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Physiological impact and Therapeutic application of Depakine or Valboric acid

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Abstract

Due to health quarantine during the recent covid-19 pandemic, most population suffered from unhealthy ways of sleep and continuous exposure of stress with chronic mood disorders and headaches. But, during the covid-19 pandemic, the epileptic patients showed seizure escalation and initiated severe symptoms treated with high and low doses of common psychoactive drugs, especially valproic acid. Several review articles focused on some clinical data of potential application of valproic acid, its benefits, and risks of high and low doses that globally prescribe too many people who suffered from the neurological illness of the central nervous system or hereditary diseases with any incident that harms the brain. Valproate is a monocarboxylic acid and an indirect γ-aminobutyric acid with a histone deacetylase inhibitor. Moreover, it has been evaluated as an equal or superior ability as an antiepileptic and anti-diabetic drug. It has a complex mechanism action for a diminution in neuronal hyper-excitability by strengthening GABAergic transmission and by constraining sodium and calcium ion passages. Worldwide, Valproate has different commercial names such as Depakine, Convulex, Epival, Kentlim, and Syonell. Exclusively, Depakine use as mono therapy and a novel choice for all types of generalized epilepsy of children. It can be used for long periods and continuously because it acts as a histone deacetylase (HDAC) inhibitor. Moreover, studies showed that Depakine did not have any narcotic effect. Still, it has biological activities to regulate gene expression and management of several therapeutic to neuropathic pain, brain plasticity, HIV therapy, schizoaffective, diabetes mellitus, autoimmune and cardiovascular diseases. Nonetheless, sodium valproic acid has a safety with major anticancer effects and antiviral or immune-modulatory effects by reducing virus replication in the body cells such as coronavirus. Consequently, this brief review article intends to evaluate the seizure threat of epilepsy and the efficacy of sodium valproate therapy by inhibition of migraine severity.

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Introduction

The Depakine form of valproic acid is licensed as a drug for treating the acute phase of bipolar disorder as anti-seizure activity (Chateauvieux *et al.,* 2010), especially the short and long seizures forms of epilepsy (Perucca *et al.,* 2006). This product was discovered in early 1968 in France and originated from Valeriana officinalis herbal (Petroff *et al.,*1999). The chemical properties of this drug allow easy delivery to the organism and cells, which can be used in three forms the acidic, salt, and semi-salt (Houghton & Bowers, 2003). One of the essential general considerations during the preparation of valproate is dissolving in either distilled water or dimethyl sulfoxide (DMSO) with a clear liquid at 25 temperature room. The half-life of valproate is between (9 – 16) hours, and it is considered "physiologically or metabolically inert" (Chateauvieux *et al.,*2010). Valproate is excreted in different ways like milk, urine (Sankar, 2007), and semen of living organisms (Swanson et al., 1978). Andonie *et al.,* (2018) was proven that valproic acid is highly safe and has a therapeutic value better than other antiepileptic drugs. Also, it can be affected in psychical manners (Negreş *et al.,*2013) by boosts the GABA neurotransmission with blocks central sodium channels and preventing the propagation of electrical impulses from end to end-neuronal synapses (Ghodke-Puranik *et al.,* 2013). Moreover, it has tonic properties related to the many indications of epilepsy, migraine, and bipolar mood (Rakitin *et al.,* 2015).

Naturally, valproate is composed of valeric acid with short-chain fatty acid its use as an adjuvant agent in cancer and neurodegenerative disease because of its action as a histone deacetylase (HDAC) inhibitor by blocks voltage-gated ion channels (Ghodke-Puranik *et al.,* 2013). Interestingly, Depakine is a selective drug of monotherapy for universal epilepsy in youths after evaluating the risk of weighty and erotogenic actions (Yerby, 2003). The helpful factor of valproate is antiviral or immunomodulatory effects by preventing RNA polymerase and reducing virus replication in cells body such as coronavirus (Unal et al., 2020). Bril *et al.,* (2011) has been successfully used valproate for years in patients to treat neuropathic pain and also suggested using valproate for the treatment of diabetic polyneuropathy. Valproic acid has also been found to motivate pancreatic insulin discharge owing to its GABA-ergic (Luef *et al.,*2003) by lowering blood glucose stages of diabetic in lab animals (Terasmaa *et al.,*2011) at a special dosage of about 600mg (Abdul Bari, 2018). Additionally, valproate is a highly effective drug, mainly as bactericidal, anti-nociceptive, anti-inflammatory, antioxidative (Ximenes *et al.,*2013), and antitumor effects, particularly in breast cancer (Heers *et al.,*2018) either alone or in combination with cytotoxic agents (Duenas-Gonzalez *et al.,*2008). The private dose of valproate increases dehydroepiandrosterone and androgen synthesis of normal theca cells in humans, and follicles progress (Wood *et al.,*2005). Therefore, valproate has been increased basal, and LH stimulated androgen secretion from minor follicles more than medium-size follicles (Glister *et al.,*2012). In vitro, valproic acid (VPA) was found to act as an anti-epileptic drug by inhibiting the steroidogenesis in bovine theca and granulosa cells and effects on the biosynthesis of the fatty acid shape of gut microbiomes such as fungi, bacteria, and yeast (Poolchanuan et al.,2020).

Several fatal cases of hyperammonemia were reported in patients treated with VPA (Verrotti *et al.,*2002). However, no often serious complications may occur at various ages, including hemorrhagic toxicity, pancreatitis, encephalopathy (Gerstner *et al.,*2008), and endocrine disorders (Fajardo *et al.,*2013). The most adverse effect of valproic acid is

hepatotoxicity (Hsu *et al.,*2009). It is essential to proactively ensure the use of valproate in women of childbearing age for it is associated with a major risk of birth defects and growing ailments in broods (Shakespeare *et al.,*2019).

Epilepsy

Epilepsy is one of the most human beings' ancient brain illnesses that knowns since a long time ago (Magiorkinis *et al.,*2010). Numerous studies have explored the concept of Epilepsy as a chronic neurological condition regarded as by spontaneous periodic seizures of cerebral sources (Sridharan, 2002). Several causes of epilepsy have been reported, such as hereditary or acquired. However, it is associated with a higher risk of cardiovascular diseases (Janszky *et al.,*2009). Epilepsy is a neurological disorder that induces brain death due to excessive liberation of glutamate, which activates the postsynaptic N-methyl-D-aspartic acid (NMDA) receptors (Cárdenas-Rodríguez *et al.,*2013).
The most basic neurotoxicity of seizures is consumed the highest amount of oxygen in the brain paralleled with other organs (Alhassan *et al.,*2017; Sudha *et al.,*2001). Furthermore, these disorders' signs have been many anatomic aspects and electroencephalographic activity (Auvin *et al.,* 2012). Its frequency ratio between 0.7–1.0%with more incidences in mature persons and children (Fiest *et al.,*2017). The common diagnostic tests for epilepsy are magnetic resonance imaging or computed tomography used to assess the electrical activity of the brain scans (Giourou *et al.,*2015).

Side effect and risk dose of valproate in different ages

Long-period administration of valproate has been related to having a numeral adverse effect. One cohort study has been investigated that the majority of treated cases showed accumulation of valproate in the circulation system of the embryo, reaching a higher concentration than in the maternal blood. These observations may be responsible for causing toxicity, and increased risk of teratogenicity in nearly three-folds (Vajda, 2012) accompanied with severe hepatotoxicity in infants and young children (Sankar, 2007). Therefore, warring should be taken in patients with liver disease to avoid hepatic toxicity (Al-Quteimat & Laila, 2020).
Tong *et al.,* (2005) approved that a high daily dose of valproate for 14 consecutive days in rats increased the level of 15-F2t-IsoP that preceded the onset of liver necrosis and steatosis. Moreover, the risk of hypoglycemia was also approved (Bari, 2018). The valproate is also approved to have teratogenic action in most animal species, but the human embryo appears to be in peak susceptibility. Several studies suggest that polytherapy is associated with a higher teratogenic risk (Ornoy, 2009). These studies may explain the brain damage in offspring during pregnancy (Chen *et al.,* 2007). However, further studies approved that valproate over dosage led to developing conditions such as somnolence, heart block or deep coma, and finally, death (Chateauvieux *et al.,* 2010). Additionally, sodium valproate has approved the action on glucose level and lipid profile in diabetic rabbits and reflected a possible hypoglycemic and dyslipidemic (Bari, 2018). Valproate has also shown minor neurologic side effects that may be of particular importance in many children with epilepsy (Perucca *et al.,* 2006). In addition, more reported cases of lip and hyper gingival pigmentation with cutaneous vacuities were

described in patients treated with valproate (Giménez-García *et al.,* 2017). Nonetheless, some researchers were pointed that valproate can directly alter the production of the clotting factors and immune thrombocytopenia with autoantibodies (Chambers *et al.,* 1999). Additionally, Watts *et al.,* (1990) reported valproic acid-induced severe anemia and mild neutropenia and evaluated the correlation between the dosage and suppression information of blood. Severe agranulocytosis was reported in the patient suffering from intracerebral hemorrhage who used valproic acid to treat surgery complications (Hsu *et al.,* 2009) . Other researchers reported that valproate-treated females were revealed a higher risk of metabolic syndrome than males (Rakitin *et al.,* 2016). Moreover, the research results dating back to the 80s explained that Polycystic ovarian syndrome and hypogonadism occurred significantly more often in women with epileptic disorders than normal females (Herzog *et al.,*1986).

Another side effects, such as signs of nausea, vomiting, and gastrointestinal distress were occurred in up to 25% of patients who take VPA and could restrict the potential use of this drug in patients with diabetes (Rakitin, 2017). Another study found that VPA attenuated diabetes-induced renal injury in a rat model of diabetic nephropathy by inhibiting the endoplasmic reticulum stress response (Sun *et al.,* 2016) and mild hyperammonemia (Gerstner *et al.,* 2008). However, some of these studies reported increased seizures during VPA-carbapenem combination therapy (Huang *et al.,* 2017). Moreover, there is an increased risk of fetal abnormalities if valproate is taken in pregnancy (Ayano, 2016). Also, it was found to stimulate Menstrual disturbances, polycystic ovaries, hyperandrogenism (Gruenberg& Post, 2008), and testosterone levels (Akdeevniz *et al.,* 2003).

Mutagenic and genotoxic effects of valproate treatment may happen in offspring epileptic females (Denli *et al.,* 2000). Several research groups paid attention to the risk of VPA on autism spectrum conditions (Hajisoltani *et al.,*2019). Furthermore, the anticonvulsant depakine has been noted patho-histological alterations in the liver when the pregnant female rats and embryos treated with it (AL–Essawi *et al.,* 2020). In addition, reproductive endocrine coordination is more disorders with valproate (Death *et al.,* 2005). These observations suggested that valproate acted potentially on digestive system disturbances, sialoadenitis, and obesity (Mauz *et al.,* 2005). Different types of tremors can be caused by anticonvulsant drugs (Morgan & Sethi, 2005).

Toxicity on blood

The administration of valproate therapy was determined by a dose which is the key to showing the presence of impairments in blood with fatal aplastic anemia (So & Wong, 2002; Coyle *et al.,* 2005). Previous research on the frequency of severe thrombocytopenia and leucopenia in patients has been appropriated of Valproic acid (Blackburn et al.,1998). Moreover, hemorrhagic complications such as blood disorders and bone marrow suppression were also reported (Fajardo *et al.,* 2013) accompanied by clotting elements deficit (Kurwale *et al.,* 2016). Blanco Serrano *et al.,* 1999) showed depakine findings that are considered poorly correlated with total serum concentrations in both clinical and toxic effects. In addition, this valproate can alter hematopoiesis by inhibiting of erythroid differentiation process (Chateauvieux *et al.,*2011). However, using high levels of VPA is the end that resulted in hyponatremia, platelets dysfunction, and aminotransferase (Wu *et al.,* 2017).

Interaction with Exogenous and medication

Prescribing advice should highlight the possibility of drug interactions when multiple drugs are suggested. Remarkably, VPA was as effective and showed a favorable tolerability profile with minimal adverse cognitive if compared with other antiepileptic treatment (Guerrini, 2006). Valproate application uses are identified to be amplified with aspirin and erythromycin (Ayano, 2016). Controlled trials of Valproic acid therapy is an enzyme inhibitor, which can be, increased the plasma concentration of tricyclic antidepressants and lamotrigine drugs (Cohen, 2015). One of the putative reasons for recommending low doses of sodium valproate with vitamins C or E is probably the fact increase the anticonvulsant activity of the drug in mice (Zalkhani & Moazedi, 2020) by inhibits the neuronal damage produced by lipid peroxidation during seizures(Barros *et al.,* 2007). Recently the advancement of a novel combination of magnesium and low-dose valproate therapy has been used as migraine prophylaxis without any side effects (Khani *et al.,* 2021). Moreover, the Epileptic patients on polytherapy showed higher mean serum levels of homocysteine(Hcy) and lower mean serum levels of folic acid than monotherapy (Eldeen *et al.,* 2012; Ghasaq Sami Mshary, 2020). VPA significantly increased sensitivity to some drugs as fludarabine, flavopiridol, bortezomib, thalidomide, and lenalidomide (Stamatopoulos *et al.,* 2009]. Patients with epilepsy suspected to be infected with COVID-19 should be isolated; the caregiver should seek treatment, especially through oral care or aspirations, for prevention and protection against COVID-19 (Kuroda, 2020). Information about the potential combination of levetiracetam with valproic acid or carbamazepine resulted in the main reduction in physical sensitivity (Andonie *et al.,* 2018). Various studies focus on diet supplements (folate and omega-3) have been allied with anticonvulsants (Yerby, 2003).

Conclusion

Recently, exposure of the population to stress is continued due to the continuity of the COVID-19 pandemic that leads to pathophysiological mood disorders (DeVane, 2003). All these cases are initiated for seizure precipitation in most epilepsies (Parihar et al., 2020). Numerous diseases, such as a schizophrenia, are achieved by antipsychotic preparations (Tekİn *et al.,* 2021). Therefore, the use of Valproate under strict regulation with standard protocols for therapy is generally recommended. Valproate, levetiracetam, and phenobarbital drugs had differing benefits and problems as long as raising the perception of the drug interaction among health care providers plus totals of most neurologists and psychiatrists in charge for mentioning of valproate who lack the awareness, experience, and other skills. The interaction of valproate with other drugs is associated with a major risk of congenital disabilities in kids. The current review article showed the association of VPA with coagulation factors deficiency, which helps evaluate the platelet function with fatal aplastic anemia. Moreover, patients having coagulation abnormalities before surgery and may require tapering and stopping VPA. Additionally, valproate has been reported also as antimigraine action but should rarely be used in bipolar disorder in pregnancy. The unlimited advantage of VPA that it is in repetitive medical use for several years, indicating slight side effects; however, severe complexities and serious consequences

of valproate have also been reported. It is worth mentioning that valproate acts as analogous to other antiepileptic drugs. Furthermore, depakine is avoided using in people with hypersensitivity from this drug (Macfarlane & Greenhalgh, 2018). Innovative information on pathophysiological mechanisms of several aspects of tremor and highlight the role of movement direction and velocity is resulted by using valproate drug (Paparella *et al.,* 2020).

Conflicts of interest

There are no conflicts of interest.

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References

Alhassan AW, Mohammed DK, Saleh MIA, Mshelia PP, Yarube IU, & Lawan I (2017). Combined effect of sodium valproate and ascorbic acid on pentylenetetrazole-induced seizures in mice. Bayero Journal of Pure and Applied Sciences. 2017;10(1):47-50. **DOI:** 10.4314/bajopas.v10i1.6

Akdeniz F, Taneli F, Noyan A, Yüncü Z, Vahip S. Valproate-associated reproductive and metabolic abnormalities: are epileptic women at greater risk than bipolar women? Prog Neuropsychopharmacol Biol Psychiatry. 2003 Feb;27(1):115-21. doi: 10.1016/s0278-5846(02)00341-x. PMID: 12551733.
Perucca E, Aldenkamp A, Tallis R, Krämer G. Role of valproate across the ages. Treatment of epilepsy in the elderly. Acta Neurol Scand Suppl. 2006;184:28-37. doi: 10.1111/j.1600-0404.2006.00668.x. PMID: 16776494.

AL–Essawi, DA HK, Ghiadh SJ, & Alhadad ASI. Depakine drug effects on some reproductive embryonic parameters and hepatic-histological changes during pregnancy of albino female rats. European Journal of Molecular & Clinical Medicine.2020;7(2):5791-5808.

Al-Quteimat O, Laila A. Valproate Interaction With Carbapenems: Review and Recommendations. Hosp Pharm. 2020 Jun;55(3):181-187. doi: 10.1177/0018578719831974. Epub 2019 Feb 22. PMID: 32508355; PMCID: PMC7243600.

Andonie DA, Seremet OC, Stefanescu E, Zanfirescu A, Grosan A, Osz, BE & Dogaru MT. The pharmacological effect of valproic acid, levetiracetam, carbamazepine and the coadministration of valproic acid-levetiracetam and carbamazepine-levetiracetam on tactile sensitivity, motor activity and the formation of conditioned reflex in rats. Farmacia. 2018;66(2):267-274.

Auvin S, Pineda E, Shin D, Gressens P, Mazarati A. Novel animal models of pediatric epilepsy. Neurotherapeutics. 2012 Apr;9(2):245-61. doi: 10.1007/s13311-012-0119-8. PMID: 22467296; PMCID: PMC3337021.

Ayano G. Bipolar disorders and valproate: Pharmacokinetics, pharmacodynamics and therapeutic effects and indications of valproate: Review of articles. Bipolar Disord. **2016;**2(109):2472-1077. DOI: 10.4172/2472-1077.1000109

Abdul Bari MA. Sodium valproate effects on lipid profile and glucose level in normal and diabetic rabbits. Iraqi JMS. 2018; 16(3): 247-257. doi: 10.22578/IJMS.16.3.4

Barros DO, Xavier SM, Barbosa CO, Silva RF, Freitas RL, Maia FD, Oliveira AA, Freitas RM, Takahashi RN. Effects of the vitamin E in catalase activities in hippocampus after status epilepticus induced by pilocarpine in Wistar rats. Neurosci Lett. 2007 Apr 18;416(3):227-30. doi: 10.1016/j.neulet.2007.01.057. Epub 2007 Jan 30. PMID: 17383094.

Blackburn SC, Oliart AD, García Rodríguez LA, Pérez Gutthann S. Antiepileptics and blood dyscrasias: a cohort study. Pharmacotherapy. 1998 Nov-Dec;18(6):1277-83. PMID: 9855327.

Blanco Serrano, B., Garcia Sanchez, M. J., Otero, M. J., Santos Buelga, D., Serrano, J., & Domínguez-Gil, A. (1999). Valproate population pharmacokinetics in children. Journal of clinical pharmacy and therapeutics. 24(1):73-80. **https://doi.org/10.1046/j.1365-2710.1999.00202.x**

Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, Feldman E, Iverson DJ, Perkins B, Russell JW, Zochodne D. American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology. 2011 May 17;76(20):1758-65. doi: 10.1212/WNL.0b013e3182166ebe. Epub 2011 Apr 11. Erratum in: Neurology. 2011 Aug 9;77(6):603. Dosage error in article text. PMID: 21482920; PMCID: PMC3100130.

Cárdenas-Rodríguez N, Coballase-Urrutia E, Rivera-Espinosa L, Romero-Toledo A, Sampieri A 3rd, Ortega-Cuellar D, Montesinos-Correa H, Floriano-Sánchez E, Carmona-Aparicio L. Modulation of antioxidant enzymatic activities by certain antiepileptic drugs (valproic acid, oxcarbazepine, and topiramate): evidence in humans and experimental models. Oxid Med Cell Longev. 2013;2013:598493. doi: 10.1155/2013/598493. Epub 2013 Dec 17. PMID: 24454986; PMCID: PMC3877618.

Chambers HG, Weinstein CH, Mubarak SJ, Wenger DR, Silva PD. The effect of valproic acid on blood loss in patients with cerebral palsy. J Pediatr Orthop. 1999 Nov-Dec;19(6):792-5. PMID: 10573351.

Chateauvieux S, Eifes S, Morceau F, Grigorakaki C, Schnekenburger M, Henry E, Dicato M, Diederich M. Valproic acid perturbs hematopoietic homeostasis by inhibition of erythroid differentiation and activation of the myelo-monocytic pathway. Biochem Pharmacol. 2011 Feb 15;81(4):498-509. doi: 10.1016/j.bcp.2010.11.011. Epub 2010 Nov 23. PMID: 21108933.

Chateauvieux S, Morceau F, Dicato M, Diederich M. Molecular and therapeutic potential and toxicity of valproic acid. J Biomed Biotechnol. 2010;2010:479364. doi: 10.1155/2010/479364. Epub 2010 Jul 29. PMID: 20798865; PMCID: PMC2926634.

Chen PS, Wang CC, Bortner CD, Peng GS, Wu X, Pang H, Lu RB, Gean PW, Chuang DM, Hong JS. Valproic acid and other histone deacetylase inhibitors induce microglial apoptosis and attenuate lipopolysaccharide-induced dopaminergic neurotoxicity. Neuroscience. 2007 Oct 12;149(1):203-12. doi: 10.1016/j.neuroscience.2007.06.053. Epub 2007 Jul 28. PMID: 17850978; PMCID: PMC2741413.

Cohen, H. (2015). Casebook in clinical pharmacokinetics and drug dosing. ISBN 978-0-07-162835-8. https://accesspharmacy.mhmedical.com/content.aspx?bookid=1514&sectionid=86298946

Coyle TE, Bair AK, Stein C, Vajpayee N, Mehdi S, Wright J. Acute leukemia associated with valproic acid treatment: a novel mechanism for leukemogenesis? Am J Hematol. 2005 Apr;78(4):256-60. doi: 10.1002/ajh.20273. PMID: 15795916.

Casucci G, Villani V, Frediani F. Central mechanism of action of antimigraine prophylactic drugs. Neurol Sci. 2008 May;29 Suppl 1:S123-6. doi: 10.1007/s10072-008-0902-9. PMID: 18545912.

Death AK, McGrath KC, Handelsman DJ. Valproate is an anti-androgen and anti-progestin. Steroids. 2005 Dec 15;70(14):946-53. doi: 10.1016/j.steroids.2005.07.003. Epub 2005 Sep 13. PMID: 16165177.

Denli M, Aydin HI, Döndaröz R, Özişik T, Erdem E & Baltaci V. Genotoxicity evaluation in female patients on valproic acid monotherapy using alkaline single cell gel electrophoresis (comet assay). East J Med. **2000;** 5(2), 61-65.

DeVane CL. Pharmacokinetics, drug interactions, and tolerability of valproate. Psychopharmacol Bull. 2003;37 Suppl 2:25-42. PMID: 14624231.

Duenas-Gonzalez A, Candelaria M, Perez-Plascencia C, Perez-Cardenas E, de la Cruz-Hernandez E, Herrera LA. Valproic acid as epigenetic cancer drug: preclinical, clinical and transcriptional effects on solid tumors. Cancer Treat Rev. 2008 May;34(3):206-22. doi: 10.1016/j.ctrv.2007.11.003. Epub 2008 Jan 15. PMID: 18226465.

Eldeen ON, Abd Eldayem SH, Shatla RH, Omara NA, & Elgammal SS. Homocysteine, folic acid and vitamin B12 levels in serum of epileptic children. Egyptian Journal of Medical Human Genetics. 2012, 13(3): 275-280. http://dx.doi.org/10.1016/j.ejmhg.2012.05.002

Fajardo Angélica, Olmos Francisco, Sarmiento Lina. Valproic acid and the risk of perioperative bleeding. Case report and literature review. Rev. colomb. anestesiol. 2013 Mar [cited 2021 May 01] ; 41(1): 61-64. Available from: http://www.scielo.org.co/scielo.php?script=sci_arttext&pid=S0120-33472013000100011&lng=en. https://doi.org/10.1016/j.rca.2012.07.009.

Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon CS, Dykeman J, Pringsheim T, Lorenzetti DL, Jetté N. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. Neurology. 2017 Jan 17;88(3):296-303. doi: 10.1212/WNL.0000000000003509. Epub 2016 Dec 16. Erratum in: Neurology. 2017 Aug 8;89(6):642. PMID: 27986877; PMCID: PMC5272794.

Gerstner T, Bell N, König S. Oral valproic acid for epilepsy--long-term experience in therapy and side effects. Expert Opin Pharmacother. 2008 Feb;9(2):285-92. doi: 10.1517/14656566.9.2.285. PMID: 18201150.

Ghasaq Sami Mshary. Physiological effect and role of dietary folic acid in regenerative medicine: Review.Mirror of Research in Veterinary Sciences and animals (MRVSA). 2020. 9 (1): 37-48. Doi: http://dx.doi.org/10.22428/mrvsa-2020-0093-03.

Ghodke-Puranik Y, Thorn CF, Lamba JK, Leeder JS, Song W, Birnbaum AK, Altman RB, Klein TE. Valproic acid pathway: pharmacokinetics and pharmacodynamics. Pharmacogenet Genomics. 2013 Apr;23(4):236-41. doi: 10.1097/FPC.0b013e32835ea0b2. PMID: 23407051; PMCID: PMC3696515.

Gimenez- Garcia Rosa, Sergio Carrasco-Molina, Belen Zambrano-Centeno. Valproic Acid - Induced Hyperpigmentation. 2017, 2(1):16-18. doi: dx.doi.org/10.20431/2456-0022.0201003.

Giourou E, Stavropoulou-Deli A, Giannakopoulou A, Kostopoulos GK, & Koutroumanidis M.. Introduction to Epilepsy and Related Brain Disorders. In Cyberphysical Systems for Epilepsy and Related Brain Disorders. 2015. (pp. 11-38). Springer, Cham.

Glister C, Satchell L, Michael AE, Bicknell AB, Knight PG. The anti-epileptic drug valproic acid (VPA) inhibits steroidogenesis in bovine theca and granulosa cells in vitro. PLoS One. 2012;7(11):e49553. doi: 10.1371/journal.pone.0049553. Epub 2012 Nov 12. PMID: 23152920; PMCID: PMC3495868.

Gruenberg A. Treatment of Bipolar Illness: A Casebook for Clinicians and Patients. By R. M. Post and G. S. Leverich. (Pp. 704; $65.00; ISBN 13: 978-0-393-70537-9.)

Norton Professional Books: New York, NY. 2008. *Psychological Medicine, 38*(11), 1676-1677. doi:10.1017/S0033291708004297

Guerrini R. Valproate as a mainstay of therapy for pediatric epilepsy. Pediatric Drugs. 2006;8(2):113-29. doi: 10.2165/00148581-200608020-00004. PMID: 16608372.

Houghton BL, Bowers JB. Valproic acid overdose: a case report and review of therapy. MedGenMed. 2003 Jan 14;5(1):5. PMID: 12827066.

Razieh Hajisoltani, Seyed Asaad Karimi, Mona Rahdar, Shima Davoudi, Mehdi Borjkhani, Narges Hosseinmardi, Gila Behzadi, Mahyar Janahmadi. Hyperexcitability of hippocampal CA1 pyramidal neurons in male offspring of a rat model of autism spectrum disorder (ASD) induced by prenatal exposure to valproic acid: A possible involvement of Ih channel current, Brain Research. 2019. Volume 1708,:188-199. https://doi.org/10.1016/j.brainres.2018.12.011.

Heers H, Stanislaw J, Harrelson J, Lee MW. Valproic acid as an adjunctive therapeutic agent for the treatment of breast cancer. Eur J Pharmacol. 2018 Sep 15;835:61-74. doi: 10.1016/j.ejphar.2018.07.057. Epub 2018 Jul 31. PMID: 30075223.

Herzog AG, Seibel MM, Schomer DL, Vaitukaitis JL, Geschwind N. Reproductive Endocrine Disorders in Women With Partial Seizures of Temporal Lobe Origin. Arch Neurol. 1986. 43(4):341–346. doi:10.1001/archneur.1986.00520040029014

Hui-Chuan Hsu, Hsiang-Kuang Tseng, Shen-Chuan Wang, Ying-Yue Wang. Valproic Acid-induced Agranulocytosis. International Journal of Gerontology. 2009. Volume 3; Issue 2:137-139. https://doi.org/10.1016/S1873-9598(09)70036-5. (https://www.sciencedirect.com/science/article/pii/S1873959809700365)

Huang CR, Lin CH, Hsiao SC, Chen NC, Tsai WC, Chen SD, Lu YT, Chuang YC. Drug interaction between valproic acid and carbapenems in patients with epileptic seizures. Kaohsiung J Med Sci. 2017 Mar;33(3):130-136. doi: 10.1016/j.kjms.2016.12.001. Epub 2017 Jan 11. PMID: 28254115.

Janszky I, Hallqvist J, Tomson T, Ahlbom A, Mukamal KJ, Ahnve S. Increased risk and worse prognosis of myocardial infarction in patients with prior hospitalization for epilepsy--the Stockholm Heart Epidemiology Program. Brain. 2009 Oct;132(Pt 10):2798-804. doi: 10.1093/brain/awp216. Epub 2009 Aug 28. PMID: 19717532.

Khani S, Hejazi SA, Yaghoubi M, Sharifipour E. Comparative study of magnesium, sodium valproate, and concurrent magnesium-sodium valproate therapy in the prevention of migraine headaches: a randomized controlled double-blind trial. J Headache Pain. 2021 Apr 7;22(1):21. doi: 10.1186/s10194-021-01234-6. PMID: 33827421; PMCID: PMC8028183.

Kuroda N. Epilepsy and COVID-19: Associations and important considerations. Epilepsy Behav. 2020 Jul;108:107122. doi: 10.1016/j.yebeh.2020.107122. Epub 2020 Apr 22. PMID: 32361677; PMCID: PMC7174174.

Kurwale N, Garg K, Arora A, Chandra PS, Tripathi M. Valproic acid as an antiepileptic drug: Is there a clinical relevance for the epilepsy surgeon? Epilepsy Res. 2016 Nov;127:191-194. doi: 10.1016/j.eplepsyres.2016.09.005. Epub 2016 Sep 4. PMID: 27610748.

Luef GJ, Lechleitner M, Bauer G, Trinka E, Hengster P. Valproic acid modulates islet cell insulin secretion: a possible mechanism of weight gain in epilepsy patients. Epilepsy Res. 2003 Jun-Jul;55(1-2):53-8. doi: 10.1016/s0920-1211(03)00091-3. PMID: 12948616.

Macfarlane A, Greenhalgh T. Sodium valproate in pregnancy: what are the risks and should we use a shared decision-making approach? BMC Pregnancy Childbirth. 2018 Jun 1;18(1):200. doi: 10.1186/s12884-018-1842-x. PMID: 29859057; PMCID: PMC5984824.

Magiorkinis E, Sidiropoulou K, Diamantis A. Hallmarks in the history of epilepsy: epilepsy in antiquity. Epilepsy Behav. 2010 Jan;17(1):103-8. doi: 10.1016/j.yebeh.2009.10.023. Epub 2009 Dec 5. PMID: 19963440.

Mauz PS, Mörike K, Kaiserling E, Brosch S. Valproic acid-associated sialadenosis of the parotid and submandibular glands: diagnostic and therapeutic aspects. Acta Otolaryngol. 2005 Apr;125(4):386-91. doi: 10.1080/00016480410024460. PMID: 15823809.

Morgan JC, Sethi KD. Drug-induced tremors. Lancet Neurol. 2005 Dec;4(12):866-76. doi: 10.1016/S1474-4422(05)70250-7. PMID: 16297844.

Negreş S, Zbârcea CE, Arsene A, Chiriţă C, Buzescu A, Velescu BŞ, Ştefănescu E, Şeremet OC, Nicolescu F. (2013), Experimental pharmacological model for inducing and quantifying depression in mouse. Farmacia. 2013. 61(6): 1102-1116. http://www.revistafarmacia.ro/201306/art-07-negres%201102-1116.pdf

Ornoy A. Valproic acid in pregnancy: how much are we endangering the embryo and fetus? Reprod Toxicol. 2009 Jul;28(1):1-10. doi: 10.1016/j.reprotox.2009.02.014. Epub 2009 Mar 13. PMID: 19490988.

Giulia Paparella, Luca Angelini, Alessandro De Biase, Antonio Cannavacciuolo, Donato Colella, Carlo Di Bonaventura, Anna Teresa Giallonardo, Alfredo Berardelli & Matteo Bologna. Clinical and Kinematic Features of Valproate-Induced Tremor and Differences with Essential Tremor. The Cerebellum, 1-10. https://doi.org/10.1007/s12311-020-01216-5

Parihar J, Tripathi M, Dhamija RK. Seizures and Epilepsy in Times of Corona Virus Disease 2019 Pandemic. J Epilepsy Res. 2020 Jun 30;10(1):3-7. doi: 10.14581/jer.20002. PMID: 32983949; PMCID: PMC7494888.

Petroff OA, Rothman DL, Behar KL, Hyder F, Mattson RH. Effects of valproate and other antiepileptic drugs on brain glutamate, glutamine, and GABA in patients with refractory complex partial seizures. Seizure. 1999 Apr;8(2):120-7. doi: 10.1053/seiz.1999.0267. PMID: 10222306.

Poolchanuan P, Unagul P, Thongnest S, Wiyakrutta S, Ngamrojanavanich N, Mahidol, C& Kittakoop P. An anticonvulsive drug, valproic acid (valproate), has effects on the biosynthesis of fatty acids and polyketides in microorganisms. Scientific reports. 2020. 10(1), 1-11. https://doi.org/10.1038/s41598-020-66251-y

Rakitin A. Does Valproic Acid Have Potential in the Treatment of Diabetes Mellitus? Front Endocrinol (Lausanne). 2017 Jun 26;8:147. doi: 10.3389/fendo.2017.00147. PMID: 28694790; PMCID: PMC5483554.
Rakitin A, Kõks S, Haldre S. Metabolic syndrome and anticonvulsants: A comparative study of valproic acid and carbamazepine. Seizure. 2016 May;38:11-6. doi: 10.1016/j.seizure.2016.03.008. Epub 2016 Mar 30. PMID: 27061880.

Rakitin A, Kõks S, Reimann E, Prans E, Haldre S. Changes in the Peripheral Blood Gene Expression Profile Induced by 3 Months of Valproate Treatment in Patients with Newly Diagnosed Epilepsy. Front Neurol. 2015 Aug 31;6:188. doi: 10.3389/fneur.2015.00188. PMID: 26379622; PMCID: PMC4553897.

Sankar R. Teratogenicity of antiepileptic drugs: role of drug metabolism and pharmacogenomics. Acta Neurol Scand. 2007 Jul;116(1):65-71. doi: 10.1111/j.1600-0404.2007.00830.x. PMID: 17587258.

Stamatopoulos, B., Meuleman, N., De Bruyn, C., Mineur, P., Martiat, P., Bron, D., & Lagneaux, L. (2009). Antileukemic activity of valproic acid in chronic lymphocytic leukemia B cells defined by microarray analysis. Leukemia. 2009. 23;(12):2281-2289. https://doi.org/10.1038/leu.2009.176

Shakespeare, J., & Sisodiya, S. M. (2019). Guidance document on valproate use in women and girls of childbearing years. Royal College of General Practitioners. https://www.rcog.org.uk/globalassets/documents/guidelines/valproate-guidance-march-2019.pdf

So CC, Wong KF. Valproate-associated dysmyelopoiesis in elderly patients. American Journal of Clinical Pathology. 2002 Aug;118(2):225-228. DOI: 10.1309/4tef-lvgx-weq9-r8w8.

Sridharan R. "Epidemiology of Epilepsy." Current Science. 82, no. 6 (2002): 664-70. Accessed May 1, 2021. http://www.jstor.org/stable/24106692.

Sudha K, Rao AV, Rao A. Oxidative stress and antioxidants in epilepsy. Clin Chim Acta. 2001 Jan;303(1-2):19-24. doi: 10.1016/s0009-8981(00)00337-5. PMID: 11163018.

Sun Xin-Yi, Han-Jiao Qin, Ze Zhang, Ye Xu, Xiao-Chun Yang, Dong-Ming Zhao,Xiao-Ning Li, Lian-Kun Sun. Valproate attenuates diabetic nephropathy

through inhibition of endoplasmic reticulum stress-induced apoptosis. Molecular Medicine Reports. 2016. 13(1): 661-668 .https://doi.org/10.3892/mmr.2015.4580

Swanson, B. N., Harland, R. C., Dickinson, R. G., & Gerber, N. (1978). Excretion of valproic acid into semen of rabbits and man. Epilepsia, 19(6), 541-546.

TekİN M, Kaya Yertutanol FD, Çevrelİ B, ÖzdoĞru AA, Kulaksiz H, Uzbay İT. Sodium valproate improves sensorimotor gating deficit induced by sleep-deprivation in low doses. Turkish Journal of Medical Sciences. 2021 Feb. DOI: 10.3906/sag-2011-229.

Anton Terasmaa, Ursel Soomets, Julia Oflijan, Marite Punapart, Mats Hansen, Vallo Matto, Kersti Ehrlich, Anne Must, Sulev Kõks & Eero Vasar. Wfs1 mutation makes mice sensitive to insulin-like effect of acute valproic acid and resistant to streptozocin. Journal of physiology and biochemistry. 2011. 67(3):381-390. https://doi.org/10.1007/s13105-011-0088-0

Tong V, Teng XW, Chang TK, Abbott FS. Valproic acid I: time course of lipid peroxidation biomarkers, liver toxicity, and valproic acid metabolite levels in rats. Toxicol Sci. 2005 Aug;86(2):427-35. doi: 10.1093/toxsci/kfi184. Epub 2005 Apr 27. PMID: 15858223.

Unal G, Turan B, Balcioglu YH. Immunopharmacological management of COVID-19: Potential therapeutic role of valproic acid. Med Hypotheses. 2020 Oct;143:109891. doi: 10.1016/j.mehy.2020.109891. Epub 2020 May 27. PMID: 32498007; PMCID: PMC7255327.

Vajda, F. (2012). Dose issues in antiepileptic therapy. Journal of Clinical Neuroscience. 2012. 19(11):1475-1477.
https://doi.org/10.1016/j.jocn.2012.05.003

Verrotti A, Trotta D, Morgese G, Chiarelli F. Valproate-induced hyperammonemic encephalopathy. Metab Brain Dis. 2002 Dec;17(4):367-73. doi: 10.1023/a:1021918104127. PMID: 12602513.

Watts RG, Emanuel PD, Zuckerman KS, Howard TH. Valproic acid-induced cytopenias: evidence for a dose-related suppression of hematopoiesis. J Pediatr. 1990 Sep;117(3):495-9. doi: 10.1016/s0022-3476(05)81105-9. PMID: 2118175.

Wood JR, Nelson-Degrave VL, Jansen E, McAllister JM, Mosselman S, Strauss JF 3rd. Valproate-induced alterations in human theca cell gene expression: clues to the association between valproate use and metabolic side effects. Physiol Genomics. 2005 Feb 10;20(3):233-43. doi: 10.1152/physiolgenomics.00193.2004. Epub 2004 Dec 14. PMID: 15598877.

Wu XT, Hong PW, Suolang DJ, Zhou D, Stefan H. Drug-induced hypersensitivity syndrome caused by valproic acid as a monotherapy for epilepsy: First case report in Asian population. Epilepsy Behav Case Rep. 2017 Jun 20;8:108-110. doi: 10.1016/j.ebcr.2017.06.003. PMID: 29204346; PMCID: PMC5707210.

Ximenes José Christian Machado, Danilo de Oliveira Gonçalves, Rafaelly Maria Pinheiro Siqueira, Kelly Rose Tavares Neves, Gilberto Santos Cerqueira, Alyne Oliveira Correia, Francisco Hélder Cavalcante Félix, Luzia Kalyne Almeida Moreira Leal, Gerly Anne de Castro Brito, Maria da Graça Naffah-Mazzacorati & Glauce Socorro de Barros Viana. Valproic acid: an anticonvulsant drug with potent antinociceptive and anti-inflammatory properties. Naunyn-Schmiedeberg's archives of pharmacology. 2013. 386(7):575-587. https://doi.org/10.1007/s00210-013-0853-4

Yerby MS. Management issues for women with epilepsy: neural tube defects and folic acid supplementation. Neurology. 2003 Sep 1;61(6 Suppl 2):S23-6. doi: 10.1212/wnl.61.6_suppl_2.s23. PMID: 14504306.

Zalkhani R, & Moazedi A. Basic and clinical role of vitamins in epilepsy. Journal of Research in Applied and Basic Medical Sciences. 2020. 6(2):104-114. http://ijrabms.umsu.ac.ir/article-1-106-en.pdf