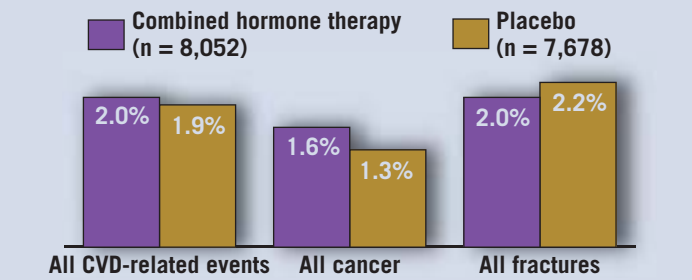


### Annualized Rates of Adverse Events During Postintervention Phase of Women's Health Initiative



Notes: Based on a mean 2.4-year follow-up of 50- to 79-year-old women after a mean 5.6-year intervention period. CVD is cardiovascular disease. Source: JAMA

# Health Risks Shifted After WHI Patients Stopped Hormone Therapy

BY MARY ANN MOON  
Contributing Writer

In the 3 years after the Women's Health Initiative clinical trial was halted early, risks and benefits related to hormone therapy changed rapidly in those who stopped taking the medication, ac-

ording to WHI investigators. Despite these alterations, the overall assessment of health risks and benefits associated with combined HT (conjugated equine estrogens plus medroxyprogesterone acetate) "continues to be weighted toward risk," said Dr. Gerardo Heiss of the

University of North Carolina, Chapel Hill, and his WHI associates.

But representatives of Wyeth Pharmaceuticals, manufacturer of Prempro, the combination HT product used in the study, said during a company-sponsored teleconference that the study does not reflect the current, lower HT dosages doctors recommend for typical HT users, who are younger, newly menopausal women.

Dr. Gary Stiles, executive vice president and chief medical officer for Wyeth, said the findings were an "ad hoc analysis without providing the full context." He noted that today's patients were "more than a decade" younger than the WHI participants, who had a mean age of 63 years at baseline. The company encourages doctors to provide lower dosages of HT drugs for the shortest time possible, he added.

The portion of the WHI trial that dealt with combined hormone therapy (HT) was stopped in 2002 at a mean of 5.6 years of follow-up because an interim analysis showed the therapy increased the risk of invasive breast cancer and failed to yield any overall health benefit. Analysis of the results accumulated to that date showed those who took HT (0.625 mg of conjugated equine estrogens and 2.5 mg of medroxyprogesterone acetate daily) for menopausal symptoms also had higher risks of cardiovascular disease, coronary heart disease, stroke, and venous thromboembolism, along with lower risks of fracture and of colorectal cancer, compared with those not on HT.

Most of the subjects were followed through the planned 8-year duration of the WHI. Results are now available on 15,730 of these women for a further 2.4 years of follow-up after discontinuation. (See box.)

The increased risk of cardiovascular disease-related events noted in the interim analysis did not persist after stopping HT, and the risk of deep vein thrombosis and pulmonary embolism also "disappeared."

But the risk of all malignancies increased, probably due to a rise in the rate of cancers other than breast and colorectal, primarily lung cancers.

The increased risk of breast cancer noted at the interim analysis did not persist after discontinuing HT, but neither did the decreased risk of colorectal cancer.

HT's protective effect against fractures also dissipated after discontinuation. Women who had taken and then stopped HT showed the same risk of hip, vertebral, and other fractures as did those who had taken placebo.

During the intervention phase of the WHI, all-cause mortality was virtually identical between subjects taking HT and those taking placebo. But in the postintervention phase, mortality was 15% higher in women who had taken and then discontinued HT.

Although this difference did not reach statistical significance because of the small number of deaths, it suggests that all-cause mortality increased after HT, the researchers said (JAMA 2008;299:1036-45).

Associate editor Lorinda Bullock contributed to this article.

## OXYCONTIN® (OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

10 mg | 15 mg | 20 mg | 30 mg | 40 mg  
60 mg\* | 80 mg\* | 160 mg\*

\*60 mg, 80 mg, and 160 mg for use in opioid-tolerant patients only

BRIEF SUMMARY OF PRESCRIBING INFORMATION (For complete prescribing information please see package insert.)

**WARNING:** OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

OxyContin can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain on a continuous, around-the-clock analgesic is needed for an extended period of time. OxyContin Tablets are NOT intended for use as a prn analgesic.

OxyContin 60 mg, 80 mg, and 160 mg Tablets, or a single dose greater than 40 mg, ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. A single dose greater than 40 mg, or total daily doses greater than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids.

OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

#### INDICATIONS AND USAGE

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain on a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin is NOT intended for use as a prn analgesic. Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Quality (formerly known as the Agency for HealthCare Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.

OxyContin is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

#### CONTRAINDICATIONS

OxyContin is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyContin is contraindicated in any patient who has or is suspected of having paralytic ileus.

#### WARNINGS

OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

OxyContin 60 mg, 80 mg, and 160 mg Tablets, or a single dose greater than 40 mg, ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. A single dose greater than 40 mg, or total daily doses greater than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids.

Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. Misuse, Abuse and Diversion of Opioids

OxyContin is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. OxyContin can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin has been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see WARNINGS and DRUG ABUSE AND ADDICTION).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

#### Interactions with Alcohol and Drugs of Abuse

OxyContin may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

#### DRUG ABUSE AND ADDICTION

OxyContin contains oxycodone, which is a full mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. There is a potential for drug addiction to develop following exposure to opioids, including oxycodone. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

"Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin, like other opioids, has been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs. OxyContin consists of a dual-polymer matrix, intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parental abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

#### Respiratory Depression

Respiratory depression is the chief hazard from oxycodone, the active ingredient in OxyContin, as with all opioid agonists. Respiratory depression is a particular problem in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

#### Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

#### Hypotensive Effect

OxyContin may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

#### PRECAUTIONS

##### General

Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Use of OxyContin is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenergic insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; hyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

##### Interactions with other CNS Depressants

OxyContin should be used with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol. Intoxicative effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of OxyContin.

##### Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

##### Ambulatory Surgery and Postoperative Use

OxyContin is not indicated for pre-emptive analgesia (administration pre-operatively for the management of postoperative pain). OxyContin is not indicated for pain in the immediate postoperative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its activity in this setting has not been established.

OxyContin is not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time. OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines).

Patients who are already receiving OxyContin Tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention (see DOSAGE AND ADMINISTRATION).

OxyContin and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common postoperative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in postoperative patients receiving opioids. Standard supportive therapy should be implemented.

##### Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

##### Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see DOSAGE AND ADMINISTRATION: Cessation of Therapy). Information for Patients/Caregivers

If clinically advisable, patients receiving OxyContin Tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be aware that OxyContin Tablets contain oxycodone, which is a morphine-like substance.
2. Patients should be advised that OxyContin Tablets were designed to work properly only if swallowed whole. OxyContin Tablets will release all their contents at once if broken, chewed, or crushed, resulting in a risk of fatal overdose.
3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
4. Patients should be advised not to adjust the dose of OxyContin™ without consulting the prescribing professional.
5. Patients should be advised that OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
6. Patients should not combine OxyContin with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
8. Patients should be advised that OxyContin is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
9. Patients should be advised that they may pass empty matrix "ghosts" (tablets) via colostomy or in the stool, and that this is of no concern since the active medication has already been absorbed.
10. Patients should be advised that if they have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
11. Patients should be instructed to keep OxyContin in a secure place away from the reach of children. When OxyContin is no longer needed, the unused tablets should be destroyed by flushing down the toilet.

##### Use in Drug and Alcohol Addiction

OxyContin is an opioid with no approved use in the management of addictive disorders. Its proper use in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia.

##### Drug-Drug Interactions

Opioid analgesics, including OxyContin™, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce respiratory depression.

Oxycodone is metabolized in part by cytochrome P450 2D6 and cytochrome P450 3A4 and in theory can be affected by other drugs.

Oxycodone is metabolized in part to oxycodone by cytochrome P450 2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polyicyclic antidepressants), such blockade has not yet been shown to be of clinical significance with this drug. Clinicians should be aware of this possible interaction, however.

##### Use with CNS Depressants

OxyContin, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

##### Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of oxycodone to evaluate its carcinogenic potential have not been conducted. Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5000 µg; chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 µg/mL and with activation 48 hours after exposure at doses of up to 5000 µg/mL, and in the in vivo bone marrow micronucleus test in mice (at plasma levels of up to 48 µg/mL). Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 µg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay (at doses of up to 50 µg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activation).

##### Pregnancy

Teratogenic Effects - Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg and 125 mg/kg, respectively. These doses are 3 and 46 times a human dose of 160 mg/day, based on mg/kg basis. The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

##### Labor and Delivery

OxyContin is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn. Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

##### Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving OxyContin because of the possibility of sedation and/or respiratory depression in the infant.

##### Pediatric Use

Safety and effectiveness of OxyContin have not been established in pediatric patients below the age of 18.

It must be remembered that OxyContin Tablets cannot be crushed or divided for administration.

##### Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% (see PHARMACOKINETICS AND METABOLISM). Of the number of subjects (445) in clinical studies of OxyContin, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen in the elderly patients who received OxyContin. Thus, the usual doses and dosing intervals are appropriate for these patients. As with all opioids, the starting dose should be reduced to 1/3 to 1/2 of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

##### Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

##### Hepatic Impairment

A study of OxyContin in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at 1/3 to 1/2 the usual doses and careful dose titration is warranted.

##### Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

##### Gender Differences

In pharmacokinetic studies, opioid-naïve females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic use at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

##### ADVERSE REACTIONS

The safety of OxyContin™ was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received OxyContin in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Serious adverse reactions which may be associated with OxyContin Tablet therapy in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension, or shock (see OVERDOSAGE).

The non-serious adverse events seen on initiation of therapy with OxyContin are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as OxyContin therapy is continued and some degree of tolerance is developed.

Clinical trials comparing OxyContin with immediate-release oxycodone and placebo revealed a similar adverse event profile for OxyContin and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were:

	OxyContin (n=227)	Immediate-Release (n=225)	Placebo (n=45)
Constipation	(2%)	(26)	(7)
Nausea	(23)	(27)	(11)
Somnolence	(23)	(24)	(4)
Dizziness	(13)	(16)	(9)
Pruritus	(13)	(12)	(2)
Vomiting	(12)	(14)	(7)
Headache	(7)	(8)	(7)
Dry Mouth	(6)	(7)	(2)
Asthenia	(6)	(7)	—
Sweating	(5)	(6)	(2)

The following adverse experiences were reported in OxyContin™-treated patients with an incidence between 1% and 5%. In descending order of frequency they were: anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, hiccups, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in postmarketing experience:

- Blood and lymphatic system disorders:** lymphadenopathy
- Cardiac disorders:** palpitations (in the context of withdrawal)
- Ear and labyrinth disorders:** tinnitus
- Endocrine disorders:** syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- Eye disorders:** abnormal vision
- Gastrointestinal disorders:** dysphagia, eructation, flatulence, gastrointestinal disorder, ileus, increased appetite, stomatitis
- General disorders and administration site conditions:** chest pain, edema, facial edema, malaise, pain, peripheral edema, thirst, withdrawal syndrome (with and without seizures)
- Immune system disorders:** anaphylactic or anaphylactoid reaction (symptoms of)
- Infections and infestations:** pharyngitis
- Injury, poisoning and procedural complications:** accidental injury
- Investigations:** hyponatremia, increased hepatic enzymes, ST depression
- Metabolism and nutrition disorders:** dehydration
- Musculoskeletal and connective tissue disorders:** neck pain
- Nervous system disorders:** abnormal gait, amnesia, hyperkinesia, hypertonia (muscular), hyposthesia, hypotonia, migraine, paresthesia, seizures, speech disorder, stupor, syncope, taste perversion, tremor, vertigo
- Psychiatric disorders:** agitation, depersonalization, depression, emotional lability, hallucination
- Renal and urinary disorders:** dysuria, hematuria, polyuria, urinary retention, urination impaired
- Reproductive system and breast disorders:** amenorrhea, decreased libido, impotence
- Respiratory, thoracic and mediastinal disorders:** cough increased, voice altered
- Skin and subcutaneous tissue disorders:** dry skin, exfoliative dermatitis, urticaria
- Vascular disorders:** vasodilation

##### OVERDOSAGE

Acute overdose with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

Deaths due to overdose have been reported with abuse and misuse of OxyContin™, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when OxyContin is abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of oxycodone overdose, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to ox