REVIEW ARTICLE

Year : 2017
Volume : 4
Issue Number : 1
Doi Number : 10.5455/JNBS.1481879445

Article history:
Received 16 December 2016
Received in revised form 29 January 2017
Accepted 27 February 2017

ALTERATION OF NEUROBEHAVIOURAL ACTIVITIES BY CARBAMAZEPINE, PHENYTOIN AND THEIR COMBINATION IN WISTAR RATS: A MINI REVIEW

WİSTAR SIÇANLARINDA KARBAMAZEPİN, FENİTOİN VE BU İKİSİNİN KARIŞIMINA BAĞLI OLARAK NÖRODAVRANIŞSAL AKTİVİTELERİN DEĞİŞİMİ: KISA BİR DEĞERLENDİRME

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Abstract

Antiepileptic drugs (AEDs) have been used for decades in the treatment of seizures in both humans and animals. There are different varieties of AEDs to choose from, the choice of an AED is determined by the seizure type, effectiveness of the drug in controlling seizure, cost and the side effects of the drug used. Epilepsy therapy could be monotherapy, that is, the use of an appropriate AED or polytherapy in which case, two or more AEDs are combined particularly in the case of refractory epilepsy. The side effects of AEDs are diverse and affect virtually all the systems of the body. This review is aimed at studying the side effects associated with the administration of carbamazepine, phenytoin and their combination on cognition and neurobehavioural generally, particularly in Wistar rats. Generally, the side effects of AEDs observed are not so detrimental because the discontinuation of the drugs usually cause a reverse of the effects observed. For this review, available informations on the effects of antiepileptic drugs on neurobehavioural activities were accessed from electronic databases.

Keywords: carbamazepine, phenytoin, learning, short-term memory, locomotion, rearing.

Özet

Antiepileptik ilaçlar (AED), hem insan hem de hayvanlardaki hastalık nöbetlerinin tedavisinde on yıllar boyunca kullanılagelmiştir. Antiepileptik ilaçların farklı türleri mevcuttur ve bu tür ilaçları seçerken geçirilen nöbet çeşidi, ilacın krizi kontrol altına alma hususundaki etkililiği ile kullanılan ilacın masrafı ve yan etkileri dikkate alınır. Epilepsi terapisi, uygun bir antiepileptik ilaç kullanımıyla yürütülen monoterapi şeklinde ya da özellikle dirençli epilepsi vakalarında başvurulan ve iki veya daha fazla antiepileptik ilacın karışımıyla gerçekleştirilen politerapi yöntemiyle uygulanabilir. Antiepileptik ilaçların yan etkileri çeşitlilik arz etmekte olup neredeyse tüm vücut sistemlerini etkiler. Bu değerlendirme, karbamazepin, fenitoin ve bu iki ilacın birleşiminin özellikle Wistar sıçanlarının bilişsel ve nörodavranışsal faaliyetleri üzerindeki yan etkilerini incelemeyi hedeflemektedir. Genel olarak antiepileptik ilaçlarla ilgili ortaya çıkan yan etkiler, ilacın kesilmesine bağlı olarak gözlemlenen ters etki sebebiyle zannedildiği kadar zararlı değildir. Bu değerlendirmede, antiepileptik ilaçların nörodavranışsal aktiviteler üzerindeki etkileriyle ilgili mevcut bilgilere elektronik veri tabanlarından erişilmiştir.

Anahtar Kelimeler: *karbamazepin, fenitoin, öğrenme, kısa süreli hafıza, hareket kabiliyeti, yetiştirme.*

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THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
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1. Introduction

The prevalence and phenomenology of naturally-occurring canine epilepsy are similar to those of humans, and it has been observed that head trauma in dogs is associated with a significant risk of developing epilepsy (Steinntze et al., 2013). Behaviour and cognition in patients with epilepsy may be affected by multiple factors including aetiology of the seizure, seizure type, frequency, duration, and severity; cerebral lesions acquired before seizure onset; age at seizure onset; intraictal and interictal physiological dysfunction due to the seizures; structural cerebral damage due to repetitive or prolonged seizures; hereditary factors; psychosocial factors; sequelae of epilepsy surgery; and untoward effects of antiepileptic drugs (AEDs) (Loring and Meador, 2001). Subtle impairment of cognitive function and behaviour occur with modest or therapeutic levels of phenytoin (PHE), valproic acid (VPA), phenobarbitone (PB) and carbamazepine (CBZ) (Balakrishnan et al., 1998). (Meador et al., 1991) reported that rather than being overtly manifest, subtle changes in cognitive and psychomotor functions do occur commonly with long-term antiepileptic drug (AED) therapy, especially phenytoin. Although the behavioural and cognitive effects of AEDs are less than the total of other factors of epilepsy, AEDs are of special concern because they are the major therapeutic modality for seizures and studying the cognitive effects of an AED should first be carried out in normal non-epileptic subjects. More importantly, a drug should theoretically be tested in well defined epilepsy syndromes with 'as homogeneous as possible' patient populations. An anti-epileptic drug theoretically can induce different cognitive effects in different epilepsy syndromes (Lagae, 2006). For instance, it is known that frontal epilepsy in a child is more prone to attention problems (Auclair et al 2005). The most common AED cognitive effects include psychomotor slowing, reduced vigilance, and impairments in memory (Loring and Meador, 2001). Phenobarbital (PB) and benzodiazepines (BZDs) possess the most marked adverse cognitive effects; major older AEDs, carbamazepine (CBZ), phenytoin (PHT), and valproate (VPA) have similar cognitive effects while the newer AEDs Gabapentine (GBP), lamotrigine (LTG), Tiagabine (TGB) and vigabatrin (VGB) produce fewer cognitive effects. Of the new AEDs, topiramate (TPM) appears to have the greatest cognitive side effect (Loring and Meador, 2001).

2. Therapy

Antiepileptic drugs (AEDs) are designed to reduce neuronal irritability and are the first choice for the treatment of new-onset epilepsy. In addition to their effects on abnormal brain activity, AEDs also decrease normal neuronal excitability, which may adversely affect cognitive function. But, the cognitive side effects of AED monotherapy are generally not pronounced when anticonvulsant blood levels are within the standard therapeutic range (Dodrill and Trompin, 1991). Cognitive side effects may be partially offset in patients with frequent seizures simply by virtue of their therapeutic effects on seizure control. The risk of significant cognitive side effects increases with higher drug dosages and with polypharmacy (Loring and Meador, 2001). The choice of an AED for any individual should take into cognisance information about seizure control, adverse effects and cost (Gamble et al, 2009).

3. Antiepileptic drugs

Both phenytoin (PHE) and carbamazepine (CBZ) are widely used potent AEDs (Tripathy et al., 2000). Phenytoin sodium (PHE) is an anticonvulsant used to control grand mal and psychomotor seizures. It can cause various neurological disorders, when given for a long time. It produces chromosomal anomalies and increased incidence of malignant melanoma (Vijay et al., 2009). PHE blocks voltage-sensitive sodium ion channels; therefore, inhibiting neuronal firing in the brain (Rykacezewka-Czerminska, 2007). Newer AEDs that may have fewer side-effects are now available, but PHE continues to occupy an important role in the pharmacological treatment of epilepsy. This is particularly so for patients on long-standing PHE regimens that may require months to years of modification of the drug regimens and doses to achieve optimal control of their disease (Chen et al., 2001).

Carbamazepine is an iminostilbene, a dibenzepine derivative that is chemically and pharmacologically related to tricyclic antidepressant agents (Bazil & Pedley, 2003). CBZ is a highly used conventional AED, which has efficacy in attenuating picrotoxin-induced convulsion (Ali et al., 2003). CBZ is the usual drug of choice for patients with newly- diagnosed partial onset seizure (Shaikh et al., 2011). Side-effects of CBZ include: drowsiness, accommodation disorders among others (Jallon, 2007).

4. Rational polypharmacy of antiepileptic drugs

Epilepsy treatment has evolved from institutionalised polytherapy to dogmatic monotherapy and then to rational polypharmacy (Kramer, 1997). Polytherapy in epilepsy is a preferred regimen in patients with intractable seizures (Loscher & Ebert, 1996). The rationale for combining some AEDs is usually based upon the presumptions concerning two aspects of efficacious treatment; the first aspect is directly related to the anticonvulsant activity of the combination drugs, while the second one takes into consideration the side-effect profile of the co-administered drugs (Czuczwer et al., 2001) & (Le Couteur & Child, 1998). It has been established that polytherapy gives an improved control of epilepsy (Sun et al., 2002). Rational polypharmacy of AEDs is one of the treatment strategies for refractory epilepsy (Cascino, 1990).

5. Role of Rational Polypharmacy in the Treatment of Refractory Epilepsy

Refractory epilepsy or intractable seizures occur when epileptic symptoms are not responding to treatment. Seizures are well controlled with a single anticonvulsant in most epileptic patients. However, about 20% of patients with primary generalised epilepsy and 35% of patients with focal epilepsy have medically intractable

seizures (Reuten & Berkovich, 1995); (Jinsook et al., 2007). Some medical approaches undertaken in the management of intractable epilepsy include the use of drugs with complementary mechanisms of action, stimulation of various components of the nervous system, biochemical manipulations, focal intracerebral drug perfusion and gene therapy (Jallon, 2007). Some of the drug combinations employed in rational antiepileptic polypharmacy include; Levetiracetam and carbamazepine (Lusczki, 2004), carbamazepine and valproate (Sun et al., 2002), lamotrigine and valproate, lamotrigine and carbamazepine, lamotrigine and diphenylhydantoin (Lusczki, 2004), carbamazepine and phenytoin (Lai et al., 1992), carbamazepine and phenytoin (Perruca &Richens, 1980), carbamazepine, phenytoin, phenobarbital and valproic acid (Bhosale et al., 2014).

6. Side-effects of Antiepileptic drugs

The incidence of adverse effects is an important issue when prescribing antiepileptic drugs (AEDs), as some of the most effective medications for seizures are associated with a considerable degree of toxicity. Studies indicate that drug tolerance by individuals is a significant limiting factor in the treatment of seizure and drug retention rates are often determined by side-effect profiles (Bootsman et al., 2009); (Chung et al 2007). Older AEDs may still be prescribed, owing to advantages that include lower cost, wide availability and long-term usage with known effects, but often exhibit greater toxicity than newer drugs (Eddy et al., 2011). Newly developed agents tend to differ in terms of mechanisms of action and pharmacokinetic properties, and are often better tolerated than older drugs. However, all AEDs have the potential to exert detrimental effects on cognitive function; a thorough appreciation of the negative cognitive effects linked to a variety of AEDs makes a crucial contribution to therapeutic successes (Meldrum, 2002). As a means of evaluating the side-effect profile of AEDs in combination, all available combinations should be tested on animals. It is widely accepted that in animal models, some neurotoxic effects produced by AEDs in combinations can easily be determined, which may be sufficient enough for further clinical use in patients (Loscher & Notting, 1991). To properly assess the neurotoxic profile of AEDs in combinations, several behavioural tests can be conducted which include; rota rod performance, chimney tests and locomotor activity in rodents (Saraswathy et al., 2015).

7. Effect of administration of carbamazepine and/or phenytoin on locomotor and rearing activities in Wistar rats

Phenytoin has been shown to significantly reduce the spontaneous motor activity, indicating the central nervous system depressant effect of the drug (Coenen et al., 1995). Phenytoin has induced muscle weakness and motor incoordination in rats indicated in impaired rota rod performance of the rats, (Aliyu et al., 2016) reported that when comparing the administration of phenytoin and carbamazepine for some motor tests in rats, the performance of rats taking carbamazepine is faster. (Nawakowska, 2011) reported decreased locomotor and rearing activities in rats administered CBZ, PHE and their combination. Decreased locomotor activity following CBZ administration was also observed in mice (Lusczki, 2004) and rats (Gillham et al., 1988). Similarly, (Lusczki, 2004) reported that combining two sodium-channel blockers may result in a considerable reduction in locomotion of the animals tested; which apparently, induced the potentiation, rather than the summation of hypo-locomotor effects produced by the combined AEDs.

8. Effects of carbamazepine and/or phenytoin on learning and memory

The complex relationship between fits, cognitive impairment, psycho-social difficulties and underlying cerebral pathology has been the subject of several investigations. There has been a growing body of evidence that a fifth factor, the presence of AEDs in the brain, contributes independently to disruption of intellectual functioning (Bourgeosis, 2004). Several non-independent factors and each to a variable extent contribute to the possible cognitive problems in epilepsy but are very difficult to study separately (Bourgeosis et al 1983). Probably the most important determinants are the epileptic process itself and the underlying brain dysfunction/pathology with symptomatic epilepsy having a worse outcome than idiopathic epilepsy (Vandelinden & Lagae, 2004). The unique contributions of the epilepsy-related factors, such as the age of onset (Tromp et al., 2003), type of seizures and epilepsy syndrome, frequency of seizures and epileptic abnormalities on the EEG are more difficult to disentangle (Aldenkamp et al., 1993). It is the combination of the underlying brain dysfunction with an epileptic syndrome at a certain age that explains the cognitive profile (Lagae, 2006). It is clear that all the older drugs can induce psychomotor slowing to a variable extent which is a basic cognitive instrument (Farwell et al., 1990). Psychomotor slowing is generally measured in reaction time studies and anti-epileptic drugs typically induce a 100—200 ms (milliseconds) increase of reaction time. This reaction time increase can be very critical in some natural situations and especially during learning situation (Riva et al., 1996) and (Forsyth et al., 1991). That AEDs also suppress epilepsy through their effect on the hippocampus may be responsible for the cognitive deficit observed, since the same part of the brain plays an important role in memory. This, therefore, makes the hippocampus and its connections, which play important roles in epileptogenesis, memory and learning, (Mathews et al., 2011); (Fitzgerald et al., 2013), to be central to the beneficial and unwanted (adverse) effects of AEDs. The administration of CBZ and/or PHE impairing learning ability has been demonstrated in some studies (Rajesh et al., 1991); (Bourgeosis, 2004). (Ogunrin et al., 2005), (Shannon & Love, 2005) and (Pulliainen & Jokolliainen, 2005) who reported impairments which are more pronounced following CBZ than with PHE administrations but (Aliyu et al., 2016) had a reversed observation with rats in their studies. Greater learning impairment was observed when the drugs were combined indicating a more cognitive deficit (Zhan, 1998); (Aliyu et al., 2016).

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Memory impairment following AED administration, including CBZ and PHE, with greater deterioration in memory following CBZ than those repeatedly-dosed with PHE (Shannon & Love, 2004), has been observed. (Wamil & McLean, 1993), reported that PHE significantly decreased the retention latency in the passive avoidance test, similar to what was recorded in this study. In addition, (Thakur et al., 2011) showed that chronic PHE treatment caused memory impairment and that neuronal damage to the hippocampus, cortex, cerebellum and midbrain by PHE may be responsible for the impairment. Different studies have shown that both phenytoin and carbamazepine seem to have negative effects on cognitive performance, particularly on tasks with significant motor and speed components; practice effects were noted and may account for much of the improvement when patients stopped taking the drugs (Pulliainen & Jokolliainen, 1994). Phenytoin has been implicated in the decline in concentration, memory, visuomotor functions and mental speed (Andrews et al., 1986); (Gillham et al., 1988); (Aman et al., 1994). These effects may be dose-related (Bourgeosis, 2004), (Aldenkamp et al., 1994) reported that there is no relationship in the cognitive-motor performance. But (Duncan et al., 1990) reported a slowed performance on information processing tasks with phenytoin in comparison with carbamazepine, but no differences for memory or selective attention. Some investigators reported more detrimental effects on memory by phenytoin than carbamazepine (Pulliainen & Jokolliainen, 1994); (Andrews et al., 1986). A double-blind placebo-controlled study indicated that attention and motor performance may improve after withdrawal (Duncan et al., 1990), and similar improvements in concentration and psychomotor performance were noted in another controlled study (May et al., 1992). (Pulliainen & Jokolliainen, 1994) concluded that the long-term effects of phenytoin on cognition are relatively few and restricted mainly to some visually guided motor functions. A number of cognitive and psychomotor effects have been linked to carbamazepine (Gillham et al., 1988). A randomized, double-blind, placebo-controlled study involving 150 epilepsy patients on AED monotherapy (mainly carbamazepine or valproate) found that drug discontinuation significantly improved performance in tests that required complex cognitive processing under time pressure, but not in more simple tasks of attention and reaction time (Henssen et al., 2006). A later study reported similar findings, with improved performance in a verbal fluency task, a Stroop task, a language task and a reaction time task after discontinuation of carbamazepine (Hessen et al., 2009). In relation to other AEDs, it has been suggested that carbamazepine has a cognitive profile that is worse than levetiracetam (Lee et al., 2011) and lamotrigine (Gillham et al., 1988) but better than phenytoin (Pulliainen & jokolliainen, 1994); (Andrews et al., 1986). However, (Coenen et al., 1995) reported that the cognitive profiles of valproate and carbamazepine were similar except for some aspects of attention and memory, in which individuals taking valproate scored better. These effects appear mild when compared with those of phenytoin and phenobarbital. A study of patients with partial epilepsy showed no impairments in selective attention and memory compared with the control, although slower information processing speed was seen with monotherapy (Gillham et al., 2000). Despite none decline in coordination, memory, concentration or mental flexibility, a lack of practice on tasks appeared to suggest subtle changes in cognitive function (Engelberts et al., 2002). It was reported that carbamazepine did not have significant negative effects on memory and attention tasks, although performance improved slightly after withdrawal in children with partial epilepsy (Prevey et al., 1996). Beneficial effects reported on memory include improved immediate memory and late recall (Bittencourt et al., 1993) and better retrieval from episodic and semantic memory in adults and adolescents (Seidel & Michelle, 1999). Controlled-release medication may be most beneficial in memory and visual information processing (Kalvia et al., 1995). Despite these encouraging findings, some investigators suggested that carbamazepine is more likely to lead to cognitive deterioration than improvement (Aldenkamp et al., 1987). Factors that may be related to a greater incidence of cognitive effects include higher dose (Hemsteadter & Witt 2010) longer duration of intake (Shehata et al. 2009) and polytherapy (Bourgeosis, 2004). Apart from its effects on epileptic patients, AEDs have been shown to impair learning, even in healthy subjects (O'Dougherty et al., 1987).

9. Conclusion

The risk of AEDs' cognitive side effects is increased with polypharmacy and at higher dosages and higher AED blood levels (Loring % Meador, 2001). The administration of carbamazepine and/or phenytoin caused cognitive impairment and alterations in neurobehaviour. This in essence indicates that learning and memory of individuals taking these drugs could be affected particularly with long term use. It is therefore important that the aforementioned parameters should be monitored so as to alleviate the expected side-effects. Additional studies are needed to compare the relative effects of all the new antiepileptic drugs to each other and to the older ones.

References

Aikiä M., Jutila L., Salmenperä T., Mervaala E., Kälviäinen R. (2006) Long-term effects of tiagabine monotherapy on cognition and mood in adult patients with chronic partial epilepsy. Epilepsy Behaviour, 8: 750–755

Aldenkamp A.P., Alpherts W.C., Moerland M.C., Ottevanger N., Van Parys J.A. (1987) Controlled release carbamazepine: cognitive side effects in patients with epilepsy. Epilepsia 28: 507–514

Aldenkamp AP, Alpherts WC, Blennow G, Elmqvist D, Heijbel J, Nilsson HL, et al.(1993) Withdrawal of antiepileptic medication in children-effects on cognitive function: the Multicenter Holmfrid Study. Neurology, 43:41—50.

Ali, A., Pillai, K. K. and Pal, S. N. (2003). Effect of folic acid and lamotrigine therapy in some rodent models of epilepsy and behaviour. Journal of Pharmacy and Pharmacology, 55(3): 387-391.

Aliyu H., Ayo, J. O., Ambali, S. F. and Zezi, A.U. Kobo, P. I. Uchendu, C. (2016). Evaluation of neurobehavioural and cognitive changes induced by carbamazepine and/or phenytoin in

Wistar rats. Global Journal of Medical Research: A Neurology and Nervous System, 16(1): 29-34.

Aman M.G., Werry J.S., Paxton J.W., Turbott S.H. (1994) Effects of phenytoin on cognitive-motor performance in children as a function of drug concentration, seizure type, and time of medication. Epilepsia 35: 172–180

Andrews D.G., Bullen J.G., Tomlinson L., Elwes R.D., Reynolds E.H. (1986) A comparative study of the cognitive effects of phenytoin and carbamazepine in new referrals with epilepsy. Epilepsia 27: 128–134

Auclair L, Isabelle J, Olivier D, David L, Eric S. (2005) Deficit of preparatory attention in children with frontal lobe epilepsy. Neuropsychologia, 43:1701—1712.

Balakrishnan, S., Bhargava, V. K. and Pandhi, P. (1998). Effect of nimodipine on thepsychomotor dysfunction induced by phenytoin in rats. Indian Journal of Pharmacology, 30: 299-305.

Bazil, C. W. and Pedley, T. A. (2003). Clinical pharmacology of antiepileptic drugs. Clinical Neuropharmacology, 26(1): 38-52.

Bhosale , U. A., Loharkar, N. R.,Yegnanarayan, R. and Quraishi, N. (2014). Study of effects of antiepileptic therapy on various biochemical and hematological parameters patients suffering of epilepsy International Journal of Basic and Clinical Pharmacology, 3(1):79-85

Bootsma H.P., Ricker L., Hekster Y.A., Hulsman J., Lambrechts D., Majoie M., et al. (2009) The impact of side effects on long term retention in three new antiepileptic drugs. Seizure 18: 327–331

Bourgeois B. (2004) Determining the effects of antiepileptic drugs on cognitive function in paediatric patients with epilepsy. Journal of Child Neurolog, 19(Suppl. 1):S15—24.

Bourgeosis B, Prensky AL, Palkes HS, et al. (1983) Intelligence in epilepsy: a prospective study in children. Annals of Neurology, 14:438—444.

Camfield CS, Chaplin S, Doyle AB, Shapiro SH, Cummings C, Camfield PR. (1979) Side effects of phenobarbital in toddlers; behavioural and cognitive aspects. Journal of Pediatrics, 95:361—365.

Cascino, G. D. (1990). Intractable partial epilepsy: evaluation and treatment. Mayo Clinic Proceedings, 65: 1578-1586.

Chen YJ, Chow JC, Lee IC. (2010) Comparison of the cognitive effect of anti-epileptic drugs in seizure-free children with epilepsy before and after drug withdrawal. Epilepsy Research, 44: 65—70.

Chung S., Wang N., Hank N. (2007) Comparative retention rates and long-term tolerability of new antiepileptic drugs. Seizure 16: 296–304

Coenen A.M.L., Konings G.M.L.G., Aldenkamp A.P., Reiner W.O., van Luijtelaar E.L.J.M. (1995) Effects of chronic use of carbamazepine and valproate on cognitive processes. Journal of Epilepsy 8: 250–254

Czuczwar, S. J. and Pizesmycki, K. (2001). Felbamate, gabapentine and topiramate as factors in the laboratory evaluation of antiepileptic drugs. Intravenous protective indices. Epilepsy Research, 9: 1-10.

Dodrill C. B,& Troupin A. S. (1991) Neuropsychological effects of carbamazepine and phenytoin: a reanalysis. 41(1): 141-3.

Duncan J.S., Shorvon S.D., Trimble M.R. (1990) Effects of removal of phenytoin, carbamazepine, and valproate on cognitive function. Epilepsia 31: 584–591

Eddy, C. M., Richards, H. E & Cavanna, A. E (2011). The cognitive impact of antiepileptic drugs. Therapeutic Advance in Neurology Disorders, 4(6): 385–407.

Engelberts N.H., Klein M., van der Ploeg H.M., Heimans J.J., Jolles J., Kasteleijn-Nolst Trenité D.G. (2002)Cognition and health-related quality of life in chronic well-controlled patients with partial epilepsy on carbamazepine monotherapy. Epilepsy Behav 3: 316–321

Farwell JR, et al. (1990) Phenobarbital for febrile seizures-effects on intelligence and on seizure recurrence. National England Journal of Medicine 322:364—369.

Fitzgerald, Z., Thayer, Z., Mohamed, A. and Miller, L. A. (2013). Examining factors related to rational drug design and rational polypharmacy. Epilepsy Research, s11: 17-43.

Gamble, C. L., Williamson, P. R. and Marson, A. G. (2009). Lamotrigine versus carbamazepine monotherapy for epilepsy. Cochrane Database of Systemic Reviews, 2: 32. Retrieved fromhttp://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001031.pub2/pd/standad11/5/2012, 4:56 am

Gillham R., Kane K., Bryant-Comstock L., Brodie M.J. (2000) A double blind comparison on lamotrigine and carbamazepine in newly diagnosed epilepsy with quality of life as an outcome measure. Seizure 9: 375–379

Gillham R.A., Williams N., Wiedmann K.D., Butler E., Larkin J.G., Brodie M.J. (1988) Concentration–effect relationships with carbamazepine and its epoxide on psychomotor and cognitive function in epileptic patients. Journal of Neurology, Neurosurgery and Psychiatry 51: 929–933

Helmstaedter C., Witt J.A. (2010) Cognitive outcome of antiepileptic treatment with levetiracetam versus carbamazepine monotherapy: A non-interventional surveillance trial. Epilepsy Behavour 18: 74–80

Hessen E., Lossius M.I., Reinvang I., Gjerstad L. (2006) Influence of major antiepileptic drugs on attention, reaction time, and speed of information processing: results from a randomized, double-blind, placebo-controlled withdrawal study of seizure-free epilepsy patients receiving monotherapy. Epilepsia 47: 2038–2045

Jallon, P. (2007). The problem of intractability: the continuing need for new medical therapies in epilepsy. Epilepsia, 39(s9): S37-S42.

Jinsook, K., Kondratyev, A. and Gale, K. (2007). Antiepileptic drug-induced neuronal cell death in immature brain: effects of carbamazepine, topiramate and levetiracetam as monotherapy versus polytherapy. Journal of Pharmacology and Experimental Therapeutics, 323: 165-173.

Kälviäinen R., Aikiä M., Saukkonen A.M., Mervaala E., Riekkinen P.J., Sr (1995) Vigabatrin vs carbamazepine monotherapy in patients with newly diagnosed epilepsy. A randomized, controlled study.Arch Neurol 52: 989–996

Krämer, G. (1997). The limitations of antiepileptic drugs monotherapy. Epilepsia, 38(s5): 9-11

Lagae, L (2006) Cognitive side effects of anti-epileptic drugs: The relevance in childhood epilepsy: Review Seizure, 15: 235—241

LeCouteur, R. A. and Child, G. (1998). Clinical management of epilepsy of dogs and cats. Problems in Veterinary Medicine, 1(4): 578-595.

Lee S.A., Lee H.W., Heo K., Shin D.J., Song H.K., Kim O.J., et al. (2011) Cognitive and behavioral effects of lamotrigine and carbamazepine monotherapy in patients with newly diagnosed or untreated partial epilepsy. Seizure 20: 49–54

Loring, D. W. and Meador K. J. (2001). Cognitive and Behavioral Effects of Epilepsy Treatment Epilepsia, 42(Suppl. 8):24–32,

Löscher, W. and Ebert, U. (1996). Basic mechanisms of seizure propagation: target for rational drug design and rational polypharmacy. Epilepsy Research, s11: 17-43.

Löscher, W. and Notting, B. (1991). The role of technical, biological and pharmacological factors in the laboratory evaluation of antiepileptic drugs. Intravenous protective indices. Epilepsy Research, 9: 1-10.

Luszczki, J. J. (2004). Effect of lamotrigine alone or in combination with conventional antiepileptic drugs on locomotor activity in mice. Indian Journal of Pharmacology, 36(5): 306-311.

Mathew, J., Gangadharam, G., Karuvilla, K. P. and Paulose, C. S. (2011). Behavioural deficit and decreased GABA receptor functional regulation in the hippocampus of epileptic rats: effects of Bacopa monnieri. Neurochemical Research, 36(1): 7-16.

May T.W., Bulmahn A., Wohlhuter M., Rambeck B. (1992)

JNBS 2017 Published by Üsküdar University www.jnbs.org

Effects of withdrawal of phenytoin on cognitive and psychomotor functions in hospitalized epileptic patients on polytherapy. Acta Neurology Scandinavia, 86: 165–170

Meador K.J, Loring DW, Huh K, et al. (1990) Comparative cognitive effects of anticonvulsants. Neurology, 23:129—137.

Meldrum, B. (2002). Do preclinical seizure models preselect certain adverse effects of antiepileptic drugs? Epilepsy Research, 50: 33-40.

Nowakoska, E., Kus, K., Polanski, A., Burda, K., Nowakoska, A. and Sadowski, C. (2011). Concomittant use of carbamazepine and olanzepine and the defect on some behavioural functions in rats. Pharmacology Reports, 63: 372-380.

O'Dougherty M., Wright F.S., Cox S., Walson P. (1987) Carbamazepine plasma concentration. Relationship to cognitive impairment. Archive of Neurology, 44: 863–867

Ogunrin, O., Adamolekun, B. and Ogunniyi, A. (2005). Cognitive effects of antiepileptic drugs in Nigerians with epilepsy. African Journal of Neurological Sciences, 24(1): 18-24.

Perucca, E. and Richens, A. (1980). Reversal by phenytoin of carbamazepine-induced water intoxication: a pharmacokinetic interaction. Journal of Neurology, Neurosurgery and Psychiatry, 43: 540-545.

Prevey M.L., Delaney R.C., Cramer J.A., Cattanach L., Collins J.F., Mattson H. (1996) Effect of valproate on cognitive functioning: comparison with carbamazepine. Archive of Neurology 53: 1008–1016

Pullaiainen, V. and Jokolainen, M. (2005). Comparing the cognitive effects of phenytoin and carbamazepine in long term monotherapy: A two year follow up. Epilepsia, 36(12): 1195-1202.

Pulliainen V., Jokelainen M. (1994) Effects of phenytoin and carbamazepine on cognitive functions in newly diagnosed epileptic patients. Acta Neurology Scandinavia 89: 81–86

Rajesh, K. R., Surendra, R. and Thangam, J. (1991). Effect of valproic acid and carbamazepine on learning and memory in rats. Indian Journal of Pharmacology, 23(30): 185-188.

Reuten, D. C. and Berkovic, S. F. (1995). Idiopathic generalized epilepsy of adolescence: are the syndromes clinically distinct? Neurology, 45: 1469-1476.

Riva. et al. (1996) Discontinuation of phenobarbital in children: effects on neurocognitive behavior. Pediatric Neurology, 14:36—40.

Rykaczewska-Czerwińska, M. (2007). Antinociceptive effect of phenytoin in rats. Pharmacology Reports, 59(1): 144-149.

Saraswathy GR, Maheswari E, Santhrani T (2015) Protective Effect of Alpha Lipoic Acid against Phenytoin Induced Behavioral Abnormalities in Rats. Journal of Molecular Biomarker and Diagnosis, 5: 241.

Seidel W.T., Mitchell W.G. (1999) Cognitive and behavioral effects of carbamazepine in children: data from benign rolandic epilepsy. Journal of Child Neurology, 14: 716–723

Shaikh, S., Bin Yaacob, H and Bin AbdRahman, R. (2011). Lamotrigine for trigeminal neuralgia: Efficacy and safety in comparison with carbamazepine. Journal of Chinese Medical Association, 74: 243-249.

Shannon, H. E. and Love, P. L. (2004). Effects of antiepileptic drugs on working memoryas assessed by spatial alteration performance in rats. Epilepsy and Behaviour, 5(6): 857-865.

Shannon, H. E. and Love, P. L. (2005). Effects of antiepileptic drugs on attention as assessed by five-choice serial reaction time task in rats. Epilepsy and Behaviour, 7(4): 620-628.

Steinmetz, S., Tipold, A. and Löscher, W. (2013). Epilepsy after head injury in dogs: A natural model of post traumatic epilepsy. Epilepsia, 54(4): 580-588.

Sun, M., Van Rijn, C. M., Liu, Y. and Wang, M. (2002). Combination of carbamazepine and valproate in different dose proportion in maximal electroshock seizure model in mice. Epilepsy Research, 51(1-2): 5-11.

Thakur, S., Saraswathy, G. R. and Maheswari, E. (2011a). Effect of vitamin C supplementation on phenytoin-induced behavioural abnormalities and regional lipid peroxidation in rats. International Journal of Pharmacy and Technology, (3)2: 2248-2269.

Tromp SC, Weber JW, et al. (2003). Relative influence of epileptic seizures and of epilepsy syndrome on cognitive function. Journal of Child Neurology,18:407—412.

Vanderlinden L, Lagae LG. (2004) Clinical predictors for outcome in infants with epilepsy. Pediatric Neurology, 31:52—55.

Vijay, P., Yeshwanth, R. and Bairy, K. L. (2009). Effect of phenytoin sodium on the biochemical Parameters of reproductive function in male albino Wistar rats. Retrieved 8/2/2010 from www.j-pbs.org/pdf/221/JPBS081001.pdf.

Wamil, W. A. and McLean, M. J. (1993). Phenytoin blocks N-methyl-D-aspartate responses in central neurones. Journal of Pharmacology and Experimental Therapeutics, 267: 218-27.

Zhan, C. A. (1998). Neurologic care of pregnant women with epilepsy. Epilepsia 39(s8): S26-S31.

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