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An Overview on Perinatal Fluoxetine Treatment for Depressed Mothers

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Abstract:

Maternal depression during pregnancy and the postpartum period (lactation) is a common debilitating condition affecting mother-fetus/-infant interactions, which can be a risk factor for cognitive and affective disorders in mothers and their children. Selective-serotonin-reuptake-inhibitor-(SSRI) pharmacotherapy is known as the first-line treatment of maternal depression. However, its use during pregnancy and lactation is a topic of concern.

Keywords: Perinatal Fluoxetine, Depression, Mothers.

Introduction:

The Food and Drug Administration (FDA) approved fluoxetine (FLX) hydrochloride (3-(p-trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine HCl; Lilly (LY) 110140) for listing as an antidepressant on December 12, 1987. FLX quickly gained a lot of popularity and was dubbed the "happiness pill" when it was initially sold as Prozac® capsules in the USA (1). FLX continues to be one of the most popular antidepressants in the world today; in the USA, 21,913,276 approvals for the drug were written in 2017. (2).

However, FLX has been linked to several negative side effects, such as vomiting, appetite loss, sexual dysfunction, trouble sleeping, anxiety, and even the possibility of developing the "serotonin syndrome." In fact, it has emerged as the preferred antidepressant in primary care over time, even though not all patients experience the intended therapeutic effect; only 50% of patients improve with this drug (1). The detrimental effects of FLX administration on the kidney, heart, and liver in both human and animal models have been the subject of numerous studies. During FLX therapy, reports of hemorrhage, lung damage, cardiac muscle damage, hepatotoxicity, and changes in liver enzyme activity have been demonstrated (3, 4).

FLX is often used as capsules once day, with a normal dosage of 20 mg, to treat obsessive-compulsive disorders, depression, and anxiety disorders (5). Following administration, FLX has a mean half-life of one to three days and is metabolized by cytochrome P450 (CYP450) enzymes in the liver. Norfluoxetine (NFLX), the primary byproduct of its metabolism, is a demethylated metabolite with a half-life of 4–16 days and similar pharmacological activity. P-trifluoromethyl phenol is another secondary metabolite that is created when the parent medication undergoes oxidative O-dealkylation (1, 2).

About three-quarters of all prescribed drugs are metabolized by the CYP450 enzymes; however, because FLLX and NFLX have long half-lives, they may interact pharmacologically with other medications (2). FLX is widely circulated due to its high lipophilicity and potent apparent binding to plasma proteins. Thus, the brain is exposed to a great amount of FLX and its metabolite, NFLX (1).

Presynaptic reuptake of serotonin through the neurotransmitter transporters is inhibited by SSRIs, which increase serotonin at the postsynaptic membrane in the synapse of the serotonergic system. This is the main

mechanism of action of SSRIs (6, 7). Although the release of serotonin transmission occurred within minutes and maximum inhibition of 5-HTT occurred after four hours, there was a time difference of 3-5 weeks between the initiation of drug therapy and signs of marked treatment improvement. That's why there are many criticisms of this hypothesis. (1, 8). Currently, many other accepted hypotheses about depression have been proposed, especially those focused on inflammation and neurogenesis (9, 10).

Role of Perinatal FLX in treatment for depressed mothers

Over the past ten years, the number of pregnant women prescribed SSRIs has more than doubled. The most popular SSRI is FLX; more than 2.1 percent of all pregnant ladies take FLX continuously or during one trimester of their pregnancy (11). In fact, FLX is among the top twenty specific prescription medications used by pregnant mothers. (12).

Both FLX and its metabolite, NFLX, pass through the placental barrier and are eliminated in breast milk. So, there is concern over the high proportion of mothers administering SSRIs and FLX because these drugs may expose the fetus and/or newborn to harmful substances (12, 13). According to studies observing SSRI accumulations in umbilical cord blood from mothers who received treatment, the fetal percentage ranges from 50 to 83 when compared to mother levels (14).

By week five of pregnancy, serotonergic nerve cells and receptors start to form in the human brain, and by week fifteen, the somata of serotonergic neurons are arranged in their normal way. While the rostral division of cell bodies, which makes up 85% of all serotonergic neurons, generates the major ascending axons and dendrites to areas across the forebrain, such as the cerebral cortex and hippocampus, the caudal division of cell bodies provides fibers to the spinal cord (15).

A parallel neurodevelopmental process has been observed in rodents. There are three basic steps in the serotonergic system's development: 1) formation and maturation of serotonergic neurons begin from GD 10 to GD 14; 2) beginning axonal formation until rich to full growth begins from GD 13 to GD 19; and 3) serotonergic connections with other brain regions begin at GD 19 to postnatal day (PND) 21 (16).

In adults, serotonin plays a role as a neurotransmitter and is engaged in basic brain processes like mood, appetite, sleep, learning, and body temperature regulation. Nonetheless, serotonin functions as a neuromodulator in the early stages of fetal development, impacting critical neurodevelopmental processes such as the proliferation of neurons and glia, cell proliferation, differentiation and migration, neuroplasticity, and synaptogenesis (13, 17). SSRI is able to pass across the blood-brain barrier of the fetus, resulting in measurable quantities of drug in the pups' blood and brain (18). According to certain theories, suppression of the serotonin transporter and excessive exposure to serotonin during a crucial period of fetal development cause changes in the monoamine systems in different parts of the brain, which have long-lasting neurotoxicity that vary with age (19).

Anxiety, depression, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and other neuropsychiatric disorders may be linked to disruptions in serotonin transmission at stages of brain development. This is believed to occur as important neurodevelopmental processes that are regulated by serotonin change (20). Recent studies have indicated a connection between prenatal SSRI exposure and greater levels of internalizing (anxious and depressed) behavior as well as a higher risk of externalizing (aggression and hyperactivity) behavior in children, adolescents, and adults (21).

The effects of the perinatal FLX on the internalizing and externalizing behaviors of rodent models have been examined using various behavioral tests. Behavior is the last product of the central nervous system and needs to serve as the foundation for the ultimate judgment of preclinical assessments of new medications or genetic alterations, even if genetics, electrophysiology, and histology are all crucial instruments for comprehending the underlying processes of innovative drug treatments. Behavioral tests for rodents have been continuously improving over time, and there are currently more than 100 tests in use (22). Mainly, six tests are utilized to gauge rodents' anxiety-like behavior: open field test (OFT), elevated zero maze (EZM), elevated plus maze (EPM), light-dark choice test, novelty-suppressed feeding (NSF), and marble burying. Generally, three activities are commonly

used to identify depression or hopeless behavior in rodents. These are the tail suspension test (TST), forced swim test (FST), and sucrose preference test (SPT) (15).

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