

the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis: Paroxetine produced no genotoxic effects in a battery of 5 *in vitro* and 2 *in vivo* assays that included the following: Bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes and in a dominant lethal test in rats.

Impairment of Fertility: Some clinical studies have shown that SSRIs (including paroxetine) may affect sperm quality during SSRI treatment, which may affect fertility in some men.

A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is 2.9 times the MRHD for major depressive disorder, social anxiety disorder, and GAD or 2.4 times the MRHD for OCD on a mg/m² basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (9 and 4.9 times the MRHD for major depressive disorder, social anxiety disorder, and GAD, 8.2 and 4.1 times the MRHD for OCD and PD on a mg/m² basis).

Pregnancy: Pregnancy Category D. See **WARNINGS – Usage in Pregnancy: Teratogenic Effects and Nonteratogenic Effects.**

Labor and Delivery: The effect of paroxetine on labor and delivery in humans is unknown.

Nursing Mothers: Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when paroxetine tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING and WARNINGS - Clinical Worsening and Suicide Risk**). Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with paroxetine tablets, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of paroxetine tablets in a child or adolescent must balance the potential risks with the clinical need.

In placebo-controlled clinical trials with paroxetine tablets, the following adverse events were reported in at least 2% of pediatric patients treated with paroxetine tablets and occurred at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia, and agitation.

Events reported upon discontinuation of treatment with paroxetine tablets in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients who received paroxetine tablets and which occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes, and fearfulness), nervousness, dizziness, nausea, and abdominal pain (see **DOSE AND ADMINISTRATION: Discontinuation of Treatment with Paroxetine Tablets**).

Geriatric Use: SSRI and SNRI, including paroxetine, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see **PRECAUTIONS, Hyponatremia**).

In worldwide premarketing clinical trials with paroxetine tablets, 17% of patients treated with paroxetine tablets (approximately 700) were 65 years of age or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients (see **CLINICAL PHARMACOLOGY and DOSE AND ADMINISTRATION**).

ADVERSE REACTIONS:

Associated with Discontinuation of Treatment: Twenty percent (1,199/6,145) of patients treated with paroxetine tablets in worldwide clinical trials in major depressive disorder and 16.1% (84/522), 11.8% (64/542), 9.4% (44/469), and 10.7% (79/735) of patients treated with paroxetine tablets in worldwide trials in social anxiety disorder, OCD, panic disorder, and GAD, and respectively, discontinued treatment due to an adverse event. The most common events (>1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for paroxetine tablets compared to placebo) included the following:

Major Depressive Disorder	OCD	Panic Disorder	Social Anxiety Disorder	Generalized Anxiety Disorder					
CNS									
Somnolence	2.3%	0.7%	-	1.9%	0.3%	3.4%	0.3%	2.0%	0.2%
Insomnia	-	1.7%	0%	1.3%	0.3%	3.1%	0%	-	-
Agitation	1.1%	0.5%	-	-	-	1.7%	0%	-	-
Tremor	1.1%	0.3%	-	-	-	1.1%	0%	-	-
Anxiety	-	-	-	-	-	1.1%	0%	-	-
Dizziness	-	-	1.5%	0%	-	1.3%	0%	1.0%	0.2%
Gastrointestinal									
Constipation	-	1.1%	0%	-	-	4.0%	0.3%	2.0%	0.2%
Nausea	3.2%	1.1%	1.9%	0%	3.2%	1.2%	4.0%	0.3%	2.0%
Diarrhea	1.0%	0.3%	-	-	-	1.0%	0%	-	-
Dry Mouth	1.0%	0.3%	-	-	-	1.0%	0%	-	-
Vomiting	1.0%	0.3%	-	-	-	1.0%	0.3%	-	-
Flatulence	-	-	-	-	-	1.0%	0.3%	-	-
Other									
Asthma	1.6%	0.4%	1.9%	0.4%	-	2.5%	0.6%	1.8%	0.2%
Abnormal ejaculation*	1.6%	0%	2.1%	0%	-	4.9%	0.6%	2.5%	0.5%
Sweating	1.0%	0.3%	-	-	-	1.1%	0%	1.1%	0.2%
Impotence*	-	-	1.5%	0%	-	-	-	-	-
Libido Decreased	-	-	-	-	-	1.0%	0%	-	-

Where numbers are not provided the incidence of the adverse events in patients treated with paroxetine tablets were not >1% or were not greater than or equal to 2 times the incidence of placebo.

* Incidence corrected for gender.

Commonly Observed Adverse Events:

Major Depressive Disorder: The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine tablets at least twice that for placebo, derived from Table 2) were: Asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, nervousness, ejaculatory disturbance, and other male genital disorders.

Obsessive Compulsive Disorder: The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine tablets at least twice that of placebo, derived from Table 3) were: Nausea, dry mouth, decreased appetite, constipation, dizziness, somnolence, tremor, sweating, impotence, and abnormal ejaculation.

Panic Disorder: The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine tablets at least twice that for placebo, derived from Table 3) were: Asthenia, sweating, decreased appetite, libido decreased, tremor, abnormal ejaculation, female genital disorders, and impotence.

Social Anxiety Disorder: The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine tablets at least twice that for placebo, derived from Table 3) were: Sweating, nausea, dry mouth, constipation, decreased appetite, somnolence, tremor, libido decreased, yawn, abnormal ejaculation, female genital disorders, and impotence.

Generalized Anxiety Disorder: The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine tablets at least twice that for placebo, derived from Table 4) were: Asthenia, infection, constipation, decreased appetite, dry mouth, nausea, libido decreased, somnolence, tremor, sweating, and abnormal ejaculation.

Incidence in Controlled Clinical Trials: The prescriber should be aware that the figures in the tables following cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the populations studied.

Major Depressive Disorder: Table 2 enumerates adverse events that occurred at an incidence of 1% or more among paroxetine-treated patients who participated in short-term (6- to 8-week) placebo-controlled trials in which patients were dosed in a range of 20 mg to 50 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

Body System	Preferred Term	Paroxetine Tablets (n = 421)	Placebo (n = 421)
Body as a Whole	Headache	18%	17%
	Asthma	15%	6%
	Pain	3%	1%
	Vasodilation	3%	1%
	Sweating	11%	2%
	Rash	2%	1%
	Nausea	26%	9%
	Dry Mouth	18%	12%
	Constipation	14%	9%
	Diarrhea	12%	2%
	Decreased Appetite	6%	2%
	Flatulence	4%	2%
	Oropharynx Disorder*	2%	0%
	Dyspepsia	2%	0%
	Myopathy	2%	1%
	Myalgia	2%	1%
	Paresthesia	1%	0%
	Headache	1%	0%
	Somnolence	23%	9%
	Dizziness	13%	6%
	Insomnia	13%	6%
	Tremor	8%	2%
	Nervousness	5%	3%
	Anxiety	5%	3%
	Impotence*	3%	0%
	Libido Decreased	3%	0%
	Drugged Feeling	2%	1%
	Confusion	1%	0%
	Yawn	4%	1%
	Blurred Vision	4%	1%
	Taste Perversion	2%	0%
	Ejaculatory Disturbance**	13%	0%
	Other Male Genital Disorders**	10%	0%
	Urinary Frequency	3%	1%
	Urinary Disorder*	3%	0%
	Female Genital Disorders**	2%	0%

* Events reported by at least 1% of patients treated with paroxetine tablets are included, except the following events which had an incidence on placebo >paroxetine tablets: Abdominal pain, agitation, back pain, chest pain, CNS stimulation, fever, increased appetite, myoclonus, pharyngitis, nervousness, respiratory disorder (includes mostly "cold symptoms" or "URI"), trauma, and vomiting.

** Includes mostly "lump in throat" and "tightness in throat."

† Percentage corrected for gender.

‡ Mostly "ejaculatory delay."

§ Includes "anorgasmia," "erectile difficulties," "delayed ejaculation/orgasm," and "sexual dysfunction," and "impotence."

¶ Includes mostly "difficulty with micturition" and "urinary hesitancy."

‡ Includes mostly "anorgasmia" and "difficulty reaching climax/orgasm."

Obsessive Compulsive Disorder, Panic Disorder, and Social Anxiety Disorder: Table 3 enumerates adverse events that occurred at a frequency of 2% or more among OCD patients on paroxetine tablets who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 mg to 60 mg/day or among patients with panic disorder on paroxetine tablets who participated in placebo-controlled trials of 10- to 12-weeks duration in which patients were dosed in a range of 10 mg to 60 mg/day or among patients with social anxiety disorder on paroxetine tablets who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 mg to 50 mg/day.

Body System	Preferred Term	Paroxetine Tablets (n = 542)	Placebo (n = 265)	Panic Disorder Paroxetine Tablets (n = 469)	Placebo (n = 324)	Social Anxiety Disorder Paroxetine Tablets (n = 425)	Placebo (n = 339)
Body as a Whole	Asthma	22%	14%	14%	5%	22%	14%
	Abdominal Pain	4%	3%	4%	3%	-	-
	Chest Pain	3%	2%	3%	2%	-	-
	Back Pain	-	-	2%	2%	-	-
	Chills	2%	1%	2%	1%	3%	1%
	Trauma	-	-	3%	1%	-	-
Cardiovascular	Vasodilation	4%	1%	4%	2%	-	-
	Palpitation	2%	0%	2%	0%	-	-
	Swelling	9%	3%	14%	6%	9%	2%
	Rash	3%	2%	-	-	-	-
	Nausea	23%	10%	23%	17%	25%	7%
	Dry Mouth	18%	12%	18%	11%	9%	3%
	Constipation	16%	6%	12%	5%	5%	2%
	Diarrhea	10%	10%	10%	7%	9%	6%
	Decreased Appetite	9%	3%	7%	3%	8%	2%
	Dyspepsia	-	-	2%	4%	2%	2%
	Flatulence	-	-	-	4%	2%	2%
	Appetite	4%	3%	2%	1%	-	-
	Vomiting	-	-	-	1%	2%	1%
	Myalgia	-	-	-	4%	3%	3%
	Insomnia	24%	13%	18%	10%	21%	16%
	Somnolence	24%	7%	19%	11%	22%	5%
	Dizziness	12%	6%	14%	10%	11%	7%
	Tremor	11%	1%	9%	1%	9%	1%
	Nervousness	9%	8%	9%	1%	8%	7%
	Libido Decreased	7%	4%	8%	1%	12%	1%
	Agitation	-	-	5%	4%	3%	1%
	Anxiety	-	-	5%	4%	5%	4%
	Abnormal Dreams	4%	1%	-	-	-	-
	Concentration Impaired	3%	2%	-	-	4%	1%
	Depersonalization	3%	0%	-	-	-	-
	Myoclonus	3%	0%	3%	2%	2%	1%
	Anorexia	2%	1%	-	-	-	-
Respiratory System	Rhinitis	-	-	3%	0%	-	-
	Pharyngitis	-	-	-	-	4%	2%
	Taste Perversion	2%	0%	-	-	5%	1%
	Abnormal Vision	4%	2%	-	-	4%	1%
	Taste Perversion	2%	0%	-	-	-	-
Special Senses	Abnormal Vision	4%	2%	-	-	4%	1%
	Taste Perversion	2%	0%	-	-	-	-
Urogenital System	Abnormal Ejaculation*	23%	1%	21%	1%	28%	1%
	Dysmenorrhea	-	-	-	-	5%	4%
	Female Genital	3%	0%	9%	1%	9%	1%
	Impotence*	8%	1%	5%	0%	5%	1%
	Urinary Frequency	3%	1%	2%	0%	-	-
	Impaired Urinary Tract Infection	2%	1%	2%	1%	-	-

* Events reported by at least 2% of OCD, panic disorder, and social anxiety disorder in patients treated with paroxetine tablets are included, except the following events which had an incidence on placebo >paroxetine tablets: [OCD] Abdominal pain, agitation, anxiety, back pain, cough increased, depression, headache, hyperkinesia, infection, parosmia, pharyngitis, respiratory disorder, rhinitis, and sinusitis. [panic disorder] Abnormal dreams, abnormal vision, chest pain, cough increased, depersonalization, depression, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, myalgia, nervousness, palpitation, paresthesia, pharyngitis, pharyngitis, pharyngitis, pharyngitis, taste perversion, trauma, urinary tract infection, and vasodilation. [social anxiety disorder] Abdominal pain, depression, headache, infection, respiratory disorder, and sinusitis.

† Percentage corrected for gender.

Generalized Anxiety Disorder: Table 4 enumerates adverse events that occurred at a frequency of 2% or more among GAD patients on paroxetine tablets who participated in placebo-controlled trials of 8-weeks duration in which patients were dosed in a range of 10 mg/day to 50 mg/day.

Body System	Preferred Term	Generalized Anxiety Disorder Paroxetine Tablets (n = 735)	Placebo (n = 529)
Body as a Whole	Asthma	14%	6%
	Headache	17%	14%
	Infection	6%	3%
	Abdominal Pain	1%	-
	Trauma	-	-
	Vasodilation	3%	1%
	Sweating	6%	2%
	Nausea	20%	5%
	Dry Mouth	11%	5%
	Diarrhea	9%	7%
	Decreased Appetite	5%	1%
	Vomiting	3%	2%
	Dyspepsia	11%	8%
	Insomnia	3%	2%
	Somnolence	15%	5%
	Dizziness	6%	5%
	Tremor	5%	1%
	Nervousness	4%	3%
	Libido Decreased	9%	2%
	Abnormal Dreams	4%	3%
Respiratory System	Respiratory Disorder	7%	5%
	Sinusitis	4%	3%
	Yawn	4%	1%
Special Senses	Abnormal Vision	2%	1%
Urogenital System	Abnormal Ejaculation*	25%	2%
	Female Genital Disorder*	4%	1%
	Impotence*	4%	3%

* Events reported by at least 2% of GAD in patients treated with paroxetine tablets are included, except the following events which had an incidence on placebo >paroxetine tablets: [GAD] Abdominal pain, back pain, trauma, dyspepsia, myalgia, and pharyngitis.

† Percentage corrected for gender.

Dose Dependency of Adverse Events: A comparison of adverse event rates in a fixed-dose study comparing 10, 20, 30, and 40 mg/day of paroxetine tablets with placebo in the treatment of major depressive disorder revealed a clear dose dependency for some of the more common adverse events associated with use of paroxetine tablets, as shown in Table 5:

Body System/Preferred Term	Placebo	Paroxetine Tablets			
	10 mg n=102	20 mg n=104	30 mg n=101	40 mg n=102	
Body As A Whole	0.0%	2.9%	10.6%	13.9%	12.7%
Asthma	0.0%	2.9%	10.6%	13.9%	12.7%
Dermatologic	2.0%	1.0%	6.7%	8.9%	11.8%
Gastrointestinal	5.9%	4.9%	7.7%	9.9%	12.7%
Constipation	2.0%	2.0%	5.8%	4.0%	4.9%
Decreased Appetite	2.0%	2.0%	5.8%	4.0%	4.9%
Diarrhea	7.8%	7.8%	19.2%	7.9%	14.7%
Dry Mouth	2.0%	10.8%	18.3%	15.8%	20.6%
Nausea	13.7%	14.7%	26.9%	34.7%	36.3%
Nervous System	0.0%	2.0%	5.8%	5.9%	5.9%
Anxiety	3.9%	6.9%	6.7%	8.9%	12.7%
Dizziness	0.0%	5.9%	5.8%	4.0%	2.9%
Nervousness	0.0%	2.9%	1.0%	5.0%	5.9%
Paresthesia	7.8%	12.7%	18.3%	20.8%	21.6%
Somnolence	2.0%	0.0%	7.7%	7.9%	14.7%
Special Senses	0.0%	2.9%	2.9%	2.0%	7.8%
Blurred Vision	0.0%	2.9%	2.9%	2.0%	7.8%
Urogenital System	0.0%	5.8%	10.6%	10.6%	13.0%
Abnormal Ejaculation	0.0%	5.8%	10.6%	10.6%	13.0%
Impotence	0.0%	1.9%	4.2%	6.4%	1.9%
Male Genital Disorders	0.0%	3.8%	8.7%	6.4%	3.7%

† Rule for including adverse events in table: Incidence at least 5% for 1 of paroxetine groups and >twice the placebo incidence for at least 1 paroxetine group.

In a fixed-dose study comparing placebo and 20, 40, and 60 mg of paroxetine tablets in the treatment of OCD, there was no clear relationship between adverse events and the dose of paroxetine tablets to which patients were assigned. No new adverse events were observed in the group treated with 60 mg of paroxetine tablets compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and 10, 20, and 40 mg of paroxetine tablets in the treatment of panic disorder, there was no clear relationship between adverse events and the dose of paroxetine tablets to which patients were assigned, except for asthma, dry mouth, anxiety, libido decreased, tremor, and abnormal ejaculation. In flexible-dose studies, no new adverse events were observed in patients receiving 60 mg of paroxetine tablets compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and 10, 20, and 40 mg of paroxetine tablets in the treatment of social anxiety disorder, for most of the adverse events, there was no clear relationship between adverse events and the dose of paroxetine tablets to which patients were assigned.

In a fixed-dose study comparing placebo and 20 and 40 mg of paroxetine tablets in the treatment of generalized anxiety disorder, for most of the adverse events, there was no clear relationship between adverse events and the dose of paroxetine tablets to which patients were assigned, except for the following adverse events: Asthenia, constipation, and abnormal ejaculation.

Adaptation to Certain Adverse Events: Over a 4- to 6-week period, there was evidence of adaptation to some adverse events with continued therapy (e.g., nausea and dizziness).

† Incidence of adverse events in patients treated with paroxetine tablets was similar to that in patients treated with placebo.

Male and Female Sexual Dysfunction with SSRIs: Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, for in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experiences and performance are likely to underestimate their actual incidence.

In placebo-controlled clinical trials involving more than 3,200 patients, the ranges for the reported incidence of sexual side effects in males and females with major depressive disorder, OCD, panic disorder, social anxiety disorder, and GAD are displayed in Table 6.

Incidence of Sexual Adverse Events in Controlled Clinical Trials	Paroxetine Tablets	Placebo
n (males)	1446	1042
Decreased Libido	6-15%	0-5%
Ejaculatory Disturbance	2-9%	0-2%
Impotence	2-9%	0-3%
n (females)	1822	1340
Decreased Libido	0-9%	0-2%
Organic Disturbance	2-9%	0-1%

There are no adequate and well-controlled studies examining sexual dysfunction with paroxetine treatment. Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Weight and Vital Sign Changes: Significant weight loss may be an undesirable result of treatment with paroxetine tablets for some patients but, on average, patients in controlled trials had little or no weight loss versus smaller changes on placebo and active control. No significant changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were observed in patients treated with paroxetine tablets in controlled clinical trials.

ECG Changes: In an analysis of ECGs obtained in 682 patients treated with paroxetine tablets and 415 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

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