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Review

Genotoxic Effects of Commonly Used Selective Serotonin Reuptake Inhibitors Antidepressants

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ABSTRACT

Depression, stemming from the Latin term 'deprimere,' meaning 'to press down,' is a constellation of symptoms characterized by disturbances in emotion, thought, behavior, and physical functions as reflections of impairments and irregularities in brain functions. As a psychiatric disorder, depression is most commonly treated through the use of antidepressants. Prior to their usage and release into the market, it is essential to investigate the genotoxic effects of these drugs. Genotoxic effects encompass deoxyribonucleic acid (DNA) damage occurring in the nucleus, chromosomes, and DNA structure, including DNA insertions, DNA breaks, gene mutations, chromosomal abnormalities, clastogenicity, and aneuploidy. With the increasing prevalence of antidepressant drug use in contemporary times, the determination of whether these medications induce genetic damage has become exceedingly crucial. Sertraline, commonly employed in the treatment of depression, belongs to the class of antidepressants known as selective serotonin reuptake inhibitors (SSRIs). This review discusses the genotoxic effects of SSRIs, with a specific focus on sertraline.

Keywords: Antidepressant drugs, genotoxic effect, selective serotonin reuptake inhibitors, sertraline

Depression is characterized by mood disorders, consisting of clusters of symptoms and manifestations, with a duration that can extend from weeks to months. It involves a significant alteration in an individual's usual functionality, demonstrating a tendency for periodic or cyclical recurrence.[1]

Such feelings may be observed as a widespread response commonly elicited in response to adverse life conditions. It is important to note that not every similar emotional state should be considered depression. In depression, these emotions are both continuous and intensely experienced at a level that disrupts the individual's daily life and functionality. Depression, with a lifetime prevalence ranging from 1.5% to 19%, poses a serious societal problem when left untreated, leading to high treatment costs, elevated mortality and morbidity rates.[2]

GENOTOXICITY OF SSRIs AND ANTIDEPRESSANTS

In 2020, the World Health Organization projected that depression would be the second leading cause of mortality among diseases due to complications associated with stress and the cardiovascular system. According to the results of epidemiological studies in Türkiye, the prevalence of clinical-level depression in the population is around 10%, and depression has become chronic in approximately one-third of patients. Globally, approximately 21% of the population is affected by depression.[3]

In Türkiye, the use of antidepressants has increased by 85% in the last four years. While 14 million 138 thousand boxes of antidepressants were consumed in 2003, this figure rose to 22 million 651 thousand in 2006 and further increased to 26 million 246 thousand in 2007. Antidepressant use in Türkiye is particularly concentrated among individuals aged 17-24.[4,5]

Antidepressants refer to psychiatric medications, dietary substances, or herbal materials (such as herbs, leaves, or fruits) used to alleviate conditions

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like depression or dysthymia (chronic depression). According to the literature, antidepressants achieve a success rate of approximately 94% in the treatment of depression. In the present day, with the increase in societal and personal problems, cases of depression have become more prevalent, leading antidepressants to become one of the most sought-after groups of drugs. Antidepressants are classified into eight groups: Selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), serotonin noradrenergic reuptake inhibitors, alpha-2 adrenoreceptor antagonists, serotonin-norepinephrine reuptake inhibitors, norepinephrine-dopamine reuptake inhibitors, and enhancing antidepressant drugs.[6,7]

The genotoxicity test involves the measurement of repairable, and therefore reversible, DNA primer damage, as well as the detection of stable and irreversible damage (i.e., gene mutations and chromosomal aberrations) that can be transmitted to the next generation when it occurs in germ cells. It can be defined as a disturbance in the mechanisms involved in maintaining the integrity of the genome. For a comprehensive assessment of genotoxicity, evaluation of three main endpoints (gene mutation, structural chromosomal aberrations, and numerical chromosomal deviations) is necessary, as each of these events plays a role in carcinogenesis and hereditary diseases. Genotoxicity tests determine whether various substances cause mutations, chromosomal abnormalities, or DNA damage. Since the late 1970s, these tests have been a cornerstone in assessing the reliability of chemicals.[8,9]

To determine the genotoxicity of antidepressants, various tests have been employed over time. These include the Ames test, somatic mutation and recombination test, mouse lymphoma assay, unscheduled DNA synthesis test, rodent dominant lethal assay, chromosomal aberration test, sister-chromatid exchange test, micronucleus test, and comet assay. Selective serotonin reuptake inhibitors are the first antidepressants developed to improve medication compliance, overcome side effects, and address safety concerns in the treatment of chronic and recurrent serious disorders that often result in physical and psychosocial impairments (e.g., major depressive disorders, panic disorders, and obsessive-compulsive disorders). The SSRIs, primarily used in the treatment of various psychological disorders, including major depressive disorder (depression), are the most widely prescribed antidepressant agents in many countries today due to their lower pharmacological side effects compared to other antidepressant agents.[10]

Unlike the MAOI and TCA groups, SSRIs directly impact the serotonin reuptake mechanism without affecting dopamine and norepinephrine levels in the brain; hence, they are termed 'selective'.[11] Released from vesicles at presynaptic nerve terminals, serotonin crosses the synaptic cleft and transmits impulses by binding to serotonin receptors on postsynaptic neurons. Subsequently, it is reabsorbed through the "serotonin reuptake transporter protein" (SERT) channel in the presynaptic neuron. This process, known as serotonin reuptake, plays a crucial role in regulating the serotonin release levels in the brain. Antidepressant agents belonging to the SSRI group block the SERT channel, preventing serotonin reuptake and leading to an increase in serotonin levels in the brain.[12] Prior studies have established that this elevation in serotonin concentration reduces depressive symptoms in patients.

Fluoxetine

Fluoxetine is an SSRI group antidepressant agent that has been widely used for many years in the treatment of major depressive disorder (in adults and children), obsessive-compulsive disorder, panic disorder, depressive mood disorder (premenstrual dysphoric disorder), and bulimia nervosa.[13]

Fluoxetine has been examined for its genotoxicity by both manufacturing companies and independent laboratories, and it has been observed that it may carry a genotoxic risk.[13,14]

Paroxetine

Paroxetine is an antidepressant that belongs to the class of SSRIs. Structurally, it differs from some other drugs with a similar mechanism of action, as it is in the phenylpiperidine class. In usual therapeutic doses, both single and repeated administrations do not affect psychomotor performance. However, at high doses, it may cause disturbances measurable through specific tests. Paroxetine, as one of the active ingredients in the SSRI group, has been declared to exhibit non-genotoxic effects.[15,16]

Escitalopram

Escitalopram is an antidepressant belonging to the SSRI class. It has been approved by the Food and Drug Administration for the treatment of depression and anxiety in adults and adolescents aged 12 and older. The medication is also used for the treatment of panic disorder, social anxiety

disorder, and obsessive-compulsive disorder. The potential genotoxicity and cytotoxicity of escitalopram have been extensively investigated using three different methods with *in vitro* human peripheral lymphocytes. From the findings, it can be concluded that escitalopram may be potentially genotoxic for peripheral lymphocytes at higher concentrations. There is only one article regarding the genotoxicity of escitalopram.[17] According to a study, an increase in the dose (0.06, 0.12, and 0.24 mg/kg/day) of escitalopram increased micronucleus frequency in both maternal and embryonic mice, and the increase was statistically significant at the highest dose. They also reported that the drug is somewhat mutagenic.[18] Another study suggests that escitalopram has genotoxic effects on both somatic and germ cells in mice.[19]

Citalopram

Citalopram is an antidepressant belonging to the SSRI group, primarily used in the treatment of major depressive disorder, generalized anxiety disorder, panic disorder, premenstrual dysphoric disorder, body dysmorphic disorder, and obsessive-compulsive disorder. It increases serotonin levels in organs such as the small intestine, leading to side effects.[20] Citalopram has both positive and negative results in terms of genotoxicity.

The Organisation for Economic Co-operation and Development guidelines for chemical testing specify that before the active ingredient used in pharmaceutical production is released into the market, it is essential to conduct the following tests:

-bacterial gene mutation test.

-cytogenetic evaluation of *in vitro* chromosomal damage in mammalian cells or *in vitro* mammalian cell gene mutation test.

-*in vivo* chromosomal damage test using rodent hematopoietic cells.

Results of the tests required for the release of drugs into the market are typically found only in reports submitted by the testing companies, and access to many of these reports is often limited. Furthermore, these reports frequently do not include trial doses, trial durations, and a detailed breakdown of the results. Therefore, it is crucial for independent laboratories to investigate the genotoxic risks of drug-active ingredients for human health. In pursuit of this goal, scientists endeavor to determine the potential clastogenic, mutagenic, and genotoxic effects of various drug-active ingredients through *in vivo* and *in vitro* testing methods. As a result of these studies, it has been identified that many drug-active ingredients possess genotoxic effects.[21,22]

Sertraline

Sertraline, an SSRI, is a derivative of phenyl naphthylamine. Its advantages over other SSRIs include the absence of significant enzyme inhibition and a shorter elimination half-life (24-26 hours). Some studies on sertraline have reported that when used in the early stages of pregnancy, it may lead to a major malformation, specifically a heart septal defect, in children who begin to walk. A study was conducted with patients using SSRIs such as fluoxetine, sertraline, and the TCA clomipramine. In this study, leukocyte isolation and DNA damage in a certain number of male and female patients using antidepressants and healthy individuals as a control group were compared through gel electrophoresis, revealing significant DNA damage in patients. The study found that fluoxetine caused the most DNA damage, while clomipramine caused the least. Additionally, the study determined that DNA damage in male patients was more significant than in female patients.[23] In another long-term *in vivo* study conducted on female rats, it was indicated that sertraline could lead to the development of thyroid and uterine tumors.[24]

Sertraline is the second most potent inhibitor of serotonin reuptake and the second most selective serotonin blocker compared to norepinephrine uptake. It is the only SSRI that binds to dopamine transporters.[23] Apart from the potential to block α1-adrenoceptors, sertraline has a low affinity for neurotransmitter receptors, and it lacks clinical relevance.[25,26] Sertraline, in addition to being the most commonly prescribed adult medication among the new generation of antidepressants called SSRIs, is also prescribed to children aged six and older and pregnant women.[27,28]

Pregnancy and the postpartum period are considered relatively high-risk intervals for depressive episodes in women, especially those with a history of psychiatric disorders. The data regarding the potential consequences of exposure to SSRIs through the placenta and breast milk on newborn adaptation and long-term neurocognitive baby development are still debatable. While most babies born to women taking SSRIs during pregnancy are normal, accumulating evidence suggests that maternal SSRI treatment during pregnancy may lead to adverse reproductive outcomes. Maternal SSRI treatment in the first trimester has been associated

with an increased risk of birth defects, particularly cardiac abnormalities.[29] It has been suggested that sertraline, especially in pregnant women, may cause severe lung problems and morphological defects in the fetus.[30]

In a study investigating the effects of sertraline on somatic growth and reflex development in rats, it was found that as the concentration of sertraline increased, the rats exhibited delayed body and organ development, decreased body weights, and slowed development of features such as tail length and head size. For a more comprehensive detection of the genotoxic effects of sertraline and the risk assessment of SSRI treatment, new and advanced studies should be conducted, including the determination of DNA repair enzyme levels and histopathological examinations of target organs. Due to the limited information available, examining the genotoxic potential of antidepressant drug active ingredients using different tests and test systems will undoubtedly contribute to increasing the limited knowledge in this field. Therefore, there is a need for *in vitro*, *in vivo*, and epidemiological studies on the genotoxicities of drug active ingredients.[31,32]

In conclusion, the focus on the genotoxicity of SSRIs and specific antidepressants like fluoxetine, paroxetine, escitalopram, citalopram, and sertraline raises concerns about potential risks associated with their use. The genotoxicity tests employed, including the Ames test, somatic mutation, and recombination test, mouse lymphoma assay, and others, serve as crucial tools in assessing the safety of these medications. While SSRIs, such as sertraline, exhibit efficacy in treating psychological disorders, the reported genotoxic effects and potential adverse outcomes during pregnancy necessitate careful consideration. Moreover, the long-term implications of antidepressant use, especially during sensitive periods like pregnancy and the postpartum period, underscore the importance of continued research to assess the risks and benefits comprehensively. Further investigations, including advanced studies on DNA repair enzyme levels and histopathological examinations, are recommended to enhance our understanding of the genotoxic potential and overall safety of antidepressant drug active ingredients. In light of the limited available information, continued *in vitro*, *in vivo*, and epidemiological studies are crucial for a more comprehensive evaluation of the genotoxicities associated with these medications.

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