

# 19. BÖLÜM

## Yasal ve Yasadışı Maddeler Gabapentinoidler

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### Giriş

Günümüzde başlıca gabapentin ve pregabalin etkin maddeleri ile temsil edilen gabapentinoidler, 2000’li yıllarda suistimal olguları nedeniyle ayrıca dikkat çeken bir konu haline gelmiştir. Her iki molekül de, gamma-aminobütirik asit (GABA) analogudur. Gabapentin, uyarıcı nörotransmitterlerin salınımını engelleyen, bu yolla da nöropatik ağrı ve nöbet bozukluklarındaki patolojik nörotransmisyonu karşı etkili bir antikonvülzandır. Pregabalin de benzer endikasyonlarda değerlendirilen, biyoyararlanımı ve etkisi gabapentininden daha fazla olan bir bileşiktir ve suistimal konusunda daha fazla gündeme gelmektedir. Gabapentinoidler genellikle iyi tolere edilir. Özellikle opioidlerin de dahil olduğu tablolar haricinde, kontrollü tedavi esnasında ciddi bir sorun oluşturduğuna ilişkin çok net bilgi mevcut değildir. Bununla birlikte, opioidlerle doz aşımı söz konusu olduğunda, pregabalinin de kullanılıyor olması, ölüm riskinde artışa yol açabilmektedir.

Aşırı doz halinde spesifik bir tedavi bulunmadığı için, semptomatik tedavi esas alınmaktadır. Etkin maddenin müstahzarlarda ve kan, idrar, saç gibi biyolojik örneklerde saptanması ve miktar tayinine yönelik çalışmalarda farklı analitik yöntemlerden yararlanılmaktadır. Günümüzde, analizlerde özellikle HPLC, GC-MS ve LC-MS/MS’in tercih edildiği görülmektedir (1).

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## KAYNAKLAR

1. Mohammadian E, Rahimpour E, Foroumadi A, et al. Derivatization of  $\gamma$ -amino butyric acid analogues for their determination in the biological samples and pharmaceutical preparations: A comprehensive review. *Critical Reviews in Analytical Chemistry*. 2021; 1–28. doi:10.1080/10408347.2021.1916733
2. Chiappini S, Schifano F. A decade of gabapentinoid misuse: An analysis of the European Medicines Agency's 'Suspected Adverse Drug Reactions' Database. *CNS Drugs*. 2016;30(7): 647–654. doi:10.1007/s40263-016-0359-y
3. WHO Collaborating Centre for Drug Statistics Methodology, Oslo N. [https://www.whocc.no/atc\\_ddd\\_index/?code=N02BG](https://www.whocc.no/atc_ddd_index/?code=N02BG).
4. Wishart DS, Feunang YD, Guo AC, et al. DrugBank 5.0: A major update to the DrugBank database for 2018. *Nucleic Acids Research*. 2018;46(D1): D1074–D1082. doi:10.1093/nar/gkx1037
5. RxMediaPharma2021. İnteraktif İlaç Bilgi Kaynağı. Üstünes L (ed), Gemaş AŞ, 2021.
6. Anton RF, Latham P, Voronin K, et al. Efficacy of gabapentin for the treatment of alcohol use disorder in patients with alcohol withdrawal symptoms. *JAMA Internal Medicine*. 2020;180(5): 728. doi:10.1001/jamainternmed.2020.0249
7. Bates RE, Leung JG, Morgan RJ, et al. Retrospective analysis of gabapentin for alcohol withdrawal in the hospital setting: The Mayo Clinic experience. *Mayo Clinic Proceedings: Innovations, Quality & Outcomes*. 2020;4(5): 542–549. doi:10.1016/j.mayocpiqo.2020.06.002
8. Mariani JJ, Pavlicova M, Choi CJ, et al. An open-label pilot study of pregabalin pharmacotherapy for alcohol use disorder. *The American Journal of Drug and Alcohol Abuse*. 2021; 1–9. doi:10.1080/00952990.2021.1901105
9. Goodman CW, Brett AS. Gabapentin and pregabalin for pain – Is increased prescribing a cause for concern? *New England Journal of Medicine*. 2017;377(5): 411–414. doi:10.1056/NEJMp1704633
10. Sosyal Güvenlik Kurumu Sağlık Uygulama Tebliği (24.03.2013). Resmî Gazete (Sayı: 28597). Erişim adresi: <https://www.mevzuat.gov.tr/mevzuat?MevzuatNo=17229&MevzuatTur=9&MevzuatTertip=5> (erişim: 27.07.2021).
11. Drugs.com. Gabapentin. Erişim adresi: <https://www.drugs.com/monograph/gabapentin.html#pharmacokinetics> (20.07.2021).
12. Drugs.com. Pregabalin. Erişim: <https://www.drugs.com/monograph/pregabalin.html#pharmacokinetics> (20.07.2021).
13. UpToDate 2021. Gabapentin. [https://www.uptodate.com/contents/gabapentin-drug-information?search=gabapentin&source=panel\\_search\\_result&selectedTitle=1~148&usage\\_type=panel&kp\\_tab=drug\\_general&display\\_rank=1](https://www.uptodate.com/contents/gabapentin-drug-information?search=gabapentin&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1) (erişim: 08.07.2021).
14. UpToDate 2021. Pregabalin. [https://www.uptodate.com/contents/pregabalin-drug-information?search=pregabalin&source=panel\\_search\\_result&selectedTitle=1~142&usage\\_type=panel&kp\\_tab=drug\\_general&display\\_rank=1#F949947](https://www.uptodate.com/contents/pregabalin-drug-information?search=pregabalin&source=panel_search_result&selectedTitle=1~142&usage_type=panel&kp_tab=drug_general&display_rank=1#F949947) (erişim:08.07.2021).
15. Ahmad KA, Shoaib RM, Ahsan MZ, et al. Microglial IL-10 and  $\beta$ -endorphin expression mediates gabapentinoids antineuropathic pain. *Brain, Behavior, and Immunity*. 2021;95: 344–361. doi:10.1016/j.bbi.2021.04.007
16. Daly C, Griffin E, Ashcroft DM, et al. Intentional drug overdose involving pregabalin and gabapentin: Findings from the National Self-Harm Registry Ireland, 2007–2015. *Clinical Drug Investigation*. 2018;38(4): 373–380. doi:10.1007/s40261-017-0616-y

17. Loudin S, Haas J, Payne M, et al. Identifying co-exposure to opiates and gabapentin during pregnancy. *The Journal of Pediatrics*. 2020;217: 196–198. doi:10.1016/j.jpeds.2019.09.029
18. Molero Y, Larsson H, D’Onofrio BM, et al. Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents, and violent crime: population based cohort study in Sweden. *BMJ*. 2019;365: l2147. doi:10.1136/bmj.l2147
19. Torrance N, Veluchamy A, Zhou Y, et al. Trends in gabapentinoid prescribing, co-prescribing of opioids and benzodiazepines, and associated deaths in Scotland. *British Journal of Anaesthesia*. 2020;125(2): 159–167. doi:10.1016/j.bja.2020.05.017
20. FDA In Brief: FDA requires new warnings for gabapentinoids about risk of respiratory depression. <https://www.fda.gov/news-events/fda-brief/fda-brief-fda-requires-new-warnings-gabapentinoids-about-risk-respiratory-depression>. Erişim: 10.07.2021.
21. Önal A, Sagirli O. Spectrophotometric and spectrofluorimetric methods for the determination of pregabalin in bulk and pharmaceutical preparation. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*. 2009;72(1): 68–71. doi:10.1016/j.saa.2008.08.009
22. Derayea SM, Attia TZ, Elnady M. Development of spectrofluorimetric method for determination of certain antiepileptic drugs through condensation with ninhydrin and phenyl acetaldehyde. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*. 2018;204: 48–54. doi:10.1016/j.saa.2018.06.027
23. Berry D, Millington C. Analysis of pregabalin at therapeutic concentrations in human plasma/serum by reversed-phase HPLC. *Therapeutic Drug Monitoring*. 2005;27(4): 451–456. doi:10.1097/01.ftd.0000158874.54100.1a
24. Ulu ST, Kel E. Highly Sensitive determination and validation of gabapentin in pharmaceutical preparations by HPLC with 4-Fluoro-7-Nitrobenzofurazan derivatization and fluorescence detection. *Journal of Chromatographic Science*. 2011;49(6): 417–421. doi:10.1093/chrscl/49.6.417
25. Yagi T, Naito T, Mino Y, et al. Rapid and validated fluorometric HPLC method for determination of gabapentin in human plasma and urine for clinical application. *Journal of Clinical Pharmacy and Therapeutics*. 2012;37(1): 89–94. doi:10.1111/j.1365-2710.2010.01243.x
26. Larsen Burns M, Kinge E, Stokke Opdal M, et al. Therapeutic drug monitoring of gabapentin in various indications. *Acta Neurologica Scandinavica*. 2019;139(5): 446–454. doi:10.1111/ane.13075
27. Hložek T, Bursová M, Coufal P, et al. Gabapentin, pregabalin and vigabatrin quantification in human serum by GC–MS after hexyl chloroformate derivatization. *Journal of Analytical Toxicology*. 2016;40(9): 749–753. doi:10.1093/jat/bkw070
28. Sadones N, Van Bever E, Van Bortel L, et al. Dried blood spot analysis of gabapentin as a valid alternative for serum: a bridging study. *Journal of Pharmaceutical and Biomedical Analysis*. 2017;132: 72–76. doi:10.1016/j.jpba.2016.09.036
29. Heltsley R, DePriest A, Black DL, et al. Urine drug testing of chronic pain patients. iv. prevalence of gabapentin and pregabalin. *Journal of Analytical Toxicology*. 2011;35(6): 357–359. doi:10.1093/anatox/35.6.357
30. Dwivedi J, Namdev KK, Chilkoti DC, et al. An improved LC-ESI-MS/MS method to quantify pregabalin in human plasma and dry plasma spot for therapeutic monitoring and pharmacokinetic applications. *Therapeutic Drug Monitoring*. 2018;40(5): 610–619. doi:10.1097/FTD.0000000000000541
31. De La Vega H, Fox K, Pardi J, et al. Validation of a high-throughput screening and quantification method for the determination of gabapentinoids in blood using a combination of LC-TOF-MS and LC-MS-MS. *Journal of Analytical Toxicology*. 2019;43(9): 696–702. doi:10.1093/jat/bkz070

32. Möller I, Held K, Klimpel D, et al. Development and validation of an LC–MS/MS method for relevant drugs in epilepsy patients using dried blood spots. *Biomedical Chromatography*. 2021; e5130. doi:10.1002/bmc.5130
33. Zeid AM, Kaji N, Nasr JJM, et al. Stacking-cyclodextrin-microchip electrokinetic chromatographic determination of gabapentinoid drugs in pharmaceutical and biological matrices. *Journal of Chromatography A*. 2017;1503: 65–75. doi:10.1016/j.chroma.2017.04.049
34. Zeid AM, Nasr JJM, Belal F, et al. Determination of three antiepileptic drugs in pharmaceutical formulations using microfluidic chips coupled with light-emitting diode induced fluorescence detection. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*. 2021;246: 119021. doi:10.1016/j.saa.2020.119021
35. Naguib IA, Ali NA, Elroby FA, et al. Green HPLC–DAD and HPTLC methods for quantitative determination of binary mixture of pregabalin and amitriptyline used for neuropathic pain management. *Journal of Chromatographic Science*. 2021;59(6): 536–547. doi:10.1093/chromsci/bmab031
36. Shah J, Kotadiya R. A critical review on analytical methods for recently approved FDC Drugs: Pregabalin and etoricoxib. *Critical Reviews in Analytical Chemistry*. 2020; 1–21. doi:10.1080/10408347.2020.1855411
37. Häkkinen M, Vuori E, Kalso E, et al. Profiles of pregabalin and gabapentin abuse by postmortem toxicology. *Forensic Science International*. 2014;241: 1–6. doi:10.1016/j.forsciint.2014.04.028
38. Cantrell FL, Mena O, Gary RD, et al. An acute gabapentin fatality: a case report with postmortem concentrations. *International Journal of Legal Medicine*. 2015;129(4): 771–775. doi:10.1007/s00414-015-1193-3
39. Hamm CE, Gary RD, McIntyre IM. Gabapentin concentrations and postmortem distribution. *Forensic Science International*. 2016;262: 201–203. doi:10.1016/j.forsciint.2016.03.028
40. Slavova S, Miller A, Bunn TL, et al. Prevalence of gabapentin in drug overdose postmortem toxicology testing results. *Drug and Alcohol Dependence*. 2018;186: 80–85. doi:10.1016/j.drugalcdep.2018.01.018
41. Tharp AM, Hobron K, Wright T. Gabapentin-related Deaths: Patterns of Abuse and Post-mortem Levels. *Journal of Forensic Sciences*. 2019;64(4): 1105–1111. doi:10.1111/1556-4029.14021
42. Kriikku P, Ojanperä I. Pregabalin and gabapentin in non-opioid poisoning deaths. *Forensic Science International*. 2021;324: 110830. doi:10.1016/j.forsciint.2021.110830
43. Johansen ME. Gabapentinoid use in the United States 2002 through 2015. *JAMA Internal Medicine*. 2018;178(2): 292. doi:10.1001/jamainternmed.2017.7856
44. Grosshans M, Mutschler J, Hermann D, et al. Pregabalin abuse, dependence, and withdrawal: A case report. *American Journal of Psychiatry*. 2010;167(7): 869–869. doi:10.1176/appi.ajp.2010.09091269
45. Lancia M, Gambelungho A, Gili A, et al. Pregabalin abuse in combination with other drugs: monitoring among methadone patients. *Frontiers in Psychiatry*. 2020;10: 1022. doi:10.3389/fpsy.2019.01022
46. Schwan S, Sundström A, Stjernberg E, et al. A signal for an abuse liability for pregabalin—results from the Swedish spontaneous adverse drug reaction reporting system. *European Journal of Clinical Pharmacology*. 2010;66(9): 947–953. doi:10.1007/s00228-010-0853-y
47. Gahr M, Freudenmann RW, Hiemke C, et al. Pregabalin abuse and dependence in Germany: results from a database query. *European Journal of Clinical Pharmacology*. 2013;69(6): 1335–1342. doi:10.1007/s00228-012-1464-6

48. Driot D, Jouanjus E, Oustric S, et al. Patterns of gabapentin and pregabalin use and misuse: Results of a population-based cohort study in France. *British Journal of Clinical Pharmacology*. 2019;85(6): 1260–1269. doi:10.1111/bcp.13892
49. Dufayet L, Care W, Deheul S, et al. Increase in pregabalin recreational use in adolescents in France. *Clinical Toxicology*. 2021; 1–4. doi:10.1080/15563650.2021.1892719
50. Tambon M, Ponté C, Jouanjus E, et al. Gabapentinoid abuse in France: Evidence on health consequences and new points of vigilance. *Frontiers in Psychiatry*. 2021;12: 639780. doi:10.3389/fpsy.2021.639780
51. Evoy KE, Covvey JR, Peckham AM, et al. Gabapentinoid misuse, abuse and non-prescribed obtainment in a United States general population sample. *International Journal of Clinical Pharmacy*. 43(4):1055-1064. doi: 10.1007/s11096-020-01217-8.
52. Ibiloye EA, Barner JC, Lawson KA, et al. Prevalence of and factors associated with gabapentinoid use and misuse among Texas Medicaid recipients. *Clinical Drug Investigation*. 2021;41(3): 245–253. doi:10.1007/s40261-021-01009-6
53. Fonseca F, Lenahan W, Dart RC, et al. Non-medical Use of prescription gabapentinoids (gabapentin and pregabalin) in five European Countries. *Frontiers in Psychiatry*. 2021;12: 676224. doi:10.3389/fpsy.2021.676224
54. Gu X, Chen T, Su T-L, et al. Investigating the prescribing trajectory and geographical drug utilisation patterns of gabapentinoids in primary care in England: An ecological study. *British Journal of Clinical Pharmacology*. 2021; bcp.14827. doi:10.1111/bcp.14827
55. Oh Gy, Slavova S, Freeman PR. Characterization of gabapentin use in Kentucky after reclassification as a Schedule V controlled substance. *Journal of the American Pharmacists Association*. 2021;61(3): e86–e92. doi:10.1016/j.japh.2020.12.012
56. Sason A, Adelson M, Schreiber S, et al. Pregabalin misuse in methadone maintenance treatment patients in Israel: Prevalence and risk factors. *Drug and Alcohol Dependence*. 2018;189: 8–11. doi:10.1016/j.drugalcdep.2018.04.025
57. Snellgrove BJ, Steinert T, Jaeger S. Pregabalin use among users of illicit drugs: a cross-sectional survey in Southern Germany. *CNS Drugs*. 2017;31(10): 891–898. doi:10.1007/s40263-017-0467-3
58. Vickers-Smith R, Sun J, Charnigo RJ, et al. Gabapentin drug misuse signals: A pharmacovigilance assessment using the FDA adverse event reporting system. *Drug and Alcohol Dependence*. 2020;206: 107709. doi:10.1016/j.drugalcdep.2019.107709
59. Mutlu E, Aşıcıoğlu F. Abuse of prescribed psychoactive drugs. *Anatolian Journal of Psychiatry*. 2020; 21(2):195-202.
60. Althobaiti YS, Alghorabi A, Alshehri FS, et al. Gabapentin-induced drug-seeking-like behavior: a potential role for the dopaminergic system. *Scientific Reports*. 2020;10(1): 10445. doi:10.1038/s41598-020-67318-6
61. Bonnet U, Scherbaum N. How addictive are gabapentin and pregabalin? A systematic review. *European Neuropsychopharmacology*. 2017;27(12): 1185–1215. doi:10.1016/j.euro-neuro.2017.08.430
62. Hägg S, Jönsson AK, Ahlner J. Current evidence on abuse and misuse of gabapentinoids. *Drug Safety*. 2020;43(12): 1235–1254. doi:10.1007/s40264-020-00985-6
63. Evoy KE, Sadrameli S, Contreras J, et al. Abuse and misuse of pregabalin and gabapentin: A systematic review update. *Drugs*. 2021;81(1): 125–156. doi:10.1007/s40265-020-01432-7
64. Evoy KE, Morrison MD, Saklad SR. Abuse and misuse of pregabalin and gabapentin. *Drugs*. 2017;77(4): 403–426. doi:10.1007/s40265-017-0700-x