Repurposing psychiatric drugs as anti-cancer agents

Jing Huang a, b, c, d, Danwei Zhao e, Zhixiong Liu a, Fangkun Liu a, *

a Department of Neurosurgery, Xiangya Hospital, Central South University (CSU), Changsha, China
b Department of Psychiatry, The Second Xiangya Hospital, Central South University, Changsha, Hunan, 410001, China
c Mental Health Institute of the Second Xiangya Hospital, Central South University, Chinese National Clinical Research Center for Mental Disorders (Xiangya), Changsha, Hunan, 410001, China
d Chinese National Technology Institute on Mental Disorders, Hunan Key Laboratory of Psychiatry and Mental Health, Changsha, Hunan, 410001, China
e Xiangya Medical School, Central South University, Changsha, Hunan, China

Abstract

Cancer is a major public health problem and one of the leading contributors 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
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 have demonstrated 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, pimozone, 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 deacetylation (HDAC) inhibition. More than 80 clinical trials have been initiated to evaluate its anticaner properties against different tumors [28]. 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 anticaner 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 pimozone and the atypical psychiatric medication olanzapine disrupt cholesterol homeostasis to kill cancer cells. There are many other examples of neuroactive drugs with antitumor 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
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 administered 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 (HDAC, 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 processes 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).

<table>
<thead>
<tr>
<th>Trial identifier</th>
<th>Eligible disease conditions</th>
<th>Treatments</th>
<th>Estimated enrollment</th>
<th>Start date</th>
<th>Clinical phase</th>
<th>Primary goal</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00530907</td>
<td>Advanced cancers</td>
<td>Valproic Acid</td>
<td>57</td>
<td>2007</td>
<td>I</td>
<td>The safety and highest tolerable dose of bevacizumab in combination with valproic acid</td>
<td>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.</td>
<td>[65]</td>
</tr>
<tr>
<td>NCT01007695</td>
<td>Breast cancer</td>
<td>Valproic Acid</td>
<td>31</td>
<td>2009</td>
<td>I</td>
<td>Determine if valproic acid levels correlate with histone acetylation in leukocytes during treatment</td>
<td>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.</td>
<td>[53,54]</td>
</tr>
<tr>
<td>NCT01898104</td>
<td>Rectal cancer</td>
<td>Valproic Acid</td>
<td>152</td>
<td>2013</td>
<td>I/II</td>
<td>Maximum tolerated dose of capecitabine, given alone or in combination with valproic acid</td>
<td>Recruiting</td>
<td>NA</td>
</tr>
<tr>
<td>NCT01552434</td>
<td>Advanced malignancy</td>
<td>Valproic Acid</td>
<td>216</td>
<td>2012</td>
<td>I</td>
<td>Maximum tolerated dose of valproic acid, tumor response</td>
<td>Recruiting</td>
<td>NA</td>
</tr>
<tr>
<td>NCT00246103</td>
<td>Solid tumor malignancies</td>
<td>Valproic Acid</td>
<td>44</td>
<td>2005</td>
<td>I</td>
<td>Maximum tolerated dose of valproic acid in combination with epirubicin</td>
<td>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.</td>
<td>[66]</td>
</tr>
<tr>
<td>NCT02446652</td>
<td>Cervical cancer</td>
<td>Valproic Acid</td>
<td>230</td>
<td>2015</td>
<td>III</td>
<td>Overall survival, objective response, toxicity, quality of life, progression free survival</td>
<td>Not yet recruiting</td>
<td>NA</td>
</tr>
<tr>
<td>NCT02446431</td>
<td>Solid tumor malignancies</td>
<td>Valproic Acid</td>
<td>20</td>
<td>2015</td>
<td>I</td>
<td>5-year event free survival, safety and tolerability</td>
<td>Recruiting</td>
<td>NA</td>
</tr>
<tr>
<td>NCT01817751</td>
<td>Recurrent high-grade glioma</td>
<td>Valproic Acid</td>
<td>66</td>
<td>2013</td>
<td>II</td>
<td>Response rate, overall survival and adverse effects</td>
<td>Recruiting</td>
<td>NA</td>
</tr>
<tr>
<td>NCT02068586</td>
<td>Uveal melanoma</td>
<td>Valproic Acid</td>
<td>90</td>
<td>2014</td>
<td>II</td>
<td>Overall survival, tolerability</td>
<td>Recruiting</td>
<td>NA</td>
</tr>
<tr>
<td>NCT02761291</td>
<td>Recurrent/metastatic nasopharyngeal carcinoma</td>
<td>Valproic Acid</td>
<td>90</td>
<td>2016</td>
<td>Recruiting</td>
<td>Toxicity, safety and tolerability</td>
<td>Recruiting</td>
<td>NA</td>
</tr>
<tr>
<td>NCT03243461</td>
<td>High grade gliomas</td>
<td>Valproic Acid</td>
<td>198</td>
<td>2017</td>
<td>III</td>
<td>Comparison of effects of valproic acid and chloroquine.</td>
<td>Not yet recruiting</td>
<td>NA</td>
</tr>
<tr>
<td>NCT00867672</td>
<td>Acute myeloid Leukemia</td>
<td>Valproic Acid</td>
<td>204</td>
<td>2011</td>
<td>II</td>
<td>Objective best response rate, survival, safety and toxicity</td>
<td>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.</td>
<td>[111]</td>
</tr>
<tr>
<td>NCT01342692</td>
<td>Myelodysplastic syndromes</td>
<td>Valproic Acid</td>
<td>320</td>
<td>2011</td>
<td>II</td>
<td>Response rate, overall survival and adverse effects</td>
<td>Completed but No Results Posted</td>
<td>NA</td>
</tr>
<tr>
<td>NCT02096289</td>
<td>Relapsed or refractory acute myeloid leukemia</td>
<td>Thioridazine</td>
<td>13</td>
<td>2014</td>
<td>I</td>
<td>Safety, tumor response, assessment of functional leukemia stem cells, pharmacogenetic analysis of thioridazine serum trough levels</td>
<td>Completed but No Results Posted</td>
<td>NA</td>
</tr>
<tr>
<td>NCT03122444</td>
<td>Triple negative breast cancer</td>
<td>Imipramine</td>
<td>24</td>
<td>2017</td>
<td>Pre-Surgical Window of Opportunity Trial</td>
<td>Decrease in the proliferation rate of triple negative breast cancer</td>
<td>Not yet recruiting</td>
<td>NA</td>
</tr>
<tr>
<td>NCT02217709</td>
<td>Non-metastatic recurrent prostate cancer</td>
<td>Phenelzine</td>
<td>46</td>
<td>2014</td>
<td>II</td>
<td>Occurrence of PSA decline to &lt;50% from baseline following at least 12 weeks of treatment with phenelzine sulfate</td>
<td>Recruiting</td>
<td>NA</td>
</tr>
<tr>
<td>NCT01253642</td>
<td>Prostate cancer</td>
<td>Phenelzine</td>
<td>20</td>
<td>2010</td>
<td>II</td>
<td></td>
<td>Terminated (low enrollment)</td>
<td>NA</td>
</tr>
</tbody>
</table>
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.

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. This finding suggests that patients with a dopamine deficit may have some protection against cancer [71]. These findings are further corroborated by evidence that polymorphisms of the DR2 modulate fluidity. It is also important roles in several neurological functions including motility, 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

---

Table 2 (continued)

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

Abbreviations: NA, not applicable.
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 [33]. 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, bupropione, chlorpromazine, and pimozide) and antidepressants (fluoxetine, fluvoxamine, nefazodone, venlafaxine, bupropione, clomipramine, and sertraline trazodone) tested negative in rodent carcinogenic assays. Antipsychotics (olanzapine, risperidone, aripiprazole, quetiapine, and ziprasidine) 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 antipsychotics, antidepressants, and anticonvulsants [92]. 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.
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 anti-neoplastic 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.

Funding

This work was supported by National Natural Science Foundation of China (81472693).

Declarations of interest

None.

Acknowledgments

The authors would like to thank the reviewers for their valuable comments and suggestions to improve the quality of the paper.

References


41.


42.

43.

44.