

ADJUVAN İLAÇLAR

Gözde DAĞISTAN ¹

İsmail Eren DURMUŞ ²

Ayten BİLİR ³

ÖZET

Adjuvan analjezikler temelde ağrı dışındaki endikasyonlar için onaylanmış ajanlar olup günümüzde birçok kanser ve kanser dışı kronik ağrı durumunda tedavide yer almaktadır. Kanser ağrısında analjezik ilaçların etkinliğini artırmak ve destek tedavisi sağlamak amacıyla Dünya Sağlık Örgütü'nün önerdiği basamak tedavisinin her basamağında kullanılmaktedirler. Kansere bağlı ağrısı olan hastalarda adjuvan analjezik tedavinin zamanlaması hakkında karar bildiren yayınlanmış kesin veriler bulunmadığından hastanın klinik takipleri doğrultusunda karar verilmesi önerilmektedir. Etkin doz aralıkları farklı olan bu ajanları kullanırken, düşük doz ile başlanıp analjezik etki elde edilene kadar yan etkiler gözetilerek dozun titre edilmesi önerilmektedir. Bu amaçla birçok farklı gruptaki adjuvan ajan kanser ağrılı hastalarda opioid ajanlara ilaveten kullanılabilir. Bu ajanlar aşağıdaki gibi sınıflandırılabilirler.

- | | | |
|---|---|--|
| 1. Antidepresanlar | 2.2. Primer olarak voltaja bağlı sodyum kanallarına etki etmeyen antikonvülzanlar | 5.2. Dexmedetomidin |
| 1.1 Trisiklik antidepresanlar | 2.2.1. Gabapentin | 6. Kas gevşeticiler |
| 1.2 Selektif serotonin geri alım inhibitörleri | 2.2.2. Pregabalin | 6.1. Santral etkili kas gevşeticiler |
| 1.3 Selektif serotonin ve noradrenalin geri alım inhibitörleri | 3. N metil D aspartat reseptör antagonistleri | 6.1.1. Baklofen |
| 2. Antikonvülzanlar | 3.1. Ketamin | 6.1.2. Benzodiazepinler |
| 2.1 Primer olarak voltaja bağlı sodyum kanallarına etki eden antikonvülzanlar | 3.2. Dekstrometorfan | 6.1.3. Tizanidin |
| 2.1.1 Fenitoin | 3.3. Memantin | 6.2. Periferik etkili kas gevşeticiler |
| 2.1.2 Karbamazepin | 3.4. Amantadin | 6.2.1. Botulinum toksini |
| 2.1.3. Okskarbazepin | 3.5. Magnezyum | 7. Glikokortikoidler |
| 2.1.4. Topiramat | 4. Lokal anestezikler | 8. Kalsiyum düzenleyiciler |
| | 5. Alfa-2 adrenerjik agonistler | 8.1. Kalsitonin |
| | 5.1. Klonidin | 8.2. Bifosfonatlar |
| | | 8.3. Donesumab |
| | | 9. Kanabinoidler |

¹ Öğr. Gör. Dr., Akdeniz Üniversitesi Tip Fakültesi, Algoloji BD., g_dagistan@hotmail.com

² Uzm. Dr., Antalya Eğitim ve Araştırma Hastanesi, Algoloji Kliniği, iedurmus@hotmail.com

³ Prof. Dr., Eskişehir Osmangazi Üniversitesi Tip Fakültesi Algoloji BD., bilirayten@gmail.com

Ancak böbrek fonksiyonunda bozulma görülmemiştir.

KANNABİNOİDLER

“Esrar”, “tibbi esrar” ve “kenevir” olarak nitelenen kannabinoidler, Amerika Birleşik Devletleri Gıda ve İlaç Dairesi (FDA) tarafından düzenlenmeyen ve hastalar tarafından yasal esrar dispanserlerinden temin edilen, doğal olarak yetiştirilen bitki materyallerini ifade eder. Altmıştan fazla kannabinoid türü mevcuttur. Bu bileşiklerin bazıları farmakolojik etkilere sahiptir. Muhtemelen sinir sistemi ve diğer dokulardaki spesifik reseptörlerle etkileşime giren endojen kannabinoid bileşiklerinin (endokannabinoidler) etkilerini taklit eder. Ağrısı opioidlere veya diğer adjuvan analjeziklere yeterince yanıt verme-yen ileri evre kanserli hastalara kannabinoidler öne-riilebilir. Bu ajanlar, sınırlı analjezik etkinliği sahip-tilir. Geniş bir yan etki profili vardır. Ayrıca hastalar veya hasta yakınları tarafından esrar olarak bilindiği için kullanımıyla ilgili endişeler doğurabilir.

Amerika Birleşik Devletleri onaylı tek kannabi-noid olan dronabinol yalnızca kemoterapinin neden olduğu bulantı ve kusma için onaylanmıştır. İkinci bir oral ajan olan nabilone, Kanada ve Birleşik Kral-lik'ta mevcuttur, ancak 2019'da Amerika Birleşik Devletleri'nde satışı durdurulmuştur.

Kanıtlar sınırlı ve çelişkili olsa da kannabinoid ilaçların analjezik etkinliği ile ilgili veriler mevcut-tur (264-270). Kanser hastalarında az sayıda çalışma yapılmıştır (267, 271-273). Bu verilere dayana-rak, kannabinoidler, refrakter ağrı için sekonder analjezikler olarak kullanılabilir. Kannabinoidlerin yapılan meta-analiz ve derlemelerde kronik ağrı ve özellikle nöropatik ağrı için etkili olduğuna dair veri-ler mevcuttur (274-277). Başka bir çalışmada ise kronik ağrısı olan kannabinoid kullanan hastalar plasebo kullanan hastalar ile karşılaştırıldığında, kannabinoid kullanımının ağrı palyasyonunda, fi-ziksel işlevde ve uyku kalitesinde çok az farka neden olduğu gösterilmiştir (278). Başka bir çalışmada kannabinoidlerin kronik ağrı için adjuvan ilaç ola-rak etkilerinin yetersiz kanıtlar nedeniyle belirsiz

kaldığı sonucuna varılmıştır (279). Bu sonuçlara da-yanarak yayınlanan kılavuzda, kanser veya kanser di-şi kronik ağrısı olan kişilerde standart bakım ve yönetime ek olarak, kannabinoidlerin eklenmesi za-yif kanıtlarla desteklenmiştir (280). Kannabinoidle-rin santral sinir sistemi üzerine etkileri, uyuşukluk, baş dönmesi, yorgunluk, oryantasyon bozukluğu, ruh hâli değişikliği (öfori veya disfori), denge kay-bı ve halüsinasyonlar olarak sınıflandırılabilir (274, 281). Ağız kuruluğu, bulantı ve kusma görülebilir. Postural senkop ve aritmiler dahil olmak üzere kar-diyoasküler yan etkiler bildirilmiştir. Bu etkilerin ortaya çıkma sıklığı bilinmemekte birlikte mijokard enfarktüsü gözlenmiştir (282).

KAYNAKLAR

- Urits I, Peck J, Orhurhu MS, et al. Off-label antidepressant use for treatment and management of chronic pain: Evolving understanding and comprehensive review. Curr Pain Headache Rep 2019;23:66. doi: 10.1007/s11916-019-0803-z.
- Lee YC, Chen PP. A review of SSRIs and SNRIs in neuropathic pain. Expert Opin Pharmacother 2010;11(17):2813-2825. doi: 10.1517/14656566.2010.507192.
- Griebeler ML, Morey-Vargas OL, Brito JP, et al. Pharmacologic interventions for painful diabetic neuropathy: An umbrella systematic review and comparative effectiveness network meta-analysis. Ann Intern Med 2014;161(9):639-649. doi: 10.7326/M14-0511.
- Dharmshaktu P, Tayal V, Kalra BS. Efficacy of antidepressants as analgesics: a review. J Clin Pharmacol 2012;52(1):6-17. doi: 10.1177/0091270010394852.
- Onghena P, Van Houdenhove B. Antidepressant-in-diced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. Pain 1992;49(2):205-219. doi: 10.1177/0091270010394852.
- Salerno SM, Browning R, Jackson JL. The effect of antidepressant treatment on chronic back pain: a meta-analysis. Arch Intern Med 2002;162(1):19-24. doi: 10.1001/archinte.162.1.19.
- Mease PJ, Dundon K, Sarzi-Puttini P. Pharmacotherapy of fibromyalgia. Best Pract Res Clin Rheumatol 2011;25(2):285-297. doi: 10.1016/j.berh.2011.01.015.
- Ferreira GE, McLachlan AJ, Lin CC, et al. Efficacy and safety of antidepressants for the treatment of back pain and osteoarthritis: systematic review and meta-analy-sis. BMJ 2021;372:1-13. doi: 10.1136/bmj.m4825.
- Lynch ME. Antidepressants as analgesics: a review of randomized controlled trials. J Psychiatry Neurosci 2001;26:30-36. PMID: 11212591.
- Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. Pain 1999;83:389-

400. doi: 10.1016/S0304-3959(99)00154-2.
11. Davies J. A strategy for chronic pain. *Practitioner* 1997;241:452-458. PMID: 9425705.
 12. Spiegel K, Kalb R, Pasternak GW. Analgesic activity of tricyclic antidepressants. *Ann Neurol* 1983;13:462-465. doi: 10.1002/ana.410130418.
 13. Galer BS. Neuropathic pain of peripheral origin: advances in pharmacologic treatment. *Neurology* 1995;45(12 Suppl 9):17-25. doi: 10.1212/wnl.45.12_suppl_9.s17.
 14. Bonezzi C, Demartini L. Treatment options in postherpetic neuralgia. *Acta Neurol Scand Suppl* 1999;173:25-35. doi: 10.1111/j.1600-0404.1999.tb07387.x.
 15. Milligan K. Prescribing antidepressants in general practice. Tricyclic antidepressants are also used for relief of chronic pain. *BMJ* 1997;15:314:827-828. PMID: 9081015.
 16. Kalso E, Tasmuth T, Neuvonen PJ. Amitriptyline effectively relieves neuropathic pain following treatment breast cancer. *Pain* 1996;64:293-302. doi: 10.1016/0304-3959(95)00138-7.
 17. Weber WE. Pharmacotherapy for neuropathic pain caused by injury to the afferent nerve fibers. *Ned Tijdschr Geneesk* 2001;28:813-817. PMID: 11370425.
 18. Arnold LM, Keck PE. Antidepressant treatment of fibromyalgia. A meta-analysis and review. *Psychosomatics* 2000;41:104-113. doi: 10.1176/appi.psy.41.2.104.
 19. Dalgiç H, Papak Ö. Trisiklik antidepressanların analjezik/antinosiseptif etki mekanizmaları. *Erciyes Tip Dergisi* 2003;25(2):98-103.
 20. Korzeniewska-Rybicka I, Plaznik A. Analgesic effect of antidepressant drugs. *Pharmacol Biochem Behav* 1998;59:331-338. doi: 10.1016/s0091-3057(97)00336-5.
 21. Hannonen P, Malmiemi K. A randomized, double-blind, placebo-controlled study of moclobemide and amitriptyline in the treatment of fibromyalgia in females without psychiatric disorder. *Br J Rheumatol* 1998;37:1279-1286. doi: 10.1093/rheumatology/37.12.1279.
 22. Bowsher D. Neurogenic pain syndromes and their management. *Br Med Bull* 1991;47:644-666. doi: 10.1093/oxfordjournals.bmb.a072498.
 23. Rigal F, Eschalier A. Activities of five antidepressants in a behavioral pain test in rats. *Life Sci* 1983;32:2965-2971. doi: 10.1016/0024-3205(83)90647-1.
 24. Clifford DB. Treatment of pain with antidepressants. *Am Fam Physician* 1985;31:181-185.
 25. Reinman W, Schlutz H, Selv N. The antinociceptive effects of morphine, desipramine, and serotonin and their combinations after intrathecal injection in the rat. *Anesth Analg* 1999; 88:141-145. PMID: 2983520
 26. Eisenach JC, Gebhart GF. Intrathecal amitriptyline. Antinociceptive interactions with intravenous morphine and intrathecal clonidine. *Anesthesiology* 1995;83:1036-1045. doi: 10.1097/00000542-199511000-00017.
 27. Aydinli, I. (2007). Sekonder analjezikler. Serdar Erdine (Ed.), Ağrı içinde (s. 605-626). İstanbul: Nobel Tıp Kitabevleri.
 28. Schreiber S, Backer MM, Pick CG. The antinociceptive effect of venlafaxine in mice is mediated through opioid and adrenergic mechanisms. *Neurosci Lett* 1999;1(273):85-88. doi: 10.1016/s0304-3940(99)00627-8.
 29. Sierralta F, Pinardi G, Mendez M, et al. Interaction of opioids with antidepressant-induced antinociception. *Psychopharmacology (Berl)* 1995;122(4):374-378. doi: 10.1007/BF02246269.
 30. Godefroy F, Weil-Fugazza J, Besson JM. Do acute or chronic tricyclic antidepressants modify morphine antinociception in arthritic rats? *Pain* 1986;25:233-244. doi: 10.1016/0304-3959(86)90099-0.
 31. Botney M, Fields HL. Amitriptyline potentiates morphine analgesia by direct action on central nervous system. *Ann Neurol* 1983;13:160-164. doi: 10.1002/ana.410130209.
 32. Montastruc JL, Tran MA. Effects of morphine clomipramine combination on a rest of experimental analgesia. *Rev Neurol (Paris)* 1985;141:669-671. PMID: 3003869.
 33. Fialip J, Marty H, Makambila MC. Pharmacokinetic patterns of repeated administration of antidepressant in animals. Their relevance in a study of the influence of clomipramine on morphine analgesia in mice. *J Pharmacol Exp Ther* 1989;248:747-751. PMID: 2918477.
 34. Ventafridda V. Antidepressants increase bioavailability of morphine in cancer patients. *Lancet* 1987;23;1:1204. doi: 10.1016/s0140-6736(87)92172-6.
 35. Pilowsky I, Hallett EC, Bassett DL, Thomas PG, Penhall RK. A controlled study of amitriptyline in the treatment of chronic pain. *Pain* 1982;14(2):169-179. doi: 10.1016/0304-3959(82)90097-5.
 36. Jaeschke R, Adachi J, Guyatt G, et al. Clinical usefulness of amitriptyline in fibromyalgia: the results of 23 N-of-1 randomized controlled trials. *J Rheumatol* 1991;18(3):447-451. doi: 10.1016/0304-3959(82)90097-5.
 37. Mercadante S, Arcuri E, Tirelli W, et al. Amitriptyline in neuropathic cancer pain in patients on morphine therapy: a randomized placebo-controlled, double-blind crossover study. *Tumori* 2002;88(3):239-242. doi: 10.1177/030089160208800310.
 38. Anderson IM, Ferrier IN, Baldwin RC, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. *J Psychopharmacol* 2008;22(4):343-396. doi: 10.1177/0269881107088441.
 39. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Beers Criteria Update Expert Panel. *J Am Geriatr Soc* 2015;63(11):2227-2246. doi: 10.1111/jgs.13702.
 40. Tomkins GE, Jackson JL, O'Malley PG, et al. Treatment of chronic headache with antidepressants: a meta-analysis. *Am JmED* 2001;111:54-63. doi: 10.1016/s0002-9343(01)00762-8.
 41. Goldenberg D, Mayskiy M, Mossey C, et al. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. *Arthritis Rheum* 1996;39(11):1852-1859. doi: 10.1002/10.1002/

- art.1780391111.
42. Rani PU, Naidu MUR, Prasad VBN, et al. An Evaluation of Antidepressants in Rheumatic Pain Conditions. *Anesth Analg* 1996;83:371-375. doi: 10.1097/00000539-199608000-00029.
 43. Tack J, Broekaert D, Fischler B, et al. A controlled crossover study of the selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome. *Gut* 2006;55:1095-1103. doi: 10.1136/gut.2005.077503.
 44. Saper JR, Silberstein SD, Lake AE 3rd, et al. Double-blind trial of fluoxetine: chronic daily headache and migraine. *Headache* 1994;34(9):497-502. doi: 10.1111/j.1526-4610.1994.hed3409497.x.
 45. Norregaard J, Volkmann H, Danneskiold-Samstøe B. A randomized controlled trial of citalopram in the treatment of fibromyalgia. *Pain* 1995; 61(3):445-449. doi: 10.1016/0304-3959(94)00218-4.
 46. Özkaya S, Aydemir E. SSRI grubu antidepressanlar ve antikanser etkileri. *Türk Bilimsel Derlemeler Dergisi* 2021;14(1):37-46.
 47. Hu XH, Bull SA, Hunkeler EM, et al. Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for depression: patient report versus physician estimate. *J Clin Psychiatry* 2004;65(7):959-965. doi: 10.4088/jcp.v65n0712.
 48. Beach SR, Kostis WJ, Celano CM, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. *J Clin Psychiatry* 2014;75(5):441-449. doi: 10.4088/JCP.13r08672.
 49. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med* 2005;352:1112. doi: 10.1056/NEJMra041867.
 50. Birmes P, Coppin D, Schmitt L, et al. Serotonin syndrome: a brief review. *CMAJ* 2003;168(11):1439-1442. PMID: 12771076.
 51. Mason PJ, Morris VA, Balcezak TJ. Serotonin syndrome. Presentation of 2 cases and review of the literature. *Medicine (Baltimore)* 2000;79(4):201-209. doi: 10.1097/00005792-200007000-00001.
 52. Bodner RA, Lynch T, Lewis L, et al. Serotonin syndrome. *Neurology* 1995;45(2):219-223. doi: 10.1212/wnl.45.2.219.
 53. Frampton JE, Plosker GL. Duloxetine: a review of its use in the treatment of major depressive disorder. *CNS Drugs* 2007;21(7):581-609. doi: 10.2165/00023210-200721070-00004.
 54. Wynn GH, Sandson N, Muniz J. (2009). Clinical Manual of Drug Interaction Principles for Medical Practice. Wynn GH, Oesterheld JR, Cozza KL, Armstrong SC (Eds), *Psychiatry* (pp 423). Washington DC: American Psychiatric Publishing.
 55. Thase ME. (2017). Venlafaxine and desvenlafaxine. Schatzberg AF, Nemeroff CB (Eds). *The American Psychiatric Association Publishing Textbook of Psychopharmacology* (pp 515). American Arlington: Psychiatric Association Publishing.
 56. Wynn GH, Sandson N, Muniz J. (2009). Clinical Manual of Drug Interaction Principles for Medical Practice. Wynn GH, Oesterheld JR, Cozza KL, Armstrong SC (Eds), *Psychiatry* (pp 426). Washington DC: American Psychiatric Publishing.
 57. Chen L, Boinpally R, Gad N, et al. Evaluation of cytochrome P450 (CYP) 3A4-based interactions of levomilnacipran with ketoconazole, carbamazepine or alprazolam in healthy subjects. *Clin Drug Investig* 2015;35(10):601-612. doi: 10.1007/s40261-015-0318-2.
 58. Norris S, Blier P. (2017). Duloxetine, milnacipran, and levomilnacipran. Schatzberg AF, Nemeroff CB (Eds), *The American Psychiatric Association Publishing Textbook of Psychopharmacology* (pp 529) Arlington: American Psychiatric Association Publishing.
 59. Asnis GM, Henderson MA. Levomilnacipran for the treatment of major depressive disorder: a review. *Neuropsychiatr Dis Treat* 2015;9(11):125-135. doi: 10.2147/NDT.S54710.
 60. Auclair AL, Martel JC, Assié MB, et al. Levomilnacipran (F2695), a norepinephrine-preferring SNRI: profile in vitro and in models of depression and anxiety. *Neuropharmacology* 2013;70:338-347. doi: 10.1016/j.neuropharm.2013.02.024.
 61. Norris S, Blier P. Duloxetine and milnacipran. (2009). Schatzberg AF, Nemeroff CB (Eds), *The American Psychiatric Publishing Textbook of Psychopharmacology* (pp 453). Washington DC: American Psychiatric Publishing.
 62. Marks DM, Shah MJ, Patkar AA, et al. Serotonin-norepinephrine reuptake inhibitors for pain control: premise and promise. *Curr Neuropharmacol* 2009;7(4):331-336. doi: 10.2174/157015909790031201.
 63. Liebowitz MR, Gelenberg AJ, Munjack D. Venlafaxine extended release vs placebo and paroxetine in social anxiety disorder. *Arch Gen Psychiatry* 2005;62:190-198. doi: 10.1001/archpsyc.62.2.190.
 64. Arnold LM, Rosen A, Pritchett YL, et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain* 2005;119(1-3):5-15. doi: 10.1016/j.pain.2005.06.031.
 65. Wernicke JF, Pritchett YL, D'Souza DN, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. *Neurology* 2006;67(8):1411-1420. doi: 10.1212/01.wnl.0000240225.04000.1a.
 66. Matsuoka H, Iwase S, Miyaji T, et al. Additive duloxetine for cancer-related neuropathic pain nonresponsive or intolerant to opioid-pregabalin therapy: A randomized controlled trial (JORTC-PAL08). *J Pain Symptom Manage* 2019;58(4):645-653. doi: 10.1016/j.jpainsymman.2019.06.020
 67. Smith EM, Pang H, Cirrincione C, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *JAMA* 2013;309(13):1359-1367. doi: 10.1001/jama.2013.2813.
 68. Frampton JE, Plosker GL. Duloxetine: a review of its use in the treatment of major depressive disorder. *CNS Drugs*. 2007;21:581-609. doi: 10.2165/00023210-200721070-00004.
 69. Torta R, Leombruni P, Borio R, et al. Duloxetine for the treatment of mood disorder in cancer patients: a 12-week case-control clinical trial. *Hum Psychopharmacol*

- 2011;26:291-299. doi: 10.1002/hup.1202.
70. Häuser W, Wolfe F, Tölle T, et al. The role of antidepressants in the management of fibromyalgia syndrome: a systematic review and meta-analysis. *CNS Drugs* 2012; 26(4):297-307. doi: 10.2165/11598970-00000000-00000.
71. Gendreau RM, Thorn MD, Gendreau JF, et al. Efficacy of milnacipran in patients with fibromyalgia. *J Rheumatol* 2005;32:1975-1985. PMID: 16206355.
72. Rouillon F, Warner B, Pezous N, et al. Milnacipran efficacy in the prevention of recurrent depression: a 12-month placebo-controlled study. Milnacipran recurrence prevention study group. *Int Clin Psychopharmacol* 2000;15:133-140. doi: 10.1097/00004850-200015030-00002.
73. Wiffen PJ, Derry S, Moore RA, et al. Antiepileptic drugs for neuropathic pain and fibromyalgia-an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2013;2013(11):CD010567. Published 2013 Nov 11. doi:10.1002/14651858.CD010567.pub2.
74. Mitra R, Jones S. Adjuvant analgesics in cancer pain: a review. *Am J Hosp Palliat Care*. 2012;29(1):70-79. doi:10.1177/1049909111413256.
75. Yajnik S, Singh GP, Singh G, Kumar M. Phenytoin as a coanalgesic in cancer pain. *J Pain Symptom Manage* 1992;7(4):209-213. doi:10.1016/0885-3924(92)90077-u
76. Obermann M. Treatment options in trigeminal neuralgia. *Ther Adv Neurol Disord* 2010;3(2):107-115. doi: 10.1177/1756285609359317.
77. Di Stefano G, Truini A, Crucchi G. Current and Innovative Pharmacological Options to Treat Typical and Atypical Trigeminal Neuralgia. *Drugs* 2018;78(14):1433-1442. doi: 10.1007/s40265-018-0964-9.
78. Rowbotham MC, Petersen KL, Davies PS, et al. "Recent developments in the treatment of neuropathic pain." *Progress in Pain Research and Management* 2000;16:833-856.
79. Gambetta E, Chichorro JG, Zamponi GW. Trigeminal neuralgia: An overview from pathophysiology to pharmacological treatments. *Mol Pain* 2020;16:1744806920901890. doi: 10.1177/1744806920901890.
80. Lake, E. (2021). Medication Management. In *Trigeminal Nerve Pain* (pp 77-87). Springer, Cham.
81. Beydoun A. Clinical use of tricyclic anticonvulsants in painful neuropathies and bipolar disorders. *Epilepsy Behav* 2002;3(3S):S18-S22. doi: 10.1016/s1525-5050(02)00017-3.
82. Ichikawa K, Koyama N, Kiguchi S, et al. Inhibitory effect of oxcarbazepine on high-frequency firing in peripheral nerve fibers. *Eur J Pharmacol* 2001;420(2-3):119-122. doi: 10.1016/s0014-2999(01)01007-x.
83. Gomez-Arguelles JM, Dorado R, Sepulveda JM, et al. Oxcarbazepine monotherapy in carbamazepine-unresponsive trigeminal neuralgia. *J Clin Neurosci* 2008;15(5):516-519. doi: 10.1016/j.jocn.2007.04.010
84. Zhou M, Chen N, He L, et al. Oxcarbazepine for neuropathic pain. *Cochrane Database Syst Rev* 2017;12(12):CD007963. doi: 10.1002/14651858.CD007963.pub3.
85. Chong MS, Libretto SE. The rationale and use of topiramate for treating neuropathic pain. *Clin J Pain* 2003;19(1):59-68. doi: 10.1097/00002508-200301000-00008.
86. Edwards KR. Efficacy and safety of topiramate in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. *Neurology* 2000;54:A81. doi: 10.1016/j.clinthera.2005.09.011.
87. Edwards KR., Potter DL, Wu SC, Kamin M, Hulihan J. Topiramate in the preventive treatment of episodic migraine: A combined analysis from pilot, double-blind, placebo-controlled trials. *CNS Spectrums*. 2003;8(06):428-432. doi:10.1017/s1092852900018733.
88. Brandes JL, Saper JR, Diamond M, et al. Topiramate for migraine prevention: a randomized controlled trial. *JAMA* 2004;291(8):965-973. doi: 10.1001/jama.291.8.965.
89. Kanda T, Kurokawa M, Tamura S, et al. Topiramate reduces abnormally high extracellular levels of glutamate and aspartate in the hippocampus of spontaneously epileptic rats (SER). *Life Sci* 1996;59(19):1607-1616. doi: 10.1016/0024-3205(96)00492-4.
90. Issa, M. A., Marshall, Z., & Wasan, A. D. (2018). Psychopharmacology for pain medicine. In *Essentials of pain medicine* (pp 427-436). Elsevier.
91. Fallon MT. Neuropathic pain in cancer. *Br J Anaesth* 2013;111(1):105-111. doi: 10.1093/bja/aet208.
92. Paice JA, Ferrell B. The management of cancer pain. *CA Cancer J Clin* 2011;61(3):157-182. doi: 10.3322/caac.20112.
93. Falk S, Bannister K, Dickenson AH. Cancer pain physiology. *Br J Pain* 2014;8(4):154-162. doi: 10.1177/2049463714545136.
94. Gomes T, Greaves S, van den Brink W, et al. Pregabalin and the Risk for Opioid-Related Death: A Nested Case-Control Study. *Ann Intern Med* 2018;169(10):732-734. doi: 10.7326/M18-1136.
95. Gomes T, Juurlink DN, Antoniou T, et al. Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case-control study. *PLoS Med* 2017;14(10):e1002396. doi: 10.1371/journal.pmed.1002396.
96. Schug SA, Chandrasena C. Pain management of the cancer patient. *Expert Opin Pharmacother* 2015;16(1):5-15. doi: 10.1517/14656566.2015.980723.
97. Sills GJ. The mechanisms of action of gabapentin and pregabalin. *Curr Opin Pharmacol* 2006;6(1):108-113. doi: 10.1016/j.coph.2005.11.003.
98. Caraceni A, Zecca E, Bonezzi C, et al. Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group. *J Clin Oncol* 2004;22(14):2909-2917. doi: 10.1200/JCO.2004.08.141.
99. Mishra S, Bhatnagar S, Goyal GN, et al. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. *Am J Hosp Palliat Care* 2012;29(3):177-182. doi: 10.1177/1049909111412539.
100. Keskinbora K, Pekel AF, Aydinli I. Gabapentin and an

- opioid combination versus opioid alone for the management of neuropathic cancer pain: a randomized open trial. *J Pain Symptom Manage* 2007;34(2):183-189. doi: 10.1016/j.jpainsymman.2006.11.013.
101. Jiang J, Li Y, Shen Q, et al. Effect of pregabalin on radiotherapy-related neuropathic pain in patients with head and neck cancer: A randomized controlled trial. *J Clin Oncol* 2019;37(2):135-143. doi: 10.1200/JCO.18.00896.
 102. Bennett MI. Effectiveness of antiepileptic or antidepressant drugs when added to opioids for cancer pain: systematic review. *Palliat Med* 2011;25(5):553-559. doi: 10.1177/0269216310378546.
 103. Peterson, S, Benzon, H. T., & Hurley, R. W. (2018). Membrane stabilizers. In Essentials of pain medicine (pp 437-444). Elsevier.
 104. Salter MW, Pitcher GM. Dysregulated Src upregulation of NMDA receptor activity: a common link in chronic pain and schizophrenia. *FEBS J* 2012;279(1):2-11. doi: 10.1111/j.1742-4658.2011.08390.x.
 105. Bouvier G, Bidoret C, Casado M, et al. Presynaptic NMDA receptors: Roles and rules. *Neuroscience* 2015;311:322-340. doi: 10.1016/j.neuroscience.2015.10.033.
 106. Zeevalk GD, Nicklas WJ. Evidence that the loss of the voltage-dependent Mg²⁺ block at the N-methyl-D-aspartate receptor underlies receptor activation during inhibition of neuronal metabolism. *J Neurochem* 1992;59(4):1211-1220. doi: 10.1111/j.1471-4159.1992.tb08430.x.
 107. Zipfel GJ, Babcock DJ, Lee JM, et al. Neuronal apoptosis after CNS injury: the roles of glutamate and calcium. *J Neurotrauma* 2000;17(10):857-869. doi: 10.1089/neu.2000.17.857.
 108. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain* 2009;10(9):895-926. doi: 10.1016/j.jpain.2009.06.012.
 109. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011;152(3 Suppl):2-15. doi: 10.1016/j.pain.2010.09.030.
 110. Shanthanna, H. Intravenous therapies in the management of neuropathic pain: a review on the use of ketamine and lidocaine in chronic pain management. *Neuropathic Pain* 2012; 41. doi: 10.5772/36882
 111. Petrenko AB, Yamakura T, Baba H, et al. The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. *Anesth Analg* 2003;97(4):1108-1116. doi: 10.1213/01.ANE.0000081061.12235.55.
 112. Kreutzwiser D, Tawfic QA. Expanding Role of NMDA Receptor Antagonists in the Management of Pain CNS Drugs 2019;33(4):347-374. doi: 10.1007/s40263-019-00618-2.
 113. Patil S, Anitescu M. Efficacy of outpatient ketamine infusions in refractory chronic pain syndromes: a 5-year retrospective analysis. *Pain Med* 2012;13(2):263-269. doi: 10.1111/j.1526-4637.2011.01241.x.
 114. Mercadante S, Arcuri E, Tirelli W, Casuccio A. Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, crossover, double-dose study. *J Pain Symptom Manage* 2000;20(4):246-252. doi: 10.1016/s0885-3924(00)00194-9.
 115. Kannan TR, Saxena A, Bhatnagar S, et al. Oral ketamine as an adjuvant to oral morphine for neuropathic pain in cancer patients. *J Pain Symptom Manage* 2002;23(1):60-65. doi: 10.1016/s0885-3924(01)00373-6.
 116. DeCaria, S. K., & Anitescu, M. (2017). Intravenous infusions for refractory cancer and chronic pain states. Benzon HT, Raja SN, Fishman SM (Eds). *Essentials of Pain Medicine* (4th edition pp 469-474). Elsevier.
 117. Bell RF, Eccleston C, Kalso EA. Ketamine as an adjuvant to opioids for cancer pain. *Cochrane Database Syst Rev* 2017;6(6):CD003351. Published 2017 Jun 28. doi: 10.1002/14651858.CD003351.pub3.
 118. Cohen SP, Bhatia A, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med* 2018;43(5):521-546. doi: 10.1097/AAP.0000000000000808.
 119. Jackson K, Ashby M, Howell D, et al. The effectiveness and adverse effects profile of "burst" ketamine in refractory cancer pain: The VCOG PM 1-00 study. *J Palliat Care* 2010;26(3):176-183. PMID: 21047040.
 120. Mercadante S, Caruselli A, Casuccio A. The use of ketamine in a palliative-supportive care unit: a retrospective analysis. *Ann Palliat Med* 2018;7(2):205-210. doi: 10.21037/apm.2018.01.01.
 121. Marchetti F, Coutaux A, Bellanger A, et al. Efficacy and safety of oral ketamine for the relief of intractable chronic pain: A retrospective 5-year study of 51 patients. *Eur J Pain* 2015 Aug;19(7):984-993. doi: 10.1002/ejp.624.
 122. Loveday BA, Sindt J. Ketamine Protocol for Palliative Care in Cancer Patients With Refractory Pain. *J Adv Pract Oncol* 2015;6(6):555-561. PMID: 27648345; PMCID: PMC5017546.
 123. Marchetti F, Coutaux A, Bellanger A, et al. Efficacy and safety of oral ketamine for the relief of intractable chronic pain: A retrospective 5-year study of 51 patients. *Eur J Pain* 2015;19(7):984-993. doi: 10.1002/ejp.624.
 124. Quibell R, Fallon M, Mihalyo M, et al. Ketamine. *J Pain Symptom Manage* 2015;50(2):268-278. doi: 10.1016/j.jpainsymman.2015.06.002.
 125. Laskowski K, Stirling A, McKay WP, et al. A systematic review of intravenous ketamine for postoperative analgesia. *Can J Anaesth* 2011;58(10):911-923. doi: 10.1007/s12630-011-9560-0.
 126. Schwenk ES, Goldberg SF, Patel RD, et al. Adverse Drug Effects and Preoperative Medication Factors Related to Perioperative Low-Dose Ketamine Infusions. *Reg Anesth Pain Med* 2016;41(4):482-487. doi: 10.1097/AAP.0000000000000416.
 127. Krystal JH, D'Souza DC, Karper LP, et al. Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. *Psychopharmacology (Berl)* 1999;145(2):193-204. doi: 10.1007/s002130051049.
 128. Okamoto Y, Tsuneto S, Tanimukai H, et al. Can gradual dose titration of ketamine for management of neuro-

- pathic pain prevent psychotomimetic effects in patients with advanced cancer? *Am J Hosp Palliat Care* 2013;30(5):450-454. doi: 10.1177/1049909112454325.
129. Nguyen L, Thomas KL, Lucke-Wold BP, et al. Dextromethorphan: An update on its utility for neurological and neuropsychiatric disorders. *Pharmacol Ther* 2016;159:1-22. doi: 10.1016/j.pharmthera.2016.01.016.
 130. Gudin J, Fudin J, Nalamachu S. Levorphanol use: past, present and future. *Postgrad Med* 2016;128(1):46-53. doi: 10.1080/00325481.2016.1128308.
 131. Taylor CP, Traynelis SF, Siffert J, et al. Pharmacology of dextromethorphan: Relevance to dextromethorphan/quinidine (Nuedexta®) clinical use. *Pharmacol Ther* 2016;164:170-182. doi: 10.1016/j.pharmthera.2016.04.010.
 132. Church J, Lodge D, Berry SC. Differential effects of dextrorphan and levorphanol on the excitation of rat spinal neurons by amino acids. *Eur J Pharmacol* 1985;111(2):185-190. doi: 10.1016/0014-2999(85)90755-1.
 133. Church J, Jones MG, Davies SN, et al. Antitussive agents as N-methylaspartate antagonists: further studies. *Can J Physiol Pharmacol* 1989;67(6):561-567. doi: 10.1139/y89-090.
 134. Franklin PH, Murray TF. High affinity [³H]dextrorphan binding in rat brain is localized to a noncompetitive antagonist site of the activated N-methyl-D-aspartate receptor-cation channel. *Mol Pharmacol* 1992;41(1):134-146. PMID: 1370704.
 135. Netzer R, Pflimlin P, Trube G. Dextromethorphan blocks N-methyl-D-aspartate-induced currents and voltage-operated inward currents in cultured cortical neurons. *Eur J Pharmacol* 1993;238(2-3):209-216. doi: 10.1016/0014-2999(93)90849-d.
 136. Palmer GC. Neuroprotection by NMDA receptor antagonists in a variety of neuropathologies. *Curr Drug Targets* 2001;2(3):241-271. doi: 10.2174/1389450013348335.
 137. Cruz MP. Nuedexta for the treatment of pseudobulbar affect: a condition of involuntary crying or laughing. *P T* 2013;38(6):325-328. PMID: 23946627; PMCID: PMC3737988.
 138. Miller A, Pratt H, Schiffer RB. Pseudobulbar affect: the spectrum of clinical presentations, etiologies and treatments. *Expert Rev Neurother* 2011;11(7):1077-1088. doi: 10.1586/ern.11.68.
 139. Duedahl TH, Rømsing J, Møiniche S, et al. A qualitative systematic review of peri-operative dextromethorphan in post-operative pain. *Acta Anaesthesiol Scand* 2006;50(1):1-13. doi: 10.1111/j.1399-6576.2006.00900.x.
 140. King MR, Ladha KS, Gelineau AM, et al. Perioperative Dextromethorphan as an Adjunct for Postoperative Pain: A Meta-analysis of Randomized Controlled Trials. *Anesthesiology* 2016;124(3):696-705. doi: 10.1097/ALN.0000000000000950.
 141. Mercadante S, Casuccio A, Genovese G. Ineffectiveness of dextromethorphan in cancer pain. *J Pain Symptom Manage* 1998;16(5):317-322. PMID: 9846026.
 142. Dudgeon DJ, Bruera E, Gagnon B, et al. A phase III randomized, double-blind, placebo-controlled study evaluating dextromethorphan plus slow-release morphine for chronic cancer pain relief in terminally ill patients. *J Pain Symptom Manage* 2007;33(4):365-371. doi: 10.1016/j.jpainsymman.2006.09.017.
 143. Witt A, Macdonald N, Kirkpatrick P. Memantine hydrochloride. *Nat Rev Drug Discov* 2004;3(2):109-110. doi: 10.1038/nrd1311.
 144. Makino KM, Porsteinsson AP. Memantine: a treatment for Alzheimer's disease with a new formulation. *Aging Health* 2011;7(3), 349-362. doi: 10.2217/ahe.11.31.
 145. Johnson JW, Kotermanski SE. Mechanism of action of memantine. *Curr Opin Pharmacol* 2006;6(1):61-67. doi: 10.1016/j.coph.2005.09.007.
 146. Sinis N, Birbaumer N, Gustin S, et al. Memantine treatment of complex regional pain syndrome: a preliminary report of six cases. *Clin J Pain* 2007;23(3):237-243. doi: 10.1097/AJP.0b013e31802f67a7.
 147. Ahmad-Sabry MH, Shareghi G. Effects of memantine on pain in patients with complex regional pain syndrome--a retrospective study. *Middle East J Anaesthesiol* 2015;23(1):51-54. PMID: 26121895.
 148. Loy BM, Britt RB, Brown JN. Memantine for the Treatment of Phantom Limb Pain: A Systematic Review. *J Pain Palliat Care Pharmacother* 2016;30(4):276-283. doi: 10.1080/15360288.2016.1241334.
 149. Alviar MJ, Hale T, Dungca M. Pharmacologic interventions for treating phantom limb pain. *Cochrane Database Syst Rev*. 2016;10(10):CD006380. Published 2016 Oct 14. doi: 10.1002/14651858.CD006380.pub3.
 150. Pickering G, Morel V. Memantine for the treatment of general neuropathic pain: a narrative review. *Fundam Clin Pharmacol* 2018;32(1):4-13. doi: 10.1111/fcp.12316.
 151. Assarzadegan F, Sistanizad M. Tolerability and efficacy of memantine as add on therapy in patients with migraine. *Iran J Pharm Res* 2017;16(2):791-797. PMID: 28979333; PMCID: PMC5603889.
 152. Bigal M, Rapoport A, Sheftell F, et al. Memantine in the preventive treatment of refractory migraine. *Headache* 2008;48(9):1337-1342. doi: 10.1111/j.1526-4610.2008.01083.x.
 153. Lindelof K, Bendtsen L. Memantine for prophylaxis of chronic tension-type headache: a double-blind, randomized, crossover clinical trial. *Cephalalgia* 2009;29(3):314-321. doi: 10.1111/j.1468-2982.2008.01720.x.
 154. Noruzzadeh R, Modabbernia A, Aghamollaii V, et al. Memantine for Prophylactic Treatment of Migraine Without Aura: A Randomized Double-Blind Placebo-Controlled Study. *Headache* 2016;56(1):95-103. doi: 10.1111/head.12732.
 155. Lipton SA. Paradigm shift in neuroprotection by NMDA receptor blockade: memantine and beyond. *Nat Rev Drug Discov* 2006;5(2):160-170. doi: 10.1038/nrd1958.
 156. Kornhuber J, Quack G, Danysz W, et al. Therapeutic brain concentration of the NMDA receptor antagonist amantadine. *Neuropharmacology* 1995;34(7):713-721. doi: 10.1016/0028-3908(95)00056-c.

157. Medrik-Goldberg T, Lifschitz D, Pud D, et al. Intravenous lidocaine, amantadine, and placebo in the treatment of sciatica: a double-blind, randomized, controlled study. *Reg Anesth Pain Med* 1999;24(6):534-540. doi: 10.1016/s1098-7339(99)90045-7.
158. Pud D, Eisenberg E, Spitzer A, et al. The NMDA receptor antagonist amantadine reduces surgical neuropathic pain in cancer patients: a double blind, randomized, placebo controlled trial. *Pain* 1998;75(2-3):349-354. doi: 10.1016/s0304-3959(98)00014-1.
159. Srebro D, Vuckovic S, Milovanovic A, et al. Magnesium in Pain Research: State of the Art. *Curr Med Chem* 2017;24(4):424-434. doi: 10.2174/0929867323666161213101744.
160. Dube L, Granry JC. The therapeutic use of magnesium in anesthesiology, intensive care and emergency medicine: a review. *Can J Anaesth* 2003;50(7):732-746. doi: 10.1007/BF03018719.
161. De Oliveira GS Jr, Castro-Alves LJ, Khan JH, et al. Perioperative systemic magnesium to minimize postoperative pain: a meta-analysis of randomized controlled trials. *Anesthesiology* 2013;119(1):178-190. doi: 10.1097/ALN.0b013e318297630d.
162. Albrecht E, Kirkham KR, Liu SS, et al. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. *Anesthesia* 2013;68(1):79-90. doi: 10.1111/j.1365-2044.2012.07335.x.
163. Murphy JD, Paskaradevan J, Eisler LL, et al. Analgesic efficacy of continuous intravenous magnesium infusion as an adjuvant to morphine for postoperative analgesia: a systematic review and meta-analysis. *Middle East J Anaesthesiol* 2013;22(1):11-20. PMID: 23833845.
164. Sousa AM, Rosado GM, Neto Jde S, et al. Magnesium sulfate improves postoperative analgesia in laparoscopic gynecologic surgeries: a double-blind randomized controlled trial. *J Clin Anesth* 2016;34:379-384. doi: 10.1016/j.jclinane.2016.05.006.
165. Choi H, Parmar N. The use of intravenous magnesium sulphate for acute migraine: meta-analysis of randomized controlled trials. *Eur J Emerg Med* 2014;21(1):2-9. doi: 10.1097/MEJ.0b013e3283646e1b.
166. Chiu HY, Yeh TH, Huang YC, et al. Effects of intravenous and oral magnesium on reducing migraine: a metaanalysis of randomized controlled trials. *Pain Physician* 2016;19(1):E97-112. PMID: 26752497.
167. Fischer SG, Collins S, Boogaard S, et al. Intravenous magnesium for chronic complex regional pain syndrome type 1 (CRPS-1). *Pain Med* 2013;14(9):1388-1399. doi: 10.1111/pme.12211.
168. Pickering G, Morel V, Simen E, et al. Oral magnesium treatment in patients with neuropathic pain: a randomized clinical trial. *Magnes Res* 2011;24(2):28-35. doi: 10.1684/mrh.2011.0282.
169. Brill S, Sedgwick PM, Hamann W, et al. Efficacy of intravenous magnesium in neuropathic pain. *Br J Anaesth* 2002;89(5):711-714. PMID: 12393768.
170. Yousef AA, Al-deeb AE. A double-blinded randomised controlled study of the value of sequential intravenous and oral magnesium therapy in patients with chronic low back pain with a neuropathic component. *Anesthesia* 2013;68(3):260-266. doi: 10.1111/anae.12107.
171. Collinsworth KA, Kalman SM, Harrison DC. The clinical pharmacology of lidocaine as an antiarrhythmic drug. *Circulation* 1974;50(6):1217-1230. doi: 10.1161/01.cir.50.6.1217.
172. Manolis AS, Deering TF, Cameron J, et al. Mexiletine: pharmacology and therapeutic use. *Clin Cardiol* 1990; 13(5):349-359. doi: 10.1002/clc.4960130509.
173. Nguyen NL, Kome AM, Lowe DK, et al. Intravenous lidocaine as an adjuvant for pain associated with sickle cell disease. *J Pain Palliat Care Pharmacother* 2015;29(4):359-364. doi: 10.3109/15360288.2015.1082009.
174. Koppert W, Ostermeier N, Sittl R, et al. Low-dose lidocaine reduces secondary hyperalgesia by a central mode of action. *Pain* 2000;85(1):217-224. doi: 10.1016/s0304-3959(99)00268-7.
175. Attal N, Rouaud J, Brasseur L, et al. Systemic lidocaine in pain due to peripheral nerve injury and predictors of response. *Neurology* 2004;62(2):218-225. doi: 10.1212/01.wnl.0000103237.62009.77.
176. Baranowski AP, De Courcey J, Bonello E. A trial of intravenous lidocaine on the pain and allodynia of postherpetic neuralgia. *J Pain Symptom Manage* 1999;17(6):429-33. doi: 10.1016/s0885-3924(99)00032-9.
177. Peixoto RD, Hawley P. Intravenous lidocaine for cancer pain without electrocardiographic monitoring: a retrospective review. *J Palliat Med* 2015;18(4):373-377. doi: 10.1089/jpm.2014.0279.
178. Kastrup J, Angelo H, Petersen P, et al. Treatment of chronic painful diabetic neuropathy with intravenous lidocaine infusion. *Br Med J (Clin Res Ed)* 1986;292(6514):173. doi: 10.1136/bmj.292.6514.173.
179. Posner IA. Treatment of fibromyalgia syndrome with intravenous lidocaine. *J Musculoskelet Pain* 1994;2(4):55-65. Doi:10.1300/J094v02n04_05.
180. Groudine SB, Fisher HA, Kaufman RP, et al. Intravenous lidocaine speeds the return of bowel function, decreases postoperative pain, and shortens hospital stay in patients undergoing radical retropubic prostatectomy. *Anesth Analg* 1998;86(2):235-239. doi: 10.1097/00000539-199802000-00003.
181. Chabal C, Jacobson L, Mariano A, et al. The use of oral mexiletine for the treatment of pain after peripheral nerve injury. *Anesthesiology* 1992;76(4):513-517. doi: 10.1097/00000542-199204000-00005.
182. Chiou-Tan FY, Tuel SM, Johnson JC, et al. Effect of mexiletine on spinal cord injury dysesthetic pain. *Am J Phys Med Rehabil* 1996;75(2):84-87. doi: 10.1097/00002060-199603000-00002.
183. Oskarsson P, Ljunggren JG, Lins PE. Efficacy and safety of mexiletine in the treatment of painful diabetic neuropathy. The Mexiletine Study Group. *Diabetes Care* 1997;20(10):1594-1597. doi: 10.2337/diacare.20.10.1594.
184. Stracke H, Meyer U, Schumacher H, et al. Mexiletine in treatment of painful diabetic neuropathy. *Med Klin (Munich)* 1994;89(3):124-131. PMID: 8196572.
185. Stracke H, Meyer UE, Schumacher HE, et al. Mexile-

- tine in the treatment of diabetic neuropathy. *Diabetes Care* 1992;15(11):1550-1555. doi: 10.2337/diacare.15.11.1550.
186. Wang JS, Backman JT, Taavitsainen P, et al. Involvement of CYP1A2 and CYP3A4 in lidocaine N-deethylation and 3-hydroxylation in humans. *Drug Metab Dispos* 2000;28(8):959-965. PMID: 10901707.
 187. Wallace MS, Laitin S, Licht D, et al. Concentration-effect relations for intravenous lidocaine infusions in human volunteers: Effects on acute sensory thresholds and capsaicin-evoked hyperpathia. *Anesthesiology* 1997;86:1262-1272. doi: 10.1097/00000542-199706000-00006.
 188. Wallace MS, Ridgeway BM, Leung AY, et al. Concentration-effect relationship of intravenous lidocaine on the allodynia of complex regional pain syndrome types I and II. *Anesthesiology* 2000;92:75-83. doi: 10.1097/00000542-200001000-00017.
 189. Baranowski AP, De Courcey J, Bonello E. A trial of intravenous lidocaine on the pain and allodynia of postherpetic neuralgia. *J Pain Symptom Manage* 1999;17:429-533. doi: 10.1016/s0885-3924(99)00032-9.
 190. Viola V, Newnham HH, Simpson RW. Treatment of intractable painful diabetic neuropathy with intravenous lignocaine. *J Diabetes Complications* 2006;20:34-39. doi: 10.1016/j.jdiacomp.2005.05.007.
 191. Labbe L, Turgeon J. Clinical pharmacokinetics of mexiletine. *Clin Pharmacokinet* 1999;37(5):361-384.
 192. Derry S, Wiffen PJ, Moore RA, et al. Topical lidocaine for neuropathic pain in adults. *Cochrane Database Syst Rev* 2014;24:2014(7):CD010958.
 193. Rowbotham MC, Davies PS, Fields HL. Topical lidocaine gel relieves postherpetic neuralgia. *Ann Neurol* 1995;37(2):246-253. doi: 10.1002/ana.410370216.
 194. Lavand'homme PM, Eisenach JC. Perioperative administration of the alpha2-adrenoceptor agonist clonidine at the site of nerve injury reduces the development of mechanical hypersensitivity and modulates local cytokine expression. *Pain* 2003;105(1-2):247-254. doi: 10.1016/s0304-3959(03)00221-5.
 195. Roh DH, Kim HW, Yoon SY, et al. Intrathecal clonidine suppresses phosphorylation of the N-methyl-D-aspartate receptor NR1 subunit in spinal dorsal horn neurons of rats with neuropathic pain. *Anesth Analg* 2008;107(2):693-700. doi: 10.1213/ane.0b013e31817e7319.
 196. Paalzow G. Analgesia produced by clonidine in mice and rats. *J Pharm Pharmacol* 1974; 1974;26(5):361-363. doi: 10.1111/j.2042-7158.1974.tb09291.x.
 197. Dennis SG, Melzack R, Gutman S, et al. Pain modulation by adrenergic agents and morphine as measured by three pain tests. *Life Sci* 1980;26(15):1247-1259. doi: 10.1016/0024-3205(80)90070-3.
 198. Aceta MD, Harris LS. (1981). Antinociceptive mechanisms and acute and chronic behavioral effects of clonidine. Lal H, Fielding S (Eds). *Psychopharmacology of clonidine* (pp 243-268). New York: Alan R Liss Inc. MID: 6276896.
 199. Chan SHH, Lai YY. Effects of aging on pain responses and analgesic efficacy of morphine and clonidine in rats. *Exp Neurol* 1982;75(1):112-119. doi: 10.1016/0014-4886(82)90011-5.
 200. Hassenbusch SJ, Gunes S, Wachsman S, et al. Intrathecal clonidine in the treatment of intractable pain: A phase I/II study. *Pain Med* 2002;3:85-91. doi: 10.1046/j.1526-4637.2002.02014.x.
 201. Siddall PJ, Molloy AR, Walker S, et al. The efficacy of intrathecal morphine and clonidine in the treatment of pain after spinal cord injury. *Anesth Analg* 2000;91:1493-1498. doi: 10.1097/00000539-200012000-00037.
 202. Rudich Z, Peng P, Dunn E, et al. Stability of clonidine in clonidine-hydromorphone mixture from implanted intrathecal infusion pumps in chronic pain patients. *J Pain Symptom Manage* 2004;28:599-602. doi: 10.1016/j.jpainsymman.2004.02.018.
 203. Ruan X, Liu H, Couch JP, et al. Recurrent cellulitis associated with long-term intrathecal opioid infusion therapy: A case report and review of the literature. *Pain Med* 2010;11:972-976. doi: 10.1111/j.1526-4637.2010.00854.x.
 204. Eisenach JC, DuPen S, Dubois M, et al. Epidural clonidine analgesia for intractable cancer pain. The epidural clonidine study group. *Pain* 1995;61:391-399. doi: 10.1016/0304-3959(94)00209-W.
 205. Lavand'homme P, De Kock M. The use of intraoperative epidural or spinal analgesia modulates postoperative hyperalgesia and reduces residual pain after major abdominal surgery. *Acta Anaesthesiol Belg* 2006;57:373-379. PMID: 17236639.
 206. Romero-Sandoval A, Eisenach JC. Clonidine reduces hypersensitivity and alters the balance of pro- and anti-inflammatory leukocytes after local injection at the site of inflammatory neuritis. *Brain, Behavior, and Immunity* 2007;21(5):569-580. doi: 10.1016/j.bbi.2006.09.001.
 207. Serednicki WT, Wrzosek A, Woron J, et al. Topical clonidine for neuropathic pain in adults. *Cochrane Database Syst Rev* 2022;5(5):CD010967. doi: 10.1002/14651858.CD010967.pub3.
 208. Weerink MAS, Struys MMRF, Hannivoort LN, et al. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. *Clin Pharmacokinet* 2017;56(8):893-913. doi: 10.1007/s40262-017-0507-7.
 209. Giovannitti JA Jr, Thoms SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: a review of current clinical applications. *Anesth Prog* 2015;62(1):31-39. doi: 10.2344/0003-3006-62.1.31.
 210. Coskuner I, Tekin M, Kati I, et al. Effects of dexmedetomidine on the duration of anaesthesia and wakefulness in bupivacaine epidural block. *Eur J Anaesthesiol* 2007;24:535-540. doi: 10.1017/S0265021506002237.
 211. Wahlander S, Frumento RJ, Wagener G, et al. A prospective, double-blind, randomized, placebo-controlled study of dexmedetomidine as an adjunct to epidural analgesia after thoracic surgery. *J Cardiothorac Vasc Anesth* 2005;19:630-635. doi: 10.1053/j.jvca.2005.07.006.
 212. Karaaslan D, Peker TT, Alaca A, et al. Comparison of buccal and intramuscular dexmedetomidine preme-

- dication for arthroscopic knee surgery. *Clin Anesth* 2006;18:589-593. doi: 10.1016/j.jclinane.2006.03.019.
213. Jaakola ML. Dexmedetomidine premedication before intravenous regional anesthesia in minor outpatient hand surgery. *J Clin Anesth* 1994;6:204-211. doi: 10.1016/0952-8180(94)90060-4.
214. Kanazi GE, Aouad MT, Jabbour-Khoury SI, et al. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. *Acta Anaesthesiol Scand* 2006; 50:222-227. doi: 10.1111/j.1399-6576.2006.00919.x.
215. Fisher B, Zornow MH, Yaksh TL, et al. Antinociceptive properties of intrathecal in rats. *Eur J Pharmacol* 1991;192:221-225. doi: 10.1016/0014-2999(91)90046-s.
216. Kaya F, Yavaşçaoğlu B, Türker G, et al. Intravenöz deksametomidin premedikasyonunun bupivakain ile uygulanan spinal anestezide duyusal blok süresine etkisi. *Uludağ Üniversitesi Tip Fakültesi Dergisi* 2008;34(3):87-92.
217. Calasans-Maia JA, Zapata-Sudo G, Sudo RT. Dexmedetomidine prolongs spinal anaesthesia induced by levobupivacaine 0.5% in guinea-pigs. *J Pharm Pharmacol* 2005; 57:1415-1420. doi: 10.1211/jpp.57.11.0006.
218. Çevikol A, Ecerkale Ö, Sancıoğlu H, ark. İntratekal Baklofen Tedavisi Uygulamalarımız: 2004-2012 Yılları Arası Olgularımızın Değerlendirilmesi. *Türk Fiz Tip Rehab Derg* 2014;60:295-301. doi: 10.5152/tfrd.2014.66933.
219. Fromn GH, Terrence CF, Glass JD. Baclofen in the treatment of trigeminal neuralgia. Double-Blind study and long term follow-up. *J Ann Neurol* 1984;15:240-244. doi: 10.1002/ana.410150306.
220. Bachhuber MA, Hennessy S, Cunningham CO, et al. Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996-2013. *Am J Public Health*. 2016;106(4):686-688. doi:10.2105/AJPH.2016.303061
221. Dasgupta N, Funk MJ, Proescholdbell S, et al. Cohort Study of the Impact of High-Dose Opioid Analgesics on Overdose Mortality. *Pain Med* 2016;17(1):85-98. doi: 10.1111/pme.12907.
222. Bandelow B, Zohar J, Hollander E, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders-first revision. *World J Biol Psychiatry* 2008;9(4):248-312. doi: 10.1080/15622970802465807.
223. Bandelow B, Michaelis S, Wedekind D. Treatment of anxiety disorders. *Dialogues Clin Neurosci* 2017;19(2):93-107. doi: 10.31887/DCNS.2017.19.2/bbandelow.
224. Riemann D, Baglioni C, Bassetti C, et al. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res* 2017;26(6):675-700. doi: 10.1111/jsr.12594.
225. 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. *J Clin Sleep Med* 2017;13(2):307-349. doi: 10.5664/jcsm.6470.
226. Wilt TJ, MacDonald R, Brasue M, et al. Pharmacologic treatment of insomnia disorder: an evidence report for a clinical practice guideline by the American College of Physicians. *Ann Intern Med* 2016;165(2):103-112. doi: 10.7326/M15-1781.
227. Srivastava M, Walsh D. Diazepam as an adjuvant analgesic to morphine for pain due to skeletal muscle spasm. *Support Care Cancer* 2003;11(1):66-69. doi: 10.1007/s00520-002-0386-8.
228. Kaufman E, Dworkin SF, LeResche L, et al. Analgesic Action of Intravenous Diazepam. *Anesthesia Progress* 1984;31(2):70-73. PMID: 6597686.
229. Majidi A, Dinpanah H, Ashoori S, et al. Comparison of morphine-midazolam versus morphine injection for pain relief in patients with limb fractures-a clinical trial. *Ulus Travma Acil Cerrahi Derg* 2015;21(1):22-26. doi: 10.5505/tjtes.2015.64494.
230. Chen X, Mou X, He Z, et al. The effect of midazolam on pain control after knee arthroscopy: a systematic review and meta-analysis. *J Orthop Surg Res* 2017;12(1):179-184. doi: 10.1186/s13018-017-0682-0.
231. Kim MH, Lee YM. Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy. *Br J Anaesth* 2001;86(1):77-79. doi: 10.1093/bja/86.1.77.
232. Delwaide PJ, Pennisi G. Tizanidine and electrophysiologic analysis of spinal control mechanisms in humans with spasticity. *Neurology* 1994;44:21-27. PMID: 7970007.
233. Hutchinson DR, Daniels F. A multinational study in general practice to evaluate the effectiveness and tolerability of tizanidine in the treatment of painful muscle spasms. *Br J Clin Res* 1990;1:39-48.
234. Malanga GA, Gwynn MW, Smith R, et al. Tizanidine is effective in the treatment of myofascial pain syndrome. *Pain Physician* 2002;5(4):422-432. PMID: 16886022.
235. Dressler D, Adib Saberi F. Botulinum toxin: mechanisms of action. *Eur Neurol* 2005;53(1):3-9. doi: 10.1159/000083259.
236. Matak I, Bölcsei K, Bach-Rojecky L, et al. Mechanisms of botulinum toxin type a action on pain. *Toxins* 2019;11(8):459. doi: 10.3390/toxins11080459.
237. Della Cuna GR, Pellegrini A, Piazz M. Effect of methylprednisolone sodium succinate on quality of life in preterminal cancer patients: a placebo-controlled, multicenter study. The Methylprednisolone Pre-terminal Cancer Study Group. *Eur J Cancer Clin Oncol* 1989;25(12):1817-1821. doi: 10.1016/0277-5379(89)90353-2.
238. Tannock I, Gospodarowicz M, Meakin W, et al. Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. *J Clin Oncol* 1989;7(5):590-597. doi: 10.1200/JCO.1989.7.5.590.
239. Mercadante SL, Berchovich M, Casuccio A, et al. A prospective randomized study of corticosteroids as adjuvant drugs to opioids in advanced cancer patients. *Am J Hosp Palliat Care* 2007;24(1):13-19. doi: 10.1177/1049909106295431.
240. Popiela T, Lucchi R, Giongo F. Methylprednisolone as palliative therapy for female terminal cancer patients. *The Methylprednisolone Female Preterminal Cancer*

- Study Group. Eur J Cancer Clin Oncol 1989;25(12):1823-1829. doi: 10.1016/0277-5379(89)90354-4.
241. Bruera E, Roca E, Cedarso L, et al. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. Cancer Treat Rep 1985;69(7-8):751-754. PMID: 2410117.
 242. Bruera E, Moyano JR, Sala R, et al. Dexamethasone in addition to metoclopramide for chronic nausea in patients with advanced cancer: a randomized controlled trial. J Pain Symptom Manage 2004;8(4):381-388. doi: 10.1016/j.jpainsympman.2004.01.009.
 243. Paulsen O, Klepstad P, Rosland JH, et al. Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial. J Clin Oncol 2014;32(29):3221-3228. doi: 10.1200/JCO.2013.54.3926.
 244. Yennurajalingam S, Frisbee-Hume S, Palmer JL, et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. J Clin Oncol 2013;31(25):3076-3082. doi: 10.1200/JCO.2012.44.4661.
 245. Haywood A, Good P, Khan S, et al. Corticosteroids for the management of cancer-related pain in adults. Cochrane Database Syst Rev 2015;24(4):1-44. doi: 10.1002/14651858.CD010756.pub2.
 246. George R, Jeba J, Ramkumar G, et al. Interventions for the treatment of metastatic extradural spinal cord compression in adults. Cochrane Database Syst Rev 2015;9:1-65. doi: 10.1002/14651858.CD006716.pub3.
 247. Lawton AJ, Lee KA, Cheville AL, et al. Assessment and Management of Patients With Metastatic Spinal Cord Compression: A Multidisciplinary Review. J Clin Oncol 2019;37(1):61-71. doi: 10.1200/JCO.2018.78.1211.
 248. Carstens JH Jr, Feinblatt JD. Future horizons for calcitonin: a U.S. perspective. Calcif Tissue Int 1991;49 Suppl 2:2-6. doi: 10.1007/BF02561368.
 249. Eastell R. Treatment of postmenopausal osteoporosis. N Engl J Med 1998;338(11):736-746. doi: 10.1056/NEJM199803123381107.
 250. Downs RW Jr, Bell NH, Ettinger MP, et al. Comparison of alendronate and intranasal calcitonin for treatment of osteoporosis in postmenopausal women. J Clin Endocrinol Metab 2000;85(5):1783-1788. doi: 10.1210/jcem.85.5.6606.
 251. Lufkin EG, Wahner HW, O'Fallon WM, et al. Treatment of postmenopausal osteoporosis with transdermal estrogen. Ann Intern Med 1992;117(1):1-9. doi: 10.7326/0003-4819-117-1-1.
 252. Overgaard K, Agnusdei D, Hansen MA, et al. Dose-response bioactivity and bioavailability of salmon calcitonin in premenopausal and postmenopausal women. J Clin Endocrinol Metab 1991;172(2):344-349. doi: 10.1210/jcem-72-2-344.
 253. Knopp-Sihota JA, Newburn-Cook CV, Homik J, et al. Calcitonin for treating acute and chronic pain of recent and remote osteoporotic vertebral compression fractures: a systematic review and meta-analysis. Osteoporos Int 2012;23(1):17-38. doi: 10.1007/s00198-011-1676-0.
 254. O'Carrigan B, Wong MH, Willson ML, et al. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev 2017;10(10):1-170. doi: 10.1002/14651858.CD003474.pub4.
 255. Hoskin P, Sundar S, Reczko K, et al. A Multicenter Randomized Trial of Ibandronate Compared With Single-Dose Radiotherapy for Localized Metastatic Bone Pain in Prostate Cancer. J Natl Cancer Inst 2015; 107(10):1-9. doi: 10.1093/jnci/djv197.
 256. Hendriks LE, Hermans BC, van den Beuken-van Everdingen MH, et al. Effect of Bisphosphonates, Denosumab, and Radioisotopes on Bone Pain and Quality of Life in Patients with Non-Small Cell Lung Cancer and Bone Metastases: A Systematic Review. J Thorac Oncol 2016;11(2):155-173. doi: 10.1016/j.jtho.2015.10.001.
 257. Cleeland CS, Body JJ, Stopeck A, et al. Pain outcomes in patients with advanced breast cancer and bone metastases: results from a randomized, double-blind study of denosumab and zoledronic acid. Cancer 2013;119(4):832-838. doi: 10.1002/cncr.27789.
 258. Martin M, Bell R, Bourgeois H, et al. Bone-related complications and quality of life in advanced breast cancer: results from a randomized phase III trial of denosumab versus zoledronic acid. Clin Cancer Res 2012;18(17):4841-4849. doi: 10.1158/1078-0432.CCR-11-3310.
 259. Patrick DL, Cleeland CS, von Moos R, et al. Pain outcomes in patients with bone metastases from advanced cancer: assessment and management with bone-targeting agents. Support Care Cancer 2015;23(4):1157-1168. doi: 10.1007/s00520-014-2525-4.
 260. Dinçel S, Sabuncuoğlu S. Osteoporoz tedavisinde kullanılan bifosfonat grubu ilaçlar ve toksisiteleri. Literatür Eczacılık Bilimleri Dergisi 2018;7(1):35-48. doi: 10.5336/pharmsci.2017-56697.
 261. Fairney A, Kyd P, Thomas E, et al. The use of cyclical etidronate in osteoporosis: changes after completion of 3 years treatment. Br J Rheumatol 1998;37(1):51-56. doi: 10.1093/rheumatology/37.1.51.
 262. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 2014;25(10):2359-2381. doi: 10.1007/s00198-014-2794-2.
 263. Black DM, Rosen CJ. Postmenopausal osteoporosis. N Engl J Med 2016;374(3):2096-2097. doi: 10.1056/NEJM-Mc1602599.
 264. Skrabek RQ, Galimova L, Ethans K, et al. Nabipalone for the treatment of pain in fibromyalgia. J Pain 2008;9(2):164-173. doi: 10.1016/j.jpain.2007.09.002.
 265. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ 2004;329(7460):1-8. doi: 10.1136/bmj.38149.566979.AE.
 266. Rog DJ, Nurmikko TJ, Friede T, et al. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 2005;65(6):812-819. doi:10.1212/01.wnl.0000176753.45410.8b.
 267. Johnson JR, Burnell-Nugent M, Lossignol D, et al. Multicenter, double-blind, randomized, placebo-cont-

- rolled, parallel-group study of the efficacy, safety, and tolerability of THC: CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage* 2010;39(2):167-179. doi: 10.1016/j.jpainsymman.2009.06.008.
268. Karst M, Salim K, Burstein S, et al. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. *JAMA* 2003;290(13):1757-1762. doi: 10.1001/jama.290.13.1757.
269. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain* 2008;9(6):506-521. doi: 10.1016/j.jpain.2007.12.010.
270. Wilsey B, Marcotte T, Deutsch R, et al. Low-dose vaporized cannabis significantly improves neuropathic pain. *J Pain* 2013;14(2):136-148. doi: 10.1016/j.jpain.2012.10.009.
271. Bowles DW, O'Bryant CL, Camidge DR, et al. The intersection between cannabis and cancer in the United States. *Crit Rev Oncol Hematol* 2012;83(1):1-10. doi: 10.1016/j.critrevonc.2011.09.008.
272. Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. *J Pain* 2012;13(5):438-449. doi: 10.1016/j.jpain.2012.01.003.
273. Lichtman AH, Lux EA, McQuade R, et al. Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as an adjunctive therapy in advanced cancer patients with chronic uncontrolled pain. *J Pain Symptom Manage* 2018;55(2):179-188. doi: 10.1016/j.jpainsymman.2017.09.001.
274. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 2015;313(24):2456-2473. doi: 10.1001/jama.2015.6358.
275. Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: A clinical review. *JAMA* 2015;313(24):2474-2483. doi: 10.1001/jama.2015.6199.
276. Andreae MH, Carter GM, Shaparin N, et al. Inhaled cannabis for chronic neuropathic pain: A meta-analysis of individual patient data. *J Pain* 2015;16(12):1221-1232. doi: 10.1016/j.jpain.2015.07.009.
277. Nugent SM, Morasco BJ, O'Neil ME, et al. The effects of cannabis among adults with chronic pain and an overview of general harms: A systematic review. *Ann Intern Med* 2017;167(5):319-331. doi: 10.7326/M17-0155.
278. Wang L, Hong PJ, May C, et al. Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. *BMJ* 2021;8;374:1-15. doi: 10.1136/bmj.n1034.
279. Noori A, Miroshnychenko A, Shergill Y, et al. Opioid-sparing effects of medical cannabis or cannabinoids for chronic pain: a systematic review and meta-analysis of randomised and observational studies. *BMJ Open* 2021;28;11(7):1-11. doi: 10.1136/bmjopen-2020-047717.
280. Busse JW, Vankrunkelsven P, Zeng L, et al. Medical cannabis or cannabinoids for chronic pain: a clinical practice guideline. *BMJ* 2021;8;374:1-10. doi: 10.1136/bmj.n2040.
281. Anderson SP, Zylla DM, McGriff DM, Arneson TJ. Impact of Medical Cannabis on Patient-Reported Symptoms for Patients With Cancer Enrolled in Minnesota's Medical Cannabis Program. *J Oncol Pract* 2019;15(4):338-345. doi: 10.1200/JOP.18.00562.
282. Pasha AK, Clements CY, Reynolds CA, et al. Cardiovascular Effects of Medical Marijuana: A Systematic Review. *Am J Med* 2021;134(2):182-193. doi: 10.1016/j.amjmed.2020.09.015.