Key Words: depression, drug, psychiatry, serotonin, side effects

Paroxetine—The Antidepressant from Hell? Probably Not, But Caution Required

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ABSTRACT *~ Paroxetine, also known by the trade names Aropax, Paxil, Pexeva, Seroxat, Sereupin and Brisdelle, was first marketed in the U.S. in 1992. Effective for major depression and various anxiety disorders, it quickly gained a sizable share of the antidepressant prescription market. By the late 1990s, paroxetine frequently was being associated with serious drug interactions and medication side effects. Most significantly, in a major Canadian epidemiological study examining the relationship between antidepressants and diseases, paroxetine was associated with a 620 percent increase in the rate of breast cancer in women who had taken it over a four-year period. Though re-analyses of this investigation discounted the magnitude of these findings, other studies have associated paroxetine with numerous side effects and adverse events not reported in clinical trials. Among these are effects on male fertility, birth defects, gestational hypertension, prolonged QT interval in infants, hyperprolactinemia, cognitive impairment in the elderly, autism, sexual side effects, weight gain, and suicidality, aggression, and akathisia in children and adolescents. Paroxetine has the highest inhibitory constant for the P450 2D6 isoenzyme of all antidepressants (Ki = 0.065–4.65 micromoles). This high affinity explains its high inhibitory interaction profile with substrates for 2D6. Paroxetine's potent 2D6 inhibition also implies that significant inhibition of the metabolism of 2D6 carcinogen substrates occurs which implies an increased probability of oncogenesis. Through 2D6 inhibition, tamoxifen metabolism is inhibited, which has been found to increase the risk of dying from breast cancer over a five-year period in women on both medications. Paroxetine also is a potent inhibitor of 3A4 with multiple 3A4 substrate interactions. Paroxetine has the highest known affinity for the serotonin transporter (0.13 nanomoles) of any currently used antidepressant. These characteristics and their potential negative consequences along with other adverse effects are considered and weighed against paroxetine's efficacious antidepressant and anxiolytic effects.* Psychopharmacology Bulletin. *2016;46(1):77–104.*

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Introduction

The presence of medication side effects is one of the most frequently reported reasons patients discontinue antidepressant medications, and antidepressant medication discontinuation is associated with poorer treatment outcomes.[1] Most studies of medication discontinuation have focused on the acute phase of treatment. It is probable that the issues involved in discontinuation due to side effects are different in the acute, continuation, and maintenance phases of treatment. Patients may be willing to tolerate some side effects, such as sexual dysfunction, early in the course of treatment, but likely they are less willing to tolerate the side effects that reduce their quality of life during ongoing treatment. It therefore is important for clinicians to continually be aware of the emergence of side effects during the continuation and maintenance phases of treatment.[2]

When Paxil (paroxetine) first was approved, it was hailed as a much needed and welcomed addition to the antidepressant/antianxiety arsenal. In addition to being a serotonin reuptake inhibitor, it also had mild to moderate noradrenergic effects through inhibiting reuptake of norepinephrine (NRI or NARI) and could be activating, which often helped depressed patients with lethargy. Additionally, paroxetine is efficacious in the treatment of generalized anxiety, panic, posttraumatic stress, social phobia, premenstrual dysphoric disorder, and obsessive-compulsive spectrum disorders.[3–4]

After a few years in Phase IV post-marketing clinical reporting, paroxetine exhibited a higher than average number of adverse events reported to both the Food and Drug Administration (FDA) and the manufacturer, GlaxoSmithKline.[2] Additionally, ongoing studies found associations between paroxetine use and serious adverse drug events, especially with long-term use and among special populations.[4,5]

Paroxetine and Breast Cancer

By the early 1990s, animal studies found that antidepressants increased the incidence and growth of breast cancer in mice. Researchers suggested that this increased incidence and tumor growth possibly was related to the inhibition of enzymes (e.g., the CPY450 2D6 isoenzyme), which are involved in the metabolism of carcinogens and estrogen, resulting in increased concentrations and serum levels of carcinogens and estrogen that are associated with breast cancer.[6,7] Boston University School of Medicine researchers subsequently published the results of a case-control study in which they interviewed 5,814 women who had been diagnosed with breast cancer during the previous year and compared

them to an equal number of women with other conditions. An initial analysis found no overall association between antidepressants and breast cancer, but additional analyses revealed a slightly increased risk in women who had taken a selective serotonin reuptake inhibitor (SSRI) in the previous year.[8] The following year, a Canadian epidemiological study of antidepressant use and breast cancer found that paroxetine had an odds ratio (OR) of 7.2 for breast cancer in women being treated for depression and/or anxiety over a four-year period. This was a several times higher OR than that of any other antidepressant or class of antidepressants in this study, including tricyclic antidepressants (TCAs), which were found to have an average OR of 2.0. Plausible pharmacokinetic and pharmacodynamic mechanisms were proposed for this increased breast cancer incidence with paroxetine, specifically potent inhibition of the 2D6 isoenzyme, which would reduce the carcinogen-scavaging function of 2D6, and increased inhibition of dopamine release in the lactotroph of the pituitary resulting in disinhibition of prolactin production and increased prolactin levels, a known risk for breast cancer.[9]

Further, paroxetine has the highest known affinity for the serotonin transporter (0.13 nM) which, through such potent antagonism, would yield the greatest availability of 5HT in the synapse and thus exhibit high inhibition of dopamine release not only in the lactotroph, but elsewhere in the central nervous system (see Table 1). Paroxetine also has the highest inhibitory constant for 2D6 of all antidepressants (Ki = 0.065–4.65 μM). This extremely high inhibitory binding constant or affinity explains paroxetine's high interaction profile with substrates for 2D6; paroxetine also is a potent inhibitor of the metabolism of 3A4 substrates.[4,10]

Researchers at Harvard Medical School, however, identified 38,273 women who had filled prescriptions for antidepressants between 1989 and 1991, another 32,949 women who had filled prescriptions for other medications during that time, and the number in each group that developed breast cancer. Following analyses, they concluded that antidepressant use, in general, including paroxetine, was not significantly associated with increased rates of breast cancer. In this study, antidepressant use was assessed over a period lasting up to 24 months. Subjects were followed for a maximum of 7.5 years; those who had a first diagnosis of breast cancer in the New Jersey Cancer Registry at least 3 months after their index date were considered incident breast cancer cases. Other covariates, including demographic, clinical, and health care utilization variables also were assessed. Based on multivariable proportional hazards models (hazard ratio; HR), use of antidepressants was unrelated to the development of breast cancer (adjusted HR = 1.04; 95% CI = 0.87–1.25). No elevated risks were found for specific antidepressants, including agents found

TABLE 1

Dissociation Constants of Antidepressants at Monoamine Transporters in Nanomoles

GENERIC DRUG	SERT	NET	DAT
Amitriptyline	4.3	35	3250
Atomoxetine	8.9	2.03	1080
Bupropion	45026	1389	2784
Citalopram	1.16	4070	28100
Clomipramine	0.28	38	2190
Desipramime	17.6	0.83	3190
Doxepin	68	29.5	12100
Duloxetine	0.8	7.5	240
Fluoxetine	0.81	240	3600
Fluvoxamine	0.79	244	3620
Imipramine	1.4	37	8500
Levominalcipran	11.2	10.2	10000+
Mianserin	4000	71	9400
Milnacipran	123	200	10000+
Mirtazapine	1500+	1250	1500+
Nefazodone	200	360	360
Nortriptyline	18	4.37	1140
Paroxetine	**0.13***	**40**	**5100**
Sertraline	0.29	420	25–48
Trazodonde	160	8500	7400
Venlafaxine	82	2480	7647
Vilazodone	1.6	56	37
Vortioxetine	1.6	113	1000+

*Highest known antidepressant affinity for the 5HTT or SERT (Serotonin Transporter); SERT, NET, and DAT are the transporters (reuptake pumps) for serotonin, norepinephrine, and dopamine, respectively. The smaller numbers indicate higher affinity for the drug at that particular transporter and represent the amount in moles of the drug in solution that occupies 50% of that particular receptor. Boldface for paroxetine.[4,10,26,67]

to be breast tumor promoters in animal studies, or for drugs associated with breast cancer in prior epidemiologic studies (e.g., paroxetine and TCAs). Moreover, no evidence was found that breast cancer was more prevalent with higher dosing of antidepressants or associated with a more severe stage of cancer at diagnosis.[11] Subsequent investigations also raised questions about the Cotterchio et al. study.[12,14,15] Additional studies yielded conflicting findings, some with no associated risk between antidepressants and breast cancer and others with some associated risk. In 2002, Sharpe and colleagues described a highly significant relationship between breast cancer and TCAs.[13] Reported in the *British Journal of Cancer*, use of TCAs appeared to double women's risk for breast cancer (OR = 2.0) which was identical to the OR for TCAs found in the Cotterchio et al. study. Other researchers then

reviewed the Sharpe et al. study and the Cotterchio et al. study, the latter of which also found an OR of 7.2 for paroxetine. It was concluded there was a theoretical biological basis for the findings from both studies for TCAs, since there was a 10-year time period between the women initially taking the medications and cancer development, but also, specifically, that Cotterchio et al. failed to control for other known breast cancer risk factors and make adjustments for the statistical comparisons, both of which could have affected their findings. It also was noted that the Cotterchio et al. conclusion that paroxetine use increased breast cancer risk was based on only 9 cases and 1 control and was not statistically significant. Further, according to these reviews, there was insufficient evidence in the two studies to recommend changes in clinical practice.[9,11–13,15]

Between 2001 and 2006, several groups of researchers published case control studies and reviews of the antidepressants and breast cancer research. Some concluded there was no association between antidepressant use and breast cancer, while others concluded there was an association and/or that the possible link between antidepressants and breast cancer risk had not been excluded, and additional studies were needed. Further, some case-control studies found that SSRI use is more common among women who developed breast cancer, while other case-control studies found no association between SSRIs and breast cancer. The latter concluded that studies up until that time had not indicated an altered risk of breast cancer associated with the use of antidepressants and there was no need for a change in practice protocols.[13,15–19]

In the 2003 study by Steingardt et al., the Ontario Cancer Registry (OCR) identified women diagnosed with primary breast cancer. Controls, randomly sampled from the female population of Ontario, were frequency matched by 5-year age groups. A mailed self-administered questionnaire included questions about lifetime use of antidepressants and potential confounders. Multivariate logistic regression yielded frequency of use findings and age-adjusted odds ratios (AOR) for risk estimates. "Ever" use of an antidepressant was reported by 14% (441/3077) of cases versus 12% (372/2994) of controls, with an AOR of 1.17 (95% CI = 1.01–1.36). An increased risk also was observed for SSRIs, with an AOR of 1.33 (95% CI = 1.07–1.66), more specifically sertraline, with an AOR of 1.58 (95% CI = 1.03–2.41) and paroxetine, with an AOR of 1.55 (95% CI = 1.00–2.40). Of 30 variables assessed by the OCR for confounding effects, none altered the risk estimate by more than 10%. The multivariate adjustment odds ratio (MVOR) included all 30 possible breast cancer risk factors and, though trending toward a positive association, was nonsignificant (MVOR = 1.2, 95% CI = 0.96–1.51). Duration or timing of antidepressant use was found to be unrelated

to risk. It was concluded that, using very parsimonious statistical methods, a modest association existed between any use of antidepressants and breast cancer. Though AOR estimates did not change, confidence intervals were widened and statistical significance was lost after adjustment for other breast cancer risk factors.[18]

In a 2006 study, Chien et al. concluded there is limited evidence that ever using antidepressants is associated with overall breast cancer risk. They found, however, that SSRIs may elevate risks of progesterone receptor negative (PR−) and estrogen receptor positive and progesterone receptor negative receptor (ER+/PR−) tumors, though further studies were needed to confirm these associations.[19] Coogan et al., after a systematic review of the literature, concluded that the evidence does not indicate the use of antidepressants increases the risk of breast cancer and, further, that there is a dearth of data on long-term SSRI use. Since these medications are commonly prescribed, it is prudent public health policy to monitor breast cancer incidence among women using this class of drug for long durations.[20] Fulton-Kehoe et al. reported in 2006 that antidepressant use and risk of breast cancer findings in the literature have been inconsistent. They conducted a population-based case-control study among women enrolled in Group Health Cooperative (GHC) in Washington State. Women diagnosed with initial primary breast cancer between 1990 and 2001 were identified (N = 2904), with five controls selected for each case (N = 14396). Antidepressant use, breast cancer risk factors, and screening mammograms were ascertained through the GHC pharmacy database and GHC records. In the year before they were diagnosed with breast cancer, about 20% of cases and controls had used TCAs (AOR = 1.06, 95% CI = 0.94–1.19); 6% of cases and controls had used SSRIs (OR = 0.98, 95% CI = 0.80–1.18). Additionally, there were no differences between cases and controls with regard to the number of filled prescriptions or the timing of antidepressant use. They concluded that the results from this and other studies did not indicate increased breast cancer risk associated with the use of antidepressants, by class, or for individual antidepressants.[14]

In a 2010 study in Canada, researchers found that breast cancer patients who were taking Paxil were more likely than those taking other antidepressants to die of breast cancer when there was a substantial overlap in their use of paroxetine for relief of depression and tamoxifen to prevent breast cancer recurrence. They also found that greater overlap of time on tamoxifen and paroxetine was associated with greater risk of death from breast cancer. This association was not seen with any other SSRI. The authors estimated that using paroxetine for 41% of a patient's time on tamoxifen (the average overlapping time among women in the study) would result in one additional breast cancer death

for every 19.7 women treated. If paroxetine was taken for the entire duration of tamoxifen treatment, it would result in one additional death for every 6.9 patients treated.[19]

In a more recent study by researchers from The City of Hope cancer research center in a trial screening of 446 drugs in wide circulation, using a new assay that can identify chemicals that disrupt the balance of aromotase and estrogen in humans, paroxetine was found to have an estrogenic effect (mimicking estrogen at estrogen receptors) that could promote the development and growth of breast tumors in women.[22] Approximately seventy percent of breast cancers in women are estrogen-sensitive or estrogen-dependent, meaning estrogen contributes to the growth of those breast tumors. The researchers, in addition to noting paroxetine's inhibition of the P450 2D6 isoenzyme, performed a further analysis that found that many of the genes whose activity is altered by paroxetine also are estrogen responsive and this paroxetine-genetic-estrogen-responsive relationship may pose another risk factor for breast cancer.[23] As many of these genes lie in the major histocompatibility complex (MHC), paroxetine may have downstream disruptive effects on synaptic pruning and over-editing of brain connections as well as polymorphic gene induction resulting in single nucleotide polymorphisms (SNPs) or even tri-nucleotide repeat polymorphisms (TNPs). This is speculation, but theoretically consistent with what is known about these phenomena.

Breast Cancer, Ovarian Cancer and Antidepressants

Cosgrove et al. performed a meta-analysis of 65 studies from 1965 to 2011 examining the relationship between antidepressants, breast cancer, and ovarian cancer. In searching English-language articles in MEDLINE, PsychINFO, the Science Citations Index, and the Cochrane Central Register of Controlled Clinical Trials through November 2010, they found 61 articles that assessed the relationship between breast and ovarian cancer and antidepressant use; articles that examined the effect of antidepressants on cell growth were included. Multi-modal screening techniques were used to investigate researchers' financial ties with industry. A random effects meta-analysis was used to pool the findings from the epidemiological literature. Thirty-three percent (20/61) of the studies reported a positive association between antidepressants and cancer. Sixty-seven percent (41/61) of the studies reported no association or antiproliferative effect. The pooled OR for the association between antidepressant use and breast/ovarian cancer in the epidemiologic studies was 1.11 (95% CI = 1.03–1.20). Importantly, researchers with industry affiliations were significantly less likely than non-affiliated researchers to conclude that antidepressants increase the risk of breast or ovarian

cancer (0/15 [0%] vs 20/46 [43.5%]; Fisher's Exact test P = 0.0012). It was concluded that pre-clinical and clinical data are mixed in terms of showing an association between antidepressant use and breast and ovarian cancer. Cosgrove et al. expostulated that the possibility that antidepressants may exhibit a bi-phasic effect, in which short-term use and/or low doses increase the risk of breast and ovarian cancer, necessitates further investigation. Results of this investigation also revealed that industry affiliations were significantly associated with negative conclusions regarding cancer risk. Researchers with ties to "Big Pharma" were much less likely to find an antidepressant-cancer relationship than those with no such ties. The findings have implications for breast cancer screening as well as the informed consent process.[17]

Sixteen years after the 2000 Cotterchie et al. study, though many additional studies have been mixed, there is significant evidence from the later studies to conclude there is a link between some antidepressants, especially paroxetine, and breast cancer. In this light, minimally it appears that treatment with paroxetine is not prudent for women with a family history of breast cancer. These women also should be advised to get genetic testing for BRCA1 and BRCA2. Women without a significant family history of breast cancer who have been maintained on paroxetine with a good therapeutic response (remission/recovery) should be left on the drug for now; and women without a family history of breast cancer who have severe depression and/or anxiety and have failed treatment on at least two other antidepressants (by definition are treatment-resistant), who are responding to paroxetine (50% reduction in symptoms) should be left on the drug with thorough patient education and consultation—if these patients choose to stay on paroxetine, they also should be considered for dose increases and/or augmentation with other agents, plus psychotherapy and possibly electroconvulsive therapy (ECT) as indicated.

Pearls of wisdom—1) Do not use paroxetine as first line treatment in an antidepressant naïve female patient who has a family history of breast cancer; 2) If a female without a strong history of breast cancer is responding well to paroxetine, continue paroxetine; 3) If a female has a strong family history of breast cancer (mother, sisters, grandmothers, or aunts), or has tested positive for BRCA1 or BRCA2, in consultation with her gynecologist, discontinue paroxetine and initiate another agent; 4) Always taper paroxetine slowly to discontinuation and/or slowly cross-taper it with another agent.[21–24,26]

Hot Flashes, Paroxetine, and Tamoxifen Treatment for BRCA

In addition to being prescribed for the treatment of depression, SSRIs are used for hot flashes, which can be an adverse effect of tamoxifen

(Nolvadex, Soltamox). Paroxetine and fluoxetine, specifically, are potent inhibitors of the cytochrome P450 2D6 enzyme that converts tamoxifen to its active metabolite, endoxifen. By inhibition of 2D6, these drugs reduce serum levels of this active metabolite and reduce tamoxifen efficacy against breast cancer recurrence.[21–24] Such effects might arise even from the use of lower doses of paroxetine. In 2013, The FDA approved Brisdelle, a low dose (7.5 mg) formulation of paroxetine, for nonhormonal treatment of hot flashes. Tamoxifen often causes hot flashes. If a woman is taking tamoxifen, she should not take paroxetine or fluoxetine to treat depression or hot flashes. The Brisdelle label warns that Brisdelle can reduce the effectiveness of tamoxifen (for breast cancer) if the two drugs are taken together.[25] It is worth noting that an FDA panel voted against approval.

In a recent study, women who were taking SSRIs with moderate to potent 2D6 enzyme inhibition had a 2-fold increase in the risk for breast cancer recurrence compared with women who were not taking these drugs concomitantly. This difference was significant—the risk for breast cancer recurrence was 7% in women who were not taking SSRIs and 16% in women who were taking SSRIs that were moderate to potent inhibitors of the 2D6 enzyme (HR = 2.2, $p = 0.0002$). The SSRIs included fluoxetine and paroxetine, highly potent 2D6 inhibitors, and sertraline, a moderately potent 2D6 inhibitor. SSRIs that were weak inhibitors of 2D6 had a breast cancer recurrence risk of 8.8% compared with the 7.5% risk in women not taking these drugs. Weak 2D6 inhibitors included citalopram (Celexa), escitalopram (Lexapro), and fluvoxamine (Luvox). It was concluded that women on tamoxifen should avoid moderate to potent 2D6 inhibiting SSRIs because they reduce the therapeutic effects of tamoxifen; weakly 2D6 inhibiting SSRIs probably are safe.

Conducted in collaboration with Indiana University researchers, this study used Medco's 11 million member database to identify 945 women older than 50 years and who were at least 70% compliant with tamoxifen therapy for two years or more. The researchers identified an additional 353 such women also taking an SSRI (most commonly paroxetine or fluoxetine); the median overlap during which they were taking both drugs was 255 days. A major limitation of both studies was that they did not account for individual genetic variations in the 2D6 isoenzyme. Some women, especially Caucasians, are poor metabolizers of tamoxifen and have reduced serum levels of the active metabolite of tamoxifen because of this genetic polymorphism. Women who effectively metabolize tamoxifen and receive the greatest protection against breast cancer recurrence, ironically, are most likely to experience side effects (e.g., hot flashes). These efficient metabolizers therefore are more likely to take an

SSRI for side effects with consequent inhibited 2D6 metabolism and a reduction of tamoxifen efficacy. SSRIs commonly are used in the U.S. for hot flashes and with approximately 30% of women on tamoxifen, significantly different from Europe where only 11% of women taking tamoxifen also are taking SSRIs.[22] Approval of Brisdelle may contribute to the continuation of this practice difference or even increase the tamoxifen+SSRIs percentages in both the U.S. and Europe.

Tamoxifen is effective and still commonly used for prevention of breast cancer recurrence. Though aromatase inhibitors, such as anastrozole (Arimidex), frequently now are being used in postmenopausal patients, many women on aromatase inhibitors develop significant side effects and switch to tamoxifen. Tamoxifen is first line treatment for premenopausal women with breast cancer. Thus, the above findings are significantly relevant in the therapeutic milieu.[21–24]

Paroxetine and Pravastatin Combination Raises Serum Glucose Levels

Paroxetine interacts with the cholesterol-lowering drug, pravastatin, and both are taken together by as many as one million people in the U.S. The resulting interaction can cause a spike in blood sugar levels. Paroxetine and pravastatin do not have this effect when taken independently. The interaction was uncovered by analyzing voluntary reports of adverse events in a database maintained by the FDA and comparing those to electronic health records held by three medical institutions with which the researchers were associated. The study used "data-mining" techniques to identify patterns of associations in large patient populations that would not readily be apparent to prescribers treating individual patients. Even though no patient on this combination reported hyperglycemia, 135 patients who did not have diabetes showed an average increase of 19 mg/dl in blood glucose after starting combination treatment.[27]

Among people with diabetes, there was a greater effect—a 48 mg/dl increase in serum levels of glucose after the drug combination was initiated. The glucose spikes were significant enough to possibly push a person who is pre-diabetic into full-blown diabetes and/or to put a diabetic patient in danger. The drug combination then was tested in laboratory mice that were first fed a high-fat, high-calorie diet putting them into a pre-diabetic and insulin-resistant condition. When these prediabetic mice were treated with the two drugs for three weeks, their blood glucose levels elevated from 128 mg/dl to 193 mg/dl. Neither paroxetine nor pravastatin alone had this effect. Undetected drug interactions presumably occur frequently but because examination of these

interactions is not part of the approval process by the FDA, their discoveries are made only after the drugs are on the market.[26,28] Up to 15 million people in the US may have prescriptions for these two drugs, and neither of these medications currently carry a warning against combinations that may increase blood glucose levels.

Pregnancy, Birth Defects, and Breast-feeding

Pregnancy Warning due to High Teratogenicity

On December 8, 2005, the FDA alerted health care professionals and patients about preliminary test results of studies for Paxil (paroxetine) suggesting that the drug increases the risk for birth defects, particularly heart defects, when women take Paxil during the first trimester. GlaxoSmithKline, at the request of the FDA, increased the pregnancy category warning from C to D for Paxil.[29]

Diav-Citrin et al. performed a prospective, controlled, multicenter, observational study that enrolled pregnant women who contacted the Israeli Teratology Information Service (Jerusalem, Israel), Servizio di Informazione Teratologica (Padua, Italy), or Pharmakovigilanz-und Beratungszentrum für Embryonaltoxikologie (Berlin, Germany) with regard to gestational exposure to paroxetine or fluoxetine between the years 1994 and 2002 in Israel and Italy, and between 2002 and 2005 in Germany.[30] The follow-up analysis of 410 paroxetine and 314 fluoxetine pregnancy exposures during the first trimester and 1467 controls, after genetic and cytogenetic anomalies were excluded, found a higher rate of major anomalies in the SSRI groups compared with controls, paroxetine 18/348 (5.2%), fluoxetine 12/253 (4.7%), and controls 34/1359 (2.5%). Cardiovascular anomalies were the main risk, paroxetine 7/348 (2.0%), with a crude OR of 3.47 (95% CI = 1.13–10.58), fluoxetine 7/253 (2.8%), with a crude OR of 4.81 (95% CI = 1.56–14.71, and controls 8/1359 (0.6%). Logistic regression analysis found only cigarette smoking of $\geqslant$ 10 cigarettes per day and fluoxetine exposure as significant variables for cardiovascular anomalies; adjusted ORs for paroxetine and fluoxetine were AOR = 2.66 (95% CI = 0.80–8.90) and AOR = 4.47 (95% CI = 1.31–15.27), respectively. The study was limited by reliance on maternal interviews as the outcome data source for most cases, no direct examination of the offspring, timing variations in follow-up, combining data from three teratological information services, lack of socioeconomic status data, non-randomization design with no blindness to exposure, and possible insufficient power for selected rare defects. The same procedure was applied to all study arms, however, and the prospective nature of the study was felt to minimize potential biases;

the relatively large number of SSRI-exposed cases gave reasonable power to the analyses.

A retrospective U.S. cohort study based on United Healthcare data done by GlaxoSmithKline reported a trend towards increased risk for cardiovascular malformations in infants of mothers taking paroxetine (n = 5956) compared to infants of mothers taking other antidepressants (n = 815) during the first trimester.[31] In infants of mothers receiving paroxetine who developed cardiovascular defects, 9 out of 12 had ventricular septal defects. Further, this study suggested there was an increased risk of all major congenital malformations for infants of mothers administered paroxetine as opposed to other antidepressants during the first trimester. Congenital malformations post first trimester exposure were 4% for paroxetine and 2% for other antidepressants. A more recent report funded by the Agency for Healthcare Research and Quality and the National Institutes of Health and published in the *New England Journal of Medicine*, however, suggested no substantial increase in the risk of cardiac malformations attributable to use of antidepressants during the first trimester based on the findings of a large, population based cohort study.[32]

Exposure to paroxetine as compared to other SSRIs late in pregnancy seems to be more frequently associated with neonatal withdrawal syndrome, including symptoms of respiratory depression, poor feeding, lethargy, and jitteriness. There also have been reports in the literature of gestational hypertension and prolonged QT interval in infants, as well.[33,34]

A 2015 meta-analysis of paroxetine treatment using Bayesian statistics and data from the U.S. National Birth Defects Prevention Study (NBDPS) confirmed previously reported associations between right ventricular outflow tract obstruction cardiac defects in infants and maternal use of fluoxetine or paroxetine early in pregnancy, and between anencephaly or atrial septal defects in infants and maternal use of paroxetine.[35] This analysis also confirmed associations between gastroschisis or omphalocele and paroxetine and between craniosynostosis and fluoxetine that were reported in the analysis of an earlier subset of NBDPS data; however, these still require corroboration in an independent data source. Reassuringly, none of five previously reported associations between sertraline and birth defects were confirmed in this analysis, particularly since about 40% of women reporting use of an SSRI in early pregnancy used sertraline. In addition, no support was found for nine other previously reported associations between maternal SSRI treatment and selected birth defects in the child.

Although this analysis supported validity of the associations observed, the increase in the absolute risks, if these associations are

causal, is small. The two strongest posterior odds ratios were seen for maternal paroxetine treatment and anencephaly (OR = 3.2) or right ventricular outflow tract obstruction cardiac defects (OR = 2.4) in the infant. Again, if causal, the absolute risks in the children of women who are treated with paroxetine early in pregnancy would increase for anencephaly from 2 per 10,000 to 7 per 10,000, and for right ventricular outflow tract obstruction cardiac defects from 10 per 10,000 to 24 per 10,000. Thus, the absolute risks for these birth defects still are low.

Other Paroxetine Birth Defects and Breast Feeding

Among other noted complications in infants exposed to paroxetine is craniosynostosis, an infant growth development defect where the skull of an infant closes too early. Craniosynostosis is diagnosed through a standard physical examination as well as by X-ray or computed tomography. The first sign is an abnormally shaped skull. Other features include signs of increased intracranial pressure, developmental delays, or mental retardation, which are caused by constriction of the growing brain. Seizures and blindness also may occur. Correa and colleagues, reporting on selected data for the National Birth Defects Prevention Study, examined information from 9,622 infants with major birth defects and 4,092 infants without major birth defects between 1997 and 2002 and found a high association between use of SSRIs and not only craniosynostosis but also other specific birth defects, including anencephaly, omphalocele, and various cardiac defects, such as atrial septal defect and ventral septal defect.[36]

In addition, paroxetine has been reported to be excreted into human milk.[37] In a study involving 23 breast-feeding mothers on paroxetine, researchers found detectable levels of the drug present in all maternal samples and in 24 of 25 breast milk samples.[38] The paroxetine concentrations in all the infant serum samples were below the lower limit of quantification, that is barely detectable, and no negative effects were observed in the infants. Nevertheless, only mild caution is recommended when paroxetine is administered to nursing women because the benefits of breastfeeding significantly outweigh the risks.[39]

Estrogen and aromatase disruptions as found recently by Chen et al. to be strongly related to paroxetine use during pregnancy would be expected to result in the teratogenic effects on developing fetuses about which these researchers cautioned as well as other birth defects. Multiple biosystems, including the skeletal, cardiac, endocrine and nervous systems, likely would be affected by such hormonal disruptions with some increase in birth defects typically found in

these systems—further supporting the classification of paroxetine as Pregnancy Category D.

Persistent Pulmonary Hypertension of the Newborn

In 2006, Chambers and colleagues published an article linking SSRI use during late pregnancy to an increased risk of persistent pulmonary hypertension (PPHN) in the newborn. This case controlled study reported a 6-fold increase in risk for developing PPHN for infants exposed to SSRIs after the 20th week of gestation when compared to infants who had not been exposed to antidepressants during pregnancy.[33,34]

On December 14, 2011, the FDA notified healthcare professionals and the public about the use of SSRI antidepressants by women during pregnancy and the potential risk of PPHN. This notification included Celexa (citalopram), Lexapro (escitalopram), Prozac, Sarafem, Symbyax (fluoxetine), Luvox, Luvox CR (fluvoxamine), Paxil, Paxil CR, Pexeva (paroxetine), Zoloft (sertraline), and Viibryd (vilazodone).[40] The initial public health advisory in July 2006 on this potential risk was based on a single published study. Since then, there have been conflicting findings from new studies evaluating this risk, making it unclear as to whether use of SSRIs during pregnancy can cause PPHN. The FDA in its 2011 notification stated it had reviewed five study results and concluded that given the conflicting results it was premature to reach any conclusion about a possible link between SSRI use during pregnancy and development of PPHN.

Paroxetine and Autism

In a 2011 study published in the *Archives of General Psychiatry*, Croen et al. followed 145,456 singleton full-term infants for a total of 904,035.50 person-years of follow-up.[41] This study used the ongoing population-based cohort, the Québec Pregnancy/Children Cohort; however, participants were followed whether or not the mother filled her prescription for an antidepressant. Also, Croen et al. did not capture whether the mother actually took the medication. They counted as statistically significant any result in which the p-value was < 0.05 and the 95% confidence interval (CI) did not cross 1.0 and they did not correct for multiple comparisons and so statistical significance may have been magnified. It was concluded that antidepressants used by mothers during pregnancy who were followed in this study increased the relative risk of autism occurring in the children of these pregnancies by 87%. The absolute risk was 0.87% (an increased risk from 1% to 1.87%, with

a 95% CI of 1.15–3.04). The increased risk of developing an autism spectrum disorder (ASD) was for exposure in the second and third trimesters only, not for exposure during the first trimester or in the year prior to getting pregnant in contradistinction to a much smaller 2011 unpublished study by these same researchers which was included in the above review and used The Kaiser Permanente Medical Care Program in Northern California. This smaller study found an increased risk of ASD from SSRI antidepressants in the year before delivery and with the strongest signal for exposure in the first trimester.

The smaller Croen et al. study included in the larger study used 298 case children with ASD (and their mothers) and 1507 randomly selected control children (and their mothers) drawn from the membership of the Kaiser Permanente Medical Care Program in Northern California. Prenatal exposure to antidepressant medications was reported for 20 case children (6.7%) and 50 control children (3.3%). In adjusted logistic regression models, there was a 2-fold increased risk of ASD associated with treatment with selective serotonin reuptake inhibitors by the mother during the year before delivery (AOR = 2.2 [95% confidence interval, 1.2–4.3]), with the strongest effect associated with treatment during the first trimester (AOR = 3.8 [95% confidence interval, 1.8–7.8]). No increase in risk was found for mothers with a history of mental health treatment in the absence of prenatal exposure to selective serotonin reuptake inhibitors. They concluded that although the number of children exposed prenatally to selective serotonin reuptake inhibitors in this population was low, results suggested that exposure, especially first trimester exposure, modestly increased the risk of ASD.

A 2014 study used a total of 966 mother-child pairs evaluated as 492 ASD, 154 developmentally disabled (DD), 320 typical development (TD) from the Childhood Autism Risks from Genetics and the Environment (CHARGE) Study, a population-based case-control study.[42] This study found that prevalence of prenatal SSRI exposure was lowest in TD children (3.4%) but did not differ significantly from ASD (5.9%) or DD (5.2%) children. Among boys, prenatal SSRI exposure was nearly 3 times as likely in children with ASD relative to TD (AOR = 2.91; 95% confidence interval [CI]: 1.07–7.93) and that the strongest association occurred with first-trimester exposure (AOR = 3.22; 95% CI: 1.17–8.84). Exposure was also elevated among boys with DD (AOR = 3.39; 95% CI: 0.98–11.75) and was strongest in the third trimester (AOR = 4.98; 95% CI: 1.20–20.62). Findings were similar among mothers with an anxiety or mood disorder.

A 2016 systematic review found that the pooled crude and adjusted odds ratios for the case children who had been exposed to SSRIs during pregnancy developing autism in the case-control studies reviewed were

P+C OR = 2.13 (95% CI: 1.66–2.73) and 1.81 (95% CI: 1.47–2.24) respectively. This review found no risk associated with other classes of antidepressants, just risk from SSRIs.[43]

Findings from published studies on SSRIs and ASD continue to be inconsistent. Potential recall bias and residual confounding by indication are concerns. Larger samples are needed to replicate studies which examine developmental delay results. Because maternal depression itself carries risks for the fetus, the benefits of prenatal SSRI use should be carefully weighed against potential harms. Further, the absolute risk of a child exposed to SSRIs during gestation of developing ASD still is small compared to the risk for ASD among children whose mothers did not take SSRIs during their pregnancies.

Anticholinergic Effects and Weight Gain

Of all the SSRIs, paroxetine is the most anticholinergic. It has a relatively high affinity for the M1 receptor (Ki = 76 nM). Thus, all of the effects associated with anticholinergic agents (e.g., dry mouth, constipation, urinary retention, blurred vision, hypohydrosis, hypolacrimation, confusion, etc.) can be expected with its use, especially in an elderly population.[5,26] Prescribers should use paroxetine cautiously in the elderly and other populations for whom anticholinergic side effects, especially cognitive confusion, would be highly deleterious. Additionally, an increase in intraocular pressures should be assumed not only from paroxetine's antichloinergicity but also from its noradrenergicity.[3–5,26] Careful, more frequent monitoring of IOPs is recommended for patients with comorbid open angle glaucoma, and paroxetine is contraindicated in patients with narrow angle glaucoma.[4,5,10] Paroxetine also has been associated with more weight gain than sertraline or fluoxetine.[44] In a review by Rosko in *Bariatric Times*, which included the previous study, patients treated with paroxetine experienced an average weight gain of 3.6 percent which was greater than those on sertraline (1.0% increase) and those on fluoxetine (who actually lost 0.2%). Further, 25.5 percent of paroxetine patients gained more than seven percent of their initial body weight compared to 6.8 percent of fluoxetine and 4.2 percent of sertraline patients.[45]

Nebes et al., however, examined use of paroxetine in an elderly population with depression and concluded that there were no significant effects on memory or increased cognitive problems, including confusion. The small increase in serum anticholinergicity seen in some elderly patients did not significantly impair cognitive function, even in those patients with a preexisting cognitive impairment.[46] Similarly, Cassano et al. conducted a double-blind, randomized, parallel-group,

multicenter study involving 242 elderly patients in Italy comparing paroxetine (20–40 mg daily) and fluoxetine (20–60 mg daily) treatment for 1 year. This study found both antidepressants suitable for long-term treatment of depression in the elderly and devoid of detrimental effects on tested cognitive functions.[47]

However, Furlan et al. found significantly different results for paroxetine as opposed to sertraline and placebo in healthy volunteers over a three-week period. In this study, paroxetine was found to demonstrate detrimental effects on delayed verbal recall and paired-associate learning on Day 14 as compared to both sertraline and placebo.[48] Paroxetine levels also were associated with mild behavioral impairment at Day 14. In contrast, sertraline plasma levels correlated positively (improvement) with immediate verbal recall on Day 7, tapping on Day 14, and delayed verbal recall scores on Day 21, and negatively (detrimentally) only with divided-attention task scores on Day 21. Positive cognitive effects of sertraline are theorized to be due to its high affinity (48 nM) for the dopamine transporter. Compared to other SSRIs, such as paroxetine (5,100 nM), sertraline's DAT affinity is 1,000 times higher (see Table 1).

Further, the Beers List of Potentially Harmful Drugs in the Elderly cautions that paroxetine is much more likely to cause confusion and psychomotor problems than other SSRIs because of its anticholinergic properties.[49]

All of the above concerns have to weighed and balanced against the net effect of the antidepressant in successfully treating a patient and the patient's possible persistent detrimental antidepressant side effects. Side effects usually present before therapeutic effects and separating them out from symptoms of depression and anxiety often is not easy. Mild cognitive impairment in the elderly is worsened by depression, and detrimental cognitive or psychomotor effects caused by initiating an antidepressant become additive at least until the antidepressant begins to be effective in relieving the depression and/or the side effects begin to remit.[50]

Other Common Side Effects

Among common side effects associated with paroxetine, some mentioned in the preceeding section, are sleepiness, yawning, dry mouth, headache, upset stomach/nausea, mild mental fogginess, dizziness, appetite loss, weight gain, nervousness and occasional jitters, delayed ejaculation, and anorgasmia. More frequently than with other SSRIs, paroxetine appears to be associated with a decrease in libido and erectile dysfunction.[51] Other common side effects include insomnia, blurred vision, occasionally increases in blood pressure, sweating, constipation, diarrhea, and feeling weak temporarily.[5,26]

Anticoagulation and Gastrointestinal Bleeding and Other Hemorrhages

Of greater concern is the possibility of anticoagulation effects with paroxetine and all SSRIs through increased serum levels of serotonin. Serotonin receptors are abundant and inhibitory on platelets. Serotonin is released from platelets in response to vascular injury and promotes vasoconstriction and a change in the shape of platelets that increases platelet agglutination or aggregation. Platelets do not produce serotonin and thus must uptake it from the serum. SSRIs inhibit platelet 5HT transporters and therefore total platelet serotonin which results in decreased clotting and increased risk of bleeding. Paton and Ferrier documented a number of studies that found a relationship between SSRI use and gastrointestinal bleeds.[52] Patients who are at risk for such bleeding must be cautioned about this possibility especially if they are receiving anticoagulant therapy (e.g., Warfarin, Xarelto, Eliquis, Pradaxa, heparin). Because of its high affinity for the serotonin transporter, paroxetine would be expected to be among the more serious offenders in this regard.

Because of the decreased clotting ability of platelets noted above there also is an increased risk of any type of hemorrhage including intracerebral hemorrhagic strokes. A recent meta-analysis of 16 observational studies (N = 506,411) confirmed that SSRIs increase the risk for brain hemorrhage in treated patients compared with controls (relative risk [RR = 1.72]; 95% confidence interval [CI], 1.16–2.55).[53] The risk for intracranial hemorrhage was elevated by combining SSRIs and anticoagulants, such as warfarin, compared to anticoagulants alone (RR = 1.56; 95% CI, 1.33–1.83). The authors concluded that the absolute risk for any stroke still is very low in patients receiving SSRIs and that only one additional intracerebral bleeding episode could be expected per 10,000 persons treated for one year. Again, paroxetine, with its very high dynamic increase of both serotonin and norepinephrine (NE increase leads to vasoconstriction), reasonably could be expected to be among, if not the worst offender in this regard.

Postpartum Hemorrhage (PPH) and Antidepressant Use

Palmsten et al. studied a cohort of 12,710 low-income women, 12% of who had current exposure to SSRIs (1,495) and 1.4% (178) who had current exposure to non-SSRIs.[54] They found the risk of postpartum hemorrhage was 2.8% among women with mood/anxiety disorders and no antidepressant exposure, 4.0% in women who currently were being treated with SSRIs, 3.8% in current non-SSRI users, 3.2% in women who recently had been treated with SSRIs, 3.1% in the recent users

of non-SSRIs, 2.5% in the past users of SSRIs, and 3.4% in the past users of non-SSRIs. Compared with no exposure, women with current exposure to SSRIs had a 1.47-fold increased risk of postpartum hemorrhage (95% confidence interval 1.33 to 1.62) and women with current non-SSRI exposure had a 1.39-fold increased risk (1.07 to 1.81). All types of SSRIs and venlafaxine, an SNRI, were significantly associated with postpartum hemorrhage. The authors concluded that exposure to SSRIs and non-SSRIs, including SNRIs and tricyclics close to the time of delivery was associated with a 1.4 to 1.9-fold increased risk for postpartum hemorrhage.

Hanley et al. conducted a population-based cohort study involving 225,973 women with 322,224 pregnancies which examined the correlation between SSRI and SNRI exposure in pregnancy and postpartum hemorrhage.[55] After adjustment for confounders, the risk of postpartum hemorrhage was increased with exposure to an SNRI (venlafaxine) in the final month of pregnancy (AOR = 1.76; 95 percent confidence interval [CI], 1.47 to 2.11), corresponding to 4.1 additional cases of PPH per 100 patients treated. These researchers found no correlation between SSRIs used in the final month of pregnancy and postpartum hemorrhage (AOR = 1.09; 95% CI, 0.98 to 1.21).

Additionally, a 2015 systematic review summarized evidence on the association between antidepressant use during pregnancy and the risk of PPH.[56] An Embase and Pubmed search was conducted. English and Dutch language studies reporting original data regarding bleeding after delivery associated with exposure to antidepressants during pregnancy were selected. Quality appraisal was conducted using the Newcastle Ottawa Scale (NOS). Out of 81 citations, 4 studies were included. Based on the NOS, 3 were considered of good quality and 1 was considered of satisfactory quality. Two studies found an increased incidence of PPH in women who used antidepressants during pregnancy. The other two studies found no overall increased risk of PPH among women who had used antidepressants while pregnant. The authors/researchers concluded that existing evidence is about antidepressant use during pregnancy and an association with an increased risk of postpartum hemorrhage is inconclusive. If there is such an association increased absolute risk will be low and its clinical relevance in need of further examination.

Hyponatremia

Hyponatremia, a less frequently reported adverse effect of SSRIs, may be more prevalent than previously reported and underestimated in elderly patients. Hyponatremia is a measured serum sodium concentration below 130 mEq/L and can produce nausea, malaise,

headaches, cramps, disorientation, confusion, generalized cognitive impairments and restlessness. Concentrations of serum sodium lower than 120 mEq/L often result in life-threatening events such as seizures, coma, and respiratory arrest. More than 1% of hospital admissions are associated with hyponatremia and there appears to be an increasing incidence of hyponatremia in SSRI-treated patients. A systematic review of case reports, observational and case-controlled studies and a clinical trial found hyponatremia associated with SSRIs ranging from 0.5% to 32%.[57] Risk factors for hyponatremia with SSRIs include older age, female gender, concomitant use of diuretics, low body weight, and lower baseline serum sodium concentration. As reviewed, hyponatremia typically developed in the first weeks of treatment and resolved within 2 weeks after SSRIs were discontinued. The authors hypothesized that SSRIs cause hyponatremia secondary to development of Syndrome of Inappropriate Antidiuretic Syndrome (SIADH). Risk factors for SSRI-induced hyponatremia include older age, female gender, current use of diuretics, low body weight, and lower baseline serum sodium concentration.

Severe cognitive impairment in SSRI-induced hyponatremia, however, can occur rapidly in the elderly. McSwann et al. reported a case of SSRI-induced hyponatremia with associated mental status impairment within the first week of SSRI intitiation.[58] Further investigation is necessary to determine SSRI-associated prevalence in younger patients, as most case and observational reports have focused on older adults.

Paroxetine, other Antidepressants and Suicidality/Aggression

People under the age of 24 who suffer from depression are warned that the use of antidepressants can increase the risk of suicidal thoughts and behavior. An FDA review of combined studies indicated that antidepressant interventions double the risk of suicidality and aggression in children and adolescents. On March 22, 2004, the FDA issued a public health advisory asking manufacturers to include a warning statement that recommends close observation of adult and child patients taking paroxetine. The FDA specifically stated that paroxetine should be avoided in children and adolescents; in cases of pediatric depressive disorder, fluoxetine was preferable.[4,59–60] In 2006, an FDA advisory committee recommended that the warning be extended to include young adults up to age 25.

More recently, results of a comprehensive review of pediatric trials conducted between 1988 and 2006 suggested the benefits of antidepressant medications outweigh their risks to children and adolescents

with major depression and anxiety disorders. The study, partially funded by NIMH, was published in the April 18, 2007, issue of the *Journal of the American Medical Association*.[59,62–63]

Since that time and from the pre-black box warning studies, most involving paroxetine, numerous investigations and data reporting have indicated an increase in completed pediatric suicides. On September 6, 2007, the Centers for Disease Control and Prevention reported that the suicide rate in American adolescents, especially girls 10 to 24 years, increased 8% from 2003 to 2004. This was the largest yearly jump in 15 years, from 4,232 suicides in 2003 to 4,599 suicides in 2004, a suicide rate of 7.32 per 100,000 people in that age range in 2004. The rate previously had dropped to 6.78 per 100,000 in 2003 from 9.48 per 100,000 in 1990. Some researchers attributed this as due to declining antidepressant prescriptions to young people since 2003, leaving more untreated cases of serious depression. Others have criticized the use of limited end points (e.g., data from two contiguous years) to make such comparisons and draw firm conclusions.[59,61]

However, a recent 2015 reanalysis of SmithKline Beecham's Study 329 (originally published by Keller and colleagues in 2001), compared the efficacy and safety of paroxetine and imipramine with placebo in the treatment of adolescents with major depression.[64] The reanalysis was undertaken using the restoring invisible and abandoned trials (RIAT) initiative to see whether access to and reanalysis of full datasets from a randomized controlled trials would have clinically relevant implications for evidence based medicine. In re-evaluating 12 double-blind randomized placebo-controlled trials in North American academic psychiatry centers from 1994 to 1998, involving a total of 275 adolescent participants with major depression who were randomized to eight weeks double-blind treatment with paroxetine (20–40 mg), imipramine (200–300 mg), or placebo, researchers found that measured results for paroxetine and imipramine were not statistically or clinically significantly different from placebo for any primary or secondary efficacy outcome. HAM-D scores decreased by 10.7 (least squares mean) (95% confidence interval 9.1 to 12.3), 9.0 (7.4 to 10.5), and 9.1 (7.5 to 10.7) points, respectively, for the paroxetine, imipramine and placebo groups ($P = 0.20$). Further, there were clinically significant increases in harmful outcomes, including suicidal ideation and behavior and other adverse events in the paroxetine group and cardiovascular problems in the imipramine group.

Then a 2016 review and meta-analysis of 70 clinical trials, using mortality and suicidality as primary outcomes and aggressive behavior and akathisia as secondary outcomes, with 18,526 patients, found that these trials had study design limitations and reporting discrepancies which may have led to serious under-reporting of harmful outcomes.[65]

For example, some outcomes appeared only in individual patient listings in the appendices and were available for only 32 trials in which the differences in mortality (all deaths were in adults, OR = 1.28 (95% confidence interval 0.40 to 4.06), suicidality, OR = 1.21 (0.84 to 1.74), and akathisia, OR = 2.04 (0.93 to 4.48) were not significant; whereas patients taking antidepressants displayed more aggressive behavior, OR = 1.93 (1.26 to 2.95)). Looking at suicidality for adults, the OR = 0.81 (0.51 to 1.28), and for aggression, OR = 1.09 (0.55 to 2.14), and OR = 2.00 (0.79 to 5.04) for akathisia. Corresponding values for children and adolescents were OR = 2.39 (1.31 to 4.33), OR = 2.79 (1.62 to 4.81), and OR = 2.15 (0.48 to 9.65). These researchers noted that in summary trial reports on the Eli Lilly website, almost all deaths were noted, but all suicidal ideation events were missing and the information on remaining outcomes was incomplete.

Sexual Side Effects

Sexual dysfunction is a frequent side effect with SSRIs and, as mentioned, paroxetine has been reported to be exceptional in this regard.[5,26,66] Common sexual side effects include problems with sexual desire, lack of interest in sex, and anorgasmia.[3–5,10,26] Although usually reversible, these sexual side effects can, in rare cases, last for months or years after the drug has been completely withdrawn. This is known as post-SSRI sexual dysfunction (PSSD).[66]

SSRI-induced sexual dysfunction affects 30% to 70% or more of individuals who take these drugs for depression.[3,4,10] Biochemical mechanisms suggested as causative include increased serotonin release resulting in agonism at inhibitory 5-HT_2 receptors, selectively decreased dopamine in both the limbic and frontal areas, selectively decreased norepinephrine, antagonism at cholinergic receptors and α_1 adrenergic receptors, inhibition of nitric oxide synthetase and elevation of prolactin levels.[4–5,26] Bupropion has no affinity for the serotonin transporter (SERT) but comparatively has *relatively selective affinity* for both the norepinephrine and dopamine transporters (NET; DAT).[67] Bupropion can increase libido and functioning (e.g., attenuate anorgasmia) by enhancing dopamine transmission in limbic and other pathways. It is proposed that these beneficial effects result from (1) increased NE and DA transmission from NET and DAT inhibition; (2) decreased serotonin transmission and serotonin-induced inhibition of limbic and prefrontal DA and spinal NE transmission; and, (3) increased NE transmission in both the cortex and sacral spinal nerve region. More potent dopamine reuptake inhibitors, central nervous system stimulants (e.g., dextroamphetamine, methylphenidate),

and dopamine agonists (e.g., pramipexole, ropinirole) also can produce these effects which also involve increased testosterone production secondary to prolactin inhibition as well as nitric oxide synthesis. Mirtazapine (Remeron) is reported to have fewer sexual side effects, most likely because it antagonizes 5-HT_2 and 5-HT_3 receptors.[68] Mirtazapine can in some cases reverse SSRI-induced sexual dysfunction and apomorphine, nefazodone (seldom used because of rare but possible hepatic failure), and nitroglycerin also have been shown to reverse some sexual dysfunction via increased nitric oxide activity, as have the phosphodiesterase 5 inhibitors (PDE-5 inhibitors) sildenafil (Viagra) and tadalafil (Cialis). PDE-5 inhibitors are contraindicated with use of nitrates and some antihypertensives. Monoamine oxidase inhibitors (MAOIs) are reported to have fewer negative effects on sexual function and sexual drive, particularly moclobemide at a 1.9% rate of occurrence, and selegiline (Emsam). Bethanechol has been reported to reverse MAOI-induced sexual dysfunction via its cholinergic agonist properties.[5,10,67] Sexual dysfunction associated with use of SSRIs, especially paroxetine, in the treatment of depression imposes a considerable medication adherence risk and hence risks therapeutic success. Bupropion, a norepinephrine and dopamine reuptake inhibitor, is recommended as an alternative treatment without adverse effects concerning sexual arousal and libido.[67,68]

Abler and colleagues investigated the neural bases of paroxetine-related subjective sexual dysfunction when compared with bupropion and placebo.[51] In a randomized, double-blind, within-subjects design, they scanned 18 healthy, heterosexual males while watching video clips of erotic and non-erotic content under steady-state conditions after taking 20 mg of paroxetine, 150 mg of bupropion, or placebo for 7 days each. Ratings of subjective sexual dysfunction increased on paroxetine compared with placebo or bupropion. Activation in areas of the anterior cingulate cortex (ACC), including subgenual, pregenual, and midcingulate cortices, in the ventral striatum and midbrain was decreased on paroxetine compared with placebo. Bupropion (Wellbutrin, Wellbutrin XL, Budeprion) did not affect subjective ratings and ACC activation and increased activity of brain regions including the posterior midcingulate cortex, mediodorsal thalamus, and extended amygdala relative to placebo and paroxetine. Regions related to processing motivational (ventral striatum), emotional, and autonomic components of erotic stimulation (ACC) in previous studies showed reduced responsiveness in subjects on paroxetine. Effects in these regions likely are part of the SSRI-related sexual dysfunction mechanism. Increased activation under bupropion points to an opposite effect when sexual functioning is impaired by paroxetine or other SSRIs.

Effects on male fertility (on spermatozoan DNA and sperm motility) have been found in men placed on paroxetine who previously had normal semen parameters. In these subjects, paroxetine induced abnormal sperm DNA fragmentation in a significant proportion of subjects, without a measurable effect on semen parameters. The fertility potential of a substantial number of men on paroxetine may be adversely affected by these changes in sperm DNA integrity.[69]

Thymoanesthesia

Closely related to sexual side effects is the phenomenon of emotional blunting, or mood anesthesia. Many SSRI users complain of apathy, lack of motivation, emotional numbness, feelings of detachment, and indifference described as a flatness or not caring much anymore. All SSRIs, SNRIs, and serotonergic TCAs can cause thymoanesthesia to varying degrees, especially at high doses.[50,67]

Other Uncommon Side Effects

Concerns with use of paroxetine include not only increased thoughts of aggression or suicide but also hypomanic/manic mood, abnormal dreams, rash, muscle pain, muscle weakness, electric shooting sensations, heart palpitations, feeling flushed, tingling sensations, and fasciculations. Again, the 2004 FDA black box warning eventually placed on all antidepressants indicated a two-fold increase in suicidal ideation and aggression in patients under the age of 24, especially in adolescents and children.[5,26,59] On December 22, 2006, a U.S. court decided in Hoorman et al. v. SmithKline Beecham Corporation that individuals who purchased Paxil or Paxil CR (paroxetine) for a minor child possibly were eligible for benefits under a $63.8 million Proposed Settlement. The lawsuit won the claim that GlaxoSmithKline promoted Paxil and Paxil CR for prescription to children and adolescents while withholding and concealing material information about the medication's safety and effectiveness for minors.[3,4,59,67]

Discontinuation Syndrome

As with other antidepressants, suddenly stopping paroxetine can lead to a discontinuation syndrome characterized by feelings of sickness, diaphoresis, asthenia, myalgia, parasthesias, fatigue, electric shock sensations, depression (including suicidality), anxiety, insomnia, headache, chills, stomachache, nausea, vomiting and diarrhea.[3] Step-wise

dose reduction involving slowly tapering down the drug over a period of at least two weeks is recommended for both discontinuation and cross tapering with another antidepressant.[26,67]

Conclusions

Paroxetine is an effective antidepressant which also has proven effective in treating generalized anxiety, panic, posttraumatic stress, social phobia, premenstrual dysphoric disorder, and obsessive-compulsive spectrum disorders. It also is being used to treat peri-menopausal or menopausal hot flashes. Currently, it has received FDA indications for major depressive disorder, social phobia, generalized anxiety disorder and hot flashes. A review of the literature, however, indicates that paroxetine has serious side and adverse drug effects ranging from congenital birth defects and heart abnormalities to breast and other possible cancers. It also may, along with other SSRIs and SNRIs, increase suicidality, aggression and akathisia in pediatric patients with incidence outcomes which initially may have been significantly underestimated in clinical trials. Women with a family history of breast cancer should only be initiated or maintained on paroxetine therapy when effective treatment cannot be rendered by other SSRIs, another class of antidepressants or anxiolytics, electroconvulsive therapy, or somatic treatments. The use of paroxetine is contraindicated in pregnancy unless the benefits significantly outweigh the risks. The use of paroxetine for depression or anxiety in women who are taking tamoxifen for the prevention of breast cancer recurrence is absolutely contraindicated as it leads to an unacceptably higher risk of breast cancer deaths in such women. Breast feeding while taking paroxetine is mildly cautioned though paroxetine likely does not pose a high risk to the nursing infant while the health benefits of breast feeding for both mother and infant appear to be significant.[39] Further, there are recognized risks to untreated depression in pregnancy. Depressed mothers often do not take good care of themselves, may drink, smoke or use illicit drugs more, and may seek less prenatal care.[3–5,39,67]

Overall, however, the problems and risks associated with paroxetine appear to possibly make it the least safe of all SSRIs and SNRIs and, if not for the low therapeutic indices of TCAs and MAOIs, possible cardiotoxicity and increased risk of serotonin syndrome, possibly the least safe of all antidepressants. These conclusions should lead practitioners to be much more cautious than with other antidepressants in recommending, initiating and continuing treatment with paroxetine, especially in females. ✤

References

1. Chong WW, Aslani P, Chen TF. Effectiveness of interventions to improve antidepressant medication adherence: a systematic review. *Int J Clin Pract*. 2011;65:954–975.
2. Zimmerman M, Galione JN, Attiullah N, Friedman M, Toba C, Boerescu DA, Ragheb M. Underrecognition of clinically significant side effects in depressed outpatients. *J Clin Psychiatry*. 71(4):484–490.
3. Preston J, O'Neal J, Talaga M. *Handbook of Clinical Psychopharmacology for Therapists*. 6th ed. Oakland, CA: New Harbinger; 2010.
4. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 3rd ed. Cambridge, United Kingdom: Cambridge University Press; 2008.
5. Stahl SM. *Essential Psychopharmacology: the Prescriber's Guide*. Cambridge, United Kingdom: Cambridge University Press; 2005.
6. Brandes LJ, Arron RJ, Bogdanovic RP, Tong J, Zaborniak CLF, et al. Stimulation of malignant growth in rodents by antidepressant drugs at clinically relevant doses. *Cancer Res*. 1992;52:3796–3800.
7. Iishi H, Tatsuta M, Miyako B, Taniguchi H. Enhancement by the tricyclic antidepressant, desipramine, of experimental carcinogenesis in rat colon induced by azoxymethane. *Carcinogenesis*. 1993;14(9):1837–1840.
8. Kelly JP, Rosenberg L, Palmer, JR, Sowmya R, Strom BL, Stolley PD, Zauber AG, Shapiro S. Risk of breast cancer according to use of antidepressants, phenothiazines, and antihistamines. *Am J Epidemiol*. 1999;150(8):861–868.
9. Cotterchio M, Kreiger N, Darlington G, Steingart A. Antidepressant medication use and breast cancer. *Am J Epidemiol*. 2000;151(10):951–957.
10. Schatzberg AF, Nemeroff CB. *Essentials of Clinical Psychopharmacology*. 2nd ed. Arlington, VA: American Psychiatric Publishing; 2006.
11. Wang PS, Walker AM, Tsuang MT, Orav EJ, Levin RL, Avorn J. Antidepressant use and the risk of breast cancer. *J Clin Epidemiol*. 2001;54:728–734.
12. Love S. Antidepressants and breast cancer risk. *Women's Health Network*. 2009;3(6):23–28.
13. Sharpe CR, Collet J-P, Belzile E, Hanley JA, Boivin J-F: The effects of tricyclic antidepressants on breast cancer risk. *Br J Cancer*. 2002:86(1):92–97.
14. Fulton-Kehoe D, Rossing MA, Rutter C, Mandelson MT, Weiss NS. Use of antidepressant medications in relation to the incidence of breast cancer. *Br J Cancer*. 2006;94(7):1071–1078.
15. Bahl S, Cotterchio M, Kreiger N. Use of antidepressant medication and the possible association with breast cancer risk. *Psychother Psychosom*. 2003;72(4):185–194.
16. Moorman PG, Grubber JM, Millikan RC, Newman B. Antidepressant medications and their association with invasive breast cancer and carcinoma in situ of the breast. *Epidemiol*. 2003;14(3):307–314.
17. Cosgrove L, Shi L, Creasey DE, Anaya-McKivergan M, Myers JA, Huybrechts KF. Antidepressants and breast and ovarian cancer risk: a review of the literature and researchers' financial associations with industry. *PLoS ONE*. 2011;6(4):e18210. doi:10.1371/journal.pone.0018210.
18. Steingart A, Cotterchio M, Kreiger N, Sloan M. Antidepressant medication use and breast cancer risk: a case-control study. *Int J Epidemiol*. 2003;32(6):961–966.
19. Chien C, Li CI, Heckbert SR, Malone KE, Boudreau DM, Daling JR. Antidepressant use and breast cancer risk. *Breast Cancer Res Treat*. 2006;95(2):131–140.
20. Coogan PF, Strom BL, Rosenberg L. SSRI use and breast cancer risk by hormone receptor status. *Breast Cancer Res Treat*. 2008;109(3):527–531.
21. Kelly CM, Juurlink DN, Gomes T, Duong-Hua M, Pritchard KI, Austin PC, et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. *BMJ*. 2010;340:c693.
22. Chen Z, Zhou D, Hsin L-Y, Kanawa N, Wong C, Yip R, Sakamuru S, Xia M, Yuan Y-C, Witt K, Teng C. AroER Tri-Screen™ is a Biologically Relevant Assay for Endocrine Disrupting Chemicals Modulating the Activity of Aromatase and/or the Estrogen Receptor. *Toxicol. Sci*. 2014;139(1): 198–209. doi:10.1093/toxsci/kfu023. First published online February 4, 2014.
23. Chen Z, Zhou D, Hsin L-Y, Kanawa N, Wong C, Yip R, Sakamuru S, Xia M, Yuan Y-C, Witt K, Teng C. Cell-Based High-Throughput Screening for Aromatase Inhibitors in the Tox21 10K. *LibraryToxicol Sci*. 2015;147(2):446–457 first published online July 3, 2015.
24. Aubert R, Stanek E, Yao J, Teagarden JR, Subar M, Epstein RS, Skaar TC, Desta Z, Flockhart DA. Risk of breast cancer recurrence in women initiating tamoxifen with CYP2D6 inhibitors. *J Clin Oncol*. 2009;27:18s.
25. US Food and Drug Administration. *FDA Approves the First Non-hormonal Treatment for Hot Flashes Associated with Menopause*. Rockville, MD: FDA News; June 28, 2013.
26. Julien RM, Advokat CD, Comaty JE. *A Primer of Drug Action: A Comprehensive Guide to the Actions, Uses, and Side Effects of Psychoactive Drugs*. 12th ed. New York, NY: Worth; 2010.

27. Tatonetti NP, Denny JC, Murphy SN, Fernald GH, Krishnan G, Castro V, Kohane I, Roden DM, Altman RB. Detecting drug interactions from adverse-event reports: interaction between paroxetine and pravastatin increases blood glucose levels. *Clin Pharmacol Ther*. 2011;90(1):133–142.
28. Preskorn SH, Flockhart D. 2010 Guide to Psychiatric Drug Interactions. *Prim Psychiatry*. 2009;16(12):45–74.
29. US Food and Drug Administration. *FDA Advising of Risk of Birth Defects with Paxil*. Rockville, MD: FDA News; 2005. http://69.20.19.211/bbs/topics/NEWS/2005/NEW01270.
30. Diav-Citrin O, Shechtman S, Weinbaum D, et al. Paroxetine and fluoxetine in pregnancy: a multicenter, prospective, controlled study. *Br J Clin Pharmacol*. 2008;66(5):695–705.
31. GlaxoSmithKline. *US Cohort Study of Paxil and Birth Defects Risk*. Retrieved from GlaxoSmithKline website for Paxil. January 5, 2012.
32. Huybrechts KF, Palmsten K, Avorn J, et al. Antidepressant use in pregnancy and the risk of cardiac defects. *N Engl J Med*. 2014;370:2397–2407.
33. Sengwee T, Mitchell AA, Louik C, Werler MC, Chambers CD, Hernández-Díaz S. Selective serotonin reuptake inhibitor use and risk of gestational hypertension. *Am J Psychiatry*. 2009;166: 320–328.
34. Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *New Engl J Med*. 2006;354(6):579–587.
35. Reefhuis J, Devine O, Friedman J, Louik C, Honeim M. Specific SSRIs and birth defects: Bayesian analysis to interpret new data in the context of previous reports. *BMJ*. 2015;351. doi:http://dx.doi.org/10.1136/bmj.h3190 (Published 08 July 2015).
36. Correa A, Cragan JD, Kucik ME, Alverson CJ, Gilboa SM, Balakrishnan R, Strickland MJ, Duke CW, O'Leary LA, Riehle-Colarusso T, Siffel C, Gambrell D, Thompson D, Atkinson M, Chitra J. Reporting birth defects surveillance data 1968–2003. *Birth Defects Res A Clin Mol Teratol*. 2007;79:65–186.
37. Stowe ZN, Cohen LS, Hostetter A, Ritchie JC, Owens MJ, Nemeroff CB. Paroxetine in human breast milk and nursing infants. *Am J Psychiatry*. 2000;157:185–189.
38. Hallberg P, Sjoblom V. The use of selective serotonin reuptake inhibitors during pregnancy and breastfeeding: a review and clinical aspects. *J Clin Psychopharmacol*. 2005;25(1):59–73.
39. Hale TW, Rowe H. *Medications and Mother's Milk,* 16th ed. Hale Publishing LP: Plano, TX, 2014.
40. US Food and Drug Administration. *FDA Drug Safety Communication: Selective serotonin reuptake inhibitor (SSRI) antidepressant use during pregnancy and reports of a rare heart and lung condition in newborn babies. Safety Announcement (December 14, 2011).The FDA is updating the public on the use of selective serotonin reuptake inhibitor (SSRI) antidepressants by women during pregnancy and the potential risk of a rare heart and lung condition known as persistent pulmonary hypertension of the newborn (PPHN)*. Rockville, MD: FDA News. No page numbers.
41. Croen LA, Grether JK, Yoshida CK, Odouli R, Hendrick V. Antidepressant Use During Pregnancy and Childhood Autism Spectrum Disorders. *Arch Gen Psychiatry*. 2011;68(11):1104–1112. doi:10.1001/archgenpsychiatry.2011.73.
42. Harrington R, Lee L-C, Crum R, Zimmerman A, Hertz-Picciotto I. Prenatal SSRI Use and Offspring with Autism Spectrum Disorder or Developmental Delay. *Pediatrics*. 2014;133(5):133;e1241; originally published online April 14, 2014; doi:10.1542/peds.2013–3406.
43. Boukhris T, Sheehy O, Mottron L, Bérard A. Antidepressant use during pregnancy and the risk of autism spectrum disorder in children. *JAMA Pediatr*. 2016;170(2):117–124. doi:10.1001/jamapediatrics.2015.3356.
44. Fava M, Judge R, Hoog SL, Nilsson ME, Koke SC. Fluoxetine versus sertraline and paroxetine in major depressive disorder: changes in weight with long-term treatment. *J Clin Psychiatry*. 2000;61:863–867.
45. Rosko T. Psychiatric medications and weight gain: a review. *Bariatric Times*. 2011;8(3):12–15.
46. Nebes RD, Pollock BG, Mulsant BH, Butters MA, Zmuda MD, Reynolds III CF. Cognitive effects of paroxetine in older depressed patients. *J Clin Psychiatry*. 1999;60(suppl. 20):26–29.
47. Cassano GB, Puca F, Scapicchio PL, Trabucchi M, Italian Study Group on Depression in Elderly Patients. Paroxetine and fluoxetine effects on mood and cognitive functions in depressed nondemented elderly patients. *J Clin Psychiatry*. 2002;63(5):396–402.
48. Furlan PM, Kallan MJ, Have TT, Pollock BG, Katz I, Lucki I. Cognitive and psychomotor effects of paroxetine and sertraline on healthy elderly volunteers. *Amer J Geriatr Psychiatry*. Autumn 2001;9(4): 429–438.
49. Potentially Harmful Drugs in the Elderly: Beers List. *PHARMACIST'S LETTER/PRESCRIBER'S LETTER* June 2012; PL Detail-Document #280610. Therapeutic Research Center, Stockton, CA:1–16.
50. Nevels RM, Gontkovsky ST. Pharmacological treatment of dementia: Do medications work? *The Cognitive Therapeutics Method: Non-Pharmacological Approaches to Slowing the Cognitive and Emotional Decline Associated with Dementia*. 2014; Gontkovsky ST, editor; Home Care Press: Palo Alto: 39–64.

51. Abler B, Seeringer A, Hartmann A, Grön G, Metzger C, Walter M, Stingl J. Neural correlates of antidepressant-related sexual dysfunction: a placebo-controlled fMRI study on healthy males under subchronic paroxetine and bupropion. *Neuropsychopharmacology*. 2011;36:1837–1847.
52. Paton C, Ferrier IN. SSRIs and gastrointestinal bleeding. *BMJ*. 2005;331. doi:http://dx.doi.org/10.1136/bmj.331.7516.529.
53. Hackam DG, Mrkobrada M. Selective serotonin reuptake inhibitors and brain hemorrhage: a meta-analysis. *Neurology*. 2012;79:1862–1865.
54. Palmsten K, Hernández-Diaz S, Huybrechts KF, Williams PL, Michels KB, Achtypes ED, Moogun H, Setoguchi S. Use of antidepressants near delivery and risk of postpartum hemorrhage: cohort study of low income women in the United States. *BMJ*. 2013;347:f4877. Published online 2013 Aug 21. doi:10.1136/bmj.f4877.
55. Bruning AH, Heller HM, Kieviet N, Bakker PC, de Groot CJ, Dolma KM, Honig A. Antidepressants during pregnancy and postpartum hemorrhage: a systematic review. *Eur J Obstet Gynecol Reprod Biol*. 2015;189:38–47. doi:10.1016/j.ejogrb.2015.03.022. Epub 2015 Mar 30.
56. Hanley GE, Smolina K, Mintzes B, Oberlander TF, Morgan SG. Postpartum Hemorrhage and Use of Serotonin Reuptake Inhibitor Antidepressants in Pregnancy. *Obstet Gynecol*. 2016;127(3). doi: 10.1097/AOG.0000000000001200.
57. Jacob S, Spinler SA. Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults. *Ann Pharmacother*. 2006 Sep;40(9):1618–1622. Epub 2006 Aug 8. doi:10.1345/aph.1G293.
58. McSwan KL, Gontkovsky ST, Splinter MY. Acute changes in mental status secondary to selective serotonin reuptake inhibitor induced hyponatremia. *Rehabil Psychol*. 2003;48:202–206.
59. Nevels RM, Dehon EE, Alexander K, Gontkovsky ST. Psychopharmacology of aggression in children and adolescents with primary neuropsychiatric disorders: a review of current and potentially promising treatment options. *Exp Clin Psychopharmacol*. 2010;18(2):184–201.
60. Vedantam S. *FDA links antidepressants, youth suicide risk*. The Washington Post. 2004, Feb 3:A01.
61. Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationships between antidepressant prescription rates and rate of early adolescent suicide. *American Journal of Psychiatry*. 2006;163(11):1898–1904.
62. Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher MD, Pincus HA, Ren L, Brent DA. Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment: A Meta-analysis of Randomized Controlled Trials. *JAMA.* 2007;297(15):1683–1696. doi:10.1001/jama.297.15.1683.
63. Jureidini J. The black box warning: decreased prescriptions and increased youth suicide? *Am J Psychiatry*. 2007;164(12):1907; author reply 1908–10. doi:10.1176/appi.ajp.2007.07091463.
64. Le Noury J, Nardo J, Healy D, Raven M, Tufanaru C, Abi-Jaoude E. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *BMJ*. 2015;351. doi:http://dx.doi.org/10.1136/bmj.h4320 (Published 16 September 2015) Cite this as: *BMJ*. 2015;351:h4320.
65. Sharma T, Guski LS, Freund N, Gøtzsche P. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. *BMJ*. 2016;352. doi:http://dx.doi.org/10.1136/bmj.i65 (Published 27 January 2016).
66. Ben-Sheetrit J, Aizenberg D, Csoka AB, Weizman A, Hermesh H. Post-SSRI sexual dysfunction: Clinical characterization and preliminary assessment of contributory factors and dose-response relationship. *J Clin Psychopharmacol*. 2015;35(3):273–278. doi:10.1097/JCP.0000000000000300.
67. Stahl SM. *Antidepressants.* Cambridge, United Kingdom: Cambridge University Press; 2009.
68. Ozmenler NK, Karlidere T, Bozkurt A. Mirtazapine augmentation in depressed patients with sexual dysfunction due to selective serotonin reuptake inhibitors. *Hum Psychopharmacol*. 2008:23(4):321–326. doi:10.1002/hup.929.
69. Tanrikut C, Feldman AS, Altemus M, Paduch DA, Schlegel PN. Adverse effect of paroxetine on sperm. *Fertil Steril*. 2010;94(3):1021–1026. Epub 2009 Jun 10.