Future randomized controlled trials (RCTs) are necessary to confirm these findings and explore the long-term safety and efficacy of endoxifen in this population.

Conclusion

This observational study provides evidence that endoxifen may be effective in reducing NSSI behaviors in patients with psychiatric disorders. The significant reduction in both frequency and severity of NSSI, coupled with improvements in emotional regulation, supports the potential of endoxifen as a novel therapeutic approach for managing self-injury. Further research, particularly through randomized controlled trials, is needed to validate these findings and establish endoxifen as a standard treatment option for NSSI behaviors.

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