Suboxone and the Opioid Epidemic

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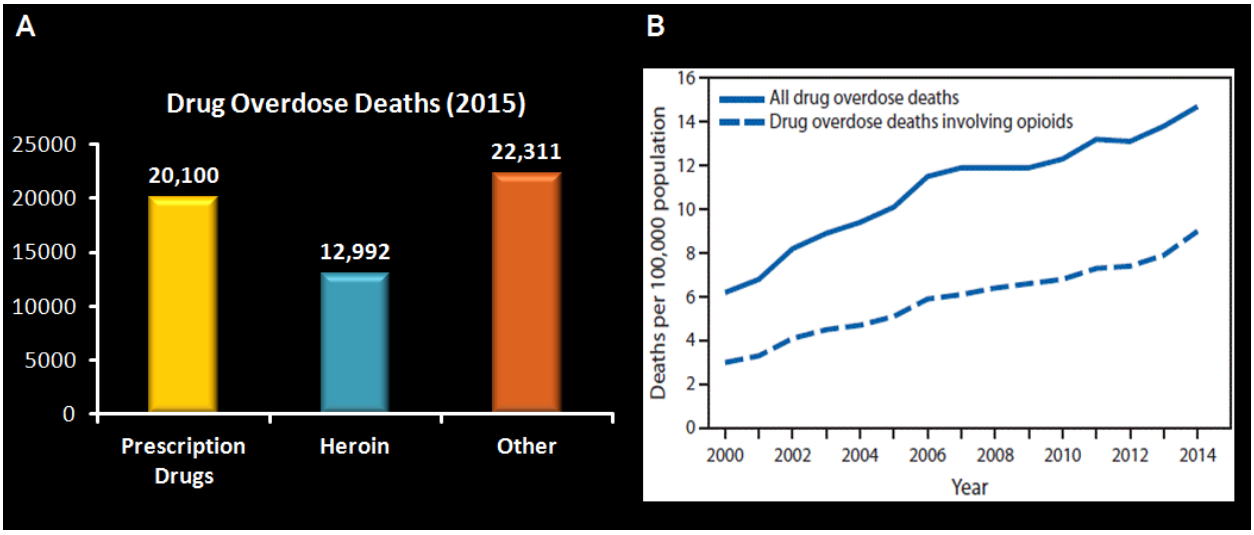
Background

Opium has been used for thousands of years, and extracts concentrated in morphine have been written about since the 1500's. It was not until the early 1800's when the morphine extract was isolated in high purity by Friedrich Sertürner, who immediately demonstrated the danger associated with opiates when used in high concentration. Sertürner injected four people, three boys and himself, all of which nearly died (Dahan, Aarts, and Smith 2010). Still, Sertürner was the first to market morphine, and ironically, did so for treatment of alcohol addiction. Today, opioids are typically prescribed in hospital care and are synthetic or semi-synthetic derivatives of morphine including heroin, and account for a significant percentage of addictions worldwide.

The United States is experiencing an opioid epidemic caused by addictions, toxicity, misprescribing and overprescribing of opioid related treatments for pain management. In the U.S., the lead cause of accidental death is drug overdoses which accounted for approximately 55,403 deaths in 2015. Of those, 36% or 20,101 were due to prescription pain relievers. Heroin, by comparison, accounted for fewer deaths at 23.5% or 12,990 in the same year (Source: CDC Health Statistics, Figure 1A)

Strikingly, drug overdose related deaths are increasing at an alarming rate. From 2000 to 2015, deaths from opioid overdoses increased by approximately **200%** which includes prescription and illicit use (Figure 1B). These deaths have increased with increasing numbers of prescriptions being written; in 2012 there were over 250 million scripts written which is enough for every adult in the US to have an opiate pill bottle (CDC 2014). Further, the number of reported addiction cases and frequency of use has also dramatically risen (Han et al. 2015). These unfortunate trends are all in the face of the introduction of Suboxone, a mixture of two synthetic opioids, that was marketed and sold as a potential treatment to mitigate this very problem. However, as will be outlined here, the label of Suboxone and the respective marketing have not alleviated the opioid epidemic, and has may have made it substantially worse.

FIGURE 1: U.S. DRUG OVERDOSE DEATHS



Panel A: 55,403 drug overdose deaths in the U.S. from prescription, heroin or other agents in 2015. **Panel B**: Increase in drug overdose deaths and opioid related deaths in the U.S. for the period 2000 to 2014.

The lethality of opioid use usually stems from respiratory depression (Dahan et al. 2001; Romberg et al. 2003). Reversal of this negative side effect can be quickly overcome by administration of antagonists for the opioid receptors (Goodman, Le Bourdonnec, and Dolle 2007). While administration of an opioid antagonist such as naloxone can save lives, the situation must be closely monitored due to its short half life. The short half life allows for an acute alleviation of respiratory depression, but an initial heavy dose of opiates can still put the patient at risk again, even without subsequent dosages (Sarton, Teppema, and Dahan 2008).

In this report, we will discuss **Suboxone**, a chemical combination of opioid analogs, and present data that supports our conclusions which include:

(a) Suboxone's current label **does not adequately disclosure** its highly addictive nature and certain other risks; and,

(b) Suboxone's marketing **does not adequately train doctors** (and patients) as to proper dosing levels and certain other dangers, which has caused misprescriptions and overprescriptions.

Further we will discuss circumstances under which, we believe, Suboxone is detrimental to the treatment of opioid addiction. Given the rise of opioid related deaths since Suboxone's approval in 2002, we believe there is now adequate data to support these conclusions.

Suboxone Introduced in 2002

In a seemingly beneficial attempt to combat this issue, Suboxone®, a trade name for the mixture of two opioid derivatives, **buprenorphine** and **naloxone**, was approved by the FDA in 2002 for a treatment for opioid addiction. At that time, buprenorphine and Suboxone were manufactured and marketed by the Reckitt Benckiser Group plc (LSE:RB), a British multinational consumer goods company that markets brands such as Calgon, Lysol and French's mustard. In 2010, the FDA approved a partnership between Reckitt Benckiser and Monosol RX, the developer of PharmFilm - which enables the delivery of drugs through a dissolvable film placed under the tongue, to market a Suboxone sublingual film product to patients.

However, in December 2014, primarily due to mounting concerns about Suboxone's potential liability from consumer or government litigation, Reckitt Benckiser spun off its pharmaceutical division which contained Suboxone, its primary revenue source, and listed the spin off on the London Stock Exchange (LSE) under the name Indivior plc (LSE: INDV).

Buprenorphine is a semi-synthetic derivative of the naturally occurring opiate **thebaine** which can be found in the opium poppy (Nyman and Hall 1976). The other constituent is naloxone (otherwise known as Narcan) which is a pure opioid antagonist and can block opioid analgesic effects (Sawynok, Pinsky, and LaBella 2017).

While naloxone is effective in the treatment of an acute overdose of opioids, it has little benefit alone in addiction treatment. Naloxone is generally regarded as a rescue medication only (van Dorp, Yassen, and Dahan 2007). The combination of an active opioid (buprenorphine) and an opioid antagonist[1] (naloxone) together, has thus been touted as a treatment for opioid addiction.

While Suboxone and buprenorphine have shown benefits in some clinical trials, many of these benefits are only attributed to *reduced "craving"* for opiates or retention in treatment programs. However, as outlined in a study done by Fudala et al., for the most important and relevant factor, *reducing illicit drug use*, **Suboxone does *not* show improvement** (Fudala et al. 2003).

As outlined below, many trials utilizing buprenorphine or **Suboxone fail to reduce opioid use** and consequently, **may simply prolong, complicate, or even worsen** the user's opioid addiction.

As such, we believe that the labeling for Suboxone does not adequately disclose its

[1] Agonists defined as activators of receptors. Antagonists defined as deactivators of receptors. Antagonists can block the effects of agonists such as opioids.

dangers and effectiveness.

Further, we believe that Suboxone's advertising and marketing has failed to adequately train doctors as to:

I. Proper diagnosis methods
II. Dosing levels, which are could often be over-prescribed to patient
III. Tapering and discontinuation regimen, which is arguably the most relevant result for addiction treatment.

Note: *The issues with Suboxone described above are similar to those raised by the FDA in 2007 in its litigation against* ***Purdue Pharma****, a privately held company based in Stamford, CT, and the makers of* ***OxyContin*** *- an opioid-based pain medication. The FDA's case resulted in a settlement consisting of (a) a $600 million fine paid by Purdue Pharma, (b) the resignation of its top 3 executives, including its CEO and (c) $34 million in fines paid personally by its top 3 executives. According to a NY Times article, the judge sought to impose jail time for the top 3 executives, but was unable to include this in the settlement terms.*

In 2015, Forbes published its list of wealthiest families in the U.S. and included for the first time, the 100% owners of Purdue Pharma, 94 year old Raymond and Beverly Sackler of Greenwich, CT whose personal net worth was estimated at $14 billion.

How did the Sacklers build the 16th largest fortune in the U.S. edging out storied families like the Busches, Mellons and Rockefellers? The short answer is by making the most popular and controversial opioid of the 21st century – OxyContin. Forbes estimates that Purdue Pharma's OxyContin has generated over $35 billion in revenue through 2015.

Suboxone's Weak Data

The statistics presented in this report cover over a decade of data since the approval of Suboxone, a drug that has represented itself as a treatment for opioid related addictions. To the best of our knowledge, studies commissioned by Suboxone's manufacturer, Reckitt Benckiser (or later, by its spin off company, Indivior), have generally presented data from relatively short periods of time.

One of the largest analyses of multiple studies conducted on opioid-addiction treatments consisted of over 5,400 participants across 31 trials. The analysis concluded that while buprenorphine used for the treatment of opioid addiction was able to retain participants in treatment programs better than placebo, **buprenorphine did not lower other opioid use** as determined by urinalysis (Mattick et al. 1996).

In many studies where urine analysis was deemed to show *negative* results, it should be noted that the semi-synthetic or synthetic[2] opioids were not screened. For instance, a journal claiming significance in diminished opiate use with Suboxone *via* urinalysis tested only for **opiates**, not **opioids** such as oxycodone, fentanyl, or meperidine (Fudala et al. 2003). A similar study, "did not always include a test for oxycodone" (Finch, Kamien, and Amass 2007). Since these opioids are some of the most widely used illicit painkillers, it is inconceivable we believe, that such studies can claim efficacy - if it does not test for them.

Another study demonstrated a significance in keeping patients in treatment from relapsing at 154 in-patient days, but **buprenorphine had only a 10% relapse-free rate**, which questions its effectiveness over the longer term (Schottenfeld, Chawarski, and Mazlan 2008).

Similarly, a study meant to assess the positive benefits of Suboxone or methadone for treatment of opioid use determined that **there was no difference among placebo**, **methadone, or Suboxone** for positive (finding employment, documented social/family improvement) or negative (missed/positive urinalysis, violation of terms of probation) events (Cradick et al. 2014).

In perhaps the most objective and reliable studies done post-Suboxone's approval, the NIH funded two studies (here and here) that were deemed "promising". This "success" was largely attributed to lowered opioid use during treatment in conjunction with greater treatment retention. However, on closer examination, the success is not so clear cut:

"Participants assigned to extended Suboxone treatment were much less likely to provide opioid-positive urine samples at ***weeks 4 and 8, but not at week 12 (when the dose had tapered off)*** *than those in the standard detoxification group.* ***Follow-up evaluations at months 6, 9 and 12 showed increased rates of opioid use in both groups*** *compared to the end of the treatment period"*

This should be alarming, as these are the results from the NIH, one of the largest and foremost research institutions worldwide. This decline in efficacy after treatment ends is highlighted strongly when looking at the actual numbers:

> *"Results showed that approximately 49 percent of participants reduced prescription painkiller abuse during extended (at least 12-week) Suboxone treatment.* ***This success rate dropped to 8.6 percent once Suboxone was discontinued."***

[2] Semi-synthetic refers to opioids that are derived from their natural source, but modified with synthetic chemistry, such as oxycodone or heroin. Synthetic refers to opioids that are not derived from a natural source, and fully synthesized in the lab, such as Fentanyl.

If the NIH has a problem finding efficacy, and demonstrates a clear weakness to the success of the treatment after retention is no longer obligated, the perspective to support Suboxone as an effective treatment option for opioid addiction is significantly weakened.

While the reductionist reasoning behind the use of an opioid and an opioid-antagonist for an opioid addiction mitigation strategy is understandable, we believe it requires additional extensive long-term studies to truly identify its potential impact in drug addiction treatment. These studies should include assessment for all opioid use, treatment-program retention, and most importantly, the ability to **eventually stop all opioid use** (including buprenorphine and naloxone). The current state of research on the subject, in our opinion, indicates that the opioid addiction problem that Suboxone represents it is solving, **does in fact, continue to exist** - even when combining Suboxone with patient treatment programs.

We believe the most logical treatment for opioid addiction is **not** another opioid such as buprenorphine - which is a merely a transfer of one opioid related addiction to another.

An oversimplified analogy of the misplaced logic for providing buprenorphine to opioid addicts, would be to *provide shots of Jack Daniel's whiskey as a treatment to alcoholics*. *Further, by only screening for opiates (and not opioids) during treatment, and then, claim a "negative urine sample" - is analogous to screening alcoholics for beer consumption, but forgetting to test for liquor*.

Suboxone Antagonism and Withdrawals

To understand why we believe that **Suboxone's withdrawal symptoms are similar to heroin**, it helps to understand (i) the role of the opioid receptors in the human brain, (ii) how various agents - buprenorphine, naloxone, morphine, and heroin affect the brain's opioid receptors, and (iii) the resulting effects on opioid addicts.

There are 3 major opioid receptors in the brain that are responsible for the therapeutic effects of commonly used opioids, **μ** ("mu"), **κ** ("kappa"), and **δ** ("delta").

Below is a simplified table outlining the pharmacodynamic[3] properties of opioids - buprenorphine, naloxone, morphine, and heroin, and their effects on the 3 opioid receptors in the human brain.

[3] **Pharmacodynamics** is the study of the biochemical and physiologic effects of drugs, especially pharmaceutical drugs. The majority of drugs either (a) mimic or inhibit normal physiological/biochemical processes or inhibit pathological processes in animals or (b) inhibit vital processes of endo-or ectoparasites and microbial organisms.

The term "**agonist**" indicates that the drug ***activates* the receptor's effects,** and the term **"antagonist"** means it ***inactives*, or *blocks*, the receptor's response.** For the purposes of this report, a *partial* agonist means it *partially* activates the receptor.

FIGURE 2: OPIOID ACTIVATIONS ON THE BRAIN'S 3 OPIOID RECEPTORS

Opioid Receptor	Effects	Bupenorphine	Naloxone	Morphine	Heroin
μ	Euphoria Analgesia	Partial Agonist	Antagonist	Agonist	Agonist
κ	Depression Sedation	Antagonist	Antagonist	Agonist	Agonist
δ	Analgesia Antidepressant	Antagonist	Antagonist	Agonist	Agonist

In general, the **μ-("mu")** receptor leads to the euphoria that opioid addicts seek.

As can be seen above, both morphine and heroin activate the **μ** receptor, while buprenorphine only partially activates. While not exceptionally important, buprenorphine does show some ability to be an inverse agonist when used in conjunction of opioids (Wang, Sun, and Sadee 2007).

Buprenorphine's ***partial agonist*** activity on **μ** and **antagonist** activity on **κ** and **δ** was the basis for the view that it may inhibit the behavior of an opioid addict. However this alone does not support a conclusion for its use in opioid addiction.

Regarding Naloxone, its overdose treatment effects are due to its ***antagonist* activity** on all the opioid receptors shown in Figure 2. Naloxone is able to bind very effectively to the receptors which results in a displacement and essential inactivation of any opioid use. This antagonistic activity can save the life of someone who overdoses by *displacing* the overdosed opioid, and hence it's inclusion in Suboxone.

However, an essential aspect to Suboxone's inadequacy as a true treatment for opioid addiction is that it can have **withdrawal symptoms similar to that of heroin** (Blum et al. 2013). *The fact that Suboxone can cause withdrawals requires it to act in a similar manner and provide similar effects to the opioids it claims to provide treatment for!*

The fact that withdrawal symptoms exist with Suboxone discontinuation is supportive evidence that **Suboxone displays serious addictive properties**. This further complicates Suboxone as a treatment since one of the most beneficial aspects Suboxone claims in most of its sponsored studies - was its increase in treatment program retention. However, this "success marker" does not adequately take into account (i) the **difficulties for patients to stop use of Suboxone,** and (ii) the fact that **buprenorphine itself acts as an opioid**. Giving patients an opioid that elicits opiate-like effects, and then claiming success when patients use less opioids seems to be a redundant measure of efficacy.

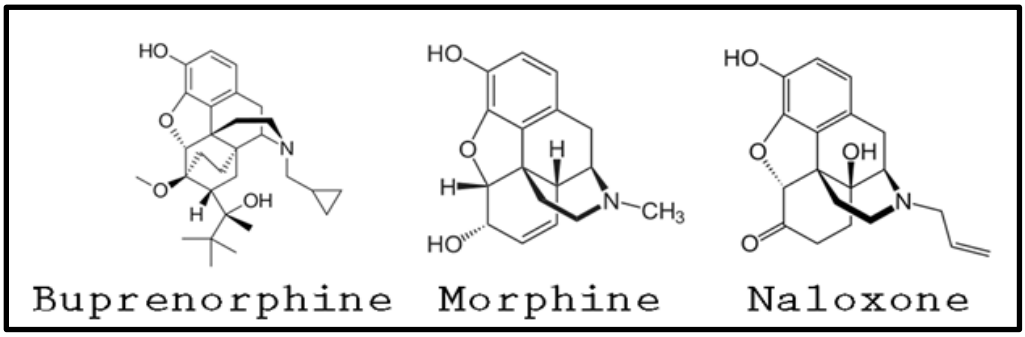
Again, the large study cited above showed moderate evidence that while Suboxone was able to keep participants in treatment programs longer than placebo, **urine analyses indicated that opioid use was similar between Suboxone users and placecbo.** This could be partially explained by the fact that buprenorphine does not directly treat addiction, but rather gives patients a weak opioid "high".

Suboxone Dangers

Buprenorphine alone can cause opioid effects such as euphoria, sedation, and analgesia (Walsh et al. 1994). This may be effective in lowering the dependence issues of an opioid addict, as the treatment partially fills the drug-seeking behavior, but *the underlying neurological mechanisms of addiction are not treated in an effective manner*, and the patient *is still using opioids.*

Based on the availability of "Suboxone addiction" treatment centers through internet searches, and the plethora of forums with posts dealing with difficulties in Suboxone addiction, it seems **common that patients find themselves addicted to Suboxone itself.** Clearly, Suboxone is not an ideal candidate for addiction treatment alone, as many patients indicate their **addiction simply changes** from the original pain medication to the Suboxone addiction treatment.

FIGURE 3: CHEMICAL STRUCTURES OF BUPRENORPHINE, MORPHINE, AND NALOXONE



One aspect of Suboxone that is deceivingly claimed as beneficial is the "**ceiling" effect** of the "high". This ceiling effect causes a limit to the "high" a user can experience with Suboxone. Therefore, patients will find that increasing the Suboxone dose actually generates diminishing returns in its euphoric effects.

While seemingly beneficial, this ceiling hides a dangerous effect of the antagonistic nature of the naloxone and buprenorphine constituents. By increasing the Suboxone dose, the patient actually **decreases sensitivity to *all* opioids** while on Suboxone (Bowdle 1998).

The concomitant use of Suboxone and any illicit opioids requires the patient to increase their illicit dose in order to achieve the same level of euphoria that the patient was accustomed to before treatment began. **This simultaneous use of Suboxone and illicit opioids** could certainly result in doses that were previously lethal, but due to Suboxone's antagonistic effects, are now non-lethal.

The danger may then be amplified if the patient *stops* Suboxone treatment for any reason, but continues using other opioids - as the opioid dose threshold required with Suboxone may now prove lethal *without* the Suboxone treatment.

Thus, we believe that **Suboxone patients are not properly informed of this danger** as it is not disclosed adequately on Suboxone's label.

Further, prescribing directions to doctors we believe, **lack an adequate explanation** of this and other risks of Suboxone.

Suboxone Labeling

Suboxone has represented itself as a treatment for opioid addiction. Reckitt Benckiser (and today, its spinoff, Indivior) was the manufacturer of buprenorphine and has funded many

of the studies that show support for Suboxone.

However, a careful review of relevant scientific literature demonstrates ample evidence that while Suboxone may show some benefits in opioid addiction recovery over the short term, there is **substantial information supporting Suboxone's negative effects** which appears to be either ignored or unknown by the FDA.

FIGURE 4: INCREASE IN EMERGENCY ROOM VISITS RESULTING FROM SUBOXONE

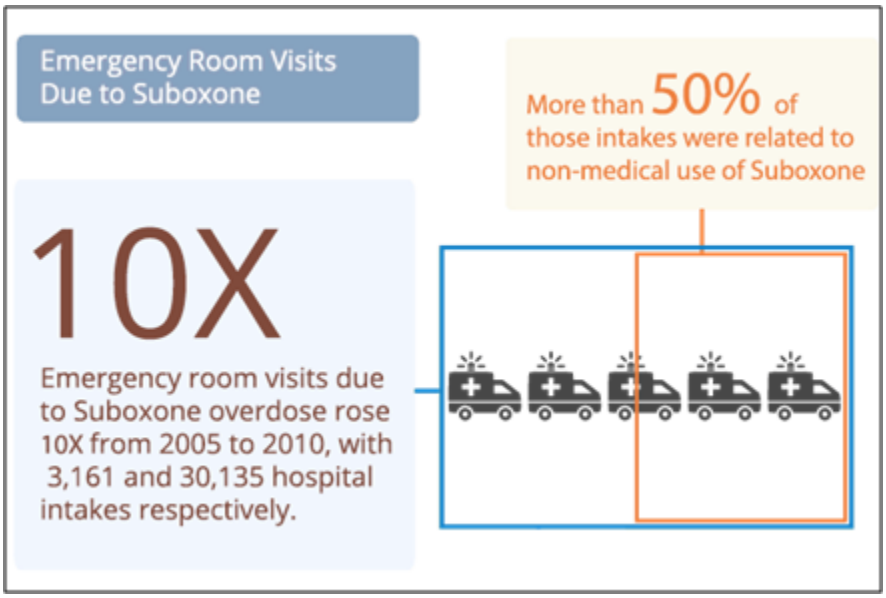


Figure 4 source

The FDA labels for Suboxone can be viewed here and here and here. Astoundingly, **very little on Suboxone's label specifically addresses "*addiction*"** and the dangers (which include the risk of death) is minimally covered.

Buprenorphine represents itself as a schedule III drug, indicating it has less abuse potential than methadone (Schedule II, is also used for opioid addiction treatment). However, buprenorphine's label discloses the following danger warnings (**which do not appear on the Suboxone labels).**

- *Chronic administration produces **opioid-type physical dependence***
- *Abrupt discontinuation or rapid dose taper may result in **opioid withdrawal syndrome***
- ***Neonatal withdrawal** has been reported following use of buprenorphine by the*

mother during pregnancy.

- *A marked and **intense withdrawal symptom 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.*

We believe that **buprenorphine's** opioid-type physical dependence, opioid-like withdrawal, and neonatal withdrawal symptoms indicate that **Reckitt Benckiser (Indivior) have falsely represents buprenorphine as a Schedule III drug.** We believe **buprenorphine** should be classified as a Schedule II drug, along with the other opioids such as morphine, codeine, hydrocodone, oxycodone, etc.

Further, the buprenorphine label indicates that "mis-use" of buprenorphine leads to addictive behavior. However, "**mis-use" is not an accurate disclosure term** we believe - as the addictive nature of buprenorphine has clearly been documented in patients under treatment with prescribed doses.

Additionally, as cited earlier, buprenorphine has a 'ceiling' dose effect which would make Suboxone treatment of little benefit. This supports our belief that **Suboxone actually promotes abuse and greater addiction.**

Suboxone's prescribing information is available online to view here, and is briefly outlined below.

- ***Day 1** Only upon moderate withdrawal symptoms should the first dose be taken.*
  - *8 mg/2 mg Suboxone sublingual film total.*
  - *Start with an initial dose of 2 mg/0.5 mg or 4 mg/1 mg buprenorphine/naloxone.*
  - *Titrate upwards in 2 or 4 mg increments of buprenorphine, at 2-hour intervals, under supervision, to total dose*
- ***Day 2** Single daily dose of up to 16 mg/4 mg Suboxone*
- ***Day 3+** Maintenance: Increments of 2 mg/0.5 mg or 4 mg/1 mg buprenorphine/naloxone until withdrawal ceases, 16 mg/4 mg per day is recommended*
- ***Stopping & Tapering**: Taper dose to avoid withdrawal symptoms*

We note that Suboxone's prescribing instructions **are very general.** To illustrate, Suboxone does not disclose ***when*** to begin the tapering process. Further, there are no instructions as to ***how*** to execute the tapering process. Tapering could be the most important step for successful discontinuation of opioid use, however Suboxone's label seems to ignore this aspect of treatment. *How, then, can an opioid-containing prescription drug be used for the treatment of opioid-based addiction, if there is no instructions on how or when to discontinue use?*

As such, it is left **to the patient to make important** (and life threatening) **tapering decisions** when using Suboxone. We believe supports our opinion that Suboxone's training of doctors is wholly inadequate and has led to overdose deaths.

Suboxone Investigations, Litigation and Contingent Liabilities

In connection with Suboxone, there are various pending investigations and litigation against Indivior (or Reckitt Benckiser) which has produced the following contingent liability reports as of November 2016.

In our opinion, there is **inadequate financial disclosures to investors** by publicly listed Reckitt Benckiser and Indivior as to potential contingent liabilities in connection with pending and expected litigation with Suboxone.

We believe there may be material contingent liabilities to these companies in connection with Suboxone and that investor protection agencies such as state attorneys general should investigate further. These are the current contingent liabilities that are disclosed by the company.

Department of Justice Investigation

- A federal criminal grand jury investigation of **Indivior initiated in December 2013** is continuing, and includes marketing and promotion practices, paediatric safety claims, and overprescribing of medication by certain physicians. The U.S. Attorney's Office for the Western District of Virginia has served a number of subpoenas relating to SUBOXONE® Film, SUBOXONE® Tablet, SUBUTEX® Tablet, buprenorphine and our competitors, among other issues. We are in the process of responding by producing documents and other information in connection with this on-going investigation, and in preliminary discussion about a possible resolution of the investigation. We are cooperating fully with the relevant agencies and prosecutors and will continue to do so.

FTC Investigation and Antitrust Litigation

- The Judge overseeing the legal privilege dispute in the FTC investigation has appointed a Special Master (an independent external lawyer) to investigate the claims of legal privilege and provide a recommendation to the Court on how the documents at issue should be treated. An initial report and recommendation relating to the first tranche of privileged documents reviewed by the Special Master was finalized in April 2016 and adopted by the Court on August 1st, 2016. Pursuant to this report and the Court's order, **Indivior** produced certain additional documents. A second tranche of documents remains under review. Following that review, the Court's decision then may be subject to appeal by either party.
- Fact discovery is continuing in the antitrust class action litigation described on our Annual Report ("Class Action Litigation"). Plaintiffs allege, among other things, that Indivior violated federal and state antitrust laws by attempting to delay generic entry of alternatives to SUBOXONE tablets, and plaintiffs further allege that Indivior unlawfully acted to lower the market share of these generic products.
- Amneal Pharmaceuticals LLC, a manufacturer of generic buprenorphine / naloxone tablets, filed a complaint against the Company in December 2015. This case has been coordinated with the Class Action litigation. Amneal's complaint contains antitrust allegations similar in nature to those set out in the class action complaints, and Amneal has also alleged violations of the Lanham Act.
- On September 22, 2016, 35 states and the District of Columbia filed a complaint against the Company in the same district where the Class Action and Amneal litigation is pending. The States' complaint is similar to the other pending complaints, and alleges violations of state and federal antitrust and consumer protection laws. On October 25, 2016, the Company was informed that the States plan to amend their complaint to add six additional states as plaintiffs. This lawsuit relates to the investigation conducted by various states, as discussed in previous filings.
- On October 12, 2016, the Company was served with a subpoena for records from the state of Connecticut Office of the Attorney General under its Connecticut civil false claims act authority. The subpoena requests documents related to the Company's marketing and promotion of SUBOXONE® products and its interactions with a non-profit third party organization. The Company is cooperating in this investigation.

ANDA Litigation

- The ruling after trial against Actavis and Par in the lawsuit involving the Orange Book-listed patents for Suboxone® Film issued on June 3rd, 2016. Ruling found the asserted claims of the '514 patent valid and infringed; the asserted claims of the '150 patent valid but not infringed; and the asserted claims of the '832 patent invalid, but found that certain claims would be infringed if they were valid.
- Based on the ruling as to the '514 patent, Actavis and Par are currently enjoined from launching a generic product. Par has appealed and Actavis is expected to appeal this ruling. The generics have also moved to reopen the judgment based on a more stringent claim construction in the Teva case. In light of the motions to reopen, Par's appeal has been deactivated until the District Court rules on the motions, and the deadline for Actavis to file a notice of appeal has been postponed.
- Trial against Dr. Reddy's, Actavis and Par in the lawsuits involving the process patent (US Patent No. 8,900,497) scheduled for November 16th and 21st -23rd, 2016.
- Trial against Dr. Reddy's in the lawsuit involving the Orange Book-listed patents for Suboxone® Film scheduled for November 7th, 16th , and 21st- -23rd, 2016, with Dr. Reddy's 30-month stay of FDA approval on ANDA No. 20-5806 expiring April 17th, 2017. Indivior believes Dr. Reddy's 30-month stay of FDA approval on ANDA No. 20-5299 also expires on April 17th, 2017, however, Dr Reddy's disputes the applicability of the stay to this ANDA.
- Trial against Alvogen in the lawsuit involving the Orange Book-listed patents and the '497 process patent for Suboxone® Film originally scheduled for April 2017 is expected to be rescheduled to a date later in the year, with Alvogen's 30-month stay of FDA approval expiring October 29th, 2017.
- By a Court order dated August 22nd, 2016, Indivior's Suboxone® Film patent litigation against Sandoz has been dismissed without prejudice because Sandoz is no longer pursuing Paragraph IV certifications for its proposed generic formulations of Suboxone® film.
- Trial against Mylan in the lawsuit involving the Orange Book-listed patents for Suboxone® Film is scheduled for September 25th, 2017, with Mylan's stay expiring March 24, 2018.
- Indivior received a Paragraph IV notification from Teva, dated February 8, 2016, indicating that Teva had filed a 505(b)(2) New Drug Application (NDA) for a

16mg/4mg strength of Buprenorphine/naloxone sublingual film. The Indivior Group and Teva agreed that infringement by Teva's 16 mg/4 mg dosage strength will be governed by the infringement ruling on the accused 8 mg/2 mg dosage strength in its ANDA currently scheduled for trial in November 2016.

- The USPTO declined to institute Teva's petitions for inter partes review of the three Orange Book-listed patents on procedural grounds.
- Dr. Reddy's has filed an inter partes review petition on each of the three Orange Book Patents. These petitions are substantively similar to those filed by Teva.
- Certain claims of the '832 patent were found invalid in an IPR proceeding, a decision that has been affirmed by the Court of Appeals for the Federal Circuit.
- In the event of a ruling in these matters that none of the claims of the asserted patents are valid and infringed by the ANDA-filers, and should there be FDA approval of one or more of the ANDAs and subsequent commercial launch of generic SUBOXONE® film, and pipeline products fail to obtain regulatory approval, there is the likelihood that revenues and operating profits of the Company will decline. In these circumstances the Directors believe they would be able to take the required steps to reduce the cost base, however this would result in a significant change to the structure of the business.

Suboxone Addiction Comments from Online Forums

The probability of relapse and continued addiction versus sobriety is not well documented over long periods of time. The prevalence of social media and forums that discuss Suboxone addiction and relapse as ongoing major issues among recovering opioid addicts is a strong indication that **Suboxone may be causing more harm than benefits.**

Further, we believe **Suboxone may be no more beneficial than simple tapered-opioid regimes.**

Since it is difficult to obtain objective data on the full effects experienced by patients with Suboxone treatment, or the extent of prescriber-patient interaction, selected discussions from online forums below describe the negative long-term and harmful results experienced by patients on prescribed Suboxone treatment.

Of note, these discussions are only a small sample of the many discussions at online forums. While not peer-reviewed or independently investigated, the sheer number of these comments cannot be ignored.

Hyperlink	Drug	Info
Drugs.com	Suboxone and Relapse	Married mother addicted to Suboxone
SuboxoneForum	Relapse after 2 years	Doctor says “You can only get off Suboxone once”.
TheFix	Suboxone Addiction	Blog states Suboxone is no less addictive than other opioids
TheDailyBeast	Suboxone in Prison	Claims Suboxone has overtaken heroin in amounts smuggled into prisons.
AddictionRecoveryGuide	Subutex (buprenorphine)	Patient addicted to buprenorphine for 4 years.
Drugs.com	Suboxone	Patient addicted to Suboxone for 2 years.
Drugs-forum.com	Suboxone	Patient put on opiates, became addicted, put on Suboxone, became addicted.

Further, there are numerous other disturbing findings from opioid addiction online forums. Above are highlights of some of the most common claims of patients having trouble with Suboxone treatment.

Since Suboxone is an opioid in itself and does not treat the addiction symptoms on the neurological level, therapy and treatment programs are highly necessary in most cases for addiction to be diminished.

Inadequate Patient Diagnosis for Suboxone Treatment

We’ve read extensively that **prescribing physicians do not always require patients to**

partake in any treatment programs, and that Suboxone treatment may only consist of one in-office visit.

Financial Incentives to Over-Prescribe Suboxone

Doctors may require patients to **pay the physician directly at $10 per pill** (single daily dose). Patients have reported a belief that doctors do this for profit.

Serious Withdrawal Symptoms with Suboxone

Many patients claim that **Suboxone is harder to quit than their prescription opioids** that brought them to addiction treatment in the first place.

Dangerous Respiratory Depression with Suboxone

Suboxone and other opioids may cause respiratory depression. Many patients state they were **prescribed benzodiazepines in parallel with Suboxone**. The combination of benzodiazepines and either Suboxone or opioids can cause significant respiratory depression which has been the cause of many deaths with patients using Suboxone. We believe many doctors are not aware of this danger.

Financial Cost of Treatment for Suboxone and Opioid Addicts

Doctors may charge hundreds of dollars to a patient for an appointment to be treated for a Suboxone addiction. Then, doctors are expected to write a new prescription or personally hand out Suboxone to the patient. The cost of such treatment may cause patients to seek heroin or other drugs due to financial problems, increasing the chance of relapse or death. Further, dangers are associated with the lack of understanding of the ceiling effects and antagonism associated with Suboxone “treatment”.

Doctors Not Committed to Get Patients Off Suboxone or Other Maintenance Drugs

There are many patients that discuss Suboxone and maintenance drugs in general, as **only a means that prolong addiction,** and that many medical prescribers are largely uninformed or have little intent of helping patients off Suboxone or such maintenance drugs. Instead, patients must seek self-help online forums, private and non-medical treatment centers to get off Suboxone and other maintenance drugs.

Suboxone’s Impact on the Brain’s Receptors Causes Craving for Opioids

Due to the conflicting partial-agonist and antagonist effects of buprenorphine and

naloxone, the ingredients in Suboxone, some patients claim that tapering with Suboxone actually causes an ***increase*** **in the need for opioids** , making the Suboxone taper actually counter-productive for quitting an opioid addiction.

Conclusions

Together, the neurological understanding of opioids and the large studies done on Suboxone treatment indicate to us that:

1. Suboxone activates the opioid receptors, induces euphoria that opioid addicts seek, and can **cause withdrawals similar to heroin.**

2. Buprenorphine, an active ingredient in Suboxone **can cause respiratory depression** (Naloxone, n.d.).

3. Suboxone's efficacy has been prematurely determined based on (1) opioid treatment retention and (2) negative illicit opioid urine samples - **not sobriety from opioids** over longer periods.

4. Many studies funded by Indivior **were inadequate** that evaluated Suboxone's efficacy based on limited data from urine samples - as they did not screen for the semi-synthetic or synthetic agonists such as oxycodone or fentanyl.

5. The antagonist activity of Suboxone on the opioid brain receptors could potentially **increase the dangers of overdose and death.**

6. Many independent studies on Suboxone have shown **no difference between placebo and Suboxone** for illicit opioid use.

Additionally, **many patient testimonials indicate that Suboxone treatment may prolong the addiction problem** and requires **extensive out-of-pocket payments**.

Prescription requirements and diagnosis for Suboxone treatment seem to be informal at best, and many doctors appear to not require patients to join an addiction treatment program.

Additionally, there is no maximum time frame for Suboxone treatment, i.e. there are no controlled trials for discontinuation of use, indicating it was not the intent of the

pharmaceutical producer to cure opioid addiction, but to provide maintenance indefinitely (which can be seen as just replacement).

Yet, even in the face of substantial independent research showing little evidence for efficacy in actually treating opioid addiction, a substantial profit has been made by Reckitt Benckiser and Indivior and this profit is being made in the face of rising deaths caused by prescription drug overdoses.

*While researching naloxone/bupenorphine treatment trials, it is essential to identify the funding source of the investigators. Multiple studies disclose funding sources as the pharmaceutical companies whose product seeks FDA approval, which can bias results.

A list of pharmaceutical-company funded research:
http://www.sciencedirect.com/science/article/pii/S037687160900115X
http://onlinelibrary.wiley.com/doi/10.1111/j.1521-0391.2011.00186.x/full
http://www.sciencedirect.com/science/article/pii/S0140673603126001

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Naloxone, Structural Formula O. F. n.d. “Naloxone Hydrochloride Is a White to Slightly off-White Powder and Is Soluble in Water, in Dilute Acids and in Strong Alkali. Chemically, Naloxone Is 17-Allyl-4, 5 α -Epoxy-3, 14- Dihydroxymorphinan-6-One Hydrochloride. Naloxone Hydrochloride Has the Molecular Formula CHNO HCl .2HO and the Molecular Weight Is 399.87.” https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM191529.pdf.

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Appendix of Media on Suboxone and the Opioid Epidemic

Suboxone: The New Drug Epidemic?

> "This is insanity," says Percy Menzies, a pharmacist and addiction expert. "Buprenorphine is one of the most abused pharmaceuticals in the world. "We took an abused drug and we said let's use it to treat addiction to heroin and opiates."

Emergency Department Visits Involving Buprenorphine

- Emergency department (ED) visits involving buprenorphine increased substantially from 3,161 in 2005 to 30,135 visits in 2010, as availability of the drug increased
- In 2010, most buprenorphine-related ED visits were classified as nonmedical use of pharmaceuticals (52 percent, or 15,778 visits), followed by patients seeking detoxification or substance abuse treatment (24 percent, or 7,372 visits) and adverse reactions (13 percent, or 4,017 visits)
- Buprenorphine-related ED visits involving nonmedical use of pharmaceuticals increased 255 percent from 4,440 visits in 2006 to 15,778 visits in 2010
- Additional drugs were involved in 59 percent of buprenorphine-related ED visits involving nonmedical use of pharmaceuticals in 2010

Drug Overdoses Spur Rise in Accidental Deaths, Says Report

> One obvious place to reduce deaths is by drug overdoses. More than 2 million Americans abuse prescription drugs, the report says,with heroin use on the upswing again.

Recovering heroin addict explains why so many people fail out of rehab after a few days

> "When I was on Suboxone [a brand name version of buprenorphine], I felt like I could do it," Peterson said. "Every time I came off of it, I wanted to get high and I couldn't get that thought out of my head long enough to focus on anything else. It was a constant, 'I need to use right now.'"

For Opioid-Addicted Infants, a New Treatment Option

[The Dangers of Long Term Suboxone Use]

Patients being prescribed Suboxone were told this prescribed medicine would be the solution to their problem of drug addiction. In addition to the fact that a patient is still physically dependent on a substance to function, there are several disturbing effects of Suboxone that are rarely discussed.

[The Suboxone Problem No One Is Talking About]

The act suggested that buprenorphine treatment be combined with regular urine screenings and counseling. The key word here is *suggested*, and it's a terrible flaw.

[Suboxone: Concerns Behind the Miracle]

When used in the short term, Suboxone is the best detox drug I have ever seen-it can immediately stabilize a patient's life, and this can be done in an outpatient setting. When used long-term, though, it is the hardest medication I have ever dealt with in terms of detoxing a patient from it.

[Addiction Treatment With a Dark Side]

Suboxone did not save Miles Malone, 20; it killed him. In 2010, a friend texted Mr. Malone an invitation to use the drug recreationally — "we can do the suboxins as soon as I give them to u, right, dude?" — and he died that night in South Berwick, Me., of buprenorphine poisoning. The friend, Shawn Verrill, was sentenced this summer to 71 months in prison.

About the Author

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Disclosures

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