Sertraline repositioning: an overview of its potential use as a chemotherapeutic agent after four decades of tumor reversal studies

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ABSTRACT

Sertraline hydrochloride is a first-line antidepressant with potential antineoplastic properties because of its structural similarity with other drugs capable to inhibit the translation-controlled tumor protein (TCTP), a biomolecule involved in cell proliferation. Recent studies suggest it could be repositioned for cancer treatment. In this review, we systematically map the findings that repurpose sertraline as an antitumoral agent, including the mechanisms of action that support this hypothesis. From experimental in vivo and in vitro tumor models of thirteen different types of neoplasms, three mechanisms of action are proposed: apoptosis, autophagy, and drug synergism. The antidepressant is able to inhibit TCTP, modulate chemotherapeutical resistance and exhibit proper cytotoxicity, resulting in reduced cell counting (in vitro) and shrunken tumor masses (in vivo). A mathematical equation determined possible doses to be used in human beings, supporting that sertraline could be explored in clinical trials as a TCTP-inhibitor.

Introduction

About nine million people die from cancer each year, being considered the second leading cause of death in the world [1]. In this context, non-cancer drugs are thoroughly reviewed for possible effects on cell proliferation, aiming to reposition them for therapeutic use in clinical practice [2,3]. A group that has been recurrently the target of studies with encouraging results are the psychotropic drugs [4–7]. Among them, the selective serotonin reuptake inhibitor (SSRIs) sertraline stands out [8,9].

Sertraline hydrochloride was approved in 1991 for the treatment of various psychiatric disorders [10], nowadays it is considered first-line for managing depression in America [11]. Afterwards, it was in 1993 that Adam Telerman and Robert Amson set the starting point for discovering the anti-tumor properties of this antidepressant [12]. Structurally, its molecule was found to be similar to other drugs capable to inhibit Translationally Controlled Tumor Protein (TCTP), a biological compound present in eukaryotic stem cells in varying amounts [13]. A great number of biological activities are credit to TCTP, including anti-apoptotic action and involvement in cell stress pathways [14]. Furthermore, years after its discovery, Telerman et al. [12] identified this protein as an important protagonist in the tumor reversal process.

Because of the importance of this protein in maintaining cell death and survival pathways in addition to evidence linking it to cancer pathophysiology [15–18], it was proposed that reducing TCTP levels could be a promising target in cancer therapy [19]. Because of its ability of secreting histamine, antihistamines and other structurally similar molecules such as antipsychotics and antidepressants were used in an attempt to inhibit TCTP. Of the drugs tested, sertraline obtained the best results, increasing the number of reversible clones in tumor lines by 30%, a result attributed to the down-regulation of TCTP [19]. In addition, experimental studies support that the antidepressant is effective in neoplasms therapeutics as it has specific antitumor characteristics [8,20,21] whereas case reports suggested that the use of sertraline could improve the clinical status of patients and even induce tumor remission [9,22].

Therefore, with evidence that sertraline can play an important role as a chemotherapeutic agent, the present study aimed to provide a short
overview of the four decades of tumor reversal studies, including the discovery of TCTP, and to map and synthesize the mechanisms of anti-tumor action attributed to sertraline, a known TCTP-inhibitor, which are essential to support future drug repositioning trials.

**TCTP: a viable target for cancer treatment**

TCTP is a protein which gene (tpt1) is composed of approximately 4000 nucleotides [23] and is present in eukaryotic stem cells [13]. It’s structure was first described by Susan MacDonald in 1995, being called the histamine-releasing factor (HRF), because of its ability to release histamine [24]. Subsequently, other biological activities were identified: maintenance of homeostasis and cell survival (anti-apoptotic action and involvement in cell stress pathways), cell cycle and development (action on microtubules and embryonic development), regulation of cell growth, protein synthesis and degradation, as well as extracellular actions as a signaling molecule in immunological reactions [14]. Few years later, TCTP was described by Amson et al. [18], in which the antidepressant tested, sertraline was the one that obtained the best results, therefore, it became one of the most studied drugs in tumor reversal models [19]. Breast cancer was the most investigated, representing 46.15% [13, 21, 35, 38], whilst experimental studies with in vitro, in vivo, or observational studies. Breast cancer was the most investigated, representing 46.15% [13, 21, 35, 38], whilst experimental studies with in vitro, in vivo, or observational studies prevailed. Only one case report and one cohort study are published [22, 39].

**Sertraline as a promising TCTP-inhibitor**

Because of the importance of TCTP for the maintenance of the path of cell death and survival and the evidences that links this protein to the pathophysiology of cancer [15–18], it was proposed that reducing its levels could be a promising target in cancer therapy [19]. Antihistamines and structurally similar molecules, such as antipsychotics and antidepressants were used to verify whether inhibition of TCTP expression would induce changes in the malignant phenotypes of different strains (colorectal, pulmonary and melanoma). Of the drugs tested, sertraline was the one that obtained the best results, therefore, it became one of the most studied drugs in tumor reversal models [19].

A specific lock-and-key interaction between sertraline and tpt1/TCTP was described by Amson et al. [18], in which the antidepressant would directly bind to tpt1/TCTP, avoiding its interaction with MDM2. Thus, promoting the interaction of TCTP autoubiquitination with MDM2 and p53, leading to MDM2 autoubiquitination and restoring p53 levels. Consequently, the reistitution of p53 levels prevents its degradation [13,33–35].

Most of these findings were obtained during experimental studies, which sought to determine the antitumoral mechanisms and outcomes of administering the antidepressant in tumor models. Fig. 2 and Table 1 summarizes available studies, including research countries, types of neoplasms tested, settings and methods. Thirteen different types of neoplasms were assessed, on in vitro, in vivo, or observational studies. Breast cancer was the most investigated, representing 46.15% [13,21, 35–38], whilst experimental studies with in vitro or in vivo approaches prevailed. Only one case report and one cohort study are published [22, 39].

**Sertraline antitumor action mechanisms**

Three proposed mechanisms are raised: apoptosis, autophagy, and drug synergism. Fig. 3 summarizes the mapping of these mechanisms from the studies, including the types of neoplasms and outcomes presented by them.

**Apoptosis**

By definition, it is the process of controlled cell death that physiologically regulates cell populations through intracellular activation of enzymes that degrade their own DNA [40]. Two pathways are described: intrinsic - which involves the B-cell lymphoma 2 (Bcl-2) family and the initiating caspases 2, 8, 9 and 10 [41,42]; and extrinsic - death initiated by receptor followed by the activation of the initiating caspases and finally the executors (3, 6 and 7) [43–45]. Different mechanisms and findings were related to it, including the inhibition of TCTP [13,19, 33–35,46], interactions on the mTOR/Akt pathway [20,21,47,48], increased caspase-3 levels [26,33,46,49,50], increase on caspase-7 levels [50], ionic changes related to Ca2+ [33,51], increased expression of tumor protein P53 (p53)[33, 52], inhibition of breast tumor initiating cells (BTIC)[36, 37] and decreased expression of Bcl-2 [26].

**Autophagy**

Autophagy is considered a survival mechanism in times of nutrient deprivation when the cell undergoes continence stress, survives by cannibalizing itself and recycling the digested content through lysosomal enzymes [53]. The administration of sertraline was reported to
induce autophagy in AML, lung, and prostate cancer [46,47,49]

**Drug synergism**

It is a drug interaction that increases the individual effect of a medication when taken together with another one. Regarding sertraline, 15 different medications are cited as synergistic: doxorubicin [21,26,54], docetaxel [36,37], pterostilbene [55,56], the Coordinated Survival Paths Protocol (CUSP9) which involves nine medications (aprepitant, artesunate, auranofin, captopril, celecoxib, disulfiram, itraconazole, ritonavir, sertraline) [22,34], thimerosal [38], dacarbazine [33], erlotinib [47], etoposid [21], olaparib [21], sorafenib [57], vilazodone [37], vincristine [26], TNF-related apoptosis-inducing ligand (TRAIL) [58] and XL413 [48].

As for the type of synergism mechanism, summation (additive) and potentiation are reported. Concerning summation mechanisms cytotoxicity [26,46,56] mTOR action [21] and the inhibition of BTIC’s [36] are highlighted. These, taken together with chemotherapeutic drugs, would act in an additive manner aiming to destroy tumor cells. For potentiation, Drinberg et al. [54] suggested that sertraline inhibits ATP-binding cassette transporters (ABC), a family of proteins which are supposed to decrease intracellular concentrations of chemotherapies. Further interactions are still to be detailed.

**Outcomes of sertraline administration in tumor settings**

The most remarkable outcome of the administration of sertraline in tumor models is the reduction in tumor cell counts after sertraline intervention (Fig. 3). Other results are decreased sphere forming assay (SFA) [33,35-37,46,50,52,55], shrunk of tumor masses [8,19,20,33,36,37], decreased relapse [21,36,54], decreased Marker of Proliferation Ki67 (MKi67) levels [33,37] and near complete remission of tumor [22].

At the present, only one study associated the administration of the SSRI with a decrease in time to relapse and an increase in MKi67 levels in ovarian cancer [39]. However, the population at this observational stage was composed mostly of patients with high-grade carcinoma with serous histology (76%), characteristics linked to the worst prognosis of the disease, whereas information on the period of administration or dosage of the drug were not provided.

**Discussion**

Drug repositioning offers the opportunity to identify new uses for substances already well established in clinical practice. Based on new tests and experimental research, they can reveal new targets and pathways to be explored further in clinical trials. When successful, this
The mechanisms of action: apoptosis, autophagy, and drug synergism. The antidepressant sertraline on experimental or observational studies presented three main repositioned as a chemotherapeutic agent as for the probable antitumor characteristics of included studies.

Table 1

| N  | Citation            | Study aims                                                                 | Cell type                              | Intervention                                                                 | Outcomes                                                                 |
|----|---------------------|----------------------------------------------------------------------------|----------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------|
| 1  | Amit et al. (2009)  | Evaluate the effects of SSRIs compared to chemotherapy on human cells of   | Human cells of lymphoma and AML       | Cells were exposed to sertraline, doxorubicin vincristine and cyclophosphamide | Synergism with doxorubicin and vincristine and apoptosis                 |
|    | (2009) [23]         | and lymphoma and AML                                                       |                                        |                                                                            |                                                                          |
| 2  | Amson et al. (2011) | Compare the effects of antihistamines drugs and SSRIs on human tumor cells | Human cells of breast cancer          | Cells were exposed to antihistamines and SSRIs and had their growth rates and TCTP levels rated | Apoptosis by TCTC inhibition                                              |
|    | (2011) [13]         |                                                                           |                                        |                                                                            |                                                                          |
| 3  | Boia-Ferreira et al. | Evaluate the effects of sertraline on TCTP levels of melanomas            | Human cells of melanoma; rats         | Exposition of cells to sertraline, followed by in vivo evaluation          | Lower tumoral growth though apoptosis by TCTP inhibition                  |
|    | (2017) [41]         |                                                                           |                                        |                                                                            |                                                                          |
| 4  | Chinnapaka et al. (2020) [51] | Evaluate the anti-prostate cancer steam cells (PCSC) targeting effects of sertraline on PCSC | Human cells of PCSC                  | Cells were cultured with sertraline at various doses. Then, cell studies were performed | Apoptosis and autophagy by free radicals of H2O2, decreased TCTP and increased caspase 3 | Cell proliferation of ovarian tumor cells and MEk67 levels. SSRIs users had a shortened time until relapse |
|    |                     |                                                                           |                                        |                                                                            |                                                                          |
| 5  | Christensen et al. (2016) [49] | Evaluate the effects of SSRIs on ovarian cancer cells and on overall survival of patients diagnosed with ovarian cancer | Human cells of ovarian cancer          | Cells were subjected to a sertraline therapy, followed by in vivo evaluation | A retrospective analysis based on medical records checked the use of SSRIs and evaluated the progression of ovarian cancer on patients |                                                                          |
|    |                     |                                                                           |                                        |                                                                            |                                                                          |
| 6  | Di Rosso et al. (2018) [38] | Evaluate the effects of sertraline and fluoxetine on lymphomas growth in vivo | Animal cells of lymphomas; mice       | Cells were injected subcutaneously on mice and drugs were administered     | Shrink palpable tumor masses through apoptosis                             |
|    |                     |                                                                           |                                        |                                                                            |                                                                          |
| 7  | Drinberg et al. (2014) [48] | Evaluate the effects of sertraline on ovarian cancer                       | Human cells of ovarian adenocarcinoma; mice | Cells were injected subcutaneously on mice and drugs were administered     | Synergism with doxorubicin; tumor regression and increased survival        |
|    |                     |                                                                           |                                        |                                                                            |                                                                          |
| 8  | Geeraerts et al. (2021) [36] | Repurpose sertraline and thimerosal as inhibitors of tumoral growth        | Human cells of breast cancer and animal cells of AML; mice | Exposition of cells to sertraline and thimerosal, followed by in vivo evaluation | Synergism with thimerosal; inhibited tumor growth                           |
|    |                     |                                                                           |                                        |                                                                            |                                                                          |
| 9  | Gil-Ad et al. (2008) | Evaluate the effects of sertraline and paroxetine on colorectal cancer     | Human cells of colorectal cancer; mice | Cells were inoculated on mice and drugs were administered                 | Apoptosis by caspase-3 pathway; shrink palpable tumor masses               |
|    | (2008) [8]          | compared to colorectal cancer growth in vivo                              |                                        |                                                                            |                                                                          |
| 10 | Gwynne et al. (2017) | Evaluate the effects of SSRIs on human cells of breast cancer               | Human cells of breast cancer; mice     | Exposition of cells to sertraline, followed by in vivo evaluation          | Synergism with docetaxel and vilazodone increasing apoptotic; inhibited tumor growth |
|    | (2017) [34]         |                                                                           |                                        |                                                                            |                                                                          |
| 11 | Hall et al. (2016)  | Evaluate the effects of SSRIs on animal cells of breast cancer              | Animal cells of breast cancer; rodents | Cells were inoculated on rodents and SSRIs were administered              | Apoptosis through BTIC s, leading to inhibited cell proliferation         |
|    | (2016) [33]         |                                                                           |                                        |                                                                            |                                                                          |
| 12 | Huang et al. (2011) | Evaluate the effects of sertraline on human cells of prostate cancer        | Human cells of prostate cancer         | Cells were treated with sertraline and cell studies were performed        | Increased calcium influx, leading to apoptosis                             |
|    | (2011) [50]         |                                                                           |                                        |                                                                            |                                                                          |
| 13 | Jiang et al. (2018) | Evaluate the effects of sertraline on animal cells of lung cancer          | Animal cells of lung cancer; mice      | Cells were inoculated on mice and drugs were administered                 | Apoptosis and apoptosis though mTOR pathway and autophagy                |
|    | (2018) [29]         |                                                                           |                                        |                                                                            |                                                                          |
| 14 | Kast et al. (2014)  | Check new approaches to GBM, according to CUSP protocol                    | Human cells of GBM                    | Exposition of cells to drugs, followed by in vitro evaluation             | Increased life expectancy in GBM patients                                 |
|    | (2014) [42]         |                                                                           |                                        |                                                                            |                                                                          |
| 15 | Kuwahara et al. (2015) [45] | Compare the antitumor effects of SSRIs to SNRIs                          | Human cells of liver cancer           | Cells were treated with SSRIs and SNRIs                                  | Apoptosis; reduced cell proliferation                                    |
|    | (2015) [45]         |                                                                           |                                        |                                                                            |                                                                          |
| 16 | Li et al. (2017)    | Identify the role of TCTP on tumor cells and mechanisms of inhibition      | Human cells of cervix cancer and breast cancer | Cells were submitted to drugs and/or radiotherapy                      | Apoptosis and decreased cell survival rate on cells treated with etoposide and sertraline |
|    | (2017) [35]         |                                                                           |                                        |                                                                            |                                                                          |
| 17 | Lin et al. (2010)   | Verify if sertraline has antitumor action                                  | Human cells of breast cancer and lymphoma; mice | Exposition of cells to sertraline, followed by in vivo evaluation       | Synergism with doxorubicin; increased apoptosis through mTOR pathway      |
|    | (2010) [24]         |                                                                           |                                        |                                                                            |                                                                          |
| 18 | Lin et al. (2013)   | Evaluate the effects of sertraline on human OS cells                      | Human cells of osteosarcoma           | Exposition of cells to sertraline                                        | Apoptosis through cytotoxicity                                            |
|    | (2013) [52]         |                                                                           |                                        |                                                                            |                                                                          |
| 19 | Reddy et al. (2008) | Evaluate the effects of sertraline on human melanoma cells                | Human cells of melanoma; rats         | Exposition of cells to sertraline, followed by in vivo evaluation       | Apoptotic shrinking of tumoral masses                                     |
|    | (2008) [22]         |                                                                           |                                        |                                                                            |                                                                          |
| 20 | Salacz et al. (2017) | Report a novel anti-cancer treatment utilizing repurposed drugs (modified CUSP/MT2) in a patient with H3 K27M mutated diffuse midline glioma (DMG) | Patient with H3 K27M mutated DMG | First, laser thermotherapy was performed, followed by standard concurrent radiotherapy and temozolomide, followed by a modified CUSP including sertraline | Near complete remission of enhancing tumor and steady clinical improvement |
|    | (2017) [25]         |                                                                           |                                        |                                                                            |                                                                          |
| 21 | Schmidt et al. (2013) [44] | Investigate protocols that could benefit the treatment of GBM             | Human GBM cells                       | Cell lines were tested with 465 pairs of drugs                          | Synergism with pterostilbene                                                |

The process can benefit the therapeutic field by saving time and resources, as well as providing a new therapeutic option for a particular disease. Our proposal was to map evidence that sertraline has the potential to be repositioned as a chemotherapeutic agent as for the probable antitumor action proposed by several studies.

From the available literature, 13 different neoplasms exposed to sertraline on experimental or observational studies presented three main mechanisms of action: apoptosis, autophagy, and drug synergism. The antidepressant played an important role in shrinking tumor masses and reducing tumor cell counting. In this context, decades of tumor reversal studies stress that these findings are reliable, as the antidepressant has shown ability to inhibit TCTP (leading to increased p53 levels and tumor reversal) [12,19,25,33], modulate chemotherapeutic resistance [54] and exhibit proper cytotoxicity [59]. A timeline was drawn to illustrate the evolution of these decades of studies aiming to repurpose the antidepressant (Supplementary Material 1).

As for the published studies, these generally involved some in vitro experimental stage, whereas the most reported outcome of that point
Fig. 3. Mapping of mechanisms of action, types of neoplasms and outcomes.

Caption: Mapping of mechanisms of action including (a) drug synergism, (b) apoptosis, (c) autophagy; (d) Types of neoplasms submitted to intervention with sertraline; (e) Outcomes of the intervention. AML, acute myeloid leukemia; BTIC, breast tumor initiating cell; Bcl-2, B-cell lymphoma 2; CUSPS9, Coordinated Survival Paths Protocol; DTIC, dacarbazine; GBM, glioblastoma multiforme; mTOR/Akt, mammalian target rapamycin/protein kinase B; OS osteosarcoma; SFA, sphere forming assay; TCTP, translationally controlled tumor protein.

Font: The Authors (2021).
was a diminished cell counting in comparison to the control group after sertraline intervention, as indicated by the reduction in SFA. This result was primarily related to apoptosis and has been directly attributed to TCTP antagonism in breast [35, 52], cervical cancer [35], colorectal cancer [19], GBM [34] leukemia [19], lung [19], melanoma [19,33] and prostate [46]. Another mechanism of action that supports this outcome was autophagy, reported in AML [49], on lung [47] and prostate [46]. Furthermore, several studies reported synergism between sertraline and other drugs in *in vitro* experiments in AML [26], breast cancer [21, 35–38], cervix cancer [35], GBM [55,56], glioma [22], liver cancer [22, 48], lung cancer [50,58], lymphoma [26], and melanoma [33]. Curiously, Amit et al. [26] reported that sertraline-treated animals had smaller tumor masses when compared to the control group in lung cancer [47] and lymphoma [21, 54, 56]. All in all, Kast et al. [34] and Salacz et al. [22] reported that repositioning the empirical use of sertraline in therapeutic regimens for GBM (such as CUSP9) was beneficial, attributing the increase in patient’s survival rates to these synergistic mechanisms.

Apart from its mechanism of action, the repositioning of sertraline as a therapeutic assistant in the treatment of neoplasms depends on its precise concentration in humans and on a safe toxicological profile. The concentrations administered in *in vivo* experimental studies ranged from 1 mg/kg/day [20] to 60 mg/kg/day [36], with an average of 22.14 mg/kg/day, mostly based on the IC50 of sertraline obtained in preliminary tests. When extrapolating the doses used by the authors in *in vivo* models, we obtain a variation of doses to be administered per day in humans between 9.13 mg/day to 913.2 mg/day [61], with average of 233.9 mg/day, being within the therapeutic range, which varies from 50 to 400 mg/day [62]. Only two concentrations were above 400mg: 547.9 mg/day [36] and 913.2 mg/day [47] as presented in Table 2. Therefore, we believe that the effective therapeutic regimens in reducing tumor cell

Table 2

| N | Author (Year) | Cancer Type | Cell Line | Treatment Details | Therapeutics | Dose performed In vivo | Outcome | Extrapolation |
|---|---------------|-------------|-----------|-------------------|--------------|------------------------|---------|--------------|
| 1 | Teymory et al. (2004) | Breast | MDA-MB231 | SCD/SCD Mice | Single injection once a day for 60 days | Sertraline (18 mg/kg), Promethazine (22.5 mg/kg) and Thioridazine (6.75 mg/kg) | Shrinking of tumor palpable masses | 164.4 mg/day |
| 2 | Reddy et al. (2000) | Melanoma | A375 | Mice | Single injection | Sertraline (1 mg/day) | Shrinking of tumor palpable masses | 9.13 mg/day |
| 3 | Gil-Ad et al. (2000) | Colorectal | HT-29 | Mice CD1 | Injection twice a week for the first 3 weeks followed by 3 times a week from the third week ahead | Sertraline (15 mg/kg) | Shrinking of tumor palpable masses | 137.8 mg/day |
| 4 | Lin et al. (2010) | Lymphoma | Pten+/− Eμ-Myc, Eμ-Myc/ Bcl-2, and Eμ-Myc/ELF4 | Mice C57BL | Injection of doxorubicin (single dose), rapamycin (daily for 5 days) and sertraline (daily for 5 days) Intravenous for 3 days, 4 times a day Gavage for 3 days | Sertraline (20 mg/kg), Doxorubicin (10 mg/kg) and Rapamycin (4 mg/kg) | Reduced relapse; increased survival rate; inhibited tumoral growth | 182.6 mg/day |
| 5 | Drienberg et al. (2014) | Ovarian | OVCAR-8 | Athymic Nude Mice | Single injection | Saline and Doxorubicin (2 mg/kg) | Sertraline (2 mg/kg) | Shrunken tumor masses | 18.2 mg/day |
| 6 | Christianen et al. (2016) | Ovarian | SK-OV-3 | Athymic Nude Mice | Single injection | Sertraline (2 mg/kg) | Increased cell proliferation and increased Ki67 levels | 91.3 mg/day |
| 7 | Hall et al. (2016) | Breast | MMTV-Neu | Mice FVB/N | Intravenous for 7 days, once a day Intra peritoneal sertraline for 7 days (single daily dose) and single docetaxel dose on the first day | Sertraline (60 mg/kg) | Reduced relapse; decreased Ki67 levels; reduced relapse | 547.9 mg/day |
| 8 | Bois-Ferrera et al. (2017) | Melanoma | B16-F10 | Mice C57BL/6 | Intraperitoneal daily for 12 days | Sertraline (10 mg/kg) | Shrinking of tumor palpable masses; decreased Ki67 levels; reduced relapse | 91.3 mg/day |
| 9 | Russo et al. (2018) | Lymphoma | EL4 | Mice C57BL/6 J | Gavage for 5 weeks | Sertraline (20 mg/kg/day) | Reduced tumor cells counting, reduced risk of developing a tumor | 182.6 mg/day |
| 10 | Jiang et al. (2018) | Lung | A549-luc | Mice NSCL | Per oral for 6 months Per oral for 6 months | Sertraline (50 mg/kg) and Erlotinib (50 mg/kg/day) | Reduced tumor cells counting | 913.2 mg/day |
| 11 | Goerar et al. (2021) | Breast | MDA-MB-231, MDA-MB-468, MCF7 and HCC70 | Mice NOD-SCID/ IL2γ−/− | Intraperitoneal injections on days 7, 9, 11, 13, 15, 20 and 24 | Sertraline (2.5 mg/kg), Artemether (40 mg/kg) or both | Inhibition of tumor growth | 22.7 mg/day |

Caption: Eight articles 1,2,3,4,5,6,8,9 performed doses that are equivalent to the standard approach on psychiatric disorders, whereas two articles 7,10 performed doses that exceed that therapeutic index; AML, Acute Myeloid Leukemia. Font: The Authors (2021).
count, reducing palpable tumor masses, and decreasing recurrences are practicable in humans.

Apart from the expected side effects of SSRI [63] and “serotonin toxicity” (provoked by up to 30 times the common daily dose) [64,65] data can be variable regarding severe symptoms, with reports of decreased level of consciousness, electrocardiographic changes, and seizures with overdoses greater than 75 times the recommended daily dose [65]. Specifically with sertraline, studies state that overdosing was not related to greater complications or morbidity, with side effects being the same as those reported with usual doses [66]. Recent reports indicate that severe cases of overdose with SSRI are increasing, but frequently happen during multiple drug abuse, especially mixed to alcohol [65,67]. Other side effects such as inhibition of platelet secretion, aggregation, and blood plug formation are under investigation, nevertheless, it is presumed, that patients with thrombocytopenia or platelet disorder could benefit from higher doses. [68]

To overcome this impasse, Lei et al. [69] synthesized a nanoliposome containing sertraline and indocyanine green (ICG), called Ser / ICG @ Lip, with the aim of increasing the concentrations administered and avoiding undesirable side effects. This technology offers a new drug delivery pathway in reason of it’s targeted-specific pharmacodynamics and simplified pharmacokinetics that may improve the therapeutic effect towards tumor therapy [70,71]. In addition, here we have identified more than thirteen instances of synergism with other drugs that could improve therapeutic regimens, reducing toxicity and side effects.

Conclusions

We conclude by suggesting that the direct action of sertraline on components linked to cellular dynamics can signal an active interference of this drug in tumor biogenesis. Evidence confirms that its repositioning could be explored, with probable safety and synergistic potential with other chemotherapeutic drugs currently available. We have also identified a Phase I clinical study (NCT02891278) which proposes the determination of the feasibility, safety, and toxicity of administering sertraline in combination with timed-sequential cytosine arabinoside (ara-C) in adults with relapsed and refractory acute myeloid leukemia (AML). The results will be decisive for the usefulness of repositioning sertraline in chemotherapy regimens in humans.

Credit author statement

João Luiz Baú-Carneiro and Francelise Bridi Cavassini elaborated the content and figures, structured, and wrote the manuscript up to the last version, reviewing it as to its important intellectual content. João Luiz Baú-Carneiro is himself the creator of all the figures. Isabella Akemi Guirao Sumida and Malu Gallon searched the databases for articles and wrote the first draft of the manuscript. Tânia Zaleski reviewed the article for important intellectual content and Marianna Boia-Ferreira was the specialist researcher to verify the quality of the selected studies as well as a key element in conducting the discussion.

Declaration of Competing Interest

The authors have declared that no competing interests exist.

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Supplementary materials

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