

Prospects for repurposing CNS drugs for cancer treatment

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Abstract

Drug repurposing is the idea of using an already approved drug for another disease or disorder away from its initial use. This new approach ensures the reduction in high cost required for developing a new drug in addition to the time consumed, especially in the tumor disorders that show an unceasing rising rate with an unmet success rate of new anticancer drugs. In our review, we will review the anti-cancer effect of some CNS drugs, including both therapeutic and preventive, by searching the literature for preclinical or clinical evidence for anticancer potential of central nervous system drugs over the last 8 years period (2010-2018) and including only evidence from Q1 journals as indicated by Scimago website (www.scimagojr.com). We concluded that Some Central Nervous system drugs show a great potential as anti-cancer in vitro, in vivo and clinical trials through different mechanisms and pathways in different types of cancer that reveal a promising evidence for the repurposing of CNS drugs for new indications.

Introduction

World Health Organization (WHO) reported that an estimated number of 10 million people will die of cancer in 2018, with the availability of treatment services for more than 90% of high-income countries compared to less than 30% of low-income countries.¹ To keep pace with this rapidly increasing rate, the development of combating strategies against cancer is of an utmost importance. The discovery of a new drug against cancer is a tedious process in terms of cost and duration, with a low

probability to enter Phase I clinical trials.² Moreover, most of the new chemotherapeutics have a negative impact on the quality of life due to their toxicity issues.³

Drug repurposing (also called *Drug repositioning*) is the idea of using a previously approved FDA (Food and Drug Administration) drug in a different disorder or disease away from its initial use. These repurposed drugs have been extensively studied for their efficacy, toxicity, and safety. This consequently leads to saving time and money and accelerate their entry to experimental clinical trials.⁴ Thalidomide is a clear example that has been initially used for the treatment of motion sickness and then was withdrawn for its teratogenic effect.⁵ Following further experimental studies, Thalidomide has been repositioned and approved by the FDA for the treatment of leprosy and multiple myeloma.⁵ This emphasizes the importance and practicality of applying the idea of drug repurposing. The Repurposing Drugs in Oncology (ReDO) project is one of the schemes that has been initiated in 2014 to highlight promising drug candidates with good toxicity profile and experimental evidence, to be subjected to clinical trials to validate their off-label usage.⁴ The project has provided a list of candidate drugs, including Losartan, Omeprazole, Statins, Nitroglycerin, Chloroquine/Hydroxychloroquine, Propranolol, Mebendazole, Cimetidine, Clarithromycin, Diclofenac, Itraconazole, in addition to other drugs that have already been introduced into clinical trials, as Ketorolac and Fluvabrex.^{4,6-14} To catch up with the growing interests and efforts in drug repositioning, the *Drug Repurposing Hub* has emerged as a platform that integrates close collaboration between the Broad Institute Cancer Program, Center for the Development of Therapeutics, and the Connectivity Map group (<https://clue.io/repurposing>). The hub collected detailed data for more than 8000 compounds, and their relevant mechanism of action, protein targets, and approved indications.

In the current review article, we are focusing on Central Nervous system (CNS) drugs repurposing for cancer. Studies emphasizing the emerging role of CNS therapies for usage against cancer is a verdict for our decision.¹⁵⁻¹⁹ This review provides a foundation upon which further research can be implemented on the use of CNS drugs in cancer.

The History of CNS drugs

CNS drugs mainly include Antipsychotic drugs (e.g., Chlorpromazine, Phenothiazine), Antidepressants (e.g., Tricyclic antidepressant, Selective Serotonin Reuptake Inhibitor), and Anticonvulsant (e.g., Potassium bromide, Valproate). We will focus on the next paragraphs on the history of the main CNS classes and their original usage (Figure 1).

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Antipsychotics and antidepressants

Usage of antidepressants started in the late 1930s after many failed attempts to develop an effective treatment for depression. In the 1950s, structure-activity relationship studies on antihistamines emphasized their potential efficacy as anti-depressants, and led to the discovery of nearly all antidepressant and antipsychotics.¹⁷⁻¹⁹ In 1952, Chlorpromazine's antipsychotic properties were discovered and marked a new era for the treatment of psychiatric disorders. Chlorpromazine was the spike from which other antidepressants developed.²⁰ There are six main classes of antidepressants including Tricyclic Antidepressants (TCA), Monoamine Oxidase Inhibitors (MAOI), Selective Serotonin Reuptake Inhibitors (SSRI), Serotonin and Norepinephrine Reuptake Inhibitors (SNRI), Norepinephrine and Dopamine Reuptake Inhibitors (NDRI), and atypical antidepressants. Imipramine, a TCA, was the first reported drug for the treatment of depression in 1957.²¹ It is also used in Attention Deficit Hyperactive Disorder (ADHD) in children, by inhibiting Norepinephrine and Serotonin reuptake.²²

Anticonvulsants and anti-epileptics

The history of anticonvulsants goes back to 1857 when Edward Sieveking discovered the potential of using Potassium Bromide in treating Catamenial epilepsy.²³ On the other hand, the antiepileptic efficacy of Barbiturates was discovered accidentally in 1912 by Albert Hauptmann, who observed its effect on reducing the frequency of seizures in epileptic patients.²⁴ The discovery of the anticonvulsant properties of Phenytoin in 1938 was a great leap forward in the treatment of epilepsy due to the fact that Phenytoin has shown efficacy in patients who did not respond to barbiturates and bromides. Moreover, usage of Phenytoin was not associated with the common sedative side effect of the other agents.^{25,26} In 1953, Carbamazepine, which was developed concurrently with the anti-depressant drug Imipramine, represented a new advance in the development of anticonvulsants.²⁷ Lastly, Valproate, which is prescribed nearly for all types of seizures nowadays, was first synthesized in 1881, but its anticonvulsant properties were identified in 1962 by Pierre Emyard.²⁸

List of drugs with potential repurposing capabilities

In the current part, we will introduce a list of drugs that are being used for CNS disorders, and showing a pre-clinical and clinical evidence for use in different types of cancer, as documented by research publications over the last 8 years (*i.e.*, 2010-2018). To maximize the reliability of those proposed drugs, we included only data extracted from Q1 journals as indicated by Scimago (www.scimagojr.com). The list of potential drugs includes Imipramine, Phenothiazines, Trifluoperazine, Pimozide, and Valproate.

Imipramine

Has shown efficacy against cancer as shown in several studies.

Glioma

A study was conducted both *in vitro* and *in vivo* to show the efficacy of Imipramine on glioma. The drug inhibited NADPH oxidase-mediated ROS *in vitro*. *In vivo*, a combination of Imipramine and Doxorubicin showed enhanced anti-invasive effect.²⁹ Whereas a combination of Imipramine and Ticlopidine exhibited a suppressing effect on the ATG7, a member of the autophagy survival signaling, resulting in cell death.³⁰

Breast Cancer

Another reported use for Imipramine is in breast cancer where it demonstrated demonstrated an inhibitory effect on the proto-oncogene FoxM1 and its associated DNA repair signals.³¹

Head and Neck squamous cell carcinoma (HNSCC)

The mechanism of HNSCC invasion depends on epithelial-mesenchymal transition (EMT) induction with Twist1 to initiate a sequenced cascade that ends up with the induction of mesenchymal-mode movement, which plays a great role in local invasion of HNSCC. Imipramine showed potential to inhibit the invasion through suppressing Twist1- and NF- κ B-mediated pathways.³²

Burkett's lymphoma

Imipramine decreased cancer cells viability in Burkett's lymphoma without affecting disseminated cells or angiogenesis both *in vivo* and *in vitro*.³³

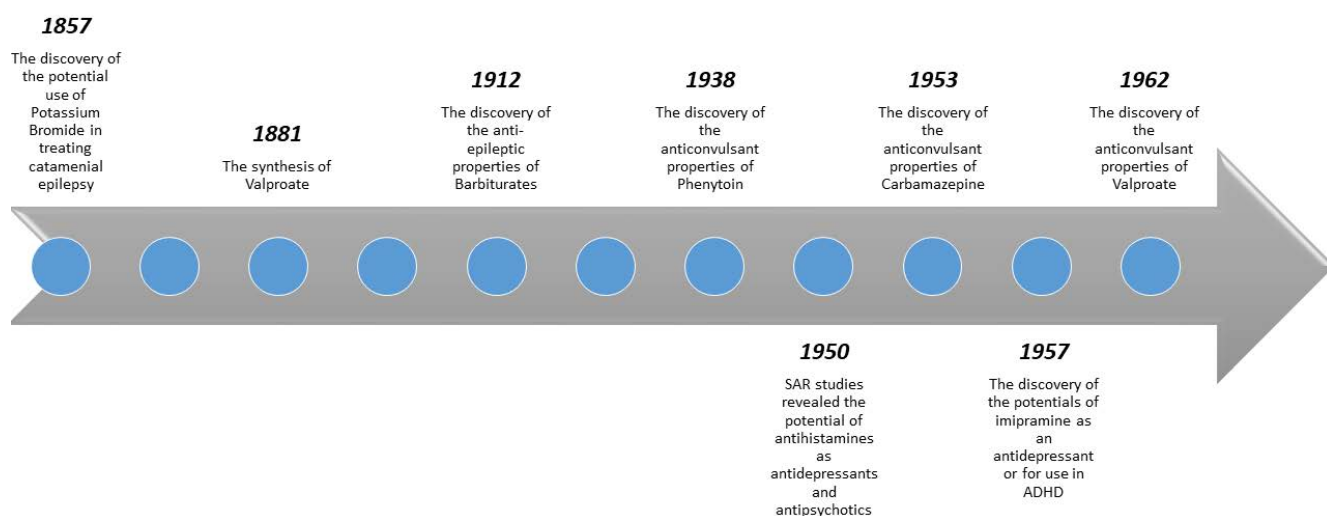


Figure 1. The History of CNS drugs.

Acute/chronic myeloid leukemia

The efficacy of Imipramine against acute myeloid leukemia cells is demonstrated through its pro-apoptotic ability by the re-activation of the tumor suppressor protein phosphatase 2A (PP2A) and blocking the NF- κ B pathway.³⁴ The same mechanism of action was demonstrated when combined with the tyrosine kinase inhibitor, Nilotinib, in chronic myeloid leukemia. Imipramine decreased the levels of ROS which in combination with Nilotinib caused a decrease in cancer cells' viability and proliferation.³⁵

Phenothiazines

Are conventional antipsychotic drug family that work mainly as D2 antagonists. Several studies revealed its possible use in cancer.

Breast cancer

Phenothiazines caused a drastic elevation in the level of the pro-apoptotic Bax, and decreased the level of the pro-survival Bcl2, thus inducing apoptosis.³⁶

Small cell lung carcinoma (SCLC)

Phenothiazines reduced cancer cell viability, and induced apoptosis via lysosomal dysfunction.³⁷

Oral cancer

Phenothiazine elicited its effect on caspase-3, caspase-9 and procaspase-8 activity in oral cancer. Moreover, it inhibited Akt and mTOR phosphorylation leading to cancer cell apoptosis and elevated levels of ROS and associated DNA damage (38).³⁸

Trifluoperazine (TFP)

Is an FDA-approved phenothiazine. Its mechanism of action, similarly, involves D2 receptor antagonism. It is mainly used for the treatment of Schizophrenia and other psychotic disorders.³⁹ TFP was repurposed in many studies for cancer.

Glioblastoma

TFP was proved to inhibit the growth of cancer cells in glioblastoma by releasing a massive irreversible amount of Ca²⁺ from IP3R channels through its binding to calmodulin subtype 2 (CaM2). Additionally, it showed an anti-proliferative effect both *in vitro* and *in vivo* xenograft models.⁴⁰ Conversely, a recent study has highlighted the effect of low-dose TFP on the attenuation of cellular apoptosis and enhancement of proliferation in glioma cells.⁴¹

Lung cancer

The ability of TFP to suppress Wnt/ β -catenin signaling in gefitinib-resistant lung cancer led to overcome the cancer resistance to gefitinib.⁴²

Metastasis

The anti-cancer effect of TFP extended to cancer metastatic cells where the migration of these cells was inhibited by impeding the angiogenesis via decreasing VEGF. This anti-angiogenic activity was due to the suppression of AKT phosphorylation and β -catenin pathway.⁴³

Pimozide

Is another old D2 blocking agent used for Tourette's Disorder.⁴⁴ Reviews from 2002 found a synergistic effect for both Pimozide and Mibefradil on T-type Ca²⁺ channels inhibition in which proliferation is reduced in breast cancer. They also suggested other mechanisms by which Pimozide can fight cancer

cells including the apoptotic effects in cancer cells and the decreased expression of Bcl-2.⁴⁵

Breast cancer

In 2018, new studies demonstrated the effect of Pimozide on breast cancer cells through the reduction of the level of STAT5 phosphorylation.⁴⁶

Hepatocellular carcinoma (HCC)

In HCC, Pimozide reduced cancer cell proliferation by cell cycle arrest at the G0/G1 phase and decreased STAT3 levels which lead to decreasing cancer cells maintenance.⁴⁷

Acute/chronic myeloid leukemia

Pimozide was combined with Sunitinib, a tyrosine kinase inhibitor, in acute myeloid leukemia leading to enhanced efficacy via the inhibition of STAT5 phosphorylation and *in vivo* apoptosis induction.⁴⁸ Likewise, in chronic myeloid leukemia, Pimozide showed the same effect when combined with tyrosine kinase inhibitors.

Valproate (Valproic acid)

Is an anti-epileptic drug acting by blocking Na⁺ channels, GABA transaminase, and Ca²⁺ channels. It is widely used in different kinds of epilepsy, migraine seizures and acute manic episodes.⁴⁹ Many studies were introduced for the beneficial role of Valproate in fighting cancer.

Lymphoma

A study elicited the depletion of Ca²⁺ into mitochondria in lymphoma via cellular inositol 1,4,5 trisphosphate (IP3) reduction and PRKAA1/2-mTOR cascade activation. This results in cancer cell retardation.⁵⁰ The safety, effectiveness, and good overall response rate of the Valproate and Hydralazine combination in cutaneous T-cell lymphoma has been evaluated in phase II clinical trial.⁵²

Prostate cancer

Valproate limited prostatic tumor growth through enhancing androgen sensitivity and elevating cellular prostatic acid phosphatase via its histone acetylation action, hence dephosphorylating ErbB-2.⁵² Furthermore, studies showed that Valproate causes the re-expression of cyclin D2, a crucial cell cycle-regulatory gene, that is frequently absent in prostate cancer.⁵³ Studies involving Valproate combined with Metformin demonstrated the synergistic anti-cancer effect, with no effect on the prostatic normal epithelium. This effective action can be due to p53 signaling pathway which surges cancer cell apoptosis.⁵⁴

Head and neck squamous cell carcinoma

Valproate has been also tested in HNSCC where it proved to up-regulate p21, thus affecting cancer cell viability, differentiation markers and proliferation cessation.⁵⁵ Caponigro F. *et al.* developed phase II clinical trials on the use of Valproate in the recurrent and metastatic forms of the HNSCC. Its efficacy was enhanced when combined with both Cisplatin and Cetuximab.⁵⁶ A recent clinical trial is studying the chemo-preventive effect of using Valproate in HNSCC, however, the results are not dispatched yet.⁵⁷

Glioblastoma

Another controversial evidence showed Valproate-induced autophagy through the ERK1/2 pathway leading to the death of glioma cells. Autophagy was also enhanced when Valproate was combined with Rapamycin or Temozolomide both *in vivo* and *in vitro*.⁵⁸ Additionally, cell cycle arrest at G2/M, ROS production,

down-regulation of paraoxonase 2, cyclin B1, cdc2 with Bcl-xL and up-regulating p27, p21 with Bim were also elicited as anti-cancer effects of Valproate in glioblastoma.⁵⁹ Valproate is currently being tested in a phase IV trial against glioma.⁶⁰

Acute myeloid leukemia (AML)

It was found that patients suffering from AML, specially AML1/ETO-positive patients, would greatly benefit from the apoptotic induction in cancer cells using Valproate.⁶¹ A new synergetic combination of both Valproate and Ellipticine, a topoisomerase II inhibitor, exhibited an apoptotic activity *in vitro*, due to improving histones H3 and H4 acetylation caused by this combination.⁶² A phase I trial is studying the side effects and the best dose of Decitabine and Valproate in treating patients with refractory or relapsed AML or previously treated chronic lymphocytic leukemia or small lymphocytic leukemia. Decitabine works against cancer cells by stopping its division, whereas Valproate may stop the growth of cancer cells by hampering enzymes essential for cellular growth. Combining Decitabine with Valproate may kill more cancer cells.⁶³ It is reported that treatment of AML with continuous Valproate and low-dose Cytarabine plus intermittent Tretinoin, a well-known anticancer drug also known as all-trans retinoic acid, has a complete hematological remission with low-frequency side effects.⁶⁴

Chronic lymphocytic leukemia

A phase I trial shows the role of Valproate in increasing the cluster of differentiation antigen 20 (CD20) expression. The basis in this study is that an increase of CD20 would render treatment with monoclonal antibodies (e.g. Rituximab) in patients with chronic lymphocytic leukemia more effective.⁶⁵

Neuroendocrine carcinoma

Valproate increased Notch signaling pathway signaling, known for its tumor suppression effect on the neuroendocrine tumors (NETs). This indicates the possibility for an anti-cancer effect in such carcinoma.⁶⁶

Bladder cancer and Hepatocellular carcinoma (HCC)

Valproate has also exhibited its anti-cancer effects on bladder cancer and HCC. In the case of bladder cancer, it was combined with Melatonin, which showed a synergetic effect through activating apoptotic, necrotic and autophagy genes. The combination increased E-cadherin, a tumor suppressor gene, and suppressed N-cadherin, which potentiate cancer formation. Moreover, it initiated Wnt and Raf/MEK/ERK pathway.⁶⁷ In the event of HCC, the activation of caspase-3, ROS, and autophagy were introduced by Valproate/Doxorubicin combination.⁶⁸

Breast cancer

A study has shown that Valproate can increase thymidine phosphorylase levels in breast cancer cells leading to synergizing the effect of Capecitabine through the histone deacetylase HDAC3.⁶⁹ A phase I trials is carried out to confirm if the hypothesis of giving Valproate before surgery for newly diagnosed breast cancer will increase breast tumor histone acetylation, leading to the inhibition of tumor growth.⁷⁰

Pancreatic and cervical cancers

Pancreatic cancer and colon cancer responded to the histone deacetylase inhibitory effect of Valproate by decreasing the Amyloid Precursor Protein (APP). Lowering the levels of APP was associated with activating the endoplasmic reticulum chaperone, GRP78 in cancer cells.⁷¹ Another mechanism of Valproate in pancreatic cancer and cervical cancer as an anti-cancer drug is

DNA damage and apoptosis through ROS production. This effect was demonstrated *in vivo* when Parvovirus H-IPV synergistically added to Valproate.⁷²

Conclusions

Drug repurposing is a promising path for fighting cancer in the existence of many challenges against the development of new anti-cancer drugs. CNS drugs showed a great potential for killing cancer cells *in vitro*, *in vivo* and as shown by few clinical trials. Imipramine, Phenothiazines, Trifluoperazine, Pimozide, and Valproate were proven as having an anti-cancer effect *via* several mechanisms of action and pathways in different types of cancer. Valproate, in particular, has a growing evidence as a potential therapeutic option against many types of cancer.

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