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Mini-review

Repurposing psychiatric drugs as anti-cancer agents

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ABSTRACT

Cancer is a major public health problem and one of the leading contributors to the global disease burden. The high cost of development of new drugs and the increasingly severe burden of cancer globally have led to increased interest in the search and development of novel, affordable anti-neoplastic medications. Antipsychotic drugs have a long history of clinical use and tolerable safety; they have been used as good targets for drug repurposing. Being used for various psychiatric diseases for decades, antipsychotic drugs are now reported to have potent anti-cancer properties against a wide variety of malignancies in addition to their antipsychotic effects. In this review, an overview of repurposing various psychiatric drugs for cancer treatment is presented, and the putative mechanisms for the anti-neoplastic actions of these antipsychotic drugs are reviewed.

1. Introduction

Cancer is a major public health problem and a leading contributor to the global disease burden [1]. The International Agency for Research on Cancer (IARC) estimates that growth and aging of the population alone are expected to contribute to 21.7 million new cancer cases and 13 million cancer-related deaths by 2030. Hereditary involvement, exposure to radiation and chemicals, unhealthy lifestyles, and other risk factors continue to increase the future burden.

Current chemotherapy treatments mainly include alkylating agents, antimetabolites, antibiotics, topoisomerase inhibitors, and mitotic inhibitors [2], which have remained largely unchanged for three decades. Anticancer agents constantly dominate the US Food and Drug Administration (FDA) drug approval list, although a temporary decline occurred in 2016 [3]. Innovations in cancer drug discovery remain a highly challenging endeavor. Only approximately 10 new cancer drugs are approved by the FDA yearly [4]. The high-cost and time-consuming nature of new drug development represent significant challenges in cancer drug discovery. Several years may be required to prove the efficiency and safety of a new drug. The analysis of 68 randomly selected approved drugs estimated that it takes 15 years and US$ 802 million to bring a new drug to the market. The total pre-approval cost is also increasing at an annual rate of 7.4% [5].

The challenges of developing new drugs suggest the need to explore alternative and novel affordable approaches to treating human cancer. The strategy of converting the indications of existing drugs from one therapeutic area to include the treatment of other diseases, which is also known as “drug repurposing” or “drug repositioning,” shortens the time required for clinical application based on existing previous drug clinical trial results and toxicology testing. This new method of drug discovery has significant advantages over traditional drug development. The use of known drugs and compounds for new indications saves time and cuts the cost of bringing a drug to market. More than 90% of drugs fail the development process. In the last few years, an increasing number of drug companies are now devoting considerable efforts to enhance the efficiency and success rates of drug repositioning. This has created a new strategy for drug discovery creation based on known drugs.

Psychiatric drugs have a long history of clinical use and tolerable

Abbreviations: MSSA, methicillin-susceptible *Staphylococus aureus*; MRSA, methicillin-resistant; *S.* SSRIs, selective, serotonin reuptake inhibitors; MAOIs, monoamine oxidase inhibitors; HDACs, histone deacetylases; CSCs, cancer stem cells; DRs, dopamine receptors.

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safety and have been used as good targets for drug repurposing. For example, thioridazine has well-recognized antimicrobial properties in addition to its antipsychotic activity, which is also common to other phenothiazine analogs [6,7]. It has shown significant in vitro activity against susceptible and multidrug-resistant strains of *Mycobacterium tuberculosis* [8], intracellular methicillin-susceptible *Staphylococcus aureus* (MSSA) [9], methicillin-resistant *S. aureus* (MRSA) [10], and vancomycin-resistant enterococci [11]. The use of thioridazine as an antipsychotic drug has been reduced because of the unfavorable side effects, but investigations and the recent discovery of its antimicrobial properties demonstrate the feasibility and reliability of its clinical efficacy. More studies could be performed to further elucidate other potential clinical uses of this agent. There are also numerous other examples such as haloperidol and its derivative bromperidol, which have currently been repurposed for the treatment of various fungal infections [12].

Psychiatric medications are also promising as a new generation of cancer chemotherapies. Several epidemiological studies have reported that patients with schizophrenia who are receiving antipsychotic drugs have a lower cancer incidence than the general population, suggesting that psychiatric medications might have positive effects on some human cancers. Decreased incidences of prostate, colon, and rectal cancers were observed in patients receiving schizophrenia drugs [13–16]. Psychiatric drugs such as phenothiazines, olanzapine, pimozide, and valproic acid are frequently used in different psychiatric conditions. Further, studies have also showed that these antipsychotic drugs can induce the death of various cancer cells in vitro and in vivo [17–19]. In this review, we present an overview of the repurposing of various psychiatric drugs for cancer treatment and review the putative mechanisms of the anti-neoplastic actions of these psychiatric drugs. In addition, we will discuss the limitations and challenges remaining, including the potential carcinogenicity, controversial clinical studies, and bad tolerance of some psychiatric drugs.

2. Anti-neoplastic properties of psychiatric medications

The high cost of developing new drugs and the increasing severity of the global burden of cancer have increased the interest in the research and development of novel, affordable anti-neoplastic medications. Psychiatric drugs have been used for various psychiatric diseases for decades and are currently reported to have potent anticancer properties against a wide variety of malignancies in addition to their antipsychotic effects.

For more than 100 years, epidemiological studies exploring the association between schizophrenia and cancer have shown conflicting results [20]. A decreased incidence of cancer among patients with schizophrenia compared with that in the general population has been reported in diverse patient populations [21–23]. The evaluation of risk for cancer development in patients with schizophrenia in a large cohort study in an Israeli population demonstrated a lower risk of cancer in patients with than in those without schizophrenia [24]. Another study exploring this association in three Jewish-Israeli populations (Israel, Europe-America, and Africa-Asia) showed that cancer standardized incidence ratios (SIRs) were significantly reduced in patients with schizophrenia for all sites [23]. A population-based study in the US also demonstrated a reduced risk of cancer among persons diagnosed with schizophrenia compared with that in the general population after controlling for known risk and demographic factors [25]. Other studies have identified higher or equivalent relative risk for cancers in patients with schizophrenia than in the general population, contributed by genetic, environmental, and other confounding factors [22]. Studies analyzing selected cancer sites also showed contradictory results, especially for women with breast cancer and men with lung cancer. For example, the increased risk of female-specific cancers such as breast cancer found in some studies may be due to the elevated prolactin effects of psychiatric medications [26,27].

These findings suggest that patients with schizophrenia may have been protected against some cancers based on numerous studies reporting a lower cancer risk in patients with schizophrenia than in the general population [21–25]. One possible explanation is that psychiatric medications may partially decrease the risk of cancer development based on their anti-neoplastic properties [28]. The molecular anticancer mechanisms of antipsychotic agents are yet to be elucidated. Valproic acid is primarily used for bipolar disorder, epilepsy, and migraine headaches. It has also been identified as a promising anti-neoplastic drug based on histone deacetylase (HDAC) inhibition. More than 80 clinical trials have been initiated to evaluate its anticancer properties against different tumors [29]. Phenothiazines are used to treat schizophrenia and psychosis, and they inhibit the growth of cancer cells [28,30–32]. Thioridazine and other phenothiazine drugs have been reported to have anticancer effects mediated by different mechanisms [31]. Sachlos et al. [30] found that thioridazine promotes cancer stem cell differentiation through the dopamine receptor (DR) pathway while Zhelev et al. [31] demonstrated that it inhibits mitochondrial DNA polymerase and decreases ATP production with selectively cytotoxicity and antiproliferative activity in leukemic cells. Another group also found that thioridazine was cytotoxic against the NCI-N87 and AGS gastric cancer cell lines through the mitochondrial pathway [33].

Treatment with the first generation typical antipsychotic drug, penfluridol, was reported to inhibit pancreatic tumor growth by inducing autophagy-mediated apoptosis [34]. Wiklund et al. [35] found that pimozide and the atypical psychiatric medication olanzapine disrupt cholesterol homeostasis to kill cancer cells. There are many other examples of neuroactive drugs with anti-tumor effects including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and monoamine oxidase inhibitors (MAOIs). Gordon et al. [36] showed that SSRIs directly induce apoptosis-associated cytotoxicity in biopsy-like Burkitt lymphoma cells. In another study, paroxetine and sertraline induced a dose-dependent inhibition of the viability and proliferation of human colon cancer cell lines and colorectal cancer cell-xenografted mice [37]. Tricyclic antidepressants were identified to inhibit the growth of neuroendocrine tumors including small cell lung cancer, pancreatic neuroendocrine tumors, and Merkel cell carcinoma [38]. Tranylcypromine is an MAOI used to treat depression that is refractory to numerous other drugs, which fail to treat the symptoms [39]. It has been shown to inhibit BHC110/LSD1 leading to tumor growth inhibition, as an important chromatin modification enzyme capable of demethylating histone [40–43].

These data suggest that psychiatric drugs might have antitumor potential for clinical treatment. These experiments also facilitated the identification of novel targeted strategies that could be rapidly evaluated in patients with a variety of tumors through the repurposing of approved drugs. Psychiatric drugs with potential anti-neoplastic effects are summarized in Table 1. Anti-psychotic drugs kill cancer cells through a variety of pathways including histone deacetylation inhibition, the DR pathway, and disruption of cholesterol homeostasis (see Table 2).

3. Psychiatric medications in brain tumors

Brain tumors are responsible for 2–3% of all cancer-related deaths diagnosed in the US annually [44]. Glioblastoma (GBM) is the most common brain tumor with a devastating and extremely

Table 1
Psychiatric drugs with potential anti-neoplastic effects.

Class Drug	References	Primary indications for use	Primary mechanism of action	Mechanism of anti-cancer effects
Valproic acid (Valproate, VPA)	[29,52,58,59]	Bipolar disorder Epilepsy Migraine headaches	Blockade of voltage-gated sodium, potassium, and calcium channels and inhibition the re-uptake of GABA.	Inhibits histone deacetylase to reduce cancer cell proliferation and induce apoptosis; induces differentiation and inhibits angiogenesis.
Phenothiazines Chloropromazine Levomepromazine Thioridazine	[28,30–32]	Schizophrenia Psychosis Antiemetic	Dopamine receptor antagonists	Promotes cancer stem cell differentiation through dopamine receptor pathway; inhibits mitochondrial DNA polymerase and decreases ATP production with selectively cytotoxicity and antiproliferative activity in leukemic cells.
Olanzapine Pimozide	[35]	Schizophrenia Bipolar disorder Tourette syndrome Resistant tics	An antagonist of the D2, D3, and D4 receptors and the 5-HT7 receptor	Disrupts cholesterol homeostasis to kill cancer cells.
Selective serotonin reuptake inhibitors (SSRI) Citalopram Fluoxetine Paroxetine Sertraline	[36,37,104]	Depression Generalized anxiety disorder Obsessive–compulsive disorder Eating disorders Stroke recovery Premature ejaculation	Serotonin reuptake inhibition	Reduces proliferation and induce apoptosis in cancer cells; down-regulates pAKT to mediate the synergistic anti-proliferative interaction with other chemo-drugs.
Tricyclic antidepressants Imipramine Trimipramine Amitriptyline	[38,105,106]	Major depression Attention-deficit hyperactivity disorder Insomnia Chronic pain	Serotonin and norepinephrine transporter blockage to enhance neurotransmission.	Inhibits cellular proliferation and induces cell apoptosis in different tumors including neuroendocrine tumors; improves the effectiveness of other chemotherapeutic agents.
MAO inhibitors Selegiline Phenelzine Tranylcypromine	[37,42,63]	Atypical depression Panic disorder Borderline personality disorder	Inhibition of monoamine oxidase, thus preventing the breakdown of monoamine neurotransmitters.	Inhibits BHC110/LSD1, as an important chromatin modification enzyme capable of demethylating histone.

aggressive clinical progression. Standard treatment of this tumor includes surgical resection, chemotherapy, and radiotherapy [45–48]. Recently, significant breakthroughs have been achieved in drug treatments for brain cancer such as chemotherapy and novel immune strategies. Despite the considerable efforts that have been made to increase the effectiveness, the clinical improvement of this devastating disease remains limited.

To target tumors in the brain, anti-tumor drugs must freely penetrate the blood-brain barrier (BBB). The low drug concentrations of systemically administrated therapeutic drugs in the brain may contribute to the limited success in brain tumor chemotherapy. The BBB restricts delivery of most chemo-drugs, and recent CNS drug discovery has been focused on developing agents that freely penetrate the brain [49,50]. Psychiatric medications have been proven to have anti-neoplastic properties against various cancers, which indicates their potential in treating brain tumors. These drugs have been used and studied in clinical settings for a long time, and freely penetrate the brain, which is very important for brain tumor therapy. Moreover, the chemical mechanism and toxicity of psychiatric medications have been extensively studied, which saves time for new drug development [51].

Several psychiatric drugs have been reported to be effective against GBM. Valproic acid has been traditionally used as an anti-epileptic drug and mood stabilizer for decades. It was also found to inhibit the growth of several tumor cells including GBM in recent years [19,52–54]. Several studies have evaluated and confirmed that this drug is promising for GBM treatment [52,55–57]. Clinical trials of valproic acid in brain tumors are included in Table 1. Research has shown that valproic acid can improve the outcome of patients with GBM together with conventional therapies, including temozolomide and radiation [55,57]. Valproic acid was also found to downregulate the expression of MGMT and sensitize GBM cells [58]. In addition to being identified as an HDAC inhibitor (HDACi, HDI), the anti-GBM activity of valproic acid is mediated by the induction of differentiation and angiogenesis inhibition [52,59]. Another antipsychotic drug pimozide was also found to attenuate GBM cell growth and stem cell survival. It was identified as a USP 1 specific inhibitor, which inhibits GMB stem cell development and radioresistance [60]. Tricyclic antidepressants, SSRIs, and phenothiazines have also been demonstrated to reduce GBM cellular proliferation and induce GBM apoptosis [61,62].

4. HDACs

Epigenetic regulation is considered one of the hallmarks of cancer development. Posttranslational modifications including acetylation, methylation, and phosphorylation may play crucial roles in cancer development by regulating gene transcription, chromatin remodeling, and nuclear architecture [63]. Histone acetylation is a well-established epigenetic modification that has been involved in various biological process including cancer initiation and progression. Histone acetylation can be targeted by HDACis. Increasing evidence indicates that HDAC inhibition has anti-neoplastic effects on various human cancers [64]. HDACis have a long history of use in psychiatry and neurology as mood stabilizers and anti-epileptics. A well-known example is valproic acid, which has been used for the treatment of bipolar disorders and schizophrenia. Although other mechanisms of valproic acid have been reported to contribute to its anti-neoplastic effects, inhibition of HDAC has been extensively studied [29].

Valproic acid was firstly used in anticancer clinical trials in 1999, and since then, several clinical trials of different leukemias and various solid tumors have been conducted. These clinical trials were designed and initiated to evaluate the effects of valproic acid as an HDACi on various cancers, and many have shown its promising anti-cancer effects [53,54,65,66]. Two randomized phase III trials of magnesium valproate chemotherapy in cisplatin-resistant recurrent ovarian and cervical cancers were started in 2007 to determine the effect of epigenetic therapy with valproate as an HDACi. Large-scale phase III clinical trials of valproic acid in cervical

Table 2
Representative clinical trials of psychiatric drugs. (update January 2018/Clinicaltrials.gov).

Trial identifier	Eligible disease conditions	Treatments	Estimated enrollment	Start date	Clinical phase	Primary goal	Results	Reference
NCT00530907	Advanced cancers	Valproic Acid	57	2007	I	The safety and highest tolerable dose of bevacizumab in combination with valproic acid	The combination of bevacizumab 11 mg/kg and valproic acid 5.3 mg/kg is safe in patients with advanced cancers. Patients with hypertension had improved overall survival.	[65]
NCT01007695	Breast cancer	Valproic Acid	31	2009	I	Determine if valproic acid levels correlate with histone acetylation in leukocytes during treatment	Valproic acid is well-tolerated and can decrease proliferation in breast tumors. Higher valproic acid levels are needed than those achieved at standard dose levels, but valproic acid levels do not predict effect directly. More parameters should be monitored such as peripheral blood histone acetylation changes.	[53,54]
NCT01898104	Rectal cancer	Valproic Acid	152	2013	I/II	Maximum tolerated dose of capecitabine, given alone or in combination with valproic acid	Recruiting	NA
NCT01552434	Advanced malignancy	Valproic Acid	216	2012	I	Maximum tolerated dose of valproic acid, tumor response	Recruiting	NA
NCT00246103	Solid tumor malignancies	Valproic Acid	44	2005	I	Maximum tolerated dose of valproic acid in combination with epirubicin	Partial responses were 22% (9/41) during the phase I part. Objective responses were 64% (9/14) in evaluable patients at the dose expansion with a median number of 6 administered cycles. Valproic acid plasma levels were associated with short-term, reversible depletion of WBC and neutrophils within 48 h. Histone acetylation in tumor samples and in PBMCs correlated with valproic acid levels and was further linked to baseline HDAC2 but not to HDAC6 expression.	[66]
NCT02446652	Cervical cancer	Valproic Acid	230	2015	III	Overall survival, objective response, toxicity, quality of life, progression free survival	Not yet recruiting	NA
NCT02446431	Solid tumor malignancies	Valproic Acid	20	2015	I	5-year event free survival, safety and tolerability	Recruiting	NA
NCT01817751	Recurrent high-grade glioma	Valproic Acid	66	2013	II	Response rate, overall survival and adverse effects	Recruiting	NA
NCT02068586	Uveal melanoma	Valproic Acid	90	2014	II	Overall survival, tolerability	Recruiting	NA
NCT02761291	Recurrent/metastatic nasopharyngeal carcinoma	Valproic Acid	Recruiting	2016	I	Toxicity, safety and tolerability	Recruiting	NA
NCT03243461	High grade gliomas	Valproic Acid	198	2017	III	Comparison of effects of valproic acid and chloroquine.	Not yet recruiting	NA
NCT00867672	Acute myeloid Leukemia	Valproic Acid	204	2011	II	Objective best response rate, survival, safety and toxicity	Effect on ORR of VPA vs no VPA (17.8 vs 17.2%): OR 1.06, CI [0.51,2.21], p = 0.88. The addition of VPA did not affect ORR or OS.	[111]
NCT01342692	Myelodysplastic syndromes	Valproic Acid	320	2011	II	Response rate, overall survival and adverse effects	Completed but No Results Posted	NA
NCT02096289	Relapsed or refractory acute myeloid leukemia	Thioridazine	13	2014	I	Safety, tumor response, assessment of functional leukemia stem cells, pharmacogenetic analysis of thioridazine serum trough levels	Completed but No Results Posted	NA
NCT03122444	Triple negative breast cancer	Imipramine	24	2017	Pre-Surgical Window of Opportunity Trial	Decrease in the proliferation rate of triple negative breast cancer	Not yet recruiting	NA
NCT02217709	Non-metastatic recurrent prostate cancer	Phenelzine	46	2014	II	Occurrence of PSA decline to≥50% from baseline following at least 12 weeks of treatment with phenelzine sulfate	Recruiting	NA
NCT01253642	Prostate cancer	Phenelzine	20	2010	II		Terminated (low enrollment)	NA

Table 2 (*continued*)

Trial identifier	Eligible disease conditions	Treatments	Estimated enrollment	Start date	Clinical phase	Primary goal	Results	Reference
						Proportion of patients who experience a PSA decline of at least 30%		
NCT02717884	Non-M3 acute myeloid leukemia (AML) blasts	Tranylcypromine	60	2015	I/II	Maximum tolerated dose determination of tranylcypromine in combination with fixed-dose of all-trans retinoic acid and with fixed-dose cytarabine	Recruiting	NA
NCT02273102	AML and MDS	Tranylcypromine	25	2015	I	Rate of toxicity in study participants receiving tranylcypromine/all-trans retinoic acid combination Therapy	Recruiting	NA
NCT02891278	Relapsed and refractory AML	Sertraline	36	2016	I	The recommended phase 2 dose and the maximum tolerated dose	Recruiting	NA
NCT02770378	Recurrent glioblastoma	Sertraline	10	2016	Proof-of-concept clinical trial	Response rate, overall survival and adverse effects	Recruiting	NA

Abbreviations: NA, not applicable.

cancer and glioma were also conducted in 2015 and 2017, respectively. Most of the clinical trials evaluated the safety, response rate, and adverse effects of valproic acid on different types of cancers, and some have shown encouraging results. A phase I study (NCT00530907) evaluated the combination of bevacizumab and valproic acid in patients with advanced cancers. Bevacizumab 11 mg/kg and valproic acid 5.3 mg/kg were safe and well-tolerated. Patients with hypertension showed improved overall survival [65]. Another clinical trial (NCT01007695) found that valproic acid was well-tolerated and decreased the proliferation of breast tumor cells. HDAC inhibition is a valid strategy for triple-negative breast cancer (TNBC) therapies [53,54]. Evaluation of valproic acid in solid tumor malignancies demonstrated 22% (9/41) partial responses during phase I and 64% (9/14) objective responses in evaluable patients at the dose expansion with a median of six administered cycles [66]. Histone acetylation in tumor samples and peripheral blood mononuclear cells (PBMCs) correlated with valproic acid levels and was further linked to baseline HDAC2 but not HDAC6 expression. Representative clinical trials of psychiatric medications as anticancer agents including valproic acid are summarized in Table 1.

5. Anti-psychotic drugs act on human cancer through the DR pathway

The cancer stem cell (CSC) hypothesis has become an important milestone in cancer therapy. CSCs share functional characteristics with stem cells including enhanced self-renewal, migration, and survival capacity, which contribute to tumor heterogeneity, therapy resistance, and metastasis. CSCs promote tumor growth and resist differentiation, and are a rare cell population that replenishes the entire tumor [67]. Increasing evidence indicates that conventional therapies are ineffective against cancer CSCs. This provides a potential strategy for cancer chemotherapy targeting human CSCs.

Identification of compounds that selectively inhibit CSCs could be promising and useful for preclinical drug screening. The antipsychiatric drug class of phenothiazines including chlorpromazine, levomepromazine, promethazine, trifluoperazine, and thioridazine was found to suppress proliferation and induce apoptosis of various tumor cells, including neuroblastoma, non-small cell lung cancer, glioma, melanoma, and leukemia [16,28,32]. After screening hundreds of small molecules, Sachlos et al. [30] found that thioridazine, an antipsychotic drug, selectively targets CSCs. Unlike other compounds, thioridazine acts by enhancing CSC differentiation rather than killing them. This suggests that thioridazine could be used as a selective anti-CSC agent.

To assess how thioridazine exerts its anti-CSC activity, Sachlos et al. [30] analyzed the expression of DRs on the surface of normal and neoplastic human pluripotent stem cells (hPSCs) because thioridazine is known to be a DR antagonist [68]. They found that all DRs were expressed on the surface of leukemia cells but not normal blood stem cells. This finding suggests that DRs expression might be upregulated in CSCs. The selectively high expression of DRs in neoplastic stem cells could be targeted by DR antagonists such as thioridazine. This finding also suggests that the DR pathway could serve as a biomarker specific to some CSCs and be promising in clinical treatment.

G protein-coupled DRs (DR1, DR2, DR3, DR4, and DR5) play important roles in several neurological functions including motivation, motor behavior, and cognition [69]. Several DRs have been clinically targeted in the treatments of various psychiatric and neurological diseases, including schizophrenia, bipolar disorder, Huntington's disease, Parkinson's disease, and Tourette's syndrome [70]. Interestingly, several studies have reported decreased incidences of most cancers in patients with Parkinson's disease, which suggests that patients with a dopamine deficiency may have some protection against cancer [71]. These findings are further corroborated by evidence that polymorphisms of the DR2 modulate the risk of colorectal cancer [72]. In addition, dopamine signaling enhances the efficacy of anticancer drugs in breast and colon cancer [73]. Further studies are required to determine whether the anti-CSC properties of phenothiazines and other antipsychotics are mediated through the DR pathway.

6. Anti-psychotic drugs kill cancer cells by disrupting cholesterol homeostasis

Cholesterol homeostasis is one of the most intensely regulated processes in the human body, which has been extensively studied for over 100 years [74]. Cholesterol plays a key role in various processes. It is an essential part of the mammalian cell membrane that contributes to cell permeability, affinity, and fluidity. It is also the precursor of all steroid hormones and bile acids. Insufficient or excessive cholesterol can lead to serious consequences including atherosclerosis and metabolic-related diseases. Cholesterol

metabolism also plays a key role in transmembrane signaling process and cell growth [75,76]. A recent study has shown that microRNA 33, which modulates cholesterol and fatty acid metabolism, regulates cell proliferation and cycle progression [77]. A new study published in Cancer Research suggests that cholesterol homeostasis could be a novel therapeutic target for prostate cancer treatment [78].

First-generation antipsychotic drugs, known as typical psychiatric medications, were believed to exert their antipsychotic efficacy through the blockade of the DR2, which causes extrapyramidal side effects and hyperprolactinemia [79]. Second-generation drugs known as atypical psychiatric medications such as risperidone and olanzapine were developed in the 1990s. The newer psychiatric medications have a broader binding profile, affecting the activity of DR as well as serotonin and histamine receptors [79]. Their therapeutic effects are associated with higher risks of adverse metabolic effects including impaired glucose metabolism, obesity, and dyslipidemia [80]. Research studies have found that antipsychotic drugs upregulate genes involved in lipid homeostasis [81]. These drugs upregulate lipogenic gene expression by disrupting intracellular trafficking and the synthesis of cholesterol [82]. The upregulation of lipogenic genes partly explains the efficacy of psychiatric medications in treating psychiatric disorders as well as their adverse metabolic effects [35,83,84]. In a study conducted in Australia, six antipsychotic drugs (reserpine, chlorpromazine, haloperidol, pimozide, risperidone, and olanzapine) were screened for their potential anticancer effects in various tumor cell lines derived from lymphoblastoma, neuroblastoma, non-small cell lung cancer, and breast adenocarcinoma. Almost all these drugs selectively inhibited cancer cells, and pimozide was found to be the most lethal agent [35]. Furthermore, the gene expression analysis of the drug-treated groups showed that olanzapine and pimozide exert their cytotoxicity by disrupting cholesterol homeostasis. They also found that the side-effects of these psychiatric medications could be reduced by co-administration with the cholesterol inhibitor mevastatin. These results indicate that psychiatric medications affecting the cholesterol homeostasis pathways could be novel chemotherapeutic agents for cancer treatment. Several clinical studies also found that olanzapine prevented chemotherapy-induced nausea and vomiting [28,85,86]. Moreover, research studies have reported that olanzapine accumulates in the lung after administered to patients, suggesting that it could be promising in lung cancer chemotherapy [87]. These studies provide a rational basis for the future anticancer use of psychiatric medications as an alternative strategy with the traditional agents [88].

7. Challenges and limitations of psychiatric drug repurposing

Several studies have confirmed the anticancer effects of psychiatric medications against different malignancies. However, challenges and limitations still exist in the repurposing of these drugs that need to be considered prior to their further clinical applications.

Psychiatric medications have been proven to possess cytotoxicity against cancer cells and have been tested in clinical trials, although most related studies were in vitro investigations using only human tumor cell lines [32,37]. However, in vivo rodent studies showed that psychiatric drugs could be effective against several cancers, including liver, pancreas, and thyroid tumors in rodents of both sexes, as well as pituitary and mammary tumors in female rodents [28]. A systematic review and assessment of psychiatric drugs from FDA rodent studies summarized the carcinogenicity of several classes psychiatric drugs including antipsychotics, antidepressants, anticonvulsants, benzodiazepines/sedative-hypnotics, and amphetamines [89]. The results demonstrated that antipsychotics (90%, 9/10 agents) and anticonvulsants (85.7%, 6/7 agents) were highly carcinogenic in preclinical in vivo studies. Another review summarized the results of investigations of the carcinogenic effects of marketed antipsychotics and antidepressants [90]. Long-term carcinogenesis assays of 25 drugs demonstrated that 32.0% (8/25) of the psychiatric drugs were carcinogenic. The authors also summarized all the carcinogenic assays and found that several antipsychotics (fluphenazine, haloperidol, buspirone, chlorpromazine, and pimozide) and antidepressants (fluoxetine, fluvoxamine, nefazodone, venlafaxine, bupropion, clomipramine, and sertraline trazodone) tested negative in rodent carcinogenic assays. Antipsychotics (olanzapine, risperidone, aripiprazole, quetiapine, and ziprasidone) and antidepressants (duloxetine, mirtazapine, paroxetine, citalopram, and phenelzine) exhibited positive responses in carcinogenesis assays. These animal-based preclinical results are not sufficient to obtain definitive and reliable conclusions for human clinical applications. Furthermore, although the mechanisms of the potential carcinogenicity of psychiatric medications have not been clearly identified, the animal-based preclinical results provide information for further investigation of their clinical applications.

Findings of clinical studies are also controversial regarding the effects of psychiatric drugs on cancer risk. A study using Danish nationwide registers assessed the associations between various antidepressants and the risk of epithelial ovarian cancer, which showed that compared with non-use and other antidepressants, the use of SSRIs was associated with reduced cancer risk [91]. Another study noted that SSRIs were associated with decreased risk of hepatocellular carcinoma [92]. However, some studies have reported contradictory results. Antipsychotic are reported to cause higher breast cancer incidence among female patients with schizophrenia. The results may be related to the hyperprolactinemia caused by antipsychotics, which should be considered seriously in future drug use [26,27]. The extensively used atypical antipsychotic drug, clozapine, can cause severe agranulocytosis and other hematological side effects [28,93]. Nielsen and Boysen [93] found that clozapine-treated patients had eight times increased risk of developing acute myeloid leukemia (AML) compared to patients with schizophrenia or schizo-affective disorder not receiving clozapine [94]. The authors also noted some limitations of their study. Firstly, only four schizophrenia patients were involved in the study. Secondly, it has been revealed that the leukemia inhibitory factor (*LIF*) gene is associated with hebephrenic schizophrenia, which has often been treated with clozapine [95]. These concerns make it difficult to clarify whether the clozapine treatment directly caused AML [94]. It is worth emphasizing that mandatory hematological monitoring should be recommended for clozapine treatment to avoid hematological abnormalities and increased risk of developing AML.

The long history of clinical use, existing drug clinical results, and toxicology of psychiatric drugs make them good candidates for drug repurposing. However, long-term administration of psychiatric medication may result in side effects. Patients administered first-generation antipsychotic drugs are more likely to experience extrapyramidal side-effects, especially with haloperidol, zotepine, and chlorpromazine. Weight gain and associated metabolic disorders have been recognized as the main problems associated with second-generation antipsychotic drugs [96,97]. Other side effects of psychiatric medications such as QTc prolongation, prolactin increase, sexual dysfunction, sedation, postural hypotension, and cardiac arrhythmia could also be unpleasant for patients [97]. Another important issue associated with long-term psychiatric medication is tolerance onset, which should always be assessed in patients administered psychiatric drugs. Prior psychiatric medications may affect the efficiency of new drug use because of cross-

tolerance issues, which partly explain why novel clinical trials have been unsuccessful [98]. The tolerance onset associated with general psychiatric drugs is relatively low and acceptable. Wheler et al. [65] found that when combined with bevacizumab (11 mg/kg intravenously [IV] once every 14 days), valproic acid (5.3 mg/kg orally [PO] daily) was safe and well tolerated in treating patients with advanced cancers. However, high-dose-induced neurotoxicity should also be monitored. In previous studies, high doses of valproic acid were reported to be associated with several neurotoxicities (20–26% of patients), including fatigue, confusion, and somnolence [99,100]. A lower dose of valproic acid showed favorable efficiency, but two patients (2/57) developed grade 3 toxicity with altered mental status [65]. Phenothiazine derivatives have been reported to possess anti-proliferative properties in various tumors in addition to their pharmacodynamic actions as psychiatric drugs; however, these actions also contribute to their intolerance and a variety of adverse effects [101–103]. All these factors have to be considered and further studies would be required to balance the benefit/risk ratio of additional clinical applications.

8. Conclusion

Faced with high cost and risks of drug development, researchers are currently focusing attention on repurposing existing drugs, including drugs that failed in clinical trials. One of the most successful cases of drug repurposing is sildenafil. After penile erections were observed in patients in phase 1 trials of sildenafil for cardiovascular disease, it was reevaluated for erectile dysfunction treatment. Repurposing drugs aids in revamping the old drugs for a new indication, making drug development more predictable with agents with known toxicity and pharmacology [104]. It also aids physicians in on and off-label drug prescription. Many medications have been found to be efficient for indications they have not been previously approved to treat. Drug repurposing provides opportunities for investigating the mechanisms of the observed effects in further trials. This could be a promising complement, as well as a more efficient and relatively rapid strategy for new drug discovery.

In this review, we have highlighted the significant antineoplastic properties of antipsychotic drugs including valproic acid, phenothiazines, olanzapine, pimozide, antidepressants and other psychiatric medications against various tumors. These drugs have been shown to arrest cancer cell proliferation and induce their apoptosis in pre-clinical studies, although further investigations are required to elucidate the precise mechanisms and targets of these psychiatric medications drugs. Furthermore, numerous drugs, including valproic acid and thioridazine, are currently under evaluation in clinical trials. These findings are very promising for generating new chemotherapeutic drugs.

In addition to the potential cytotoxicity of psychiatric medications against cancer cells, these drugs provide additional benefits for cancer chemotherapy. Cancer is a severe disease and a leading cause of death worldwide. A large proportion of patients with cancer developmental disorders [36,105,106]. Therefore, the use of these drugs in patients with cancer who have co-morbidities of depression, anxiety, or other mental problems appears attractive. Moreover, some psychiatric medications could be beneficial for the prevention and control of chemotherapy-related adverse effects. Olanzapine has been suggested to be effective in controlling nausea and emesis in several phase III trials [37].

Despite the above findings, there are still several concerns with the use of psychiatric medications for cancer chemotherapy. The use of some psychiatric medications is found to reduce the risk of developing cancer. SSRIs are considered to inhibit colon cancer cell growth and may be prescribed for chemopreventive purposes [38]. However, female patients with schizophrenia who are receiving psychiatric medications such as risperidone, paliperidone, and amisulpride have been shown to exhibit a significantly high risk of breast cancer [107]. Increasing experimental and epidemiological data have demonstrated that the anti-dopamine activity of psychiatric medications can cause potential hyperprolactinemia [108]. Another concern with psychiatric medications use in cancer therapy is their possible, unexpected and frequent adverse effects. Although psychiatric medications have been clinically used for several years, they are known to induce a wide range of adverse effects [109,110]. The common adverse effects are extrapyramidal syndrome, postural hypotension, cardiac arrhythmia, and metabolic syndrome. Further investigation needed to assess the precise mechanism, efficiency, and adverse effects.

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Declarations of interest

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