

Implications of Antidepressants Use in Breast Cancer: A Brief Review

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ABSTRACT

We review herein the available data regarding the potential relationship between antidepressants and breast cancer. According to some studies, the biological rationale leading correlation among antidepressants and mammary carcinogenesis is represented by the increase in prolactin levels and by the promotion of cell proliferation. However, these studies seem to be spoiled by an unsatisfactory statistical design and by the lack of a good control for confounding elements. Thus, experimental and clinical data remain controversial, even though recent studies tend to exclude a causative link between depressive disorders and breast malignancies. We have also investigated whether the concomitant use of selective serotonin re-uptake inhibitors and hormonal therapy influences cancer-related risk of death in ER-positive breast cancer patients treated with adjuvant anti-estrogen therapy. Even here an unequivocal consensus seems to be lacking, most of the studies suggest that women in hormonal adjuvant therapy experiencing depression can be safely treated with SSRI, without a negative impact on breast cancer prognosis. Whether depression and antidepressant have a role in breast tumour development, a reverse correlation is undeniably present. We reviewed the Literature to assess if there is a relationship between antidepressants and breast cancer risk and if antidepressants use may affect breast cancer patients' prognosis. We also provide a thorough list of potential pharmacological interactions between the molecules currently used for breast cancer treatment and antidepressants.

Key words: breast cancer, depression, antidepressants, drugs interactions

INTRODUCTION

The potential relationship between depression and breast cancer has been extensively explored over the last decades. The assumed biological rationale behind this association leans to an intricate network involving the nervous, immune and endocrine system (1). In fact, reduced cytotoxic T lymphocytes, Natural Killers and inflammatory cytokines activity, along with higher cortisol levels typically associated with depression, may represent a proliferative drive for cancer cells. Experimental and clinical data remain controversial, even though recent studies tend to exclude a causative link between depressive disorders and breast malignancies (2).

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Similarly, a correlation between antidepressants and breast cancer has been postulated. Researches mainly focused on Selective Serotonin Re-uptake Inhibitors (SSRI), the most prescribed antidepressant category, which increase circulating prolactin (PRL) levels, thus stimulating cell proliferation, differentiation and angiogenesis, finally leading to an increased risk of breast cancer. Again, several controversial findings made this hypothesis unclear. Moreover, many studies investigated antidepressants influence on breast cancer recurrence and survival (3).

Whether depression and antidepressant may have a role in breast tumour development, a reverse correlation between these entities is undeniably present, since a cancer diagnosis represents a major risk of mood-related disorders. Therefore, given the progressively increasing amount of women diagnosed with breast cancer, every oncologist should be aware of the potential drug-to-drug interactions between antidepressants and antineoplastic agents, and to properly manage them in a multidisciplinary team with neurologist, psychiatrist and psychologist (4-5).

In this paper, we aimed to assess if a relationship between antidepressants and breast cancer risk exist and if antidepressants use may affect breast cancer patients' prognosis. A systematic review of the Literature has been performed by inserting on Pubmed the keywords "breast cancer" AND "antidepressant" AND "depression". Only the more recent and relevant results to our research issue were selected.

We also provide a thorough list of potential pharmacological interactions between the molecules currently used for breast cancer treatment and antidepressants.

DISCUSSION

During the last decades, a plethora of experimental and epidemiological studies unsuccessfully tried to discover a potential pathogenic role between antidepressants and breast cancer.

Antidepressants biological effects may potentially lead to breast cancerogenesis, since all these medications seem to increase circulating PRL levels, hamper the immune system and promoting cell proliferation (6).

However, a growing number of evidences seem to disconfirm that higher PRL levels are associated with breast cancer development in humans (7,8).

Additionally, immune system de-regulation in antidepressants users may occur by enhancing immune cells activity (6).

Fluoxetine treatment increases the number of brain breast cancer metastases in murine model, an effect accompanied by elevated permeability of the blood-brain barrier, pro-inflammatory changes in the brain, and glial activation. This suggests a possible role of brain-resident immune cells and glia in promoting increased development of brain metastases (9). Raloxifene/Fluoxetine combination had a better effect than Raloxifene or Fluoxetine alone against induced breast cancer in rats and may represent a new therapeutic modality for management of breast cancer (10).

Apart from pre-clinical experiments, a plethora of epidemiologic studies explored whether antidepressants use may increase the risk of breast cancer in the healthy population (11-14) (*table 1*). No conclusive data are available, and a recent prospective trial conducted on a large cohort of 4014 women both in pre-menopausal and post-menopausal subjects failed to demonstrate this relationship (3).

Scarce evidences exist about antidepressants use and the onset of a specific breast cancer subtype, defined on the basis of hormonal receptors and HER2 status. Two studies did not showed correlation between antidepressants and ER positive breast cancer (15,16), whereas another one reported a significant increase of Estrogen Receptor (ER) positive/ Progesteron Receptor (PR) negative breast tumour risk in patients on SSRIs (17).

Experimental and epidemiological data does not seem to support the hypothesis that antidepressants increase the risk of breast cancer, even though these evidences come from a plethora of studies with satisfactory statistical design, adequate exposure definitions and good control for confounding elements (12). The relationship between breast cancer and antidepressant use needs to be further evaluated.

Several studies investigated whether the concomitant use of SSRI and hormonal therapy influences cancer-related risk of death in early-stage ER-positive breast cancer patients treated with adjuvant anti-estrogen therapy (Tamoxifen or aromatase inhibitors).

A large UK cohort trial conducted on 23.669 breast cancer patients found a 27% increase of breast cancer mortality in women taking SSRIs. SSRIs users had a higher breast cancer-specific mortality than non-users with no apparent dose-response relationship. Nonetheless, data are lacking about patients' adherence to SSRI and anti-cancer treatment (1).

An adherence study and a nested case-control study considered Swedish women who were diagnosed with ER-positive breast cancer from July 2007 and July 2011.

Table 1 - Studies about association between ADs use and breast cancer risk

Study	Study characteristics	No of cases/controls	Results
Cotterchio et al.(5)	Population-based Case-Control study 1995-1996 Canada	750 cases 750 controls	ADs not associated with increased breast cancer risk
Ikuko Kato et al. (6)	Cohort study 1985-1991 New York and Florida	566 breast cancer cases total population 15270 cases	ADs associated with increased breast cancer risk
Wang et al.(7)	Retrospective Cohort study 1989-1996 USA	571 breast cancer cases 38273 ADs users 32949 ADs nonusers	ADs associated with increased breast cancer risk
Moorman et al. (8)	Population-based Case-Control study 1993-2000 USA	938 cases 771 controls	ADs not associated with increased breast cancer risk
Coogan et al. (9)	Hospital-based Case Control study 1988-2002 USA	2138 cases 2858 controls	ADs not associated with increased breast cancer risk
Gonzalez-Perez et al. (10)	Registry-based Nested Case-Control study 1995-2001 UK	3708 cases 20000 controls	ADs not associated with increased breast cancer risk
Chien et al. (11)	Population-based Case-Control study 1997-1999 Location: USA	975 cases 1007 controls	ADs not associated with increased breast cancer risk
Wernli et al. (12)	Population-based Case-Control study 2003-2006 USA	2908 cases 2927 controls	ADs not associated with increased breast cancer risk
Haukka et al. (13)	Registry-based Cohort study 1998-2005 USA	1365 cases 418588 controls	ADs associated with increased breast cancer risk
Ashbury et al. (14)	Registry-based Nested Case-Control study 2003-2006 Canada	1701 cases 17017 controls	ADs not associated with increased breast cancer risk
Walker et al. (15)	Registry-based Case Control UK	1642 cases 3262 controls	ADs not associated with increased breast cancer risk

The adherence study, conducted on 9104 patients, demonstrated that short-term SSRIs users (3-18 months) were less compliant to endocrine therapy than long-term SSRIs users (≥ 18 months). In the nested case-control study, 445 cases (breast cancer deaths) and 11.125 controls (25 for each case) were included. The endpoint study was the odds ratio of breast cancer death in relation to short-term and long-term SSRIs exposure. No association between concomitant use of SSRIs and oral hormone therapy and breast cancer-specific survival emerged. In particular, no difference was observed between long-term SSRI users and non-users, whereas patients with concomitant short-term SSRI use had a worse breast cancer survival than non-users. However, the poor adherence to endocrine therapy was clearly associated with worse prognosis. These results underline the importance of a proper management of depressed breast cancer patients in

order to improve their compliance towards both anti-depressants and anti-cancer treatment (4).

Additionally, a cohort study conducted on women with early breast cancer diagnosed in Denmark from 1998 to 2011 demonstrated that treatment with anti-depressants had significantly increased risk of receiving non-guideline therapy for breast cancer and significantly worse overall survival including breast cancer-specific survival. Of the 45.352 recruited women, 744 (2%) had a previous hospital contact for depression and 6068 (13%) had been treated with antidepressants before cancer diagnosis. However, the survival of women with and without previous depression overlapped in both groups, if women with depression received adjuvant treatment according to guidelines. But worse prognosis had those given antidepressants before breast cancer due to the risk of not receiving the standard adjuvant therapy (13).

Table 2 - Interactions between ADs and drugs used in hormone-receptor positive/HER2 negative breast cancer.
 Green tiles: no interaction; Yellow tiles: potential interaction; Red tiles: major interaction. TAM Tamoxifen;
 LETRO Letrozole; ANA: Anastrozole; FULV: Fulvestrant; PALB: Palbociclib; RIB: Ribociclib.

DRUG NAME	TAM	LETRO	ANA	EXE	FULV	EVE	PALB	RIB
Imipramine	Yellow	Green	Green	Green	Green	Green	Green	Yellow
Clomipramine	Yellow	Green	Green	Green	Green	Green	Green	Yellow
Trimipramine	Yellow	Green	Green	Green	Green	Green	Green	Yellow
Amitriptyline	Yellow	Green	Green	Green	Green	Green	Green	Yellow
Nortriptyline	Yellow	Green	Green	Green	Green	Green	Green	Yellow
Maprotiline	Yellow	Green	Green	Green	Green	Green	Green	Yellow
Fluoxetine	Red	Green	Green	Green	Green	Green	Green	Red
Citalopram	Red	Yellow	Green	Green	Green	Green	Yellow	Red
Paroxetine	Red	Green	Green	Green	Green	Green	Green	Green
Sertraline	Red	Green	Green	Green	Green	Green	Yellow	Red
Escitalopram	Red	Green	Green	Green	Green	Green	Yellow	Red
Mianserine	Yellow	Green	Green	Green	Green	Green	Green	Green
Trazodone	Yellow	Green	Green	Green	Green	Yellow	Green	Yellow
Nefazodone	Yellow	Green	Green	Green	Green	Red	Red	Red
Mirtazapine	Yellow	Green	Green	Green	Green	Green	Yellow	Yellow
Venlafaxine	Red	Green	Green	Green	Green	Green	Yellow	Yellow
Reboxetina	Green	Green	Green	Green	Green	Green	Yellow	Yellow
Duloxetine	Red	Green	Green	Green	Green	Green	Green	Green
Agomelatina	Yellow	Green	Green	Green	Green	Green	Green	Green
Hypericum	Red	Green	Green	Red	Green	Red	Red	Red
Vortioxetina	Green	Green	Green	Green	Green	Green	Green	Green
Selegiline	Green	Green	Green	Green	Green	Green	Green	Green

Despite univocal consensus is lacking, most of the abovementioned studies suggest that women on hormonal adjuvant therapy experiencing depression can be treated with SSRI without a negative impact on breast cancer prognosis. No data currently support the hypothesis that antidepressants may affect breast cancer patients' outcome.

The potential drug-to-drug interactions between the molecules currently approved for the treatment of breast cancer and the most prescribed anti-depressants are depicted in *tables 2-4*.

Drugs used for the management of hormone receptor positive breast cancer are those displaying more interactions with antidepressants. Specifically, the selective estrogenic receptor modulator Tamoxifen seriously interacts with 9 of the considered antidepressants, of which 5 are SSRIs (Fluoxetine, Citalopram, Paroxetine, Sertraline and Escitalopram), 2 are

Serotonin and Noradrenalin Reuptake Inhibitors (SNRIs) (Venlafaxin and Duloxetine), one is a serotonin H2 receptor inhibitor (Nefazodone) and one is the herbal medication Hypericum perforatum.

Tamoxifen undergoes an extensive hepatic metabolism, involving mainly 2D6 cytochrome 450 (CYP2D6), which transform the drug in its active metabolite Endoxifen (14,18). Since SSRIs inhibits CYP2D6, their co-administration with tamoxifen may decrease circulating Endoxifen levels, thus hampering anti-cancer efficacy of the drug. This drug-to-drug interaction may especially occur when tamoxifen is used along with strong or moderate CYP2D6 inhibitors; such are fluoxetine, paroxetine, sertraline and duloxetine (19). Additionally, a slight increase of tamoxifen-induced QT interval prolongation exists when the drug is co-administered with citalopram, escitalopram and venlafaxine (20,21). CYP3A4 plays also a role in early stages of hepatic

Table 3 - Interactions between ADs and drugs used in HER2 positive breast cancer.
 Green tiles: no interaction; Yellow tiles: potential interaction; Red tiles: major interaction. TRAST Trastuzumab;
 PERT: Pertuzumab; LAP: Lapatinib.

DRUG NAME	TRAST	PERT	LAP	TD-M1
Imipramine	Green	Green	Yellow	Green
Clomipramine	Green	Green	Yellow	Yellow
Trimipramine	Green	Green	Yellow	Green
Amitriptyline	Green	Green	Yellow	Green
Nortriptyline	Green	Green	Yellow	Green
Maprotiline	Green	Green	Yellow	Yellow
Fluoxetine	Green	Green	Yellow	Yellow
Citalopram	Green	Green	Red	Yellow
Paroxetine	Green	Green	Green	Yellow
Sertraline	Green	Green	Yellow	Yellow
Escitalopram	Green	Green	Red	Yellow
Mianserina	Green	Green	Yellow	Green
Trazodone	Green	Green	Yellow	Green
Nefazodone	Green	Green	Yellow	Yellow
Mirtazapine	Green	Green	Yellow	Green
Venlafaxine	Green	Green	Yellow	Yellow
Reboxetina	Green	Green	Yellow	Yellow
Duloxetine	Green	Green	Green	Yellow
Agomelatina	Green	Green	Green	Green
Hypericum	Green	Green	Yellow	Yellow
Vortioxetina	Green	Green	Green	Yellow
Selegiline	Green	Green	Green	Green

tamoxifen metabolism. Both Nefazodone and Hypericum may affect tamoxifen circulating levels, by inhibiting or inducing CYP3A4, respectively (22,23). However, the CDK4/6 inhibitor Ribociclib, displays 6 major interactions. As for tamoxifen, a QT interval prolongation potentially resulting in “torsade de point” represents the main concern for the concomitant use of Ribociclib and antidepressants (24).

Amongst targeted drugs for HER2 positive breast cancer treatment, the receptor tyrosin-kinase Lapatinib presents interactions with Citalopram and Escitalopram, leading to possible heart toxicity (25). Despite several potential interactions, we have not found any major interaction between the antibody-drug conjugate Trastuzumab Emtansine (TD-M1) and antidepressants. Additionally, anti-HER2 monoclonal antibodies (Trastuzumab and Pertuzumab) have

an excellent interaction profile with the given antidepressants. Except for anthracyclines and Eribulin melisate, both interacting with Citalopram and Escitalopram with increased risk of cardiotoxicity, the other chemotherapeutic agents commonly employed for the treatment of breast cancer, can be safely administered with anti-depressants (26,27).

Given the high rate of mood disorders amongst cancer patients, the oncologists should be aware of the potential correlation between these diseases and of the pharmacologic interactions, should gain awareness of the potential drug-to-drug interactions which may hamper anticancer treatment efficacy or significantly increase their toxicities, and should manage breast cancer patients with a multi-modal approach that involves the surgeon and a dedicated psychiatrist / psychologist.

Table 4 - Interactions between ADs and chemotherapeutic agents.
 Green tiles: potential interaction; Red tiles: major interaction; ANTR: Antracyclines; TAX: Taxanes; CYCLO: Cyclofosfamide; MTX: Metotrecate; 5-FU: 5-Fluorouracil; CAPE: Capecitabine; VNB: Vinorelbine; EM: Eribulin mesilate.

	ANTR*	TAX**	CYCLO	MTX	5-FU	CAPE	VNB	EM
Imipramine	Green	Green	Green	Green	Green	Green	Green	Yellow
Clomipramine	Green	Green	Green	Green	Green	Green	Green	Yellow
Trimipramine	Green	Green	Green	Green	Green	Green	Green	Yellow
Amitriptyline	Green	Green	Green	Green	Green	Green	Green	Yellow
Nortriptyline	Green	Green	Green	Green	Green	Green	Green	Yellow
Maprotiline	Green	Green	Green	Green	Green	Green	Green	Yellow
Fluoxetine	Green	Green	Green	Green	Green	Green	Green	Green
Citalopram	Red	Green	Green	Green	Green	Green	Green	Red
Paroxetine	Green	Green	Green	Green	Green	Green	Green	Green
Sertraline	Green	Green	Green	Green	Green	Green	Green	Yellow
Escitalopram	Red	Green	Green	Green	Green	Green	Green	Red
Mianserina	Green	Green	Green	Green	Green	Green	Green	Green
Trazodone	Green	Green	Green	Green	Green	Green	Green	Yellow
Nefazodone	Green	Green	Green	Green	Green	Green	Green	Green
Mirtazapine	Green	Green	Green	Green	Green	Green	Green	Green
Venlafaxine	Green	Green	Green	Green	Green	Green	Green	Yellow
Reboxetina	Green	Green	Green	Green	Green	Green	Green	Green
Duloxetine	Green	Green	Green	Yellow	Green	Green	Green	Green
Agomelatina	Green	Green	Green	Green	Green	Green	Green	Green
Hypericum	Green	Yellow	Yellow	Green	Green	Green	Yellow	Green
Vortioxepina	Green	Green	Green	Green	Green	Green	Green	Green
Selegiline	Green	Green	Green	Green	Green	Green	Green	Green

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