

Antidepressant drugs as a complementary therapeutic strategy in cancer

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Abstract

In the last decade, it has been increasingly recognized that antidepressant drugs may exert a range of effects, in addition to their well-documented ability to modulate neurotransmission. Although as a group they act on monoaminergic systems and receptors in different ways, a number of studies have demonstrated that at least some antidepressants might have other properties in common, including immunomodulatory, cyto/neuroprotective, analgesic and anti-inflammatory activities. These properties are partly related to the influence of antidepressants on glial cell function.

Recently, emerging information about the possible anticancer properties of antidepressants has sparked increased interest within scientific community, and there is now evidence that these drugs affect the key cellular mechanisms of carcinogenesis. This review examines the putative cellular targets for the anticancer action of antidepressant drugs, and presents examples of the interaction between antidepressants and anticancer drugs. By reviewing the current state of research in this area, we hope to focus the attention of oncologists and researchers engaged in the study of cancer on the role that antidepressant drugs could play in the complementary therapy of cancer.

Keywords: Cancer, energy metabolism dysfunction in cancer, apoptosis, antidepressants

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Introduction

Nowadays, various antidepressants are used in clinical practice. According to their influence on the monoaminergic systems they are divided into several groups: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, serotonin and norepinephrine disinhibitors, serotonin antagonists/reuptake inhibitors, norepinephrine and dopamine reuptake inhibitors and selective norepinephrine reuptake inhibitors. Besides major depression, antidepressant drugs are applied in the therapy of such disorders as dysthymia, schizoaffective disorders, anxiety disorders, panic disorders, social phobia, anorexia, bulimia, post-traumatic stress disorders, migraine, chronic pain syndromes, neuropathic pain, spinal cord injury and neurodegenerative disorders with neuroinflammation.¹

Antidepressants also have an important position in the therapy of cancer patients because half suffer from major depression or depressed mood.²

In the last 20–25 years, the number of oncological patients treated with antidepressants has remarkably increased.

Since antidepressants were used concurrently with cytostatics, some observations suggested that antidepressants influenced the effectiveness of anticancer therapy.

At the same time, first reports about putative anticancer properties of antidepressant drugs began to appear in world literature.³ Interest in the, at that time, novel properties of antidepressant drugs stimulated further studies; however, these brought unequivocal and sometimes contradictory results, depending on the experimental model and antidepressant drug used.⁴

Knowledge about adjuvant drugs, including antidepressants used in anticancer treatment is invaluable, since substances that would enhance the effect of chemotherapeutics in case of weak response or resistance to chemotherapy are constantly searched for, especially in aggressive cancer phenotypes.

The role of antidepressant drugs in anticancer therapy is still controversial and needs further studies, because the outcome of their combined treatment is uncertain. It could happen that co-administration of a certain anticancer drug with an antidepressant may either enhance or weaken the chemotherapeutic effect.

Anticancer properties of antidepressant drugs

Experimental data suggest that antidepressants, in particular TCAs and SSRIs, show anticancer properties in different tumour cell lines. Table 1 summarizes the most important findings in this area.

Putative strategic targets of anticancer activity of antidepressant drugs

Programmed cell death. Experimental and epidemiological studies have indicated that cancer progression is a result of deregulation of proliferation and cell death.⁵ Cell death, which may occur by apoptosis, is the effect of failure of cytoprotective mechanisms against intra/extracellular stressors⁶ (Figure 1).

Apoptosis. It has been suggested that an increasing number of cancer cells in the organism during carcinogenesis is correlated with a decrease in the number of apoptotic cells and with an increase in cell proliferation.⁷ It is known that cancer cells are characterized by resistance to cell death mediators.⁸ The most important reasons why cancer cells can avoid apoptosis include:

1. *In the intrinsic pathway:* inactivation of apoptotic protease activating factor;
2. *In the extrinsic pathway:* decreased expression of death receptors responsible for mediation of tumour necrosis factor activity: (TNFR1), TRAILR1/R2, FAS, decreased content of caspase 8, high level of FLICE inhibitory protein;
3. *In both pathways:* high content of the inhibitor of apoptosis protein family. Moreover, cancer cells demonstrate a higher content of antiapoptotic proteins: Bcl-2, Bcl-XL, Mcl-1, an increased permeability of the outer mitochondrial membrane and an ability to inhibit caspase activity.⁹

Experimental studies have indicated that some antidepressants can induce apoptosis via different pathways. In C6 cells, desipramine (TCAs) elicited apoptosis via the endoplasmic reticulum stress-dependent pathway (C/EBP homologous protein [CHOP]) manifested by chromatin condensation and nuclear shrinkage. Increased expression of the endoplasmic reticulum stress regulator CHOP/GADD153 and its target molecule GADD34 was also noted. Furthermore, an enhanced activity of apoptosis executors, such as caspase 3 and 9 with no alteration of caspase 8 activity was observed. These findings indicate a dominant role of the intrinsic apoptotic pathway in the anticancer properties of desipramine.^{10,11} In another experimental model, MG63 human osteosarcoma cells, desipramine induced [Ca (2+)] independent apoptosis by increasing caspase 3 activation associated with p38 mitogen-activated protein kinase (MAPK).¹² Similar observations were made in the study on PC3 human prostate cancer. Desipramine induced apoptosis through its ability to increase the cytosolic (Ca2+) level and activation of c-Jun NH₂-terminal kinase phosphorylation without any effect on extracellular signal-regulated kinase (ERK) and p38

MAPK. Arimochi and Morita¹³ also found that desipramine induced apoptotic cell death through non-mitochondrial and mitochondrial pathways in different types of human colon carcinoma cells. In human colon adenocarcinoma grade II HT29 cells, apoptosis was not connected with cytochrome c leakage from mitochondria or the disruption of mitochondrial membrane potential. On the other hand, desipramine significantly increased caspase 8 activity without any effect on caspase 9 in HT29 cells and caused non-oxidative apoptotic damage of colon carcinoma HCT116, which may suggest the initiation of a novel mitochondrial apoptotic pathway.

Imipramine, another TCA, also possesses apoptotic properties. This drug induced apoptosis in U-937 cells as the result of an increase in caspase 2 and 3 activity, and caused disruption of cell lysosomes due to accumulation of phospholipids.¹⁴ The SSRI fluoxetine demonstrated an apoptotic action in the study on rat glioma cell lines, human neuroblastoma cell lines, Burkitt lymphoma cells and an ovarian carcinoma cell line OVCAR-3.^{15,16} This drug increased permeability of the mitochondrial membrane, leading to cytochrome c release and enhanced activity of caspase 3 through the reactive oxygen species (ROS)-dependent activation of nuclear factor (NF)-κB. Moreover, fluoxetine increased mitochondrial Bax protein level and decreased cytosolic Bid and Bcl-2, while up-regulating p 53 protein concentration.

Sertraline (an SSRI) was found to have a proapoptotic action in A375 human melanoma, a common malignant tumour poorly responsive to chemotherapy and radiation. Sertraline decreased expression of AKT, a protein protective against cell apoptosis. These results suggest that sertraline acts as an AKT inhibitor in melanoma cells, leading to cancer cell death.¹⁷

Autophagy. Among three forms of cell death: apoptosis, autophagy and necrosis, only autophagy can play either pro-survival or pro-death role acting as a guardian or an executioner, as pro-survival process autophagy plays a crucial role in cell homeostasis during periods of starvation or stress caused by carcinogenesis.¹⁸ Nowadays, it is also suggested that this process may contribute to the suppression of tumour function by limiting chromosomal instability, preventing the accumulation of oncogenic mutations, restricting oxidative stress and reducing local inflammation. At a morphological level, autophagy is associated with the formation of large cytoplasmic autophagosomes, which distinguish autophagy from apoptosis – I type of PCD. Autophagic cell death is induced by excess autophagosome formation or/and cross-talk between autophagy and cell death (apoptosis or necrosis) signals.⁶ The results of the recent studies suggest that the role of autophagy in oncogenesis depends on the stage of cancer progression. In early stages, autophagy plays a protective role but later it acts as a tumour suppressor by acting pro-autophagic genes and blocking anti-autophagic genes.¹⁹

Since it has been found that some forms of cell death may be modulated pharmacologically a new anticancer therapy is still looking for.²⁰ Some antidepressants are among drugs

Table 1 Anticancer effects of antidepressant drugs in different experimental models

Type of antidepressant drug	Type of cancer	Experimental model	Outcome	Authors
Citalopram, Fluoxetine (SSRI)/Citalopram:20 or 40 mg/kg twice-daily i.p. Fluoxetine: 10 or 20 mg/kg once-daily i.p. during 30 days	Colonic tumours	Mice (<i>in vivo</i>)	Fluoxetine and citalopram was found to suppress cell division in dimethylhydrazine-induced colonic tumours	Tutton and Barkla ⁸⁵
Clomipramine (TCA) 10 or 20 mg/kg i.p.	Solid tumours	Mice (<i>in vivo</i>)	Clomipramine enhanced the cytotoxicity of antitumour drugs in drug-resistant tumours	Merry <i>et al.</i> ⁸³
Clorgyline (MAO-A) (1 µmol/L)	Prostate cancer	Prostate cancer cells E-CA-88 (<i>in vitro</i>)	Clorgyline in high-grade PCa cells inhibited growth of prostate cancer cells	Flamand <i>et al.</i> ⁸⁴
Fluoxetine (SSRI) 10 mg/kg/day i.p. during 14 days	Melanoma cells	Mice (<i>in vivo</i>)	Fluoxetine prevented from melanoma-induced oxidative changes in mice spleen	Kirkova <i>et al.</i> ⁴⁵
Imipramine (TCA; 80 µmol/L) Clomipramine (TCA; 35 µmol/L) Citalopram (TCA; 220 µmol/L)	Human acute myeloid leukaemia cells (HL-60)	Cell line (<i>in vitro</i>)	Imipramine, clomipramine and citalopram caused a loss in cell viability by activating the apoptotic system in HL-60 cells	Xia <i>et al.</i> ⁸⁶
Chlorimipramine (TCA) (0.9–1400 µmol/L)	Human glioma cell lines (biopsy material)	Cell line (<i>in vitro</i>)	Chlorimipramine inhibited of glioma oxygen consumption	Daley <i>et al.</i> ³⁵
Paroxetine (SSRI)Fluoxetine (SSRI)Clomipramine (TCA)(6–50 µmol/L)	Rat glioblastoma cells (G6), Human neuroblastoma cells (SH-SY5Y)	Cell line (<i>in vitro</i>)	Antidepressants induced apoptosis in neuronal and glial cell lines	Levkovitz <i>et al.</i> ¹⁶
Desipramine (TCA; 50–75 µmol/L)	Human colon adenocarcinoma cells HT29	Cell line (<i>in vitro</i>)	Antidepressants reduced the viability of HT 29 cells through either a non-mitochondrial or a mitochondrial pathway	Arimochi and Morita ¹³
Chlorimipramine (TCA) (1, 10, 100, 200 µmol/L)	Glioma cells (G6)	Cell line (<i>in vitro</i>)	Chlorimipramine enhanced cytotoxicity of antitumour drug (imatinib), inhibited tumour growth and enhanced cell death C6 glioma line	Blir <i>et al.</i> ⁸⁷
Fluoxetine (SSRI) (1, 2.5, 5 µmol/L)	Lung cancer cells (A549), colon cancer cells (HT29), neuroblastoma cells (SKNAS), medulloblastoma/rhabdo-myosarcoma cells (TE671), astrocytoma cells (MOGGCCM), breast cancer cells (T47D)	Cell line (<i>in vitro</i>)	Fluoxetine reduced growth of cancer cells, exhibited antiproliferative effects, inhibited phosphorylation of ERK1/2 kinases, decreased expression of c-fos, c-jun, cyclin A, cyclin D1 and increased expression of p21 and p53 genes which resulted in slowing of the cell progression	Stepulak <i>et al.</i> ⁴⁰
Clomipramine (TCA; 0.5–0.9 mmol/L)Amitriptyline (TCA; 0.14–0.5 mmol/L)	Anaplastic astrocytoma cells IPSB-18	Cell line (<i>in vitro</i>)	Antidepressants exhibited antineoplastic properties and with combination with dexamethasone (synergistic effect) inhibited cellular respiration and increased cell death in anaplastic astrocytoma cell line IPSB-18	Higgins and Pilkington ⁸³
Fluoxetine (SSRI; 15–25 µmol/L)	Human epithelial ovarian cancer cells (OVCA9-3), (SK-OV-3)	Cell line (<i>in vitro</i>)	Fluoxetine induced mitochondrial membrane permeability change and formation reactive oxygen species, increased mitochondrial Bax level, decreased cytosolic Bid and Bcl-2 level and in consequence caused cell death of ovarian cancer cells	Lee <i>et al.</i> ⁸⁸
Maprotyline (NSRI; 50 µmol/L) Fluoxetine (SSRI; 50 µmol/L)	Human Burkitt lymphoma cells	Cell line (<i>in vitro</i>)	Maprotyline and fluoxetine induced autophagic programmed cell death in the chemoresistant Burkitt's lymphoma cell line	Cloonan and Williams ²¹
Desipramine (TCA; 10, 20 µmol/L)	Rat glioma cells (G6)	Cell line (<i>in vitro</i>)	Desipramine induced typical apoptotic morphology of chromatin condensation in rat glioma C6 cells and activated intracellular caspase 9 and 3	Ma <i>et al.</i> ¹⁰
Clomipramine (TCA) Nortriptyline (TCA) Amitriptyline (TCA) (6.25–200 µmol/L)	Melanoma cells	Cell lines, Primary cell cultures (<i>in vitro</i>)	Antidepressants exerted activity against melanoma cells, related to the lysosomal effects based on their cationic amphiphilic properties or effects at the mitochondrial membrane	Parker <i>et al.</i> ⁸⁹

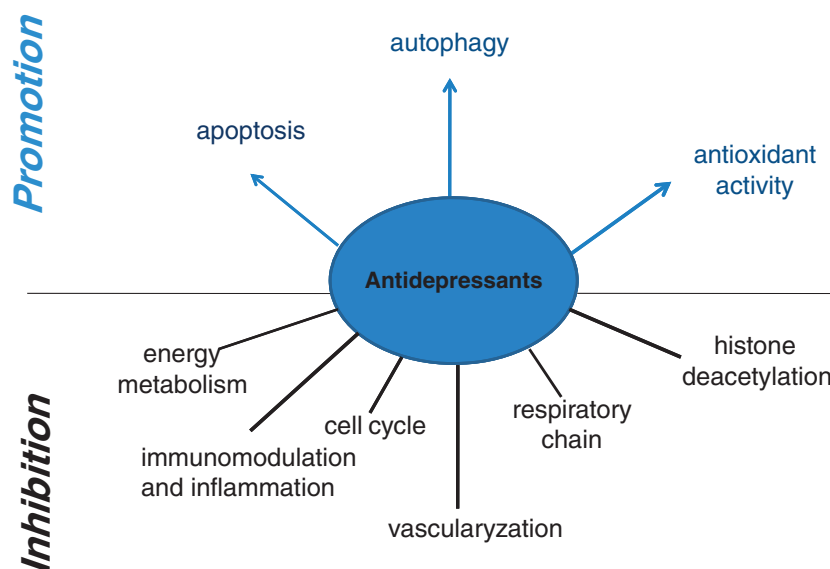


Figure 1 Putative cellular points of anticancer activity of antidepressants. Anticancer activity of antidepressant drugs is probably connected with inhibition and/or promotion of several uncontrolled cancer processes like: energy metabolism, cell cycle, vascularization, histone deacetylation, apoptosis, autophagy and oxidation processes. (A color version of this figure is available in the online journal)

with proautophagic properties. Cloonam and Williams²¹ have shown that two antidepressants, maprotyline and fluoxetine overcome the 'apoptotic block' and induced autophagy in DG-75 cells of chemoresistant Burkitt's lymphoma cell line. The maximal effect, namely 50–60% cells, was observed after 72-h of exposure to the antidepressant. This effect was not accompanied by alterations in caspase activity, DNA fragmentation or poly-ADP ribose polymerase cleavage. The authors suggest that maprotyline and fluoxetine may be used as new proautophagic agents either alone or in combination with other drugs in the treatment of resistant forms of Burkitt's lymphoma.

The relationship between autophagy and cancer is still not clear. In opposite to Cloonam and Williams' study,²¹ in other experimental models, autophagy might even show an opposite protumour activity.²² At present is not yet understood what factors determine whether autophagy is a cytoprotective or cytotoxic process, and therefore further studies are required.²³ Investigation of this issue may be important for success of cancer therapy case of cancers with an aggressive phenotype which have lost their accessible apoptotic pathways and are resistant to the standard therapy.²¹

Mitochondria. Mitochondria play a pivotal role in energy metabolism, redox homeostasis, regulation of proliferation, apoptosis and intracellular signal transduction.^{23,24} Recently, it has also been suggested that mitochondrial dysfunction is involved in the pathophysiology of neurodegenerative, psychiatric and oncological diseases.²⁵ In cancer cells, mitochondrial dysfunction may appear at different levels, and may comprise such processes as: mitochondrial

DNA mutations, oncogenic stress, loss of p53 tumour suppressor activity and aberrant expression of metabolic enzymes.²⁶ A recent study that focused on mitochondria as a target for cancer therapy pointed out that antidepressants may act as mitocans and alleviate mitochondrial dysfunction in cancer cells.²⁷

Energy metabolism. Recent experimental studies have indicated metabolic chaos in the cells of brain tumours, such as glioma. Cancer (transformed) cells typically display dramatic bioenergetic remodelling caused by their lack of metabolic flexibility, an increased efficiency of aerobic glycolytic machinery and a reduction in oxidative phosphorylation. These alterations are due to a disturbed function of mitochondrial enzymatic systems.^{28–30} Antidepressants are able to affect mitochondrial bioenergetic processes in cancer cells, and this may constitute a new strategic target for cancer therapy.

Some studies have shown that chlorimipramine and desipramine elicit negative influence on bioenergetic mitochondrial function by reducing the level of adenosine triphosphate (ATP) by about 50% in cancer cells in comparison to controls.^{31–33}

Interesting observations were made in a study on hypericin, a weak inhibitor of monoamine oxidase A and B (MAO-A, MAO-B) isolated from the medicinal herb *Hypericum perforatum*. Hypericin is a photosensitizer and inhibits mitochondrial succinoxidase, cell proliferation and mitochondrial function. As a result, it may be used as a safe photodynamic antitumour agent.³⁴ Experiments demonstrated that hypericin decreased the intracellular ATP level by about 60% in the human glioblastoma cell

line SNB-19, compared to control, and decreased the photo-generated pH by about 0.5 units. In mouse mammary carcinoma cells EMT6, hypericin also presented similar features, reducing the total cellular ATP level by approximately 50% and acting to inhibit respiration.³⁴

Respiratory chain. Some experimental data suggest that antidepressants influence oxygen consumption in cancer cells, thereby causing a decrease in membrane potential concomitant with an increase in superoxide and hydrogen peroxide production. These factors are responsible for DNA damage.^{25,26}

In *in vitro* experiments, clomipramine, desipramine, norfluoxetine and tianeptine decreased the activity of respiratory complex I by about 50% of the control activity. The effect of these drugs on the activity of respiratory complex II/III was more selective. Clomipramine, desipramine and norfluoxetine decreased its activity by more than 70%, while clomipramine reduced activity of the mitochondrial complex IV (responsible for transferring electrons to molecular oxygen atoms) by more than 99%.^{24,28} In the IPSB-18 cancer cells (anaplastic astrocytoma cell line), clomipramine, norclomipramine and amitriptyline were also shown to inhibit cellular respiration in glioma cells. Moreover, it was reported that combined therapy of clomipramine and dexamethasone produced a synergistic effect manifested by an increase in cell death. Such an effect seems to be promising for glioma treatment.³³ Similar effects on the respiratory chain in the C6 glioma line were induced by chlorimipramine. Chlorimipramine decreased O₂ consumption in glioma cells by about 95% within 5 min when compared to the control cell culture.³⁵ Desipramine, amitriptyline, imipramine, citalopram, venlafaxine, mirtazapine and moclobemide diminished the activities of mitochondrial enzymes (enzymes of the electron transport chain complexes I, II, IV) in an isolated fraction from pig brain. In addition, some results have shown that antidepressants may act as inhibitors of complex I and IV in the electron transport chain. This also supports the suggestion that mitochondria may be a candidate for a new biomarker of cancer and a cellular metabolic target for antidepressants in cancer treatment.²⁷

Cell cycle. The p53 protein, a tumour suppressor called 'the guardian of the genome' plays an important role in cell cycle regulation. It is a factor that can induce growth arrest and apoptotic cell death in response to a number of cellular stressors. The level of p53 is low in normal cells, but it is activated in response to DNA damage or hypoxia.³⁶ On the other hand, the inactivation of p53 gene as a result of methylation of a CpG dinucleotide is the main event in the mechanism of carcinogenesis.³⁷ In cancer cells, p53 may play an important role as a factor that induces apoptosis and also sensitizes the cells to ionizing radiation and cytostatics.³⁸ Susceptibility of cancer cells to a drug depends on the cell cycle phase and mutations of the p53 gene.³⁶

Nowadays, experimental studies demonstrate that antidepressant drugs may destroy cancer cells through their influence on the cell cycle. Fluoxetine was found to arrest

cells at the G0/G1 phase and as a result, sensitized cells of human cervical cancer (SiH) and breast cancer (MDA MB231) to the cytotoxic effect of cyclophosphamide – one of the most popular cytostatic drugs. Cell cycle inhibition by fluoxetine reached about 75.1–94.4% in MDA MB 231 cells and 69–93.5% in SiHa cells after 12- or 24-h incubation. It was shown that this drug arrested cell cycle by cyclin E accumulation, cyclin A downregulation and fluctuations in p27, p21 and CKS 1 – complex factors involved in the G1/S transition.³⁹ In the A549 and HT29 cell lines, fluoxetine also inhibited progression of cell cycle. The slowing down cell cycle progression was due to a decrease in c-fos, c-jun, cyclin A, cyclin D expression and increased p21 and p53 expression.³⁸ Another antidepressant, desipramine inhibited cell cycle progression in Ca3/7 mouse skin squamous cell carcinoma. Moreover, desipramine decreased the levels of Bcl-2 and survivin, a protein known as the 'baculoviral inhibitor of apoptosis'. The results of the above mentioned studies clearly demonstrate that the inhibition of cell cycle in cancer cells seems to be a promising way to arrest cancer development.

Antioxidant activity. All cells are continuously exposed to free radicals and oxidative stress which is caused by an imbalance between production of pro-oxidants and antioxidants.^{40,41} ROS generated in mitochondria are the second messengers in signalling pathways and are involved in cellular pathological events.^{42,43} Disruption of redox homeostasis activates many transcription factors including NF- κ B, AP-1, p53, hypoxia-inducible factor 1 (HIF-1), peroxisome proliferator-activated receptor - γ and β -catenin/Wnt. The activation of these transcription factors can lead to the expression of over 500 genes connected with such processes as apoptosis, cell cycle arrest, proliferation, chemoresistance, radioresistance, angiogenesis and transformation of normal cells to tumour cells in breast, cervical, gastric, liver and lung cancer and melanoma.⁴⁴ It is also suggested that oxidative stress contributes to the three stages of carcinogenic process: initiation, promotion and progression.⁴³

Kirkova *et al.*⁴⁵ examined whether fluoxetine is able to modify the changes induced by melanoma in the endogenous antioxidant defense system. Experiments showed that 14-day administration of fluoxetine to healthy CB7BL/6 mice did not affect spleen antioxidant status. This antidepressant did not change the level of total glutathione or the activities of endogenous antioxidant enzymes in the spleen: glutathione peroxidase and superoxide dismutase. Moreover, this experiment showed that a 14-day antidepressant pretreatment prevented development of inoculated B16F10 melanoma cells. This effect suggests that fluoxetine possesses anti-melanogenic potential via its antioxidant activities and that it prevents melanoma-induced oxidative changes in the mouse spleen. It has also been suggested that drugs with antioxidant properties may inhibit skin carcinogenesis and selectively induce apoptosis in cancer cells.⁴⁵ These findings are the basis for the concept of a unique therapy called 'oxidation therapy' of solid tumours, which focuses on the generation of cytotoxic ROS.

Vascularization. In 1974 Dr Rakesh K Jain¹² used an experimental cancer model to investigate how much of an injected drug reached a tumour connected to the circulatory system through one vein and one artery. He found that the majority of the drug did not access the tumour, but that which did was distributed unequally and that in some spaces there was no drug whatsoever. Tumours were found to be able to stimulate the growth of new vessels to create a tangled knot, in which the vessels were randomly connected and had an abnormal structure, and their function was disrupted. In addition, the blood flow in some vessels was weak but in others it was rapid or periodically reversed; some sections of tumour were leaky but some were impenetrable. Moreover, pores in the vessel walls were 100 times bigger than normal. Due to these factors, the endogenous tumour environment was characterized by ischaemia and high acidity, and cancer cells became more aggressive under anaerobic conditions. These experiments showed that the complicated structure of tumours hindered the effective administration of anticancer drugs. Observations accumulated over many years revealed that normalization of this chaotic vessel microenvironment was an effective means of cancer treatment.

Experiments such as the one mentioned above showed that angiogenesis plays a pivotal role in tumour growth, invasion and metastasis.⁴⁶ A key factor in neo-angiogenesis is the vascular endothelial growth factor (VEGF), the receptors of which are often overexpressed in many cancers, especially in brain tumours associated with areas of high angiogenesis and vascular density.⁴⁷ Experimental studies demonstrate that some substances with antidepressant properties also have antiangiogenic/angiopreventive activities. Hyperforin, which inhibits VEGF production, is one of such chemicals. It is an active substance of St John's wort, a medicinal plant used for the treatment of mild depression. It was suggested that hyperforin might influence inhibition of the inflammatory process associated with angiogenesis and might modify immune cell stimulation.^{48,49}

Some classes of antidepressants increase VEGF expression in the hippocampus and enhance VEGF signalling mediated by the Flk-1 receptor, which underlies neurogenic and neuroprotective effects in the CNS.⁵⁰ On the other hand, it has also been noted that due to proangiogenic properties, antidepressants can induce carcinogenesis. Taking into consideration these results it is difficult to say whether antidepressant drugs actually inhibit or promote carcinogenesis. An interesting opinion was proposed by Kubera *et al.*⁵¹ who studied the influence of desipramine or fluoxetine pretreatment on metastasis of B16F10 melanoma in young and old C57BL/6 mice. They found that inoculation of tumour cells in young animals caused a faster tumour growth and a higher mortality than in the older mouse group. Kubera *et al.*⁵¹ also showed that 'antidepressant pretreatment inhibited primary tumour growth in young animals but increased primary tumour growth in aged animals in comparison to age-matched controls'.

Recent studies also emphasized the role of ROS in the increased production of angiogenic factors, like IL-8, VEGF,

matrix metalloproteinase and inducible nitric oxide synthase. Their signalling is an implication of inflammatory processes in angiogenesis. The role of quiescent stem cells via HIF/VEGF pathways is another interesting problem associated with the promotion of tumorigenesis.⁵²

Immunomodulation and inflammation. In the 19th century, Rudolf Virchow noted that inflammatory cells were present within tumours and that tumour cells developed at sites of chronic inflammation. In recent years, three related aspects, namely oxidative stress, immunomodulation and inflammation have been the subject of epidemiological and experimental studies in relation to cancer. At present, inflammation is regarded as 'a secret killer' and 'a double-edged sword' of the immune system. It is known that chronic inflammation may predispose an individual to various chronic illnesses including cancer and that it may induce malignancy of precancerous conditions.⁵³⁻⁵⁵ Moreover, inflammatory cells produce soluble mediators, such as metabolites of arachidonic acid, cytokines and chemokines, which may activate carcinogenesis.^{56,57}

Experimental data suggest that cancer cells are able to 'deceive' the immune system because oncogenic changes induce a chronic inflammatory microenvironment within and around tumours.⁵⁸ It is also known that leukocytes, cytotoxic T lymphocytes and natural killer (NK) cells play an important role in constraining tumour development.⁵⁴ As a result, these immune cells are thought to combat cancer. Yet the fact that malignant tumours are often diagnosed in patients with autoimmune disorders caused by B lymphocyte hyperactivity indicates an interesting and more complex relationship between the immune system and cancer.^{56,58}

An elevated NF- κ B activity in tumours has been shown in some studies. This basic transcription factor regulates more than 150 effector genes and is associated with resistance to chemotherapy and radiation.⁵⁸ Ben-Neriah and Karin⁵⁹ demonstrated that TNF blockade influenced inactivation of cancer cells, while NF- κ B triggered programmed cell death in cancer cells in Mdr2 knockout mice suffering from chronic hepatitis which had transformed into liver cancer. It should be emphasized that only one study presents the directly inhibitory effect of antidepressant drug on NF- κ B activation in tumour cells. Namely, fluoxetine induced such effect in colon cancer which was associated with the significant attenuation of colon cancer development and tumorigenesis in mice.⁶⁰

Usage of antidepressant drugs with cytostatics in combined therapy of cancer diseases may be accounted for their immunomodulatory properties in the periphery and central nervous system.^{91,92} An influence of antidepressants on the immune system activity is complex and involves several direct as well as indirect effects among those the most important are as follows:

1. Antidepressant are able to modulate activity of immunocompetent cells directly via acting on the receptors of the neurotransmitters such as serotonin, dopamine and norepinephrine.⁶¹ Direct effects of antidepressant drugs on immune cells (NK cells,

macrophages, splenocytes, lymphocytes T and B) indicate also in *in vitro* studies.⁵⁴ It has been shown that antidepressants are able to suppress production of the pro-inflammatory cytokines (IFN- γ , TNF- α , IL-1 β) and to increase the production of the anti-inflammatory cytokine IL-10 by peripheral immunocompetent cells.^{51,90,93} In turn, cytokines are known as the essential mediators in communication between the endocrine, immune and central nervous system. Cytokines regulate immune response mainly by their influence on immune cells in the periphery and by the activation of the hypothalamic-pituitary-adrenal (HPA) axis.^{58,62}

2. Besides the effects mediated by cytokines and nervous system, the indirect influence of antidepressants on immune system activity is due to normalization of HPA hyperactivity which is a marker of glucocorticoid (GC) resistance. Ineffective action of GCs on target tissues could lead to immune activation. Antidepressants restore the negative feedback inhibition of the HPA axis by increasing GC and mineralocorticoid receptor expression and function which is important for their antidepressive effect⁶³ but also may have significance for their anticancer properties.

Recent studies suggest that an individual stress response partially mediated by hyperactivity of HPA axis can influence tumour biology. The promoting role of GCs for development of epithelial cancer is discussed. High expression of GR and increased GC-mediated gene expression were observed in oestrogen-independent breast cancer characterized by more rapid progression. Moreover, the results of the studies in animal models of human breast cancer suggest that GCs inhibit tumour cell apoptosis. It is thought that antiapoptotic mechanisms in tumour cells may be determinants of resistance to synthetic GC therapy although the high concentration of endogenous GCs is also likely to initiate an increased GR-mediated antiapoptotic signals in malignant epithelial cells.⁶⁴ The above-mentioned data indicate that understanding the role of GC signalling in human cancer biology and an influence of antidepressant drugs on this pathway seem to be important and need further investigation in order to better recognize the controversial influence of antidepressants on 'immunological portrait of cancer'.

Histone deacetylase (HDAC). Experimental data indicate that HDAC inhibitors are a promising new important class of anticancer chemotherapeutics.⁹⁴ These compounds are able to arrest the cell cycle, induce both apoptosis and autophagy in *in vivo* and *in vitro* experimental models, promote chromatin remodelling and kill transformed cells. Moreover, they can radiosensitize human tumour cells, acting like adjuvants in radiotherapy.⁶⁵ The HDAC inhibitors can also induce the expression of fewer than 10% of genes, some of which are involved in the inhibition of tumour growth.⁶⁶

In *in vitro* and *in silico* studies, amitriptyline (TCA) exerted a potential anti-myeloma effect by inhibiting

HDAC activity. Studies by Mao *et al.*⁶⁷ have shown that amitriptyline downregulates HDAC3, -6, -7, -8 activities and forms strong van der Waals interactions with five residues of HDAC 7 (Phe162, His192, Phe221, Leu293, His326). The inhibition of HDAC leads to hyperacetylation of the transcription factor NF- κ B,⁶⁸ which prevents NF- κ B/p65 binding to the cyclin D promoter. Furthermore, it was shown that amitriptyline inhibited cyclin D2 transactivation. A disturbed activity of cyclin D2 detected in 50% of patients with multiple myeloma is associated with poor prognosis in this cancer.^{69,70} Thus, the potential of amitriptyline to restore the capability of multiple myeloma cells to undergo programmed cell death through HDAC inhibition seems to be partly responsible for its promising effect in this group of patients.^{95,96}

Promotion of carcinogenesis by antidepressant drugs

Some rodent *in vivo* models have shown a stimulatory effect of antidepressant drugs on carcinogenesis has been demonstrated. In rats, clomipramine promoted mammary tumour growth. Brandes *et al.*⁷¹ also found that in rats, fluoxetine and amitriptyline promoted growth of fibrosarcomas, melanomas and mammary tumours; however, there were no differences in survival among antidepressant- and saline-treated groups. A similar effect in rats treated with fluoxetine or amitriptyline was observed in 7,12-dimethylbenz(a)anthracene-induced cancer. In comparison to the control group, the frequency of mammary tumours in the antidepressant-treated rats increased up to 2.5 times. In one *in vitro* study, fluoxetine and amitriptyline stimulated DNA synthesis in fibrosarcoma cells. Both drugs increased thymidine incorporation into DNA by 30–40% over baseline values, which support the hypothesis that some antidepressants may promote tumour growth.

Promotion of carcinogenesis by antidepressants was also demonstrated in clinical studies where it was observed that the use of paroxetine (SSRI) might be associated with a substantially increased risk of breast and ovarian cancer.^{65,66} Other authors suggested that the use of TCAs for 2–5 years in the past might be associated with a small dose-dependent increase in the risk of prostate cancer and liver cancer⁷² and might have a possible promoting effect on Hodgkin's lymphoma.⁷³ Interesting results were obtained by Brandes *et al.*⁷¹ who reported that clomipramine, amitriptyline, imipramine (TCA) and trazodone might play a role in the development of mammary neoplasms in humans, through stimulation of prolactin secretion. This effect probably explains the unexpected properties of the aforementioned antidepressants because it has been established that prolactin promotes induction and growth of mammary tumours in rats and mice and that moreover, high levels of prolactin are associated with a two-fold increase in the risk of breast cancer.⁸¹ Brandes *et al.*⁷¹ also reported that TCAs and fluoxetine (SSRI) were structurally similar to a prototype of the antioestrogen binding site and an intracellular histamine receptor ligand that is known to be a tumour growth stimulator.

Interaction of antidepressants with anticancer drugs

Some interesting findings indicating that particular antidepressants may influence anticancer drug metabolism should attract the attention of oncologists. It was found that some SSRIs might be able to interact with anticancer drugs through the inhibition of one or more cytochrome P450 isoenzymes (CYPs).^{75,76} Among the antidepressants there are strong inhibitors of CYP2D6, an isoenzyme of cytochrome P450, such as fluoxetine, paroxetine and a weak inhibitor venlafaxine.⁷⁶ Kelly *et al.*⁷⁷ reported progression of breast cancer in women who were treated with antidepressants, in particular paroxetine concomitantly with tamoxifen whereas in patients treated with the other antidepressants that are not such strong inhibitors, such as sertraline, fluvoxamine and particularly venlafaxine this effect was not observed.

On the other hand, support and enhancement of anticancer drug action by some antidepressant drugs were also noted. Peer and Margalit⁷⁸ demonstrated that fluoxetine (Prozac) was a highly effective chemosensitizer. In *in vitro* studies, they showed that fluoxetine enhanced the cytotoxicity of anticancer drugs, such as doxorubicin, mitomycin C, vinblastine and paclitaxel by 10- to 100-fold in drug-resistant (but not drug-sensitive) cells. Moreover, fluoxetine increased drug accumulation in multidrug resistant cells and inhibited drug efflux from those cells. In an experimental *in vivo* model, fluoxetine enhanced doxorubicin accumulation within tumours (12-fold).

It is important to note that any clinician wishing to use antidepressants in cancer treatment should take into consideration other factors, such as the patient's age, menopausal period, phase of cancer, cardiovascular diseases, surgical treatment (in women with mammary tumours), genetic background, rate of metabolism, smoking and alcoholism which may influence the rate of cancer progression. TCAs act as potassium channel blockers and may, therefore, enhance cardiovascular disturbances and mortality, leading to a false conclusion about their procarcinogenic action.⁷⁹

Summary and conclusion

Though the anticancer properties of antidepressant drugs have been demonstrated in many studies, the influence of these drugs on cancer and immunity is still controversial. This widespread opinion is probably large due to an insufficient knowledge about the underestimated adjuvant role of antidepressants in anticancer therapy and the fact that a small number of reports have suggested that antidepressants may promote cancer. It seems that these conflicting results may be due to different experimental models used in the studies and failures in the interpretation of some results.⁴ As a result of the emergence of conflicting results, where in one experimental model antidepressants appeared to promote tumour growth and in another they seemed to reveal anticancer properties, researchers all over the world began to carry out epidemiological studies to elucidate this issue. A study conducted between 2003 and 2006 in Canada demonstrated that prolonged SSRI use did not have a latent effect on breast cancer risk and that there was no evidence for an increased risk of breast cancer caused by the use of

SSRIs.⁸⁰ Furthermore, other studies showed that antidepressants might afford protection against lung, colon and prostate cancer.^{97,98}

On the basis of the presented results, it seems that antidepressant drugs may occupy an important position in anticancer treatment as an adjuvant therapy (Figure 1). *In vivo* experimental studies, which have greater significance for the evaluation of potential drug efficacy in human therapy have yielded some interesting results. They have shown that some antidepressant drugs:

1. significantly decrease the incidence of pituitary adenomas in rats and fibroadenomas in female rats (fluoxetine);
2. have an antineoplastic effect in colonic tumours in mice and rats (fluoxetine, citalopram)⁴⁷ and in murine tumour models (clomipramine), and reduce tumour size of actinomycin D-resistant solid tumours in mice;⁸¹
3. enhance the cytotoxicity of antitumour drugs in drug-resistant tumours (clomipramine);^{82,83}
4. have an antioxidant action and inhibit skin carcinogenesis in mice (fluoxetine);⁴⁵
5. inhibit growth of prostate cancer in mice through antiproliferative action (clorgiline).⁸⁴

In summary, since antidepressant drugs are prescribed in cancer patients because of depression, chronic cancer pain, anxiety, insomnia, hot flashes and appetite disturbances, the influence of antidepressant drugs on cancer and their interaction with anticancer drugs should not be ignored. Knowledge about the adjuvant role of antidepressant drugs and their action as chemosensitizers is necessary for oncologists who want to use these drugs in therapy of cancer.

Authors contribution

PhD AB (first author) prepared manuscript and she was an originator of this work. Prof. EO checked this text and made corrections.

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