

## Incidence of Drug Interactions

While overdose with the use of buprenorphine alone is uncommon, caution is advised in its concomitant use with CNS depressants, sedatives, and hypnotics, especially benzodiazepines and alcohol, due to the potential additive effects on CNS depression.<sup>14</sup>

When taken alone, there is less risk of fatal respiratory depression with SUBOXONE than full-opioid agonists, because of the “ceiling effect” achieved with buprenorphine. However, when buprenorphine is used in combination with other CNS medications, the benefit of the ceiling effect may be overridden and the patient may be at greater risk for respiratory depression.

As evidenced in a study conducted with rats, the “ceiling effect” of buprenorphine was not evident when buprenorphine was combined with high doses (20 mg/kg) of diazepam.<sup>15</sup> This combination altered the usual effect of buprenorphine on respiratory depression, making it appear similar to the effect of a full opioid agonist. Although the combination of buprenorphine and benzodiazepines is not contraindicated, SUBOXONE and SUBUTEX should be prescribed with caution to patients taking benzodiazepines or other drugs that act on the central nervous system, regardless of whether these medications are prescribed by a physician or taken as drugs of abuse. When these medication are taken together, consider reducing the dose of one or both. Clinical observation of patients should be especially vigilant when considering this combination of medications.

This is of even greater concern when CNS drugs are used at higher than prescribed doses or administered parenterally. One clinical study showed the interaction between buprenorphine and benzodiazepines was likely based on a pharmacodynamic and not a pharmacokinetic mechanism.<sup>16</sup>

SUBOXONE overdose can cause pinpoint pupils, sedation, hypotension, respiratory depression and death.

In a situation where a patient taking buprenorphine has overdosed and is unconscious, the primary management should be the reestablishment of adequate ventilation with mechanical assistance of respiration, if required. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Recent data suggest that an initial naloxone bolus dose of 3 mg/70 kg, followed by 4 mg/70 kg/h over 90-minutes’ infusion, is needed to maintain persistent reversal of buprenorphine-induced respiratory depression. If an infusion is not possible, repeat bolus dose as needed.<sup>17</sup>

SUBOXONE has potential for abuse and produces dependence of the opioid type, with a milder withdrawal syndrome than full agonists. Caution: Federal law prohibits the use of this drug by any person other than the patient for whom it was prescribed.

Cytolytic hepatitis and hepatitis with jaundice have been observed in the addicted population receiving buprenorphine.

There are no adequate and well-controlled studies of SUBOXONE (a Category C medication) in pregnancy.

Caution should be exercised when driving cars or operating machinery.

Always store buprenorphine-containing medications safely and out of the reach and sight of children. Destroy any unused medication appropriately.

The most commonly reported adverse events with SUBOXONE include: headache (36%, placebo 22%), withdrawal syndrome (25%, placebo 37%), pain (22%, placebo 19%), insomnia (14%, placebo 16%), nausea (15%, placebo 11%), and constipation (12%, placebo 3%). Please see full Prescribing Information for a complete list.

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# MEDICAL ADVISORY & BEST-PRACTICES UPDATE

## Managing Unintentional Pediatric Exposures

Prescription buprenorphine use in treatment of opioid dependence is increasing. Although the depressive respiratory effects of buprenorphine are less than that of full opioid agonists (the “ceiling” effect), there must be continued vigilance and awareness around the risk of pediatric exposure.

The incidence of unintentional buprenorphine exposure in children  $\leq 6$  years of age is 7.5 per 1,000 unique recipients of drug dispensed, according to the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) system. Richard C. Dart, MD, PhD, Executive Director of the RADARS system stresses that “many people do not realize that prescription opioids inadvertently end up in the hands of children.”<sup>1</sup>

One retrospective review, from November 2002 to December 2005, showed that in children  $< 6$  years old, unintentional buprenorphine ingestions are generally well tolerated, with respiratory depression and significant CNS depression occurring in only 7% of patients.<sup>2</sup>

Of the 86 cases reviewed, 37% of children remained asymptomatic, and 56% had a minor effect (agitation, drowsiness, vomiting, and/or miosis without respiratory or CNS depression). Children  $< 2$  years of age were more likely to experience clinical effects ( $P=.028$ ). No child ingesting  $< 4$  mg of buprenorphine experienced a severe effect. Similarly, all of the children who ingested  $> 4$  mg experienced some effect.<sup>2</sup>

Although these data attest to the safety profile of buprenorphine, everyone—including the patient, physician, the manufacturer, and regulators—must work to minimize unintentional exposures. The best deterrents are patient education and safe storage and disposal of medication.

If pediatric exposure to SUBOXONE or SUBUTEX\* is suspected, determine the amount ingested. Children ingesting  $< 4$  mg of buprenorphine are not likely to have a severe effect. However, prudent precautionary measures include monitoring in an emergency department setting for a minimum of 6 hours, especially in the following cases: children  $< 2$  years of age;  $> 2$  mg was confirmed ingested; or if the dose cannot be determined with certainty.<sup>2</sup>

If respiratory depression occurs, one protocol recommends that naloxone be administered intravenously, at the initial dose of 0.1 mg/kg, and then repeated every 2 minutes until reversal is achieved.<sup>3</sup> (A separate protocol for adults is defined on Page 4.)

## SUBOXONE: Optimizing Dosage

Correct dosing is pivotal to the success of your patients’ treatment.

- Dosing that is too low can result in cravings and withdrawal symptoms, which may cause your patient to drop out of treatment and/or use additional opioids or other drugs (eg, Benzodiazepines)
- Dosing that is too high can lead to overmedication or the potential for diversion

Overmedication may occur with inappropriately high doses of SUBOXONE (particularly in the presence of other CNS depressant medications). Higher doses may increase the incidence of adverse effects such as respiratory depression, sedation, and nausea/vomiting.

\*SUBOXONE (buprenorphine HCl/naloxone HCl dihydrate) (CIII)/SUBUTEX (buprenorphine HCl) (CIII) sublingual tablets.

**Children can be safeguarded from unintentional exposure if medication is stored and disposed of properly. Physicians and their staff can play a key part by educating patients. Some helpful tips:**

- Adults should not take medications in front of children, who may want to imitate
- Medication should be kept in child-resistant containers and caps should be replaced securely after use
- Medication should be kept out of the reach and sight of children
- Medication should not be discarded in wastebaskets that are accessible at a child’s height
- Medication should never be referred to as “candy” to a child

### Tips for immediate disposal of expired or unused medications<sup>4</sup>:

- Take medications out of their original containers
  - Mix them with an undesirable substance such as coffee grounds or cat litter, so they are not diverted after disposal
- OR
- Return medications to community pharmaceutical take-back programs for proper disposal

Safety data in the United States are limited to doses ≤24 mg daily. Results of clinical studies generally indicate there is little clinical advantage in using doses higher than those within this dose range.<sup>5,6</sup>

There is considerable evidence to suggest that the generally effective daily SUBOXONE dosage is approximately 16 mg/day. This dosage may vary; however, few patients require dosages higher than 24 mg/day.<sup>5,6</sup>

## Periodic Patient Evaluation

Patients should be seen at reasonable intervals (at least weekly during initial treatment) based upon the individual circumstance of the patient. Periodic assessment is necessary to determine compliance with the dosing regimen, effectiveness of treatment plan, and ability of the patient to handle the prescribed medication. Once a stable dose is achieved and toxicological tests are free of illicit drugs, less frequent office visits may be initiated. A monthly schedule may be reasonable for patients on a stable dose of the prescribed medication(s) who are making progress toward treatment objectives.<sup>7</sup>

Continuation or modification of opioid therapy should depend on the physician’s evaluation of progress toward stated treatment objectives such as<sup>7</sup>

- Absence of toxicity
- Absence of medical or behavioral adverse effects
- Responsible handling of medications
- Compliance with all elements of the treatment plan (including recovery-oriented activities, psychotherapy and/or other psychosocial modalities)
- Abstinence from illicit drug use

If reasonable treatment goals are not being achieved, the physician should re-evaluate the appropriateness of continued treatment.<sup>7</sup>

Dose monitoring in line with current, evidence-based data should not only produce the desired clinical outcome but also prevent patients from having more medication than necessary. Because of the limited physiological withdrawal, slow dissociation from the mu-opioid receptor and long plasma half-life of buprenorphine, in some circumstances, having a higher than necessary total daily dose will result in the patient having excess medication.

Excess medication may tempt an individual to become “entrepreneurial” for the purposes of generating additional income or seeking to “provide treatment” to others who can not access or afford treatment. While the latter may be well-intended, any transfer of a controlled substance to another person is illegal.

### ■ High Receptor Occupancy Supports Dosing Within the Suggested Range

At low doses (2 mg), mu-opioid receptor occupancy is approximately 41%. At 8-mg,\* 16-mg, and 32-mg doses, receptor occupancy increases to 83%, 92%, and 98%, respectively.<sup>6,8</sup> In a study by Greenwald et al, it was shown that opioid receptor availability between 16 mg and 32 mg did not significantly change; however, following the 32-mg dose, area under the curve

\*Note: 8-mg data are derived from Comer et al,<sup>8</sup> in which the combination product of SUBOXONE (8 mg/2 mg) was used.

### The “STOP—THINK” TRAFFIC LIGHT Analogy for Maintenance Dosing

*Following successful induction, the goal should be to stabilize the patient with a clinically effective (ie, maintenance) dose of SUBOXONE. “The dosage should be progressively adjusted in increments/decrements of 2 mg or 4 mg to a level that maintains the patient in treatment and suppresses opioid withdrawal effects.”<sup>9</sup>*

#### ● 4 mg–16 mg (Expected)

*The recommended target dose of SUBOXONE is 16 mg/day. Clinical studies have shown that this is a clinically effective dose. Although doses as low as 12 mg may be effective in some patients,<sup>9</sup> for most patients, a 16-mg dose should alleviate withdrawal symptoms and block the effects of other opioid agonists for at least 24 hours.*

#### ● 16 mg–24 mg (Think)

*The upper limit of the recommended daily dosage of buprenorphine in the United States is 24 mg. The reported lack of significant increase in brain mu-receptor occupancy between doses of 16 mg and 32 mg would infer that there should be little difference in occupancy at doses between 16 mg and 24 mg in most patients. When a patient expresses a need for a higher dose, consider the possible causes (eg, environmental stressors or psychosocial issues that increase cravings): Is there any possibility that drug interactions are affecting buprenorphine metabolism? What are the specific complaints about the dosage? Are the buprenorphine effects wearing off throughout the day? If so, use clinical judgment to guide dosing intervals. Before increasing the patient’s dose, explore other alternatives.*

#### ● >24 mg (Stop and Reassess)

*Currently available data on doses greater than 24 mg show no significant advantages (ie, blockade, cravings, or suppression of withdrawal) compared to the 16-mg dose.<sup>6,8</sup> (See section on Considerations for Dosing Above the Suggested Range.)*

**Current practice-based evidence indicates that a patient requiring daily dosages of 24 mg or greater should be the exception.**

(AUC) plasma levels increased with each dose and resulted in a longer duration of action.<sup>6</sup> This longer duration of action may allow patients to skip a dose and thereby have excess buprenorphine to sell or give away.

### ■ Considerations for Dosing Above the Suggested Range

Well-controlled studies establishing the safety and efficacy of SUBOXONE/SUBUTEX doses above the suggested range are lacking. There have been 53 deaths reported to Reckitt Benckiser in the United States in patients who received SUBOXONE/SUBUTEX between January 2003 (when SUBOXONE became commercially available) and December 31, 2007.<sup>10</sup> In a majority of cases, concomitant medications, including those with CNS or respiratory depressant activity (eg, benzodiazepines, alcohol, barbiturates, SSRIs), were also ingested. In some cases, the presence of heroin, cocaine, and other drugs of abuse were noted in the medical examiners’ reports. Four cases (2 miscarriages, 1 heart attack, 1 suicide) involved SUBOXONE/SUBUTEX alone; however, buprenorphine was not considered causal in any of these cases. For some patients, SUBOXONE/SUBUTEX was prescribed off-label (eg, for pain treatment), and significant medical and/or psychiatric comorbidity (eg, posttraumatic stress disorder, depression, and/or anxiety) was also present.

## The Importance of Counseling

Psychosocial counseling is an essential component of treatment for opioid dependence.

Because it is such a crucial element, the Drug Addiction Treatment Act of 2000 requires that physicians seeking to obtain the certification to prescribe SUBOXONE must be able to provide or refer patients for counseling.<sup>11</sup>

Combination therapy that integrates pharmacotherapy and psychotherapy is proven to enhance patient success. Counseling has been shown to increase retention rates and lower the occurrence of relapse.<sup>12</sup> Higher retention rates have demonstrated significant improvements in<sup>13</sup>:

- Reducing illicit drug use (excluding alcohol)
- Reducing injection drug use-related risk
- Maintaining employment
- Maintaining personal relationships

To treat patients most effectively, it is important to remember that the chance of relapse can be higher with short-term medical withdrawal (ie, detoxification) treatment because patients have less time to learn the skills necessary to maintain an opioid-free lifestyle.

- Pharmacotherapy is only 1 aspect of treatment
- Inclusion of psychosocial counseling greatly improves the likelihood of successful treatment outcome
- Each patient’s needs are unique

By incorporating psychotherapy along with SUBOXONE treatment, the specific behavioral and physical needs of each patient can be addressed.

The counselor partners with the physician in monitoring patient adherence and finding the appropriate dosage based on patient compliance and symptomatology. Such monitoring is also a crucial safeguard against diversion of the medication (see following section, “Safety Concerns”).

As supplement to services typically provided by the physician, counselors can integrate motivational enhancement therapy, cognitive behavioral therapy, prevention education, and intervention in case of relapse.<sup>11</sup>

## Safety Concerns: Misuse and Diversion

It is well-known that a portion of the population is vulnerable to dependence when exposed to opioids on a chronic basis. A minority of this segment of the population will go on to exhibit addictive behaviors that will result in health and social problems: **These are the patients for whom SUBOXONE is indicated.** While SUBOXONE is an appropriate treatment for many, it is incumbent on the patient, physician, clinical support staff, manufacturers, and regulators to take great care to limit the diversion and misuse of the medication.

Despite the favorable safety profile of buprenorphine, SUBOXONE has potential for abuse and produces dependence of the opioid type.

However, safety and diversion concerns should be balanced against the therapeutic benefit that buprenorphine brings to opioid-dependent patients who take their medication appropriately and as prescribed.

When monitoring patients taking SUBOXONE, certain behaviors may indicate misuse and diversion. These behaviors include:

- Requests for early refills
- Lost or misplaced prescriptions
- Dose escalation
- Requests to change from SUBOXONE to SUBUTEX
- Alternative route of administration
- Obtaining medication from others

Also, signs of reluctance to cooperate with the treatment plan, including missed appointments or refusal to participate in counseling, may indicate that the patient is misusing or diverting prescriptions. Urine testing may be useful to identify noncompliance and concurrent drug use.

To guard against diversion, there are certain actions that can be taken:

- Performing random tablet counts
- Protection of prescription pad
- Limiting quantities and refills prescribed
- Utilization of State Prescription Monitoring Programs

Another option may be to work with a caretaker or a counselor to verify and manage medication (see previous section, “The Importance of Counseling”).