Letter to Editor:
The Neuropsychiatric Side Effects of Oseltamivir, an Early Solution in the Coronavirus

Ideh Ghafour[1], **Forouzan Elyasi**[2*]

1. Psychiatry and Behavioral Sciences Research Center, Addiction Institute, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
2. Department of Psychiatry, Sexual and Reproductive Health Research Center, Addiction Institute, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.

*** Corresponding Author:**
Forouzan Elyasi, MD.
Address: Department of Psychiatry, Sexual and Reproductive Health Research Center, Addiction Institute, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
Phone: +98 (113) 3370885
E-mail: forouzan.elyasi@gmail.com

Dear Editor

December 2019 ended with a report of an outbreak of pneumonia with unknown cause in Wuhan, China. The disease attracted global attention, and subsequently, researchers identified a novel coronavirus (SARS-CoV-2) only seven days after the first case of infection identified on January 7, 2020 [1]. People with coronavirus disease 2019 (COVID-19) often suffer from respiratory symptoms and, to a lesser extent, gastrointestinal symptoms. Fever, cough, dyspnea, myalgia, dizziness, headache, sore throat, rhinorrhea, chest pain, and diarrhea are symptoms of this disease. The main routes of transmission of the virus are short-range expiratory droplets and indirect transmission [2]. Recent studies show that patients 60 years or older are at higher risk, and children are less likely to become infected. The infected children have milder symptoms or will remain asymptomatic [3]. One of the issues requiring special attention in this era is the complications, such as neuropsychiatric side effects and interactions of used drugs [4]. Oseltamivir is one of the antiviral drugs used in the treatment of COVID-19 [5].

The oseltamivir has also been recommended in Iran in the annex to the "National Guidelines for Novel Coronavirus". It is in the prime version of the Flowchart of Diagnosis and Treatment of COVID-19 at the outpatient and inpatient levels, released by the Center for Infectious Disease Management and Research of the Ministry of Health and Medical Education on February 26, 2020 [6]. In the prime version of the Flowchart, the drug had been recommended at a dose of at least 75 mg twice a day for 5 days in the antiviral outpatient dual therapy and triple/quadruple therapies on admission. Still, this drug was removed from the fourth version of the Flowchart.

Oseltamivir (Tamiflu) is a neuraminidase inhibitor that blocks the release of flu virus-laden droplets from infected cells in the respiratory tract. Zanamivir, peramivir, and laninamivir are other drugs of this group. The oseltamivir is globally one of the most effective flu treatments approved by the US Food and Drug Administration (FDA) to treat influenza [7]. The drug is usually well-tolerated regardless of the patient's age and other comorbidities. The most common side effects of this drug are nausea, vomiting, gastrointestinal discomfort, which is experienced by 10%-15% of adults receiving therapeutic doses [8]. However, there are case reports of the psychiatric side effects of this drug in Japan and other countries in recent years. Of all the side effects reported with this drug, neuropsychiatric symptoms and body aches had the greatest adverse effect on patients' satisfaction with treatment

Citation Ghafour I, Elyasi F. The Neuropsychiatric Side Effects of Oseltamivir: An Early Solution in the Coronavirus. Pharmaceutical and Biomedical Research. 2020; 6 (Special Issue on COVID-19):61-64. http://dx.doi.org/10.18502/pbr.v6i(S2).5654

doi: http://dx.doi.org/10.18502/pbr.v6i(S2).5654

[9]. The oseltamivir-induced behavioral abnormalities have been reported in more than 100 children and adolescents in Japan by 2007 [10]. Up to 10% of the drug passes through the blood-brain barrier, responsible for the neuropsychiatric side effects of the drug [11]. The psychiatric side effects are more common in children and adolescents [8]. These side effects often start suddenly (within 48 hours of starting treatment) and improve rapidly [12, 13]. However, there are also reports of late-onset [11, 14].

The psychiatric side effects of this drug mainly include delirium (and delirium-like conditions) and suicidal attempts. Some of the other side effects of oseltamivir reported in the articles include cognitive impairment, sudden anger, episodes of fear, putting unusual objects in the mouth [7], impaired consciousness, tremor, anxiety symptoms, parasomnias, [11] crying, nervousness/restlessness, and body aches [9]. Cases from Japan consist of neuropsychiatric events like jumping or falling from a height [7].

There has been a case report of oseltamivir-induced mania in China in 2010 [15] and an oseltamivir-induced major depressive episode in a 15-year-old teenage girl in South Korea. The girl 5 days after the administration of oseltamivir (75 mg twice daily) had insomnia, decreased sleep needs, reduced appetite, and loss of concentration, agitation, depression, irritability, and impulsive suicidal thoughts [13]. A 22-year-old man with influenza A (H1N1) in South Korea in 2015, five days after treatment with oseltamivir (75 mg), showed some side effects, including mood swings, suicidal thoughts, auditory hallucinations, memory problems, and insomnia. Also, the patient's psychiatric symptoms persisted up to two days after the drug discontinuation, even more severely, so that the patient exposed the delirium of guilt and the thoughts of nihilism [14]. Review research (2008) reported oseltamivir-induced psychiatric side effects, higher in males [16]. In most cases, the patient had no premorbid medical or psychiatric history [7]. However, these case reports have limitations in using scales like Naranjo ADR scales or any description about confounders like drug-drug interaction or the direct effect of the viral illness.

There is no definite information about the cause of such side effects. Studies have mentioned the roles of neurotransmitter changes, including an increase in dopamine release in the medial prefrontal cortex (mPFC) in rats, which may be in favor of such changes in patients receiving oseltamivir [17]. Oseltamivir carboxylate can penetrate the blood-brain barrier from the blood, but a study has shown that active drug flow by anion transporters restricts the cerebral release. As a result, differences in the activity of anion transporters can justify interpersonal differences in the experience of drug-related psychiatric side effects [13]. Besides, a study (2008) showed that the brain and plasma concentrations of oseltamivir carboxylate were higher in younger rats than in older ones, which could justify higher psychiatric complications at younger ages [18].

Finally, researchers believe that it is difficult to distinguish the effects of treatment from the symptoms of the underlying disease [13]. Studies have not reported any increase in neuropsychiatric side effects following oseltamivir use [17, 19]. Infectious diseases such as influenza can be associated with behavioral symptoms and can cause hallucinations, delirium, or abnormal behaviors, especially if they have encephalitis or encephalopathy [12]. Also, patients with influenza may show psychiatric symptoms due to immunological reactions rather than virus penetration into the central nervous system [20].

Some prospective clinical trials showed no elevation in these complications compared with placebo [19]. There have also been articles demonstrating that oseltamivir is associated with the reduced risk of neuropsychiatric complications [8]. Therefore, further studies need to investigate the underlying mechanism of psychiatric complications. At present, there is a need for close observation and follow-up of the patient at the time of oseltamivir administration [14].

Most side effects of medications are reported voluntarily by the patients, and it is difficult to estimate the true extent of psychiatric side effects with oseltamivir, but overall it seems uncommon. FDA considers insufficient evidence to conclusively establish a link between oseltamivir and psychiatric side effects. However, the patients treated with this drug should be closely monitored for evidence of abnormal behavior. If neuropsychiatric side effects occur, the decision to continue or discontinue the drug should be made based on the risks and benefits to each patient [21].

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Writing – original draft, writing – review & editing: Ideh Ghafour; Writing – review & editing, conceptualization: Forouzan Elyasi; Supervision: Both authors.

Conflict of interest

The authors declared no conflict of interest.

References

[1] Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). J Gen Intern Med. 2020; 35:1545–9. [DOI:10.1007/s11606-020-05762-w] [PMID] [PMCID]

[2] Chen Q, Quan B, Li X, Gao G, Zheng W, Zhang J, Zhang Z, Liu C, Li L, Wang C, Zhang G. A report of clinical diagnosis and treatment of nine cases of coronavirus disease 2019. J Med Virol. 2020; 92(6):683-7. https://onlinelibrary.wiley.com/doi/full/10.1002/jmv.25755

[3] Velavan TP, Meyer CG. The COVID-19 epidemic. Trop Med Int Health. 2020; 25(3):278-80. [DOI:10.1111/tmi.13383] [PMID] [PMCID]

[4] Zarghami M. Psychiatric aspects of Coronavirus (2019-nCoV) infection. Iran J Psychiatry Behav Sci. 2020; 14(1):e102957. [DOI:10.5812/ijpbs.102957]

[5] Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and Corona Virus Disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 2020; 55(3):105924. [DOI:10.1016/j.ijantimicag.2020.105924] [PMID] [PMCID]

[6] Ministry of Health and Medical Education. COVID-19 Diagnostic and therapeutic flowchart for outpatient and inpatient service levels [Internet]. 2020 [Updated 2020 Feb; Cited 2020 Apr]. Available from: http://dme.behdasht.gov.ir/uploads/Felo_Tashkish.pdf

[7] Chen R, Fang Z, Huang YJBid. Neuropsychiatric events in an adult patient with influenza a (H3N2) treated with oseltamivir (Tamiflu): A case report. BMC Infect Dis. 2019; 19(1):224. [DOI:10.1186/s12879-019-3827-4] [PMID] [PMCID]

[8] Huh K, Kang M, Shin DH, Hong J, Jung J. Oseltamivir and the risk of neuropsychiatric events: a national, population-based study. Clin Infect Dis. 2020; 71(9):e406–e414. [DOI:10.1093/cid/ciaa055] [PMID]

[9] Antipov EA, Pokryshevskaya EB. The effects of adverse drug reactions on patients' satisfaction: evidence from publicly available data on tamiflu (oseltamivir). Int J Med Inform. 2019; 125:30-6. [DOI:10.1016/j.ijmedinf.2019.02.005] [PMID]

[10] Izumi Y, Tokuda K, O'Dell KA, Zorumski CF, Narahashi T. Neuroexcitatory actions of Tamiflu and its carboxylate metabolite. Neurosci Lett. 2007; 426(1):54-8. [DOI:10.1016/j.neulet.2007.08.054] [PMID] [PMCID]

[11] Haque SF, Nizami S. Neuropsychiatric symptoms in the pediatric population after administration of oseltamivir. Am J Psychiatry Resid J. 2017; 12(2):18-9. [DOI:10.1176/appi.ajp-rj.2017.120207]

[12] FDA. US Food and Drug Administration (FDA) [Internet]. 2008 [Updated 2020 April]. Available from: https://www.fda.gov/media/76542/download

[13] Chung S, Joung YS. Oseltamivir (tamiflu) induced depressive episode in a female adolescent. Psychiatry Investig. 2010; 7(4):302-4. [DOI:10.4306/pi.2010.7.4.302] [PMID] [PMCID]

[14] Jeon SW, Han C. Psychiatric symptoms in a patient with influenza A (H1N1) treated with oseltamivir (Tamiflu): A case report. Clin Psychopharmacol Neurosci. 2015; 13(2):209-11. [DOI:10.9758/cpn.2015.13.2.209] [PMID] [PMCID]

[15] Ho LN, Chung JP, Choy KL. Oseltamivir-induced mania in a patient with H1N1. Am J Psychiatry. 2010; 167(3):350. [DOI:10.1176/appi.ajp.2009.09101421] [PMID]

[16] Toovey S, Rayner C, Prinssen E, Chu T, Donner B, Thakrar B, et al. Assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir. Drug Safety. 2008; 31(12):1097-114. [DOI:10.2165/0002018-200831120-00006] [PMID]

[17] Allen SN, Demler TL, Trigoboff E, Opler LA. Oseltamivir use in psychiatric inpatients taking clozapine: Effect on neuropsychiatric events. Innov Clin Neurosci. 2011; 8(5):12-13. [PMCID] [PMID]

[18] Ose A, Kusuhara H, Yamatsugu K, Kanai M, Shibasaki M, Fujita T, et al. P-glycoprotein restricts the penetration of oseltamivir across the blood-brain barrier. Drug Metab Dispos. 2008; 36(2):427-34. [DOI:10.1124/dmd.107.018556] [PMID]

[19] Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: A meta-analysis of randomised controlled trials. Lancet. 2015; 385(9979):1729-37. [DOI:10.1016/S0140-6736(14)62449-1]

[20] Matheson NJ, Harnden A, Perera R, Sheikh A, Symmonds-Abrahams M. Neuraminidase inhibitors for preventing and treating influenza in children. Cochrane Database Syst Rev. 2007; (1). [DOI:10.1002/14651858.CD002744.pub2]

[21] Satoh K, Nonaka R, Ogata A, Nakae D, Uehara SI. Effects of oseltamivir phosphate (Tamiflu) and its metabolite (GS4071) on monoamine neurotransmission in the rat brain. Biol Pharm Bull. 2007; 30(9):1816-8. [DOI:10.1248/bpb.30.1816] [PMID]

This Page Intentionally Left Blank