AN INDEPENDENT SUPPLEMENT BY MEDIAPLANET TO THE MIAMI HERALD

No.1/September 2011

MEDIA PLANET

ADDICTION RECOVERY

3 TIPS FOR OVERCOMING ADDICTION

COMBATING A CHRONIC DISEASE

Pharmacist Jake Nichols, comes forward to discuss his firsthand experience with prescription drug abuse and how he came out on the other side

PHOTO: VANESSA PHOTOGRAPHY, BOSTON, MA

Supporting a loved one
What you can do provide positive reinforcement

Consequences of addiction
The hard truth about how addiction can affect your life long-term

Medical advancements
The latest developments in treating the disease

CHALLENGES

TIPS 1 EARLY INTERVENTION IS ESSENTIAL

Not all addictions look alike, and similarly, there is not a one-size-fits-all treatment option to cure this chronic disease.

The full scope of addiction

Addiction is a brain disease which results from drug or alcohol use. No one who comes into our University of Florida treatment programs (floridarecoverycenters.com) ever says they took prescription medications or smoked or started taking drugs with the idea that they would become addicted. They can usually tell you when they started, but not when they lost control and became addicted. Addiction, or continued compulsive use of a drug despite numerous, obvious, harmful consequences, is generally a chronic and relapsing disease without a specific cure.

Prevention is the single most effective "treatment" but often ignored or misunderstood. Telling someone who has a mother or father who suffered from the disease of addiction to not smoke or drink, is prevention. Helping pregnant women and mothers avoid drugs, smoking, and alcohol is prevention. Similarly, it is important to understand that use often becomes abuse, which often becomes addiction seamlessly and without warning. Our repeated experience with one drug epidemic after another should encourage us to consider that all drugs of abuse, including prescription medications, are dangerous until proven safe and effective. Early intervention and prevention are essential to recovery and to survival. Furthermore, focusing on prevention and intervention goes a long way toward fighting the stigma and denial associated with the disease.

Scientific advancements

Basic science has helped us understand more precisely how and where drugs of abuse act or work in the brain. Scans now allow us to see where the drugs meet the brain in real time. Science has also helped us understand dependence and withdrawal. But while now commonplace, successful treatments for withdrawal have not cured addicts or addiction.

If detoxification was a cure for addiction, we would have cured alcoholism decades ago. Scientists have even come to understand that withdrawal is not necessary for addiction to occur and that elimination of withdrawal, while a first step, is not recovery. We understand where, in the brain, drugs "hijack" the user and distort the perceived importance of the user's family, friends, health, motivation and relationships. But, we cannot seem to figure out when the switch goes off and addiction occurs.

Risk factors

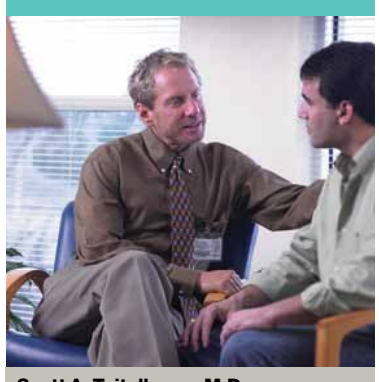
Not all people have the same risks. Some risks are genetic and others environmental. Some are related to psychiatric illnesses or trauma and others to intrauterine or second- and third-hand exposure early in life. Some are related to pain. Drugs harm the abuser but also those who happen to be driving nearby or even riding a bicycle or walking. We all know about DUIs and driving under the influence of alcohol, but are learning about driving and illicit drugs causing accidents and emergencies for the users and innocent bystanders. Addiction, untreated, is often fatal.

Medical progress and treatment works but cannot ensure success without the user working the program. Unlike strep throat or other infectious diseases, we do not have a medicine or medicines that can be given, even against the person's will, and cure the disease. In addiction treatment, there is nothing more critical or important in the long run, than motivation to change. It takes years for drugs to change the person, so we should not be surprised if it takes years for them to return back to their old self.

Craving for cocaine or other drugs is an acquired, new drive in users. Treatment can help separate craving from use. Our work with impaired health professionals has helped us understand that treatment and recovery are difficult, involve time, energy and work and the best outcomes are found when the treatment can be given for years. In impaired physicians, nationwide, treatment works and it is expected that over 80 percent of the treated physicians can be drug-free and back to work.

Mark S. Gold, M.D.
University of Florida Distinguished Professor and Chairman of the Department of Psychiatry, Gainesville, Florida

"Basic science has helped us understand more precisely how and where drugs of abuse act or work in the brain."



Scott A. Teitelbaum, M.D.
Director, University of Florida College of Medicine's Florida Recovery Center, Gainesville, FL, President, Florida Society of Addiction Medicine

"In addiction treatment, there is nothing more critical or important in the long run, than motivation to change."

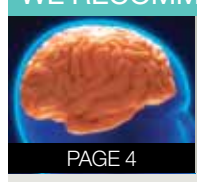
How you can support

So, if you know someone using drugs, suggest that they stop and go to a meeting. Suggest that we do not know who can use and stop and who will progress to addiction. It took nearly 500 years from when Christopher Columbus brought tobacco smoking to our shores to recognize that tobacco caused addiction, cancer, heart disease and so on. It took even longer to realize the second and third-hand effects on the rest of us. Now, in examining the effects of tobacco and other drugs on the unborn, we see that early exposure can change risk of abuse and dependence. Some of us may be born with a high risk of alcohol or drug abuse, but some of the risk may not be due to genes per se but rather exposure changing gene expression. We are, in essence, making drug craving, liking and wanting more common and not providing equally compelling alternatives like healthy eating, exercise, prayer, sports, music and helping others.

Everyone knows someone who has been in addiction treatment and for whom recovery has worked. Unfortunately, recovery is personal and is anonymous. So it is up to all of us to prevent, de-stigmatize, and intervene. Help someone find the strength to quit, go to an AA meeting, find treatment and recovery.

MARK S. GOLD, M.D.
SCOTT A. TEITELBAUM, M.D.
editorial@mediaplanet.com

WE RECOMMEND



PAGE 4

James C. Burman, M.D.
Comparing an addiction to other common diseases

"As we truly medicalize the disease of addiction, we continually recognize the need to tailor treatment to the individual."

A real-life account p. 3
How a pharmacist overcame his addiction to prescription drugs.

MEDIA PLANET

ADDICTION RECOVERY, FIRST EDITION, SEPTEMBER 2011

Publisher: Anthony Chiaravallo
anthony.chiaravallo@mediaplanet.com
Business Developer: Mandy Wilczynski
mandy.wilczynski@mediaplanet.com
Designer: Ariela Anelli
ariela.anelli@mediaplanet.com
Managing Director: Eric Alexander
eric.alexander @mediaplanet.com
Editorial Manager: Luciana Colapinto
luciana.colapinto@mediaplanet.com

Contributors: James C. Berman, M.D., Mark S. Gold, M.D., B. Doublas Hoey, PD, Jake Nichols, Bernardo Savariego, M.D., Scott A. Teitelbaum, M.D., Cynthia Moreno Tuohy

Distributed within:
Miami Herald, September 2011
This section was created by Mediaplanet and did not involve the Miami Herald or its Editorial Departments.

FOLLOW US ON FACEBOOK & TWITTER!
facebook.com/MediaplanetUSA
twitter.com/MediaplanetUSA

Mediaplanet's business is to create new customers for our advertisers by providing readers with high-quality editorial content that motivates them to act.

Addressing a public health crisis

Board certified by the American Board of Psychiatry and Neurology for over 30 years, Dr. Bernardo Savariego treats people struggling with addiction in a private office setting. A strong advocate of treating addiction with evidence-based medicine, he also guides his patients to complementary psychosocial support.

In your experience, how severe a problem is opioid dependence and addiction?
Nationally, the statistics are grim and definitely point to a public health crisis. The government's newest figures on substance abuse show that approximately 2.3 million Americans have escalated into opioid addiction.

In my own private practice here in Miami, we see patients from all walks of life who struggle with this medical disease. We treat adolescents, parents with children, high-achieving professionals and retirees. Most started out misusing prescription opioid painkillers like oxycodone or hydrocodone, often using pills they got from family members or friends. Since these drugs are legal and approved by the FDA, people often did not understand their danger. Most people do not realize that misusing prescription painkillers is physically as damaging to their brains as abusing heroin.

Why do so many patients relapse who receive short-term "detoxes?" How do you help your patients avoid this cycle?
The high failure rate of short-term treatment is easy to understand when you realize that opioid addiction is a chronic, physical medical disease. It's a lot like adult-onset diabetes or high blood pressure in the sense that, while the condition may initially be caused by poor lifestyle choices, it becomes a long-term physical disease. After prolonged opioid use there are changes in the brain that may take a year or more to reverse. That is why the World Health Organization classifies addiction as a "brain disease."

Lasting recovery requires physical healing in the brain coupled with the patient's working through emotional issues with counseling and other psychosocial support. This healing and rebuilding take time. Every patient is different, and treatment needs to be tailored to each person's particular needs.

"Approximately 2.3 million Americans have escalated into opioid addiction."

Bernardo Savariego, M.D.
Addiction Psychiatrist, Professor in Psychiatry, University of Miami School of Medicine

How does medication help patients with opioid dependence issues?
I use medication because it helps to manage the physical cravings that an addicted person feels. Thanks to Federal legislation—the Drug Addiction Treatment Act of 2000—it is now possible to treat opioid addiction in the privacy of a doctor's office. Without the threat of physical cravings or opioid withdrawal, patients can focus on the other parts of their lives that need attention. I have found that combining medication with long-term counseling support gives my patients the best chance of regaining what they had lost to addiction.

TIPS 2

BREAK THE WALL OF SILENCE

PRESCRIPTION DRUGS
Addiction to prescription medication is more common than one might think.
PHOTO: ISTOCKPHOTO.COM

True story: pharmacist overcomes addiction

My name is Jake Nichols, and I am a pharmacist in Massachusetts as well as a person in recovery from drug addiction. That may sound jarring—how could a well-educated medical professional have become addicted to drugs?—and at one time I would never have thought this possible. But it did happen to me, as it can happen to anyone. Here's my story.

After graduating from the Massachusetts College of Pharmacy in 2000, I had moved into a fulfilling professional life, teaching at two universities and managing hospital clinical pharmacy programs. I loved knowing that I was directly helping a diverse population of needy, low-income patients. I eventually moved on to new challenges and found myself working in managed care.

But financial constraints forced cutbacks, and my position was eliminated. Jobless, I became depressed and began using drugs heavily. I teetered "on the edge" for over a year, even after finding another pharmacist position. Working alone most of the time, I found ample opportunity to steal drugs from my employer. I used amphetamines and then increasingly Vicodin, an opioid painkiller. I was caught when another pharmacist saw a faxed invoice and realized I was diverting drugs. My employer, the Board of Pharmacy, the DEA, and local as well as state police intervened, and I lost my professional license. It was quite humbling to find myself in a courtroom listening to a judge outlining the charges against me.

At a residential facility I was treated with the medication Suboxone. It removed my cravings, and without the threat of opioid withdrawal I was able to begin focusing on the steps I needed to take to reclaim my life. I realized, oddly, that although addiction runs in my family, I had trusted my medical education to keep myself safe. But addiction is a chronic brain disease that needs a medical solution. Like diabetes or asthma, addiction is long-term and potentially life-threatening.

I am extremely grateful for having been given the chance to redeem my life. I remain under the close supervision of the Board of Pharmacy. My wife was unaware of my addiction and suffered enormously when I was caught in my lies. We also faced severe financial difficulties as a result of the chaos my addiction caused, and for a time we feared foreclosure on our home. But she has had the grace to continue to believe in me, and we now have a beautiful little boy.

TURNING PAIN INTO PROGRESS
Jake Nichols shares his story of struggle to help others suffering from addiction.
PHOTO: NAME SURNAME

I have a new calling in my life—to help break the wall of silence around the plague of drug addiction among medical professionals. This subject remains taboo, but it shouldn't be. I know from personal experience that many healthcare professionals struggle with addiction but are afraid to ask for help. Here in Massachusetts I am active in trying to modernize the laws that govern addiction among pharmacists and nurses. I am also working to increase education about the medical nature of addiction in medical, nursing and pharmacy schools.

One day, addiction will be recognized as the disease it is, patients will not be stigmatized, treatment will be readily available, and people in recovery will be applauded throughout our communities. For myself, I will continue to work towards that day.

JAKE NICHOLS
editorial@mediaplanet.com

Change on the horizon for addiction treatment

Historically, addiction has been regarded as a moral failure, a sin or a display of weakness on the part of the user. It is widely believed that if people want to stop abusing drugs or alcohol "enough," they can "just stop"—stop destroying their bodies, stop hurting their families and stop draining society.

Modern medicine, sound research techniques and sophisticated brain imaging technology has directly disproved this belief and reinforces the reality that addiction to drugs or alcohol is a brain disease that has many similarities to other chronic medical diseases such as diabetes, hypertension and asthma.

Prescription drug abuse affects people of all ages. Cravings, loss of control, physical dependence and tolerance: these established patterns of behavioral and physiological symptoms are associated with substance use disorders. Researchers and addiction professionals have also pinpointed a definitive and unique pattern of neurobiological adaptations that take place in the brain. We now know that chronic abuse of a psychoactive substance attacks the brain, resulting in long-lasting adaptations, damage to the cerebral cortex and limbic system and disruptions in neurotransmission.

This new understanding does not mean that a person addicted to drugs or alcohol is helpless to change his or her behavior, but it does mean that people seeking help need more comprehensive and long-term treatment than originally thought. Effective addiction treatment requires biologically-based interventions that are used in conjunction with traditional psychotherapeutic techniques, such as talk-therapy and support groups. It can take years to get the body back to its "normal" state given that many of these neurobiological adaptations can persist for years after the last use of drugs and alcohol. Accordingly, addiction treatment services must also be accessible long-term.

Cynthia Moreno Tuohy
Executive Director of NAADAC, the Association of Addiction Professionals

"Prescription drug abuse affects people of all ages."

Prior to the Affordable Care Act (ACA), signed into law by President Obama in March 2010, comprehensive addiction treatment services were limited to those who had medical insurance with optional substance use disorder treatment benefits: leaving most people to pay for treatment out of pocket. Under the new law, services such as screening, early intervention, treatment and recovery support for clients with substance use disorders will be provided in the same manner and in the same, primary care settings as services for diabetes, asthma or any other illness. The change will bring needed help to many as it also increases awareness that drug dependence is a chronic, treatable disease. The health care legislation, as it currently stands, also accommodates for broader coverage for Americans with substance use disorders by providing coverage for those previously uninsured, requiring insurance plans to cover substance use disorders, praohibiting denial of coverage due to a pre-existing condition—including substance use disorders—and providing greater access to treatment through Medicaid.

In 2008, 23.1 million Americans aged 12 and older needed treatment for a substance use problem, and yet only 2.3 million—one in ten—received care at a specialty treatment center. Many of those who do not receive, but could benefit from treatment, do not have health insurance or other means to pay for it. As we move toward implementation of new health care regulations, more people will be able to get the care they need.

More information is available at naadac.org.

CYNTHIA MORENO TUOHY
editorial@mediaplanet.com

INSIGHT

STEP 3 PARTNER WITH YOUR PHARMACIST

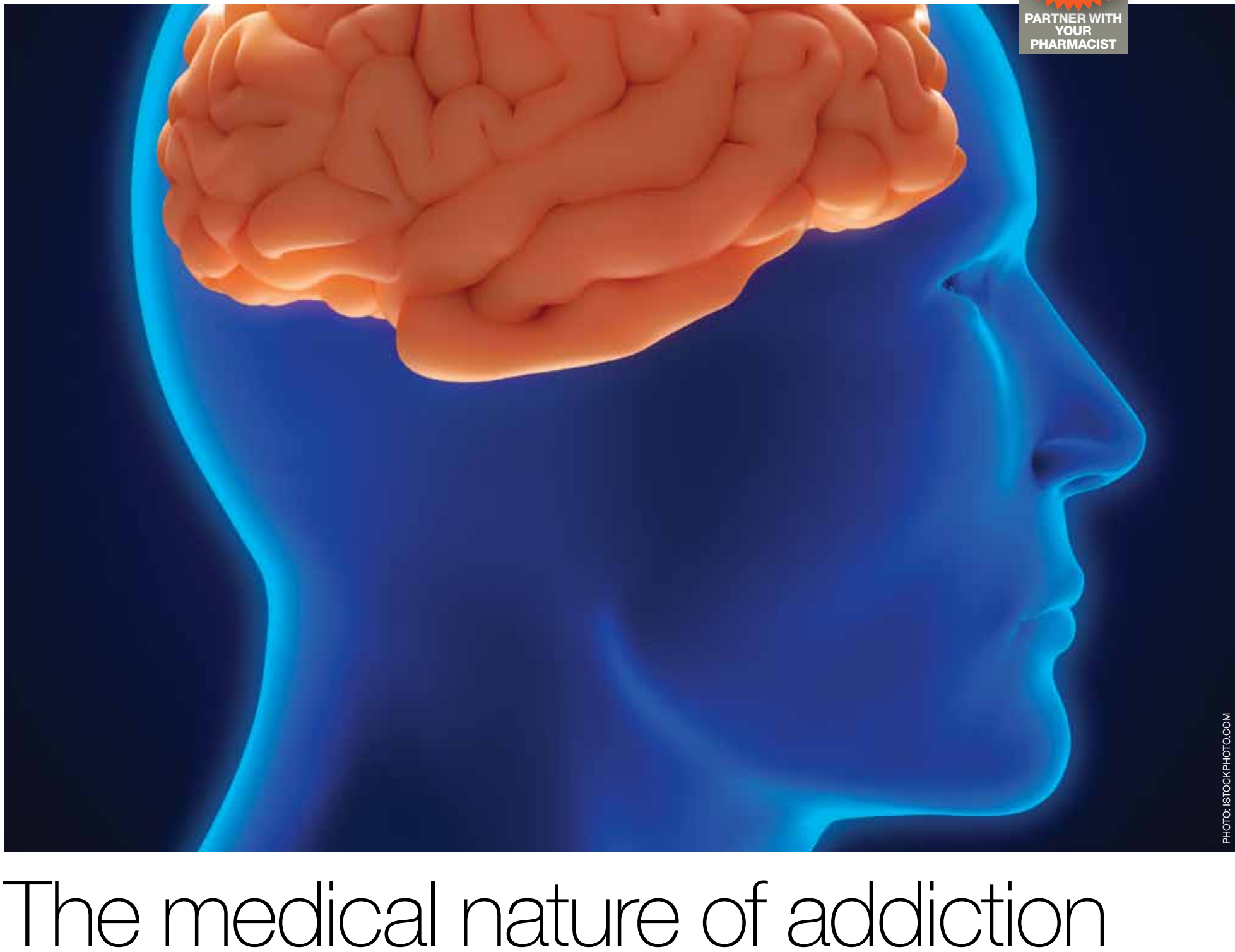


PHOTO: ISTOCKPHOTO.COM

The medical nature of addiction

James C. Berman, M.D., University of Pennsylvania Health System has been a Board certified internist for over 25 years, Dr. Berman has also been certified since 1987 to treat addiction by the American Society of Addiction Medicine. He directs Penn Addiction Medicine at the University of Pennsylvania Health System.

To date, the medical community as a whole has lacked any meaningful understanding regarding addiction. Consequently, its treatment has been marginalized, relegated to the domain of non-medical entities. Within the past decade, however, the tireless work of relatively anonymous pioneering neuroscientists has established that addiction is a complex brain disease. Moreover, NIDA, under the dynamic stewardship of Nora Volkow, M.D., has championed the medical nature of addiction with an international voice that resonates throughout the medical community.

As the emphasis on evidence-based medicine for addiction has increased, it is incumbent upon physicians to generate and ultimately embrace the treatments and strategies derived from the evidence. Addiction is a chronic, progressive, primary disease, characterized by relapse which, if left untreated or mistreated, can and will result in death.

Interestingly, heart disease, lung disease, diabetes, and cancer are characterized in exactly the same way. Yet relapse, an accepted aspect of all other chronic diseases, is viewed with judgment, prejudice, and disdain when addiction is the disease. As physicians, the vast majority of us spend most of our professional lives treating or attempting to prevent relapses associated with chronic diseases. Let us hope that the burgeoning science of addiction coupled with evidence-based medicine will lead physicians to re-evaluate their responsibilities towards addicted patients. The disease of addiction, albeit with its unique individual nuances, is merely another spoke on the wheel of chronic diseases.

Unequivocally, the hallmark of treatment for chronic diseases is pharmacotherapy. There is a robust literature supporting the efficacy of pharmacotherapy in the disease of addiction. Nonetheless, these medications are not a panacea. Rather they are marvelous tools, which can be extracted from a toolbox that continues to grow. Hence, pharmacotherapy does not eliminate the need for psychosocial support. On the contrary, it magnifies the necessity for such non-medical support in order to maximize treatment success.

> "Addiction is a chronic, progressive, primary disease, characterized by relapse which, if left untreated or mistreated, can and will result in death . . . we continually recognize the need to tailor treatment to the individual."

As we truly medicalize the disease of addiction, we continually recognize the need to tailor treatment to the individual. Medicalization leads to demarginalization, which affords our patients the best care we can offer. Ultimately, as addiction treatment moves into mainstream medical practice, a team approach using various modalities, under the auspices of organized medicine, should be the standard of care for addicted patients.

JAMES C. BERMAN
editorial@mediaplanet.com

Working with your community pharmacist to prevent drug abuse

When used as directed, prescription medicine can play a critical role in treating a range of conditions. With the power of prescription medicines comes great responsibility for their use and storage.

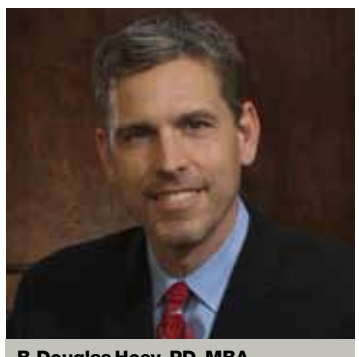
A new campaign, Safeguard My Meds (safeguardmymeds.org), offers tools and resources to help keep medicines safe, including a variety of downloadable print, video and online materials and tips.

For instance, some tips suggest maintaining a list of medicines at home, keeping them in a locked storage container in a cool, dry place, keeping them out of the reach of children and pets, and never sharing medicines with others.

Protecting your medicines

A national survey shows that while an overwhelming majority of Americans say that it is extremely or very important to safely store and dispose of prescription medicine, many may not be doing everything they can to protect their medicines. Most of those surveyed indicated that they keep prescription medicine in an unlocked cabinet, closet or drawer in their homes. Moreover, respondents frequently said they store prescription medicine in the bathroom or kitchen, two areas in which temperatures and conditions could compromise a drug's integrity and are often unsecured and easily accessed by anyone entering the home.

There can be dangerous consequences when prescriptions aren't stored securely, particularly for young people. According to the U.S. Office of National Drug Control Policy, for young people ages 12-17, prescriptions have become the second most abused illegal drug (behind marijuana) with controlled substances playing a major role. In tfact, one in five U.S. high school students says they have abused a prescription medicine at least once in their lives. A majority (70 percent) of those young people say they are acquiring those drugs from a friend or relative, not the street corner as once thought.



B.Douglas Hoey, PD, MBA
NCPA Executive Vive President and CEO

> "There can be dangerous consequences when prescriptions aren't stored securely, particularly for young people."

Storing and disposing

As medication experts, community pharmacists can play a major role in reversing this trend. Talk to your community pharmacist about how to store, use and dispose of prescription or over-the-counter medicine properly. When medications are no longer needed, look for local disposal options at community pharmacies nationwide participating in the voluntary Dispose My Meds program.

As of September 2011, nearly 1,400 independent community pharmacies from 47 states are listed on disposemymeds.org and have returned an estimated 50,000 pounds of drugs for disposal. These pharmacies help consumers properly dispose of unused and unwanted drugs, often at no cost. There may be certain restrictions on what can be returned (in particular, the pharmacist cannot accept controlled substances for disposal), so patients should always check with their local pharmacist.

Your community pharmacist looks forward to talking to you soon.

The National Community Pharmacists Association (NCPA®) represents the interests of America's community pharmacists, including the owners of more than 23,000 independent community pharmacies, pharmacy franchises, and chains. Together they represent a $93 billion health-care marketplace, have more than 315,000 employees including 62,400 pharmacists, and dispense over 41 percent of all retail prescriptions.

To learn more go to ncpanet.org or read NCPA's blog, The Dose, at ncpanet.wordpress.com.

B. DOUGLAS HOEY, PD, MBA
editorial@mediaplanet.com

If you think you, or someone you know, may be dependent on prescription pain medicines or heroin...

Learn the latest thinking

Did you know that dependence on prescription pain medicines or heroin is a chronic disease?

Dependence on opioids (addiction to prescription pain medicines or heroin) is a long-term brain disease.

Because opioid dependence is a medical condition, it can be treated effectively with medication combined with counseling and support.

Visit **suboxone.com** for a quiz that can help you have a discussion with your doctor.

Ask about medical treatment

Ask about SUBOXONE® (buprenorphine and naloxone) Sublingual Film (CIII), a proven medical treatment available in the privacy of a doctor's office

SUBOXONE Film includes a medication called buprenorphine, which has been shown to help people stay in treatment and reduce cravings.

Take the first step—find a certified doctor and ask about SUBOXONE Film

To find a doctor certified to prescribe SUBOXONE Film, visit **suboxone.com**.

Exclusive savings available with SUBOXONE Film treatment

Visit **suboxone.com** to download a copay card.

For more information about living with opioid dependence, the importance of counseling, and treatment with SUBOXONE Film, visit **suboxone.com**.

SUBOXONE® (buprenorphine and naloxone) Sublingual Film (CIII) is indicated for maintenance treatment of opioid dependence as part of a complete treatment plan to include counseling and psychosocial support. Treatment should be initiated under the direction of physicians qualified under the Drug Addiction Treatment Act.

Important Safety Information

Do not take SUBOXONE Sublingual Film if you are hypersensitive to buprenorphine or naloxone.

SUBOXONE Sublingual Film can be abused in a manner similar to other opioids, legal or illicit.

Chronic use of buprenorphine can cause physical dependence. SUBOXONE contains an opioid that can cause physical dependence. Do not stop taking SUBOXONE without talking to your doctor. You could become sick with uncomfortable withdrawal signs and symptoms because your body has become used to this medicine.

SUBOXONE Sublingual Film can cause serious life-threatening breathing problems, overdose, and death, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other central nervous system (CNS) depressants (ie, sedatives, tranquilizers, or alcohol). It is extremely dangerous to self-administer nonprescribed benzodiazepines or other CNS depressants while taking SUBOXONE Sublingual Film.

Liver function should be monitored before and during treatment.

Keep SUBOXONE Sublingual Film out of the sight and reach of children. Children who take SUBOXONE Sublingual Film can have severe, possibly fatal, breathing problems.

Do not inject or take SUBOXONE Sublingual Film before the effects of opioids (eg, heroin, hydrocodone, methadone, morphine, oxycodone) have subsided as you may experience withdrawal symptoms.

Neonatal withdrawal has been reported. Use of SUBOXONE Sublingual Film in pregnant women or during breast-feeding should only be considered if the potential benefit justifies the potential risk. Caution should be exercised when driving vehicles or operating hazardous machinery, especially during dose adjustment as patients may experience drowsiness and slow reaction time.

Adverse events commonly observed with the sublingual administration of SUBOXONE Sublingual Film are numb mouth, sore tongue, redness of the mouth, headache, nausea, vomiting, sweating, constipation, signs and symptoms of withdrawal, insomnia, pain, swelling of the limbs, disturbance of attention, palpitations, and blurred vision.

Cytolytic hepatitis, jaundice, and allergic reactions, including anaphylactic shock, have been reported.

This is not a complete list of potential adverse events associated with SUBOXONE Sublingual Film. Please see full Prescribing Information for a complete list.

To report an adverse event associated with taking SUBOXONE Sublingual Film, please call 1-877-782-6966. You are encouraged to report adverse events of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see full Product Information on the following pages.

Reckitt Benckiser Pharmaceuticals Inc.

Manufactured for Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA 23235 by MonoSol Rx LLC, Warren, NJ 07059

TF08144 09/11

Suboxone® Sublingual Film (buprenorphine and naloxone) C III

Reckitt Benckiser Pharmaceuticals Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SUBOXONE® sublingual film safely and effectively. See full prescribing information for SUBOXONE sublingual film.

SUBOXONE (buprenorphine and naloxone) sublingual film for sublingual administration CIII.

Initial U.S. Approval: 2002

INDICATIONS AND USAGE

SUBOXONE sublingual film is indicated for maintenance treatment of opioid dependence. Prescription use of this product is limited under the Drug Addiction Treatment Act. (1)

DOSAGE AND ADMINISTRATION

Administer SUBOXONE sublingual film sublingually as a single daily dose. (2)

The recommended daily dose for maintenance is 16/4 mg.

DOSAGE FORMS AND STRENGTHS

Sublingual film: 2 mg buprenorphine with 0.5 mg naloxone and 8 mg buprenorphine with 2 mg naloxone. (3)

CONTRAINDICATIONS

Hypersensitivity to buprenorphine or naloxone. (4)

WARNINGS AND PRECAUTIONS

- Buprenorphine can be abused in a similar manner to other opioids. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits. (5.1)
- Significant respiratory depression and death have occurred in association with buprenorphine, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other CNS depressants (including alcohol). (5.2)
- Consider dose reduction of CNS depressants, SUBOXONE sublingual film, or both in situations of concomitant prescription. (5.3)
- Store SUBOXONE sublingual film safely out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children. (5.4)
- Chronic administration produces opioid-type physical dependence. Abrupt discontinuation or rapid dose taper may result in opioid withdrawal syndrome. (5.5)
- Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events. (5.6)
- Do not administer SUBOXONE sublingual film to patients with known hypersensitivity to buprenorphine or naloxone. (5.7)
- A marked and intense opioid withdrawal syndrome is highly likely to occur with parenteral misuse of SUBOXONE sublingual film by individuals physically dependent on full opioid agonists or by sublingual administration before the agonist effects of other opioids have subsided. (5.8)
- Neonatal withdrawal has been reported following use of buprenorphine by the mother during pregnancy. (5.9)
- SUBOXONE sublingual film is not appropriate as an analgesic. There have been reported deaths of opioid naïve individuals who received a 2 mg sublingual dose. (5.10)
- Caution patients about the risk of driving or operating hazardous machinery. (5.11)

ADVERSE REACTIONS

Adverse events commonly observed with the sublingual administration of the SUBOXONE sublingual film was oral hypoesthesia, glossodynia, oral mucosal erythema, headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, pain, and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Reckitt Benckiser Pharmaceuticals Inc. at 1-877-782-6966, FDA at 1-800-FDA-1088, or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over or under dosing. (7.1)
- Use caution in prescribing SUBOXONE sublingual film for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse. (7.3)

USE IN SPECIFIC POPULATIONS

- SUBOXONE sublingual film is not indicated for use during pregnancy unless potential benefit justifies potential risk. (8.1)
- Buprenorphine passes into the mother's milk. Breast-feeding is not advised while taking SUBOXONE sublingual film. (8.3)
- Safety and effectiveness of SUBOXONE sublingual film in patients below the age of 16 has not been established. (8.4)
- Administer SUBOXONE sublingual film with caution to elderly or debilitated patients. (8.5)
- Administer SUBOXONE sublingual film with caution to patients with liver dysfunction. (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised August 2010

FULL PRESCRIBING INFORMATION:
CONTENTS*

* Sections and subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SUBOXONE sublingual film is indicated for maintenance treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.

Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

2 DOSAGE AND ADMINISTRATION

SUBOXONE sublingual film is administered sublingually as a single daily dose. SUBOXONE sublingual film should be used in patients who have been initially inducted using SUBUTEX® (buprenorphine) sublingual tablets.

2.1 Maintenance

- SUBOXONE sublingual film is indicated for maintenance treatment. The recommended target dosage of SUBOXONE sublingual film is 16/4 mg buprenorphine/naloxone/day as a single daily dose.
- The dosage of SUBOXONE sublingual film should be progressively adjusted in increments/decrements of 2/0.5 mg or 4/1 mg buprenorphine/naloxone to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms.
- The maintenance dose of SUBOXONE sublingual film is generally in the range of 4/1 mg buprenorphine/naloxone to 24/6 mg buprenorphine/naloxone per day depending on the individual patient. Dosages higher than this have not been demonstrated to provide any clinical advantage.

2.2 Method of Administration

Place the SUBOXONE sublingual film under the tongue. If an additional sublingual film is necessary to achieve the prescribed dose, place the additional sublingual film sublingually on the opposite side from the first film. Place the sublingual film in a manner to minimize overlapping as much as possible. The sublingual film must be kept under the tongue until the film is completely dissolved. SUBOXONE sublingual film should NOT be chewed, swallowed, or moved after placement.

Proper administration technique should be demonstrated to the patient.

2.3 Clinical Supervision

Treatment should be initiated with supervised administration, progressing to unsupervised administration as the patient's clinical stability permits. SUBOXONE sublingual film is subject to diversion and abuse. When determining the prescription quantity for unsupervised administration, consider the patient's level of stability, the security of his or her home situation, and other factors likely to affect the ability to manage supplies of take-home medication.

Ideally patients should be seen at reasonable intervals (e.g., at least weekly during the first month of treatment) based upon the individual circumstances of the patient. Medication should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits. Periodic assessment is necessary to determine compliance with the dosing regimen, effectiveness of the treatment plan, and overall patient progress.

Once a stable dosage has been achieved and patient assessment (e.g., urine drug screening) does not indicate illicit drug use, less frequent follow-up visits may be appropriate. A once-monthly visit schedule may be reasonable for patients on a stable dosage of medication who are making progress toward their treatment objectives. Continuation or modification of pharmacotherapy should be based on the physician's evaluation of treatment outcomes and objectives such as:

1. Absence of medication toxicity.
2. Absence of medical or behavioral adverse effects.
3. Responsible handling of medications by the patient.
4. Patient's compliance with all elements of the treatment plan (including recovery-oriented activities, psychotherapy, and/or other psychosocial modalities).
5. Abstinence from illicit drug use (including problematic alcohol and/or benzodiazepine use).

If treatment goals are not being achieved, the physician should re-evaluate the appropriateness of continuing the current treatment.

2.4 Unstable Patients

Physicians will need to decide when they cannot appropriately provide further management for particular patients. For example, some patients may be abusing or dependent on various drugs, or unresponsive to psychosocial intervention such that the physician does not feel that he/she has the expertise to manage the patient. In such cases, the physician may want to assess whether to refer the patient to a specialist or more intensive behavioral treatment environment. Decisions should be based on a treatment plan established and agreed upon with the patient at the beginning of treatment.

Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with, or referred to, more intensive and structured treatment.

2.5 Stopping Treatment

The decision to discontinue therapy with SUBOXONE sublingual film after a period of maintenance should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuation of buprenorphine has been used, but the data are insufficient to determine the best method of dose taper at the end of treatment.

2.6 Switching between SUBOXONE (buprenorphine and naloxone) Sublingual Tablets and SUBOXONE Sublingual Film

Patients being switched between SUBOXONE (buprenorphine and naloxone) sublingual tablets and SUBOXONE sublingual film should be started on the same dosage as the previously administered product. However, dosage adjustments may be necessary when switching between products. Because of the potentially greater relative bioavailability of SUBOXONE sublingual film compared to SUBOXONE (buprenorphine and naloxone) sublingual tablets, patients switching from SUBOXONE (buprenorphine and naloxone) sublingual tablets to SUBOXONE sublingual film should be monitored for over-medication. Those switching from SUBOXONE sublingual film to SUBOXONE (buprenorphine and naloxone) sublingual tablets should be monitored for withdrawal or other indications of under-dosing. In clinical studies, pharmacokinetics of SUBOXONE sublingual film was similar to the respective dosage strengths of SUBOXONE (buprenorphine and naloxone) sublingual tablets, although not all doses and dose combinations met bioequivalence criteria.

3 DOSAGE FORMS AND STRENGTHS

SUBOXONE sublingual film is supplied as an orange rectangular sublingual film with a white printed logo in two dosage strengths:

- buprenorphine/naloxone 2 mg/0.5 mg, and
- buprenorphine/naloxone 8 mg/2 mg.

4 CONTRAINDICATIONS

SUBOXONE sublingual film should not be administered to patients who have been shown to be hypersensitive to buprenorphine or naloxone as serious adverse reactions, including anaphylactic shock, have been reported *[see Warnings and Precautions (5.7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Abuse Potential

Buprenorphine can be abused in a manner similar to other opioids, legal or illicit. Prescribe and dispense buprenorphine with appropriate precautions to minimize risk of misuse, abuse, or diversion, and ensure appropriate protection from theft, including in the home. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits. *[see Drug Abuse and Dependence (9.2)]*.

5.2 Respiratory Depression

Buprenorphine, particularly when taken by the IV route, in combination with benzodiazepines or other CNS depressants (including alcohol), has been associated with significant respiratory depression and death. Many, but not all, post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines involved misuse by self-injection. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other CNS depressant drugs. Patients should be warned of the potential danger of self-administration of benzodiazepines or other depressants while under treatment with SUBOXONE sublingual film. [see *Drug Interactions* (7.3)]

In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.

SUBOXONE sublingual film should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression).

5.3 CNS Depression

Patients receiving buprenorphine in the presence of opioid analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics, or other CNS depressants (including alcohol) may exhibit increased CNS depression. Consider dose reduction of CNS depressants, SUBOXONE sublingual film, or both in situations of concomitant prescription. *[see Drug Interactions (7.3)]*.

5.4 Unintentional Pediatric Exposure

Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it. Store buprenorphine-containing medications safely out of the sight and reach of children and destroy any unused medication appropriately. *[see Disposal of Unused SUBOXONE Sublingual Film (17.2)]*.

5.5 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset. Buprenorphine can be abused in a manner similar to other opioids. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. *[see Drug Abuse and Dependence (9.3)]*

5.6 Hepatitis, Hepatic Events

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of death, hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. Withdrawal of buprenorphine has resulted in amelioration of acute hepatitis in some cases; however, in other cases no dose reduction was necessary. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Liver function tests, prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, SUBOXONE sublingual film may need to be carefully discontinued to prevent withdrawal signs and symptoms and a return by the patient to illicit drug use, and strict monitoring of the patient should be initiated.

5.7 Allergic Reactions

Cases of hypersensitivity to buprenorphine and naloxone containing products have been reported both in clinical trials and in the post-marketing experience. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. The most common signs and symptoms include rashes, hives, and pruritus. A history of hypersensitivity to buprenorphine or naloxone is a contraindication to the use of SUBOXONE sublingual film.

5.8 Precipitation of Opioid Withdrawal Signs and Symptoms

Because it contains naloxone, SUBOXONE sublingual film is highly likely to produce marked and intense withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine, or methadone. Because of the partial agonist properties of buprenorphine, SUBOXONE sublingual film may precipitate opioid withdrawal signs and symptoms in such persons if administered sublingually before the agonist effects of the opioid have subsided.

5.9 Neonatal Withdrawal

Neonatal withdrawal has been reported in the infants of women treated with buprenorphine during pregnancy. From post-marketing reports, the time to onset of neonatal withdrawal signs ranged from Day 1 to Day 8 of life with most cases occurring on Day 1. Adverse events associated with the neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation, and myoclonus, and there have been reports of convulsions, apnea, respiratory depression, and bradycardia.

5.10 Use in Opioid Naïve Patients

There have been reported deaths of opioid naive individuals who received a 2 mg dose of buprenorphine as a sublingual tablet for analgesia. SUBOXONE sublingual film is not appropriate as an analgesic.

5.11 Impairment of Ability to Drive or Operate Machinery

SUBOXONE sublingual film may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during treatment induction and dose adjustment. Patients should be cautioned about driving or operating hazardous machinery until they are reasonably certain that SUBOXONE sublingual film therapy does not adversely affect his or her ability to engage in such activities.

5.12 Orthostatic Hypotension

Like other opioids, SUBOXONE sublingual film may produce orthostatic hypotension in ambulatory patients.

5.13 Elevation of Cerebrospinal Fluid Pressure

Buprenorphine, like other opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions, and other circumstances when cerebrospinal pressure may be increased. Buprenorphine can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

5.14 Elevation of Intracholedochal Pressure

Buprenorphine has been shown to increase intracholedochal pressure, as do other opioids, and thus should be administered with caution to patients with dysfunction of the biliary tract.

5.15 Effects in Acute Abdominal Conditions

As with other opioids, buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

5.16 General Precautions

SUBOXONE sublingual film should be administered with caution in debilitated patients and those with myxedema or hypothyroidism, adrenal cortical insufficiency (e.g., Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Adverse Events in Clinical Trials - SUBOXONE sublingual film

The safety of SUBOXONE sublingual film is supported by clinical trials using SUBUTEX (buprenorphine) sublingual tablets and SUBOXONE (buprenorphine and naloxone) sublingual tablets, and other trials using buprenorphine sublingual solutions, as well as an open-label study in 194 patients treated with SUBOXONE sublingual film. In total, safety data from clinical studies are available from over 3000 opioid-dependent subjects exposed to buprenorphine at doses in the range used in the treatment of opioid dependence. Few differences in the adverse event profile were noted among SUBOXONE sublingual film, SUBOXONE (buprenorphine and naloxone) sublingual tablets, SUBUTEX (buprenorphine) sublingual tablets and a buprenorphine ethanolic sublingual solution.

The most common adverse event (>1%) associated with the sublingual administration of the SUBOXONE sublingual film was oral hypoesthesia. Other adverse events were constipation, glossodynia, oral mucosal erythema, vomiting, intoxication, disturbance in attention, palpitations, insomnia, withdrawal syndrome, hyperhidrosis, and blurred vision.

Other adverse event data were derived from larger, controlled studies of SUBOXONE (buprenorphine and naloxone) and SUBUTEX (buprenorphine) tablets and of buprenorphine sublingual solution. In a comparative study of SUBOXONE (buprenorphine and naloxone) and SUBUTEX (buprenorphine) sublingual tablets, adverse event profiles were similar for subjects treated with 16/4 mg SUBOXONE (buprenorphine and naloxone) sublingual tablets or 16 mg SUBUTEX (buprenorphine) sublingual tablets. The following adverse events were reported to occur by at least 5% of patients in a 4-week study of SUBOXONE (buprenorphine and naloxone) sublingual tablets and SUBUTEX (buprenorphine) sublingual tablets.

Table 1. Adverse Events (≥5%) by Body System and Treatment Group in a 4-week Study

Body System/ Adverse Event (COSTART Terminology)	SUBOXONE (buprenorphine and naloxone) sublingual tablets 16/4 mg/day N=107 n (%)	SUBUTEX (buprenorphine) sublingual tablets 16 mg/day N=103 n (%)	Placebo N=107 n (%)
Body as a Whole			
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)
Pain abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)
Pain back	4 (3.7%)	8 (7.8%)	12 (11.2%)
Withdrawal syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)
Cardiovascular System			
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)
Digestive System			
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)
Nervous System			
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)
Respiratory System			
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)
Skin And Appendages			
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)

Abbreviations: COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms.

The adverse event profile of buprenorphine was also characterized in the dose-controlled study of a buprenorphine ethanolic solution, over a range of doses in four months of treatment. Table 2 shows adverse events reported by at least 5% of subjects in any dose group in the dose-controlled trial.

Table 2. Adverse Events (≥5%) by Body System and Treatment Group in a 16-week Study

Body System/ Adverse Event (COSTART Terminology)	Buprenorphine Dose				
	Very Low* N=184 n (%)	Low* N=180 n (%)	Moderate* N=186 n (%)	High* N=181 n (%)	Total* N=731 n (%)
Body as a Whole					
Abscess	9 (5%)	2 (1%)	3 (2%)	2 (1%)	16 (2%)
Asthenia	26 (14%)	28 (16%)	26 (14%)	24 (13%)	104 (14%)
Chills	11 (6%)	12 (7%)	9 (5%)	10 (6%)	42 (6%)
Fever	7 (4%)	2 (1%)	2 (1%)	10 (6%)	21 (3%)
Flu syndrome	4 (2%)	13 (7%)	19 (10%)	8 (4%)	44 (6%)
Headache	51 (28%)	62 (34%)	54 (29%)	53 (29%)	220 (30%)
Infection	32 (17%)	39 (22%)	38 (20%)	40 (22%)	149 (20%)
Injury accidental	5 (3%)	10 (6%)	5 (3%)	5 (3%)	25 (3%)
Pain	47 (26%)	37 (21%)	49 (26%)	44 (24%)	177 (24%)
Pain back	18 (10%)	29 (16%)	28 (15%)	27 (15%)	102 (14%)
Withdrawal syndrome	45 (24%)	40 (22%)	41 (22%)	36 (20%)	162 (22%)
Digestive System					
Constipation	10 (5%)	23 (13%)	23 (12%)	26 (14%)	82 (11%)
Diarrhea	19 (10%)	8 (4%)	9 (5%)	4 (2%)	40 (5%)
Dyspepsia	6 (3%)	10 (6%)	4 (2%)	4 (2%)	24 (3%)
Nausea	12 (7%)	22 (12%)	23 (12%)	18 (10%)	75 (10%)
Vomiting	8 (4%)	6 (3%)	10 (5%)	14 (8%)	38 (5%)
Nervous System					
Anxiety	22 (12%)	24 (13%)	20 (11%)	25 (14%)	91 (12%)
Depression	24 (13%)	16 (9%)	25 (13%)	18 (10%)	83 (11%)
Dizziness	4 (2%)	9 (5%)	7 (4%)	11 (6%)	31 (4%)
Insomnia	42 (23%)	50 (28%)	43 (23%)	51 (28%)	186 (25%)
Nervousness	12 (7%)	11 (6%)	10 (5%)	13 (7%)	46 (6%)
Somnolence	5 (3%)	13 (7%)	9 (5%)	11 (6%)	38 (5%)
Respiratory System					
Cough increase	5 (3%)	11 (6%)	6 (3%)	4 (2%)	26 (4%)
Pharyngitis	6 (3%)	7 (4%)	6 (3%)	9 (5%)	28 (4%)
Rhinitis	27 (15%)	16 (9%)	15 (8%)	21 (12%)	79 (11%)
Skin and Appendages					
Sweat	23 (13%)	21 (12%)	20 (11%)	23 (13%)	87 (12%)
Special Senses					
Runny eyes	13 (7%)	9 (5%)	6 (3%)	6 (3%)	34 (5%)

*Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes:
1 mg solution would be less than a tablet dose of 2 mg
4 mg solution approximates a 6 mg tablet dose
8 mg solution approximates a 12 mg tablet dose
16 mg solution approximates a 24 mg tablet dose

6.2 Adverse Events – Post-marketing Experience with Suboxone Sublingual Tablets

The most frequently reported post-marketing adverse event not observed in clinical trials was peripheral edema.

7 DRUG INTERACTIONS

7.1 Cytochrome P-450 3A4 (CYP3A4) Inhibitors and Inducers

Buprenorphine is metabolized to norbuprenorphine primarily by cytochrome CYP3A4; therefore, potential interactions may occur when SUBOXONE sublingual film is given concurrently with agents that affect CYP3A4 activity. The concomitant use of SUBOXONE sublingual film with CYP3A4 inhibitors (e.g., azole antifungals such as ketoconazole, macrolide antibiotics such as erythromycin, and HIV protease inhibitors) should be monitored and may require dose-reduction of one or both agents.

The interaction of buprenorphine with CYP3A4 inducers has not been studied; therefore, it is recommended that patients receiving SUBOXONE sublingual film be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., efavirenz, phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered [see Clinical Pharmacology (12.3)].

7.2 Antiretrovirals

Three classes of antiretroviral agents have been evaluated for CYP3A4 interactions with buprenorphine. Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to induce or inhibit the P450 enzyme pathway, thus no interactions with buprenorphine are expected. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine and etravirine are known CYP3A inducers whereas delaviridine is a CYP3A inhibitor. Significant pharmacokinetic interactions between NNRTIs (e.g., efavirenz and delavirdine) and buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects. It is recommended that patients who are on chronic buprenorphine treatment have their dose monitored if NNRTIs are added to their treatment regimen. Studies have shown some antiretroviral protease inhibitors (PIs) with CYP3A4 inhibitory activity (nelfinavir, lopinavir/ritonavir, ritonavir) have little effect on buprenorphine pharmacokinetic and no significant pharmacodynamic effects. Other PIs with CYP3A4 inhibitory activity (atazanavir and atazanavir/ritonavir) resulted in elevated levels of buprenorphine and norbuprenorphine and patients in one study reported increased sedation. Symptoms of opioid excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly. Monitoring of patients taking buprenorphine and atazanavir with and without ritonavir is recommended, and dose reduction of buprenorphine may be warranted.

7.3 Benzodiazepines

There have been a number of post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines. In many, but not all, of these cases, buprenorphine was misused by self-injection. Preclinical studies have shown that the combination of benzodiazepines and buprenorphine altered the usual ceiling effect on buprenorphine-induced respiratory depression, making the respiratory effects of buprenorphine appear similar to those of full opioid agonists. SUBOXONE sublingual film should be prescribed with caution to patients taking benzodiazepines or other drugs that act on the CNS, regardless of whether these drugs are taken on the advice of a physician or are being abused/misused. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking SUBOXONE sublingual film, and should also be cautioned to use benzodiazepines concurrently with SUBOXONE sublingual film only as directed by their physician.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of SUBOXONE sublingual film or buprenorphine/naloxone in pregnant women. SUBOXONE sublingual film should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects:

Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (IM) (3:2) administration of mixtures of buprenorphine and naloxone. Following oral administration to rats and rabbits, no teratogenic effects were observed at buprenorphine doses up to 250 mg/kg/day and 40 mg/kg/day, respectively (estimated exposure approximately 150 times and 50 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis). No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated exposure approximately 20 times and 35 times, respectively, the recommended human daily dose of 16 mg on a mg/m² basis). Acephalus was observed in one rabbit fetus from the low-dose group and omphalocele was observed in two rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Following oral administration of buprenorphine to rats, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). In the rabbit, increased post-implantation losses occurred at an oral dose of 40 mg/kg/day. Following IM administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day.

Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the recommended human daily sublingual dose of 16 mg on a mg/m² basis) were not statistically significant.

In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

Non-teratogenic Effects:

Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Fertility, peri-, and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), and after SC doses of 0.1 mg/kg/day and up (approximately 0.06 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

8.3 Nursing Mothers

Buprenorphine passes into breast milk. Breast-feeding is not advised in mothers treated with buprenorphine products.

An apparent lack of milk production during general reproduction studies with buprenorphine in rats caused decreased viability and lactation indices.

8.4 Pediatric Use

The safety and effectiveness of SUBOXONE sublingual film have not been established in pediatric patients.

8.5 Geriatric Use

Clinical studies of SUBOXONE sublingual film, SUBOXONE (buprenorphine and naloxone) sublingual tablets, or SUBUTEX (buprenorphine) sublingual tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone is unknown. Since both drugs are extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. However, it is not known whether both drugs are affected to the same degree. Therefore, dosage should be adjusted and patients should be watched for signs and symptoms of precipitated opioid withdrawal.

8.7 Renal Impairment

No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine. The effects of renal failure on naloxone pharmacokinetics are unknown.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Buprenorphine is a Schedule III narcotic under the Controlled Substances Act.

Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

9.2 Abuse

Buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. 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.

Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with or referred for more intensive and structured treatment.

Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines.

The physician may be able to more easily detect misuse or diversion by maintaining records of medication prescribed including date, dose, quantity, frequency of refills, and renewal requests of medication prescribed.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper handling and storage of the medication are appropriate measures that help to limit abuse of opioid drugs.

9.3 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset *[see Warnings and Precautions (5.5)]*.

A neonatal withdrawal syndrome has been reported in the infants of women treated with buprenorphine during pregnancy *[see Warnings and Precautions (5.9)]*.

10 OVERDOSAGE

The manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression, and death.

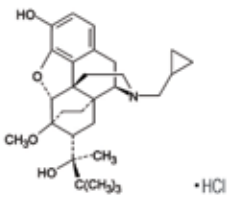
In the event of overdose, the respiratory and cardiac status of the patient should be monitored carefully. When respiratory or cardiac functions are depressed, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, IV fluids, vasopressors, and other supportive measures should be employed as indicated.

In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.

11 DESCRIPTION

SUBOXONE (buprenorphine and naloxone) sublingual film is an orange film, imprinted with a logo identifying the product and strength in white ink. It contains buprenorphine HCl, a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist, and naloxone HCl dihydrate, an opioid receptor antagonist, at a ratio of 4:1 (ratio of free bases). It is intended for sublingual administration and is available in two dosage strengths, 2 mg buprenorphine with 0.5 mg naloxone and 8 mg buprenorphine with 2 mg naloxone. Each sublingual film also contains polyethylene oxide, hydroxypropyl methylcellulose, maltitol, acesulfame potassium, lime flavor, citric acid, sodium citrate, FD&C yellow #6, and white ink.

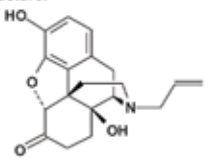
Chemically, buprenorphine HCl is (2S)-2-[17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol hydrochloride. It has the following chemical structure:



• HCl

Buprenorphine HCl has the molecular formula $C_{29}H_{41}NO_4$ • HCl and the molecular weight is 504.10. It is a white or off-white crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol, and practically insoluble in cyclohexane.

Chemically, naloxone HCl dihydrate is 17-Allyl-4, 5α -epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride dihydrate. It has the following chemical structure:



HCl • $2H_2O$

Naloxone hydrochloride dihydrate has the molecular formula $C_{19}H_{21}NO_4$ • HCl • $2H_20$ and the molecular weight is 399.87. It is a white to slightly off-white powder and is freely soluble in water, soluble in alcohol, and practically insoluble in toluene and ether.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SUBOXONE sublingual film contains buprenorphine and naloxone. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is a potent antagonist at mu-opioid receptors and produces opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists when administered parenterally.

12.2 Pharmacodynamics

Subjective Effects:

Comparisons of buprenorphine to full opioid agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect.

In opioid-experienced subjects who were not physically dependent, acute sublingual doses of buprenorphine/naloxone tablets produced opioid agonist effects which reached a maximum between doses of 8/2 mg and 16/4 mg buprenorphine/naloxone.

Opioid agonist ceiling-effects were also observed in a double-blind, parallel group, dose-ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg), placebo and a full agonist control at various doses. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid-experienced subjects who were not physically dependent. Both active drugs produced typical opioid agonist effects. For all measures for which the drugs produced an effect, buprenorphine produced a dose-related response. However, in each case, there was a dose that produced no further effect. In contrast, the highest dose of the full agonist control always produced the greatest effects. Agonist objective rating scores remained elevated for the higher doses of buprenorphine (8-32 mg) longer than for the lower doses and did not return to baseline until 48 hours after drug administration. The onset of effects appeared more rapidly with buprenorphine than with the full agonist control, with most doses nearing peak effect after 100 minutes for buprenorphine compared to 150 minutes for the full agonist control.

Physiologic Effects:

Buprenorphine in IV (2, 4, 8, 12 and 16 mg) and sublingual (12 mg) doses has been administered to opioid-experienced subjects who were not physically dependent to examine cardiovascular, respiratory, and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared to placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O_2 saturation, or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3-hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed.

The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O_2 saturation to the same degree.

Effect of Naloxone:

Physiologic and subjective effects following acute sublingual administration of buprenorphine tablets and buprenorphine/naloxone tablets were similar at equivalent dose levels of buprenorphine. Naloxone had no clinically significant effect when administered by the sublingual route, although blood levels of the drug were measurable. Buprenorphine/naloxone, when administered sublingually to an opioid-dependent cohort, was recognized as an opioid agonist, whereas when administered intramuscularly, combinations of buprenorphine with naloxone produced opioid antagonist actions similar to naloxone. This finding suggests that the naloxone in buprenorphine/naloxone tablets may deter injection of buprenorphine/naloxone tablets by persons with active substantial heroin or other full mu-opioid dependence. However, clinicians should be aware that some opioid-dependent persons, particularly those with a low level of full mu-opioid physical dependence or those whose opioid physical dependence is predominantly to buprenorphine, abuse buprenorphine/naloxone combinations by the intravenous or intranasal route. In methadone-maintained patients and heroin-dependent subjects, IV administration of buprenorphine/naloxone combinations precipitated opioid withdrawal signs and symptoms and was perceived as unpleasant and dysphoric. In morphine-stabilized subjects, intravenously administered combinations of buprenorphine with naloxone produced opioid antagonist and withdrawal signs and symptoms that were ratio-dependent; the most intense withdrawal signs and symptoms were produced by 2:1 and 4:1 ratios, less intense by an 8:1 ratio.

12.3 Pharmacokinetics

Absorption:

Table 3 shows the pharmacokinetic parameters of buprenorphine, norbuprenorphine, and naloxone after administration of SUBOXONE sublingual film in randomized, crossover studies. The pharmacokinetics of the SUBOXONE sublingual film is similar to the pharmacokinetics of the respective dosage strengths of SUBOXONE (buprenorphine/naloxone) sublingual tablets, although not all doses and dose combinations met bioequivalence criteria.

Table 3 Pharmacokinetic parameters of buprenorphine, norbuprenorphine, and naloxone after the sublingual administration of SUBOXONE sublingual film

Dose	Analyte	Mean SD	C_{max} (ng/mL)	T_{max} (h)	AUC_{inf} (h•ng/mL)	$t_{1/2}$ (h)
2 mg/0.5 mg	Buprenorphine	Mean	0.947	1.72	8.654	33.41
		SD	0.374	0.60	2.854	13.01
	Norbuprenorphine	Mean	0.312	2.26	14.52	56.09
		SD	0.140	2.03	5.776	31.14
	Naloxone*	Mean	54.1	0.77	137.3	5.00
		SD	23.0	0.26	43.10	5.52
8 mg/2 mg	Buprenorphine	Mean	3.37	1.53	30.45	32.82
		SD	1.80	0.66	13.03	9.81
	Norbuprenorphine	Mean	1.40	2.17	54.91	41.96
		SD	1.08	2.63	36.01	17.92
	Naloxone*	Mean	193	0.81	480.8	6.25
		SD	91.2	0.19	201.0	3.14

*Naloxone C_{max} expressed as pg/mL. Naloxone AUC_{inf} expressed as h•pg/mL

Distribution:

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Naloxone is approximately 45% protein bound, primarily to albumin.

Metabolism:

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by the CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in-vitro; however, it has not been studied clinically for opioid-like activity. Naloxone undergoes direct glucuronidation to naloxone-3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.

Elimination:

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated). Based on all studies performed with SUBOXONE sublingual film, buprenorphine has a mean elimination half-life from plasma ranging from 24 to 42 hours and naloxone has a mean elimination half-life from plasma ranging from 2 to 12 hours.

Drug-drug Interactions:

CYP3A4 Inhibitors and Inducers: Subjects receiving SUBOXONE sublingual film should be monitored if inhibitors of CYP3A4 such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin) or HIV protease inhibitors and may require dose-reduction of one or both agents. The interaction of buprenorphine with all CYP3A4 inducers has not been studied, therefore it is recommended that patients receiving SUBOXONE sublingual film be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered *[See Drug Interactions (7.1)]*.

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine, has been found to be a moderate CYP2D6 inhibitor in in-vitro studies employing human liver microsomes. However, the relatively low plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic doses are not expected to raise significant drug-drug interaction concerns.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity:

Carcinogenicity data on SUBOXONE sublingual film are not available.

A carcinogenicity study of buprenorphine/naloxone (4:1 ratio of the free bases) was performed in Alderley Park rats. Buprenorphine/naloxone was administered in the diet at doses of approximately 7, 31, and 123 mg/kg/day for 104 weeks (estimated exposure was approximately 4, 18, and 44 times the recommended human sublingual dose of 16/4 mg buprenorphine/naloxone based on buprenorphine AUC comparisons). A statistically significant increase in Leydig cell adenomas was observed in all dose groups. No other drug-related tumors were noted.

Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3, and 35 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) for 27 months. As in the buprenorphine/naloxone carcinogenicity study in rat, statistically significant dose-related increases in Leydig cell tumors occurred. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

Mutagenicity:

The 4:1 combination of buprenorphine and naloxone was not mutagenic in a bacterial mutation assay (Ames test) using four strains of *S. typhimurium* and two strains of *E. coli*. The combination was not clastogenic in an *in vitro* cytogenetic assay in human lymphocytes or in an IV micronucleus test in the rat.

Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (*S. cerevisiae*) for recombinant, gene convertant, or forward mutations; negative in *Bacillus subtilis* "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay.

Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5mg/plate) in a third study. Results were positive in the Green-Tweets (*E. coli*) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both in vivo and in vitro incorporation of [^{3}H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.

Impairment of Fertility:

Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately 28 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) had no adverse effect on fertility.

16 HOW SUPPLIED / STORAGE AND HANDLING

SUBOXONE sublingual film is supplied as an orange rectangular sublingual film with a white printed logo in child-resistant polyester/foil laminated pouches:

- NDC 12496-1202-3 (buprenorphine/naloxone 2 mg/0.5 mg/film; content expressed in terms of free base) - 30 films per carton
- NDC 12496-1208-3 (buprenorphine/naloxone 8 mg/2 mg/film; content expressed in terms of free base) - 30 films per carton

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

Patients should be advised to store buprenorphine-containing medications safely and out of sight and reach of children. Destroy any unused medication appropriately *[see Disposal of Unused SUBOXONE Sublingual Film (17.2)]*.

Rx only

17 PATIENT COUNSELING INFORMATION

17.1 Safe Use

Before initiating treatment with SUBOXONE, explain the points listed below to caregivers and patients. Instruct patients to read the Medication Guide each time SUBOXONE is dispensed because new information may be available.

- Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other CNS depressants (including alcohol) while taking SUBOXONE sublingual film. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their physician. *[see Warnings and Precautions (5.2), Drug Interactions (7.3)]*
- Patients should be advised that SUBOXONE sublingual film contains an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their films in a safe place, and to protect them from theft.
- Patients should be instructed to keep SUBOXONE sublingual film in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients should be advised that if a child is exposed to SUBOXONE sublingual film, medical attention should be sought immediately.
- Patients should be advised never to give SUBOXONE sublingual film to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death.
- Patients should be advised that selling or giving away this medication is against the law.
- Patients should be cautioned that SUBOXONE sublingual film may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving or operating machinery. Caution should be taken especially during drug induction and dose adjustment and until individuals are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities. *[see Warnings and Precautions (5.11)]*
- Patients should be advised not to change the dosage of SUBOXONE sublingual film without consulting their physician.
- Patients should be advised to take SUBOXONE sublingual film once a day.
- Patients should be informed that SUBOXONE sublingual film can cause drug dependence and that withdrawal signs and symptoms may occur when the medication is discontinued.
- Patients seeking to discontinue treatment with buprenorphine for opioid dependence should be advised to work closely with their physician on a tapering schedule and should be apprised of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist/partial agonist medication-assisted treatment.
- Patients should be cautioned that, like other opioids, SUBOXONE sublingual film may produce orthostatic hypotension in ambulatory individuals. *[see Warnings and Precautions. (5.12)]*
- Patients should inform their physician if any other prescription medications, over-the-counter medications, or herbal preparations are prescribed or currently being used. *[see Drug Interactions (7.1, 7.2 and 7.3)]*
- Women of childbearing potential who become pregnant or are planning to become pregnant, should be advised to consult their physician regarding the possible effects of using SUBOXONE sublingual film during pregnancy. *[see Use in Specific Populations (8.1)]*
- Patients should be warned that buprenorphine passes into breast milk. Breast-feeding is not advised in mothers treated with buprenorphine products. *[see Use in Specific Populations (8.3)]*.
- Patients should inform their family members that, in the event of emergency, the treating physician or emergency room staff should be informed that the patient is physically dependent on an opioid and that the patient is being treated with SUBOXONE sublingual film.
- Refer to the Medication Guide for additional information regarding the counseling information.

17.2 Disposal of Unused SUBOXONE Sublingual Film

Unopened SUBOXONE sublingual films should be disposed of as soon as they are no longer needed:

1. Remove the SUBOXONE film from its foil pouch.
2. Drop the SUBOXONE film into the toilet.
3. Repeat steps 1 and 2 for each SUBOXONE film. Flush the toilet after all unneeded films have been put into the toilet.

Foil pouches or cartons should not be flushed down the toilet.

RA017 09/2010
Revised 9/01/2010

Manufactured for Reckitt Benckiser
Pharmaceuticals Inc.,
Richmond, VA 23235 by:
MonoSol Rx, LLC,
Warren, NJ 07059

Distributed by:
Reckitt Benckiser Pharmaceuticals Inc.
Richmond, VA 23235