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# A Novel Sustained-Release *In-Situ* Implant of Fluvoxamine Ameliorates Depressive-Like Behaviours in a CUMS Mouse Model

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**Abstract**

Nearly 280 million individuals worldwide suffer from depression, a serious mental health condition. Numerous antidepressants are available; however, treatment results are still not ideal because of factors like low adherence, frequent dosage schedules, delayed start, and uneven efficacy among patient populations. Because it blocks the serotonin transporter (SERT) and modifies sigma-1 receptor activation, fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), is used extensively. However, pharmacokinetic restrictions that need two or three daily dosages frequently limit its therapeutic potential. This makes a strong case for the creation of innovative drug delivery methods that guarantee continuous drug release, preserve steady plasma levels, and eventually enhance long-term effectiveness and patient adherence. To get around the drawbacks of traditional dosage, the current study set out to create and assess a fluvoxamine *in situ*-forming implant (FISFI) as a sustained-release delivery method. In order to deliver fluvoxamine with a prolonged release in a chronic unpredictable mild stress (CUMS) mouse model of depression, the implant was created using biodegradable polymers. According to the study, both therapy groups showed notable improvements in both biochemical and behavioral indicators. With the lowest immobility durations (63.21 ± 17.95 s), the strongest sucrose preference at day 33, and the lowest

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serotonin restoration (~648 pg/mg), the FISFI group demonstrated similar efficacy. Individual results for the implant group were more consistent, indicating less variability. These findings demonstrate that fluvoxamine uses sigma-1 receptor activation and serotonergic modulation to produce strong antidepressant-like effects. By incorporating fluvoxamine into a biodegradable polymeric depot, FISFI may improve clinical results by lowering patient burden and delivering reliable therapeutic effects.

**Keywords:** Fluvoxamine, Sustained-release implant, *In situ* forming system, Depression, Mental health, Socioeconomic

## Introduction

Nearly 280 million individuals worldwide suffer from depression, a multifactorial psychiatric illness thtat lowers quality of life and increases disability, chronic illnesses and early mortality [1]. Depression continues to be a major contributor to the worldwide disease burden despite tremendous advancements in psychiatry and neuroscience, highlighting the urgent need for novel and efficient treatment approaches [2].

Antidepressants which work by altering the brain's monoaminergic systems are the main pharmacological treatment for depression [3]. Nevertheless, these medications frequently have a delayed beginning of action, varying efficacy in different patient groups frequent dosage regimens, and adverse drug reactions, all of which lead to poor adherence and treatment failure (4).

Compared to monoamine oxidase inhibitors and tricyclic antidepressants, selective seroton reuptake inhibitors (SSRIs) have a better safety record, making them the preferred first line treatment (5). One of the often prescribed SSRIs, fluvoxamine, works by specifically blocking the serotonin transporter, which raises the amount of extracellular serotonin in the synaptic cleft and enhances mood regulation (6). However, frequent dosing typically two or three times per day is required due to its short elimination half-life, which presents a significant obstacle to long term adherence (7).

Recent studies have concentrated on developing cutting-edge drug delivery systems that can maximise antidepressant treatment in order to overcome these obstacles. Because they allow for regulated and prolonged drug release, lower dose frequency, and maintain constant plasma drug concentrations, sustained release devices are especially appealing. A promising delivery method is represented by *in situ* forming implants, which are usually made of biodegradable polymers that, when injected, change from sol to gel. Developing a depot at the administration site. The pharmacokinetic limitations of traditional formulations can be addressed while maintaining steady serotonergic regulation by adding fluvoxamine to such a system.

As a preclinical tool for examining the biology of depression and assessing possible treatment approaches, the chronic unexpected mild stress (CUMS) paradigm in rodents has received substantial validation. The goal of this study is to develop and assess a fluvoxamine *in situ*-forming implant (FISFI) for enhanced antidepressant efficacy and sustained release.

## Materials and Methods

### *Materials*

The study used fluvoxamine maleate, a medicinal component for implant formulation from TCI Chemicals, Chennai. Poly Lactic-Co-Glycolic Acid (PLGA 50:50) from Nomisma Healthcare, Vadodara Gujarat, for sustained release trials and N-Methyl pyrrolidone from Sisco Research Laboratories (P) Ltd., Taloja, Maharashtra. Reliability and reproducibility were guaranteed by the analytical grade of the materials selected. For implant assessment, phosphate-buffered saline was utilized. To ensure stability, the materials were handled aseptically, glassware was sterilized, and storage was done according to recognized guidelines. This method is relevant to the development of

implant drug delivery system and represents regulatory compliance

### *Animals*

An investigation of depression was conducted using Male C57BL/6 mice of 8-12 weeks old. The mice were kept in the CCSEA approved Animal facility, Centre for Toxicology and Development Research . After a week of acclimatization, the mice were kept in polypropylene cages and their health and behavior were observed. The humidity (30-70%) and temperature (19-23ºC) of the experimental room were monitored and recorded during the experiments . Daily monitoring was carried out, and standard rodent feed was supplied. Consistent physiological baselines and reduced stresses were guaranteed by the strict animal care approach as per national regulation, assuring both scientific validity and ethical responsibility (IAEC Approval number : IAEC/72/SRIHER/891/2024).

### *Implant preparation*

A biodegradable polymeric technology was used to construct the fluvoxamine *in situ* forming implant (FISFI), which provides prolonged medication release. To develop a transparent polymer solution, the PLGA 50/50 was dissolved in N-methyl pyrrolidone(NMP). To enhance injectability and dispersion, polyethene glycol 6000 (PEG 6000) was then added. Drug was dissolved. To guarantee consistency and reproducibility, the implant was injected into phosphate-buffered saline (PBS) after the formulation's homogeneity and viability were evaluated. Because of its therapeutic use, biocompatibility and predictable breakdown kinetics, PLGA was selected. To maximize fluvoxamine trapping and prolonged release, the formulation approach was somewhat modified from earlier *in situ* implant techniques with both reliability and translational potential. This method provides a strong platform for assessing fluvoxamine's antidepressant effectiveness in a depression paradigm caused by CUMS (8).

### *Experimental design*

The purpose of the study was to assess the antidepressant effects of fluvoxamine administered conventionally versus through an -forming implant. A negative control, intraperitoneal fluvoxamine (CUMS + FLU), and *in situ* implant fluvoxamine (CUMS + FISFI) were the three groups into which 18 male C57BL/6 mice were split. The chronic unpredictable mild stress (CUMS) regimen was started after the mice had been acclimated for a week. Fluvoxamine was given subcutaneously every three days for three weeks and intraperitoneally for 21 days following two weeks of CUMS exposure. At prearranged intervals, behavioral evaluations were conducted. Brain tissues were removed following euthanasia in order to measure serotonin levels using ELISA method (9,10). This made it possible to directly compare the neurochemical results, behavioral recovery, and antidepressant efficacy of sustained-release and traditional fluvoxamine formulations. successively for 3 weeks as mentioned in Figure 1.

### *The chronic unpredictable mild stress (CUMS)*

The multiple stressors that contribute to human depression were mimicked by inducing

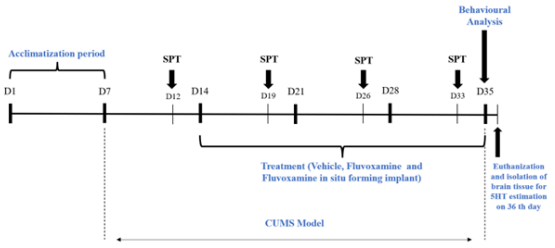


Figure 1:Study design

depression-like behaviors in mice using the chronic unpredictable mild stress (CUMS) paradigm. The process, which was modified from Frisbee *et al*. (2015), involved applying one stressor every day for four weeks in a row. Predator noise, wet cages, slanted cages, damp bedding, forced swimming, empty cage confinement, and disturbance of the light/dark cycle were among the stressors. The stressor

schedule was changed to keep things unpredictable. Because it produces core depression-like symptoms such as behavioral despair and anhedonia, which can be measured using tests such as the tail suspension test and sucrose preference, the CUMS technique has received extensive validation. The paradigm ensures translational relevance and reproducibility in assessing antidepressant therapies by using several mild stresses to produce strong behavioral and biochemical changes without causing excessive morbidity or mortality. Each of the animals was then exposed to one of the stressors listed below which was performed on a randomized schedule and delivered (Table 1).

Table 1:Unpredictable chronic mild stress (UCMS)

| Week | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
|---|---|---|---|---|---|---|---|
| 1 | Wet cage | Dampened saw dust | Empty Cage | Predator sound | Tilted cage | Swim stress | Disruption of Light / dark cycle |
| 2 | Swim stress | Tilted cage | Wet cage | Disruption of Light / dark cycle | Dampened saw dust | Empty Cage | Predator sound |
| 3 | Tilted Cage | Predator sound | Swim Stress | Dampened saw dust | Empty Cage | Disruption of Light / dark cycle | Wet cage |
| 4 | Disruption of Light / dark cycle | Empty Cage | Dampened saw dust | Wet cage | Swim Stress | Predator sound | Tilted Cage |

***Behavioural and biochemical assessments***

In comparison to traditional treatment, the study assessed the fluvoxamine implant's antidepressant effectiveness. To evaluate treatment outcomes and depression-like traits, behavioral tests were performed. Mice were given two pre-weighed bottles of 1% sucrose solution and water for an hour in order to measure anhedonia using the sucrose preference test (SPT). Behavioral despair was evaluated using the tail suspension test (TST), where decreased immobility is suggestive of antidepressant-like effects. Animals were put to death by isoflurane overdose following behavioral testing, and their brains were removed for biochemical analysis. A commercially available enzyme-linked immunosorbent test (ELISA) was used to measure the levels of serotonin. To track overall health, weekly body weight and feed intake were noted. These biochemical and behavioral endpoints offered a thorough assessment of the antidepressant effectiveness of the fluvoxamine implant (11).

***Statistical analysis***

Data was analyzed using GraphPad Prism software (version 10), which included one-way analysis of variance (ANOVA) for group comparisons and the Shapiro-Wilk test for normality. When an ANOVA revealed significant differences, pairwise group comparisons were conducted using Tukey's post hoc test. P-values were corrected for multiple testing, and a 95% confidence interval was retained.

For behavioral data, repeated measures ANOVA was utilized, which shed light on the treatment's long-term consequences. The statistical design ensured biologically significant and statistically confirmed therapy effects by adhering to preclinical psychopharmacology requirements. Strong results from behavioral and biochemical endpoints were ensured by the analysis, which made it possible to distinguish clearly between the control, standard fluvoxamine, and implant-treated groups. This supported the fluvoxamine *in situ* implant's translational potential.

## Results and Discussion

### *Body weight*

The study examined the body weight of experimental animals with a focus on fluvoxamine *in situ*-forming implants (FISFI), standard fluvoxamine administration, and control (CUMS only). All animals maintained their clinical normalcy throughout the four-week stress paradigm. Body weight fluctuated slightly in the CUMS-only group, which may have been caused by changed metabolic processes and decreased food consumption. Both fluvoxamine-treated groups, however, kept their body weights constant, suggesting that the drug's administration did not result in any unfavorable systemic effects or extra metabolic strains. Since new drug delivery methods can occasionally change food habits or cause local or systemic toxicity, the FISFI group's lack of noticeable weight loss is remarkable. Because it alleviates depressive-like states, fluvoxamine, especially in its sustained-release implant form, may indirectly restore stress-induced metabolic disturbances, as seen by the increased weight stability in treated groups. Given that weight loss or increase frequently coincides with the course and treatment of major depressive illness, this finding is pertinent to patients with this condition. In this preclinical scenario, the FISFI formulation showed such a profile, offering therapeutic advantages in behavioral testing while preserving body weight stability. All things considered, the study backs the use of sustained-release implants as a good substitute for traditional antidepressant medication.

### *Sucrose preference test*

A behavioral test called the sucrose preference test (SPT) is used to assess anhedonia, a primary symptom of depression in both human and animal models. In a study, sucrose preference was noted at baseline and then during the CUMS paradigm on days 12, 19, 26, and 33. The findings demonstrated notable group-dependent variations, emphasizing fluvoxamine's antidepressant properties as well as the *in-situ* implant formulation's enhanced benefit. When compared to controls, both fluvoxamine-treated groups' preferences for sucrose were noticeably better.

The FISFI group's better performance indicates that fluvoxamine's antidepressant effects were maintained and even strengthened over time by the sustained-release delivery mechanism. The restoration of serotonergic transmission in reward-associated brain areas may be the cause of the observed increase in sucrose preference following fluvoxamine therapy. Because irregular drug exposure can make treatment more difficult, these findings are important for clinical depression. When compared to the conventional intraperitoneal route, the FISFI formulation offers superior and long-lasting behavioral advantages, bolstering the clinical promise of sustained-release fluvoxamine implants as a cutting-edge depression treatment approach.The finding demonstrated notable group dependent variations, emphasizing fluvoxamine's antidepressant properties as well as the *in situ* implant formulation's enhanced benefit (Table 2)

Table 2:Effect of fluvoxamine and FISFI on sucrose preference (%) in CUMS-induced mice across different experimental weeks. Values are expressed as mean ± SD (n = 6).

| Week | Day | Group | Mean (SPT%) | SD |
|---|---|---|---|---|
| Baseline | 7th Day | G1 | 62.54 | 41.56 |
| Baseline | 7th Day | G2 | 74.39 | 29.04 |
| Baseline | 7th Day | G3 | 51.85 | 16.85 |
| 1 | 12th Day | G1 | 78.6 | 19.45 |
| 1 | 12th Day | G2 | 94.4 | 13.61 |
| 1 | 12th Day | G3 | 77.7 | 31.20 |
| 2 | 19th Day | G1 | 64.1 | 13.54 |
| 2 | 19th Day | G2 | 62.2 | 14.21 |
| 2 | 19th Day | G3 | 59.8 | 14.41 |
| 3 | 26th Day | G1 | 28.5 | 19.83 |
| 3 | 26th Day | G2 | 86.1 | 22.15 |
| 3 | 26th Day | G3 | 79.4 | 23.13 |
| 4 | 33rd Day | G1 | 65.6 | 19.51 |
| 4 | 33rd Day | G2 | 79.4 | 23.13 |
| 4 | 33rd Day | G3 | 94.4 | 13.61 |

***Tail suspension test***

A behavioral paradigm for evaluating behavioral distress in rodents is the tail suspension test (TST). In current study, mice given fluvoxamine intraperitoneally or the fluvoxamine *in situ*-forming implant (FISFI) demonstrated markedly reduced immobility, suggesting strong antidepressant effects. Comparable efficacy was suggested by the study's lack of significant differences between the intraperitoneal fluvoxamine and FISFI groups. Nonetheless, the FISFI group's quantitatively reduced immobility indicates a higher level of behavioral recovery. The findings lend credence to the clinical potential of FISFI in enhancing behavioral recovery via sustained and reliable serotonergic regulation. The outcomes are also influenced by fluvoxamine's pharmacokinetics. Stable plasma levels and continuous serotonergic modulation are the outcomes of the FISFI formulation, which guarantees continuous drug release from the PLGA depot. This mechanistic benefit is especially crucial for depression, as therapy results are negatively impacted by noncompliance. Comparable efficacy was suggested by the study's lack of significant differences between the intraperitoneal fluvoxamine and FISFI groups, though the implant-treated mice showed numerically lower immobility times (Table 3).The tail suspension test revealed a significant reduction in immobility time in both treatment groups compared to the negative control ($p < 0.0001$), while no significant difference was observed between the standard and FISFI formulations (Figure 2)

Table 3:Effect of fluvoxamine and FISFI on immobility time (s) in the tail suspension test. Data are presented as mean ± SD (n = 6). Statistical significance was determined using one-way ANOVA followed by Tukey's post hoc test.

| Group | Immobility (s) Mean ± SD | n |
|---|---|---|
| Negative Control | 145.60 ± 22.75 | 6 |
| Standard Treatment | 74.69 ± 16.75 | 6 |
| Test Compound | 63.21 ± 17.95 | 6 |

| TUKEY'S MULTIPLE COMPARISONS TEST | 95.00% CI of diff. | BELOW THRESHOLD ? | SUMMARY | Adjusted P Value | |
|---|---|---|---|---|---|
| NEGATIVE CONTROL vs. STANDARD | 41.93 to 99.89 | Yes | **** | <0.0001 | A-B |
| NEGATIVE CONTROL vs.TEST ITEM | 53.41 to 111.4 | Yes | **** | <0.0001 | A-C |
| STANDARD vs. TEST ITEM | -17.50 to 40.46 | No | ns | 0.5707 | B-C |

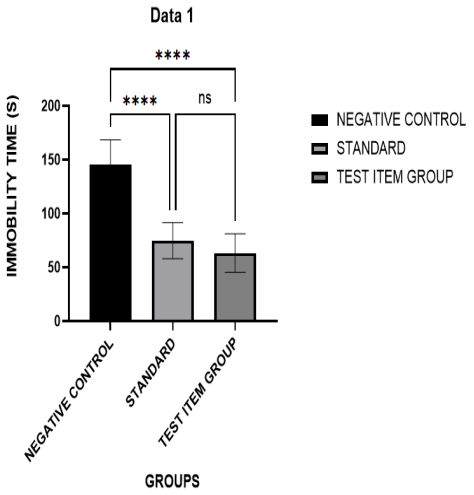


Figure 2:Comparison of immobility times in the tail suspension test among groups. Data are expressed as mean ± SD (n = 6). Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test. **p < 0.0001 vs. negative control; ns = non-significant.

Despite a notable decrease in immobility when compared to the negative control, the study revealed that FISFI, has antidepressant efficacy that is comparable to conventional fluvoxamine intraperitoneal medication This treatment effect is biologically significant and confirms earlier findings that drugs that decrease immobility in stress-based paradigms improve mood regulation and stress resilience. To prove their promise as cutting-edge antidepressant techniques, more research into their molecular underpinnings is required.

***Serotonin estimation***

According to research, long-term stress interferes with serotonin transmission, which results in symptoms similar to depression. Following four weeks of chronic unpredictable mild stress (CUMS) and fluvoxamine therapy, serotonin levels were assessed in brain tissue homogenates. The findings confirmed the negative effects of extended stress exposure on serotonergic signaling by demonstrating a significant decrease in serotonin in the CUMS-only group. Nonetheless, serotonin levels were significantly restored in both therapy groups. Serotonin levels in the FISFI group showed a more equal distribution among subjects, indicating that sustained-release administration produces more consistent neurotransmitter regulation. In the treatment of depression, where variations in plasma medication concentrations may result in novel symptoms or adverse effects, this stability is ideal. Given the brief half-life of fluvoxamine, the sustained-release profile of the FISFI formulation offers an advantage by sustaining consistent serotonergic regulation over prolonged periods of time. The formulation's potential to address one of the primary neurochemical deficiencies in depression is further demonstrated by the serotonin restoration seen in mice treated with FISFI. Serotonin levels were significantly reduced in the CUMS-only group, while both treatment groups showed marked restoration, with the implant formulation demonstrating more consistent values across subjects (Table 4; Figure 3).

Table 4:Effect of fluvoxamine and FISFI on brain serotonin concentrations (pg/mg) in CUMS-induced mice. Data are expressed as mean ± SD (n = 6)

| Animal Groups | Serotonin | O.D Value | | | | Concentration of Serotonin (pg/mg of tissue) | STDev |
|---|---|---|---|---|---|---|---|
| | | Trial 1 | Trial 2 | Trial 3 | Average | | |
| Group 1 | NC – 1 | 0.423 | 0.479 | 0.438 | 0.447 | 341 | 29.0 |
| | NC – 2 | 0.434 | 0.467 | 0.474 | 0.458 | 346 | 21.4 |
| | NC – 3 | 0.512 | 0.523 | 0.512 | 0.516 | 370 | 6.4 |
| | NC – 4 | 0.563 | 0.467 | 0.472 | 0.501 | 364 | 54.0 |
| | NC – 5 | 0.503 | 0.567 | 0.519 | 0.530 | 385 | 33.3 |
| | NC – 6 | 0.501 | 0.545 | 0.504 | 0.517 | 379 | 24.6 |
| Group 2 | Str+Std – 7 | 1.312 | 1.267 | 1.223 | 1.267 | 691 | 44.5 |
| | Str+Std – 8 | 1.189 | 1.297 | 1.264 | 1.250 | 684 | 55.3 |
| | Str+Std – 9 | 1.356 | 1.323 | 1.389 | 1.356 | 729 | 33.0 |
| | Str+Std – 10 | 1.367 | 1.245 | 1.267 | 1.293 | 702 | 65.0 |
| | Str+Std – 11 | 1.202 | 1.278 | 1.234 | 1.238 | 687 | 38.2 |
| | Str+Std – 12 | 1.101 | 1.112 | 1.167 | 1.127 | 639 | 35.4 |
| Group 3 | Str+Form – 13 | 1.234 | 1.116 | 1.126 | 1.159 | 645 | 65.4 |
| | Str+Form – 14 | 1.167 | 1.156 | 1.121 | 1.148 | 640 | 24.0 |
| | Str+Form – 15 | 1.123 | 1.086 | 1.067 | 1.092 | 616 | 28.5 |
| | Str+Form – 16 | 1.280 | 1.108 | 1.103 | 1.164 | 647 | 100.8 |
| | Str+Form – 17 | 1.134 | 1.034 | 1.045 | 1.071 | 616 | 54.8 |
| | Str+Form – 18 | 1.036 | 1.112 | 1.146 | 1.098 | 627 | 56.3 |

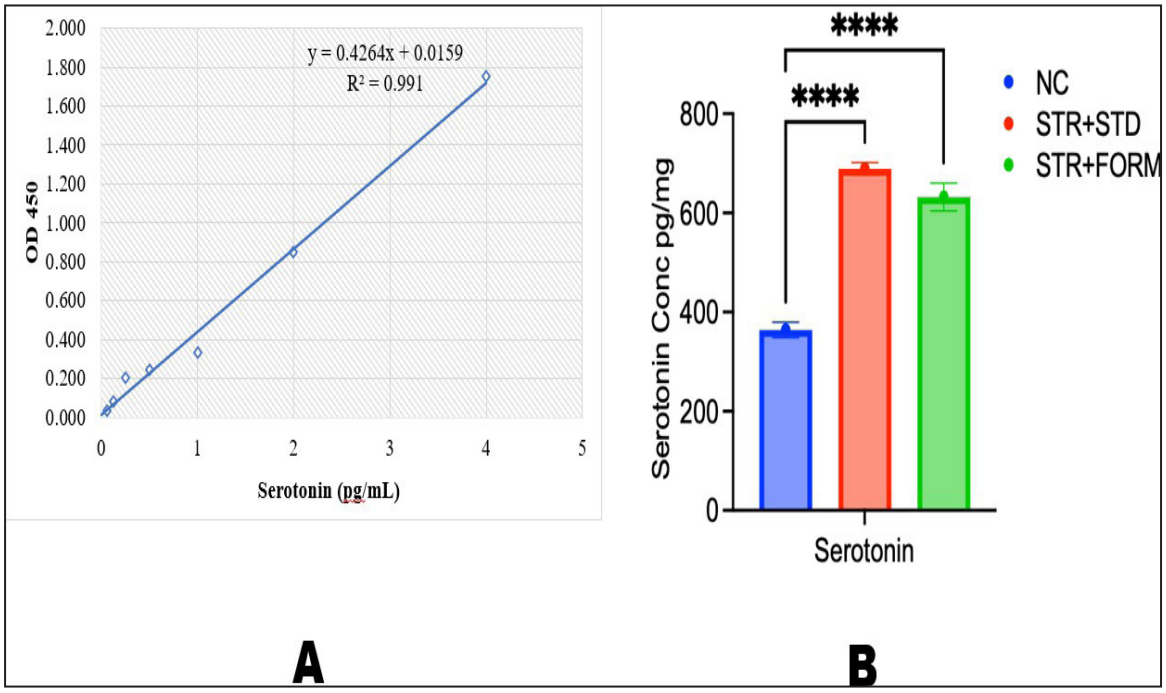


Figure 3:Serotonin estimation using ELISA. (A) Standard calibration curve for serotonin ($R^2 = 0.991$). (B) Comparative serotonin concentrations in brain homogenates of NC (CUMS only), STR+STD (CUMS + standard fluvoxamine i.p.), and STR+FORM (CUMS + FISF

***Pathological examinations***

The study assessed the fluvoxamine *in situ*-forming implant's (FISFI) safety in treating long-term illnesses including depression. The animals remained clinically normal, showing no signs of aberrant behaviors, skin lesions, or postural problems, even though there was no morbidity noted. All groups showed consistent body weight maintenance over the course of the four-week study period , with no discernible intergroup variations. With no discernible morphological changes or discolorations across groups, the study also verified that there were no obvious abnormalities in the brain. The slow and persistent release of fluvoxamine, which maintains consistent drug levels and lowers the risk of peak-related adverse events, is responsible for the implant's good safety profile. This pharmacological benefit is especially pertinent to the treatment of depression, as treatment-emergent side effects frequently impair patient adherence. Given that preclinical models show no signs of toxicity or disease, FISFI may provide a secure and practical substitute for standard human dosage schedules.

**Conclusion**

A study using a chronic unpredictable moderate stress mice paradigm showed the antidepressant efficacy and safety of a new fluvoxamine in situ-forming implant (FISFI). Stress-induced anhedonia and behavioral despair were successfully reduced by FISFI, with results that were on par with or marginally better than those of traditional fluvoxamine treatment. As evidence of its capacity to maintain serotonergic neurotransmission, it also raised serotonin levels in the brain. Translational assessments, pharmacokinetic profiles, and thorough histopathology should all be a part of future research.

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