

DUYGUDURUM DÜZENLEYİCİLERİ

102.

BÖLÜM

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GİRİŞ

Duygudurum düzenleyicileri (DDD)'nin bipolar bozukluğun belirlenmiş dört bölümünden (mani, depresyon, maninin önlenmesi ve depresyonun önlenmesi) hepsini ya da herhangi bir bölümünü tedavi edebilen ilaçlar olduğu öne sürülebilir (1).

Bipolar bozukluğun çocukta ve ergenlerde tedavisiyle ilgili kanıtlar sınırlıdır ve genel olarak sanki küçük yetişkinlermiş gibi erişkin literatüründeki kanıtların adaptasyonu ile tedavi edilirler (2). Tablo 1'de Amerikan Gıda ve İlaç Dairesi (FDA) tarafından çocuklarda ve ergenlerde bipolar bozukluk tedavisinde kullanımı onaylanan ilaçlar verilmiştir.

LİTYUM

Lityum, doğada kolaylıkla ulaşılabilen en hafif metal olup sıklıkla ilaç endüstrisinde LiCO₃ şeklinde bileşikleri kullanılmaktadır. Bipolar bozukluğun

manik epizodunda faydalı olduğu 1949'da Avustralyalı psikiyatrist Cade tarafından kanıtlanmış (4), 1970'lerde bipolar bozukluk tedavisi için yetişkin hastalarda FDA onayı verilmiştir. Lityum, erişkinde, bipolar bozukluğun manik epizodu kadar sürdürüm tedavisinde de yaygın olarak kullanılmaktadır (5). Depresif epizotlarda etkinliğinin daha az olduğu öne sürülmekle birlikte, unipolar depresyonda antidepresanlar için güçlendirme tedavisi olarak da tercih edilmektedir (1) ve intihar riskini azalttığı düşünülmektedir. Ancak bu kullanımları için resmen onaylanmamıştır. Lityumun ayrıca nörodejeneratif değişimleri hafiflettiği ve demansa karşı önleyici olabileceği düşünülmektedir (4).

Çocuk ve ergen bipolar hastalarda, akut mani ve sürdürüm tedavisinde tek FDA onayı bulunan DDD'dir. Bipolar bozukluğu olan çocuklarla ve ergenlerle yapılan çalışmalarda, psikotik özellikler yoksa veya madde kullanımı eşlik ediyorsa Lit-

Tablo 1. Çocukta ve Ergende Bipolar Bozukluk Tedavisinde FDA Onayı Alan İlaçlar (2 ve 3)

İlaç	Bipolar Bozukluğun epizodu	Yaş	Günlük doz mg/gün
Lityum	Karma/manik/sürdürüm	12-17	900-1200
Risperidon	Karma/manik	10-17	0.5-6
Olanzapin	Karma/manik	13-17	5-20
Aripiprazol	Karma/manik	10-17	10-30
Asenapin	Karma/manik	10-17	5-10
Ketiapin	Karma/manik	10-17	400-600
Olanzapin/fluoksetin kombinasyonu	Depresif epizod	10-17	3/25-12/50
Lurasidon	Depresif epizod	10-17	20-80

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yarlı sodyum kanal blokeri olan riluzol ile bipolar depresyon, tedaviye dirençli unipolar depresyon ve anksiyete tedavisinde umut verici sonuçlar bildirilmiştir ancak yüksek maliyeti ve sık görülen hepatotoksik yan etkileri kullanımını sınırlamaktadır (1).

Antihipertansif ve antiaritmik olarak işlev gören kalsiyum kanal blokerleri vasküler düz kaslar üzerindeki L tipi kanallar üzerine etki gösterirken, nöronlar üzerine yerleşik L tipi kanalların işlevi tartışmalıdır. Bir L tipi kalsiyum kanal blokeri olan dihidropiridin ile ilgili bipolar bozuklukta faydalı olduğuna dair anektodal kanıtlar sunulmuştur (1).

Bunun dışında kolinerjik sistem (fizostigmin, donepezil, skopolamin), melatonerjik sistem (ramelton, agomelatin), glukokortikoid sistem (mifepriston, ketokonazol, metirapon), immünolojik ve inflamatuvar sistem (selekoksisib), pürinerjik sistem (allopurinol) yeni ilaç arayışları için uygun hedefler olabilirler (59).

İnozitol ve L-metilfolat (MTHF)

Bipolar bozukluk ve tedaviye dirençli bipolar depresyonda atipik antipsikotik veya DDD'ye eklenerek güçlendirilmesi önerilebilir (1).

KAYNAKÇA

1. Stahl S. (2015) Stahl'ın Temel Psikofarmakolojisi. (Tunç ALKIN, Çev.Ed.). İstanbul. İstanbul Tıp Kitabevi
2. Stepanova E, Findling RL. Psychopharmacology of Bipolar Disorders in Children and Adolescents. *Pediatr Clin N Am.* 2017; 64:1209-1222
3. Ruegg H, Adler C, Duran L.R.P. *Curr Treat Options Psych.* 2019; 6: 75. doi:10.1007/s40501-018-0162-0
4. Grant B, Salpekar JA, Using Lithium in Children and Adolescents with Bipolar Disorder: Efficacy, tolerability, and practical Considerations. *J.A. Pediatr Drugs.* 2018; 20:303. doi:10.1007/s40272-018-0289-x
5. Katzung B.G. (2018). *Basic & Clinical Pharmacology.* (14th edition).USA: Mc Graw-Hill Education
6. Amerio A, Ossola P, Scagnelli F. Safety and efficacy of lithium in children and adolescents: A systematic review in Bipolar Illness. *European psychiatry.* 2018; 54, 85-97
7. Campbell M, Adams PB, Small AM et al. Lithium in hospitalized aggressive children with conduct disorder: A double-blind and placebo-controlled study. *J Am Acad Child Adolesc Psychiatry.*1995; 34:445-453.
8. Malone RP, Delaney MA, Luebbert JF et al. A double-blind placebo-controlled study of lithium in hospitalized aggressive children and adolescents with conduct disorder. *Arch Gen Psychiatry.*2000; 57:649-654
9. Hedy SA, Swoboda HD. Lithium Toxicity. *StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing;*

2019. Available from <http://www.ncbi.nlm.nih.gov/books/NBK499992/> PubMed PMID: 29763168.
10. Dell'Osso L, Del Grande C, Gesi C et al. A new look at an old drug: neuroprotective effects and therapeutic potentials of lithium salts. *Neuropsychiatr Dis Treat.* 2016;12:1687-1703.
11. Findling RL, Frazier JA, Kafantaris V et al, The Collaborative Lithium Trials (CoLT): specific aims, methods, and implementation. *Child Adolesc Psychiatry Ment Health* 2008;2(1):21
12. Gitlin, M, Lithium side effects and toxicity: prevalence and management strategies. *Int J Bipolar Disord.* 2016; 4, 27
13. Elbe D, Black TR, McGrane IR, Procyshyn RM. *Clinical Handbook of Psychotropic Drugs for Children and Adolescents.*(2019) (4th edition).Canada: Hogrefe publishing.
14. Aiff H, Attman P, Aurell M et al, Effects of 10-30 years of lithium treatment on kidney function. *J Psychopharmacol.* 2015;29(5):608-14.
15. Bosquet S, Desscombes E, Gauthier T et al, Nephrotic syndrome during lithium therapy. *Nephrol Dial Transplant.* 1997;12:2728-31
16. Alexander MP, Farag YM, Mittal BV et al, Lithium toxicity: A double-edged sword. *Kidney Int.* 2008;73:233-7.
17. Schreiner A, Waldherr R, Rohmeiss P, Focal segmental glomerulosclerosis and lithium treatment. *Am J Psychiatry.* 2000; 157 (5),834.
18. Petersen CE, Amaral S, Frosch E. Lithium-induced nephrotic syndrome in a prepubertal boy. *J Child Adolesc Psychopharmacol.* 2008;18:210-3
19. Kala GK, Mogri M, Weber-Shrikant E. Lithium-induced membranous glomerulonephropathy in a pediatric patient. *Pediatr Nephrol.* 2009;24:2267-9.
20. Hayes JF, Marston L, Walters K et al. Adverse renal, endocrine, hepatic and metabolic events during maintenance mood stabilizer treatment for bipolar disorder: a population-based cohort study. *PLoS ONE.* 2016. Doi:10.1371/journal.pmed.1002058
21. Consoli A, Deniau E, Huynh C et al, Treatments of child and adolescent bipolar disorders. *Eur. Child Adolesc Psychiatry.* 2007; 16:187-198
22. KR Munshi, A Thampy, The syndrome of irreversible lithium-effectuated neurotoxicity. *Clinical Neuropharmacology.* 2005; 28 (1),38-49
23. Kallner G, Petterson U, Renal, thyroid and parathyroid function during lithium treatment: laboratory tests in 207 people treated for 1-30 years. *Acta Psychiatr Scand.* 1995; 91:48-51
24. Kusalic M, Engelsmann F, Effect of lithium maintenance therapy on thyroid and parathyroid function. *J Psychiatry Neurosci.* 1999; 24:227-233
25. Bretaudeau Deguigne M, Hamel JF, Boels D. Early digestive tract decontamination in acute-on-chronic lithium poisoning does not call conventional therapy into question. *Clinical Toxicology.*2013; 51(8):809
26. Findling RL, Kafantaris V, Pavuluri M et al. Post-acute effectiveness of lithium in pediatric bipolar I disorder. *J Child Adolesc Psychopharmacol.* 2013;23(2):80-90.
27. Yacobi S, Ornoy A. Is lithium a real teratogen? What can we conclude from the prospective versus retros-

- pective studies? A review. *Isr J Psychiatry Relat Sci.* 2008;45(2):95-106
28. Nagamine M, Yoshino A, Ishii M et al. Lithium induced Hashimoto's encephalopathy: a case report. *Bipolar Disord* 2008; 10:846848. 37
 29. Kesebir S, Akdeniz F, Vahip S. Lityum zehirlenmesi. *Turk Psikiyatri Derg* 2001; 12:315-319
 30. Yang Y, Guo Y, Aiguo Z. Neuroleptic malignant syndrome in a patient treated with Lithium carbonate and haloperidol. *Shanghai Archives of Psychiatry.*2014;26(6):368-370
 31. Hsu CW, Lee Y, Lee CY et al. Neurotoxicity and nephrotoxicity caused by combined use of lithium and risperidone: a case report and literature review. *BMC Pharmacology and toxicology* 2016;17:59
 32. Gajwani P, Kemp DE, Muzina DJ et al. Acute treatment of mania: an update on new medications. *Curr Psychiatry Rep.* 2006 Dec;8(6):504-9
 33. Davico C, Canavese C, Vittarini R. Anticonvulsants for psychiatric Disorders in children and adolescents: a systematic rev of their efficacy. *Front Psychiatry.* 2018; 9:270
 34. Findling RL, Youngstrom EA, Young AS. Progress in diagnosis and treatment of bipolar disorder among children and adolescents: an international perspective. *Evidence-based mental health* 2018; 21(4):177-81
 35. Methaneethorn J. A Systematic Review of Population Pharmacokinetics of Valproic Acid. *Br J Clin Pharmacol.* 2018; 84(5), 816-834
 36. Ayano,G. Bipolar Disorders and Valproate: Pharmacokinetics, Pharmacodynamics, Therapeutic Effects and Indications of Valproate: Review of Articles. *Bipolar Disord.* 2016; 2:109.
 37. Tomson T, Battino D, Perucca E. Valproic acid after five decades of use in epilepsy: time to reconsider the indications of a time-honoured drug. *Lancet Neurol.* 2016;15(2):210-218
 38. Hellings JA, Weckbaugh M, Nickel et al. A double-blind, placebo-controlled study of valproate for aggression in youth with pervasive developmental disorders. *J Child Adolesc Psychopharmacol.* 2005;15:682-92. doi: 10.1089/cap.2005.15.682
 39. Canitano R. Mood Stabilizers in children and adolescents with Autism Spectrum Disorders. *Clin Neuropsychopharmacol.* 2015; 38:177-18
 40. Hollander E, Chaplin W, Soorya L et al. Divalproex sodium vs placebo for the treatment of irritability in children and adolescents with autism spectrum disorders. *Neuropsychopharmacology.*2010; 35:990-98
 41. Blader JC, Schooler NR, Jensen PS et al. Adjunctive divalproex versus placebo for children with ADHD and aggression refractory to stimulant monotherapy. *Am J Psychiatry.*2009;166:1392-1401
 42. Taylor D, Barnes TRE, Young AH (2018). *The Maudsley Prescribing Guidelines in psychiatry.* (13th edition) UK: Wiley Blackwell
 43. Brodie MJ. Tolerability and Safety of Commonly Used Antiepileptic Drugs in Adolescents and Adults: A Clinician's Overview. *CNS Drugs* 2017; DOI 10.1007/s40263-016-0406-8
 44. Mikkonen K, Vainionpaa LK, Pakarinen AJ. Long term reproductive endocrine health in young woman with epilepsy during puberty. *Neurology.*2004; 62:445-450
 45. Nelson-DeGrave VL, Wickenheisser JK, Cockrell JE. Valproate potentiates androgen biosynthesis in human ovarian theca cells. *Endocrinology .* 2004; 145:799-808
 46. Zhao S, Xiaoyin W, Wang Y et al. Effects of Valproate on reproductive endocrine function in male patients with epilepsy: A systematic review and meta-analysis. *Epilepsy & Behavior* 2018;85:120-128
 47. Rashid M, Kashyap A, Undela K. Valproic acid and Stevens-Johnson syndrome: a systematic review of descriptive studies. *International Journal of Dermatology.*2019;58(9):1014-1022
 48. Joshi NH, Deshpande AN, Deshpande NC, Rathore AS. Comparative evaluation of oral hygiene status and gingival enlargement among epileptic and healthy children as related to various antiepileptic drugs. *J Indian Soc Periodontol.*2017;21(2):125-129. doi:10.4103/jisp.jisp_48_17
 49. *Bipolar disorder:assessment and management.* NICE Clinical Guidelines, No.185. Copyright@NICE2019.
 50. Axelson D. Pediatric bipolar disorder: Overview of choosing treatment.2019;www.uptodate.com.
 51. Whalen K (2019) *Lippincott Illustrated Reviews: Pharmacology* (7.th edition). Philadelphia: WaltersvKluwer
 52. Stahl S. M. (2017). *Stahl's Essential Psychopharmacology prescriber's guide* (6th edition). UK: Cambridge University press.
 53. Zaccara G, Franciotta D, Perucca E. Idiosyncratic Adverse Reactions to Antiepileptic Drugs. *Epilepsia.* 2007;48(7):1223-1244
 54. Wilding JP. Combination therapy for obesity. *Journal of Psychopharmacology.*2017;31(11):1503-1508
 55. Vitiello B, Riddle MA, Yenokyan G et al. Treatment moderators and a predictors of outcome in Treatment of Early Age Mania (TEAM) study. *J Am Acad Child Adolesc Psychiatry* 2012;51(9):867-78
 56. Geller B, Luby JL, Joshi P et al. A randomized controlled trial of risperidone, lithium, or divalproex sodium for initial treatment of bipolar I disorder, manic or mixed phase, in children and adolescents. *Arch Gen Psychiatry* 2012;69(5):515-28
 57. Papolos DF, Teicher MH, Faedda GL. Clinical experience using intranasal ketamin in the treatment of pediatric bipolar disorder/fear of harm phenotype. *J Affect Disord* 2013;147:431
 58. Konstantakopoulos G. Challenges with bipolar disorder drug discovery.. *Expert Opinion on Drug Discovery.*2016; 11(5):425-428
 59. Fornaro M, Kardash L, Novella S et al. Progress in bipolar disorder drug design toward the development of novel therapeutic targets:a clinician's perspective. *Expert opinion on drug discovery.*2018;13(3):221-22