Review Article

Hacettepe University Journal of the Faculty of Pharmacy
Volume 45 / Number 1 / March 2025 / pp. 71-78

The Epigenetic Effects Associated with Selective Serotonin Reuptake Inhibitors Treatment

Ayla Kenar[1]
ORCID: 0009-0001-4074-4704
Merve Arıcı[2]
ORCID: 0000-0001-5850-1578
Fedaa Abo Ras[1,3]
ORCID: 0000-0002-2290-1622
Mahmoud Abudayyak[3]*
ORCID: 0000-0003-2286-4777

[1]Istanbul University, Institute of Graduate Studies in Health Sciences, Department of Pharmaceutical Toxicology, Istanbul, Türkiye

[2]Istinye University, Faculty of Pharmacy, Department of Pharmaceutical Toxicology, Istanbul, Türkiye

[3]Istanbul University, Faculty of Pharmacy, Department of Pharmaceutical Toxicology, Istanbul, Türkiye

Corresponding author:
Mahmoud ABUDAYYAK
Istanbul University, Faculty of Pharmacy, Department of Pharmaceutical Toxicology, Istanbul, Türkiye
E-mail: abudiak1987@yahoo.com mfirat.kenanoglu@istanbul.edu.tr
Tel: +90 2124400000/ 13561

Received Date: 02.08.2024
Accepted Date: 17.02.2025

DOI: 10.52794/hujpharm.1527051

ABSTRACT

Depression is the most predominant psychiatric disorder worldwide. Selective serotonin reuptake inhibitors (SSRIs) are well-known drugs among the extensively used antidepressants. Additionally, SSRIs are used in the treatment of other behavioral disorders. The etiology of major depressive disorder (MDD) involves gene-environment interactions. Epigenetic modifications have a crucial role in managing treatment and prognostic benefits. It was shown that there is a clear relationship between SSRIs and epigenetic modifications. The epigenetic mechanisms underlying antidepressant drug treatment remain incompletely understood. Numerous studies have reported correlations between epigenetic modifications in genes such as BDNF, MAOA, SLC6A4, HTR1A, and HTR1B, as well as genome-wide methylation patterns, and treatment with selective serotonin reuptake inhibitors (SSRIs) in adult patients. Similarly, evidence suggests that prenatal and early-life exposure to SSRIs is associated with adverse outcomes, potentially affecting a child's physiological, emotional, and psychological development by altering methylation patterns in specific genes compared to non-exposed ones. These findings point to the potential use of epigenetic profiles as biomarkers to predict antidepressant treatment response, as well as to explain their toxicities and side effects. This review examines the impact of SSRI exposure on epigenetic modifications.

Keywords: selective serotonin reuptake inhibitors, epigenetic modifications, methylation.

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are well-known drugs among antidepressants, with extensive use because of their ability to treat many mental disorders. They provide improvement for depressive and other behavioral disorders such as anxiety, obsessive-compulsive disorder, panic disorder, and bulimia nervosa. SSRIs are safer alternatives to tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) [1].

Several studies have suggested an association between epigenetic modification and the clinical symptoms of depression. The epigenetic regulation of gene expression elicited by environmental stimuli continuously changes its expression. Exposure to prenatal and adult stress could be associated with epigenetic alteration of genes involved in mood regulation. In the same way, these epigenetic changes may serve to identify and treat symptom groups specifically for mental disorders [2]. This review focuses on the impact of SSRI treatment on epigenetic modifications in adults with depressive and behavioral disorders.

2. Material and Methods

A comprehensive literature review was conducted using databases accessible through the Istanbul University Library, including ScienceDirect, ClinicalKey, UpToDate, and Web of Science. Additional searches were performed in Google Scholar, Scopus, the National Thesis Center, and PubMed using relevant keywords. Search terms included "SSRI" in combination with "epigenetic," "methylation," or "chromatin," as well as "Fluoxetine" (along with other drugs listed in Table 1) paired with the same terms

3. Results and Discussion

3.1. Epigenetic modifications and SSRIs

The term 'epigenetics', first defined by Conrad Waddington in 1942, now refers to the examination of non-genotoxic and heritable alterations in the gene expression profile without any changes in DNA sequence [3]. Epigenetic mechanisms are fundamental to regulating gene expression in cellular processes such as embryogenesis, cellular differentiation, development, homeostasis, genomic imprinting, and disease pathogenesis through processes such as DNA methylation, histone modifications, and microRNA regulation [4, 5] (Table 1).

3.2. The effect of exposure to SSRIs during early life on epigenetic modifications

SSRIs are among the most used antidepressants during pregnancy, as their mechanism of action involves inhibiting the reuptake of monoamines and increasing their concentration outside the nerves in the brain. In the fetus, catecholamines and serotonin play a critical role in managing and regulating neuronal proliferation, migration, differentiation, neurogenesis, cerebral cortex maturation, and neuroendocrine development. Since SSRIs may cross the placenta and blood-brain barrier, and enter the breast milk, they may adversely affect the fetal brain leading to functional, developmental, behavioral, cognitive, and mental disorders [6,7].

SSRIs play a role in changing the level of DNA methylation during fetal development; the level of DNA methylation in cord blood was compared between neonates born to mothers who suffered from untreated depression or anxiety and neonates born to mothers who used SSRIs. Altered DNA methylation levels were observed in 42 CpG sites of mothers' DNA who did not receive any treatment. These changes were not observed in neonates born to mothers exposed to SSRIs. It was also found that DNA methylation at only one CpG site altered gene expression. Researchers concluded that SSRIs could change DNA methylation patterns and at the same time may reduce depression that negatively affects DNA methylation [8]. Another study demonstrated that cord blood DNA methylation of *NR3C1* was associated with increased cortisol levels in mothers with depression and who used SSRIs. However, in the same study, the hypothesis of altered levels of methylation DNA methylation in cord blood due to depression in mothers was not proven. This was attributed to the fact that DNA extracted from umbilical cord blood does not fully reflect methylation changes in the tissues of the newborn's central nervous system [9].

Fluoxetine (FLX), an antidepressant in the SSRI class, is widely prescribed for the treatment of anxiety disorders during pregnancy due to its relatively reduced side effects. Studies have reported that RNA expression patterns, regulatory enzyme gene expression, and behavioral changes were observed in

the offspring of female rats exposed to FLX before pregnancy. FLX alters the serotonergic transmission pathway by inhibiting serotonin transporter and increasing synaptic serotonin levels. This inhibition of serotonin reuptake may affect the oocytes, leading to a change in gene expression patterns; FLX has been shown to increase the RNA expression of *HTR2C* and influence the RNA expression of RNA-editing enzymes in the brains of offspring. The impact of FLX on newborns varies based on their sex, as it increases the aggressiveness of males and delays the initiation of maternal behavior in females [10].

Meyer et al. [11] reported changes in levels of serotonin receptors (HT-5), serotonin transporter (HTT-5), and tryptophan hydroxylase (TPH2) mRNA in the cerebral cortex following exposure to sertraline. Also, an unexplained increase in cortical mRNA levels of TPH2 and 5-HT2C receptors was observed. However, these molecular changes did not result in alterations in the behavioral phenotype in mice.

Exposure to FLX throughout pregnancy and lactation reveals brain DNA reprogramming effects through abnormal DNA methylation patterns, notably in the hippocampus and cortex, post-weaning. Given the hippocampus' pivotal role in learning, memory, and stress response, it demonstrates heightened sensitivity to environmental changes, maintaining early-induced epigenetic patterns throughout life [12]. Additionally, another study conducted on pregnant and breastfeeding rats also supports the possibility that SSRIs modulate epigenetic mechanisms. demonstrating that early exposure to FLX leads to permanent genetic changes that may cause late-onset concerns. [13].

Boulle et al. [6] demonstrated that FLX was also administered to offspring during the postnatal period, which is equivalent to the 3rd trimester of human neural development. Results indicated that developmental FLX treatment led to a rise in H3K27me3-enrichment at promoter IV of the brain-derived neurotrophic factor (BDNF) gene in prenatally stressed female offspring. These results suggest that the lasting neurochemical effects of developmental exposure to fluoxetine may be linked to prolonged epigenetic repression of gene transcription. Another study investigated DNA methylation in cord blood in relation to prenatal depressive symptoms (PND) and escitalopram use. The study found a relationship between PND and suboptimal fetal growth, suggesting epigenetic programming effects on the fetus. However, differential methylation (DM) was not directly associated with PND alone. Nonetheless, differences in cord blood methylation were observed in infants whose mothers experienced anxiety and were treated with SSRIs [14].

It has been shown that early life stress and chronic stress in adults modulate epigenetic mechanisms. A study examining the epigenetic mechanisms of the BDNF gene in the hippocampus, which may underlie the effects of postpartum maternal separation stress and adult self-control stress, found decreased levels of BDNF gene expression, acetylated histone H3 and H4 in the BDNF promoter, and an increase in HDAC5 mRNA. Treatment with escitalopram restored these alterations, indicating that these epigenetic mechanisms are involved in escitalopram's action [15].

Exposure to antidepressants during the prenatal period, compared to unexposed infants, revealed a significant relationship between higher *SLC6A4* methylation at CpG9 and CpG10 in infants exposed to antidepressants. This may suggest that prenatal exposure to SSRIs, due to the mother's treatment, could mitigate the negative physiological effects of the mother's situation [16].

Citalopram is one of the SSRIs commonly prescribed to pregnant women. Perinatal exposure to citalopram induced an increase in mRNA expression of brain angiogenesis inhibitor 3 (BAI3) and its ligands in the early postnatal dentate gyrus of both male and female offspring. This provides evidence for alterations in BAI signaling in individuals with depression and schizophrenia [17]. Moreover, exposure to citalopram during early neuronal differentiation has been shown to induce gene expression and DNA methylation of several genes, including *BDNF, DDIT4*, and *GDF11*. This suggests that citalopram exposure is linked to neurodevelopment and depression [18] (Table 1).

3.3. The effect of SSRIs in adults on epigenetic modifications

Several studies have demonstrated interactions between depressive symptoms and epigenetic mechanisms. An association has been observed between SSRIs and genes including *BDNF, MAOA, SLC6A4, HTR1A, HTR1B, IL6, IL11*, as well as whole-genome methylation [19] (Table 1).

ISSN: 2458 - 8806

BDNF:

BDNF plays a critical role in neuronal survival, synaptic plasticity, cognition, and response to antidepressants [19]. It promotes the growth and differentiation of nerve cells, maintains their survival and normal functionality, and prevents their death [20]. A significant correlation has been observed between decreased BDNF levels and the diagnoses of depression and anxiety. Since decreased BDNF levels in the brain may result in the atrophy and loss of cells in the hippocampus and prefrontal cortex, antidepressants work by increasing BDNF expression, reversing neuronal atrophy, and preventing cell loss [21]. Blaze et al. [22] reported that levels of BDNF *IV* gene methylation are higher in rats with prenatally stressed mothers compared to rats with non-stressed mothers. The research suggests that the *BDNF* gene contains distinct variants controlled by specific promoter regions. The most common of these variants is BDNF-IV, and alterations in its expression are associated with depressive and behavioral disorders, as well as epigenetic modifications. The exon-IV promoter region is a key candidate for epigenetic regulation, as it includes specific binding sites for some epigenetic-related proteins.

A study on patients with MDD treated with citalopram for 8 weeks indicated significantly increased mRNA expression of *BDNF* in patients with depression. However, no significant alterations in *BDNF* mRNA levels were observed after treatment. This suggests a relationship between mRNA expression levels and treatment response. Chromatin immunoprecipitation (ChIP) results showed a substantial reduction in H3K27me3 levels at promoter region- VI of BDNF in all patients receiving citalopram treatment for 8 weeks [23]. Serum BDNF levels were decreased in untreated depressed patients but increased during treatment with sertraline and escitalopram. After 8 weeks of treatment with sertraline or escitalopram, patients with higher levels of baseline serum BDNF showed greater improvements than patients with lower levels of BDNF. This suggests that individuals with relatively higher pre-treatment levels of BDNF may experience a more significant reduction in depressive symptoms. However, no statistically significant relationship was found between serum BDNF levels and depression severity before treatment. It has been suggested that adequate BDNF levels during treatment with antidepressants are necessary to achieve the therapeutic effects of antidepressants by enhancing activity-dependent neuronal plasticity, facilitating neural adaptations, and increasing the effects of antidepressants on serotonin levels in the hippocampus [24]. Furthermore, it was found that FLX could exacerbate depressive behavior by upregulating the expression of BDNF promoter region IV in the hippocampus [25]

In another study, an association was found between DNA methylation and SSRI response in MDD patients treated with escitalopram for 8 weeks. Additionally, three DMPs located on the *CHN2* and *JAK2* genes were closely linked to alterations in mRNA expression. These alterations may serve as potential biomarkers for SSRI treatment response [26] (Table 1).

MAO-A:

Monoamine oxidase (*MAO-A*) plays an important role in regulating monoamine neurotransmitter levels. It also influences mood, stress reactions, and brain developmental functions [17]. Domschke et al. [27] investigated the association between *MAO-A* methylation and antidepressant response in 94 patients with major depressive disorder. According to their results, while there is no significant major effect of *MAO-A* methylation in depression, *MAO-A* DNA hypomethylation may be a potential biomarker for escitalopram treatment in female patients with major depressive disorder (Table 1).

SLC6A4:

SLC6A4 plays a crucial role in the therapeutic response of antidepressant treatment. Iga et al. [28] investigated the association between SLC6A4 methylation at CpG sites in patients with major depressive disorder (MDD), both before and after eight weeks of treatment with different antidepressants including escitalopram, fluvoxamine, and sertraline. According to the findings, before treatment, patients with MDD exhibited significantly elevated expression of serotonin receptor (5-HTT) protein compared to unaffected controls. After treatment, these levels were significantly reduced. Methylation at CpG-2, CpG-3, and CpG-5 in *SLC6A4* may be associated with depressive symptoms. Similarly, treatments with paroxetine and fluvoxamine induced differential DNA methylation at CpG 3 [29] (Table 1).

DNA Methylation:

DNA methylation is an important epigenetic mechanism that regulates gene expression. Zhou et al. [30] identified several genes with both hypomethylation and hypermethylation, along with altered mRNA expressions in patients treated with escitalopram. In an experiment conducted on Balb/c mice, the efficacy of the antidepressant FLX was enhanced when histone deacetylase (HDAC) was inhibited. In FLX-exposed mice, HDAC inhibitors raised the levels of H4 histone acetylcholinesterase, and RNA polymerase II at promoter 3 of the *BDNF* gene, thereby enhancing *BDNF* transcription from this promoter. Inhibition of HDAC activity also reduced *BDNF*-stimulated tropomyosin kinase B receptor activation in fluoxetine-treated mice, thereby abrogating the behavioral effects of FLX. These data obtained from an animal model with strong responsiveness to fluoxetine suggest that HDAC inhibitors could serve as a potent adjunct to fluoxetine treatment for adolescents with minimal response to fluoxetine monotherapy and for those at risk of suicidality, as well as for adults not responding to an SSRI [31]. In another study, comprehensive analyses of DNA methylation were performed to investigate the relationship between clinical responses to paroxetine treatment and levels of DNA methylation. Results indicate the possible association between differential DNA methylation of *PPFIA4* and *HS3ST1* genes and clinical responses to paroxetine [32] (Table 1).

A genome-wide association study (GWAS) evaluated the potential differences in DNA methylation after FLX treatment in children and adolescents and found that 21 CpG sites showed a significant relationship with the response to FLX treatment. Also, *RHOJ* and *OR2L13* were identified at critical CpG sites which play a critical role in DNA methylation differences between blood and brain. This suggests that the methylation in specific genes may serve as possible biomarkers for the prediction of antidepressant treatment response [33]. Additionally, increased DNA methylation in patients treated with sertraline (including those exposed to trauma) was associated with a higher risk of premature mortality in these patients [34] (Table 1).

HTR1A and HTR1B:

The serotonin receptors 1A and 1B (HTR1A, HTR1B) play important roles in both the pathogenesis of major depressive disorder (MDD) and the clinical effects of SSRIs. DNA methylation of the HTR1A and HTR1B promoters was evaluated in patients treated with escitalopram. Two of the 96 CpG sites assessed were identified as potential predictors of antidepressant treatment response. Four CpG hypomethylation sites at HTR1A/1B, influenced by stress, were found to correlate with a poor response to antidepressant medications. Furthermore, it has been shown that age, environment, and antidepressant treatment may influence DNA methylation status. However, no significant effect of HTR1A and HTR1B genotypes on antidepressant treatment response and DNA methylation status was observed [35]. However, Gassó et al. [36] reported a negative correlation between the methylation levels of the *HTR1B* promoter and the response to FLX treatment in children and adolescents (Table 1).

P11:

Several studies have highlighted the role of p11 in the underlying mechanism of depression in both experimental models and humans. Certain classes of antidepressants result in increased p11 levels in specific brain regions. Additionally, p11 gene therapy has been effective in reversing depression-like behavior in mice. An association between decreased p11 levels and increased DNA methylation has been observed in rodent models. This effect was reversed by treatment with escitalopram. Exposure to escitalopram induced hypomethylation, which led to an increase in p11 gene expression and a decrease in the mRNA levels of two DNA methyltransferases [37] (Table 1).

4. Conclusion

In conclusion, epigenetic modifications can offer valuable insights into the management of SSRI treatment. Tailoring antidepressant therapy to the specific epigenomic profile of patients with major depressive disorder (MDD) has the potential to enhance treatment efficacy and shorten the overall treatment duration.

Conflict of Interest

All authors declare that there are no conflicts of interest.

ISSN: 2458 - 8806

Table 1. The epigenetic effects of SSRI drugs and the affected genes.

Drug	Gene	Epigenetic mechanism	Model	References
Fluoxetine	*HTR2C*	increased mRNA expression	Rat	Zaidan et al. 2018 [10]
	ADAR, ADARB1	decreased mRNA expression	Rat	Zaidan et al. 2018 [10]
	BDNF	decreased mRNA levels of promoter-IV, increased H3K27me3 at promoter-IV	Rat	Boulle et al. 2016 [6]
	BDNF	increased DNA methylation of *BDNF* promoter-IV	Mice	Jin et al. 2017 [25]
	BDNF	increased acetylated histon H4 protein at promoter-III	Mice	Schmaus, 2014 [31]
		decreased **Global methylation** in hyppocampus, hypothalamus and PAG, increased in cortex	Rat	Toffoli et al. 2014 [12]
		increased **global methylation** in hyppocampus	Rat	Silva et al. 2018 [13]
	RHOJ, OR2L13	differential DNA methylation	Human	Martinez-Pinteño et al. 2021 [33]
Sertraline	*BDNF*	decreased methylation of exon I	Human	Xing et al. 2021 [20]
	5-HTT, TPHR	increased mRNA expression	Mice	Meyer et al. 2018 [11]
		increased DNA methylation	Human	Katrinli et al. 2023 [34]
Escitalopram	*DNMT1, DNMT3A*	decreased DNA methylation	Rat	Melas et al. 2012 [37]
	P11	increased mRNA expression	Rat	Melas et al. 2012 [37]
	CHN2, JAK2	decreased DNA methylation, decreased mRNA expression	Human	Ju et al. 2019 [26]
	MAO-A	differential DNA methylation	Human	Domschke et al. 2015 [27]
	HTR1A, HTR1B	decreased DNA methylation at two CpG sites	Human	Wang et al. 2018 [35]
	many genes including *CBL, MPZL3, RAB31*	differential DNA methylation	Human	Zhou et al. 2023 [30]
Citalopram	*BDNF*	decreased in H3K27me3 levels at promoter-IV	Human	Lopez et al. 2013 [23]
	BAI3	increased mRNA expression	Rodent	Unroe et al. 2021 [17]
	many genes including BDNF, DDIT4	differential DNA methylation	*In vitro*	Spildrejorde et al. 2024 [18]
Paroxetine	*SLC6A4*	differential DNA methylation at CpG 3	Human	Okada et al 2014 [29]
	HS3ST1, PPFIA4	differential DNA methylation	Human	Takeuchi et al. 2017 [32]
Fluvoxamine	*SLC6A4*	differential DNA methylation at CpG 3	Human	Okada et al 2014 [29]

Statement of Contribution of Researcher

Design – A.K., F.A.R..; Supervision – M.Ab.; Data Collection and/or Processing – A.K., F.AR.; Literature Search – A.D., Y.N..; Writing – A.K., F.A.R..; Critical Reviews – M.A., M.Ab.

References

1- Chigome AK, Matsangaise MM, Chukwu BO, Matlala M, Sibanda M, Meyer JC. Review of selective serotonin reuptake inhibitors. *SA Pharmaceutical Journal* 2017; 84(6), 52-59. https://hdl.handle.net/10520/EJC-b3bd72247

2- Chmielewska N, Szyndler J, Maciejak P, Płaźnik A. Epigenetic mechanisms of stress and depression. *Psychiatr Pol.* 2019;53(6), 1413-1428. https://doi.org/10.12740/PP/94375

3- Singh D, Singh P, Srivastava P, Kakkar D, Pathak M, Tiwari AK. Development and challenges in the discovery of 5-HT1A and 5-HT7 receptor ligands. *Bioorg Chem.* 2023;131,106254. https://doi.org/10.1016/j.bioorg.2022.106254

4- Portela A, Esteller M. Epigenetic modifications and human disease. *Nat Biotechnol.* 2010;28(10),1057-1068. https://doi.org/10.1038/nbt.1685

5- Cacabelos R, Tellado I, Cacabelos P. in Ramón Cacabelos, The Epigenetic Machinery in the Life Cycle and Pharmacoepigenetics, In Translational Epigenetics, Pharmacoepigenetics, *Academic Press,* Volume 10, 2019, Pages 1-100, ISSN 25425358, ISBN 9780128139394, https://doi.org/10.1016/B978-0-12-813939-4.00001-2

6- Boulle F, Pawluski JL, Homberg JR, Machiels B, Kroeze Y, Kumar N, et al. Developmental fluoxetine exposure increases behavioral despair and alters epigenetic regulation of the hippocampal BDNF gene in adult female offspring. *Horm Behav*. 2016; 80,47-57. https://doi.org/10.1016/j.yhbeh.2016.01.017

7- Dubovicky M, Belovicova K, Csatlosova K, Bogi E. Risks of using SSRI/SNRI antidepressants during pregnancy and lactation. *Interdiscip Toxicol*. 2017;10(1), 30. https://doi.org/10.1515/intox-2017-0004

8- Non AL, Binder AM, Kubzansky LD, Michels KB. Genome-wide DNA methylation in neonates exposed to maternal depression, anxiety, or SSRI medication during pregnancy. *Epigenetics*. 2014;9(7),964-972. https://doi.org/10.4161/epi.28853

9- Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics*. 2008;3(2),97-106. https://doi.org/10.4161/epi.3.2.6034

10- Zaidan H, Ramaswami G, Barak M, Li JB, Gaisler-Salomon I. Pre-reproductive stress and fluoxetine treatment in rats affect offspring A-to-I RNA editing, gene expression and social behavior. *Environ Epigenet*. 2018;4(2),dvy021. https://doi.org/10.1093/eep/dvy021

11- Meyer LR, Dexter B, Lo C, Kenkel E, Hirai T, Roghair RD, Haskell SE. Perinatal SSRI exposure permanently alters cerebral serotonin receptor mRNA in mice but does not impact adult behaviors. *J Matern Fetal Neonatal Med.* 2018;31(11),1393-1401. https://doi.org/10.1080/14767058.2017.1317342

12- Toffoli LV, Rodrigues Jr GM, Oliveira JF, Silva AS, Moreira EG, Pelosi GG et al. Maternal exposure to fluoxetine during gestation and lactation affects the DNA methylation programming of rat's offspring: modulation by folic acid supplementation. *Behav Brain Res.* 2014;265,142-147. https://doi.org/10.1016/j.bbr.2014.02.031

13- Silva AS, Toffoli LV, Estrada VB, Veríssimo LF, Francis-Oliveira J, Moreira EG, et al. Maternal exposure to fluoxetine during gestation and lactation induces long lasting changes in the DNA methylation profile of offspring's brain and affects the social interaction of rat. *Brain Res Bull*. 2018;142,409-413. https://doi.org/10.1016/j.brainresbull.2018.09.007

14- Kallak TK, Bränn E, Fransson E, Johansson Å, Lager S, Comasco E, et al. DNA methylation in cord blood in association with prenatal depressive symptoms. *Clin Epigenetics*. 2021;13(1),1-14. https://doi.org/10.1186/s13148-021-01054-0

15- Seo MK, Ly NN, Lee CH, Cho HY, Choi CM, Lee JG, et al. Early life stress increases stress vulnerability through BDNF gene epigenetic changes in the rat hippocampus. *Neuropharmacology* 2016;105,388-397 https://doi.org/10.1016/j.neuropharm.2016.02.009

16- Gartstein MA, Hookenson KV, Brain U, Devlin AM, Grunau RE, Oberlander TF. Sculpting infant soothability: the role of prenatal SSRI antidepressant exposure and neonatal SLC6A4 methylation status. *Dev Psychobiol*. 2016;58(6),745-758. https://doi.org/10.1002/dev.21414

17- Unroe KA, Glover ME, Shupe EA, Feng N, Clinton SM. Perinatal SSRI exposure disrupts G protein-coupled receptor BAI3 in developing dentate gyrus and adult emotional behavior: relevance to psychiatric disorders. *Neuroscience*. 2021; *471*, 32-50. https://doi.org/ 0.1016/j.neuroscience.2021.07.007

18- Spildrejorde M, Leithaug M, Samara A, Aass HCD, Sharma A, Acharya G, ... & Lyle R. Citalopram exposure of hESCs during neuronal differentiation identifies dysregulated genes involved in neurodevelopment and depression. *Front. cell dev. biol.* 2024;*12*, 1428538. https://doi.org/ 10.3389/fcell.2024.1428538

19- Webb LM, Phillips KE, Ho MC, Veldic M, Blacker CJ (2020). The relationship between DNA methylation and antidepressant medications: a systematic review. *Int J Mol Sci.* 2020;21(3), 826. https://doi.org/10.3390/ijms21030826

20- Xing Y, Sun T, Li G, Xu G, Cheng J, Gao S. The role of BDNF exon I region methylation in the treatment of depression with sertraline and its clinical diagnostic value. *J Clin Lab Anal*. 2021;35(11),e23993. https://doi.org/10.1002/jcla.23993

ISSN: 2458 - 8806

21- Martinowich K, Manji H, Lu B. New insights into BDNF function in depression and anxiety. *Nat Neurosci*. 2007;10(9),1089-1093. https://doi.org/10.1038/nn1971

22- Blaze J, Asok A, Borrelli K, Tulbert C, Bollinger J, Ronca AE, et al. Intrauterine exposure to maternal stress alters Bdnf IV DNA methylation and telomere length in the brain of adult rat offspring. *Int J Dev Neurosci*. 2017:62,56-62. https://doi.org/10.1016/j.ijdevneu.2017.03.007

23- Lopez JP, Mamdani F, Labonte B, Beaulieu MM, Yang JP, Berlim MT, et al. Epigenetic regulation of BDNF expression according to antidepressant response. *Mol Psychiatry*. 2013;18(4),398-399. https://doi.org/10.1038/mp.2012.38

24- Wolkowitz OM, Wolf J, Shelly W, Rosser R, Burke HM, Lerner GK, et al. Serum BDNF levels before treatment predict SSRI response in depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2011;35(7),1623-1630. https://10.1016/j.pnpbp.2011.06.013

25- Jin HJ, Pei L, Li YN, Zheng H, Yang S, Wan Y, et al. Alleviative effects of fluoxetine on depressive-like behaviors by epigenetic regulation of BDNF gene transcription in mouse model of post-stroke depression. *Sci Rep*. 2017;7(1),1-15. https://doi.org/10.1038/s41598-017-13929-5

26- Ju C, Fiori LM, Belzeaux R, Theroux JF, Chen GG, Aouabed Z, et al. Integrated genome-wide methylation and expression analyses reveal functional predictors of response to antidepressants. *Transl Psychiatry*. 2019;9(1),254. https://doi.org/10.1038/s41398-019-0589-0

27- Domschke K, Tidow N, Schwarte K, Ziegler C, Lesch KP, Deckert J, et al. Pharmacoepigenetics of depression: no major influence of MAO-A DNA methylation on treatment response. *J Neural Transm*. 2015;122(1),99-108. https://doi.org/10.1007/s00702-014-1227-x

28- Iga J, Watanabe SY, Numata S, Umehara H, Nishi A, Kinoshita M, et al. Association study of polymorphism in the serotonin transporter gene promoter, methylation profiles, and expression in patients with major depressive disorder. *Hum Psychopharmacol*. 2016;31,193–199. https://doi.org/10.1002/hup.2527

29- Okada S, Morinobu S, Fuchikami M, Segawa M, Yokomaku K, Kataoka T, ... & Mimura M. The potential of SLC6A4 gene methylation analysis for the diagnosis and treatment of major depression. *J Psychiatr Res.* 2024;*53*, 47-53. https://doi.org/10.1016/j.jpsychires.2014.02.002

30- Zou Z, Zhang Y, Huang Y, Wang J, Min W, Xiang M, ... & Li T. Integrated genome-wide methylation and expression analyses provide predictors of diagnosis and early response to antidepressant in panic disorder. *J Affect Disord.* 2023;*322*, 146-155. https://doi.org/10.106/j.jad.10.049

31- Schmauss C. An HDAC-dependent epigenetic mechanism that enhances the efficacy of the antidepressant drug fluoxetine. *Sci Rep*. 2015;5(1),1-8. https://doi.org/10.1038/srep08171

32- Takeuchi N, Nonen S, Kato M, Wakeno M, Takekita Y, Kinoshita T, Kugawa F. Therapeutic response to paroxetine in major depressive disorder predicted by DNA methylation. *Neuropsychobiology* 2018;75(2),81-88. https://doi.org/10.1159/000480512

33- Martinez-Pinteño A, Rodriguez N, Blázquez A, Plana MT, Varela E, Gassó P, et al. DNA methylation of fluoxetine response in child and adolescence: preliminary results. *Pharmgenomics Pers Med*. 2021;459-467. https://doi.org/10.2147/PGPM.S289480

34- Katrinli S, King AP, Duval ER, Smith AK, Rajaram N, Liberzon I, Rauch SA. DNA methylation GrimAge acceleration in US military veterans with PTSD. *Neuropsychopharmacology*. 2023;*48*(5), 773-780.

35- Wang P, Lv Q, Mao Y, Zhang C, Bao C, Sun H, et al. HTR1A/1B DNA methylation may predict escitalopram treatment response in depressed Chinese Han patients. *J Affect Disord.* 2018;228,222-228. https://doi.org/10.1016/j.jad.2017.12.010

36- Gassó P, Rodríguez N, Blázquez A, Monteagudo A, Boloc D, Plana MT, et al. Epigenetic and genetic variants in the HTR1B gene and clinical improvement in children and adolescents treated with fluoxetine. *Prog Neuropsychopharmacol Biol Psychiatry*. 2017;75,28-34. https://doi.org/10.1016/j.pnpbp.2016.12.003

37- Melas PA, Rogdaki M, Lennartsson A, Björk K, Qi H, Witasp A, et al. Antidepressant treatment is associated with epigenetic alterations in the promoter of P11 in a genetic model of depression. *Int J Neuropsychopharmacol.* 2012;15(5),669-679. https://doi.org/10.1017/S1461145711000940