Are Antidepressants Carcinogenic? A Review of Preclinical and Clinical Studies

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Background: Antidepressants are widely prescribed for mood and anxiety disorders, though reports in the oncology and epidemiology literature have suggested these agents may possess tumor initiating and/or promoting properties, raising questions about safe long-term use in patients. The author conducted a review of the preclinical and clinical literature on the connection between antidepressants and carcinogenesis.

Method: A MEDLINE search was conducted for English-language articles published from 1966 to 2002 using the search terms *antidepressants*, *tumors*, *carcinogenesis*, and *cancer*, as well as specific antidepressant names. Additional studies were ascertained through cross-references.

Results: Preclinical studies found evidence for both tumor promotion and suppression, though the majority of studies predominantly examined tricyclic antidepressants (TCAs), with 1 report suggesting that TCAs with a nitrogen atom in the central ring are genotoxic. Of 13 clinical studies, 3 found a significant increase, 4 noted a trend increase, and 6 found no increase in risk for cancer with antidepressant (mostly TCA) use. Methodologic differences could account for some of the discrepancies found in the clinical studies, while questions about the validity for humans of the preclinical models raise doubt about the significance of those findings.

Conclusion: While there is some suggestive evidence of an association between antidepressant use and cancer, the link is, at this time, questionable but deserving of further study, especially with newer agents. Clinicians should not withhold antidepressant medication when indicated, as the risks of untreated depressive and anxiety disorders exceed the as yet unsubstantiated risk of tumor formation in such patients.

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Antidepressants are prescribed for treatment of mood, anxiety, and other disorders (e.g., pain) that may be chronic and require maintenance therapy. Patients commonly ask whether the medication they are being prescribed has any long-term effects, especially the potential for tumor formation or growth. This is an important question, particularly in the context of antidepressant treatment of patients already diagnosed with cancer or those immunologically compromised (e.g., patients with acquired immunodeficiency syndrome, transplant recipients). Some reports in the oncology and epidemiology literature have suggested that antidepressants may be linked with tumor formation or growth, raising concern about prescribing such medications on a chronic basis. While pharmaceutical companies include information about carcinogenicity and mutagenicity in the *Physicians' Desk Reference*, this article reviews published preclinical and clinical studies that have examined the connection between antidepressants and cancer, specifically whether antidepressants may be carcinogenic.

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CARCINOGENESIS

Carcinogenesis is an abnormal alteration of cellular differentiation, apoptosis (cell death), or both, resulting from an interaction between genetic and environmental factors.[1–8] The process of carcinogenesis can be divided into 3 phases: initiation, promotion, and progression.[1] Initiation is an irreversible alteration in the genetic makeup of a cell that results from an agent, i.e., carcinogen, attacking and damaging DNA (genotoxicity) and leading to the potential to develop into a neoplastic clone of cells.[3] Mutations in critical genes responsible for the maintenance of DNA integrity create an environment conducive to excessive unrepaired mutations.[7] Other genes implicated in this process are those that regulate tumor suppression, apoptosis, phase I (cytochrome P450 [CYP450]) and phase II (e.g., glutathione and *N*-acetyltransferase) activity, and behaviors (e.g., tobacco use, diet, alcohol consumption, etc.).[1] In the promotion phase, continued mutations are induced via ongoing exposure to a toxic agent (external or

Table 1. Effects of Antidepressants in Preclinical Studies of Carcinogenesis

Medication	Tumor Model	Effect	Hypothesized Mechanism
Isocarboxazid[9]	Lung	Increased incidence in mice	Hydrazine damage to DNA
Phenelzine[10]	Ames test; induction of base pair substitutions in *Salmonella* DNA	Mutagenic in both models	Hydrazine damage to DNA
Isocarboxazid[10]	Liver/lung of mice; sister chromatid exchanges in bone marrow of mice	Increased DNA damage in liver/lung; increased sister chromatid exchanges	Hydrazine damage to DNA
Clomipramine[11]	Vincristine-resistant leukemic mice	Potentiation of chemotherapeutic effect	Calmodulin inhibition by clomipramine
Clomipramine, imipramine[12]	Human hypernephroma in vitro	Inhibition of growth	Interaction with nucleotides, cell membranes, or energy-linked mitochondrial reactions
Imipramine[13]	Sarcoma in stressed rats	Attenuation of tumor growth	Catecholaminergic and/or opioid changes modifying stress
Fluoxetine, citalopram[14]	Rat jejunal/colonic tumors; xenografts of human colorectal tumors in mice	Increased mitotic rate in jejunal tumor; reduced mitotic rate in colonic and xenografted tumors	Blockade of serotonin-induced proliferative signals
Fluoxetine[15]	Three in vitro and xenografted (mice) prostate carcinoma lines	Inhibition of growth in all models	Blockade of serotonin-induced proliferative signals
Clomipramine[16]	Actinomycin D–resistant osteogenic sarcoma in mice	Augmentation of actinomycin-D inhibition	Increased intracellular actinomycin-D
Fluoxetine, amitriptyline[17]	Fibrosarcoma and melanoma in mice; mammary tumors in rat	Stimulation of tumor growth	Binding to antiestrogen binding site/ histamine receptor with modulation of CYP450 activity and subsequent changes in cellular proliferative signals
Fluoxetine[18]	2-year rodent model	Decreased incidence of pituitary adenomas and female mammary adenomas and fibroadenomas	Reduced body weight in high-dose (10 mg/kg) group
Clomipramine, desipramine, imipramine[19,20]	*Drosophila* wing development	Genotoxic; amitriptyline, maprotiline, nortriptyline, protriptyline not genotoxic	Nitrogen atom in central ring converted to N-nitroso compounds
Desipramine[21]	Induced colonic tumors in rats	Increased incidence	Changes in norepinephrine, growth hormone, or cAMP
Amitriptyline, fluoxetine[3]	Inhibition of apoptosis in human and murine tumor cell lines	Inhibition of growth acutely with high dose and chronically at low dose	Inhibition of DNA fragmentation induced by UV light
Paroxetine[22]	Multiple in vitro tests; 2-year rodent studies	No genotoxic effects in vitro; increased liver tumors in male mice	Liver tumor finding without dose-related trends characterized as "fortuitous"
Sertraline[23]	Rodent models	Increase in benign liver tumors in male mice	Adaptive change due to hepatic microsomal enzyme induction
Fluoxetine, citalopram, paroxetine[24]	Cultured Burkitt lymphoma cells	Inhibition of apoptosis	Blockade of serotonin transporter

Abbreviations: cAMP = cyclic adenosine monophosphate, CYP450 = cytochrome P450.

internal), and this process may generate oxygen-based free radicals, disrupt apoptosis regulatory proteins, and/or inhibit intercellular communication.[2] In the progression phase, genotypically and phenotypically altered cells develop microscopic and macroscopic changes.

Monro and MacDonald[4] note that in addition to the Ames assay, which tests the ability of a substance to mutate a strain of the *Salmonella typhinium* bacteria, the standard approach to identification of carcinogenicity since the early 1970s has been to conduct "bioassays," which test different dose levels of an agent in 50 male and 50 female animals of 2 rodent species, with exposure to the agent in question beginning soon after weaning and continuing on a daily basis for most of the animal's lifespan. Additional models include measuring the effect of agents on cancer cell lines in vitro and in vivo, including xenografts of human tumors in animals.

PRECLINICAL STUDIES

Table 1 summarizes the effects of antidepressants, including hypothesized mechanisms, in preclinical studies of carcinogenesis.

Early reports[9,10,25,26] indicated that monoamine oxidase inhibitors (MAOIs) with a hydrazine group (iproniazid, phenelzine, isocarboxazid) could potentially be carcinogenic, including findings of lung tumors in mice fed isocarboxazid[9] and the acceleration of cell division in rats with induced colonic tumors treated with nialamide.[26] In addition, phenelzine was mutagenic in the Ames test as well as in induction of base-pair substitutions in a bacterial DNA repair test, and isocarboxazid damaged DNA in liver and lungs of mice and increased the frequency of sister chromatid exchanges in mouse bone marrow.[10]

Studies investigating tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) began appearing in the literature in the 1980s. Tsuruo et al.[11] found that clomipramine was able to potentiate the chemotherapeutic effect of vincristine in mice with vincristine-resistant leukemia, while Sauter[12] reported that imipramine and clomipramine inhibited the growth of human hypernephroma cells in vitro. Basso et al.[13] investigated the effects of imipramine on rats inoculated with sarcoma cells, some of whom were subjected to an animal model of depression, "chronic variable stress," and found that imipramine attenuated tumor growth in the animals subjected to this depression paradigm.

Tutton and Barkla[14] examined the effects of fluoxetine and citalopram on cell proliferation and tumor growth in jejunal and colonic tumors of rats and in xenografts of human colorectal tumors in mice, and they found a significantly reduced mitotic rate in 3 of 6 doses of the drugs in the colonic tumors and a reduced tumor volume in the xenografts. Abdul et al.[15] evaluated the effect of fluoxetine in an in vitro study of 3 prostate carcinoma lines and in vivo with xenografts in athymic nude mice, finding that fluoxetine inhibited proliferation of the 3 in vitro cell lines in a dose dependent manner while also significantly inhibiting the growth rate in the xenografts (at a dose of 2 mg/kg/day). The authors of both of the latter 2 studies[14,15] note that serotonin can be a stimulant to cell division in a variety of cell types, with some of these cells having a serotonin-uptake mechanism, which, upon inhibition, would block serotonin from entering the cytoplasm and thereby reduce proliferative signals.

Finally, Merry et al.[16] noted that clomipramine augmented the effect of actinomycin D in reducing osteogenic sarcoma in mice with actinomycin D–resistant tumors, though clomipramine alone did not inhibit growth.

In contrast to the above reports suggesting antitumor effects of TCAs and SSRIs, the following studies indicate potential enhancement of tumor growth, in particular, the work of Brandes and colleagues.[17,27]

In 1992, Brandes et al.[17] reported that amitriptyline and fluoxetine stimulated the growth of malignancies in 3 rodent models at dosages relevant to treatment of depression in humans (100–150 mg/day of amitriptyline, 20–80 mg/day of fluoxetine). The effects of amitriptyline or fluoxetine were studied on tumor growth in mice that were transplanted with fibrosarcoma or melanoma cells or in rats that developed induced mammary tumors. Eight of 20 amitriptyline- or fluoxetine-treated mice developed fibrosarcoma tumors by day 5 compared with none of 20 saline controls, while 20 of 21 rats given amitriptyline or fluoxetine developed 33 mammary tumors by week 15 compared with 5 tumors in 4 of 7 rats receiving saline, indicating that in both of these tumor models, tumor latency decreased 30% to 40%, and in the mammary model, tumor frequency increased 2-fold.

Further, stimulation of melanoma was observed in mice. Brandes et al.[17] noted that the chemical structure of TCAs and fluoxetine is similar to agents that bind to a growth regulatory intracellular histamine receptor that itself is associated with antiestrogen binding sites (AEBS) in cell nuclei and microsomes. They[17,27] also report evidence that agents that bind to this AEBS-histamine receptor are involved in cellular proliferation, possibly by modulating lipid/eicosanoid metabolism, and inhibit normal growth but enhance tumor growth in vitro and in vivo.[27]

In an extension of their hypothesis, LaBella and Brandes[27] note that ligands that bind to the AEBS-histamine receptor modulate the activity of CYP450 enzymes, which in turn are believed to influence cellular proliferation via the maintenance of steady-state levels of endogenous lipid mediators of gene expression. On the basis of their findings and review of the literature, Brandes and colleagues[17,27] opine that standard tests of carcinogenicity or mutagenicity may not be adequate to determine the potential of a drug to act as a tumor promoter when cancer already exists or to accelerate the development of neoplasms in the presence of initiators, such as chemicals or viruses.

The provocative findings of Brandes and associates[17,27] led to a series of reports and editorial comment.[18,28–33] Bendele et al.[18] published the results of 3 studies conducted with dietary fluoxetine (dosages up to 10 mg/kg) in rodent carcinogenesis models over a period of 2 years finding no evidence of an increase in the incidence of any type of tumor in the treated versus control rodents, with statistically significant decreases found in the incidences of pituitary adenomas in rats of both sexes and a decrease in mammary adenomas and fibroadenomas in the female rats. Further, Pande[28] asserted that the tumor models used by Brandes et al. were of the immunogenic type and may not be representative of spontaneous human cancers.

Brandes and Cheang[29] noted that their own analysis of the Bendele et al.[18] study showed that there was a significant increase over controls in lung, skin, lymphoreticular, and pheochromocytoma tumors in the mice fed low- to mid-range doses of fluoxetine and that a bell-shaped phenomenon occurs, with lower doses increasing and higher doses decreasing tumor growth, as they note with other medications (e.g., tamoxifen).

Hoffman and Long[30] subsequently argued that Brandes and Cheang's reanalysis[29] was flawed because their selection and pooling of the tumor incidence data were questionable, though Brandes and Cheang[31] rebutted this criticism and expressed the opinion that immunosuppression may be another factor linking fluoxetine with certain cancers, citing reports implicating fluoxetine in cases of recurrent herpes infection[34] as well as cutaneous pseudolymphoma.[35]

Van Schaik and Graf[19,20] evaluated TCAs in a genotoxicity assay that involved wing development in *Drosophila melanogaster*. Clomipramine, imipramine, and desipramine were genotoxic whereas amitriptyline, nortriptyline, protriptyline, and maprotiline were not, with the suggestion that the nitrogen atom at position 5 of the central ring of the former 3 compounds confers genotoxicity. Iishi et al.[21] reported that desipramine increased the incidence of induced colon tumors in rats, while in vitro studies[3] using inhibition of apoptosis as a mechanism of tumor promotion found that acute treatment with amitriptyline and fluoxetine inhibited UV light–induced DNA fragmentation, though at doses much higher than those prescribed for depression, while in a 3-day, low-dose paradigm, amitriptyline inhibited DNA fragmentation at concentrations lower than serum levels in a human taking 100 mg/day.

Kelvin et al.[22] reported carcinogenicity studies with paroxetine and found no genotoxic effects in the in vitro studies, but they noted an increased incidence of malignant liver tumors in the intermediate-dose group of male mice that was without significant dose-related trends, a finding characterized as "fortuitous." Davies and Klowe[23] discussed the results of carcinogenicity studies with sertraline, noting that the tests were negative in rats, but there was a slight increase in benign liver tumors in male mice, a finding they considered to be secondary to hepatic enzyme induction by sertraline and not posing a risk to humans. In a more recent study, Serafeim et al.[24] examined the effects of fluoxetine, citalopram, and paroxetine on serotonin-driven apoptosis in cultured cell lines of Burkitt lymphoma, finding that these SSRIs inhibited the apoptotic process implicating the serotonin transporter as a target for promoting programmed cell death.

In regards to other antidepressants, Tucker[36] reported that lifetime administration of bupropion in rats led to focal hepatic hyperplasia, though the incidence of hepatocellular carcinomas was random and not elevated relative to the background incidence in the rat strains used. Carcinogenicity studies related to venlafaxine, mirtazapine, nefazodone, fluvoxamine, and tranylcypromine were not identified by MEDLINE search.

CLINICAL STUDIES

Thirteen epidemiologic studies were found that assessed cancer risk in antidepressant users; 3 were prospective, and 10 were retrospective (Table 2).

Friedman,[37] responding to Brandes's concern about antidepressant tumor promotion,[50] reported data from a long-term follow-up study for the National Cancer Institute that screened for potential carcinogenic effects of medications. Patients who filled at least 1 prescription for amitriptyline (N = 1957) or imipramine (N = 308) were followed for 19 years; there was no indication of any increase in cancer rates as measured by observed-to-expected cases except at the 15-year timepoint, when there were 4 cases of liver cancer in the amitriptyline group (1.05 expected), though there was no further increase by 19-year follow-up; this was felt to be a chance finding in the context of the study screening multiple drugs at multiple cancer sites. Friedman[37] noted, however, that the dosages of antidepressants and/or the statistical power of the study may not have been sufficient to detect a small effect and the analyses did not consider duration of drug use or time since last drug use. Friedman's study also looked at whether there was any difference in cancer rates between controls and patients with a diagnosis of depression and did not find any association.

Four studies examined the relationship between antidepressants and ovarian cancer. Harlow and Cramer[38] looked at data from 2 case-control studies on the relationship between antidepressant (amitriptyline, imipramine, protriptyline, phenelzine, amitriptyline-chlordiazepoxide, or amitriptyline-perphenazine) use, ascertained by either open-ended questions regarding any medication use or questions specifying "antidepressant" use, and epithelial ovarian cancer. The daily dose, length of use, and mood status were not determined in patients or controls. An increased risk of cancer was found for prior use of an antidepressant exceeding 1 to 6 months (adjusted odds ratio [OR] = 2.1, 95% confidence interval [CI] = 0.9 to 4.8) and for women whose first use occurred before 50 years of age (OR = 3.5, 95% CI = 1.3 to 9.2). Harlow and Cramer[38] hypothesized that antidepressants, via hepatic microsomal enzyme induction, might induce estrogen metabolism and secondarily raise serum gonadotropin levels leading to ovarian stimulation, though acknowledging the possibility that women with ovarian cancer might also recall their use of medications in the remote past better than healthy women or may have selectively agreed to participate more often than did controls.

In a subsequent case-control study,[39] the same authors determined names of medications, age at first use, and duration of use, in addition to asking patients whether they were ever diagnosed with depression that required medication or medical consultation; antidepressant (TCA, SSRI, or MAOI) or other psychotropic use for 6 months or longer was associated with an increased risk (OR = 1.6, 95% CI = 1.1 to 2.3) of invasive ovarian cancer. Additionally, the risk was greatest for women whose first use was premenopausally for more than 2 years (OR = 2.9, 95% CI = 1.3 to 6.6) and for the dopamine/norepinephrine reuptake inhibitors (bupropion, nortriptyline, desipramine, pemoline, amphetamines) (OR = 2.9, 95% CI = 1.3 to 6.4) versus the serotonergic agents, though the association of psychotropic medication use in general and the risk of ovarian cancer was no different in women with or without a history of depression. The authors note the potential selection bias in their study given the stigma associated with

Table 2. Clinical Studies of Antidepressants and Carcinogenesis

Medications	Cancer Type (N)/ Controls (N)	Study Design	Medication Ascertainment Method	Depression Status	Result
Amitriptyline, imipramine[37]	Any (amitriptyline, N = 1957; imipramine, N = 308)	P	Health plan pharmacy record; no dosage control	No difference in risk for cancer	No association
Amitriptyline, amitriptyline-chlordiazepoxide, amitriptyline-perphenazine, imipramine, protriptyline, phenelzine[38]	Epithelial ovarian (N = 432)/random community controls (N = 444)	R	Self-report; dose/duration not controlled	Not controlled	Increased; OR = 2.1 (95% CI = 0.9 to 4.8) for use > 1–6 mo; OR = 3.5 (CI = 1.3 to 9.2) for use prior to age 50
TCAs, SSRIs, MAOIs[39]	Epithelial ovarian (N = 563)/ random community controls (N = 523)	R	Self-report of use > 6 mo; dosage not controlled	Self-report of depression; no difference in risk for cancer	No risk for SSRIs; increased risk for NE/DA reuptake inhibitors (OR = 2.9, CI = 1.3 to 6.4)
TCAs, SSRIs[40]	Epithelial ovarian (N = 748)/ cancer (N = 1496) and noncancer (N = 1496) controls	R	Self-report of use for at least 4 d/wk for at least 4 wk	Not controlled	No increase in risk
Amitriptyline, desipramine, nortriptyline, phenelzine[41]	Breast (N = 151)/medicine and surgery ward patients (N = 151)	R	Self-report of use > 1 mo; no validation of use	Not controlled	No increase in risk
TCAs[42]	Breast (N = 302)/health plan controls (N not specified)	R	Health plan pharmacy records	Not controlled	No association
Antidepressants[43]	Recurrence of primary breast (N = 831), colon (N = 351), or melanoma (N = 285) or new primary tumor/each matched to 5 controls with similar cancer site/stage	P	Health plan pharmacy records of prescriptions filled for an antidepressant (N = 260); no validation of use	Not controlled	No increase in recurrence or in development of new primary tumor after 2.2 y
TCAs, fluoxetine, paroxetine, trazodone, maprotiline, bupropion, venlafaxine[44]	Breast (N = 5814)/cancer (N = 5095) and noncancer (N = 5814) controls	R	Self-report of use at least 4 d/wk for at least 4 wk	Not controlled	No increase in risk except for a borderline significant risk in SSRI users in the year prior to diagnosis
Fluoxetine, sertraline, paroxetine, amitriptyline, imipramine, doxepin[45]	Breast (N = 629)/population controls (N = 641)	R	Self-administered questionnaire of regular use at least 2 wk	Self-report of depression; no difference in risk	OR = 2.1 (CI = 0.9 to 5.0) for TCA use > 2 y; OR = 0.7 (CI = 0.2 to 2.2) for SSRIs except paroxetine; OR = 7.2 (CI = 0.9 to 58.3), of borderline significance
TCAs, fluoxetine, MAOIs, bupropion[46]	Breast cancer rates in patients prescribed an antidepressant (N = 38,273)/those prescribed other medications (N = 32,949)	R	Government prescription program records; determination of days exposed	Not controlled	No increased risk, including by dose or duration
TCAs[47]	Breast (N = 5882)/ population controls (N = 23,517)	R	Government prescription plan records; calculation of moles/d of antidepressant taken	Not controlled	Trend elevated risk (RR = 2.02, 95% CI = 1.34 to 3.04) in those exposed in years 11–15 prior to diagnosis
TCAs, SSRIs, MAOIs, tetracyclics[48]	Any (N = 39,807)	P	Government prescription database	Not controlled	Increased risk (standardized incidence ratio = 2.5, CI = 1.4 to 4.2) of non-Hodgkin lymphoma with ≥ 5 TCA prescriptions
TCAs[49]	Esophageal (N = 293) or gastric (N = 261) adenocarcinoma/ population controls (N = 675)	R	Structured interview about specific antidepressant use at least once/wk for 6 mo or longer	Not controlled	Nonsignificant increased risk (OR = 1.6, CI = 0.7 to 3.7) of esophageal cancer in short-term and recent (< 5 y) users

Abbreviations: CI = confidence interval, DA = dopamine, MAOI = monoamine oxidase inhibitor, NE = norepinephrine, OR = odds ratio, P = prospective, R = retrospective, RR = relative risk, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

the use of psychotropic medication and recommend that future studies use structured diagnostic instruments to assess past and present psychiatric disorders.

Coogan et al.[40] conducted a study of patients with epithelial ovarian cancer (N = 748), cancer controls (N = 1496), and noncancer controls (N = 1496) and evaluated use, by structured nurse interview, of different categories of psychotropic medications, though only 5 patients used SSRIs. The ORs were not increased for women who had used any class of drug, including TCAs, for at least 5 years, regular use being defined as taking medication at least 4 days per week for at least 4 weeks, or for women who had used the medications for 10 or more years previously. Patients in this study were not formally evaluated or matched for diagnosis of depression, and the small number of regular users of TCAs and especially SSRIs limited the authors' ability to evaluate risk by time or age since first use, duration of use, or any specific drugs individually.

The potential relationship between breast cancer and antidepressant use has been the subject of 7 reports. Wallace et al.[41] conducted a study between 1974 and 1978 of 151 women with breast cancer and 151 matched controls who were asked about any psychotropic medication taken for longer than 1 month, though no validation of medication use was obtained. The antidepressants assessed were amitriptyline, nortriptyline, desipramine, and phenelzine, though only 12 cases took antidepressants; the cases were significantly different from controls in having a more frequent family history of breast cancer and nulliparity, later mean age at onset of menopause, later mean age at first live birth, and less frequent history of surgical menopause. There was no evidence of a tumor-promoting effect as measured by any differences in mean age at onset of cancer versus controls or in clinical stage at presentation, though the authors acknowledge limitations to their findings due to the limited number of subjects and lack of confirmation of actual medication use.

Danielson et al.[42] looked at exposure to medication (computer database) in the 6 months prior to a diagnosis of breast cancer in a group of 302 women and found no difference in the incidence of cancer in users of TCAs (agents not specified) versus nonusers, though, as they indicate, the evaluation of relatively recent drug use can only address tumor promotion by these medications. Additionally, the use of medications prior to 1976 could not be ascertained, and information was lacking on possible confounding factors (e.g., age at menarche, parity, etc.)

Weiss et al.[43] examined the relationship between use of "antidepressants" and tumor recurrence or development of a second primary tumor in 1467 patients with a history of breast or colon cancer or melanoma who were matched to 5 controls with similar cancer site and stage. Follow-up of patients averaged 2.2 years, and 18% of cases filled prescriptions for at least 1 antidepressant as determined by pharmacy records; the study was designed to have an 80% power to detect a doubling of risk for a recurrent or new cancer with drug use. The use of an antidepressant was unrelated to risk of tumor recurrence or a second primary tumor, though a limitation was that the small number of cases exposed to antidepressants precluded an analysis of the effect of individual drugs or dose equivalents and it was not possible to determine whether patients actually took the medications dispensed.

Kelly et al.[44] conducted a study of medication use in 5814 women with primary breast cancer, 5095 women with other malignancies, and 5814 women with other medical conditions in the period 1977 to 1996. Regular antidepressant (TCAs mostly, especially amitriptyline, SSRIs, and smaller numbers of trazodone, bupropion, and venlafaxine) use was defined as at least 4 days/week for a minimum of 4 weeks beginning 1 year or more prior to diagnosis (determined by subject interview), though women were not assessed formally for depression per se. Breast cancer patients were more likely to be older at the birth of their first child, be Jewish, and have a family history of breast cancer and benign breast disease compared with controls. Overall, there was no evidence of increased breast cancer risk for any of the drugs, though for SSRIs (fluoxetine, sertraline, paroxetine), the relative risk (RR) was 2.0 (95% CI = 1.0 to 4.3) when duration of use of 1 to 2 years was assessed, but there was no further increase in RR with longer duration of use (RR = 1.3, 95% CI = 0.5 to 3.7 for 3 or more years of use). There was, however, a borderline statistically significant elevated RR of 1.8 (95% CI = 1.0 to 3.3) for use of SSRIs that continued into the year prior to diagnosis but without a tendency for the risk to increase with longer duration of use; all the SSRI users had taken the medication for less than 5 years, and there were only 62 regular users of SSRIs.

Cotterchio et al.[45] investigated antidepressant use, determined by self-administered questionnaire, and breast cancer risk in a population-based case-control study of women (cases: N = 629, controls: N = 641) diagnosed in 1995 and 1996. These researchers looked at antidepressant use for at least 2 weeks and controlled for a history of depression; they found an age-adjusted increased risk between the use of TCAs for at least 2 years and breast cancer (OR = 2.5, 95% CI = 1.2 to 5.1), as well as an increased risk in the multivariate analysis (OR = 2.1, 95% CI = 0.9 to 5.0), while the risk for paroxetine, though of borderline statistical significance, was elevated 7-fold, with the authors hypothesizing that paroxetine's potential to stimulate prolactin secretion and/or inhibit CYP450 2D6 might be etiologic. No associations were found between time since first and last use of antidepressants and breast cancer risk.

Lawlor[51] commented that the positive findings regarding use of paroxetine and TCAs for greater than 2 years

are not statistically significant and could have occurred by chance given the multiple subgroup analyses that were undertaken and the potential for recall bias regarding antidepressant use. Further, Beebe et al.[52] argued that only 9 cases and 1 control patient took paroxetine, and none could have had more than 3 years of exposure, that no breast carcinogen has been reported to have such a short latency period, that there was no evidence from paroxetine toxicology or carcinogenicity studies of an increase in pathology lesions consistent with hyperprolactinemia, and that human studies implicating prolactin as a risk factor for breast cancer are inconsistent, with much smaller risks observed. Additionally, Beebe et al.[52] point out that a more recent review[53] found only a weak and nonsignificant risk of breast cancer, with poor metabolizer genotype or phenotype weakening the hypothesis implicating paroxetine's CYP450 2D6 inhibition as a mechanism in carcinogenesis.

Wang et al.[46] conducted a retrospective cohort study of 38,273 women who filled a prescription for an antidepressant (determined by state and federal entitlement program databases) versus 32,949 who filled a prescription for any other medication in 1989 and 1991 and found that use of antidepressants was unrelated to breast cancer diagnosis. Further, there were no elevated risks with any specific antidepressants (highest number of prescriptions were for amitriptyline followed by fluoxetine) nor any connection between intensity of use and cancer stage, though they did note that antidepressant users had more conditions potentially related to cancer development, including use of estrogens, benign breast disorders, obesity, and alcohol abuse/dependence. Additionally, the authors acknowledge the limited determination and validation of antidepressant use.

Most recently, Sharpe et al.[47] reported results of a study on the prior use of TCAs for up to 15 years and breast cancer, which included 5882 cases and 23,517 controls. They determined TCA exposure by calculating the number of moles/day consumed in 5 different time epochs and found that there was a trend toward an increase in the risk for breast cancer in those women with the highest exposure in years 11 to 15 (RR = 2.02, 95% CI = 1.34 to 3.04) and that this increased risk could be attributed to the use of 6 "genotoxic"[19,20] TCAs (clomipramine, desipramine, doxepin, amoxapine, imipramine, and trimipramine), suggesting that these TCAs could be tumor initiators, though they note their results may have been confounded by other risks for breast cancer associated with TCA use (e.g., as noted in the study by Wang et al.[46]) for which they did not control.

Dalton et al.[48] used a population-based cohort study of 39,807 adults prescribed any type of antidepressant (prescription database) between 1989 and 1995 and estimated cancer risk as determined by linkage to diagnosis in a national cancer registry. Among SSRI users, no increase in risk was found, though this class of drug had not been available very long and the follow-up was relatively short, while there was an increased risk of non-Hodgkin's lymphoma among TCA users, with the risk higher in those receiving 5 or more prescriptions. Study limitations included lack of information on diagnoses for which antidepressants were prescribed and daily dosage as well as potential selection bias, e.g., being prescribed an antidepressant for symptoms of depression that were really an epiphenomenon of undiagnosed cancer.

Finally, Vaughan et al.[49] used personal interview data from a multicenter, population-based, case-control study to evaluate whether medications, including "TCAs" (amoxapine, nortriptyline, amitriptyline, maprotiline, doxepin, trimipramine, imipramine, protriptyline), that relax the lower esophageal sphincter and thereby promote reflux were associated with a risk of developing esophageal or gastric adenocarcinomas. They noted a nonsignificant increased risk of esophageal carcinoma in short-term (less than 5 years) TCA users but not in gastric cancer; this association was reduced when recent users (within 5 years) were excluded. The authors note the chief limitation of their study as reliance on self-report of past medication use and suggest that future studies distinguish associations with the underlying condition and related lifestyle changes versus use of the various antidepressants.

DISCUSSION

Antidepressants play a pivotal role in the psychiatric armamentarium, being prescribed not only in the treatment of mood and anxiety disorders, but also in eating, attention-deficit, and pain disorders, all of which can be chronic conditions requiring maintenance treatment similar to other medical conditions, e.g., diabetes or hypertension. As a result, patients will be exposed to these medications over periods of years, raising the question of long-term safety, as with the use of antipsychotics and tardive dyskinesia. Further, these psychiatric conditions themselves are often associated with risk factors that may lead to the development of medical illness, e.g., smoking in schizophrenics.

An additional question is whether the underlying condition, in this case depression, is associated with an increased risk of medical illness independent of confounding factors such as smoking or alcohol use. Kiecolt-Glaser and Glaser,[54] for example, review potential ways in which depression and/or stress may be carcinogenic, including adverse effects on natural killer cell function, DNA repair mechanisms, apoptosis, and frequency of sister chromatid exchanges.

Though beyond the scope of this article, there is a separate body of research on the possible connection between depression and/or personality variables and risk of developing cancer, though the results of these studies have been

quite variable due to a number of methodological differences and shortcomings and have been the subject of reviews and editorial commentaries.[55–60]

The preclinical studies of antidepressants reveal disparate findings including tumor promotion, suppression, and null effect. The critical question, however, is whether preclinical models serve as a proxy for human carcinogenicity. Potential problems with these preclinical models include (1) differences in bioavailability, kinetics, and metabolism between animals and humans, with such differences leading to tumorigenic effects in animals but not humans[2,4,6]; (2) multiple sources of variability in animal studies that may distort outcomes, e.g., genetic differences between strains, weight changes, necropsy examination[61]; (3) the use of the "maximum tolerated dose" in bioassays, which disturbs homeostasis and/or leads to toxicity that in humans would be expressly avoided, in addition to which, the use of the maximum tolerated dose could lead to differences in the bioavailability, metabolism, and kinetics of the drug[4]; (4) marked interspecies differences in organ susceptibility to cancer, with some rodent strains having high spontaneous rates of tumors in organs in which cancer in humans is rare[4]; (5) bioassays producing conflicting results with increases in one tumor type accompanied by decreases in another type.

While all agents, therefore, that are carcinogenic in humans have also been tumorigenic in animals, the converse, i.e., that all carcinogens in animals are likewise carcinogens in humans, is not true.[2] Further, though transgenic rodent models have been proposed[4] as an alternative to standard bioassays, Shureiqi et al.[1] question whether such a genetic model is any better at recapitulating human tumor development.

The clinical studies reviewed have likewise shown variable findings, with 3 of 13 studies[38,39,48] finding an increased cancer risk in primarily TCA users. Only 3 clinical studies determined depression status, and antidepressant use may have been underreported due to the stigma of taking psychotropic medication. Additionally, prescriptions filled for an antidepressant does not guarantee that patients actually took the medication as prescribed, and in some studies[44,46] users of antidepressants had possible increased cancer risks independent of antidepressant usage, including family history of breast cancer, obesity, tobacco use, and alcohol consumption.

Further, prompted by a media report that used 2 studies[45,47] to proclaim antidepressants increase the risk for breast cancer, Kurdyak et al.[62] noted how the conclusions of these and other studies could be weakened by potential confounding factors, the multiple statistical comparisons employed, and post hoc analysis. Findings of potential increased risks with groups (e.g., TCAs, SSRIs) rather than individual drugs are also problematic given potential differences among individual agents in absorption, distribution, metabolism, and excretion. Though the findings of Sharpe et al.[47] implicating specific TCAs as genotoxic[19,20] are provocative, Kurdyak et al.[62] note that this conclusion was based upon post hoc analysis and is, therefore, questionable.

Complicating epidemiologic studies, patients may be prescribed different antidepressants for varying lengths of time, especially as newer agents are introduced onto the market, thereby potentially confounding attribution risk to an individual agent. Finally, LaBella and Brandes[27] question the ability of epidemiologic studies to accurately find links between a single agent and development of tumors, as humans, they argue, are exposed to numerous chemical agents in the environment and medications and the long latency period between exposure and development of cancer is confounded by multiple competing risks.

Given these questions and limitations, it is premature to conclude that there is any connection between antidepressant, predominantly TCA, use and carcinogenesis. Steingart and Cotterchio[63] had come to this conclusion in an earlier review of 8 preclinical and 4 clinical studies. Whether newer agents carry any risk will require further study over long periods of time, given latency issues described earlier. Such studies would need to prospectively control for multiple confounding factors including depression itself, tobacco and other substance use/abuse, diet, family history, weight, etc. and require validation of medication use (including duration, dose, and class of agent). None of the clinical studies reviewed met all these criteria. Further, given the morbidity and mortality of untreated or undertreated psychiatric illness, there is no reason to withhold antidepressant medication out of concern for a remote and uncertain risk of cancer development or cancer recurrence.[64]

Media reports of new study findings should not be accepted at face value,[62] as this could lead to patient and clinician misunderstanding and inappropriate discontinuation of vital medication. Finally, as the vast majority of the literature on this topic is published in journals of oncology and epidemiology, and, as a result, is not typically read by psychiatrists, the fostering of communication and collaboration between psychiatry and the oncology/epidemiology fields would improve clinician knowledge and patient care.

CONCLUSION

The risk of tumor development as a result of antidepressant use is, at this time, questionable, though relative lack of long-term data on newer agents makes this conclusion tentative and future preclinical and clinical studies need to address past shortcomings. There is no present basis for recommending a change in antidepressant prescribing practices out of concern for possible antidepressant-related tumor initiation or promotion.

Drug names: amitriptyline (Elavil and others), amitriptyline and chlordiazepoxide (Limbitrol and others), bupropion (Wellbutrin and others), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Sinequan and others), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), isocarboxazid (Marplan), maprotiline (Ludiomil and others), mirtazapine (Remeron and others), nefazodone (Serzone), nortriptyline (Aventyl, Pamelor, and others), paroxetine (Paxil), pemoline (Cylert and others), phenelzine (Nardil), protriptyline (Vivactil), sertraline (Zoloft), tamoxifen (Nolvadex and others), tranylcypromine (Parnate), trazodone (Desyrel and others), trimipramine (Surmontil), venlafaxine (Effexor), vincristine (Oncovin, Vincasar PFS, and others).

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