BÖLÜM 32

ÇOCUK NÖROLOJİ HASTALARINDA BİREYSEL TEDAVİLER VE GEN TEDAVİLERİ

Yiğithan GÜZİN [1]
Pınar GENÇPINAR [2]

GİRİŞ

Son yıllarda çocukluk çağı nadir hastalıklarının moleküler tanı ve tedavi olanakları büyük ölçüde artmıştır. Modern genetik ve moleküler tanı yöntemleri ile etkilenen hastaları doğru bir şekilde tanımlamak ve karakterize etmek mümkün olmaktadır. [1]

Pediatrik nöroloji alanında, hassas tıp özellikle genetik ve moleküler teşhislerdeki ilerlemelerle birlikte, nörolojik bozuklukları olan çocuklar için daha hedefe yönelik ve özelleştirilmiş tedavilerin mümkün hale gelmesiyle önem kazanmıştır. Bu yaklaşım, nadir veya karmaşık durumlara sahip hastaların sonuçlarını ve yaşam kalitesini artırmada büyük bir potansiyele sahiptir.[2]

Bu bölümde pediatrik nöroloji pratiğinde hedefe yönelik tedavilerden bahsedilecektir.

EPİLEPSİ

Tuberoskleroz Kompleksi

Tüberoskleroz kompleksi (TSC), cilt, merkezi sinir sistemi, kalp, akciğerler ve böbrek gibi birden çok organı etkileyebilen otozomal dominant kalıtan, multisistemik bir nörokütanöz genetik hastalıktır.[3] *TSC1* veya *TSC2* genlerindeki patojenik varyantlardan kaynaklanır, bu da mTOR yolunun aşırı aktivasyonuna ve birçok organda benign tümöral oluşumlara neden olur.[4] mTOR yolu, protein translasyonunu, hücre döngüsü ilerlemesini ve hipoksiye yanıtı düzenlemek için önemlidir.[5–7] TSC'de epilepsinin yönetimi zor olabilir. TSC ve epilepsi hastalarının yaklaşık yüzde 60'ında dirençli epilepsi görülmektedir. Bu tür hastalar için tedavi seçenekleri arasında ketojenik diyet, vigabatrin, vagus sinir stimülasyonu, epilepsi cerrahisi, everolimus ve kannabidiol bulunur.[8,9]

Everolimus

Everolimus (Afinitor®), mTOR (rapamisinin analoğu) serin/treonin kinaz sinyal iletim yolunun oral bir protein kinaz inhibitörüdür.[10] Everolimus, cerrahi rezeksiyon için aday olmayan TSC ile ilişkili subependimal dev hücreli tümörlerin(-SEGA) tedavisinde ve TSC ile ilişkili nöbetleri olan 2 yaşından büyük hastalarda ek tedavi olarak diğer tedavilere yanıt vermeyen hastalarda sıklıkla kullanılmaktadır.[11]

2011 yılında SEGA'ları ve/veya renal anjiyomiyolipomları olan, komplikasyon riski taşıyan ancak cerrahiye uygun olmayan TSC hastalarının

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telafi edilir. Bu durum SMA'lı hastalarda fenotipik değişkenliğin tamamını olmasa da bir kısmını açıklayan bir mekanizmadır. [144] SMA' da temel tedavi destekleyici tedavidir. Son zamanlarda, SMA umut verici yeni tedaviler geliştirilmiştir. Nusinersen ve risdiplam gibi hastalık modifiye edici tedaviler artık mevcuttur.

Nusinersen

SMN1 ve *SMN2'nin* kodlamasında farklı olan tek bir nükleotit vardır. *SMN2'nin* ürettiği protein miktarı *SMN1'in* ürettiğinden daha az olsa da, bu düşük miktar SMA'nın ciddiyetinin *SMN2'nin* kopya sayısıyla modüle edilmesi için yeterlidir [145,146]

Nusinersen, SMN2'ye yönelik bir antisens oligonükleotittir. [147] *SMN2'yi* değiştirir, ekson 7'nin dahil edilmesi için pre-RNA eklemesini sağlar ve fonksiyonel SMN proteininin ekspresyonunu arttırır. Nusinersen tedavisi 5q –SMA'larda Aralık 2016'da FDA tarafından onaylanmıştır.[148]

Nusinersen, 5 ml(12mg) 'lik çözelti içinde intratekal olarak uygulanır. 0. gün, 14. gün, 28. gün ve 63. gün olmak üzere dört yükleme dozu halinde verilir. Sonraki idame dozları her dört ayda bir uygulanır.[149] En sık görülen yan etkiler lomber ponksiyon ile ilişkili yan etkiler olan baş ağrısı ve sırt ağrısıdır.[149] Tromobositopeni, renal toksisite ve hiponatremi nusinersenin diğer bilinen yan etkileridir.[150]

Risdiplam

Risdiplam (Evrysdi®), SMA tedavisinde kullanılan ilk oral ilaçtır. SMN2 kopya sayısı 2,3,4 olan non-5q SMA hastalarında ≥ 2 ay ve üstü kullanılabilmektedir.[151] SMN2 pre-mRNA uçbirleştirme değiştirici olan risdiplam tam uzunlukta SMN proteini üretimini arttırır. İntratekal tedavi ve gen terapilerinden daha güçlü sistemik etkileri vardır. Geniş sistemik etkileri, non-invaziv oluşu ve 2 aylıktan itibaren kullanılabilmesi en önemli avantajıdır. Yan etki profili ile ilgili çalışmalar halen devam etmektedir.[152]

Zolgensma

Onasemnogene abeparvovec, insan SMN geninin tamamen işlevsel bir kopyasını, hedef motor nöron hücrelerine aktaran adeno-ilişkili virüs vektörü bazlı bir gen terapisidir. Tek intravenöz uygulama sonucunda hastanın motor nöronlarında SMN proteininin ekspresyonu ile sonuçlanır. [153,154]

Onasemnogene abeparvovec'in güvenliği ve etkinliği, 2 hafta ile 8 ay arasında infantil başlangıçlı SMA'lı 36 pediatrik hastayı içeren bir klinik çalışmaya dayanmaktadır. İnfantil başlangıçlı SMA hastalarının doğal seyri ile karşılaştırıldığında, onasemnogene abeparvovec ile tedavi edilen hastaların baş kontrolü ve desteksiz oturma becerisi gibi gelişimsel motor becerilerinde önemli bir iyileşme görülmüştür. [153,154] Onasemnogene abeparvovec genel olarak iyi tolere edilmektedir. Onasemnogene abeparvovec'in en yaygın yan etkileri karaciğer enzimlerinde yükselme ve kusmadır. Hepatotoksisite, genellikle profilaktik prednizolonla hafifletilebilen bilinen bir yan etkidir. Bu nedenle, hastaların karaciğer fonksiyonları onasemnogene abeparvovec uygulamasından sonra en az 3 ay boyunca izlenmelidir. [155]

KAYNAKLAR

1. Ziegler A. [Precision medicine in pediatric neurology exemplified by the new treatment forms]. *Nervenarzt*. 2022;93(2):122-134. doi:10.1007/s00115-021-01251-5
2. Shellhaas RA, deVeber G, Bonkowsky JL. Gene-Targeted Therapies in Pediatric Neurology: Challenges and Opportunities in Diagnosis and Delivery. *Pediatr Neurol*. 2021;125:53-57. doi:10.1016/j.pediatrneurol.2021.09.011
3. Rodrigues DA, Gomes CM, Costa IMC. Tuberous sclerosis complex. *An Bras Dermatol*. 2012;87(2):184-196. doi:10.1590/s0365-05962012000200001
4. Curatolo P, Specchio N, Aronica E. Advances in the genetics and neuropathology of tuberous sclerosis complex: edging closer to targeted therapy. *Lancet Neurol*. 2022;21(9):843-856. doi:10.1016/S1474-4422(22)00213-7
5. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. *Lancet (London, England)*. 2008;372(9639):657-668. doi:10.1016/S0140-6736(08)61279-9
6. Tee AR, Fingar DC, Manning BD, Kwiatkowski DJ,

Cantley LC, Blenis J. Tuberous sclerosis complex-1 and -2 gene products function together to inhibit mammalian target of rapamycin (mTOR)-mediated downstream signaling. *Proc Natl Acad Sci U S A*. 2002;99(21):13571-13576. doi:10.1073/pnas.202476899

7. Child ND, Benarroch EE. mTOR: its role in the nervous system and involvement in neurologic disease. *Neurology*. 2014;83(17):1562-1572. doi:10.1212/WNL.0000000000000922
8. Chu-Shore CJ, Major P, Camposano S, Muzykewicz D, Thiele EA. The natural history of epilepsy in tuberous sclerosis complex. *Epilepsia*. 2010;51(7):1236-1241. doi:10.1111/j.1528-1167.2009.02474.x
9. Jeong A, Nakagawa JA, Wong M. Predictors of Drug-Resistant Epilepsy in Tuberous Sclerosis Complex. *J Child Neurol*. 2017;32(14):1092-1098. doi:10.1177/0883073817737446
10. Houghton PJ. Everolimus. *Clin cancer Res an Off J Am Assoc Cancer Res*. 2010;16(5):1368-1372. doi:10.1158/1078-0432.CCR-09-1314
11. Hasskarl J. Everolimus. *Recent results cancer Res Fortschritte der Krebsforsch Prog dans les Rech sur le cancer*. 2018;211:101-123. doi:10.1007/978-3-319-91442-8_8
12. Cappellano AM, Senerchia AA, Adolfo F, et al. Successful everolimus therapy for SEGA in pediatric patients with tuberous sclerosis complex. *Child's Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg*. 2013;29(12):2301-2305. doi:10.1007/s00381-013-2170-0
13. Bissler JJ, Kingswood JC, Radzikowska E, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet (London, England)*. 2013;381(9869):817-824. doi:10.1016/S0140-6736(12)61767-X
14. Samueli S, Abraham K, Dressler A, et al. Efficacy and safety of Everolimus in children with TSC - associated epilepsy - Pilot data from an open single-center prospective study. *Orphanet J Rare Dis*. 2016;11(1):145. doi:10.1186/s13023-016-0530-z
15. Franz DN, Belousova E, Sparagana S, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet (London, England)*. 2013;381(9861):125-132. doi:10.1016/S0140-6736(12)61134-9
16. Agricola K, Stires G, Krueger DA, Capal JK, Franz DN, Ritter DM. Diabetes in Individuals With Tuberous Sclerosis Complex Treated With mTOR Inhibitors. *Pediatr Neurol*. 2021;120:7-10. doi:10.1016/j.pediatrneurol.2021.03.007
17. Friedman D, Bogner M, Parker-Menzer K, Devinsky O. Vigabatrin for partial-onset seizure treatment in patients with tuberous sclerosis complex. *Epilepsy Behav*. 2013;27(1):118-120. doi:10.1016/j.yebeh.2012.12.033
18. French JA. Vig abatrin. 1999;(8).
19. Tong X, Ratnaraj N, Patsalos PN. Vigabatrin extracellular pharmacokinetics and concurrent gamma-aminobutyric acid neurotransmitter effects in rat frontal cortex and hippocampus using microdialysis. *Epilepsia*. 2009;50(2):174-183. doi:10.1111/j.1528-1167.2008.01863.x
20. Zhang B, McDaniel SS, Rensing NR, Wong M. Vigabatrin inhibits seizures and mTOR pathway activation in a mouse model of tuberous sclerosis complex. *PLoS One*. 2013;8(2):e57445. doi:10.1371/journal.pone.0057445
21. Bresnahan R, Gianatsi M, Maguire MJ, Tudur Smith C, Marson AG. Vigabatrin add-on therapy for drug-resistant focal epilepsy. *Cochrane database Syst Rev*. 2020;7(7):CD007302. doi:10.1002/14651858.CD007302.pub3
22. Curatolo P. Vigabatrin for refractory partial seizures in children with tuberous sclerosis. *Neuropediatrics*. 1994;25(1):55. doi:10.1055/s-2008-1071586
23. Xu Z, Gong P, Jiao X, et al. Efficacy of vigabatrin in the treatment of infantile epileptic spasms syndrome: A systematic review and meta-analysis. *Epilepsia open*. 2023;8(2):268-277. doi:10.1002/epi4.12703
24. Appleton RE, Peters AC, Mumford JP, Shaw DE. Randomised, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms. *Epilepsia*. 1999;40(11):1627-1633. doi:10.1111/j.1528-1157.1999.tb02049.x
25. Riikonen R. Recent advances in the pharmacotherapy of infantile spasms. *CNS Drugs*. 2014;28(4):279-290. doi:10.1007/s40263-014-0139-5
26. Schonstedt V, Stecher X, Venegas V, Silva C. Vigabatrin-induced MRI changes associated with extrapyramidal symptoms in a child with infantile spasms. *Neuroradiol J*. 2015;28(5):515-518. doi:10.1177/1971400915598082
27. Westall CA, Wright T, Cortese F, Kumarappah A, Snead OC 3rd, Buncic JR. Vigabatrin retinal toxicity in children with infantile spasms: An observational cohort study. *Neurology*. 2014;83(24):2262-2268. doi:10.1212/WNL.0000000000001069
28. Fong CY, Osborne JP, Edwards SW, et al. An investigation into the relationship between vigabatrin, movement disorders, and brain magnetic resonance imaging abnormalities in children with infantile spasms. *Dev Med Child Neurol*. 2013;55(9):862-867. doi:10.1111/dmcn.12188
29. Leonard H, Downs J, Benke TA, Swanson L, Olson H, Demarest S. CDKL5 deficiency disorder: clinical features, diagnosis, and management. *Lancet Neurol*. 2022;21(6):563-576. doi:https://doi.org/10.1016/S1474-4422(22)00035-7
30. Hanefeld F. The clinical pattern of the rett syndrome. *Brain Dev*. 1985;7(3):320-325. doi:https://doi.org/10.1016/S0387-7604(85)80037-1
31. Weaving LS, Christodoulou J, Williamson SL, et al. Mutations of CDKL5 Cause a Severe Neurodevelopmental Disorder with Infantile Spasms and Mental Retardation. *Am J Hum Genet*. 2004;75(6):1079-1093. doi:https://doi.org/10.1086/426462
32. Tao J, Van Esch H, Hagedorn-Greiwe M, et al. Mutations in the X-linked cyclin-dependent kinase-li-

ke 5 (CDKL5/STK9) gene are associated with severe neurodevelopmental retardation. *Am J Hum Genet*. 2004;75(6):1149-1154. doi:10.1086/426460
33. Lin C, Franco B, Rosner MR. CDKL5/Stk9 kinase inactivation is associated with neuronal developmental disorders. *Hum Mol Genet*. 2005;14(24):3775-3786. doi:10.1093/hmg/ddi391
34. Kalscheuer VM, Tao J, Donnelly A, et al. Disruption of the serine/threonine kinase 9 gene causes severe X-linked infantile spasms and mental retardation. *Am J Hum Genet*. 2003;72(6):1401-1411. doi:10.1086/375538
35. Fehr S, Wilson M, Downs J, et al. The CDKL5 disorder is an independent clinical entity associated with early-onset encephalopathy. *Eur J Hum Genet*. 2013;21(3):266-273. doi:10.1038/ejhg.2012.156
36. Lamb YN. Ganaxolone: First Approval. *Drugs*. 2022;82(8):933-940. doi:10.1007/s40265-022-01724-0
37. Vossler DG. Ganaxolone: A New Treatment for CDKL5 Deficiency Disorder. *Epilepsy Curr*. 2022;22(6):348-350. doi:10.1177/15357597221125238
38. Klepper J. Glucose transporter deficiency syndrome (GLUT1DS) and the ketogenic diet. *Epilepsia*. 2008;49 Suppl 8:46-49. doi:10.1111/j.1528-1167.2008.01833.x
39. Koch H, Weber YG. The glucose transporter type 1 (Glut1) syndromes. *Epilepsy Behav*. 2019;91:90-93. doi:10.1016/j.yebeh.2018.06.010
40. Castellotti B, Ragona F, Freri E, et al. Screening of SLC2A1 in a large cohort of patients suspected for Glut1 deficiency syndrome: identification of novel variants and associated phenotypes. *J Neurol*. 2019;266(6):1439-1448. doi:10.1007/s00415-019-09280-6
41. Klepper J, Akman C, Armeno M, et al. Glut1 Deficiency Syndrome (Glut1DS): State of the art in 2020 and recommendations of the international Glut1DS study group. *Epilepsia open*. 2020;5(3):354-365. doi:10.1002/epi4.12414
42. Suls A, Dedeken P, Goffin K, et al. Paroxysmal exercise-induced dyskinesia and epilepsy is due to mutations in SLC2A1, encoding the glucose transporter GLUT1. *Brain*. 2008;131(Pt 7):1831-1844. doi:10.1093/brain/awn113
43. Ramm-Pettersen A, Nakken KO, Haavardsholm KC, Selmer KK. GLUT1-deficiency syndrome: Report of a four-generation Norwegian family with a mild phenotype. *Epilepsy Behav*. 2017;70(Pt A):1-4. doi:10.1016/j.yebeh.2017.02.016
44. Pons R, Collins A, Rotstein M, Engelstad K, De Vivo DC. The spectrum of movement disorders in Glut-1 deficiency. *Mov Disord*. 2010;25(3):275-281. doi:10.1002/mds.22808
45. Roubergue A, Apartis E, Mesnage V, et al. Dystonic tremor caused by mutation of the glucose transporter gene GLUT1. *J Inherit Metab Dis*. 2011;34(2):483-488. doi:10.1007/s10545-010-9264-6
46. Klepper J, Leiendecker B. GLUT1 deficiency syndrome--2007 update. *Dev Med Child Neurol*. 2007;49(9):707-716. doi:10.1111/j.1469-8749.2007.00707.x
47. Kossoff EH, Zupec-Kania BA, Auvin S, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. *Epilepsia open*. 2018;3(2):175-192. doi:10.1002/epi4.12225
48. Klepper J, Leiendecker B. Glut1 deficiency syndrome and novel ketogenic diets. *J Child Neurol*. 2013;28(8):1045-1048. doi:10.1177/0883073813487600
49. Nordli DRJ, De Vivo DC. The ketogenic diet revisited: back to the future. *Epilepsia*. 1997;38(7):743-749. doi:10.1111/j.1528-1157.1997.tb01460.x
50. van der Louw E, van den Hurk D, Neal E, et al. Ketogenic diet guidelines for infants with refractory epilepsy. *Eur J Paediatr Neurol EJPN Off J Eur Paediatr Neurol Soc*. 2016;20(6):798-809. doi:10.1016/j.ejpn.2016.07.009
51. Kass HR, Winesett SP, Bessone SK, Turner Z, Kossoff EH. Use of dietary therapies amongst patients with GLUT1 deficiency syndrome. *Seizure*. 2016;35:83-87. doi:10.1016/j.seizure.2016.01.011
52. De Giorgis V, Masnada S, Varesio C, et al. Overall cognitive profiles in patients with GLUT1 Deficiency Syndrome. *Brain Behav*. 2019;9(3):e01224. doi:10.1002/brb3.1224
53. Hao J, Kelly DI, Su J, Pascual JM. Clinical Aspects of Glucose Transporter Type 1 Deficiency: Information From a Global Registry. *JAMA Neurol*. 2017;74(6):727-732. doi:10.1001/jamaneurol.2017.0298
54. Møller RS, Heron SE, Larsen LHG, et al. Mutations in KCNT1 cause a spectrum of focal epilepsies. *Epilepsia*. 2015;56(9):e114-20. doi:10.1111/epi.13071
55. Barcia G, Fleming MR, Deligniere A, et al. De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy. *Nat Genet*. 2012;44(11):1255-1259. doi:10.1038/ng.2441
56. Liu R, Sun L, Wang Y, Wang Q, Wu J. New use for an old drug: quinidine in KCNT1-related epilepsy therapy. *Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol*. 2023;44(4):1201-1206. doi:10.1007/s10072-022-06521-x
57. Milligan CJ, Li M, Gazina E V, et al. KCNT1 gain of function in 2 epilepsy phenotypes is reversed by quinidine. *Ann Neurol*. 2014;75(4):581-590. doi:10.1002/ana.24128
58. Grace AA, Camm AJ. Quinidine. *N Engl J Med*. 1998;338(1):35-45. doi:10.1056/NEJM199801013380107
59. Fitzgerald MP, Fiannacca M, Smith DM, et al. Treatment Responsiveness in KCNT1-Related Epilepsy. *Neurother J Am Soc Exp Neurother*. 2019;16(3):848-857. doi:10.1007/s13311-019-00739-y
60. Spagnoli C, Salerno GG, Iodice A, Frattini D, Pisani F, Fusco C. KCNQ2 encephalopathy: A case due to a de novo deletion. *Brain Dev*. 2018;40(1):65-68. doi:10.1016/j.braindev.2017.06.008
61. Pisano T, Numis AL, Heavin SB, et al. Early and effective treatment of KCNQ2 encephalopathy. *Epilepsia*. 2015;56(5):685-691. doi:10.1111/epi.12984
62. Malerba F, Alberini G, Balagura G, et al. Genotype-phenotype correlations in patients with de novo KCNQ2 pathogenic variants. *Neurol Genet*. 2020;6(6):e528. doi:10.1212/NXG.0000000000000528

63. Schubert-Bast S, Hofstetter P, Fischer D, Schloesser R, Ramantani G, Kieslich M. Sodium channel blockers in KCNQ2-encephalopathy: Lacosamide as a new treatment option. *Seizure*. 2017;51:171-173. doi:10.1016/j.seizure.2017.08.005
64. Arya R, Glauser TA. Pharmacotherapy of focal epilepsy in children: a systematic review of approved agents. *CNS Drugs*. 2013;27(4):273-286. doi:10.1007/s40263-013-0048-z
65. Singh NA, Westenskow P, Charlier C, et al. KCNQ2 and KCNQ3 potassium channel genes in benign familial neonatal convulsions: expansion of the functional and mutation spectrum. *Brain*. 2003;126(Pt 12):2726-2737. doi:10.1093/brain/awg286
66. Numis AL, Angriman M, Sullivan JE, et al. KCNQ2 encephalopathy: delineation of the electroclinical phenotype and treatment response. *Neurology*. 2014;82(4):368-370. doi:10.1212/WNL.0000000000000060
67. Matta JA, Ashby MC, Sanz-clemente A, Roche KW, Isaac JTR. Article mGluR5 and NMDA Receptors Drive the Experience- and Activity-Dependent NMDA Receptor NR2B to NR2A Subunit Switch. *Neuron*. 2011;70(2):339-351. doi:10.1016/j.neuron.2011.02.045
68. Traynelis SF, Wollmuth LP, McBain CJ, et al. Glutamate receptor ion channels: structure, regulation, and function. *Pharmacol Rev*. 2010;62(3):405-496. doi:10.1124/pr.109.002451
69. Lemke JR, Lal D, Reinthaler EM, et al. Mutations in GRIN2A cause idiopathic focal epilepsy with rolandic spikes. *Nat Genet*. 2013;45(9):1067-1072. doi:10.1038/ng.2728
70. Lesca G, Rudolf G, Bruneau N, et al. GRIN2A mutations in acquired epileptic aphasia and related childhood focal epilepsies and encephalopathies with speech and language dysfunction. *Nat Genet*. 2013;45(9):1061-1066. doi:10.1038/ng.2726
71. 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
72. Bouhadoun S, Poulin C, Berrahmoune S, Myers KA. A retrospective analysis of memantine use in a pediatric neurology clinic. *Brain Dev*. 2021;43(10):997-1003. doi:10.1016/j.braindev.2021.05.012
73. Schiller K, Berrahmoune S, Dassi C, et al. Randomized placebo-controlled crossover trial of memantine in children with epileptic encephalopathy. *Brain*. 2023;146(3):873-879. doi:10.1093/brain/awac380
74. Ditzler K. Efficacy and tolerability of memantine in patients with dementia syndrome. A double-blind, placebo controlled trial. *Arzneimittelforschung*. 1991;41(8):773-780.
75. Kuns B, Rosani A, Varghese D. Memantine. In: ; 2023.
76. Delatycki MB, Bidichandani SI. Friedreich ataxia- pathogenesis and implications for therapies. *Neurobiol Dis*. 2019;132:104606. doi:10.1016/j.nbd.2019.104606
77. Alper G, Narayanan V. Friedreich's ataxia. *Pediatr Neurol*. 2003;28(5):335-341. doi:10.1016/s0887-8994(03)00004-3
78. Lodi R, Tonon C, Calabrese V, Schapira AH V. Friedreich's ataxia: from disease mechanisms to therapeutic interventions. *Antioxid Redox Signal*. 2006;8(3-4):438-443. doi:10.1089/ars.2006.8.438
79. Strawser C, Schadt K, Hauser L, et al. Pharmacological therapeutics in Friedreich ataxia: the present state. *Expert Rev Neurother*. 2017;17(9):895-907. doi:10.1080/14737175.2017.1356721
80. Lodi R, Rajagopalan B, Bradley JL, et al. Mitochondrial dysfunction in Friedreich's ataxia: from pathogenesis to treatment perspectives. *Free Radic Res*. 2002;36(4):461-466. doi:10.1080/10715760290021324
81. Martelli A, Puccio H. Dysregulation of cellular iron metabolism in Friedreich ataxia: from primary iron-sulfur cluster deficit to mitochondrial iron accumulation. *Front Pharmacol*. 2014;5:130. doi:10.3389/fphar.2014.00130
82. Rötig A, de Lonlay P, Chretien D, et al. Aconitase and mitochondrial iron-sulphur protein deficiency in Friedreich ataxia. *Nat Genet*. 1997;17(2):215-217. doi:10.1038/ng1097-215
83. Palau F. Friedreich's ataxia and frataxin: molecular genetics, evolution and pathogenesis (Review). *Int J Mol Med*. 2001;7(6):581-589. doi:10.3892/ijmm.7.6.581
84. Delatycki MB, Corben LA. Clinical features of Friedreich ataxia. *J Child Neurol*. 2012;27(9):1133-1137. doi:10.1177/0883073812448230
85. Cook A, Giunti P. Friedreich's ataxia: clinical features, pathogenesis and management. *Br Med Bull*. 2017;124(1):19-30. doi:10.1093/bmb/ldx034
86. Lynch DR, Schadt K, Kichula E, McCormack S, Lin KY. Friedreich Ataxia: Multidisciplinary Clinical Care. *J Multidiscip Healthc*. 2021;14:1645-1658. doi:10.2147/JMDH.S292945
87. Abeti R, Baccaro A, Esteras N, Giunti P. Novel Nrf2-Inducer Prevents Mitochondrial Defects and Oxidative Stress in Friedreich's Ataxia Models. *Front Cell Neurosci*. 2018;12:188. doi:10.3389/fncel.2018.00188
88. Abeti R, Uzun E, Renganathan I, Honda T, Pook MA, Giunti P. Targeting lipid peroxidation and mitochondrial imbalance in Friedreich's ataxia. *Pharmacol Res*. 2015;99:344-350. doi:10.1016/j.phrs.2015.05.015
89. Sahdeo S, Scott BD, McMackin MZ, et al. Dyclonine rescues frataxin deficiency in animal models and buccal cells of patients with Friedreich's ataxia. *Hum Mol Genet*. 2014;23(25):6848-6862. doi:10.1093/hmg/ddu408
90. Shan Y, Schoenfeld RA, Hayashi G, et al. Frataxin deficiency leads to defects in expression of antioxidants and Nrf2 expression in dorsal root ganglia of the Friedreich's ataxia YG8R mouse model. *Antioxid Redox Signal*. 2013;19(13):1481-1493. doi:10.1089/ars.2012.4537
91. Lee A. Omaveloxolone: First Approval. *Drugs*. 2023;83(8):725-729. doi:10.1007/s40265-023-01874-9
92. Program M. New Drug Evaluation : Omaveloxolone Oral Capsules. 2023;(February).
93. Dravet C. The core Dravet syndrome phenotype. *Epilepsia*. 2011;52 Suppl 2:3-9. doi:10.1111/j.1528-1167.2011.02994.x
94. Anwar A, Saleem S, Patel UK, Arumaithurai K, Malik P. Dravet Syndrome: An Overview. *Cureus*. 2019;11(6):e5006. doi:10.7759/cureus.5006

95. Catterall WA, Kalume F, Oakley JC. NaV1.1 channels and epilepsy. *J Physiol*. 2010;588(Pt 11):1849-1859. doi:10.1113/jphysiol.2010.187484
96. Strzelczyk A, Schubert-Bast S. A Practical Guide to the Treatment of Dravet Syndrome with Anti-Seizure Medication. *CNS Drugs*. 2022;36(3):217-237. doi:10.1007/s40263-022-00898-1
97. Li W, Schneider AL, Scheffer IE. Defining Dravet syndrome: An essential pre-requisite for precision medicine trials. *Epilepsia*. 2021;62(9):2205-2217. doi:10.1111/epi.17015
98. Nickels KC, Wirrell EC. Stiripentol in the Management of Epilepsy. *CNS Drugs*. 2017;31(5):405-416. doi:10.1007/s40263-017-0432-1
99. Fisher JL. The effects of stiripentol on GABA(A) receptors. *Epilepsia*. 2011;52 Suppl 2(0 2):76-78. doi:10.1111/j.1528-1167.2011.03008.x
100. Stiripentol for Dravet syndrome. *Aust Prescr*. 2020;43(3):102. doi:10.18773/austprescr.2020.029
101. Zulfiqar Ali Q, Marques P, Selvarajah A, Tabarestani S, Sadoway T, Andrade DM. Starting stiripentol in adults with Dravet syndrome? Watch for ammonia and carnitine. *Epilepsia*. 2020;61(11):2435-2441. doi:10.1111/epi.16684
102. *See Full Prescribing Information for Complete Boxed Warning.* •.; 2020.
103. Gil-Nagel A, Falip M, Sánchez-Carpintero R, et al. The contribution of fenfluramine to the treatment of Dravet syndrome in Spain through Multi-Criteria Decision Analysis. *Epilepsy Behav*. 2022;132:108711. doi:10.1016/j.yebeh.2022.108711
104. Schoonjans A-S, Ceulemans B. An Old Drug for a New Indication: Repurposing Fenfluramine From an Anorexigen to an Antiepileptic Drug. *Clin Pharmacol Ther*. 2019;106(5):929-932. doi:10.1002/cpt.1469
105. Schoonjans A-S, Ceulemans B. A critical evaluation of fenfluramine hydrochloride for the treatment of Dravet syndrome. *Expert Rev Neurother*. 2022;22(5):351-364. doi:10.1080/14737175.2021.1877540
106. McCoy B, Wang L, Zak M, et al. A prospective open-label trial of a CBD/THC cannabis oil in dravet syndrome. *Ann Clin Transl Neurol*. 2018;5(9):1077-1088. doi:10.1002/acn3.621
107. Koubeissi M. Anticonvulsant Effects of Cannabidiol in Dravet Syndrome. *Epilepsy Curr*. 2017;17(5):281-282. doi:10.5698/1535-7597.17.5.281
108. Gao C, Pielas M, Jiao F, et al. Epilepsy in Dravet Syndrome-Current and Future Therapeutic Opportunities. *J Clin Med*. 2023;12(7). doi:10.3390/jcm12072532
109. Rett A. [On a unusual brain atrophy syndrome in hyperammonemia in childhood]. *Wien Med Wochenschr*. 1966;116(37):723-726.
110. Burd L, Randall T, Martsolf JT, Kerbeshian J. Rett syndrome symptomatology of institutionalized adults with mental retardation: comparison of males and females. *Am J Ment Retard*. 1991;95(5):596-601.
111. Silva-Reis SC, Sampaio-Dias IE, Costa VM, et al. Concise Overview of Glypromate Neuropeptide Research: From Chemistry to Pharmacological Applications in Neurosciences. *ACS Chem Neurosci*. 2023;14(4):554-572. doi:10.1021/acschemneuro.2c00675
112. Keam SJ. Trofinetide: First Approval. *Drugs*. 2023;83(9):819-824. doi:10.1007/s40265-023-01883-8
113. Darwish M, Youakim JM, Harlick J, DeKarske D, Stankovic S. A Phase 1, Open-Label Study to Evaluate the Effects of Food and Evening Dosing on the Pharmacokinetics of Oral Trofinetide in Healthy Adult Subjects. *Clin Drug Investig*. 2022;42(6):513-524. doi:10.1007/s40261-022-01156-4
114. Chung J, Smith AL, Hughes SC, et al. Twenty-year follow-up of newborn screening for patients with muscular dystrophy. *Muscle Nerve*. 2016;53(4):570-578. doi:10.1002/mus.24880
115. Bello L, Pegoraro E. The "Usual Suspects": Genes for Inflammation, Fibrosis, Regeneration, and Muscle Strength Modify Duchenne Muscular Dystrophy. *J Clin Med*. 2019;8(5). doi:10.3390/jcm8050649
116. Manzur AY, Kinali M, Muntoni F. Update on the management of Duchenne muscular dystrophy. *Arch Dis Child*. 2008;93(11):986-990. doi:10.1136/adc.2007.118141
117. Mah JK. Current and emerging treatment strategies for Duchenne muscular dystrophy. *Neuropsychiatr Dis Treat*. 2016;12:1795-1807. doi:10.2147/NDT.S93873
118. Reserved AR, Editor FD. Duchenne and Becker muscular dystrophy : Glucocorticoid and disease-modifying treatment. Published online 2023:1-22.
119. Markati T, Oskoui M, Farrar MA, Duong T, Goemans N, Servais L. Emerging therapies for Duchenne muscular dystrophy. *Lancet Neurol*. 2022;21(9):814-829. doi:10.1016/S1474-4422(22)00125-9
120. Kole R, Krieg AM. Exon skipping therapy for Duchenne muscular dystrophy. *Adv Drug Deliv Rev*. 2015;87:104-107. doi:10.1016/j.addr.2015.05.008
121. Lim KRQ, Maruyama R, Yokota T. Eteplirsen in the treatment of Duchenne muscular dystrophy. *Drug Des Devel Ther*. 2017;11:533-545. doi:10.2147/DDDT.S97635
122. van Deutekom JCT, van Ommen G-JB. Advances in Duchenne muscular dystrophy gene therapy. *Nat Rev Genet*. 2003;4(10):774-783. doi:10.1038/nrg1180
123. fda-grants-accelerated-approval-first-drug-duchenne-muscular-dystrophy @ www.fda.gov. https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-drug-duchenne-muscular-dystrophy
124. Eteplirsen. In: ; 2022:1-7.
125. Anwar S, Yokota T. Golodirsen for Duchenne muscular dystrophy. *Drugs Today (Barc)*. 2020;56(8):491-504. doi:10.1358/dot.2020.56.8.3159186
126. Heo Y-A. Golodirsen: First Approval. *Drugs*. 2020;80(3):329-333. doi:10.1007/s40265-020-01267-2
127. fda-grants-accelerated-approval-first-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation @ www.fda.gov. https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation
128. Servais L, Mercuri E, Straub V, et al. Long-Term Safety and Efficacy Data of Golodirsen in Ambulatory Patients with Duchenne Muscular Dystrophy Amenable

to Exon 53 Skipping: A First-in-human, Multicenter, Two-Part, Open-Label, Phase 1/2 Trial. *Nucleic Acid Ther*. 2022;32(1):29-39. doi:10.1089/nat.2021.0043
129. Dhillon S. Viltolarsen: First Approval. *Drugs*. 2020;80(10):1027-1031. doi:10.1007/s40265-020-01339-3
130. Roshmi RR, Yokota T. Viltolarsen: From Preclinical Studies to FDA Approval. *Methods Mol Biol*. 2023;2587:31-41. doi:10.1007/978-1-0716-2772-3_2
131. Bushby K, Finkel R, Wong B, et al. Ataluren treatment of patients with nonsense mutation dystrophinopathy. *Muscle Nerve*. 2014;50(4):477-487. doi:10.1002/mus.24332
132. Welch EM, Barton ER, Zhuo J, et al. PTC124 targets genetic disorders caused by nonsense mutations. *Nature*. 2007;447(7140):87-91. doi:10.1038/nature05756
133. Dent KM, Dunn DM, von Niederhausern AC, et al. Improved molecular diagnosis of dystrophinopathies in an unselected clinical cohort. *Am J Med Genet A*. 2005;134(3):295-298. doi:10.1002/ajmg.a.30617
134. Namgoong JH, Bertoni C. Clinical potential of ataluren in the treatment of Duchenne muscular dystrophy. *Degener Neurol Neuromuscul Dis*. 2016;6:37-48. doi:10.2147/DNND.S71808
135. Kolb SJ, Kissel JT. Spinal Muscular Atrophy. *Neurol Clin*. 2015;33(4):831-846. doi:10.1016/j.ncl.2015.07.004
136. Mostacciuolo ML, Danieli GA, Trevisan C, Müller E, Angelini C. Epidemiology of spinal muscular atrophies in a sample of the Italian population. *Neuroepidemiology*. 1992;11(1):34-38. doi:10.1159/000110905
137. Pearn J. Incidence, prevalence, and gene frequency studies of chronic childhood spinal muscular atrophy. *J Med Genet*. 1978;15(6):409-413. doi:10.1136/jmg.15.6.409
138. Thieme A, Mitulla B, Schulze F, Spiegler AW. Epidemiological data on Werdnig-Hoffmann disease in Germany (West-Thüringen). *Hum Genet*. 1993;91(3):295-297. doi:10.1007/BF00218278
139. Ogino S, Wilson RB. Genetic testing and risk assessment for spinal muscular atrophy (SMA). *Hum Genet*. 2002;111(6):477-500. doi:10.1007/s00439-002-0828-x
140. Friesen WJ, Massenet S, Paushkin S, Wyce A, Dreyfuss G. SMN, the product of the spinal muscular atrophy gene, binds preferentially to dimethylarginine-containing protein targets. *Mol Cell*. 2001;7(5):1111-1117. doi:10.1016/s1097-2765(01)00244-1
141. Kerr DA, Nery JP, Traystman RJ, Chau BN, Hardwick JM. Survival motor neuron protein modulates neuron-specific apoptosis. *Proc Natl Acad Sci U S A*. 2000;97(24):13312-13317. doi:10.1073/pnas.230364197
142. Lefebvre S, Bürglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell*. 1995;80(1):155-165. doi:10.1016/0092-8674(95)90460-3
143. Butchbach MER. Copy Number Variations in the Survival Motor Neuron Genes: Implications for Spinal Muscular Atrophy and Other Neurodegenerative Diseases. *Front Mol Biosci*. 2016;3:7. doi:10.3389/fmolb.2016.00007
144. Hsieh-Li HM, Chang JG, Jong YJ, et al. A mouse model for spinal muscular atrophy. *Nat Genet*. 2000;24(1):66-70. doi:10.1038/71709
145. Hua Y, Vickers TA, Baker BF, Bennett CF, Krainer AR. Enhancement of SMN2 exon 7 inclusion by antisense oligonucleotides targeting the exon. *PLoS Biol*. 2007;5(4):e73. doi:10.1371/journal.pbio.0050073
146. Passini MA, Bu J, Richards AM, et al. Antisense oligonucleotides delivered to the mouse CNS ameliorate symptoms of severe spinal muscular atrophy. *Sci Transl Med*. 2011;3(72):72ra18. doi:10.1126/scitranslmed.3001777
147. Hoy SM. Nusinersen: First Global Approval. *Drugs*. 2017;77(4):473-479. doi:10.1007/s40265-017-0711-7
148. Chiriboga CA, Swoboda KJ, Darras BT, et al. Results from a phase 1 study of nusinersen (ISIS-SMN(Rx)) in children with spinal muscular atrophy. *Neurology*. 2016;86(10):890-897. doi:10.1212/WNL.0000000000002445
149. Hoy SM. Nusinersen: A Review in 5q Spinal Muscular Atrophy. *CNS Drugs*. 2021;35(12):1317-1328. doi:10.1007/s40263-021-00878-x
150. Neil EE, Bisaccia EK. Nusinersen: A Novel Antisense Oligonucleotide for the Treatment of Spinal Muscular Atrophy. *J Pediatr Pharmacol Ther JPPT Off J PPAG*. 2019;24(3):194-203. doi:10.5863/1551-6776-24.3.194
151. Paik J. Risdiplam: A Review in Spinal Muscular Atrophy. *CNS Drugs*. 2022;36(4):401-410. doi:10.1007/s40263-022-00910-8
152. Kakazu J, Walker NL, Babin KC, et al. Risdiplam for the Use of Spinal Muscular Atrophy. *Orthop Rev (Pavia)*. 2021;13(2):25579. doi:10.52965/001c.25579
153. Stevens D, Claborn MK, Gildon BL, Kessler TL, Walker C. Onasemnogene Abeparvovec-xioi : Gene Therapy for Spinal Muscular Atrophy. Published online 2020. doi:10.1177/1060028020914274
154. fda-approves-innovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-rare-disease @ www.fda.gov. https://www.fda.gov/news-events/press-announcements/fda-approves-innovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-rare-disease
155. Blair HA. Onasemnogene Abeparvovec: A Review in Spinal Muscular Atrophy. *CNS Drugs*. 2022;36(9):995-1005. doi:10.1007/s40263-022-00941-1