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The Relationship between Antipsychotic Medications and Cancer: A Review Article

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ABSTRACT

Background: Cancer is a global problem and causes lots of deaths across the world. Due to the high cost of manufacturing and developing new drugs, there is more willingness to use medications that may have anti-neoplastic effects.

Objectives: Antipsychotic drugs have a long history of clinical use. Currently, there are several reports about the anti-cancer effects of antipsychotic drugs in different types of malignancies.

Methods: In this study, the effects and mechanisms of several antipsychotic drugs on different types of cancer were investigated. The current investigations show that some antipsychotic drugs might inhibit the proliferation of cancer cells and some others can be used to ease the symptoms caused by cancer.

Results: The anticancer effects of all antipsychotic drugs haven't been thoroughly investigated and it is reported that few drugs may reverse the effects and increase the risk of neoplasm.

Conclusions: Although some studies have revealed that antipsychotic drugs might beneficially affect cancer cells, high quality clinical trials are still needed to confirm these results.

Key words: Antipsychotic Agents, Neoplasms, Medication Therapy Management

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Introduction

Cancer is one of the major global health problems and according to international cancer research agency (IARC) statistics; the number of people with cancer will reach 21.7 million till 2030 that will result in 13 million deaths *[1]*.

Current chemotherapy treatments have been unchanged through the past three decades and these medications include alkylating agents, antimetabolites, antibiotics, topoisomerase inhibitors, and mitotic inhibitors *[2]*.

Drugs that are used in treating Psychiatric disorders have a long history of clinical usage and can be considered as a choice in cancer therapy. In particular, Thioridazine is well-recognized to have antimicrobial

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properties in addition to its antipsychotic activity *[1, 3]*.

A number of studies have also been done about the anti-cancer effects of antipsychotic-drugs. It has been reported that patients with schizophrenia who received antipsychotic drugs, had a lower risk of getting cancer *[4-6]*. Antipsychotic medications are proposed by vivo and in vitro to cause cancer cells' death in different routes, *[7]*.

The effect of antipsychotic drugs on cancer

1. Aripiprazole (ARI)

Aripiprazole is one of the antipsychotic drugs used in schizophrenia and other psychiatric disorders. This drug exerts its effect through binding the dopamine and serotonin receptors. This drug has a few side effects and can also be used in cancer *[7-10]*.

It has been shown that ARI can cause cell death and inhibit cancer stem-like cells (CSC) growth. ARI can also inhibit survivin expression and thereby causes CSCs to become sensitive to chemotherapeutic agents. ARI and its active metabolite dehydroaripiprazole (DARI) inhibit P-glycoprotein and breast cancer resistance protein (BCRP). In addition, it can decrease the efflux and increase the gastrointestinal absorption of chemotherapy agents *[11-13]*.

2. Chlorpromazine (CPZ)

Chlorpromazine is an antipsychotic drug that belongs to the phenothiazine class. This drug has been used in the treatment of certain mental/mood disorders, including schizophrenia and the manic phase of bipolar disorder *[14]*.

It has been revealed that CPZ has inhibitory effects on tumor growth in several cancers, including hepatocellular carcinoma, glioma, leukemia, and melanoma *[15-17]*. this drug might also reduce the risk of prostate cancer in men with schizophrenia *[4]*. It also might have an anti-proliferative effect on leukemia cells in culture without any influence on normal lymphocyte viability *[16, 18]*; CPZ also induces apoptosis in a B16 mouse melanoma cell line and other different types of cultured cells, including melanoma cells *[18]*.

In glioma cells, CPZ augments p21 expression is a cyclin-dependent kinase inhibitor and finally, it causes cell cycle stop in the G2/M-phase. In colorectal cancer cells, it is shown that CPZ induces apoptosis through the p53 gene which is a Tumor suppressor gene *[17]*.

This drug has also a synergistic effect on tamoxifen decreasing cell growth and metabolic activity both in tamoxifen-sensitive and tamoxifen-resistant human breast cancer cells *[18]*. Besides, due to the anti-emetic, analgesia, and sedative effects, CPZ can be used as a concomitant medication in cancer patients *[19]*. The anti-cancer effects of CPZ become noticeable in long-term and high doses; however, long-term use or high doses of CPZ can cause a serious movement disorder that may not be reversible *[13]*.

3. Clozapine (CLZ)

Clozapine is an atypical antipsychotic drug that is used for schizophrenia treatment. Little information is available about the beneficial effect of clozapine in preventing cancer progression.

Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) is a phosphatase enzyme that converts phosphatidylinositol 3, 4, 5-trisphosphate to phosphatidylinositol 4, 5-bisphosphate and thereby antagonizes the action of phosphoinositide 3-kinase (PI3K). Mutations or deletions in the gene of this enzyme can activate the calcium-calmodulin pathway through subunit p110γ of PI3K that can lead to multiple cancers. Studies have found that CLZ can suppress cell growth by blocking the IP3-dependent calcium release and inhibiting the calcium-calmodulin pathway *[20, 21]*. This drug has several side effects such as agranulocytosis, neutropenia and weight gain *[22]*. Studies have shown that the risk of acute myeloid leukemia (AML) in patients treated by CLZ was eight times more than those who did not receive this

drug. The mechanism of clozapine-induced AML remains unknown but a recent study found that clozapine possesses cytotoxic effects on human bone marrow stromal cells *[23]*.

4. Fluphenazine (FPH)

Fluphenazine, one of the phenothiazine derivatives, is a useful drug in different psychotic disorders like schizophrenia, mania, severe anxiety, and disturbed behavior. In addition to being a neuroleptic drug;, FPH has anti-nausea and anti-vomiting effects.

Several studies have indicated that FPH can act as a P-glycoprotein inhibitor and can be an auxiliary agent in cancer treatment *[24]*. However, this drug has some side effects on the central nervous system that can limit the usage of FPH in cancer therapy *[25]*.

In-vitro studies have indicated that FPH inhibits the proliferation of human myeloblastic leukemia cells (HL-60). Besides, this drug has a cytotoxic effect against the intraperitoneal L-1210 and P-388 leukemia murine tumor models. It has also been shown that FPH is able to induce apoptosis in a B16 mouse melanoma cell line and it can reduce melanoma tumor growth in vivo *[26]*.

5. Fluspirilene (FPL)

Fluspirilene is an antipsychotic drug that belongs to the diphenylbutylpiperidines group which is used to treat schizophrenia.

Studies have shown that FPL can inhibit phosphorylation of cyclin-dependent kinase2 (Cdk2), a protein in the cell cycle, and causes cells to cease at the G1 phase of the cell cycle; therefore, FPL can have inhibitory activity against hyperproliferation in hepatocellular carcinoma HepG2 and Huh7 cells. This drug can also inhibit xenograft hepatocellular carcinoma (HCC) in animal models *[27]*. Furthermore, FPL was shown to inhibit the p53-MDM2 (murine double minute 2) interaction by binding to the p53-binding pocket of the MDM2 protein, causing p53 activation and inhibition of human tumor cells growth *[28]*.

6. Haloperidol (HPD)

Haloperidol is an antipsychotic drug that has been used in treating Schizophrenia, mania and other psychiatric disorders.

Hepatocellular carcinoma is the second cause of cancer deaths in the world. Haloperidol can play an important role in human HCC. Also, HPD can bolster induced ferroptosis by stimulating cellular iron accumulation, GSH depletion, and lipid peroxidation. Heme oxygenase-1 (HO-1) has been proposed to demonstrate cytoprotective effects against various stress-related conditions. Subsequently, HPD can elevate the HO-1 expression in ferroptosis *[13, 29]*.

The drug can have an inhibitory effect on sigma receptors. Sigma-1 receptor increases the synthesis of vascular endothelial growth factor (VEGF) through its effect on voltage-dependent potassium channels hERG (a gene that codes for a protein known as $K_v11.1$). Recent studies have shown the inhibition of the sigma-1 receptor can have antiproliferative and cytotoxic effects. It is reported that HPD has some rare but serious side effects, including fainting, slow heartbeat, severe dizziness, chest pain, and a very severe allergic reaction *[30]*.

It should be noted that HPD injection is not approved for the treatment of patients with dementia-related psychosis due to the risk of increased mortality *[13]*.

7. Olanzapine (OLA)

Olanzapine is used to treat multiple mental disorders such as schizophrenia *[31]*. This drug is the blocker of several receptors, including dopaminergic (D3 and D4), serotonergic 5HT3, adrenergic (alpha1), and histaminergic receptors. 5HT3 plays an important role in nausea and emesis; OLA can also be efficacious in the treatment of cancer-induced vomiting by blocking the 5-Hydroxytryptamine3 (5HT3) receptor. By considering that this drug can act as a dopamine antagonist, OLA can be used as an auxiliary cancer treatment drug *[32]*.

Low circulating levels of adiponectin and high levels of lectin can increase the risk of breast cancer by interrupting cell proliferation processes in cancer cells. Olanzapine and clozapine can both prevent this process by reducing adiponectin levels *[33]*.

Additionally, OLA can suppress the expression of the survivin in pulmonary and pancreas cancer stem cells and make them more sensitive to treatment agents like cisplatin and gemcitabine. The most important disadvantages of OLA are the potential long-term adverse effects, including increased blood, sugar tardive dyskinesia, and weight gain *[34]*.

8. Penfluridol (PFD)

Penfluridol is a first-generation antipsychotic drug. It has been used in the treatment of schizophrenia since 1970. Researches indicate that the anti-tumor effect of PFD in glioblastoma is by AKT-mediated suppression of Glioma-Associated Oncogene Homolog1 (GLI1) which is a transcriptional factor that acts as an effector of the hedgehog signaling pathway which is also overexpressed in glioblastoma tumors. These new findings can suggest PFD as a treatment of glioblastoma *[35]*. This drug can also induce apoptosis in xenograft pancreatic tumors by inhibiting their proliferation *[36]*.

Recent studies have indicated that PFD can have an effect on the suppression of mammary tumor metastases by inhibiting integrin b4, focal adhesion kinase (Fak), paxillin, Rac proteins (Rac1, 1b, 2, 3), and rho-associated, coiled-coil-containing protein kinase 1 (ROCK1) signals expression. These mechanical signals are caused by extracellular matrix (ECM) stiffness in the mammary epithelium *[37]*.

9. Pimozide (PMZ)

Pimozide, which is of the diphenylbuty-lpiperidines class, is used in different mental problems including schizophrenia and bipolar disorder. This drug acts as a dopamine (D2) receptor antagonist *[38]*.

There are several in vitro studies that show inhibitory effects of PMZ on pulmonary, brain and breast cancer cells. This drug inhibits proliferation and metastasis of cancer cells by preventing fibroblasts differentiation into myofibroblast. Myofibroblast is the agent that helps the growth of tumors especially breast tumors *[39]*.

Studies have shown that PMZ can reduce the ability of HCC survival by regulating the canonical Wnt pathway (Wnt/β-catenin pathway), epithelial cell adhesion molecule (EpCAM), and protein expression. The overexpression of EpCAM plays an important role in cancer formation *[40]*.

PMZ can inhibit the proliferation of MDA-MB-231 breast and A549 lung cancer cell lines *[39]*.

Furthermore, the beneficial effects of PMZ have been identified in the treatment of metastatic melanoma by suppression of dopaminergic pathways. Further studies are needed to confirm its beneficial effects *[41]*.

10. Quetiapine (QUE)

Quetiapine, another atypical antipsychotic drug, is used in several mental disorders such as schizophrenia, depression, and bipolar disorders.

It can be useful in cancer-related complications by inhibiting osteoclastogenesis and preventing breast cancer-related bone loss via the suppression of the Receptor activator of nuclear factor kappa-B ligand (RANKL)-mediated mitogen-activated protein kinase (MAPK) signaling pathway *[42]*.

Quetiapine can also be useful in the treatment of tamoxifen insomnia *[43]*. Furthermore, another study on xenograft glioma indicated that treating with QUE can suppress Glioblastoma stem cells (GSCs) initiated tumor growth. Combination therapy of QUE and temozolomide is shown to have asynergistic effect on glioma suppression *[44]*.

11. Risperidone (RIS)

Risperidone which is an atypical antipsychotic drug is widely used in psychotic disorders. It is a blocker of several receptors including dopaminergic (D2), adrenergic (α2) and serotonin (5HT2) receptors *[45]*.

This drug in combination with Rumenic acid can inhibit the proliferation of prostate cancer cells (PC3) in vitro and delay the growth of prostate cancer tumors in vivo *[46]*. Likewise, RIS reduces Tamoxifen-induced hot flushes in patients with breast cancer *[45]*.

Risperidone also has been applied in resistant breast cancers. RIS accumulates in high-levels in the tissues that can lead to pharmacokinetic interactions of RIS with breast cancer resistance protein (BCRP) substrates. Additionally, RIS can also inhibit the P-glycoprotein (P-gp); therefore, these dual effects of RIS can affect the efflux of chemotherapy drugs from the target tissue [47].

Few reports have shown that there is more breast cancer risk in RIS consumers but some other studies dismissed the relationship and expressed that RIS has little effect in increasing the risk of breast cancer *[48]*. Therefore, further researches are needed to prove this claim.

12. Sulpiride (SUL)

Sulpiride, a benzamide derivate, is one of the typical antipsychotic drugs which is used widely in patients with schizophrenia. This drug has fewer side effects than other typical antipsychotics such as haloperidol and chlorpromazine *[49]*.

Due to its D2 receptor antagonistic property, SUL can be used as an adjuvant therapy in cancer. SUL can significantly augment the anticancer effect of dexamethasone in treating breast cancer and it can also suppress the growth of cancer stem cells (CSCs) *[50]*.

13. Th ioridazine (THZ)

Thioridazine, a phenothiazine derivate, is a powerful antipsychotic drug that is used in psychotic disorders *[51]*. It is another D2 antagonist and some previous studies have indicated that patients with schizophrenia receiving dopamine antagonists had a lower risk for rectal, colon, prostate and uterus cancer. THZ has antineoplastic effects through inducing oxidative stress, apoptosis, inhibiting tumor angiogenesis, and interacting with the Protein kinase B (PKB), also known as Akt and extracellular-regulated kinase (ERK) signaling pathways in ovarian cancer *[14, 52]*.

Recent reports have also indicated that THZ has an efficient and selective role in the inhibition of the growth and repair of stem cells without causing any harmful effects on cells with normal growth *[44]*.

Furthermore, THZ inhibits the growth of lung cancer NCI-H1299 cell line by sensitizing tumor cells to chemotherapy. This drug can reduce the phosphorylation of AKT, an important protein for cell survival, *[53]*, and it can also cause apoptosis in leukemia cells and melanoma B16 cell lines *[54]*. It can also decrease the viability of cancer cells and induces apoptosis by the mitochondrial pathway in gastric cancer *[55]*. Combination therapy is a cornerstone of cancer therapy. The combined therapy of THZ and loratadine is described as a promising therapy compared to THZ alone in gastrointestinal malignancy *[7]*.

It should be noted that THZ has the potential to prolong the corrected QT (QTc) interval which is associated with torsade de pointes (TdP) and sudden death.

14. Trifluoperazine (TFP)

Trifluoperazine**,** another phenothiazine antipsychotic agent, inhibits DNA Double-Strand Break Repair Pathway; therefore, it can cause bleomycin cytotoxicity in non–small-cell-lung carcinoma. The drug is a calmodulin antagonist and it might suppress DNA repair through a calmodulin-dependent pathway carcinoma *[56]*. Other calmodulin inhibitors such as adriamycin *[57]* and cisplatin enhance the cytotoxic effects of TFP *[58]*.

Studies have shown that the combination of TFP with cisplatin or gefitinib was capable to erase the drug resistance of lung cancer *[45]*.

Resistance to radiotherapy is a major problem in patients who suffer from solid tumors. TFP can also enhance ionizing radiation (IR) induced cell death

through breakage of DNA double-strand and the inhibition of DNA repair, and thus it can be used as an adjuvant to IR *[16, 59]*.

Conclusion

Antipsychotic drugs can be beneficial in cancer therapy using different pathways, including malignant cells growth inhibition and improvement of the chemotherapy efficacy in cancers. They can also affect several stages of the cell cycle. It is proposed that the addition of antipsychotic drugs at a sufficient dose to an anti-cancer agent or radiotherapy regimens of lower doses can enhance cancer treatment with slighter side effects; therefore, it can improve patients' quality of life *[13]*.

The anticancer effects of all antipsychotic drugs have not been thoroughly investigated and it is reported that few drugs may reverse the effects and increase the risk of neoplasm. Nevertheless, some antipsychotic drugs can be considered as cancer therapy medications because of their beneficial effects. However, in order to confirm the anti-neoplastic effects of antipsychotic-drugs, further comprehensive investigations are needed.

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Authors' contributions

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Conflict of Interest

The authors declare that there is no potential conflict of interests in this review.

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