BÖLÜM 23

Anksiyolitik ve Sedatif Hipnotikler

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GİRİŞ

Anksiyolitik ilaçlar temel olarak sedatif (sakinleştirici) ve hipnotik (uyku getirici) etkileri mevcuttur. Düşük dozlarda sakinleştirici, yüksek dozlarda uyku getirici etkileri baskındır. Ruhsal hastalıkların çoğunluğunda kullanılmaktadırlar. Benzodiazepinler, Z-İlaçlar, Adrenerjik sistem üzerine etkili ilaçlar, Buspiron, GABA analogları, Antihistaminikler, Barbitüratlar ve Melatoninerjik ilaçlar olmak üzere birçok alt gruba ayrılmaktadırlar. En sık kullanılanlar ise benzodiazepinlerdir. Anksiyolitik ve sedatif hipnotik ilaçlar güncel literatür bilgisinden yararlanılarak etki düzeneklerine göre gruplara ayrılarak anlatılmıştır(1).

BENZODİAZEPİNLER

Etki Mekanizması ve Süresi

Benzodiazepin ilaçlar, farmakolojik olarak Gama Amino Bütirik Asit (GABA) nörotransmitteri üzerinden etki etmektedirler. GABA, beyinin ana inhibitör nörotranmitteridir. GABA, Glutamat amino asitten Glutamik Asit Dekarboksilaz (GAD) enzimini aracılığıyla sentezlenir. Sentezden sonra, sinaptik veziküller içine taşınır ve sinaps aralığına salgılanıncaya kadar bu veziküllerde depolanır. GABA, sinaps aralığına salgılandıktan sonra ise GABA reseptörlerine bağlanır ve post sinaptik hücrede inhibitör etki yapar. GABA'nın GABA-A, GABA-B, GABA-C olmak üzere 3 ana reseptörü bulunmaktadır. A ve C reseptörleri ligand kapılı iyon kanalları iken, B reseptörü G-protein kenetli reseptörlerdir. Ayrıca GABA-A reseptörlerinin α, γ, Δ olmak üzere çeşitli alt reseptörleri mevcuttur. Benzodiazepin ilaçlar, GABA-A'nın bazı alt reseptörlerine bağlanarak GABA benzeri etki göstermektedirler. GABA'nın etkisi ise; sinaptik aralıkta GABA Taşıyıcıları (GAT), hücre içinde ise GABA Transaminaz (GABA-T) enzimi aracılığıyla sonlandırılmaktadır(2). Şekil 1'de GABA'nın farmakolojisi özet olarak anlatılmıştır.

Benzodiazepinler kimyasal yapılarına, emilim hızlarına ve yağda çözünme derecelerine göre kısa, orta ve uzun etkili (yarı ömürlü) şeklinde sınıflandırılmaktadır. Kısa-orta yarı ömürlü olanlar genellikle hipnotik olarak kullanılırken orta-uzun yarı ömürlü olanlar ise anksiyolitik olarak kullanılmaktadır. Tablo 1'de yarı ömürlerine göre benzodiazepinler gösterilmiştir(3).

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ğunun akut tedavisinde denenmiştir ve sonuçlar plaseboya göre üstün bulunmuştur(113).

Gepiron ve Tandospiron, buspiron gibi bir azopiron grubunda olup 5-HT1A parsiyel agonistlerdir. Buspironun anksiyolitik etkisinin olması ve kullanımının onaylanması sonrası gepiron ve tandospiron araştırılmaktadır. Yapılan çalışmalar faz 2 aşamasındadır henüz faz 3'e geçilememiştir(114,115). Vilazodon ve vortioksetin FDA tarafından major depresif bozuklukta kullanımı onaylanmış antidepresan ilaçlardır. Serotonin geri alım inhibitör etkileri yanında 5-HT1A agonist etkileri mevcuttur. Mevcut çalışmaların bazılarında anksiyete belirtilerini azaltmakla beraber anksiyete bozukluklarında kullanımı ile ilgili ikna edici veri henüz bulunmamıştır(116–118).

SONUÇ

Anksiyete ve uykusuzluk, ruhsal hastalıklarda ve hastalık dışında günlük yaşamdaki psikososyal stresörlerde görülen en sık belirtilerdendir. Uzun süreli devam etmesi durumunda hayat kalitesini azaltmakta ve işlevselliği etkilemektedir. Benzodiazepin ilaçlar halen uzun süredir en sık kullanılan ilaçlardır. Son yıllarda benzodiazepin dışındaki ilaçların kullanımı artmaya başlamıştır. Mevcut ilaçlar kullanılırken bağımlılık, etki süresi ve özel gruplarda tolere edilebilirlik ve yan etki konusunda dikkatli olunmalıdır. Bu alanda yeni ilaç araştırma ve denemeleri halen sürmektedir.

KAYNAKLAR

1. Zwanzger P, Singewald N, Bandelow B. [Pharmacotherapy of anxiety disorders-Guideline-conform treatment and new developments]. *Der Nervenarzt*. Nervenarzt; 2021;92(5): 433–440. doi:10.1007/S00115-020-01051-3
2. STAHL SM. *Stahl'ın Temel Psikofarmakolojisi, Sinirbilimsel Temeli ve Pratik Uygulaması*.. 4.Baskı. ALKIN T (ed.) İstanbul: İstanbul Tıp Kitapevi; 2015. 1–608 p.
3. SADOCK BJ. *Kaplan Sadock Psikiyatri*.. 11th ed. BOZKURT A (ed.) İstanbul: Güneş Tıp Kitapevi; 2016. 910–1060 p.
4. Öztürk O, Uluşahin A. Mental Health and Disorders [Ruh Sağlığı ve Bozuklukları]. *Nobel Tıp Kitabevleri*. Nobel Tıp Kitabevleri; 2018; 1–788. https://nobeltip.com/product/224/ruh-sagligi-ve-bozukluklari
5. Seldenrijk A, Vis R, Henstra M, et al. [Systematic review of the side effects of benzodiazepines]. *Nederlands tijdschrift voor geneeskunde*. Ned Tijdschr Geneeskd; 2017;161(43). https://pubmed.ncbi.nlm.nih.gov/29076441/
6. Karcıoğlı Ö. Benzodiazepin Zehirlenmeleri. *Acilde Klinik Toksikoloji*. 2009. p. 193–212. https://www.researchgate.net/publication/294086853_Benzodiazepin_Zehirlenmeleri/citation/download
7. Joint Formulary Committee. British national formulary. 67, March-September 2014. Pharmaceutical Press,; 2014;
8. Soyka M. Treatment of Benzodiazepine Dependence. *The New England journal of medicine*. N Engl J Med; 2017;376(12): 1147–1157. doi:10.1056/NEJMRA1611832
9. Markota M, Rummans TA, Bostwick JM, et al. Benzodiazepine Use in Older Adults: Dangers, Management, and Alternative Therapies. *Mayo Clinic proceedings*. Mayo Clin Proc; 2016;91(11): 1632–1639. doi:10.1016/J.MAYOCP.2016.07.024
10. Picton JD, Brackett Marino A, Lovin Nealy K. Benzodiazepine use and cognitive decline in the elderly. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists*. Am J Health Syst Pharm; 2018;75(1): e6–e12. doi:10.2146/AJHP160381
11. Shyken JM, Babbar S, Babbar S, et al. Benzodiazepines in Pregnancy. *Clinical obstetrics and gynecology*. Clin Obstet Gynecol; 2019;62(1): 156–167. doi:10.1097/GRF.0000000000000417
12. Stahl SM, Grady MM, Munter N. *Stahl'ın temel psikofarmakolojisi : reçete kılavuzu*.. 5th ed. Uzbay IT (ed.) İstanbul Tıp Kitapevleri ; 2017. 871 p.
13. Dokkedal-Silva V, Berro LF, Galduróz JCF, et al. Clonazepam: Indications, Side Effects, and Potential for Nonmedical Use. *Harvard review of psychiatry*. Harv Rev Psychiatry; 2019;27(5): 279–289. doi:10.1097/HRP.0000000000000227
14. Jiang S, Brownell KC, Kamper JE, et al. Clonazepam for Catatonia Incompletely Responsive to Lorazepam. *Journal of the Academy of Consultation-Liaison Psychiatry*. Elsevier; 2021;62(1): 97–101. doi:10.1016/J.PSYM.2020.09.009
15. Amore M, D'Andrea M, Fagiolini A. Treatment of Agitation With Lorazepam in Clinical Practice: A Systematic Review. *Frontiers in psychiatry*. Front Psychiatry; 2021;12. doi:10.3389/FPSYT.2021.628965
16. Pelzer ACM, van der Heijden FMMA, den Boer E. Systematic review of catatonia treatment. *Neuropsychiatric disease and treatment*. Neuropsychiatr Dis Treat; 2018;14: 317–326. doi:10.2147/NDT.S147897
17. Smith S, Ketheesan S, Touma E, et al. Lorazepam challenge test for catatonia. *Emergency medicine Australasia : EMA*. Emerg Med Australas; 2021;33(4): 763–764. doi:10.1111/1742-6723.13780
18. Hui D, Frisbee-Hume S, Wilson A, et al. Effect of Lorazepam With Haloperidol vs Haloperidol Alone on Agitated Delirium in Patients With Advanced Cancer

Receiving Palliative Care: A Randomized Clinical Trial. *JAMA*. JAMA; 2017;318(11): 1047–1056. doi:10.1001/JAMA.2017.11468
19. Ait-Daoud N, Hamby AS, Sharma S, et al. A Review of Alprazolam Use, Misuse, and Withdrawal. *Journal of addiction medicine*. J Addict Med; 2018;12(1): 4–10. doi:10.1097/ADM.0000000000000350
20. Garakani A, Murrough JW, Freire RC, et al. Pharmacotherapy of Anxiety Disorders: Current and Emerging Treatment Options. *Frontiers in Psychiatry*. Frontiers Media SA; 2020;11: 595584. doi:10.3389/FPSYT.2020.595584
21. Sateia MJ, Buysse DJ, Krystal AD, et al. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. *Journal of Clinical Sleep Medicine : JCSM : Official Publication of the American Academy of Sleep Medicine*. American Academy of Sleep Medicine; 2017;13(2): 307. doi:10.5664/JCSM.6470
22. Nutt DJ, Stahl SM. Searching for perfect sleep: the continuing evolution of GABAA receptor modulators as hypnotics. *Journal of psychopharmacology (Oxford, England)*. J Psychopharmacol; 2010;24(11): 1601–1612. doi:10.1177/0269881109106927
23. Louzada LL, Machado F v., Nóbrega OT, et al. Zopiclone to treat insomnia in older adults: A systematic review. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. Eur Neuropsychopharmacol; 2021;50: 75–92. doi:10.1016/J.EURONEURO.2021.04.013
24. Najib J. Eszopiclone, a nonbenzodiazepine sedative-hypnotic agent for the treatment of transient and chronic insomnia. *Clinical therapeutics*. Clin Ther; 2006;28(4): 491–516. doi:10.1016/J.CLINTHERA.2006.04.014
25. Rösner S, Englbrecht C, Wehrle R, et al. Eszopiclone for insomnia. *The Cochrane database of systematic reviews*. Cochrane Database Syst Rev; 2018;10(10). doi:10.1002/14651858.CD010703.PUB2
26. Xiang T, Cai Y, Hong Z, et al. Efficacy and safety of Zolpidem in the treatment of insomnia disorder for one month: a meta-analysis of a randomized controlled trial. *Sleep Medicine*. Elsevier; 2021;87: 250–256. doi:10.1016/J.SLEEP.2021.09.005
27. Bomalaski MN, Claflin ES, Townsend W, et al. Zolpidem for the Treatment of Neurologic Disorders: A Systematic Review. *JAMA neurology*. JAMA Neurol; 2017;74(9): 1130–1139. doi:10.1001/JAMANEUROL.2017.1133
28. Chen LE, Zhao AD, Zhang QJ, et al. Investigation of the usefulness of zaleplon at two doses to induce afternoon-sleep under noise interference and its effects on psychomotor performance and vestibular function. *Military Medical Research*. Mil Med Res; 2016;3(1). doi:10.1186/S40779-016-0075-4
29. Goldschmied JR, Sengupta A, Sharma A, et al. Treatment of Insomnia with Zaleplon in HIV+ Significantly Improves Sleep and Depression. *Psychopharmacology Bulletin*. MedWorks Media Inc.; 2021;51(3): 50. /pmc/articles/PMC8374930/
30. Oliver E, Mayor Jr F, D'Ocon P. Beta-blockers: Historical Perspective and Mechanisms of Action. *Revista espanola de cardiologia (English ed.)*. Rev Esp Cardiol (Engl Ed); 2019;72(10): 853–862. doi:10.1016/J.REC.2019.04.006
31. Steenen SA, van Wijk AJ, van der Heijden GJMG, et al. Propranolol for the treatment of anxiety disorders: Systematic review and meta-analysis. *Journal of Psychopharmacology (Oxford, England)*. SAGE Publications; 2016;30(2): 128. doi:10.1177/0269881115612236
32. Argolo FC, Cavalcanti-Ribeiro P, Netto LR, et al. Prevention of posttraumatic stress disorder with propranolol: A meta-analytic review. *Journal of Psychosomatic Research*. Elsevier; 2015;79(2): 89–93. doi:10.1016/J.JPSYCHORES.2015.04.006
33. Liu X, Lou X, Cheng X, et al. Impact of metoprolol treatment on mental status of chronic heart failure patients with neuropsychiatric disorders. *Drug Design, Development and Therapy*. Dove Press; 2017;11: 305. doi:10.2147/DDDT.S124497
34. Armstrong C, Kapolowicz MR. A Preliminary Investigation on the Effects of Atenolol for Treating Symptoms of Anxiety. *Military Medicine*. Oxford Academic; 2020;185(11–12): e1954–e1960. doi:10.1093/MILMED/USAA170
35. Naguy A. Clonidine Use in Psychiatry: Panacea or Panache? *Pharmacology*. Karger Publishers; 2016;98(1–2): 87–92. doi:10.1159/000446441
36. Hudson N, Burghart S, Reynoldson J, et al. Evaluation of low dose prazosin for PTSD-associated nightmares in children and adolescents. *The Mental Health Clinician*. College of Psychiatric and Neurologic Pharmacists (CPNP); 2021;11(2): 45. doi:10.9740/MHC.2021.03.045
37. Reist C, Streja E, Tang CC, et al. Prazosin for treatment of post-traumatic stress disorder: a systematic review and meta-analysis. *CNS Spectrums*. Cambridge University Press; 2021;26(4): 338–344. doi:10.1017/S1092852920001121
38. Breen A, Blankley K, Fine J. The efficacy of prazosin for the treatment of posttraumatic stress disorder nightmares in U.S. military veterans. *Journal of the American Association of Nurse Practitioners*. Blackwell Publishing Ltd; 2017;29(2): 65–69. doi:10.1002/2327-6924.12432
39. Howland RH. Buspirone: Back to the future. *Journal of Psychosocial Nursing and Mental Health Services*. Slack Incorporated; 2015;53(11): 21–24. doi:10.3928/02793695-20151022-01
40. Wilson TK, Tripp J. Buspirone. *xPharm: The Comprehensive Pharmacology Reference*. StatPearls Publishing; 2022; 1–5. doi:10.1016/B978-008055232-3.61355-8
41. Kowacs DP, Folchini CM, de Moura Vieira KR, et al. Use of Buspirone in the Treatment of Nonpharmacological Bruxism: About 4 Cases. *Clinical neuropharmacology*. NLM (Medline); 2021;44(6): 247–249. doi:10.1097/WNF.0000000000000486
42. Loane C, Politis M. Buspirone: What is it all about? *Brain Research*. Elsevier; 2012;1461: 111–118. doi:10.1016/J.BRAINRES.2012.04.032
43. Cruz MRS, Hidalgo PC, Lee MS, et al. Buspirone for the treatment of dementia with behavioral disturbance. *International Psychogeriatrics*. Cambridge

University Press; 2017;29(5): 859–862. doi:10.1017/S1041610216002441
44. Mahmood I, Sahajwalla C. Clinical Pharmacokinetics and Pharmacodynamics of Buspirone, an Anxiolytic Drug. *Clinical Pharmacokinetics 1999 36:4*. Springer; 2012;36(4): 277–287. doi:10.2165/00003088-199936040-00003
45. Strawn JR, Mills JA, Cornwall GJ, et al. Buspirone in Children and Adolescents with Anxiety: A Review and Bayesian Analysis of Abandoned Randomized Controlled Trials. *Journal of Child and Adolescent Psychopharmacology*. Mary Ann Liebert, Inc.; 2018;28(1): 2. doi:10.1089/CAP.2017.0060
46. Church MK. Allergy, histamine and antihistamines. *Handbook of Experimental Pharmacology*. Springer New York LLC; 2017;241: 321–331. doi:10.1007/164_2016_85
47. Parsons ME, Ganellin CR. Histamine and its receptors. *British Journal of Pharmacology*. John Wiley & Sons, Ltd; 2006;147(S1): S127–S135. doi:10.1038/SJ.BJP.0706440
48. Chu DK, Oykhman P, Sussman GL. How to use antihistamines. *CMAJ*. Canadian Medical Association; 2021;193(14): E478–E479. doi:10.1503/CMAJ.201959/TAB-RELATED-CONTENT
49. Hydroxyzine. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. National Institute of Diabetes and Digestive and Kidney Diseases; 2017; https://www.ncbi.nlm.nih.gov/books/NBK548128/
50. Ghanizadeh A, Zare S. A preliminary randomised double-blind placebo-controlled clinical trial of hydroxyzine for treating sleep bruxism in children. *Journal of Oral Rehabilitation*. John Wiley & Sons, Ltd; 2013;40(6): 413–417. doi:10.1111/JOOR.12049
51. Mahr F, Billman M, Essayli JH, et al. Selective Serotonin Reuptake Inhibitors and Hydroxyzine in the Treatment of Avoidant/Restrictive Food Intake Disorder in Children and Adolescents: Rationale and Evidence. *https://home.liebertpub.com/cap*. Mary Ann Liebert, Inc., publishers 140 Huguenot Street, 3rd Floor New Rochelle, NY 10801 USA ; 2022;32(2): 117–121. doi:10.1089/CAP.2021.0038
52. Wong HCG. Long-term use of diphenhydramine. *CMAJ : Canadian Medical Association Journal*. Canadian Medical Association; 2015;187(14): 1078. doi:10.1503/CMAJ.1150066
53. Badr B, Naguy A. Cyproheptadine: a psychopharmacological treasure trove? *CNS Spectrums*. Cambridge University Press; 2021; 1–3. doi:10.1017/S1092852921000250
54. Simon L v., Keenaghan M. Serotonin Syndrome. *Pain Medicine: An Essential Review*. StatPearls Publishing; 2022;11(9): 201–202. https://www.ncbi.nlm.nih.gov/books/NBK482377/
55. Prakash S, Rathore C, Rana K, et al. Chronic serotonin syndrome: A retrospective study. *World Journal of Psychiatry*. Baishideng Publishing Group Inc; 2021;11(4): 124. doi:10.5498/WJP.V11.I4.124
56. Abdel-Hamid IA, Elsaied MA, Mostafa T. The drug treatment of delayed ejaculation. *Translational Andrology and Urology*. AME Publications; 2016;5(4): 576. doi:10.21037/TAU.2016.05.05
57. Allison M, Hale C. A Phase I Study of the Pharmacokinetics and Pharmacodynamics of Intranasal Doxylamine in Subjects with Chronic Intermittent Sleep Impairment. *Drugs in R and D*. Springer International Publishing; 2018;18(2): 129–136. doi:10.1007/S40268-018-0232-1/FIGURES/4
58. Khorasani F, Aryan H, Sobhi A, et al. A systematic review of the efficacy of alternative medicine in the treatment of nausea and vomiting of pregnancy. *https://doi.org/10.1080/01443615.2019.1587392*. Taylor & Francis; 2019;40(1): 10–19. doi:10.1080/01443615.2019.1587392
59. Dooley DJ, Taylor CP, Donevan S, et al. Ca2+ channel alpha2delta ligands: novel modulators of neurotransmission. *Trends in pharmacological sciences*. Trends Pharmacol Sci; 2007;28(2): 75–82. doi:10.1016/J.TIPS.2006.12.006
60. Sills GJ. The mechanisms of action of gabapentin and pregabalin. *Current Opinion in Pharmacology*. Elsevier; 2006;6(1): 108–113. doi:10.1016/J.COPH.2005.11.003
61. Cross AL, Viswanath O, Sherman A l. Pregabalin. *The Essence of Analgesia and Analgesics*. StatPearls Publishing; 2022; 298–301. doi:10.1017/CBO9780511841378.072
62. Goodman CW, Brett AS. A Clinical Overview of Off-label Use of Gabapentinoid Drugs. *JAMA Internal Medicine*. American Medical Association; 2019;179(5): 695–701. doi:10.1001/JAMAINTERNMED.2019.0086
63. Houghton KT, Forrest A, Awad A, et al. Biological rationale and potential clinical use of gabapentin and pregabalin in bipolar disorder, insomnia and anxiety: protocol for a systematic review and meta-analysis. *BMJ Open*. BMJ Publishing Group; 2017;7(3): 13433. doi:10.1136/BMJOPEN-2016-013433
64. Generoso MB, Trevizol AP, Kasper S, et al. Pregabalin for generalized anxiety disorder: An updated systematic review and meta-analysis. *International Clinical Psychopharmacology*. Lippincott Williams and Wilkins; 2017;32(1): 49–55. doi:10.1097/YIC.0000000000000147
65. Olivares JM, Álvarez E, Carrasco JL, et al. Pregabalin for the treatment of patients with generalized anxiety disorder with inadequate treatment response to antidepressants and severe depressive symptoms. *International Clinical Psychopharmacology*. Lippincott Williams and Wilkins; 2015;30(5): 265–271. doi:10.1097/YIC.0000000000000087
66. Baldwin DS, den Boer JA, Lyndon G, et al. Efficacy and safety of pregabalin in generalised anxiety disorder: A critical review of the literature. *Journal of Psychopharmacology*. SAGE Publications Ltd; 2015;29(10): 1047–1060. doi:10.1177/0269881115598411
67. Pande AC, Pollack MH, Crockatt J, et al. Placebo-controlled study of gabapentin treatment of panic disorder. *Journal of clinical psychopharmacology*. J Clin Psychopharmacol; 2000;20(4): 467–471. doi:10.1097/00004714-200008000-00011
68. Pande AC, Davidson JRT, Jefferson JW, et al. Treatment of social phobia with gabapentin: a placebo-controlled study. *Journal of clinical psychopharmacology*. J Clin Psychopharmacol; 1999;19(4): 341–348. doi:10.1097/00004714-199908000-00010
69. Lavigne JE, Heckler C, Mathews JL, et al. A Randomized, Controlled, Double-Blinded Clinical Trial of Gabapentin 300mg versus 900mg versus Placebo for Anxiety Symptoms in Breast Cancer Survivors. *Breast cancer re-*

search and treatment. NIH Public Access; 2012;136(2): 479. doi:10.1007/S10549-012-2251-X

70. Önder E, Tural Ü, Gökbakan M. Does gabapentin lead to early symptom improvement in obsessive-compulsive disorder? *European Archives of Psychiatry and Clinical Neuroscience 2008 258:6*. Springer; 2008;258(6): 319–323. doi:10.1007/S00406-007-0798-Z
71. Randinitis EJ, Posvar EL, Alvey CW, et al. Pharmacokinetics of pregabalin in subjects with various degrees of renal function. *Journal of clinical pharmacology*. J Clin Pharmacol; 2003;43(3): 277–283. doi:10.1177/0091270003251119
72. Bockbrader HN, Wesche D, Miller R, et al. A Comparison of the Pharmacokinetics and Pharmacodynamics of Pregabalin and Gabapentin. *Clinical Pharmacokinetics 2010 49:10*. Springer; 2012;49(10): 661–669. doi:10.2165/11536200-000000000-00000
73. Bonnet U, Scherbaum N. How addictive are gabapentin and pregabalin? A systematic review. *European Neuropsychopharmacology*. Elsevier; 2017;27(12): 1185–1215. doi:10.1016/J.EURONEURO.2017.08.430
74. Zacny JP, Paice JA, Coalson DW. Subjective, psychomotor, and physiological effects of pregabalin alone and in combination with oxycodone in healthy volunteers. *Pharmacology, biochemistry, and behavior*. Pharmacol Biochem Behav; 2012;100(3): 560–565. doi:10.1016/J.PBB.2011.10.023
75. *[On the history of barbiturates] - PubMed*. [Online] https://pubmed.ncbi.nlm.nih.gov/27086450/
76. López-Muñoz F, Ucha-Udabe R, Alamo C. The history of barbiturates a century after their clinical introduction. *Neuropsychiatric Disease and Treatment*. Dove Press; 2005;1(4): 329. /pmc/articles/PMC2424120/
77. 'Özçelik F 'Erdem. M 'Bolu, A 'Gülsün, M. Melatonin : Genel Özellikleri ve Psikiyatrik Bozukluklardaki Rolü. *Psikiyatride Güncel Yaklaşımlar-Current Approaches in Psychiatry*. 2013;5(2): 179–2013.
78. Xie Z, Chen F, Li WA, et al. A review of sleep disorders and melatonin. *https://doi.org/10.1080/01616412.2017.1315864*. Taylor & Francis; 2017;39(6): 559–565. doi:10.1080/01616412.2017.1315864
79. Kuriyama A, Honda M, Hayashino Y. Ramelteon for the treatment of insomnia in adults: a systematic review and meta-analysis. *Sleep Medicine*. Elsevier; 2014;15(4): 385–392. doi:10.1016/J.SLEEP.2013.11.788
80. Ramelteon. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. National Institute of Diabetes and Digestive and Kidney Diseases; 2018; https://www.ncbi.nlm.nih.gov/books/NBK548437/
81. Low TL, Choo FN, Tan SM. The efficacy of melatonin and melatonin agonists in insomnia – An umbrella review. *Journal of Psychiatric Research*. Pergamon; 2020;121: 10–23. doi:10.1016/J.JPSYCHIRES.2019.10.022
82. Buoli M, Grassi S, Serati M, et al. Agomelatine for the treatment of generalized anxiety disorder. *Expert opinion on pharmacotherapy*. Expert Opin Pharmacother; 2017;18(13): 1373–1379. doi:10.1080/14656566.2017.1359257
83. Macisaac SE, Carvalho AF, Cha DS, et al. The mechanism, efficacy, and tolerability profile of agomelatine. *https://doi.org/10.1517/14656566.2014.862233*. Taylor & Francis; 2014;15(2): 259–274. doi:10.1517/14656566.2014.862233
84. Nishimon S, Nishimon M, Nishino S. Tasimelteon for treating non-24-h sleep-wake rhythm disorder. *https://doi.org/10.1080/14656566.2019.1603293*. Taylor & Francis; 2019;20(9): 1065–1073. doi:10.1080/14656566.2019.1603293
85. Dunayevich E, Erickson J, Levine L, et al. Efficacy and tolerability of an mGlu2/3 agonist in the treatment of generalized anxiety disorder. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. Neuropsychopharmacology; 2008;33(7): 1603–1610. doi:10.1038/SJ.NPP.1301531
86. Kent JM, Daly E, Kezic I, et al. Efficacy and safety of an adjunctive mGlu2 receptor positive allosteric modulator to a SSRI/SNRI in anxious depression. *Progress in neuro-psychopharmacology & biological psychiatry*. Prog Neuropsychopharmacol Biol Psychiatry; 2016;67: 66–73. doi:10.1016/J.PNPBP.2016.01.009
87. Krystal JH, Mathew SJ, Dsouza DC, et al. Potential psychiatric applications of metabotropic glutamate receptor agonists and antagonists. *CNS drugs*. CNS Drugs; 2010;24(8): 669–693. doi:10.2165/11533230-000000000-00000
88. Engin E, Treit D, Dickson CT. Anxiolytic- and antidepressant-like properties of ketamine in behavioral and neurophysiological animal models. *Neuroscience*. Neuroscience; 2009;161(2): 359–369. doi:10.1016/J.NEUROSCIENCE.2009.03.038
89. Papakostas GI, Salloum NC, Hock RS, et al. Efficacy of Esketamine Augmentation in Major Depressive Disorder: A Meta-Analysis. *The Journal of clinical psychiatry*. J Clin Psychiatry; 2020;81(4). doi:10.4088/JCP.19R12889
90. Fava M, Freeman MP, Flynn M, et al. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). *Molecular psychiatry*. Mol Psychiatry; 2020;25(7): 1592–1603. doi:10.1038/S41380-018-0256-5
91. Glue P, Medlicott NJ, Harland S, et al. Ketamine's dose-related effects on anxiety symptoms in patients with treatment refractory anxiety disorders. *Journal of psychopharmacology (Oxford, England)*. J Psychopharmacol; 2017;31(10): 1302–1305. doi:10.1177/0269881117705089
92. Abdallah CG, Coplan JD, Jackowski A, et al. A pilot study of hippocampal volume and N-acetylaspartate (NAA) as response biomarkers in riluzole-treated patients with GAD. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. Eur Neuropsychopharmacol; 2013;23(4): 276–284. doi:10.1016/J.EURONEURO.2012.05.009
93. Sugiyama A, Saitoh A, Iwai T, et al. Riluzole produces distinct anxiolytic-like effects in rats without the adverse effects associated with benzodiazepines. *Neuropharmacology*. Neuropharmacology; 2012;62(8): 2489–2498. doi:10.1016/J.NEUROPHARM.2012.02.012
94. Aboujaoude E, Barry JJ, Gamel N. Memantine augmentation in treatment-resistant obsessive-compulsive disorder: An open-label trial. *Journal of Clinical Psychopharmacology*. 2009;29(1): 51–55. doi:10.1097/JCP.0b013e318192e9a4
95. Myers KM, Carlezon WA, Davis M. Glutamate recep-

tors in extinction and extinction-based therapies for psychiatric illness. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. Neuropsychopharmacology; 2011;36(1): 274–293. doi:10.1038/NPP.2010.88
96. Bailey JE, Papadopoulos A, Lingford-Hughes A, et al. D-Cycloserine and performance under different states of anxiety in healthy volunteers. *Psychopharmacology*. Psychopharmacology (Berl); 2007;193(4): 579–585. doi:10.1007/S00213-007-0817-9
97. Hoffmann E, Nomikos GG, Kaul I, et al. SAGE-217, A Novel GABA A Receptor Positive Allosteric Modulator: Clinical Pharmacology and Tolerability in Randomized Phase I Dose-Finding Studies. *Clinical pharmacokinetics*. Clin Pharmacokinet; 2020;59(1): 111–120. doi:10.1007/S40262-019-00801-0
98. Wise T, Patrick F, Meyer N, et al. Cholinergic Modulation of Disorder-Relevant Neural Circuits in Generalized Anxiety Disorder. *Biological psychiatry*. Biol Psychiatry; 2020;87(10): 908–915. doi:10.1016/J.BIOPSYCH.2019.12.013
99. Simen A, Whitlock M, Qiu R, et al. An 8-Week, Randomized, Phase 2, Double-Blind, Sequential Parallel-Group Comparison Study of Two Dose Levels of the GABAA Positive Allosteric Modulator PF-06372865 Compared With Placebo as an Adjunctive Treatment in Outpatients With Inadequate Response to Standard of Care for Generalized Anxiety Disorder. *Journal of clinical psychopharmacology*. J Clin Psychopharmacol; 2019;39(1): 20–27. doi:10.1097/JCP.0000000000000997
100. Smith K, Leiras C. The effectiveness and safety of Kava Kava for treating anxiety symptoms: A systematic review and analysis of randomized clinical trials. *Complementary therapies in clinical practice*. Complement Ther Clin Pract; 2018;33: 107–117. doi:10.1016/J.CTCP.2018.09.003
101. Rana T, Behl T, Sehgal A, et al. Exploring the role of neuropeptides in depression and anxiety. *Progress in neuro-psychopharmacology & biological psychiatry*. Prog Neuropsychopharmacol Biol Psychiatry; 2022;114. doi:10.1016/J.PNPBP.2021.110478
102. Yoon S, Kim YK. The Role of the Oxytocin System in Anxiety Disorders. *Advances in experimental medicine and biology*. Adv Exp Med Biol; 2020;1191: 103–120. doi:10.1007/978-981-32-9705-0_7
103. Acheson DT, Feifel D, Kamenski M, et al. Intranasal oxytocin administration prior to exposure therapy for arachnophobia impedes treatment response. *Depression and anxiety*. Depress Anxiety; 2015;32(6): 400–407. doi:10.1002/DA.22362
104. Michelson D, Hargreaves R, Alexander R, et al. Lack of efficacy of L-759274, a novel neurokinin 1 (substance P) receptor antagonist, for the treatment of generalized anxiety disorder. *The international journal of neuropsychopharmacology*. Int J Neuropsychopharmacol; 2013;16(1): 1–11. doi:10.1017/S1461145712000065
105. Iftikhar K, Siddiq A, Baig SG, et al. Substance P: A neuropeptide involved in the psychopathology of anxiety disorders. *Neuropeptides*. Neuropeptides; 2020;79. doi:10.1016/J.NPEP.2019.101993
106. Sayed S, van Dam NT, Horn SR, et al. A Randomized Dose-Ranging Study of Neuropeptide Y in Patients with Posttraumatic Stress Disorder. *The international journal of neuropsychopharmacology*. Int J Neuropsychopharmacol; 2018;21(1): 3–11. doi:10.1093/IJNP/PYX109
107. Mathé AA, Michaneck M, Berg E, et al. A Randomized Controlled Trial of Intranasal Neuropeptide Y in Patients With Major Depressive Disorder. *The international journal of neuropsychopharmacology*. Int J Neuropsychopharmacol; 2020;23(12): 783–790. doi:10.1093/IJNP/PYAA054
108. Griebel G, Beeské S, Stahl SM. The vasopressin V(1b) receptor antagonist SSR149415 in the treatment of major depressive and generalized anxiety disorders: results from 4 randomized, double-blind, placebo-controlled studies. *The Journal of clinical psychiatry*. J Clin Psychiatry; 2012;73(11): 1403–1411. doi:10.4088/JCP.12M07804
109. Ballaz SJ, Bourin M, Akil H, et al. Blockade of the cholecystokinin CCK-2 receptor prevents the normalization of anxiety levels in the rat. *Progress in neuro-psychopharmacology & biological psychiatry*. Prog Neuropsychopharmacol Biol Psychiatry; 2020;96. doi:10.1016/J.PNPBP.2019.109761
110. Zwanzger P, Domschke K, Bradwejn J. Neuronal network of panic disorder: the role of the neuropeptide cholecystokinin. *Depression and anxiety*. Depress Anxiety; 2012;29(9): 762–774. doi:10.1002/DA.21919
111. Eser D, Baghai T, Schule C, et al. Neuroactive steroids as endogenous modulators of anxiety. *Current pharmaceutical design*. Curr Pharm Des; 2008;14(33): 3525–3533. doi:10.2174/138161208786848838
112. Lenze EJ, Hershey T, Newcomer JW, et al. Antiglucocorticoid therapy for older adults with anxiety and co-occurring cognitive dysfunction: results from a pilot study with mifepristone. *International journal of geriatric psychiatry*. NIH Public Access; 2014;29(9): 962. doi:10.1002/GPS.4085
113. Liebowitz MR, Hanover R, Draine A, et al. Effect of as-needed use of intranasal PH94B on social and performance anxiety in individuals with social anxiety disorder. *Depression and anxiety*. Depress Anxiety; 2016;33(12): 1081–1089. doi:10.1002/DA.22546
114. Lin J, Su Y, Wang C, et al. Effects of tandospirone augmentation in major depressive disorder patients with high anxiety: A multicenter, randomized, parallel-controlled, open-label study. *Journal of psychiatric research*. J Psychiatr Res; 2018;99: 104–110. doi:10.1016/J.JPSYCHIRES.2018.01.020
115. Kaur Gill A, Bansal Y, Bhandari R, et al. Gepirone hydrochloride: a novel antidepressant with 5-HT1A agonistic properties. *Drugs of today (Barcelona, Spain : 1998)*. Drugs Today (Barc); 2019;55(7): 423–437. doi:10.1358/DOT.2019.55.7.2958474
116. Yee A, Ng CG, Seng LH. Vortioxetine Treatment for Anxiety Disorder: A Meta-Analysis Study. *Current drug targets*. Curr Drug Targets; 2018;19(12): 1412–1423. doi:10.2174/1389450118666171117131151
117. Schneier FR, Moskow DM, Choo TH, et al. A randomized controlled pilot trial of vilazodone for adult separation anxiety disorder. *Depression and anxiety*. Depress Anxiety; 2017;34(12): 1085–1095. doi:10.1002/DA.22693
118. Zareifopoulos N, Dylja I. Efficacy and tolerability of vilazodone for the acute treatment of generalized anxiety disorder: A meta-analysis. *Asian Journal of Psychiatry*. Elsevier Science B.V.; 2017;26: 115–122. doi:10.1016/J.AJP.2017.01.016