

# Chapter 4

## NEW GENERATION ANTIEPILEPTIC DRUGS IN THE TREATMENT OF EPILEPSY

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### INTRODUCTION

Antiepileptic drugs are classified as classical (benzodiazepines, ethosuximide, carbamazepine, phenytoin, phenobarbital, valproic acid, primidone) and the new generation (zonisamide, vigabatrin, thiagabine, felbamate, lamotrigine, topiramate, oxcarbazepine, eslicarbazepine acetate, briveracetam, levetiracetam, retigabine, gabapentin, pregabalin, lacosamide, etc). New antiepileptic drugs (NAD) have been developed to alleviate the drug side effects of classical antiepileptic treatments. Although the new antiepileptic group has advantages in terms of side effect profile, drug interaction, and teratogenicity, they have not been demonstrated to be more effective than classical antiepileptics. The aim of this compilation is to guide the clinicians by explaining the effects and side effects of new antiepileptic drugs

### NEW TREATMENTS IN EPILEPSY

#### Zonisamide (ZNS)

Zonisamide, 1,2-benzisoxazole-3-methanesulfonamide, a benzisoxazole derivative, is a new generation and broad-spec-

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cated as 600-1200 mg/day. Oral bioavailability is 60%. It reaches its maximum dose in the blood in approximately two hours after oral administration (33).

Side effects include weight gain, fatigue, dizziness, blurred vision, somnolence, urinary retention, confusion, QT prolongation, tremor, nausea, increased nail and skin pigmentation (7).

## **Conclusion**

The rate of patients receiving new generation antiepileptic therapies has increased significantly in recent years. New generation antiepileptic drugs are better tolerated compared to classical antiepileptic therapies and therefore offer new alternatives for patients who are adversely affected by the side effects of classical antiepileptic therapies. As experiences grow, it is clear that these drugs may replace classic antiepileptics.

**Keywords:** Epilepsy, new generation antiepileptic drug

## **REFERENCES**

1. Brodie MJ, Ben-Menachem E, Chouette I, Giorgi L. Zonisamide: its pharmacology, efficacy and safety in clinical trials. *Acta Neurol Scand Suppl* 2012;(194):19–28.
2. Patsalos EP. Zonisamide. *The Epilepsy Prescriber's Guide to Antiepileptic Drugs* Cambridge, United Kingdom; New York, N.Y: Cambridge University Press; 2018. p.339-49.
3. Xixis KI, RM. Second Generation Antiepileptic Drugs, in: A.M.Husain, *Practical Epilepsy* New York: Demos Medical Publishing; 2016; p.277-302.
4. Schulze-Bonhage A. Zonisamide in the treatment of epilepsy. *Expert Opin Pharmacother* 2010;11(1):115–26.
5. Sills G, Brodie M. Pharmacokinetics and drug interactions with zonisamide. *Epilepsia* 2007;48(3):435–41.
6. Raucci U, Spalice A, Basile LA, Guardala C, Nasta L, Terenzi S, et al. New drugs in the treatment of childhood epilepsy: vigabatrin (study of 61 subjects) *J Pediatr Med Chir* 1994;16:575-8.
7. Abou-Khalil B. New Generation Antiepileptic Drugs. In: Azar MZ ed. *Epilepsy Board Review*. New York: Springer; 2017. p.225-33.
8. Santos CC. Third-Generation Antiepileptic Drugs, in: A.M.Husain, *Practical Epilepsy*, New York: Demos Medical Publishing; 2016; p.303-16.
9. Kalviainen R, Nousiainen I, Mantyjarvi M, et al. Vigabatrin, a gabargic antiepileptic drug, causes concentric visual field defects. *Neurology*. 1999;53:922-6.

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10. Toggweiler S, Wieser HG. Concentric visual field restriction under vigabatrin therapy: extent depends on the duration of drug intake. *Seizure*. 2001;10:420-3.
11. Patsalos PN, Duncan JS. New antiepileptic drugs: a review of their current status and clinical potential. *CNS Drugs* 1994; 2:40-77.
12. Chadwick D, Leiderman DB, Sauermann W, et al. Gabapentin in generalized seizures. *Epilepsy Res*. 1996;25:191-7.
13. Perucca E, Gram L, Avanzini G, et al. Antiepileptic drugs as a cause of worsening seizures. *Epilepsia*. 1998; 39; p.5-17.
14. Patsalos EP. *Gabapentin. The Epilepsy Prescriber's Guide to Antiepileptic Drugs* Cambridge, United Kingdom; New York, N.Y: Cambridge University Press; 2018. p.109-19.
15. Theodore WH: *Felbamate. Epilepsy: A comprehensive textbook* (Eds: Engel J, Pedley TA) Lippincott - Raven Philadelphia 1997, 1509-1514.
16. Azar NJ, Bangalore-Vittal N, Arain A, et al. Tiagabine-induced stupor in patients with psychogenic nonepileptic seizures: nonconvulsive status epilepticus or encephalopathy? *Epilepsy Behav*. 2013;27:330-2.
17. Koeppe MJ, Edwards M, Collins J, et al. Status epilepticus and tiagabine therapy revisited. *Epilepsia*. 2005;46:1625-32.
18. Dam M. Practical aspects of oxcarbazepine treatment. *Epilepsia* 1994;35 (Suppl 3):23-5.
19. Davis Rick . Valproic Acid A Reappraisal of its Pharmacological Properties and Clinical Efficacy in Epilepsy . *Drugs* 1994;47(2): 332-72.
20. Bertram G. Katzung . *Basic and Clinical Pharmacology* . Lancet medical . (1996) 9th ed. pp:387-89.
21. Grant SM, Faulds D. Okskarbazepin Farmakolojisi ve Epilepsi, Trigeminal Nevralji ve Affektif Hastalıklardaki Terapotik Potansiyeli. *Drugs Rep* .1992;43(6):873-888
22. Krauss GL, Edwards HB, Lin B. Lacosamide for the treatment of epilepsy. *Ann Med* 2012;44(7):674-9.
23. Casas-Fernández C, Martínez-Bermejo A, Rufo-Campos M, Smeyers-Durá P, Herranz-Fernández JL, Ibáñez-Micó S, et al. Efficacy and tolerability of lacosamide in the concomitant treatment of 130 patients under 16 years of age with refractory epilepsy: a prospective, open-label, observational, multicenter study in Spain. *Drugs R D* 2012;12(4):187-97.
24. Pina-Garza JE, Schwarzman L, Wiegand F, et al. A pilot study of topiramate in childhood absence epilepsy. *Acta Neurol Scand*. 2011; 123:54-9.
25. Privitera M. Topiramate: a new antiepileptic drug. *Ann Pharmacother* 1997; 31:1164-1173.
26. Xixis KI, RM. *Second Generation Antiepileptic Drugs*, in: A.M. Husain, *Practical Epilepsy* New York: Demos Medical Publishing; 2016; p.277-302.
27. Mikati MA, El Banna D, Sinno D, et al. Response of infantile spasms to levetiracetam. *Neurology*. 2008;70(7):574-5.

28. Genton P, Gelisse P. Antimyoclonic effect of levetiracetam. *Epileptic Disord.* 2000; 2(4):209-12.
29. Frucht SJ, Louis ED, Chuang C, et al. A pilot tolerability and efficacy study of levetiracetam in patients with chronic myoclonus. *Neurology.* 2001;57(6):1112-4.
30. Sirsi D, Safdieh JE. The safety of levetiracetam. *Expert Opin Drug Saf.* 2007;6(3):241-50.
31. Martin L, Rabasseda X, Leeson P, Castaner J. Pregabalin. *Drugs of the Future* 1999;24(8):862-870.
32. Kavoussi R. From molecule to medicine. *European Neuropsychopharmacology* 2006;16:S128-S133.
33. Santos CC. Third-Generation Antiepileptic Drugs, in: A.M. Husain, *Practical Epilepsy*, New York: Demos Medical Publishing; 2016; p.303-16.
34. French JA, Kugler AR, Robbins JL, Knapp LE, Garofalo EA. Dose response trial of pregabalin adjunctive therapy in patients with partial seizures. *Neurology* 2003; 60(10):1631-7.
35. Arroyo S, Anhut H, Kugler AR, Lee CM, Lloyd E, Knapp LE, et al. Pregabalin add-on treatment: a randomized, double-blind, placebo controlled, dose-response study in adults with partial seizures. *Epilepsia* 2004; 45(1):20-7.
36. Patsalos EP, Perampanel. *The Epilepsy Prescriber's Guide to Antiepileptic Drugs* (s.). Cambridge, United Kingdom; New York, N.Y: Cambridge University Press; 2018. p.204-13.
37. Hanada T. The AMPA receptor as a therapeutic target in epilepsy: preclinical and clinical evidence. *J Receptor Ligand Channel Res.* 2014;7:39-50.
38. Patsalos EP. Felbamate. *The Epilepsy Prescriber's Guide to Antiepileptic Drugs* Cambridge, United Kingdom; New York, N.Y: Cambridge University Press; 2018. p.90-8.
39. Patsalos EP, Eslicarbazepine. *The Epilepsy Prescriber's Guide to Antiepileptic Drugs* Cambridge, United Kingdom; New York, N.Y: Cambridge University Press; 2018. p.71-80.
40. Mims KN. A New Antiepileptic Drug and Drugs in Development. in: A.M. Husain, *Practical Epilepsy*; New York: Demos Medical Publishing; 2016. p.317-23.
41. Patsalos EP. Brivaracetam. *The Epilepsy Prescriber's Guide to Antiepileptic Drugs* Cambridge, United Kingdom; New York: Cambridge University
42. Klitgaard H, Matagne A, Nicolas JM, et al. Brivaracetam: rationale for discovery and preclinical profile of a selective SV2A ligand for epilepsy treatment. *Epilepsia.* 2016;57:538- 48.
43. Nicolas JM, Hannestad J, Holden D, et al. Brivaracetam, a selective high-affinity synaptic vesicle protein 2A (SV2A) ligand with preclinical evidence of high brain permeability and fast onset of action. *Epilepsia.* 2016;57:201-9.
44. Stockis A, Watanabe S, Scheen AJ, et al. Effect of rifampin on the disposition of brivaracetam in human subjects: further insights into brivaracetam hydrolysis. *Drug Metab Dispos.* 2016;44:792-9.

45. Devinsky O, Cilio MR, Cross H, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia*. 2014;55:791-802.
46. Gloss D, Vickrey B. Cannabinoids in epilepsy. *Cochrane Database Syst Rev* 2014. Available at: <http://onlinelibrary.wiley.com/doi/10.1002/CD009270.pub3/full>. Accessed March 5, 2016.
47. Ibeas-Bih C, Chen T, Nunn AV, et al. Molecular targets of cannabidiol in neurological disorders. *Neurotherapeutics*. 2015;12:699-730.
48. Devinsky O, Thiele E, Laux L, et al. Efficacy and safety of Epidiolex (cannabidiol) in children and young adults with treatment-resistant epilepsy: Update from the expanded access program, 2015. *American Epilepsy Society Annual Meeting*. Abstract. Available at: [https://www.aesnet.org/meetings\\_events/annual\\_meeting\\_abstracts/view/2414222](https://www.aesnet.org/meetings_events/annual_meeting_abstracts/view/2414222). Accessed May 19, 2016.
49. Kirchner GI, Meier-Wiedenbach I, Manns MP. Clinical pharmacokinetics of everolimus. *Clin Pharmacokinet*. 2004;43:83-95.
50. Curatolo P, Moavero R. mTOR inhibitors as a new therapeutic option for epilepsy. *Expert Rev Neurother*. 2013;13:627-38.
51. Tavazoie SF, Alvarez VA, Ridenour DA, et al. Regulation of neuronal morphology and function by the tumor suppressors Tsc1 and Tsc2. *Nat Neurosci*. 2005;8:1727-34.
52. Tavazoie SF, Alvarez VA, Ridenour DA, et al. Regulation of neuronal morphology and function by the tumor suppressors Tsc1 and Tsc2. *Nat Neurosci*. 2005;8:1727-34.
53. Bialer M, Johannessen SI, Levy RH, et al. Progress report on new anti-epileptic drugs: a summary of the Twelfth Eilat Conference (EILAT XII). *Epilepsy Res*. 2015;111:85-141.
54. Jozwiak S, Kotulska K, Berkowitz N, et al. Safety of everolimus in patients younger than 3 years of age: results from EXIST-1, a randomized, controlled clinical trial. *J Pediatr*. 2016;172:151-155.e151.
55. Amada N, Yamasaki Y, Williams CM, et al. Cannabidiol (CBD) suppresses pentylenetetrazole (PTZ)-induced increases in epilepsy-related gene expression. *Peer J*. 2013;1:e214.
56. De Petrocellis L, Orlando P, Moriello AS, et al. Cannabinoid actions at TRPV channels: effects on TRPV3 and TRPV4 and their potential relevance to gastrointestinal inflammation. *Acta Physiol (Oxf)*. 2012;204:255-66.