BÖLÜM
6

COVID-19 TEDAVİSİ İLAÇLARI VE PSİKOFARMAKOLOJİ-1

Evren ŞAVLI[1]

Giriş

COVID-19 Tedavisi İlaçları ve Psikofarmakoloji'nin I.Bölümünde Yeni Korona Virüs Hastalığı-19'un (COVID-19) organ- sistemler üzerindeki etkilerine ve buna bağlı etkileşim görülebilecek psikotrop tedavi ilaçlarına değinilmiştir. II. ve III. bölümlerinde ise COVID-19'un değişik safhalarında kullanılan, bazı yeniden konumlandırılmış (repurposed) deneysel tedaviler etki mekanizmalarına göre sıralanarak sunulmuştur. COVID-19 deneysel tedavileri arasında yazım aşamasında en büyük klinik araştırmalarda incelenmekte olan ilaçlara yer verilmeye çalışılmıştır **(klorokin, hidroksiklorokin, lopinavir/ritonavir, remdesivir, favipiravir, tosilizumab, interferon beta (İFN-beta), immün plazma tedavisi ve azitromisin)**. Bu ilaçların nöropsikiyatrik yan etkileri, psikotrop ilaçlar ile etkileşimleri değerlendirilmeye çalışılmış ve konuya ilişkin Liverpool Üniversitesi Liverpool Drug Interaction Group'a ait tablo (Tablo 1) II.Bölümün sonuna eklenmiştir.

COVID-19'un Organ-Sistemler Üzerindeki Etkileri

COVID-19'un çoklu organ hasarı ile seyrettiği gösterilmiştir: karaciğer, böbrek, akciğerler, kalp, immün ve hematolojik sistem gibi (1). Psikotrop tedavilerin etkileşimi açısından değerlendirildiğinde bu organ ve sistemler üzerindeki hastalığa bağlı etkilerin uygulanacak ilaçların farmakokinetiğini (emilim, dağılım, metabolizma ve/ya da atılım) ve farkodinamiğini (bazı psikotropların yan etkilerine olan artmış duyarlılık) değiştirebileceği unutulmamalıdır.

Kalp Üzerindeki Hastalık Etkileri

COVID-19'un kalpte daha çok aritmojenik etkiler oluşturduğu öne sürülmektedir (2). Li ve arkadaşlarının yayınladıkları meta-analiz sonuçlarına göre COVID-19'lu hastaların en az %8'inde akut kardiyak hasarın görüldüğü (3) belirtilmektedir. Bir başka meta-analiz çalışmasında ise COVID-19'lu hastalarda COVID-19'un şiddetli seyretmesinin akut kardiyak hasar ile ilgili olabileceği ve akut kardiyak hasarın ise ölümle bağlantılı olduğu belirtilmektedir. Kardiyak hasar biyomarkerlarının başlıca sağ kalamayanlarda arttığı ifade edilen bu çalışmada COVID-19'lu hastalarda miyokardit gelişiminin önlenmesi için etkin bir şekilde kalp sağlığının takip edilmesi gerekliliğinin altı çizilmektedir (4) .

[1] Dr. Öğr. Üyesi Evren ŞAVLI, Ordu Üniversitesi Tıp Fakültesi Tıbbi Farmakoloji AD. evsavli@yahoo.com

doz azaltımı düşünülmesi ya da kullanımlarından kaçınılması gerektiği belirtilmektedir (10,31).

Sonuç

COVID-19'lu hastaların psikotrop ilaçlar ile tedavilerini tasarlarken SARS-CoV-2'nin sistemler üzerindeki tutulumları ve tedavisinde kullanılan deneysel ilaçların etkileşimleri göz önünde tutulmalıdır.

KAYNAKLAR

1. Gavriatopoulou M, Korompoki E, Fotiou D, et al. Organ-specific manifestations of COVID-19 infection. *Clin Exp Med*. 2020;20(4):493-506. Doi: 10.1007/s10238-020-00648-x.
2. Wu CI, Postema PG, Arbelo E, et al. SARS-CoV-2, COVID-19, and inherited arrhythmia syndromes. *Heart Rhythm*. 2020;17(9):1456-1462. Doi: 10.1016/j.hrthm.2020.03.024
3. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol*. 2020;109(5):531-538. Doi: 10.1007/s00392-020-01626-9
4. Li JW, Han TW, Woodward M, et al. The impact of 2019 novel coronavirus on heart injury: A Systematic review and Meta-analysis. *Prog Cardiovasc Dis.* 2020;63(4):518-524. Doi: 10.1016/j.pcad.2020.04.008.
5. Kuba K, Imai Y, Rao S. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. *Nat Med.* 2005;11:875–879
6. Zheng YY, Ma YT, Zhang JY, et al. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. 2020;17:259–260
7. Postema PG, Neville J, de Jong JSSG, et al. Safe drug use in long QT syndrome and Brugada syndrome: comparison of website statistics. *Europace*. 2013;15:1042–1049.
8. Gérard A, Romani S, Fresse A, et al. French Network of Pharmacovigilance Centers. "Off-label" use of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine in COVID-19: A survey of cardiac adverse drug reactions by the French Network of Pharmacovigilance Centers. *Therapie.* 2020;75(4):371-379. Doi: 10.1016/j.therap.2020.05.002.
9. Stockley IH. (2008*). Stockley's Drug Interactions: a Source Book of Interactions, Their Mechanisms, Clinical Importance and Management.* (Eighth edit.). London; Chicago: Pharmaceutical Press
10. Bilbul M, Paparone P, Kim AM, et al. Psychopharmacology of COVID-19. *Psychosomatics.* 2020;61(5):411-427. Doi: 10.1016/j.psym.2020.05.006.)
11. Beach SR, Celano CM, Sugrue AM, et al: QT prolongation, torsades de Pointes, and psychotropic medications: a 5-year update. *Psychosomatics* 2018;59(2):105-122. Doi: 10.1016/j.psym.2017.10.009.
12. Tisdale JE, Chung MK, Campbell KB, et al. American Heart Association Clinical Pharmacology Committee of the Council on Clinical Cardiology and Council on Cardiovascular and Stroke Nursing. Drug-Induced Arrhythmias: A Scientific Statement From the American Heart Association. *Circulation.* 2020;142(15):e214-e233. Doi: 10.1161/CIR.0000000000000905.
13. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. *Am J Hematol*. 2020;95(7):834-847. Doi: 10.1002/ajh.25829.
14. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497-506. Doi: 10.1016/S0140-6736(20)30183-5.)
15. Oyesanmi O, Kunkel EJS, Monti DA, et al. Hematologic side effects of psychotropics. *Psychosomatics* 1999;40(5):414-21. Doi: 10.1016/S0033-3182(99)71206-5.)
16. Murru A, Popovic D, Pacchiarotti I, et al. Management of adverse effects of mood stabilizers. *Curr Psychiatry Rep*. 2015;17(8):603. Doi: 10.1007/s11920-015-0603-z.
17. Schneider-Thoma J, Efthimiou O, Bighelli I, et al. Second-generation antipsychotic drugs and short-term somatic serious adverse events: a systematic review and meta-analysis. *Lancet Psychiatry.* 2019;6(9):753-765. Doi: 10.1016/S2215-0366(19)30223-8.
18. de Leon J, Sanz EJ, Norén GN, et al. Pneumonia may be more frequent and have more fatal outcomes with clozapine than with other second-generation antipsychotics. *World Psychiatry.* 2020;19(1):120-121. Doi: 10.1002/wps.20707.
19. Siskind D, Honer WG, Clark S, et al. Consensus statement on the use of clozapine during the COVID-19 pandemic. *J Psychiatry Neurosci.* 2020;45(4):200061. Doi: 10.1503/jpn.200061.
20. Cicala G, Barbieri MA, Spina E, et al. A comprehensive review of swallowing difficulties and dysphagia associated with antipsychotics in adults. *Expert Rev Clin Pharmacol*. 2019;12(3):219-234. Doi: 10.1080/17512433.2019.1577134.
21. Dzahini O, Singh N, Taylor D, et al. Antipsychotic drug use and pneumonia: Systematic review and meta-analysis. *J Psychopharmacol.* 2018;32(11):1167-1181. Doi: 10.1177/0269881118795333.
22. Clark SR, Warren NS, Kim G, et al. Elevated clozapine levels associated with infection: A systematic review. *Schizophr Res.* 2018;192:50-56. Doi: 10.1016/j.schres.2017.03.045.
23. Husain Z, Almeciga I, Delgado JC, et al. Increased FasL expression correlates with apoptotic changes in granulocytes cultured with oxidized clozapine. *Toxicol Appl Pharmacol*. 2006;214(3):326-34. Doi: 10.1016/j.taap.2006.01.008
24. Regen F, Herzog I, Hahn E, et al. Clozapine-induced agranulocytosis: Evidence for an immune-mediated mechanism from a patient-specific in-vitro approach. *Toxicol Appl Pharmacol.* 2017;316:10-16. Doi: 10.1016/j.taap.2016.12.003.
25. Sun GQ, Zhang L, Zhang LN, et al. Benzodiazepines

or related drugs and risk of pneumonia: A systematic review and meta-analysis. *Int J Geriatr Psychiatry*. 2019;34(4):513-521. Doi: 10.1002/gps.5048

26. Ostuzzi G, Papola D, Gastaldon C, et al. Correction to: Safety of psychotropic medications in people with COVID-19: evidence review and practical recommendations. *BMC Med.* 2020;18(1):291. Doi: 10.1186/s12916-020-01757-w.
27. Dragioti E, Solmi M, Favaro A, et al. Association of Antidepressant Use With Adverse Health Outcomes: A Systematic Umbrella Review. *JAMA Psychiatry*. 2019;76(12):1241-1255. Doi: 10.1001/jamapsychiatry.2019.2859.
28. Kunutsor SK, Seidu S, Khunti K. Depression, antidepressant use, and risk of venous thromboembolism: systematic review and meta-analysis of published observational evidence. *Ann Med.* 2018;50(6):529-537. Doi: 10.1080/07853890.2018.1500703.
29. Lee IC, Huo TI, Huang YH. Gastrointestinal and liver manifestations in patients with COVID-19. *J Chin Med Assoc*. 2020;83(6):521-523. Doi: 10.1097/JCMA.0000000000000319.
30. Xie H, Zhao J, Lian N, et al. Clinical characteristics of non-ICU hospitalized patients with coronavirus disease 2019 and liver injury: A retrospective study. *Liver Int*. 2020;40(6):1321-1326. Doi: 10.1111/liv.14449
31. Goldberg J, Ernst C. (2019). *Managing the side effects of psychotropic medications.* (Second edit.). Washington DC: American Psychiatric Association Publishing
32. Telles-Correia D, Barbosa A, Cortez-Pinto H, et al. Psychotropic drugs and liver disease: a critical review of pharmacokinetics and liver toxicity. *World J Gastrointest Pharmacol Ther* 2017;8(1):26-38. Doi: 10.4292/wjgpt.v8.i1.26.
33. Laporte JR, Healy D. *In The Midst Of The Sars-Cov-2 Pandemia, Caution Is Needed Wıth Commonly Used Drugs That Increase The Risk Of Pneumonıa.* (05.12.2020 tarihinde https://webcache.googleusercontent.com/search?q=cache:riwhzvx8fM8J:https://rxisk.org/medications-compromising-covid-infections/+&cd=1&hl=tr&ct=clnk&gl=tr adresinden ulaşılmıştır.)
34. Trifiró G, Sultana J, Spina E. Are the safety profiles of antipsychotic drugs used in dementia the same? An updated review of observational studies. *Drug Saf.* 2014;37(7):501-20. Doi: 10.1007/s40264-014-0170-y.
35. Knol W, van Marum RJ, Jansen PA, et al. Antipsychotic drug use and risk of pneumonia in elderly people. *J Am Geriatr Soc*. 2008;56(4):661-6. Doi: 10.1111/j.1532-5415.2007.01625.x
36. Trifirò G, Gambassi G, Sen EF, et al. Association of community-acquired pneumonia with antipsychotic drug use in elderly patients: a nested case-control study. *Ann Intern Med*. 2010;152(7):418-25, W139-40. Doi: 10.7326/0003-4819-152-7-201004060-00006.
37. Mehta S, Pulungan Z, Jones BT, et al. Comparative safety of atypical antipsychotics and the risk of pneumonia in the elderly. *Pharmacoepidemiol Drug Saf*. 2015;24(12):1271-80. Doi: 10.1002/pds.3882.
38. Nosè M, Recla E, Trifirò G, et al. Antipsychotic drug exposure and risk of pneumonia: a systematic review and meta-analysis of observational studies. *Pharmacoepidemiol Drug Saf*. 2015;24(8):812-20. Doi: 10.1002/pds.3804.
39. Chatterjee S, Carnahan RM, Chen H, et al. Anticholinergic Medication Use and Risk of Pneumonia in Elderly Adults: A Nested Case-Control Study. *J Am Geriatr Soc*. 2016;64(2):394-400. Doi: 10.1111/jgs.13932.
40. Paul KJ, Walker RL, Dublin S. Anticholinergic medications and risk of community-acquired pneumonia in elderly adults: a population-based case-control study. *J Am Geriatr Soc*. 2015;63(3):476-85. Doi: 10.1111/jgs.13327.
41. Taipale H, Tolppanen AM, Koponen M, et al. Risk of pneumonia associated with incident benzodiazepine use among community-dwelling adults with Alzheimer disease. *CMAJ*. 2017;189(14):E519-E529. Doi: 10.1503/cmaj.160126.
42. Obiora E, Hubbard R, Sanders RD, et al. The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: a nested case-control and survival analysis in a population-based cohort. *Thorax.* 2013;68(2):163-70. Doi: 10.1136/thoraxjnl-2012-202374.
43. Vozoris NT, Wang X, Austin PC, et al. Serotonergic antidepressant use and morbidity and mortality among older adults with COPD. *Eur Respir J.* 2018;52(1):1800475. Doi: 10.1183/13993003.00475-2018
44. Gabapentin and risk of severe respiratory depression. *Drug Ther Bull.* 2018;56(1):3-4. Doi: 10.1136/dtb.2018.1.0571
45. European Medicines Agency (EMA) (2017). *Pharmacovigilance Risk Assessment Committee (PRAC) recommendations on signals.* (05.12.2020 tarihinde https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-6-9-june-2017-prac-meeting_en.pdf adresinden ulaşılmıştır)
46. U.S. Food and Drug Administration (FDA) (2020). *FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise,Horizant) and pregabalin (Lyrica, Lyrica CR) When used with CNS depressants or in patients with lung problems.* (05.12.2020 tarihinde https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin adresinden ulaşılmıştır)
47. FDA (2020). *FDA In Brief: FDA requires new warnings for gabapentinoids about risk of respiratory depression.* (05.12.2020 tarihinde https://www.fda.gov/news-events/fda-brief/fda-brief-fda-requires-new-warnings-gabapentinoids-about-risk-respiratory-depression adresinden ulaşılmıştır)
48. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683-690. Doi: 10.1001/jamaneurol.2020.1127.
49. Li YC, Bai WZ, Hashikawa T. Response to Commentary on "The neuroinvasive potential of SARS-CoV-2 may play a role in the respiratory failure of COVID-19 pa-

tients". *J Med Virol*. 2020;92(7):707-709. Doi: 10.1002/jmv.25824.
50. Kotfis K, Williams Roberson S, Wilson J, et al. COVID-19: What do we need to know about ICU delirium during the SARS-CoV-2 pandemic? *Anaesthesiol Intensive Ther*. 2020;52(2):132-138. Doi: 10.5114/ait.2020.95164.
51. Helms J, Kremer S, Merdji H, et al. Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med*. 2020;382(23):2268-2270. Doi: 10.1056/NEJMc2008597.
52. Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. *Age Ageing*. 2011;40(1):23-9. Doi: 10.1093/ageing/afq140.
53. Wu YC, Tseng PT, Tu YK, et al. Association of delirium response and safety of pharmacological interventions for the management and prevention of delirium: a network meta-analysis. *JAMA Psychiatry.* 2019;76(5):526-535. Doi: 10.1001/jamapsychiatry.2018.4365.
54. DeBattista C. (2015). Antidepressant Agents.In Weitz M, Lebowitz H (Eds), *Basic and Clinical Pharmacology* (13th ed., pp. 778). New York: McGraw-Hill Education
55. Stahl SM. (2015). *Stahl'ın Temel Psikofarmakolojisi Sinirbilimsel Temeli Ve Pratik Uygulaması 4.baskı.* (Tunç Alkın, Çev. Ed.). İstanbul: İstanbul Tıp Kitabevi
56. Alper K, Schwartz KA, Kolts RL, et al. Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approval reports. *Biol Psychiatry.* 2007;62(4):345-54. Doi: 10.1016/j.biopsych.2006.09.023.
57. Johannessen Landmark C, Henning O, Johannessen SI. Proconvulsant effects of antidepressants - What is the current evidence? *Epilepsy Behav*. 2016;61:287-291. Doi: 10.1016/j.yebeh.2016.01.029.
58. Kanner AM. The use of psychotropic drugs in epilepsy: what every neurologist should know. *Semin Neurol*. 2008;28(3):379-88. Doi: 10.1055/s-2008-1079342.
59. Wu CS, Wang SC, Yeh IJ, et al. Comparative risk of seizure with use of first- and second-generation antipsychotics in patients with schizophrenia and mood disorders. *J Clin Psychiatry*. 2016;77(5):e573-9. Doi: 10.4088/JCP.15m09898.
60. Fanelli V, Fiorentino M, Cantaluppi V, et al. Acute kidney injury in SARS-CoV-2 infected patients. *Crit Care* 2020;24(1):155. Doi: 10.1186/s13054-020-02872-z.