

## Bölüm 17

# PARKİNSON HASTALIĞINDA İLAÇ-İLAÇ ETKİLEŞİMLERİ

Dilara NEMUTLU SAMUR<sup>1</sup>  
Gül ÖZBEY<sup>2</sup>

### GİRİŞ

İlaç-ilaç etkileşimleri (İİE), bir ilacın birlikte uygulandığı diğer ilacın etkilerini artırması, azaltması ve/veya değiştirmesi olarak tanımlanabilir <sup>(1)</sup>. İİE, ilaçların etkililiklerini ve güvenilirliklerini değiştirebildiklerinden advers etkilerin sık ve önlenemez nedenleri arasında yer alır <sup>(2,3)</sup>. Farmakodinamik İİE, ilaçların farmakolojik aktivitelerini oluşturdukları reseptörler, biyolojik ya da fizyolojik olaylar düzeyinde gerçekleşir ve ilaçların etkilerinin artmasına ya da azalmasına neden olur <sup>(4)</sup>. Farmakokinetik İİE ise absorpsiyon, dağılım, metabolizma, ekskresyon adı verilen farmakokinetik olaylar sırasında görülür ve ilaçların serum konsantrasyonlarının değişmesi ile ilaç etkisinin azalması ya da toksik etkilerin artması ile sonuçlanabilir. Farmakokinetik İİE, farmakodinamik İİE'ne göre daha sık görülmektedir <sup>(4)</sup>.

Birçok kaynağa göre farklı sınıflandırılan İİE, Lexicomp® ilaç etkileşimleri veri tabanında 5 grupta incelenmektedir: X (kombinasyondan kaçın), D (tedaviyi modifiye et), C (tedaviyi izle), B (tedavinin değişmesine gerek yok), A (bilinen etki-leşim yok) <sup>(5)</sup>. İİE ile ilgili bilgiler, klinisyenlerin reçetelenmiş ilaçlar ile ilgili potansiyel riskleri tahmin etmelerini sağladığı için önemlidir <sup>(6)</sup>. İİE, bir ilacın başka bir ilaçla birlikte verilmesi ile ilacın farmakolojik aktivitesinde bir değişikliğin meydana gelmesi sonucu etkinin artması, azalması veya istenmeyen klinik sonuçların ortaya çıkması gibi sonuçlar doğurabildiği gibi, diğer komorbid durumların kötüleşmesine veya tedavinin etkisizleşmesine de neden olabilir <sup>(7)</sup>. Örneğin; ayrı ayrı verilen iki ilacın oluşturdukları yanıtların toplamı, aynı dozlarda birlikte verildiklerinde oluşan etkiye eşit ise aditif etkileşimden bahsedilir <sup>(8)</sup>. Birlikte verilen iki ilacın etkisi, ayrı ayrı verilen aynı dozların oluşturduğu yanıtların toplamından daha büyük ise pozitif sinerjistik etkiden ve birlikte verilen iki ilacın etkisi, ayrı ayrı verilen aynı dozların oluşturduğu yanıtların toplamından daha az ise negatif

<sup>1</sup> Dr. Öğr. Üyesi Dilara NEMUTLU SAMUR Alanya Alaaddin Keykubat Üniversitesi Tıp Fakültesi Tıbbi Farmakoloji AD. dilaranemutlu@gmail.com

<sup>2</sup> Doç. Dr. Gül ÖZBEY Akdeniz Üniversitesi Tıp Fakültesi Tıbbi Farmakoloji AD. gulozbey@gmail.com

Bu kitap bölümünü oluştururken taradığımız ilaç veri tabanları ve detaylı literatür araştırmaları, PH’de çoklu ilaç kullanımına bağlı olarak görülen İİE konusunda yalnızca teorik değerlendirmelerin mevcut olduğunu, İİE’ne yönelik aydınlatıcı klinik verilerin eksik olduğunu göstermiştir. Bu bağlamda PH’de İİE ile ilgili daha fazla çalışma yapılmalı ve PH’de akılcı ilaç kullanımına yönelik stratejiler daha açık ve yol gösterici bir şekilde literatürde yer almalıdır. PH hastalarında elektronik reçete oluşturulurken İİE’ni sunabilecek yazılımlar geliştirilmesi, ilaç tedavilerinin optimizasyonu sağlayarak özellikle geriatrik PH hastalarında polifarmasiye bağlı İİE’ni azaltabilir <sup>(62)</sup>.

## KAYNAKLAR

1. Askari M, Eslami S, Louws M, Wierenga PC, Dongelmans DA, Kuiper RA, Abu-Hanna A. Frequency and nature of drug-drug interactions in the intensive care unit. *Pharmacoepidemiology and Drug Safety*2013; 22(4):430-7. Doi: 10.1002/pds.3415.
2. Montane E, Arellano AL, Sanz Y, Roca J, Farre M. Drug-related deaths in hospital inpatients: A retrospective cohort study. *British Journal of Clinical Pharmacology*2018; 84(3):542-552. Doi: 10.1111/bcp.13471.
3. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA*2003; 289(13):1652-8. Doi: 10.1001/jama.289.13.1652.
4. Palleria C, Di Paolo A, Giofre C, Caglioti C, Leuzzi G, Siniscalchi A, De Sarro G, Gallelli L. Pharmacokinetic drug-drug interaction and their implication in clinical management. *Journal of Research in Medical Sciences*2013; 18(7):601-10.
5. Lexicomp Online, *Drug-Drug Interactions*. Lexi-Comp, Inc.: Hudson, Ohio.
6. Bitner A, Zalewski P, Klawe JJ, Newton JL. Drug Interactions in Parkinson’s Disease: Safety of Pharmacotherapy for Arterial Hypertension. *Drugs - Real World Outcomes*2015; 2(1):1-12. Doi: 10.1007/s40801-015-0008-7.
7. Santos TRA, Silveira EA, Pereira LV, Provin MP, Lima DM, Amaral RG. Potential drug-drug interactions in older adults: A population-based study. *Geriatrics & Gerontology International*2017; 17(12):2336-2346. Doi: 10.1111/ggi.13070.
8. Trevor AJ, Katzung BG, Kruidering-Hall M, *Katzung & Trevor’s Pharmacology: Examination & Board Review*. Vol. 11th edition. 2015, New York: McGraw Hill Medical.
9. Delafuente JC. Understanding and preventing drug interactions in elderly patients. *Critical Reviews in Oncology/Hematology*2003; 48(2):133-43. Doi: 10.1016/j.critrevonc.2003.04.004.
10. Jost WH, Brück C. Drug interactions in the treatment of Parkinson’s disease. *Journal of Neurology*2002; 249 Suppl 3:lii/24-9. Doi: 10.1007/s00415-002-1305-0.
11. Poewe W. Non-motor symptoms in Parkinson’s disease. *European Journal of Neurology*2008; 15 Suppl 1:14-20. Doi: 10.1111/j.1468-1331.2008.02056.x.
12. McLean G, Hindle JV, Guthrie B, Mercer SW. Co-morbidity and polypharmacy in Parkinson’s disease: insights from a large Scottish primary care database. *BMC Neurology*2017; 17(1):126. Doi: 10.1186/s12883-017-0904-4.
13. Braga M, Pederzoli M, Antonini A, Beretta F, Crespi V. Reasons for hospitalization in Parkinson’s disease: a case-control study. *Parkinsonism & Related Disorders*2014; 20(5):488-92; discussion 488. Doi: 10.1016/j.parkreldis.2014.01.022.
14. Wang X, Zeng F, Jin WS, Zhu C, Wang QH, Bu XL, Luo HB, Zou HQ, Pu J, Zhou ZH, Cui XP, Wang QS, Shi XQ, Han W, Wu Q, Chen HS, Lin H, Zhang LL, Zhang M, Lian Y, Xu ZQ, Zhou HD, Zhang T, Wang YJ. Comorbidity burden of patients with Parkinson’s disease and Parkinsonism between 2003 and 2012: A multicentre, nationwide, retrospective study in China.

- Scientific Reports*2017; 7(1):1671. Doi: 10.1038/s41598-017-01795-0.
15. Santos García D, Suárez Castro E, Expósito I, de Deus T, Tuñas C, Aneiros A, López Fernández M, Núñez Arias D, Bermúdez Torres M. Comorbid conditions associated with Parkinson's disease: A longitudinal and comparative study with Alzheimer disease and control subjects. *Journal of the Neurological Sciences*2017; 373:210-215. Doi: 10.1016/j.jns.2016.12.046.
  16. Gil-Prieto R, Pascual-García R, San-Roman-Montero J, Martínez-Martin P, Castrodeza-Sanz J, Gil-de-Miguel A. Measuring the Burden of Hospitalization in Patients with Parkinson's Disease in Spain. *PLoS One*2016; 11(3):e0151563. Doi: 10.1371/journal.pone.0151563.
  17. Park HY, Park JW, Sohn HS, Kwon JW. Association of Parkinsonism or Parkinson Disease with Polypharmacy in the Year Preceding Diagnosis: A Nested Case-Control Study in South Korea. *Drug Safety*2017; 40(11):1109-1118. Doi: 10.1007/s40264-017-0559-5.
  18. Potashkin J, Huang X, Becker C, Chen H, Foltynie T, Marras C. Understanding the Links Between Cardiovascular Disease and Parkinson's Disease. *Movement Disorders*2020; 35(1):55-74. Doi: <https://doi.org/10.1002/mds.27836>.
  19. Kotagal V, Albin RL, Müller ML, Koeppe RA, Studenski S, Frey KA, Bohnen NI. Advanced age, cardiovascular risk burden, and timed up and go test performance in Parkinson disease. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*2014; 69(12):1569-75. Doi: 10.1093/gerona/glu070.
  20. Mullapudi A, Gudala K, Boya CS, Bansal D. Risk of Parkinson's Disease in the Users of Antihypertensive Agents: An Evidence from the Meta-Analysis of Observational Studies. *Journal of Neurodegenerative Diseases*2016; 2016:5780809. Doi: 10.1155/2016/5780809.
  21. Csoti I, Jost WH, Reichmann H. Parkinson's disease between internal medicine and neurology. *Journal of Neural Transmission (Vienna, Austria : 1996)*2016; 123(1):3-17. Doi: 10.1007/s00702-015-1443-z.
  22. Lang Y, Gong D, Fan Y. Calcium channel blocker use and risk of Parkinson's disease: a meta-analysis. *Pharmacoepidemiology and Drug Safety*2015; 24(6):559-66. Doi: 10.1002/pds.3781.
  23. Jhang KM, Huang JY, Nfor ON, Tung YC, Ku WY, Jan CF, Liaw YP. Flunarizine related movement disorders: a nationwide population-based study. *Scientific Reports*2019; 9(1):1705. Doi: 10.1038/s41598-018-37901-z.
  24. Sica DA. Centrally acting antihypertensive agents: an update. *Journal of Clinical Hypertension (Greenwich, Conn.)*2007; 9(5):399-405. Doi: 10.1111/j.1524-6175.2007.07161.x.
  25. Karalliedde L, Clarke SFJ, Gotel U, Karalliedde J. (2016). *Adverse drug interactions : a Handbook for Prescribers* (Second edition). Boca Raton London : CRC Press.
  26. Rizek P, Kumar N, Jog MS. An update on the diagnosis and treatment of Parkinson disease. *CMAJ*2016; 188(16):1157-1165. Doi: 10.1503/cmaj.151179.
  27. Riederer P, Bartl J, Laux G, Grünblatt E. Diabetes type II: a risk factor for depression-Parkinson-Alzheimer? *Neurotoxicity Research*2011; 19(2):253-65. Doi: 10.1007/s12640-010-9203-1.
  28. May M, Schindler C. Clinically and pharmacologically relevant interactions of antidiabetic drugs. *Therapeutic Advances in Endocrinology and Metabolism*2016; 7(2):69-83. Doi: 10.1177/2042018816638050.
  29. Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. *The Lancet. Neurology*2004; 3(3):169-78. Doi: 10.1016/s1474-4422(04)00681-7.
  30. Chen J, Guan Z, Wang L, Song G, Ma B, Wang Y. Meta-analysis: overweight, obesity, and Parkinson's disease. *International Journal of Endocrinology*2014; 2014:203930-203930. Doi: 10.1155/2014/203930.
  31. Palacios N, Gao X, McCullough ML, Jacobs EJ, Patel AV, Mayo T, Schwarzschild MA, Ascherio A. Obesity, diabetes, and risk of Parkinson's disease. *Movement disorders : Official Journal of the Movement Disorder Society*2011; 26(12):2253-2259. Doi: 10.1002/mds.23855.
  32. Beeler JA, Faust RP, Turkson S, Ye H, Zhuang X. Low Dopamine D2 Receptor Increases Vulnerability to Obesity Via Reduced Physical Activity, Not Increased Appetitive Motivation. *Biological Psychiatry*2016; 79(11):887-897. Doi: 10.1016/j.biopsych.2015.07.009.
  33. Cheung BM, Cheung TT, Samaranyake NR. Safety of antiobesity drugs. *Therapeutic Advances*

- in Drug Safety*2013; 4(4):171-81. Doi: 10.1177/2042098613489721.
34. Minár M, Valkovič P. Thyroid-induced worsening of parkinsonian tremor resistant to drugs and subthalamic nucleus deep brain stimulation. *Case Reports in Neurological Medicine*2014; 2014:489275. Doi: 10.1155/2014/489275.
  35. Munhoz RP, Teive HA, Troiano AR, Hauck PR, Herdoiza Leiva MH, Graff H, Werneck LC. Parkinson's disease and thyroid dysfunction. *Parkinsonism & Related Disorders*2004; 10(6):381-3. Doi: 10.1016/j.parkreldis.2004.03.008.
  36. Umehara T, Matsuno H, Toyoda C, Oka H. Thyroid hormone level is associated with motor symptoms in de novo Parkinson's disease. *Journal of Neurology*2015; 262(7):1762-8. Doi: 10.1007/s00415-015-7780-x.
  37. Prakash KM, Kek PC. Hyperthyroidism "masked" the levodopa response in newly diagnosed Parkinson's disease patients. *Parkinsonism & Related Disorders*2010; 16(10):691-2. Doi: 10.1016/j.parkreldis.2010.07.009.
  38. Yapici Eser H, Bora HA, Kuruoğlu A. Depression and Parkinson disease: prevalence, temporal relationship, and determinants. *Turkish Journal of Medical Sciences*2017; 47(2):499-503. Doi: 10.3906/sag-1603-101.
  39. Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. *Movement Disorders : Official Journal of the Movement Disorder Society*2008; 23(2):183-9; quiz 313. Doi: 10.1002/mds.21803.
  40. Shulman LM, Taback RL, Rabinstein AA, Weiner WJ. Non-recognition of depression and other non-motor symptoms in Parkinson's disease. *Parkinsonism & Related Disorders*2002; 8(3):193-7. Doi: 10.1016/s1353-8020(01)00015-3.
  41. Starkstein SE, Brockman S. Management of Depression in Parkinson's Disease: A Systematic Review. *Movement Disorders Clinical Practice* 2017; 4(4):470-477. Doi: 10.1002/mdc3.12507.
  42. Ryan M, Eatmon CV, Slevin JT. Drug treatment strategies for depression in Parkinson disease. *Expert Opinion on Pharmacotherapy*2019; 20(11):1351-1363. Doi: 10.1080/14656566.2019.1612877.
  43. Jankovic J. Parkinson's disease: clinical features and diagnosis. *Journal of Neurology, Neurosurgery, and Psychiatry*2008; 79(4):368-76. Doi: 10.1136/jnnp.2007.131045.
  44. Dissanayaka NN, Sellbach A, Matheson S, O'Sullivan JD, Silburn PA, Byrne GJ, Marsh R, Mellick GD. Anxiety disorders in Parkinson's disease: prevalence and risk factors. *Movement Disorders : Official Journal of the Movement Disorder Society*2010; 25(7):838-45. Doi: 10.1002/mds.22833.
  45. Broen MP, Narayan NE, Kuijf ML, Dissanayaka NN, Leentjens AF. Prevalence of anxiety in Parkinson's disease: A systematic review and meta-analysis. *Movement Disorders : Official Journal of the Movement Disorder Society*2016; 31(8):1125-33. Doi: 10.1002/mds.26643.
  46. Kano O, Ikeda K, Cridebring D, Takazawa T, Yoshii Y, Iwasaki Y. Neurobiology of Depression and Anxiety in Parkinson's Disease. *Parkinson's Disease*2011; 2011:143547. Doi: 10.4061/2011/143547.
  47. Pontone GM, Williams JR, Anderson KE, Chase G, Goldstein SR, Grill S, Hirsch ES, Lehmann S, Little JT, Margolis RL, Palanci J, Rabins PV, Weiss HD, Marsh L. Pharmacologic treatment of anxiety disorders in Parkinson disease. *The American Journal of Geriatric Psychiatry* 2013; 21(6):520-528. Doi: 10.1016/j.jagp.2012.10.023.
  48. Kummer A, Teixeira AL. Neuropsychiatry of Parkinson's disease. *Arquivos de Neuro-Psiquiatria*2009; 67:930-939.
  49. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. *Nature Reviews. Neuroscience*2017; 18(7):435-450. Doi: 10.1038/nrn.2017.62.
  50. Emre M. Dementia associated with Parkinson's disease. *The Lancet. Neurology*2003; 2(4):229-37. Doi: 10.1016/s1474-4422(03)00351-x.
  51. Goldman JG, Holden S. Treatment of psychosis and dementia in Parkinson's disease. *Current Treatment Options in Neurology*2014; 16(3):281. Doi: 10.1007/s11940-013-0281-2.
  52. Szeto JY, Lewis SJ. Current Treatment Options for Alzheimer's Disease and Parkinson's Disease

- Dementia. *Current Neuropharmacology* 2016; 14(4):326-38. Doi: 10.2174/1570159x14666151208112754.
53. Masuda Y. Cardiac effect of cholinesterase inhibitors used in Alzheimer's disease--from basic research to bedside. *Current Alzheimer Research* 2004; 1(4):315-21. Doi: 10.2174/1567205043332009.
  54. Bergman J, Lerner V. Successful use of donepezil for the treatment of psychotic symptoms in patients with Parkinson's disease. *Clinical Neuropharmacology* 2002; 25(2):107-10. Doi: 10.1097/00002826-200203000-00009.
  55. Emre M, Tsolaki M, Bonuccelli U, Destée A, Tolosa E, Kutzelnigg A, Ceballos-Baumann A, Zdravkovic S, Bladström A, Jones R. Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. *The Lancet. Neurology* 2010; 9(10):969-77. Doi: 10.1016/s1474-4422(10)70194-0.
  56. Aarsland D, Ballard C, Walker Z, Bostrom F, Alves G, Kossakowski K, Leroi I, Pozo-Rodriguez F, Minthon L, Londo E. Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. *The Lancet. Neurology* 2009; 8(7):613-8. Doi: 10.1016/s1474-4422(09)70146-2.
  57. Brennan L, Pantelyat A, Duda JE, Morley JF, Weintraub D, Wilkinson JR, Moberg PJ. Memantine and Cognition in Parkinson's Disease Dementia/Dementia With Lewy Bodies: A Meta-Analysis. *Movement Disorders Clinical Practice* 2016; 3(2):161-167. Doi: <https://doi.org/10.1002/mdc3.12264>.
  58. Seeman P, Caruso C, Lasaga M. Memantine agonist action at dopamine D2High receptors. *Synapse (New York, N.Y.)* 2008; 62(2):149-53. Doi: 10.1002/syn.20472.
  59. Thanvi BR, Lo TCN, Harsh DP. Psychosis in Parkinson's disease. *Postgraduate Medical Journal* 2005; 81(960):644-646. Doi: 10.1136/pgmj.2004.032029.
  60. Fénelon G, Mahieux F, Huon R, Ziegler M. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. *Brain : a Journal of Neurology* 2000; 123 ( Pt 4):733-45. Doi: 10.1093/brain/123.4.733.
  61. Zahodne LB, Fernandez HH. Parkinson's psychosis. *Current Treatment Options in Neurology* 2010; 12(3):200-211. Doi: 10.1007/s11940-010-0072-y.
  62. Forta – Fit for the Aged. (2012). (15.01.2021, <https://www.umm.uni-heidelberg.de/klinische-pharmakologie/forschung/forta-projekt/>).