Review Cancer Lett. 2023 Mar 11;560:216125. doi: 10.1016/j.canlet.2023.216125.

Online ahead of print.

Valproate and lithium: Old drugs for new pharmacological approaches in brain tumors?

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PMID: 36914086 DOI: 10.1016/j.canlet.2023.216125

Abstract

Beyond its use as an antiepileptic drug, over time valproate has been increasingly used for several other therapeutic applications. Among these, the antineoplastic effects of valproate have been assessed in several in vitro and in vivo preclinical studies, suggesting that this agent significantly inhibits cancer cell proliferation by modulating multiple signaling pathways. During the last years various clinical trials have tried to find out if valproate co-administration could enhance the antineoplastic activity of chemotherapy in glioblastoma patients and in patients suffering from brain metastases, demonstrating that the inclusion of valproate in the therapeutic schedule causes an improved median overall survival in some studies, but not in others. Thus, the effects of the use of concomitant valproate in brain cancer patients are still controversial. Similarly, lithium has been tested as an anticancer drug in several preclinical studies mainly using the unregistered formulation of lithium chloride salts. Although, there are no data showing that the anticancer effects of lithium chloride are superimposable to the registered lithium carbonate, this formulation has shown preclinical activity in glioblastoma and hepatocellular cancers. However, few but interesting clinical trials have been performed with lithium carbonate on a very small number of cancer patients. Based on published data, valproate could represent a potential complementary therapeutic approach to enhance the anticancer activity of brain cancer standard chemotherapy. Same advantageous characteristics are less convincing for lithium carbonate. Therefore, the planning of specific phase III studies is necessary to validate the repositioning of these drugs in present and future oncological research.

Keywords: Adverse drug reactions; Brain; Cancer; Clinical studies; Drug repositioning; Lithium carbonate; Lithium chloride; Preclinical research; Therapeutic drug monitoring; Valproate; Valproic acid.

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