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Is the Use of the Drug Buprenorphine and Naloxone (Suboxone) as Effective in Suppressing Opioid Dependency and Its Withdrawal Symptoms, or Is It Simply a Surrogate for the Opiate With the Addictive Results?

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Is the use of the drug Buprenorphine and Naloxone (Suboxone) is effective in suppressing opioid dependency and its withdrawal symptoms, or is it simply a surrogate for the opiate with the same addictive results?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not the use of the drug Buprenorphine and Naloxone (Suboxone) is effective in suppressing opioid dependency and its withdrawal symptoms, or is it simply a surrogate for the opiate with the same addictive results.

Study Design: Review of three primary studies in the English language published in 2010 and 2011.

Data sources: Randomized, controlled and double blind clinical trials evaluating the effectiveness of Suboxone in signs and symptoms of opioid withdrawal were found using the EBSCO Host and Lexi-Comp databases.

Outcome(s) Measured: Likability of the drug versus the placebo using Visual Analog Scale (VAS), side effects, withdrawal symptoms using Clinical Opiate Withdrawal Scale (COWS), abuse potential, and drug questionnaires.

Results: Three randomized controlled trials were included in this review. Suboxone was shown to be effective in the prevention of signs and symptoms of withdrawal. However, when compared to heroin participants, were significantly less willing to take low or high dose Suboxone again. Previous studies reported that addition of naloxone to bupornephrine reduced the potential of misuse.

Conclusions: All three RCT proved the effectiveness of Suboxone in the management of signs and symptoms of opioid withdrawal with no reports of misuse. Limitations in Middleton's study resulted in difficultly determining if the observed difference in abuse potential between intranasal buprenorphine and Suboxone was accurate with the studies done. Strain's study showed that there was a significant decrease in observable withdrawal signs after administration of Suboxone when compared to baseline. The higher progressive ratio breakpoint for high dose Suboxone was similar to low dose bupornephrine in Comer's study. This suggested that the naloxone component attenuated the euphoric effects of buprenorphine, resulting in decrease misuse potential.

Key Words: Suboxone, opioid, abuse, withdrawal

INTRODUCTION

Opioid dependency is characterized by the continued use of opioids despite significant opioid-induced problems. Dependency can result from the overuse of prescription drugs or from illicit drug use.[1]This paper encompasses three randomized controlled trials comparing buprenorphine/naloxone (Suboxone) effects versus placebo effects on patients going through drug withdrawal, while also looking at the abuse potential for Suboxone alone. Suboxone is known to be an effective opioid dependence pharmacotherapy, but there have been reports of misuse as well.

This topic is relevant to practice everywhere because it is a disease that a practitioner in any specialty will encounter. According to the Department of Health and Human Services, approximately 213,000 individuals aged 12 years and older are dependent on or abuse heroin, and 1,707,000 individuals 12 years and older are dependent on prescription pain medications.[3] Not only is opioid dependence or abuse extremely common, the amount of medical costs is astounding. In 1996, it was estimated that the total cost of heroin addiction, including medical costs, were $21.9 billion, while also accounting for most emergency department visits.[2] Opioid dependence accounted for 66% of visits in the ED from 2004 to 2007.[3] From 2005 to 2007, there was a 55% increase in ED visits for drug-related suicide attempts involving opioids; 16% of ED visits for drug-related suicide attempts in 2007 involved opioids.[3] In 2000, the US Congress passed the Drug Addiction Treatment Act, which allows qualified physicians to treat opioid addiction with schedule III-V narcotics approved by the US Food and Drug Administration for opioid dependence treatment.[2] This allowed for opioid treatment outside of methadone clinics, resulting in patients with opioid dependence history to be treated by their primary care physician.

Opioid dependency is a national problem and can include misuse of morphine, heroin, codeine, meperidine, and hydromorphine. When a patient takes these drugs they will feel an initial "rush" which is followed by a sense of wellbeing. Physical signs to look for in a patient you suspect is on opioids will be: pupillary constriction, respiratory depression, slurred speech, hypotension, bradycardia, and hypothermia.[4]According to the DSM criteria, dependence is considered when a patient has three or more of the following, occurring at any time in a 12-month period: tolerance, withdrawal, repeated excessive use, persistent failed efforts to cut down, excessive time spent trying to obtain substance, reduction in important social, occupational, or recreational activities, and continued used despite awareness that substance is the cause of psychological or physical difficulties.[4]Withdrawal symptoms include: anxiety, pupillary dilation, diaphoresis, tachycardia, fever, diarrhea, insomnia, yawning, vomiting, piloerection, muscle aches, seizures, hypertension and abdominal cramps.[4]

The recommended method of treatment for opioid dependence include: methadone, buprenorphine, Suboxone, combined with therapy. For the purpose of this paper the focus will be Suboxone, which can help reduce physical withdrawal symptoms and cravings. When a person takes an opiate, the drug attaches to mu receptors, which then releases dopamine, which results in pleasurable feelings.[5] As the opioids leave the receptors, the pleasurable feelings start to fade away and withdrawal symptoms, such as, cravings start to occur.[5]Suboxone contains two active ingredients, buprenorphine and naloxone. Buprenorphine is a schedule III partial agonist at the mu opioid receptor that will attach to the empty opioid receptors, thus reducing the withdrawal symptoms.[5]There have been studies that show buprenorphine alone can have abuse liability, as it can produce euphoria.[4] Naloxone is an opioid antagonist that was added to buprenorphine in effort to prevent the potential for intravenous misuse. Therefore, this method of treatment is

being proposed to see if adding naloxone to buprenorphine will decrease the incidence of misuse while also preventing withdrawal symptoms.

OBJECTIVE

The objective of this systematic review is to determine if the use of the drug Suboxone is effective in suppressing opioid dependency and its withdrawal symptoms, or is it simply a surrogate for the opiate with the same addictive results?

METHOD

In order to find adequate information for the research of this topic, a set of criteria was used for the selection of studies selected. Common interventions among all of the studies included an experimental group which received Suboxone or bupornephrine compared to the control group, which received a placebo. The comparison interventions in each of the three randomized controlled trials were the effects of the placebo pill versus the effects of Suboxone or bupornephrine while the patient was going through withdrawal. Outcomes measured in the three randomized control studies were the likability of the drug versus the placebo using Visual Analog Scale (VAS), side effects, withdrawal symptoms using Clinical Opiate Withdrawal Scale (COWS), and abuse potential.[2,3,5] All studies included in this paper were randomized control trials obtained from EBSCO between September 2012-January 2013. Key words used in literature search were: “opioid dependence,” “opioid withdrawal,” “buprenorphine,” and “naloxone”. All articles were published in peer-reviewed journals and were written in English. Articles were carefully chosen based on their clinical relevance, along with following the criteria of being patient-oriented evidence that matters. For demographics, inclusion and exclusion criteria, and population refer to Table 1. Statistics reported in these studies included p-values and ANOVA.

Middleton's study evaluated patients with opioid abuse that was confirmed by a urinalysis. Intervention for this study was a randomized, double blinded, 3.5 week in-patient study. On session days, subjects received a powder from crushed placebo, buprenorphine (2 or 8 mg) or Suboxone (2/0.5 or 8/2).[2] Baseline data collected 30 minutes prior and 6 hours after drug administration.

Strain's study was a randomized control trial in which placebo versus Suboxone was studied. The population in this study was 74% male, average age 40 years old and 64% white.[3]The intervention was started by giving patients 30 mg SC morphine to develop a baseline. After day eight, patients were given Suboxone (4/1) at 9am, 11am, and 8pm, while another group was given a matching placebo. Protocol allowed for flexible dosing for Suboxone between 12/3mg-24/6 mg to control withdrawal symptoms.[3]

In Comer's randomized control trial, patients were placed in a qualification phase, where participants who did not self-administer intravenously at least 4 mg buprenorphine more frequently than placebo were discontinued from the study.[6] The next three weeks patients were either given a placebo, Suboxone (4/1), or buprenorphine 2mg-16mg depending on withdrawal symptoms.

Table 1. Demographics & Characteristics of Included Studies.

Study	Type	#Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Middleton (2011)	Double blinded RCT	12	31 +/- 2.27 yrs	31 +/- 2.27 yrs Good health per: Physical exam ECG (normal) Medical History Lab tests UA confirmed illicit drug use	Seizure disorders Respiratory disorders History of asthma Head injury HTN CVD Abnormal ECG Req. daily prescribed med.	2	On session days, subjects received a powder from crushed placebo, buprenorphine (2 or 8 mg) or bup./naxolone (2/.5 or 8/2). Baseline data collected 30 minutes prior and 6 hours after drug administration

Strain (2011)	RCT	38	25 - 56 yrs (μ: 41yrs)	18 - 65 yrs DSM-IV (-) pregnancy MMSE >24 (-) oral herpes No dental caries No recent studies	Patient on placebo with COWS > 12	4	Induction of bup./naxolone on the first day at: 4/1 mg dosed at 9am, 11am, and 8 pm for a total of 12/3 bup./naxolone, another group given a matching placebo.
Comer (2010)	Double-blinded RCT	19	21 - 45 yrs	Daily IV heroin Daily heroin expense: $30-145 Duration: 2 - 32 yrs	Participants who did not self-administer IV 4 mg buprenorphine more frequently than placebo were d/c from the study	7	2 week qualification phase and 3 week experimental phase. Qualification phase: 2 mg sublingual buprenorphine Experimental phase: 1st week: SL bup. stabilization period 2nd wk: double-blind test

OUTCOMES MEASURED

Outcomes measured were those of patient-oriented evidence that matters. In Middleton's study subjective outcomes were measured with VAS, where zero equaled "not at all" and 100 equaled "extremely."[1] Addiction Research Center Inventory short form and street value questionnaire were also completed. Strains study measured primary outcomes using COWS. Measure of secondary outcomes included VAS, with ratings of "feeling high," "good effects," and "bad effects."[3] Participants were specifically asked to rate how the drug made them feel rather than how they felt in general.[3] In Comer's study, outcomes measured were comparing control versus experimental in the following areas: "drug liking," and potential abuse using drug effects questionnaire, VAS, and subjective opioid withdrawal scale.[6]

RESULTS

In Middleton's study, using VAS, participants were asked to rate "How much do you like the drug?" Results showed significant dose-dependence effects ($p<0.0001$). Compared to the placebo, a significant increase in ratings of "liking" was observed 45 minutes after administration of Suboxone (8/2), with a Turkey test $P< 0.05$.[2] However, low doses were not

significantly different from the placebo. In table 2, peak analysis of VAS measures revealed a significant dose effects for "high," "drug effect," "like," "good," and "bad" ($p<0.01$).[2] Both formulations produced a time and dose dependent increases on subjective effects. Patients reported a higher street value for buprenorphine 8 mg compared to Suboxone 8/2mg, but these differences were not statistically significant.[2] Peak analyses revealed that all active doses differed from the placebo, with a p-value of <0.5.[2] Based on the tests done it is difficult to determine if there is higher abuse potential between intranasal buprenorphine and Suboxone when compared to placebo.

The incidence of adverse events occurred, but no serious side effects were noted. Table 3 notes adverse events that presented during this study. Along with those adverse events one subject complained of blurred vision during the session.[2]

Table 2. Peak Scores for subjective measures (n=10)

Subjective VAS	B/N 2/0.5: mean (SEM)	B/N 8/2mg: Mean (SEM)	Placebo Mean (SEM)
Like	25 (6.10)	43.6 (6.10)	2.7 (1.48)
Drug Effect	30.5 (5.62)	36.3 (5.97)	4.1 (1.86)
High	23.1 (6.38)	35.5 (6.27)	3.3 (1.51)
Good	24.5 (6.13)	35.5 (6.17)	3.3 (1.54)
Bad	9.6 (3.32)	8.4 (2.83)	.6 (0.50)

Table 3. Safety: Adverse Events

Side Effect	Percent Affected
Vomiting	40%
Constipation	50%
Headache	40%

The Strain study measured the primary outcomes using COWS, and secondary outcomes using VAS. Prior to induction of the first soluble film COWS scores were elevated with a mean of 9.6. and after administration of Suboxone the COWS scores decreased to a mean of 5.7, which remained low for five days.[3] The ratings showed that there was a significant decrease in observable withdrawal signs when compared to baseline. Ratings of high, bad effects, and sick

were measured by VAS and remained low throughout the treatment period. There were significant time-related variations ($p<0.0001$) with a peak liking of Suboxone at 51.4.[3]

Safety evaluation was conducted throughout the study. Of the 38 participants, 18 of those received Suboxone. Of those 18, four of the participants had mild non-ulcerous irritations of the oral mucosa that were not present at baseline.[3] One patient had elevation in liver enzyme tests; however follow up tests showed a decline back to normal levels. Previous studies have noted that patients with a history of Hepatitis C whom receive buprenorphine treatment have elevated liver enzymes. However, no participants in this study with a history of Hepatitis C had elevated liver enzymes. The results proved that the use of buprenorphine and Suboxone films to be safe and effective methods for opioid dependency treatment.

Table 4.COWS Score Pre and Post Administration of B/N or Buprenorphine.

	B/N 4/1mg	Buprenorphine
Pre-treatment COWS score (mean)	10.1	9.1
Post-Treatment COWS score (mean)	5.7	4.2

The randomized control study conducted by Comer included 12 participants who were included in the final analysis. Based on mean drug progressive ratio breakpoints, reinforcing effects for heroin, high dose Suboxone, low dose buprenorphine were greater when compared to the placebo. Low dose Suboxone demonstrated reinforcing effects lower than that for heroin ($p=0.0001$).[6] High dose Suboxone had reinforcing effects that were also lower when compared to heroin ($p=0.055$).[6] When individual doses were compared, participants preferred intravenous high dose buprenorphine over all other buprenorphine formulations. According to the Drug Effects Questionnaire, participants reported a higher liking for heroin, high dose Suboxone and low or high dose buprenorphine over the placebo ($p <0.0001$).[6] For all buprenorphine formulations participants were willing to take the drug again when compared to the placebo, however, participants were significantly less willing to take low or high dose Suboxone again

when compared to heroin. Results of VAS showed that low dose Suboxone was the only formulation that differed significantly and had similar results when compared to the placebo. Low dose Suboxone and the placebo did not significantly differ in the following categories: good effects, feeling high, liking the drug, feeling sedated, and amount of money they would pay for the drug. Table 5 displays the results for mean subjective VAS scores, where 0 equals "not at all" and 100 equal "extremely."

Seven adverse events were reported in participants. Adverse events that were encountered included: urticaria, nausea, vomiting, dizziness, and chest discomfort.[6] Most side effects were mild and transient and resolved with any type of treatment.

Table 5. Mean subjective VAS

VAS measure (mean +/- SE)	Placebo	Low Dose Suboxone	High Dose Suboxone	Heroin
Good effects	1.75 ± 0.90	12.67±3.07	30.61±4.20	41.11±5.24
High	2.06±1.08	12.19±2.94	31.56±3.65	36.81±5.04
Liked the Drug	1.19±0.62	10.50±2.44	27.28±3.97	41.56±5.42
Would pay	0.25±0.13	1.72±0.51	5.81±0.91	8.50±1.10
Bad effects	3.14±1.47	4.00±2.14	5.03±3.49	0.00±0.00

DISCUSSION

The three randomized controlled trials demonstrated the effectiveness of Suboxone in response to withdrawal symptoms. However, results also showed that patients have similar responses to Suboxone when compared to heroin. Although buprenorphine is believed to show even closer results to that of heroin, it still leaves the question as to the abuse potential for Suboxone.

In Middleton's trial, based on the current results, it is not evident that observed differences with regard to abuse potential between the formulations are clinically relevant at the doses studied.[2] When high doses of Suboxone were compared to the placebo, participants had a better liking of the drugs, which leads one to believe the potential misuse. When compared to buprenorphine, participants had a better liking of that, which shows that by adding naloxone to

buprenorphine does help decrease the "high" effect. The doses used in this study were considered lower doses, with Suboxone doses at 2/.5 and 8/2mg. It is noted that patients who are going to misuse drugs are going to do so at higher dosings.[2] Therefore, it would have benefited researchers to give higher doses of Suboxone to test for abuse potential. Buprenorphine alone could lead to misuse via the intranasal route due to the increase in euphoric effects, along with the quicker onset of action.[2]Even though participants reported higher street value and drug liking for buprenorphine, when compared to Suboxone, the subjective ratings and street values were not statistically significant.[2] Limitations noted in this study were the doses of buprenorphine and Suboxone along with the small sample size of ten participants.

The results of the clinical trials done by Strain suggest that soluble film formulations were effective in suppressing opioid withdrawal.[3] Suboxone was able to attenuate signs and symptoms of withdrawal without belief of addiction potential due to the effects of naloxone. There was significant reduction in overall COWS scores, which demonstrates that the induction of Suboxone is effective. Suboxone was shown to be effective in reducing withdrawal signs and symptoms, while also having less abuse potential when compared to bupornephrine alone.[3] A pervious study done, received results from a questionnaire of 145 participants in a needle exchange program. Of those 145 participants 8% abused Suboxone compared to the 82% who reported abused bupornephrine.[6] A limitation this trial could have benefited from was having a longer stabilizations period using morphine, which would have strengthened the aspect of the study design.[5] Another limitation to this study was in respect to the absence of precipitated withdrawal of symptoms and a fixed dose schedule of Suboxone. In a clinical setting a physician will work with the patient and adjust dosing in regards to their withdrawal symptoms. Overall the results of this study noted that Suboxone was effective and safe under the dose-induction period.

Clear advantages of soluble film formulations is that they can have the can be given as a single dose, in a soluble stripe form where physicians can easily track a dose of the medication.[5] The rapid solubility can be an advantage in setting where monitoring administration of the medication is necessary.[5]

Comer's study identified conditions under which Suboxone had less potential to be abused intravenously when compared to buprenorphine or heroin.[6] After completing the study it was noted that participants were willing to pay a less amount of money for Suboxone when compared to buprenorphine or heroin.[6] There was a reduced administration by injection for participants on higher maintenance doses, which suggests that Suboxone dosing is an important factor in preventing misuse.[6] If a patient is maintained on the correct dose and they are not experiencing withdrawal signs and symptoms they are less likely to misuse the drug. When high doses of intravenous Suboxone were injected it was comparable to the effects of heroin. The higher progressive ratio breakpoint for high dose Suboxone was similar to low dose bupornephrine.[6] This suggests that in bupornephrine dependence injection drug users, the naloxone component attenuated the euphoric effects of buprenorphine.[6] This also leads researcher to believe that Suboxone, when compared to bupornephrine, will indeed decrease the misuse.[6] The stringent criteria for enrollment and the selective population of opioid dependent users resulted in a small, specific population of participants, which could result in a lack of trend across the maintenance doses in subjective effects and might not be representative of the entire opioid-dependent population.[6]

While Suboxone is commonly used across the United States for opioid dependency, there are limitations to its use. In regards to insurance companies, there are some physicians that will take any insurance and allow it to cover for the treatment of opioid dependence, while others will

only take cash.[5] With that being said, most insurance companies will cover Suboxone for treatment of opioid dependency. The contraindications to the use of Suboxone are hypersensitivities to bupornephrine or naloxone.[7] Hypersensitivity reactions that have been reported in the past are the following: bronchospasm, angioneurotic edema, and anaphylactic shock.[7] Suboxone is a pregnancy category C and is currently not used in patients who are pregnant, due to the risk of neonatal withdrawal syndrome.[7] It is also not recommended to take Suboxone while breastfeeding because it is not known whether naloxone is excreted in breast milk or not.[7]

CONCLUSION

In conclusion, these studies provide evidence that Suboxone is effective in preventing signs and symptoms of opioid withdrawal symptoms with limited findings of misuse. In the United States, Suboxone is available by prescription from qualified physicians and reports of misuse have been limited.[6] In Australia and Finland, the introduction of Suboxone has also been associated with lower rates of misuse.[6]However, in further studies that do take place, a recommendation that would benefit researchers would be the include a large population study and high doses of Suboxone. Future studies of Suboxone should include the study of sublingual films rather than tablets, primarily because this is what physicians are prescribing to their patients. In order to study the abuse potential it would be effective to monitor the same formulations given in the office. With any drug there is potential for misuse and abuse, Suboxone has been proven to have lower abuse liability when compared to what was previously available. The effects of naloxone have proven to be effective in blocking the effects of bupornephrine, ultimately reducing the risk of misuse.[4] Close monitoring by physicians and practitioners, along with therapy, is imperative for success in treatment of opioid dependency.

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