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"Antiepileptic Drugs And Cancer Risk In Epileptic Patients"

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Abstract:
The relationship between epilepsy and cancer has been widely debated, particularly regarding whether individuals with epilepsy have a higher risk of cancer and whether antiepileptic drugs (AEDs) influence cancer development positively or negatively. Evidence from animal studies, genotoxicity research, and clinical epidemiological observations offers insights into this association. In rodent studies, phenobarbital and phenytoin have been shown to promote tumor development. Phenobarbital was linked to liver tumors, while phenytoin caused lymphoid cell and liver tumors in rats. Epidemiological studies in humans have suggested possible associations between phenobarbital and hepatocellular carcinoma, as well as lung cancer. Additionally, a connection between antiepileptic drugs and brain tumors has been reported. Phenytoin has been implicated in certain cancers, including lymphoma, myeloma, and neuroblastoma, the latter in cases of fetal hydantoin syndrome. Despite extensive long-term data on these AEDs, evidence of carcinogenicity in humans remains inconsistent, leading to their classification as possibly carcinogenic. In contrast, valproate exhibits antiproliferative effects on specific cancer cell lines in both in vitro and in vivo studies. However, human epidemiological studies exploring valproate's cancer-suppressive potential remain limited, although preliminary reports suggest its use in treating hematological and solid tumors. Valproate's anticancer activity is attributed to histone deacetylase inhibition and is independent of hormone or multidrug resistance mechanisms. Newer AEDs, based on regulatory testing and post-marketing surveillance, do not show evidence of carcinogenicity, suggesting a favorable safety profile. The interplay between cancer and epilepsy remains a compelling area for future clinical and experimental investigations.

Key Words: *Epilepsy, Antiepileptic drugs (AEDs), Cancer risk, Phenobarbital, Phenytoin, Valproate, Tumor development, Hepatocellular carcinoma, Lung cancer, Brain tumors, Lymphoma, Neuroblastoma, Histone deacetylase inhibition, Carcinogenicity, Fetal hydantoin syndrome, Antiproliferative effects ETC.*

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I. Literature Of Paper:

• **"Antiepileptic Drugs A Clinician's Manual"** by Ali A. Asadi-Pooya and Michael R. Sperling: This comprehensive manual provides a practical guide for clinicians managing epilepsy using antiepileptic drugs (AEDs).

• **"Cancer: Principles and Practice of Oncology"** by Vincent T. DeVita Jr., Theodore S. Lawrence, and Steven A. Rosenberg: Known as the gold standard in oncology, this book provides a comprehensive overview of cancer biology, diagnosis, and treatment.

II. Introduction:

Individuals with a history of epilepsy make up approximately 1–2% of the general population (Bell and Sander, 2002; Sander, 2003). Enhancing their overall health requires not only effective seizure management but also addressing various coexisting health conditions. Comorbidities are common in epilepsy and have been the focus of considerable recent research (Gaitatzis et al., 2004). There is ongoing interest in understanding whether epilepsy or its treatment may contribute to the development and progression of other health issues. These comorbidities include neuropsychiatric disorders like dementia, learning disabilities, and depression, as well as non-neurological conditions, including cancer. Cancer ranks as the second leading cause of death globally and often complicates chronic medical conditions, including epilepsy. This has led to concerns about whether epilepsy itself, or the treatments used, might increase cancer risk. Long-term drug exposure, in particular, has been identified as a modifiable risk factor. Consequently, assessing the carcinogenic potential of medications used to treat epilepsy is an essential aspect of drug safety evaluation. The carcinogenicity of antiepileptic drugs (AEDs)

has been a subject of research since the late 1960s and 1970s, with studies encompassing experimental, epidemiological, and clinical approaches (Peraino et al., 1971; White et al., 1979). While the question remains unresolved, it has received less attention in recent years. This article reviews existing experimental and clinical data on cancer risk in individuals with epilepsy and underscores the need for further investigations into this important area.[SELF]

III. Carcinogenicity Test:

A critical event in the process of carcinogenesis is the mutational alteration of proto-oncogenes, tumor-suppressor genes, or other genes that regulate cell proliferation. Additionally, epigenetic changes, including DNA methylation, nuclear protein acetylation, mRNA alternative splicing, and protein modifications such as phosphorylation or nitrosylation, can play a role in initiating carcinogenesis (Hanahan and Weinberg, 2000). Among these, the regulation of nuclear protein acetylation, specifically histone acetylation and deacetylation, holds particular relevance to this discussion and will be explored further in this review. The cumulative effect of these molecular changes is the creation of cancer cells capable of sustaining autonomous growth signals, resisting inhibitory signals, evading programmed cell death, promoting angiogenesis, maintaining unlimited replication potential, and invading surrounding tissues and metastasizing. The range of pharmaceutical agents suspected or confirmed to possess carcinogenic properties is extensive. Generally, the carcinogenicity of these agents is assessed through three main approaches. Carcinogenicity is typically evaluated through three types of studies: (i) laboratory animal experiments, where rodents are exposed to the agent either at standard doses over time or more commonly at maximum tolerated doses; (ii) genotoxicity tests that assess the agent's ability to cause chromosomal damage or abnormalities in vitro; and (iii) long-term epidemiological studies tracking drug users in human populations. In rodents, carcinogenesis tends to follow a relatively straightforward mechanism, often involving a limited number of oncogenic events. In contrast, human carcinogenesis is far more complex, generally requiring a combination of at least five distinct genetic alterations to transform normal cells into malignant ones (Hahn and Weinberg, 2002). Consequently, carcinogenicity findings from animal studies, which have suggested tumor development at various sites for several drugs, have not always been corroborated by human epidemiological data.[49]

IV. Epidemiological Approaches To Human Carcinogenicity:

Carcinogenicity studies for antiepileptic drugs (AEDs) can be conducted using samples from individuals with cancer or epilepsy. Retrospective case–control studies in cancer patients are theoretically advantageous but are rarely feasible due to issues like recall bias and the absence of epilepsy history in cancer registry records or death certificates (Bell et al., 2004). More commonly, researchers estimate cancer incidence or mortality within epilepsy cohorts (Clemmesen and Hjalgrim-Jensen, 1978; White et al., 1979; Shirts et al., 1986; Olsen et al., 1989; Lamminpaa et al., 2002). Ideally, such cohorts should be large and monitored prospectively over several decades, considering the extended timeline for cancer development and the rarity of specific cancer types. Nested case–control studies within these cohorts may also be possible if sufficient data and a large sample size are available. However, long-term prospective studies are often impractical. Instead, researchers have frequently relied on retrospective follow-ups by tracing records back to earlier time points (Clemmesen and Hjalgrim-Jensen, 1978; White et al., 1979; Olsen et al., 1989; Lamminpaa et al., 2002).[2]Examples of such cohorts include institutionalized epilepsy patients whose records date back to admission (Clemmesen and Hjalgrim-Jensen, 1978; White et al., 1979; Olsen et al., 1989), hospital clinic patients, individuals applying for driving licenses (unpublished data, Lowe et al., 1986), and data sourced from pharmacy or insurance prescription records (Friedman and Ury, 1980, 1983; Selby et al., 1989; Lamminpaa et al., 2002). Cancer incidence and mortality in these cohorts are often determined using cancer registries or demographic databases. However, such studies may face challenges in verifying epilepsy diagnoses, medication compliance, and exposure duration. Additionally, important confounding factors such as smoking, alcohol use, and age at menarche and menopause are often overlooked in retrospective designs.[21]Given the challenges of studying cancer comorbidities in epilepsy, the most practical approach involves analyzing large prescription-based cohorts cross-referenced with cancer registry data (Lamminpaa et al., 2002). Cancer incidence and mortality in these cohorts are compared with community, regional, or national figures using standardized incidence ratios (SIR) and standardized mortality ratios (SMR). A SIR or SMR greater than 1 suggests a potential carcinogenic effect, while values less than 1 indicate a possible protective effect. To confirm a positive drug–cancer association, the relative risk should be substantial (e.g., >3), statistically significant, and sustained over time (Selby et al., 1989).[11]However, some associations may be misleading due to "protopathic bias," where a drug prescribed for symptoms resembling a neoplasm appears linked to cancer development when it is not the causative agent (Horwitz, 1985). Including a time lag between drug exposure and the assessment of associations can help mitigate this bias (Selby et al., 1989). Associations that strengthen over time support the notion that cancer risk increases with age and are less likely to result from protopathic bias.[32]The International Agency for Research on Cancer (IARC) continually evaluates

experimental and human data on carcinogens (IARC, 1987). Based on the evidence, the IARC classifies substances into four categories: Group 1, carcinogenic to humans; Group 2A, probably carcinogenic to humans; Group 2B, possibly carcinogenic to humans; Group 3, unclassifiable regarding carcinogenicity; and Group 4, probably not carcinogenic to humans.

V. Epidemiological Approaches To Human Carcinogenicity:

Traditional antiepileptic drugs (AEDs), introduced before the 1980s, include phenobarbital, phenytoin, carbamazepine, and sodium valproate. These medications continue to serve as the cornerstone of epilepsy management (Sander, 2004). Globally, more than 85% of individuals with epilepsy rely on these treatments, with phenobarbital being the most widely used. However, a significant treatment gap exists worldwide, leaving a large proportion of people with epilepsy without access to effective care (Meinardi et al., 2001).[44]

Phenobarbital:

Phenobarbital was among the earliest drugs shown to exhibit carcinogenic effects in animal studies. In the initial research, a significant increase in liver tumor incidence was observed when phenobarbital was administered following exposure to 2-acetylaminofluorene but not when given independently (Peraino et al., 1971). Subsequent studies confirmed its hepatocarcinogenic potential (Driver and McLean, 1986; Becker, 1985; Diwan et al., 1988), although these effects varied depending on the animal's species, sex, and age. Based on these findings, phenobarbital was identified as a non-carcinogenic agent on its own but classified as an indirect genotoxic promoter of liver tumors (Yamagi et al., 1984; Diwan et al., 1995). Additionally, phenobarbital has been shown to promote thyroid neoplasms (Becker, 1985).[55]These early animal experiments raised concerns about the potential carcinogenic risks associated with barbiturates among healthcare providers, leading to epidemiological studies examining cancer incidence and mortality in individuals using these drugs (Clemmesen and Hjalgrim-Jensen, 1978; Gold et al., 1978; Annegers et al., 1979; White et al., 1979; Shirts et al., 1986; Olsen et al., 1989, 1990, 1995; Selby et al., 1989; Goldbaher et al., 1990; Gurney et al., 1997; Lamminpaa et al., 2002).[39]

Phenytoin:

Early anecdotal reports suggested an association between phenytoin use and the occurrence of lymphoma (Salztein and Ackerman, 1959; Hyman and Sommers, 1966), prompting carcinogenicity studies in animals (Kruger, 1970; Kruger and Harris, 1972). Some investigations in specific rodent strains revealed that prolonged phenytoin exposure led to lymphoma, likely due to chronic antigenic stimulation and the drug's immunosuppressive effects. Additionally, phenytoin was linked to liver tumor development through a mechanism similar to that observed with phenobarbital (Chhabra et al., 1993; Diwan et al., 2001). However, other studies failed to demonstrate carcinogenic effects associated with phenytoin (Levo et al., 1975; Maeda et al., 1988).[71]

Valproate:

In Wistar rats, valproate administration resulted in the development of uterine adenocarcinomas (Watkins et al., 1992). Interestingly, an antitumor effect of valproate was identified accidentally during investigations into its teratogenic potential, particularly regarding human neural tube defects (Blaheta et al., 2004). Subsequent in vitro studies using neuroectodermal cell lines, such as neuroblastoma cells, demonstrated its antiproliferative and differentiating properties (Regan, 1985; Blaheta and Cinatl, 2002). These effects were later observed in other cell lines, including glioma, breast cancer, prostate cancer, teratocarcinoma, and leukemia progenitors (Cinatl et al., 1997; Knupfer et al., 1998; Blaheta and Cinatl, 2002), and eventually confirmed through in vivo experiments (Michaelis et al., 2004).[41]

Carbamazepine:

Limited research exists on the carcinogenicity of carbamazepine. However, prolonged administration at doses exceeding 25 mg/kg/day for more than two years in Sprague–Dawley rats caused hepatocellular tumors in females and benign interstitial tumors of the testes in males (Ciba Geigy, Product Information, 1987).[43]

Newer Aeds:

Newer antiepileptic drugs (AEDs), launched within the past 20 years, include vigabatrin, lamotrigine, gabapentin, felbamate, topiramate, tiagabine, zonisamide, levetiracetam, and pregabalin (Sander, 2004; Bialer et al., 2004). Unlike conventional AEDs, these drugs underwent carcinogenicity testing during their development. Gabapentin, when administered in high doses (250–2000 mg/kg) to male Wistar rats for extended periods, resulted in non-invasive, non-metastatic acinar pancreatic carcinoma (Sigler et al., 1995). This outcome, however, was deemed not relevant to humans since human pancreatic carcinomas are ductal rather than acinar. Similarly, high doses of pregabalin led to increased incidences of hemangiosarcomas in mice, though this effect was considered

species-specific, with no evidence of a similar risk in humans (European Medicines Evaluation Agency, 2003; Pfizer, 2004). Felbamate was associated with testicular interstitial cell tumors in male rats (McGee et al., 1998). Other newer AEDs have not shown carcinogenic potential in preclinical animal studies.[44]

VI. Genotoxicity Studies:

Extensive genotoxicity studies have been conducted on conventional AEDs such as phenobarbital, phenytoin, and sodium valproate. Most studies reported no significant abnormalities in genotoxic assays (Schaumann et al., 1989a, b; Schaumann et al., 1990; Whysner et al., 1996). However, some studies highlighted an increased frequency of sister chromatid exchanges in individuals with epilepsy treated with phenytoin (Hu et al., 1990; Taneja et al., 1992; Kaul and Goyle, 1999; Kaul et al., 2001). Regulatory guidelines now mandate genotoxicity testing for all pharmaceutical agents, which has been performed for newer AEDs from the outset.[41]

VII. Human Carcinogenicity Of Antiepileptic Drugs:

Phenobarbital:

A comprehensive review was conducted analyzing various studies assessing the carcinogenic potential of phenobarbital.

• Community-Based Screening And Prescription Studies:

- A large, multidrug, community-based screening study (Friedman and Ury, 1980, 1983; Selby et al., 1989).
- Two prescription-linked studies examining antiepileptic drug (AED) or barbiturate usage (Friedman and Ury, 1980, 1983; Lamminpaa et al., 2002).

• Cohort Studies:

Five historical cohort studies investigating cancer risk in individuals with epilepsy treated with phenobarbital (Clemmesen and Hjalgrim-Jensen, 1978, 1981; White et al., 1979; Olsen et al., 1989, 1995; Lamminpaa et al., 2002).[70]

• Perinatal Exposure Studies:

Four studies exploring barbiturate exposure during the perinatal period and its association with childhood brain tumors (Gold et al., 1978; Annegers et al., 1979; Goldbaher et al., 1990; Olsen et al., 1990; Gurney et al., 1997).

• Incidence-Based Studies:

One population incidence-based study (Shirts et al., 1986). Findings revealed increased standardized incidence ratios (SIRs) for cancer (ranging from 1.1 to 1.5) in most studies, although statistical significance was reached in only one case (White et al., 1979). A significant association with brain tumors was observed (SIR 2.9–5.7), primarily during the initial years of the studies. This pattern suggests a protopathic bias, where seizures were likely caused by pre-existing brain tumors rather than phenobarbital itself.[66]For systemic cancers, data were inconsistent. Nordic studies indicated elevated SIRs for hepatocellular carcinoma, but these findings were confounded by other risk factors, such as thorotrast exposure and cirrhosis (Clemmesen and Hjalgrim-Jensen, 1978, 1981; Olsen et al., 1989, 1995). Interestingly, an inverse relationship between epilepsy and liver cancer was reported in England (White et al., 1979). Elevated SIRs for lung cancer were noted in several studies, though smoking emerged as a confounding factor (Shirts et al., 1986). Conversely, decreased cancer risks in urinary bladder and skin sites were also reported (Clemmesen and Hjalgrim-Jensen, 1978, 1981; Olsen et al., 1989, 1995).[31]Perinatal exposure to barbiturates showed a threefold increased risk of childhood brain tumors in early studies (Gold et al., 1978). However, subsequent research questioned this association due to confounding factors and lack of reproducibility (Annegers et al., 1979; Goldbaher et al., 1990; Olsen et al., 1990; Gurney et al., 1997).[36]

VIII. Complicate The Assessment:

Lymphoreticular Malignancies:

Phenytoin has been associated with lymphadenopathy that mimics lymphoma, termed "pseudolymphoma." This condition typically resolves after drug withdrawal (Anthony, 1970). However, some cases progressed to true lymphoma (Abbondanzo et al., 1995).[48]Histopathological analyses identified atypical lymphoid hyperplasia, often requiring immunohistochemical studies to distinguish between benign and malignant conditions (Jeng et al., 1996; Choi et al., 2003).

Epidemiological Evidence:

While some institutionalized cohort studies reported increased SIRs for lymphomas, the association with phenytoin was not statistically significant (White et al., 1979; Olsen et al., 1989).[7]Multidrug studies in Northern California and Finland, as well as community studies, found no significant link between phenytoin use and lymphomas (Friedman and Ury, 1980; Shirts et al., 1986; Selby et al., 1989; Lamminpaa et al., 2002).

Multiple Myeloma:

Anecdotal reports linked phenytoin to myeloma (Matzner and Polliack, 1978; Rymard et al., 1981), but two case-control studies found no association (Friedman, 1986; Linet et al., 1987).

Neuroblastoma:

Several reports associated prenatal phenytoin exposure with neuroblastoma, particularly in children with fetal hydantoin syndrome (Ehrenbard and Chaganti, 1981). However, confounding factors such as exposure to multiple AEDs, smoking, and alcohol were common (Sherman and Roizen, 1976; Ramilo and Harris, 1979). Later studies failed to replicate this association (Koren et al., 1989).

Antitumor Potential:

- In vitro and in vivo studies demonstrated differentiation and antiproliferative effects on cancer cells.
- A small, uncontrolled trial showed therapeutic benefits of valproate in myelodysplastic syndromes, either alone or combined with all-trans retinoic acid (Kuendgen et al., 2004).

Clinical Trials:

Ongoing Phase I and II trials are investigating valproate's role in treating malignant disorders. A multicenter trial by the German-Speaking Society of Pediatric Oncology and Hematology is exploring its benefits in pediatric gliomas (Driever et al., 1999).

IX. Epilepsy And Cancer Survival:

Several antiepileptic drugs (AEDs), including phenobarbital, phenytoin, and carbamazepine, are potent inducers of hepatic drug-metabolizing enzymes. Many cancer chemotherapeutic agents are either metabolized in the liver or converted from prodrugs to active drugs within the liver. Consequently, the increased standardized mortality ratio (SMR) associated with cancer and potentially decreased cancer survival may be attributed to the induction of metabolism of these chemotherapeutic agents by enzyme-inducing AEDs (Vecht et al., 2003). Early anecdotal reports on drug interactions between AEDs and cytotoxic agents have been supplemented by systematic pharmacokinetic studies in recent years (Baker et al., 1992; Hassan et al., 1993; Zamboni et al., 1998; Crews et al., 2002; Grossman et al., 1998; Kuhn, 2002; Chang et al., 2003). These interactions have been reviewed elsewhere (Vecht et al., 2003), with those affecting the efficacy of cancer chemotherapeutic agents summarized in Table 1. Enzyme-inducing AEDs have been shown to reduce the area under the plasma concentration-time curves, decrease maximal plasma concentrations, and enhance hepatic clearance of many cytotoxic agents (Baker et al., 1992; Zamboni et al., 1998; Villikka et al., 1999; Mathijssen et al., 2002).

X. Mechanistic Considerations:

Cancer Risk:

The classical view of hepatocarcinogenicity associated with phenobarbital involves its enzyme-inducing properties on the cytochrome P450 system, which facilitates the conversion of xenobiotics into reactive, carcinogenic intermediates (White et al., 1979; Olsen et al., 1993). More recently, research has attributed the tumor-promoting effects of phenobarbital to its impact on gap junction-mediated intercellular communication. This process allows cells to interact and inhibit the proliferation of surrounding cells. Phenobarbital has been shown to reduce gap junction intercellular communication, thus freeing tumor precursor cells from the inhibitory effects of other cells (Sugie et al., 1987; Warner et al., 2003). Phenytoin has been linked to various immunological reactions in humans. Studies have noted a reduction in immunoglobulin levels in approximately 20% of long-term users (Bardana et al., 1983). Additionally, it inhibits the endogenous production of interferon-g, contributing to its carcinogenic potential, particularly concerning lymphoreticular neoplasia (Kruger, 1972). Phenytoin also influences the immune system in utero, demonstrated by increased glucocorticoid receptor expression in the peripheral blood lymphocytes of children with foetal hydantoin syndrome. This may partly explain the tendency of such children to develop neuroectodermal tumors. Teratogenic studies indicate that phenytoin modulates cellular responses to oxidative stress. Consequently, oxidative mechanisms have been proposed as intrinsic to phenytoin's carcinogenic and teratogenic risks (Fleischmann et al., 1990; Wells et al., 1997).[56]If cancer incidence were truly increased among patients with epilepsy, AEDs might be implicated. However, other factors must be considered, as lifestyle choices could also contribute to increased cancer risk. For instance, higher

smoking rates among people with epilepsy may be linked to anxiety caused by unpredictable seizures. While some studies support this premise, the overall evidence remains limited (Kobau et al., 2004). Furthermore, there is insufficient evidence to fully explain an increased cancer risk solely due to lifestyle patterns associated with epilepsy. The association between brain cancers and epilepsy largely reflects the fact that brain tumors can lead to epilepsy. Nonetheless, concerns persist regarding a potential mild, persistent association between tumor-promoting effects of AEDs and cancer risk (Shirts et al., 1986).[32]Genetic predisposition may partially explain the association between epilepsy and cancer. For example, mutations in the tumor suppressor gene leucine-glioma-inactivated-1 have been linked to autosomal dominant familial temporal lobe epilepsy, though this has not been associated with an increased risk of malignancies (Gu et al., 2002; Fertig et al., 2003; Brodtkorb et al., 2003). Additionally, certain disorders such as Down's syndrome, tuberous sclerosis, and neurofibromatosis are associated with both epilepsy and a higher predisposition to cancer, but these conditions are relatively rare and do not account for a significant portion of the association between epilepsy and cancer (Zipursky and Doyle, 1993; Ravindranath, 2003; Fatihi et al., 2003; Creange et al., 1999).[44]

XI. Cancer Protection:

An inverse association between enzyme-inducing AED use and urinary bladder carcinoma has been explained by the induction of metabolism to non-carcinogenic compounds of carcinogenic chemicals in cigarette smoke, which may otherwise contribute to the development of carcinoma at this site (Olsen et al., 1989, 1995). Additionally, a low standardized incidence ratio (SIR) of melanomas in a pharmacoe- pidemiological study was attributed to reduced exposure of institutionalized individuals with epilepsy to sunlight (Clemmesen and Hjalgrim-Jensen, 1978).[23]The mechanisms underlying the anti-tumor effects of valproate have been extensively studied and reviewed (Blaheta and Cinatl, 2002; Gottlicher, 2004). Valproate, as one of several histone deacetylase (HDAC) inhibitors, plays a role in oncological treatment by altering the tertiary structure of DNA, enhancing transcription factor accessibility, and promoting cell differentiation and apoptosis. Valproate preferentially inhibits class 1 HDACs and induces degradation of class 2 HDACs, while also inhibiting angiogenesis by reducing endothelial nitric oxide synthase expression (Michaelis et al., 2004). In breast cancer cell lines such as MCF-7, valproate clears estrogen receptor-alpha through pathways independent of estrogen hormone interactions (Olsen et al., 2004). Furthermore, subtherapeutic concentrations of valproate can promote tumor cell growth, which can be mitigated by the addition of an estrogen receptor antagonist (Olsen et al., 2004). The antiproliferative effects of valproate are independent of the expression of P-glycoprotein and multidrug resistance protein-1 (Tang et al., 2004), which are associated with multidrug resistance in cancer. Valproate has also been shown to downregulate protein kinase C in several tumor cell lines (Yao et al., 1999; Chen et al., 2000) and increase the expression of genes regulated by the extracellular regulated kinase-activated protein-1 pathway (Cinatl et al., 2002). Additionally, it inhibits glycogen synthase kinase 3 beta (GSK3), which negatively regulates signaling pathways involved in cellular proliferation (Rogawski and Loscher, 2004). Lamotrigine shares similar effects on GSK3, whereas carbamazepine affects signaling mechanisms upstream of GSK3, contributing to potential carcinoma-suppressing actions of these AEDs (Mai et al., 2002; Rogawski and Loscher, 2004).[71]

XII. Conclusion:

Based on available evidence, phenobarbital has been classified as carcinogenic in both mice and rats and is considered possibly carcinogenic to humans (Group 2B) by the International Agency for Research on Cancer (IARC, 1987). Similarly, phenytoin has demonstrated carcinogenicity in animals; however, the evidence in humans is inadequate, and it is classified as possibly carcinogenic to humans (Group 2B) (IARC, 1987). While the current IARC assessment does not rule out further evaluation of carcinogenic potential, this remains an area that requires more rigorous investigation. Studies conducted thus far have limitations, particularly due to the prolonged duration needed to accurately assess cancer incidence and the lack of proper controls for potential confounders. Additionally, with a relatively small number of studies available, variations in subject selection, choice of controls, cancer incidence assessment methods, treatment duration, type of AED treatment, and coding procedures have been observed. Given the concerns regarding carcinogenicity, newer, non-hepatic drug-metabolizing enzyme-inducing AEDs should preferably be used instead of enzyme-inducing AEDs in individuals undergoing cancer treatment with cytotoxic drugs. The question of cancer incidence in people with epilepsy remains an open issue. Specifically for valproate, further epidemiological studies and clinical trials investigating its potential antiproliferative effects are warranted.

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