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Is amisulpride safe when prescribed to breast and prostate cancer patients?

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ABSTRACT

In the last decades, the potential association between antidepressants and cancer risk has been increasingly investigated. Fundamental researches, performed on animal models and cell tumoral lines, have highlighted several biological mechanisms possibly supporting this association. Nevertheless, the epidemiological studies investigating the risk of cancer in patients receiving selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) have provided conflicting and inconclusive results. Therefore, the prescription of several antidepressants in oncologic patients still remains a matter of discussion.

The aim of this review is to present and discuss available evidence concerning the association between the risk of breast and prostate cancer and the use of antidepressant medications. Thus, consistencies, differences, and contradictions of available data are reported. A special focus is addressed to amisulpiride, a widely prescribed drug still poorly investigated with regard to the risk of cancer occurrence and recurrence. Overall, there is no definitive evidence of increased risk of breast and prostate cancer among patients exposed to SSRIs and TCAs. The association between amisulpiride and cancer risk has been to date scarcely explored and considered in clinical settings. Nevertheless, the hyperprolactinemia frequently resulting from its adoption has been repeatedly associated, to increased cancer risk and poorer prognosis in cancer patients. Thus, the use of amisulpiride among cancer patients should be carefully considered.

Introduction

Breast and prostate cancers are among the most common cancers in human population. Antidepressant medications are widely used and their prescription has steadily increased over recent decades [1]. Depressed patients affected by breast and prostate cancer are often treated with antidepressants [2,3]. Results from animal studies are compatible with the hypothesis that antidepressants may promote cancer growth, a biologically plausible phenomenon considering that the chemical structure of tricyclic (TCA) and selective serotonin reuptake inhibitors (SSRI) is similar to an anti-estrogen binding site. Few epidemiological studies have reported that selective antidepressants may be associated with a slight increase of breast cancer risk, while many others have failed to detect an association [4]. Data on the risk of recurrence among breast and prostate cancer patients treated with antidepressants are inconclusive [5]. In this respect, since many studies used prescription databases as source of information on exposure, the concurrent treatment with SSRIs and tamoxifen of patients affected by breast cancer might have been overlooked. It is now well-established that among SSRIs only citalopram, escitalopram, mirtazapine and venlafaxine are safe in combination with tamoxifen, while the other SSRIs, in particular paroxetine and fluoxetine, reduce the concentration of endoxifen, the active metabolite of tamoxifen, with the consequence, at least theoretically, of increasing the risk of recurrence [5]. The same applies to bupropion. It is therefore important when prescribing antidepressants drugs to patients with neoplastic diseases, to consider the benefit/risk ratio. Many studies were conducted on SSRIs and TCAs (tricyclic antidepressants) due to their wide use, while other drugs, such as amisulpride at low dosage or levo-sulpiride used as a prokinetic, were often not contemplated. The aim of this paper, after a brief review of data on antidepressant drugs and breast and prostate cancer risk, is to give a warning against the possible underestimation of the risk of cancer recurrence due to amisulpiride prescribed as an antidepressant to breast and prostate cancer patients.

Antidepressant drugs and risk of breast and prostate cancer

Laboratory studies

The intracellular action of antidepressants was explored in several non-human studies. TCA and SSRI are chemically similar to an anti-estrogen binding site that stimulates breast cancer growth in animals [6,7]. Findings from non-human studies

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suggested that antidepressants may have an antitumor effect [8] due to their ability to inhibit cellular proliferation. On the other hand, TCAs were regarded as possibly carcinogenous due to their putative genotoxic activity [9].

Moreover, sertraline has cytotoxic effect on prostate cancer cells via alteration of cytosolic-free Ca(2+) levels and also induces apoptosis [10].

With regard to the link between other SSRIs and the risk of prostate cancer, a study [11] was carried out specifically to evaluate the effect of paroxetine on growth and apoptosis induction in prostate cancer cell lines. The results confirmed the effects of paroxetine on growth and apoptosis induction in prostate cancer cell lines.

The potential genotoxic or carcinogenic effect of a number of psychotropic drugs was studied [12–14]. Possible mechanisms of action include the interaction with the cytochrome P450 enzyme system, the impaired concentration of prolactin levels, and modulation of immune system [15].

Epidemiologic studies

A huge case-control study [16] examined whether previous tricyclic usage was associated with reduced incidence of brain (with glioma as a sub-category), breast, colorectal, lung and prostate cancers. According to this study TCA use may be associated with a reduction of the risk of glioma and colorectal cancer. These protective effects appear to be specific to these particular types of cancer, since it was not observed for other cancers. In the early 1980s a case-control study [17], found a nearly 3-fold increased risk of breast cancer associated with the use of antidepressant medications (TCAs and MAOIs). A positive association was found in a cohort study conducted by Kato et al. [18] involving 15.270 women who participated in mammography screening. The use of any type of psychotropic medication at baseline was associated with an increased risk of breast, endometrial and ovarian cancers. In a population-based case-control study [19] designed specifically to examine the association between the use of AD and risk of breast cancer, the authors demonstrated a significantly higher breast cancer risk for 'ever' using SSRI, in particular paroxetine and sertraline.

Haukka et al. [20] in a cohort record-linkage study investigating cancer incidence at 19 sites in relation to the use of several antidepressants, reported an estimated RR of 1.53 (CI = 1.14–2.05) for breast cancer for subjects with more than 4 years of SSRI use compared to non-users. The most frequent cancers were breast, prostate, lung, colon, and brain cancer. In general, only few associations between the utilization of AD and cancer could be detected. Periods of 4 years and longer of exposure to AD showed a weak association with increased breast cancer incidence. However, no clear evidence of either beneficial or harmful association between usage of antidepressant and cancer was found. Among the different SSRIs, paroxetine has been speculated to increase the risk of breast cancer [21]. Haque et al. [22], in a retrospective cohort study of 109,004 female health-plan members who used various antidepressants, investigated whether breast cancer risk was higher among women who used paroxetine relatively to those who used other antidepressants. The authors found that women who used paroxetine for two or more years did not have a greater risk of developing breast cancer compared to women who used the same medication for a shorter period. A retrospective cohort study conducted by Wang et al. [23] suggested that the use of TCAs was unrelated to the development of breast cancer.

Large population-based case-control studies that used self-reported SSRI exposure information [24–26], and studies that ascertained SSRI use from a prescription database suggest that use of antidepressants was not associated with an increased risk of breast cancer [27].

Previously, Kelly et al. [28], in a case control study, found no association between TCA use and breast cancer risk; however they found an elevated OR estimate for recent use of SSRIs. These studies were limited by a lack of subjects with prolonged use of SSRIs [29] and by the possibility of disease-exposure bias. In a retrospective cohort study [30] authors studied the relationship between breast cancer and exposure to one or more antidepressant drugs in the six months prior to diagnosis, including diazepam, phenothiazines, tricyclic antidepressants, thiazides and thyroid/levothyroxine sodium. No association was observed between TCA use and breast cancer. In a population-based case-control study on 975 breast cancer cases Chien et al. observed that SSRIs may elevate risk of PR- and ER+/PR- tumors, though further studies are needed to confirm these associations [3]. In a study on 7.330 breast cancer patients, designed to assess the risk of breast cancer in connectin to tricyclic antidepressants, the authors did not find supporting evidence of an increased risk of breast cancer among women exposed to TCAs for up to 20 years [31].

An interesting topic is the difference between the ever use of antidepressants vs. prolonged use (over 12 months). In this regard, results obtained with similar methodologies vary. In a population based case-control study [32] including 1701 women with primary invasive breast cancer, Ashbury et al. found no association between prolonged SSRI use and breast cancer risk. Previous findings confirmed this lack of association [33,34].

Similarly, Moorman et al. found that antidepressant use in general was not related to an increased risk of breast cancer, though an increased risk of breast cancer may be associated with long-term use of SSRIs [35]. The systematic review of epidemiological evidence done some years ago by Bahl et al. found that a modest association between antidepressant and breast cancer cannot be excluded [1]. A similar review, conducted in the same period by Lawlor et al., concluded that epidemiologic evidence does not support an association between antidepressants and breast cancer [36]. It is noteworthy adding that in a study by Cosgrove [37] on antidepressants linked to breast and ovarian cancers, researchers with industry affiliations were found to be significantly less likely (0/15) to conclude that antidepressants increase the risk of breast or ovarian cancer ($p = .0012$, Fisher exact), compared to researchers without said ties (20/46). The authors of this study suggest that there may be a modest increase in the risk of breast/ovarian cancer with the use of ADs, especially SSRIs. A recent (and the only) formal meta-analysis by Eom [38] confirms that no definitive evidence of an association exists. In fact, out of 14 case-control studies included in the analysis, not a single one estimated an O.R. significantly different from unity, and, out of four cohort studies conducted so far, only two estimated a R.R. significantly different from 1 (1.50 and 1.75, respectively), the overall R.R. estimate by the meta-analysis being 1.02 (.96–1.08).

All these studies indicate a lack of association between breast cancer and previous SSRI treatments or at most a weak association. This does not apply to the risk of recurrence because of the aforementioned tamoxifen interaction with some CYP2D6 inhibitors [5]. Some time has passed between the first use of SSRIs in oncology settings and reports on such interaction. During such period the risk of recurrence has probably increased.

Epidemiological evidence will stem from descriptive and analytic studies. In the meantime, the precautionary principle suggests that appropriate action should be taken to prevent possible iatrogenic recurrent cancer cases.

Antidepressant drugs and risk of prostate cancer

Advances in the knowledge of the biology of prostate cancer have allowed to assume a possible role of neuroendocrine cells in prostate cancer progression through the secretion of a variety of