

# OTİZM SPEKTRUM BOZUKLUKLARINDA UYGULANAN TEDAVİLER VE ETKİNLİKLERİ

## 106. BÖLÜM

Mehmet Akif CANSIZ<sup>1</sup>

### OTİZM SPEKTRUM BOZUKLUKLARINDA TEDAVİNİN TARİHSEL SÜRECİ

Otizm ifadesinin Eugen Bleuer tarafından şizofreninin semptomlarının tanımlanmasında kullanılmıştır birlikte otistik semptomlara yönelik tedavi arayışları da başlamıştır. 1920'lerde otizmde diyet kısıtlamaları ile tedavi başlanmıştır (1). 1950'lerde Bruno Bettelheim "buzdolabı anne" teorisi ile parentektomi uygulaması denenmiştir (2). 1960'larda otizm çalışmalarının hız kazanmasıyla daha işlevsel tedaviler gelişmeye başlamıştır. Edimsel Ayırık Denemelerle Öğretim Paradigması aracılığı ile otizmli çocukların beceri kazanabileceği görüşleri ortaya çıkmıştır. 1970'lerin sonlarına doğru farmakoterapi ön planda iken 1987'de Ivar Lovass otizmde yoğun davranışsal tedavileri üzerinde çalışmalarını sunmuştur (3). 1997 yılında otizmli çocuklar için özelleştirilmiş tedavi programları uygulamaları görülmüştür. Amerika'da 94-142 sayılı kamu kanununun yürürlüğe girmesi, okullara tüm çocuklar için eğitim hizmeti verme yükümlülüğü getirmiştir. Bu kanunla birlikte de OSB olan çocukların eğitimi ve tedavisi ile ilgili hizmet ve araştırmalar artmıştır. Avrupa Birliği ülkelerinde de benzer yıllarda UNESCO ve Birleşmiş Milletler raporları doğrultusunda ortak hareketler artmıştır.

Türkiye'de 1982 Anayasası temel olarak üç madde ile otizmli çocukların eğitimi ve tedavisi ile ilgili dayanak oluşturmaktadır. Md. 42: "...Devlet, durumları sebebiyle özel eğitime ihtiyacı olanları topluma yararlı kılacak tedbirleri alır..."

olarak düzenlenmiş ve bununla ilgili sosyal destek mekanizması işletilmiştir. Md. 50: "...bedeni ve ruhi yetersizliği olanlar çalışma şartları bakımından özel olarak korunurlar..." otizmli bireylerin çalışma haklarıyla ilgili kamusal yükümlülükler getirmiştir. Md. 61: "...Devlet, sakatların korunmalarını ve toplum hayatına intibaklarını sağlayıcı tedbirleri alır... Devlet, korunmaya muhtaç çocukların topluma kazandırılması için her türlü tedbiri alır. Bu amaçlarla gerekli teşkilat ve tesisleri kurar veya kurdurur." ile mevcut tedbir yükümlülüğü devlete aittir. 2005 yılında çıkan yasa ile özel eğitim gerektiren hastalıklarda ve durumlarda eğitim alan çocukların özel eğitim kurumlarında aldığı eğitim ve rehabilitasyonların masrafları Millî Eğitim Bakanlığı'na karşılanması kararı alınmıştır. 2016 yılında ise otizmli çocukların bu merkezlerdeki eğitime devlet katkısı 8 saat bireysel eğitim, 4 saat grup eğitimi olarak artırılmıştır. Yine 2016 yılında yayımlanan 3 yıllık eylem planında bakanlık kurum ve kuruluşlarının otizmli çocukların tanı, tedavi, takip, eğitim ve çalışma alanlarıyla ilgili görev ve sorumlulukları açıkça belirtilmiş ve farkındalık çalışmalarının artışı sağlanmıştır. Bu kapsamında Aile ve Sosyal Politikalar Bakanlığı, Çalışma ve Sosyal Güvenlik Bakanlığı (Daha sonra bu iki bakanlık tek bakanlık olarak Aile, Çalışma ve Sosyal Hizmetler Bakanlığı adını almıştır), Sağlık Bakanlığı, Millî Eğitim Bakanlığı ve Yüksek Öğretim Bakanlığı'na görev dağılımı yapılmıştır. Bu görevler, farkındalık çalışmaları ve kurumlar arası iş birliği; erken tanı, tedavi ve müdahale

<sup>1</sup> Öğretim Görevlisi Doktor, Yozgat Bozok Üniversitesi Tıp Fakültesi Çocuk ve Ergen Ruh Sağlığı ve Hastalıkları AD, m.akif.cansiz@bozok.edu.tr ORCID iD: 0000-0003-1102-4676

takviyelerin değerlendirildiği son meta-analizde non-spesifik diyetin herhangi bir yararı olmadığı gösterilmiştir (180). Şelasyon ise etkisiz olmasının yanı sıra bireyin ihtiyacı olan ağır metallerden de yoksun bırakması nedeniyle mortal seyredebilen bir uygulamadır (181). Nörofeedback ise daha çok nörogelişimsel hastalıklarda profesyoneller haricindeki uygulayıcıların sıkılıkla tavsıye ettikleri bir yöntemdir. Ancak diğer nörogelişimsel hastalıklarla da benzer olarak otizmde de herhangi bir fayda saptanmamıştır (182). Lofthouse ve ark. 2012 yılında 13 oral alınabilen ve 6 oral alınmayan tamamlayıcı ve alternatif tedavilerin OSB'de etkinliğiyle ilgili yapılan çalışmaları derlemiş ve “önerilebilir”, “kabul edilebilir” ve “önerilmek” şeklinde bir sınıflandırma oluşturmuşlardır. Buna göre;

**Önerilen tedaviler:** Melatonin (uyku için), Multivitaminler (diyetle az alınıyorsa önerilen günlük dozlarda) ve masaj.

**Kabul edilebilir tedaviler:** Vitamin B6/Magnezyum, Folik Asit, Omega-3, Probiyotikler ve Gastrointestinal ilaçlar (bağırsak problemleri varsa), demir takviyesi (demir eksikliği tespit edilmişse), şelasyon (ağır metal toksisitesi göstergelmişse), L-Karnozin, akupunktur, egzersiz ve müzik terapisidır.

**Önerilmeyen tedaviler:** Yüksek doz Vitamin C, Siproheptadin, Immun Terapiler, Neurofeedback'tır (183).

Daha az girişimsel işleme maruz bırakılmasına, istenmeyen etkilerinin az olması, reklamının daha fazla yapılmıyor olması, uygulayıcıların yanlış yönlendirmesi veya profesyonel desteği ulaşmadaki güçlükler nedeniyle aileler bu tip uygulamalara sıkılıkla başvurmaktadır. Ciddi bir zaman ve ekonomik yükünün olması otizmli çocuğa sahip ailelerin umutlarının ve mali birikimlerinin istismar edilmesine sebep olmaktadır. Bundan dolayı ailelere kapsamlı bilgi verilmeli, aile, çocuk, okul ve diğer destek sistemleri ile iletişim yolları açık tutulmalı ve alternatif tedavi arayışları anlayışla karşılanıp aileler bilimsel verilerle bilgilendirilmelidirler.

## KAYNAKÇA

1. Dohan FC, Grasberger JC, Lowell FM, Johnston HT Jr., Arbegast AW. Relapsed schizophrenics: more rapid improvement on a milk- and cereal-free diet. *The British journal of psychiatry : the journal of mental science*. 1969;115(522):595-6.
2. Herbert JD, Sharp IR, Gaudiano BA. Separating fact from fiction in the etiology and treatment of autism. A scientific review of the evidence. *The Scientific Review of Mental Health Practice*. 2002;1(1).
3. Lovaas OI, Schreibman L, Koegel RL. A behavior modification approach to the treatment of autistic children. *Journal of autism and childhood schizophrenia*. 1974;4(2):111-29.
4. Otizm Spektrum Bozukluğu Olan Bireylere Yönelik Ulusal Eylem Planı (2016-2019). In: Kurulu YP, editor. Ankara: Resmi Gazete; 2016.
5. TÜSEV. Spektrum Bozukluğu Olan Bireylere Yönelik Ulusal Eylem Planı. Ekseninde Kamu-STK İlişkileri - Vaka Analizi. İstanbul: Türkiye Üçüncü Sektör Vakfı, 2017.
6. Clinical Guideline. Autism: the management and support of children and young people on the autism spectrum. United Kingdom: <http://guidance.nice.org.uk>, 2013.
7. Council NR. Educating children with autism: National Academies Press; 2001.
8. Howlin P. Outcomes in autism spectrum disorders. 2005.
9. Cohen DJ, Volkmar FR. Handbook of autism and pervasive developmental disorders: John Wiley & Sons Inc; 1997.
10. Maglione MA GD, Das L, Timbie J, Kasari C, Technical Expert Panel, Network. HAIRBA-B. Nonmedical interventions for children with ASD: recommended guidelines and further research needs. 2012;2(169-78).
11. French L, Kennedy EM. Annual Research Review: Early intervention for infants and young children with, or at-risk of, autism spectrum disorder: a systematic review. *Journal of Child Psychology and Psychiatry*. 2018;59(4):444-56.
12. Green J, Garg S. Annual Research Review: The state of autism intervention science: progress, target psychological and biological mechanisms and future prospects. *Journal of child psychology and psychiatry, and allied disciplines*. 2018;59(4):424-43.
13. Odom SL, Boyd BA, Hall LJ, Hume KA. Comprehensive treatment models for children and youth with autism spectrum disorders. *Handbook of Autism and Pervasive Developmental Disorders*, Fourth Edition. 2014.
14. Amy S Weitlauf MLM, Brittany Peters, Nila Sathe, Rebekah Travis, Rachel Aiello, Edwin Williamson, Jeremy Veenstra-VanderWeele, Shanthi Krishnaswami, Rebecca Jerome, and Zachary Warren. Therapies for Children With Autism Spectrum Disorder. Rockville: Comparative Effectiveness Review; 2014.
15. Myers SM JC. Management of children with autism spectrum disorders. 2007;120(5):1162-82.
16. Committee on Educational Interventions for Children with Autism. *Educating Children with Autism*. Washington, DC: National Academy Press, 2001.

17. Smith T. Applied behavior analysis and early intensive intervention. *Autism spectrum disorders*. 2011;1037-55.
18. Lovaas OI. Behavioral treatment and normal educational and intellectual functioning in young autistic children. *Journal of consulting and clinical psychology*. 1987;55(1):3-9.
19. Lovaas I. The ME book. Austin, TX: Pro-Ed. 1981.
20. Mukaddes NM. Eğitsel Tedavi Yaklaşımları. Otizm Spektrum Bozuklukları. 2 ed. İstanbul: Nobel Tip Yayınevi; 2017. p. 129-50.
21. Schreibman L. Intensive behavioral/psychoeducational treatments for autism: research needs and future directions. *J Autism Dev Disord*. 2000;30(5):373-8.
22. Cohen H, Amerine-Dickens M, Smith T. Early intensive behavioral treatment: replication of the UCLA model in a community setting. *Journal of developmental and behavioral pediatrics : JDBP*. 2006;27(2 Suppl):S145-55.
23. Magiati I, Charman T, Howlin P. A two-year prospective follow-up study of community-based early intensive behavioural intervention and specialist nursery provision for children with autism spectrum disorders. *Journal of child psychology and psychiatry, and allied disciplines*. 2007;48(8):803-12.
24. Reichow B, Hume K, Barton EE, Boyd BA. Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). *The Cochrane database of systematic reviews*. 2018;5(5):Cd009260.
25. Zwaigenbaum L, Bauman ML, Choueiri R, Kasari C, Carter A, Granpeesheh D, et al. Early Intervention for Children With Autism Spectrum Disorder Under 3 Years of Age: Recommendations for Practice and Research. *Pediatrics*. 2015;136(Supplement 1):S60-S81.
26. Tiede G, Walton KM. Meta-analysis of naturalistic developmental behavioral interventions for young children with autism spectrum disorder. *Autism*. 2019;23(8):2080-95.
27. Smith T, Iadarola S. Evidence Base Update for Autism Spectrum Disorder. *Journal of clinical child and adolescent psychology : the official journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association, Division 53*. 2015;44(6):897-922.
28. Waddington H, van der Meer L, Sigafoos J, Whitehouse A. Examining parent use of specific intervention techniques during a 12-week training program based on the Early Start Denver Model. *Autism*. 0(0):1362361319876495.
29. Zhou B, Xu Q, Li H, Zhang Y, Wang Y, Rogers SJ, et al. Effects of Parent-Implemented Early Start Denver Model Intervention on Chinese Toddlers with Autism Spectrum Disorder: A Non-Randomized Controlled Trial. *Autism research : official journal of the International Society for Autism Research*. 2018;11(4):654-66.
30. Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, et al. Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver Model. *Pediatrics*. 2010;125(1):e17-23.
31. Rogers SJ, Estes A, Lord C, Munson J, Rocha M, Winter J, et al. A Multisite Randomized Controlled Two-Phase Trial of the Early Start Denver Model Compared to Treatment as Usual. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2019;58(9):853-65.
32. Vivanti G, Dissanyake C, Team TVA. Outcome for Children Receiving the Early Start Denver Model Before and After 48 Months. *Journal of Autism and Developmental Disorders*. 2016;46(7):2441-9.
33. Estes A, Munson J, Rogers SJ, Greenson J, Winter J, Dawson G. Long-Term Outcomes of Early Intervention in 6-Year-Old Children With Autism Spectrum Disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2015;54(7):580-7.
34. Charman T. Editorial: Trials and Tribulations in Early Autism Intervention Research. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2019;58(9):846-8.
35. Schopler E. Parents of psychotic children as scapegoats. *Journal of Contemporary Psychotherapy*. 1971;4(1):17-22.
36. Mesibov GB, Shea V, Schopler E. The TEACCH approach to autism spectrum disorders: Springer Science & Business Media; 2005.
37. Virués-Ortega J, Arnold-Saritepe A, Hird C, Phillips K. The TEACCH program for people with autism: Elements, outcomes, and comparison with competing models. *Handbook of treatments for autism spectrum disorder*: Springer; 2017. p. 427-36.
38. Smith IM, Flanagan HE, Garon N, Bryson SE. Effectiveness of community-based early intervention based on pivotal response treatment. *J Autism Dev Disord*. 2015;45(6):1858-72.
39. Hardan AY, Gengoux GW, Berquist KL, Libove RA, Ardel CM, Phillips J, et al. A randomized controlled trial of Pivotal Response Treatment Group for parents of children with autism. *Journal of child psychology and psychiatry, and allied disciplines*. 2015;56(8):884-92.
40. Ventola P, Friedman HE, Anderson LC, Wolf JM, Oosting D, Foss-Feig J, et al. Improvements in social and adaptive functioning following short-duration PRT program: a clinical replication. *J Autism Dev Disord*. 2014;44(11):2862-70.
41. Brock ME, Dueker SA, Barczak MA. Brief Report: Improving Social Outcomes for Students with Autism at Recess Through Peer-Mediated Pivotal Response Training. *J Autism Dev Disord*. 2018;48(6):2224-30.
42. Pierce K, Schreibman L. Multiple peer use of pivotal response training to increase social behaviors of classmates with autism: results from trained and untrained peers. *Journal of applied behavior analysis*. 1997;30(1):157-60.
43. Pierce K, Schreibman L. Increasing complex social behaviors in children with autism: effects of peer-implemented pivotal response training. *Journal of applied behavior analysis*. 1995;28(3):285-95.
44. Fossum KL, Williams L, Garon N, Bryson SE, Smith IM. Pivotal response treatment for preschoolers with autism spectrum disorder: Defining a predictor profile. *Autism research : official journal of the International Society for Autism Research*. 2018;11(1):153-65.
45. Greenspan SI, Wieder S, Simons R. The child with special needs: Encouraging intellectual and emotional growth: Addison-Wesley/Addison Wesley Longman; 1998.
46. Wieder S, Greenspan SI. Climbing the Symbolic Ladder in the DIR Model Through Floor Time/Interactive Play. *Autism*. 2003;7(4):425-35.

47. Pajareya K, Nopmaneejumruslers K. A one-year prospective follow-up study of a DIR/Floortime™ parent training intervention for preschool children with autistic spectrum disorders. *Journal of the Medical Association of Thailand*. 2012;95(9):1184.
48. Rentz EA. Autism spectrum disorders: Developmental, individual-difference, relationship-based (DIR)/Floortime outcomes: Fordham University; 2015.
49. Bondy AS, Frost LA. The picture exchange communication system. *Seminars in speech and language*. 1998;19(4):373-88; quiz 89; 424.
50. Bondy A, Frost L. The Picture Exchange Communication System. *Behavior modification*. 2001;25(5):725-44.
51. Laugeson EA, Ellingsen R. Social skills training for adolescents and adults with autism spectrum disorder. *Adolescents and adults with autism spectrum disorders*: Springer; 2014. p. 61-85.
52. Kohler FW, Strain PS, Goldstein H. Learning Experiences... An Alternative Program for preschoolers and parents: Peer-mediated interventions for young children with autism. Hibbs & PS Jensen (Eds), *Psychosocial treatments for child and adolescent disorders: Empirically based strategies for clinical practice*. 2005:659-87.
53. Kaiser AP, Yoder PJ, Keetz A. Evaluating milieu teaching. 1992.
54. Case-Smith J, Arbesman M. Evidence-based review of interventions for autism used in or of relevance to occupational therapy. *The American journal of occupational therapy : official publication of the American Occupational Therapy Association*. 2008;62(4):416-29.
55. Case-Smith J, Weaver LL, Fristad MA. A systematic review of sensory processing interventions for children with autism spectrum disorders. *Autism*. 2015;19(2):133-48.
56. Zimmer M, Desch L. Sensory integration therapies for children with developmental and behavioral disorders. *Pediatrics*. 2012;129(6):1186-9.
57. Weitlauf AS, Sathe N, McPheeters ML, Warren ZE. Interventions Targeting Sensory Challenges in Autism Spectrum Disorder: A Systematic Review. *Pediatrics*. 2017;139(6).
58. Konstantareas MM, Lunsky YJ. Sociosexual knowledge, experience, attitudes, and interests of individuals with autistic disorder and developmental delay. *J Autism Dev Disord*. 1997;27(4):397-413.
59. TUFAN AE. Otizm Bozukluğunda İlaç Tedavisi. In: Se-merci B, editor. *Çocuk ve Ergen Psikofarmakolojisi*. 1 ed. İstanbul: Pedam Yayınları; 2015. p. 87-100.
60. Scahill L, McDougle CJ, Aman MG, Johnson C, Handen B, Bearss K, et al. Effects of risperidone and parent training on adaptive functioning in children with pervasive developmental disorders and serious behavioral problems. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2012;51(2):136-46.
61. Weissman L, Bridgemohan C, Patterson MC. Autism spectrum disorder in children and adolescents: Pharmacologic interventions. UpToDate Version. 2014;27.
62. Towbin KE. Strategies for pharmacologic treatment of high functioning autism and Asperger syndrome. *Child and adolescent psychiatric clinics of North America*. 2003;12(1):23-45.
63. McDougle CJ, Scahill L, Aman MG, McCracken JT, Tierney E, Davies M, et al. Risperidone for the core symptom domains of autism: results from the study by the autism network of the research units on pediatric psychopharmacology. *American Journal of Psychiatry*. 2005;162(6):1142-8.
64. Owen R, Sikich L, Marcus RN, Corey-Lisle P, Manos G, McQuade RD, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*. 2009;124(6):1533-40.
65. (aripiprazole). A. Abilify (aripiprazole). US Food & Drug Administration (FDA) approved product information. . In: Medicine UNLo, editor. 2014.
66. Rasmussen L, Bilenberg N, Thomsen Ernst M, Abitz Boysen S, Pottegård A. Use of Psychotropic Drugs among Children and Adolescents with Autism Spectrum Disorders in Denmark: A Nationwide Drug Utilization Study. *Journal of clinical medicine*. 2018;7(10).
67. Rossignol DA. Novel and emerging treatments for autism spectrum disorders: a systematic review. *Ann Clin Psychiatry*. 2009;21(4):213-36.
68. Park SY, Cervesi C, Galling B, Molteni S, Walyzada F, Ameis SH, et al. Antipsychotic Use Trends in Youth With Autism Spectrum Disorder and/or Intellectual Disability: A Meta-Analysis. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2016;55(6):456-68. e4.
69. Malone RP, Cater J, Sheikh RM, Choudhury MS, Delaney MA. Olanzapine Versus Haloperidol in Children With Autistic Disorder: An Open Pilot Study. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2001;40(8):887-94.
70. Miral S, Gencer O, Inal-Emiroglu FN, Baykara B, Baykara A, Dirik E. Risperidone versus haloperidol in children and adolescents with AD. *European child & adolescent psychiatry*. 2008;17(1):1-8.
71. Alfredsson G, Harnryd C, Wiesel FA. Effects of sulpiride and chlorpromazine on autistic and positive psychotic symptoms in schizophrenic patients--relationship to drug concentrations. *Psychopharmacology*. 1985;85(1):8-13.
72. Crespi BJ. Comparative psychopharmacology of autism and psychotic-affective disorders suggests new targets for treatment. *Evolution, medicine, and public health*. 2019;2019(1):149-68.
73. Owen R, Sikich L, Marcus RN, Corey-Lisle P, Manos G, McQuade RD, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*. 2009;124(6):1533-40.
74. Marcus RN, Owen R, Kamen L, Manos G, McQuade RD, Carson WH, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2009;48(11):1110-9.
75. Findling RL, Mankoski R, Timko K, Lears K, McCartney T, McQuade RD, et al. A randomized controlled trial investigating the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder. *The Journal of clinical psychiatry*. 2014;75(1):22-30.

76. Hirsch LE, Pringsheim T. Aripiprazole for autism spectrum disorders (ASD). The Cochrane database of systematic reviews. 2016(6):Cd009043.
77. McCracken JT, McGough J, Shah B, Cronin P, Hong D, Aman MG, et al. Risperidone in children with autism and serious behavioral problems. *The New England journal of medicine*. 2002;347(5):314-21.
78. Levine SZ, Kodesh A, Goldberg Y, Reichenberg A, Furukawa TA, Kolevzon A, et al. Initial severity and efficacy of risperidone in autism: Results from the RUPP trial. *European psychiatry : the journal of the Association of European Psychiatrists*. 2016;32:16-20.
79. McDougle CJ, Scahill L, Aman MG, McCracken JT, Tierney E, Davies M, et al. Risperidone for the core symptom domains of autism: results from the study by the autism network of the research units on pediatric psychopharmacology. *The American journal of psychiatry*. 2005;162(6):1142-8.
80. Shea S, Turgay A, Carroll A, Schulz M, Orlik H, Smith I, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*. 2004;114(5):e634-41.
81. Fung LK, Mahajan R, Nozzolillo A, Bernal P, Krasner A, Jo B, et al. Pharmacologic Treatment of Severe Irritability and Problem Behaviors in Autism: A Systematic Review and Meta-analysis. *Pediatrics*. 2016;137 Suppl 2:S124-35.
82. Nagaraj R, Singh P, Malhi P. Risperidone in children with autism: randomized, placebo-controlled, double-blind study. *Journal of child neurology*. 2006;21(6):450-5.
83. Hollander E, Wasserman S, Swanson EN, Chaplin W, Schapiro ML, Zagursky K, et al. A Double-Blind Placebo-Controlled Pilot Study of Olanzapine in Childhood/Adolescent Pervasive Developmental Disorder. *Journal of Child & Adolescent Psychopharmacology*. 2006;16(5):541-8.
84. Kemner C, Willemse-Swinkels SH, de Jonge M, Tuyman-Qua H, van Engeland H. Open-label study of olanzapine in children with pervasive developmental disorder. *Journal of clinical psychopharmacology*. 2002;22(5):455-60.
85. Zuddas A, Ledda MG, Fratta A, Muglia P, Cianchetti C. Clinical effects of clozapine on autistic disorder. *The American journal of psychiatry*. 1996;153(5):738.
86. Yalcin O, Kaymak G, Erdogan A, Tanidir C, Karacetin G, Kilicoglu AG, et al. A Retrospective Investigation of Clozapine Treatment in Autistic and Nonautistic Children and Adolescents in an Inpatient Clinic in Turkey. *Journal of child and adolescent psychopharmacology*. 2016;26(9):815-21.
87. Rothamel M, Szymoniak F, Pollet C, Beherec L, Quesada P, Leclerc S, et al. Eleven Years of Clozapine Experience in Autism Spectrum Disorder: Efficacy and Tolerance. *J Clin Psychopharmacol*. 2018;38(6):577-81.
88. Wicinski M, Wecliewicz MM. Clozapine-induced agranulocytosis/granulocytopenia: mechanisms and monitoring. *Current opinion in hematology*. 2018;25(1):22-8.
89. Piven J, Tsai GC, Nehme E, Coyle JT, Chase GA, Folstein SE. Platelet serotonin, a possible marker for familial autism. *J Autism Dev Disord*. 1991;21(1):51-9.
90. Cook EH, Jr., Charak DA, Arida J, Spohn JA, Roizen NJ, Leventhal BL. Depressive and obsessive-compulsive symptoms in hyperserotonemic parents of children with autistic disorder. *Psychiatry research*. 1994;52(1):25-33.
91. McDougle CJ, Naylor ST, Cohen DJ, Aghajanian GK, Heninger GR, Price LH. Effects of tryptophan depletion in drug-free adults with autistic disorder. *Archives of general psychiatry*. 1996;53(11):993-1000.
92. Clomipramine in the treatment of patients with obsessive-compulsive disorder. The Clomipramine Collaborative Study Group. *Archives of general psychiatry*. 1991;48(8):730-8.
93. Gordon CT, State RC, Nelson JE, Hamburger SD, Rapoport JL. A double-blind comparison of clomipramine, desipramine, and placebo in the treatment of autistic disorder. *Archives of general psychiatry*. 1993;50(6):441-7.
94. Remington G, Sloman L, Konstantareas M, Parker K, Gow R. Clomipramine versus haloperidol in the treatment of autistic disorder: a double-blind, placebo-controlled, crossover study. *J Clin Psychopharmacol*. 2001;21(4):440-4.
95. Hollander E, Phillips A, Chaplin W, Zagursky K, Novotny S, Wasserman S, et al. A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent autism. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2005;30(3):582-9.
96. Herscu P, Handen BL, Arnold LE, Snape MF, Bregman JD, Ginsberg L, et al. The SOFIA Study: Negative Multi-center Study of Low Dose Fluoxetine on Repetitive Behaviors in Children and Adolescents with Autistic Disorder. *J Autism Dev Disord*. 2019.
97. Reddiough DS, Marraffa C, Mouti A, O'Sullivan M, Lee KJ, Orsini F, et al. Effect of Fluoxetine on Obsessive-Compulsive Behaviors in Children and Adolescents With Autism Spectrum Disorders: A Randomized Clinical Trial. *Jama*. 2019;322(16):1561-9.
98. McDougle CJ, Naylor ST, Cohen DJ, Volkmar FR, Heninger GR, Price LH. A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. *Archives of general psychiatry*. 1996;53(11):1001-8.
99. Martin A, Koenig K, Anderson GM, Scahill L. Low-dose fluvoxamine treatment of children and adolescents with pervasive developmental disorders: a prospective, open-label study. *J Autism Dev Disord*. 2003;33(1):77-85.
100. McDougle CJ, Brodkin ES, Naylor ST, Carlson DC, Cohen DJ, Price LH. Sertraline in adults with pervasive developmental disorders: a prospective open-label investigation. *J Clin Psychopharmacol*. 1998;18(1):62-6.
101. Hellings JA, Kelley LA, Gabrielli WF, Kilgore E, Shah P. Sertraline response in adults with mental retardation and autistic disorder. *The Journal of clinical psychiatry*. 1996;57(8):333-6.
102. Coleman DM, Adams JB, Anderson AL, Frye RE. Rating of the Effectiveness of 26 Psychiatric and Seizure Medications for Autism Spectrum Disorder: Results of a National Survey. *Journal of child and adolescent psychopharmacology*. 2019;29(2):107-23.
103. King BH, Hollander E, Sikich L, McCracken JT, Scahill L, Bregman JD, et al. Lack of efficacy of citalopram in children with autism spectrum disorders and high le-

- vels of repetitive behavior: citalopram ineffective in children with autism. *Archives of general psychiatry*. 2009;66(6):583-90.
104. Namerow L, Thomas P, Bostic JQ, Prince J, Monuteaux MC. Use of citalopram in pervasive developmental disorders. *Journal of developmental and behavioral pediatrics : JDBP*. 2003;24(2):104-8.
  105. Couturier JL, Nicolson R. A retrospective assessment of citalopram in children and adolescents with pervasive developmental disorders. *Journal of child and adolescent psychopharmacology*. 2002;12(3):243-8.
  106. Williams K, Brignell A, Randall M, Silove N, Hazell P. Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). *The Cochrane database of systematic reviews*. 2013(8):Cd004677.
  107. Owley T, Walton L, Salt J, Guter SJ, Jr., Winnega M, Leventhal BL, et al. An open-label trial of escitalopram in pervasive developmental disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2005;44(4):343-8.
  108. de Boer T. The pharmacologic profile of mirtazapine. *The Journal of clinical psychiatry*. 1996;57 Suppl 4:19-25.
  109. Posey DJ, Guenin KD, Kohn AE, Swiezy NB, McDougle CJ. A naturalistic open-label study of mirtazapine in autistic and other pervasive developmental disorders. *Journal of child and adolescent psychopharmacology*. 2001;11(3):267-77.
  110. Coskun M, Karakoc S, Kircelli F, Mukaddes NM. Effectiveness of mirtazapine in the treatment of inappropriate sexual behaviors in individuals with autistic disorder. *Journal of child and adolescent psychopharmacology*. 2009;19(2):203-6.
  111. Nguyen M, Murphy T. Mirtazapine for excessive masturbation in an adolescent with autism. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2001;40(8):868-9.
  112. Coskun M, Mukaddes NM. Mirtazapine treatment in a subject with autistic disorder and fetishism. *Journal of child and adolescent psychopharmacology*. 2008;18(2):206-9.
  113. Naguy A, Alrashidi F, AlShalabi SR. Mirtazapine for inappropriate sexual behaviors in autism. *American journal of therapeutics*. 2019;26(6):e751-e3.
  114. Kelsey JE. Dose-response relationship with venlafaxine. *J Clin Psychopharmacol*. 1996;16(3 Suppl 2):21S-6S; discussion 6S-8S.
  115. Hollander E, Kaplan A, Cartwright C, Reichman D. Venlafaxine in children, adolescents, and young adults with autism spectrum disorders: an open retrospective clinical report. *Journal of child neurology*. 2000;15(2):132-5.
  116. Carminati GG, Gerber F, Darbellay B, Kosel MM, Deriaz N, Chabert J, et al. Using venlafaxine to treat behavioral disorders in patients with autism spectrum disorder. *Progress in neuro-psychopharmacology & biological psychiatry*. 2016;65:85-95.
  117. Marshall BL, Napolitano DA, McAdam DB, Dunleavy IJ, Tessing JL, Varrell J. Venlafaxine and increased aggression in a female with autism. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2003;42(4):383-4.
  118. Carrey N, Baath S. Trazodone for sleep in children. *Child Adolesc Psychopharmacol News*. 1996;1:10-1.
  119. Johnson CR. Sleep problems in children with mental retardation and autism. *Child and adolescent psychiatric clinics of North America*. 1996;5(3):673-84.
  120. Owens JA, Rosen CL, Mindell JA, Kirchner HL. Use of pharmacotherapy for insomnia in child psychiatry practice: A national survey. *Sleep medicine*. 2010;11(7):692-700.
  121. Gedye A. Trazodone reduced aggressive and self-injurious movements in a mentally handicapped male patient with autism. *J Clin Psychopharmacol*. 1991;11(4):275-6.
  122. Kem DL, Posey DJ, McDougle CJ. Priapism associated with trazodone in an adolescent with autism. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2002;41(7):758.
  123. Volkmar F, Siegel M, Woodbury-Smith M, King B, McCracken J, State M. Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2014;53(2):237-57.
  124. Howes OD, Rogdaki M, Findon JL, Wickers RH, Charman T, King BH, et al. Autism spectrum disorder: Consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. *Journal of psychopharmacology* (Oxford, England). 2018;32(1):3-29.
  125. Sturman N, Deckx L, van Driel ML. Methylphenidate for children and adolescents with autism spectrum disorder. *The Cochrane database of systematic reviews*. 2017;11:Cd011144.
  126. Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. *Archives of general psychiatry*. 2005;62(11):1266-74.
  127. Posey DJ, Aman MG, McCracken JT, Scahill L, Tierney E, Arnold LE, et al. Positive effects of methylphenidate on inattention and hyperactivity in pervasive developmental disorders: an analysis of secondary measures. *Biological psychiatry*. 2007;61(4):538-44.
  128. Arnold LE, Aman MG, Cook AM, Witwer AN, Hall KL, Thompson S, et al. Atomoxetine for hyperactivity in autism spectrum disorders: placebo-controlled crossover pilot trial. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2006;45(10):1196-205.
  129. Harfterkamp M, van de Loo-Neus G, Minderaa RB, van der Gaag RJ, Escobar R, Schacht A, et al. A randomized double-blind study of atomoxetine versus placebo for attention-deficit/hyperactivity disorder symptoms in children with autism spectrum disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2012;51(7):733-41.
  130. Kilincaslan A, Mutluer TD, Pasabeyoglu B, Tutkunkardas MD, Mukaddes NM. Effects of Atomoxetine in Individuals with Attention-Deficit/Hyperactivity Disorder and Low-Functioning Autism Spectrum Disorder. *Journal of child and adolescent psychopharmacology*. 2016;26(9):798-806.
  131. Aman MG, Smith T, Arnold LE, Corbett-Dick P, Tumulu R, Hollway JA, et al. A review of atomoxetine effects in young people with developmental disabilities. *Research in developmental disabilities*. 2014;35(6):1412-24.

132. Hirota T, Veenstra-VanderWeele J, Hollander E, Kishi T. Antiepileptic Medications in Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. *Journal of Autism and Developmental Disorders*. 2014;44(4):948-57.
133. Mukaddes NM. İlaç Tedavileri. Otizm Spektrum Bozuklukları. 2 ed. İstanbul: Nobel Tip Yayinevi; 2017. p. 151-77.
134. Gillberg C, Amaral D, Dawson G, Geschwind D. Autism as a medical disorder. David G Amaral. 2011.
135. Hollander E, Soorya L, Wasserman S, Esposito K, Chaplin W, Anagnostou E. Divalproex sodium vs. placebo in the treatment of repetitive behaviours in autism spectrum disorder. *The international journal of neuropsychopharmacology*. 2006;9(2):209-13.
136. Hollander E, Chaplin W, Soorya L, Wasserman S, Novotny S, Rusoff J, et al. Divalproex sodium vs placebo for the treatment of irritability in children and adolescents with autism spectrum disorders. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2010;35(4):990.
137. Hellings JA, Weckbaugh M, Nickel EJ, Cain SE, Zarcone JR, Reese RM, et al. A double-blind, placebo-controlled study of valproate for aggression in youth with pervasive developmental disorders. *Journal of child and adolescent psychopharmacology*. 2005;15(4):682-92.
138. Belsito KM, Law PA, Kirk KS, Landa RJ, Zimmerman AW. Lamotrigine therapy for autistic disorder: a randomized, double-blind, placebo-controlled trial. *J Autism and Developmental Disorders*. 2001;31(2):175-81.
139. Rezaei V, Mohammadi MR, Ghanizadeh A, Sahraiyan A, Tabrizi M, Rezazadeh SA, et al. Double-blind, placebo-controlled trial of risperidone plus topiramate in children with autistic disorder. *Progress in neuro-psychopharmacology & biological psychiatry*. 2010;34(7):1269-72.
140. Hardan AY, Jou RJ, Handen BL. A retrospective assessment of topiramate in children and adolescents with pervasive developmental disorders. *Journal of child and adolescent psychopharmacology*. 2004;14(3):426-32.
141. Wasserman S, Iyengar R, Chaplin WF, Watner D, Waldoks SE, Anagnostou E, et al. Levetiracetam versus placebo in childhood and adolescent autism: a double-blind placebo-controlled study. *International clinical psychopharmacology*. 2006;21(6):363-7.
142. Wang M, Jiang L, Tang X. Levetiracetam is associated with decrease in subclinical epileptiform discharges and improved cognitive functions in pediatric patients with autism spectrum disorder. *Neuropsychiatric disease and treatment*. 2017;13:2321-6.
143. Jaselskis CA, Cook EH, Fletcher KE. Clonidine treatment of hyperactive and impulsive children with autistic disorder. *Journal of clinical psychopharmacology*. 1992.
144. Ming X, Gordon E, Kang N, Wagner GC. Use of clonidine in children with autism spectrum disorders. *Brain and Development*. 2008;30(7):454-60.
145. Handen BL, Sahl R, Hardan AY. Guanfacine in Children with Autism and/or Intellectual Disabilities. *Journal of Developmental & Behavioral Pediatrics*. 2008;29(4):303-8.
146. Lawrence Scahill, M.S.N., Ph.D. „, James T. McCracken, M.D. „, Bryan H. King, M.D. „, Carol Rockhill, M.D. „, Bhavik Shah, M.D. „, Laura Politte, M.D. „, et al. Extended-Release Guanfacine for Hyperactivity in Children With Autism Spectrum Disorder. *American Journal of Psychiatry*. 2015;172(12):1197-206.
147. Kolmen BK, Feldman HM, Handen BL, Janosky JE. Naltrexone in young autistic children: a double-blind, placebo-controlled crossover study. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1995;34(2):223-31.
148. Feldman HM, Kolmen BK, Gonzaga AM. Naltrexone and communication skills in young children with autism. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1999;38(5):587-93.
149. Campbell M, Anderson LT, Small AM, Adams P, Gonzalez NM, Ernst M. Naltrexone in autistic children: behavioral symptoms and attentional learning. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1993;32(6):1283-91.
150. Campbell M, Anderson LT, Small AM, Locascio JJ, Lynch N, Choroco M. Naltrexone in autistic children: a double-blind and placebo-controlled study. *Psychopharmacology bulletin*. 1990.
151. Willemse-Swinkels SH, Buitelaar JK, Nijhof GJ, van Engeland H. Failure of naltrexone hydrochloride to reduce self-injurious and autistic behavior in mentally retarded adults: double-blind placebo-controlled studies. *Archives of general psychiatry*. 1995;52(9):766-73.
152. King BH, Wright DM, Handen BL, Sikich L, Zimmerman AW, McMahon W, et al. Double-Blind, Placebo-Controlled Study of Amantadine Hydrochloride in the Treatment of Children With Autistic Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2001;40(6):658-65.
153. Chez MG, Burton Q, Dowling T, Chang M, Khanna P, Kramer C. Memantine as adjunctive therapy in children diagnosed with autistic spectrum disorders: an observation of initial clinical response and maintenance tolerability. *Journal of child neurology*. 2007;22(5):574-9.
154. Erickson CA, Posey DJ, Stigler KA, Mullett J, Katschke AR, McDougle CJ. A retrospective study of memantine in children and adolescents with pervasive developmental disorders. *Psychopharmacology*. 2007;191(1):141-7.
155. Karahmadi M, Tarrahi MJ, Vatankhah Ardestani SS, Omranifard V, Farzaneh B. Efficacy of Memantine as Adjunct Therapy for Autism Spectrum Disorder in Children Aged <14 Years. *Advanced biomedical research*. 2018;7:131.
156. Hardan AY, Hendren RL, Aman MG, Robb A, Melmed RD, Andersen KA, et al. Efficacy and safety of memantine in children with autism spectrum disorder: Results from three phase 2 multicenter studies. *Autism*. 2019;23(8):2096-111.
157. Kumar H, Sharma B. Memantine ameliorates autistic behavior, biochemistry & blood brain barrier impairments in rats. *Brain research bulletin*. 2016;124:27-39.
158. Gupta S, Rimland B, Shilling PD. Pentoxifylline: brief review and rationale for its possible use in the treatment of autism. *Journal of child neurology*. 1996;11(6):501-4.

159. Akhondzadeh S, Fallah J, Mohammadi MR, Imani R, Mohammadi M, Salehi B, et al. Double-blind placebo-controlled trial of pentoxifylline added to risperidone: effects on aberrant behavior in children with autism. *Progress in neuro-psychopharmacology & biological psychiatry*. 2010;34(1):32-6.
160. Marchezan J, Winkler Dos Santos EGA, Deckmann I, Riesgo RDS. Immunological Dysfunction in Autism Spectrum Disorder: A Potential Target for Therapy. *Neuroimmunomodulation*. 2018;25(5-6):300-19.
161. Andersen IM, Kaczmarska J, McGrew SG, Malow BA. Melatonin for insomnia in children with autism spectrum disorders. *Journal of child neurology*. 2008;23(5):482-5.
162. Paavonen EJ, Nieminen-von Wendt T, Vanhala R, Aronen ET, von Wendt L. Effectiveness of melatonin in the treatment of sleep disturbances in children with Asperger disorder. *Journal of child and adolescent psychopharmacology*. 2003;13(1):83-95.
163. Giannotti F, Cortesi F, Cerquiglini A, Bernabei P. An open-label study of controlled-release melatonin in treatment of sleep disorders in children with autism. *J Autism Dev Disord*. 2006;36(6):741-52.
164. Garstang J, Wallis M. Randomized controlled trial of melatonin for children with autistic spectrum disorders and sleep problems. *Child: care, health and development*. 2006;32(5):585-9.
165. Wright B, Sims D, Smart S, Alwazeer A, Alderson-Day B, Allgar V, et al. Melatonin versus placebo in children with autism spectrum conditions and severe sleep problems not amenable to behaviour management strategies: a randomised controlled crossover trial. *J Autism Dev Disord*. 2011;41(2):175-84.
166. Gringras P, Nir T, Breddy J, Frydman-Marom A, Findling RL. Efficacy and Safety of Pediatric Prolonged-Release Melatonin for Insomnia in Children With Autism Spectrum Disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2017;56(11):948-57-e4.
167. Rossignol DA, Frye RE. Melatonin in autism spectrum disorders: a systematic review and meta-analysis. *Developmental medicine and child neurology*. 2011;53(9):783-92.
168. Guenole F, Godbout R, Nicolas A, Franco P, Claustre B, Baleye JM. Melatonin for disordered sleep in individuals with autism spectrum disorders: systematic review and discussion. *Sleep medicine reviews*. 2011;15(6):379-87.
169. Sturmey P. Secretin is an ineffective treatment for pervasive developmental disabilities: a review of 15 double-blind randomized controlled trials. *Research in developmental disabilities*. 2005;26(1):87-97.
170. Williams K, Wray JA, Wheeler DM. Intravenous secretin for autism spectrum disorders (ASD). The Cochrane database of systematic reviews. 2012(4):Cd003495.
171. McDougle CJ, Landino SM, Vahabzadeh A, O'Rourke J, Zurcher NR, Finger BC, et al. Toward an immune-mediated subtype of autism spectrum disorder. *Brain research*. 2015;1617:72-92.
172. Siniscalco D, Bradstreet JJ, Antonucci N. Therapeutic role of hematopoietic stem cells in autism spectrum disorder-related inflammation. *Frontiers in immunology*. 2013;4:140.
173. Lv YT, Zhang Y, Liu M, Qiuwaxi JN, Ashwood P, Cho SC, et al. Transplantation of human cord blood mononuclear cells and umbilical cord-derived mesenchymal stem cells in autism. *Journal of translational medicine*. 2013;11:196.
174. Bradstreet JJ, Sych N, Antonucci N, Klunnik M, Ivankova O, Matyashchuk I, et al. Efficacy of fetal stem cell transplantation in autism spectrum disorders: an open-labeled pilot study. *Cell transplantation*. 2014;23 Suppl 1:S105-12.
175. Wong HH, Smith RG. Patterns of complementary and alternative medical therapy use in children diagnosed with autism spectrum disorders. *Journal of autism and developmental disorders*. 2006;36(7):901-9.
176. Findling RL, Maxwell K, Scotece-Wojtila L, Huang J, Yamashita T, Wiznitzer M. High-dose pyridoxine and magnesium administration in children with autistic disorder: an absence of salutary effects in a double-blind, placebo-controlled study. *Journal of autism and developmental disorders*. 1997;27(4):467-78.
177. James S, Montgomery P, Williams K. Omega-3 fatty acids supplementation for autism spectrum disorders (ASD). *Cochrane Database of Systematic Reviews*. 2011(11).
178. Handen BL, Melmed RD, Hansen RL, Aman MG, Burnham DL, Bruss JB, et al. A double-blind, placebo-controlled trial of oral human immunoglobulin for gastrointestinal dysfunction in children with autistic disorder. *Journal of autism and developmental disorders*. 2009;39(5):796-805.
179. Millward C, Ferriter M, Calver SJ, Connell-Jones GG. Gluten-and casein-free diets for autistic spectrum disorder. *Cochrane database of systematic reviews*. 2008(2).
180. Fraguas D, Diaz-Caneja CM, Pina-Camacho L, Moreno C, Duran-Cutilla M, Ayora M, et al. Dietary Interventions for Autism Spectrum Disorder: A Meta-analysis. *Pediatrics*. 2019;144(5).
181. Brown MJ, Willis T, Omalu B, Leiker R. Deaths resulting from hypocalcemia after administration of edetate disodium: 2003-2005. *Pediatrics*. 2006;118(2):e534-e6.
182. Zivoder I, Martic-Biocina S, Kosic AV, Bosak J. Neurofeedback application in the treatment of autistic spectrum disorders (ASD). *Psychiatr Danub*. 2015;27:S391-S4.
183. Lofthouse N, Hendren R, Hurt E, Arnold LE, Butter E. A review of complementary and alternative treatments for autism spectrum disorders. *Autism research and treatment*. 2012;2012:870391.