



**TITLE: Suboxone for Short-term Detoxification: A Review of the Clinical Evidence**

**DATE: 7 September 2011**

**CONTEXT AND POLICY ISSUES:**

Opioid dependence is defined as a strong desire to use the substance, difficulty in controlling its use, the presence of a physiological withdrawal state, tolerance of the use of the drug, neglect of alternative pleasures and interests and persistent use of the drug, despite harm to oneself and others.<sup>1</sup> Opioid dependence is a complex disease involving physiological, psychological, genetic, behavioral and environmental factors.<sup>2</sup> Treatment of opioid dependence includes three approaches: stabilization, detoxification and maintenance.<sup>3</sup> Stabilization is usually achieved by opioid substitution treatments to ensure that the drug use becomes independent of mental state (such as craving and mood) and independent of circumstances (such as finance and physical location). The next stage is detoxification that is to withdraw from opioids. The final step is maintenance to prevent relapse.<sup>3</sup>

Addiction to opioids, usually to heroin, remains a continuing problem in the United States and is increasing in Europe.<sup>4</sup> It is estimated that there were more than 80,000 regular illegal opioid users in Canada in 2003.<sup>5</sup> The most prevalent treatment used was methadone maintenance treatment (MMT). The number of illegal drug-related overdose deaths in Canada was 958 in 2002.<sup>5</sup> Although the opioid-dependence treatment system in Canada has expanded in recent years, especially with respect to the availability of MMT, the treatment utilization rates are still lower than in most Western Europe countries. Rates of current treatment utilization as well as the relatively high number of overdose deaths suggest that there is still room for improvement in the Canadian health and social care system with respect to opioid use.<sup>5</sup>

Detoxification refers to the process by which the effects of opioid drugs are eliminated in a safe and effective manner, such that withdrawal symptoms are minimized.<sup>1</sup> Appropriate use of the detoxification agents plays a crucial role in increasing the successful detoxification rate, while minimizing the side effects and withdrawal symptoms.<sup>1</sup> Methadone or buprenorphine are recommended first-line treatments in opioid detoxification.<sup>1</sup>

Suboxone (buprenorphine/naloxone) was approved by Health Canada in 2007 for substitution treatment in opioid drug dependence in adults.<sup>6</sup> It is a fixed combination of buprenorphine (a partial  $\mu$ -opioid receptor agonist) with naloxone (an opioid antagonist) in a 4:1 ratio.<sup>7</sup> Suboxone is

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recommended for the treatment of opioid dependence for patients in whom methadone is contraindicated (such as patients at high risk of, or with QT prolongation, or hypersensitivity to methadone).<sup>8</sup> The purpose of this review is to gather additional clinical information regarding the comparative clinical efficacy and safety of short term (<4 weeks) use of suboxone compared with other opioid detoxification agents such as buprenorphine alone, methadone, and clonidine, and placebo.

**RESEARCH QUESTIONS:**

What is the comparative clinical effectiveness of short-term suboxone use versus alternative treatments for drug detoxification?

**KEY MESSAGE:**

Limited evidence showed higher treatment success rate with suboxone compared to clonidine in short term detoxification for patients with opioid dependence.

**METHODS:**

**Literature search strategy**

A limited literature search was conducted on key resources including Medline, Embase, PubMed, The Cochrane Library (2011, Issue 8), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 01, 2001 and August 04, 2011.

**Selection Criteria and Methods**

**Table 1: Selection Criteria**

<b>Population</b>	Patients with opioid dependence/ addiction
<b>Intervention</b>	Suboxone for short term detoxification(≤4 weeks)
<b>Comparator</b>	<ol style="list-style-type: none"> <li>1. Other alternative detoxification agents, e.g. buprenorphine, methadone, lofexidine, clonidine or placebo</li> <li>2. Suboxone use for &gt; 4 weeks</li> </ol>
<b>Outcomes</b>	Mortality (all cause), opioid urine test result, retention on study(or dropout), serious adverse event (SAE), adverse event (AE), withdrawal due to adverse event, self-reported other drug use, social functioning (e.g. criminality, employment, HIV risk behavior) measured by a valid method, quality of life (QOL).
<b>Study Designs</b>	Health technology assessment (HTA), systematic review, meta-analysis, randomized controlled trial (RCT), non-randomized study

## Exclusion Criteria

Studies were excluded if they did not meet the selection criteria.

## Critical Appraisal of Individual Studies

The quality of the included studies was assessed using the SIGN 50 check list.<sup>9</sup>

## SUMMARY OF EVIDENCE:

### Quantity of Research Available

Two hundred forty one articles were identified from the literature search, and 2 additional articles were identified by searching the grey literature. From these, 22 potentially relevant articles were selected for full-text screening. Of these 22, three RCT reports were included. No relevant health technology assessments, systematic reviews, meta-analyses or non-randomized studies were identified. The selection process is described in Appendix 1.

### Summary of Study Characteristics

The characteristics of the included studies are summarized in Table 2.

**Table 2: Characteristics of Included Studies**

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size	Intervention	Comparators	Main Clinical Outcomes
Woody, et al. <sup>10</sup> 2008, USA	RCT, 2 or 14 week treatment. (with 12 months post-treatment follow-up)	Patients with opioid dependence and sought outpatient treatment. Age: 14-21 years old (N=152)	Suboxone use for 2 weeks. Dose titration (buprenorphine /naloxone): 2mg/0.5mg to 6mg/1.5mg over 3 days, then maintained and adjusted if needed (N=78)	Suboxone treatment for 12 weeks. Dose titration: same as intervention group (N=74)	Opioid urine test results, rate of patient retention in the study, mortality, SAE and AE .
Ling, et al. <sup>11</sup> 2005, USA	RCT Treatment length: 13 day	Patients with opioid-dependence and seeking short-term treatment. Average age: 38 years old, (N=344)	Suboxone. Dose: using a 3-day rapid induction. 8mg/2mg from day 1 then maintained and adjusted if needed (N=234)	Clonidine Dose: on day 1, oral 0.05–0.1 mg every 4–6 h for 24 h (< 0.6mg in total); Clonidine transdermal patch. (N=110)	Treatment success rate, mortality, SAE, AE, use of ancillary medications, dropout.

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size	Intervention	Comparators	Main Clinical Outcomes
Fudala, et al., <sup>4</sup> 2003	RCT, 4-week treatment.	Patients with opioid-addiction. Average age:37 years old (N=323)	Suboxone (16 mg/4mg), qd. (N=110)	Buprenorphine, 16 mg, qd (N=106) or placebo, qd.(N=110)	Opioid urine test result. SAE, AE

AE: adverse event, h: hour, qd: once a day, RCT: randomized controlled trial, SAE: serious adverse event

### Summary of Critical Appraisal

Quality assessment was done for all three included RCTs<sup>4,10,11</sup> Research questions were adequately addressed in all three RCTs. Patients randomization was adequately addressed in one RCT<sup>10</sup> and not adequately described in the other two RCTs.<sup>4,11</sup> Allocation concealment was adequately reported in one study,<sup>10</sup> but not addressed in the other two. One study was double-blinded but the blinding process was terminated early. Drop-outs were adequately reported in all three RCTs. Intention to treat (ITT) analysis was adequate in most cases. The main results of the appraisal are summarized in Table 3.

**Table 3: Summary of Critical Appraisal of Included RCTs**

First Author, Publication Year	Strength	Limitations
Woody, et al., <sup>10</sup> 2008	Randomization method, allocation concealment and ITT analyses were adequately addressed. Valid primary outcome measurement	Blinding process was not adequately addressed
Ling, et al., <sup>11</sup> 2005	ITT analyses were adequately addressed. Valid primary outcome measurement	Randomization was not adequately addressed. Blinding process was not described
Fudala, et al., <sup>4</sup> 2003	Valid primary outcome measurement	Randomization was not adequately addressed. Blinding process was terminated early Analysis not strictly ITT

ITT: intent to treat

### Summary of Findings

Three<sup>4,10,11</sup> relevant RCTs were identified from literature search. The first RCT<sup>10</sup> compared short term suboxone detoxification (for 2 weeks) with suboxone treatment for 14 weeks. The second one<sup>11</sup> compared suboxone with clonidine. The last one<sup>4</sup> compared suboxone with buprenorphine monotherapy or placebo.

Woody et al.<sup>10</sup> conducted a RCT to evaluate the efficacy of 2-week use of suboxone versus 12-week use of suboxone in 152 patients with opioid-addiction. Patients were 15 to 21 years old. The trial duration was 12 weeks. Patients were randomized to a 2-week or a 12-week of suboxone

treatment. Patients in the 2-week group were prescribed a dose of up to 14 mg /day and then the dose was gradually decreased to day 14. Patients in the 12-week arm were prescribed a dose of up to 24 mg per day for 9 weeks and then in the following 3 weeks the dose was gradually decreased. All were offered weekly individual and group counseling. The primary outcome was opioid urine test results. Secondary outcomes included the rate of patient retention in the study, AE, and non-study drug use. Urine tests for opioid were done at weeks 4, 8, and 12. Compared with 12-week treatment group, it was reported that patients in the 2-week group had higher proportions of opioid-positive urine test result at week 4 ( $P < 0.001$ ) and week 8 ( $P < 0.001$ ) but not at week 12 ( $P = 0.18$ ). By week 12, 16 (21%) of 78 patients in 2-week group remained in treatment versus 52 (70%) of 74 patients in 12-week group ( $P < 0.001$ ). During weeks 1 through 12, patients in the 12-week suboxone group reported less opioid use ( $P < 0.001$ ), less injecting ( $P = 0.01$ ), and less non-study addiction treatment ( $P < 0.001$ ). High levels of opioid use occurred in both groups at follow-up. Four (two from each treatment group) of 83 patients who tested negative for hepatitis C at baseline were positive for hepatitis C at week 12. No serious adverse events attributable to suboxone were reported and no patients were withdrawn due to adverse events. Headaches were the most common events reported by about 18 % of patients in both groups. Other AEs were reported by less than 10% of patients and included nausea, insomnia, stomach ache, vomiting, and anxiety. One non-treatment related death occurred in a 19-year-old patient in the 12-week suboxone group. The main results are summarized in Table 4. The authors concluded that 12-week suboxone treatment provided improved outcome compared with 2-week suboxone treatment.

**Table 4. Results from Woody et al.<sup>10</sup>**

Outcomes		2-week suboxone treatment (N= 78)	12-week suboxone treatment (N=74)	P value
Opioid positive urine test results (% , 95%CI)	At week 4	61 ( 47-75)	26 (14-38)	0.001
	At week 8	54 (38-70)	23 (11-35)	0.001
	At week 12	51 (35-67)	43 (29-57)	0.18
	At 6-12 months Follow up	Not reported	Not reported	0.002 (lower in 12-week treatment)
Retention in the study (% , 95%CI)	At week 4	45 (34-56)	84(75-93)	$P < 0.001$
	At week 8	27(17-37)	74(64-84)	$P < 0.001$
	At week 12	21(12-30)	70(59-81)	$P < 0.001$
Mortality		0	1 death (due to overdose of methadone use after dropped out)	Not estimable

Ling et al.<sup>11</sup> investigated the clinical effectiveness of suboxone and clonidine for opioid detoxification in community treatment programs. Patients with opioid-dependence seeking short-term treatment were randomly assigned in a 2:1 ratio to a 13-day detoxification using respectively suboxone or clonidine. Interventions also included use of ancillary medications as needed and standard counseling. Two hundred and thirty one out-patients (157 in suboxone, 74 in clonidine) and 113 in-patients (77 in suboxone, 36 in clonidine) were included. The primary outcome was the

success rate which was defined as the proportion of participants who were both retained in the study for the entire duration and provided an opioid-free urine sample on the last visit. Main secondary outcomes included use of ancillary medications, side effects and withdrawal. For in-patients, 59 (77%) of the 77 assigned to the suboxone achieved treatment success compared to eight (22%) of the 36 assigned to clonidine ( $P < 0.0001$ ), whereas for out-patients, 46 (29%) of the 157 patients assigned to the suboxone achieved treatment success compared to four (5%) of the 74 assigned to clonidine ( $P < 0.0001$ ). In the in-patient group, four serious adverse events (including a death) occurred in each arm. Respiratory failure was the cause of death for a patient in the suboxone group, whereas bacterial endocarditis was the cause of death for a participant in the clonidine group. Neither death was attributed to study medication. The three adverse events reported in the suboxone group include suicidal behavior for two patients and severe vomiting in one. The three adverse events reported in the clonidine group include severe vomiting in one patient, a motor vehicle accident in one and cellulitis in another. In the out-patient sites, 18 SAEs occurred, with 14 occurring in the suboxone group and four in the clonidine group. No death was reported in the out-patient group. Overall AE, per-protocol analysis showed less AE was reported in suboxone group (1.5 /patient/day) than clonidine group (2.4/patient/day,  $P < 0.0001$ ) in in-patients. In out-patients, the AE was also reported to be statistically significantly less in suboxone group (0.7/patient/day) than in the clonidine group (1.2/patient/day,  $P < 0.0001$ ). For the in-patients, ancillary medications were prescribed at similar levels in both suboxone and clonidine groups. However, for the out-patients, more patients used ancillary medication in clonidine group than in the suboxone group ( $P < 0.01$ ). The main results are summarized in Table 5. The author concluded that suboxone for opioid detoxification provided more benefit than clonidine.

**Table 5. Results from Ling et al.<sup>11</sup>**

Outcomes	In-patients			Outpatients		
	Suboxone (N=77)	Clonidine (N=36)	P	Suboxone (N=157)	Clonidine (N=74)	P
Treatment success: number of patients (%)	59 (77)	8 (22)	<0.0001	46 (29)	4 (5)	<0.0001
Mortality	1 (not related to study drug, but due to respiratory failure)	1 (not related to study drug, but due to bacterial endocarditis)	Not estimable	0	0	Not estimable
SAE(number of SAE)	4	4	Not reported	14	4	Not reported
AE (number of AE/patient/day)	1.5	2.4	<0.0001	0.7	1.2	<0.001

AE: adverse event, SAE: serious adverse event

In a multicenter, double-blind RCT,<sup>4</sup> 326 patients with opioid-addiction were randomized to one of the three groups: suboxone (buprenorphine: 16 mg/naloxone: 4mg/day, n=110), buprenorphine alone (16 mg/day n=106), or placebo (n=110) for four-week treatment. The primary outcomes

were the percentage of urine samples negative for opioid and the subjects' self-reported craving for opioid. The double-blind trial was terminated early because suboxone and buprenorphine alone were found to have greater efficacy than placebo. When blinding was terminated, 323 had received at least one dose of study medication, and 243 had completed the trial. The three subjects (one in each group) who had not received study medication after randomization were excluded from the analyses. The differences among the three groups in retention rate were not significant (see table 6). Overall, the subjects received medication for 90 percent of the days that they remained in the study. It was reported that the proportion of opioid negative urine samples was greater in the suboxone and buprenorphine groups (17.8% and 20.7% respectively) than in the placebo group (5.8%,  $P < 0.001$  for both comparisons); the two active-treatment groups also reported less opioid craving ( $P < 0.001$  for both comparisons with placebo). The main results are presented in Table 6. The author concluded that suboxone and buprenorphine alone are safe and reduce the use of opioid and the craving for opioid among opioid-addicted patients who receive these medications in an office-based setting.

**Table 6: Results from Fudala, et al.<sup>4</sup>**

Outcomes	Suboxone (N=109)	Buprenorphine (N=105)	Placebo (N=109)	P
Opioid-negative urine test result (%)	17.8	20.7	5.8	<0.001 for both suboxone versus placebo and buprenorphine versus placebo
Retention in the study	Not reported	Not reported	Not reported	Not significant

**Limitations**

Among the three trials included in this review, two RCTs<sup>10,11</sup> were not blinded. One RCT<sup>4</sup> was double blinded, but the blinding process was terminated early. Lack of sufficient blinding and allocation concealment may impact internal validity. For one RCT<sup>4</sup> some patients were excluded from the study for safety reasons. The dosage used in the included studies was not well controlled and ancillary medications were also allowed to be used in the trials. The intervention (dose and duration) and comparators were all different among the identified studies. Each trial was conducted in different clinical setting, one was office-based, one was community based and one included both out-patients and in-patients. Results may not be generalizable.

**CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:**

The evidence comparing the clinical effectiveness of short term suboxone detoxification with other alternative medications in the treatment of patients with opioid dependence/addiction is limited. Data indicated that short term (2- week) suboxone treatment showed a lower treatment success rate compared with 12 week treatment. But the treatment success rate was found to be higher in patients treated with suboxone than with clonidine or placebo in short term detoxification. However, the data identified in this review should be interpreted with caution due to various potential limitations

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## REFERENCES:

1. National Collaborating Centre for Mental Health. Drug misuse: opioid detoxification [Internet]. London: The British Psychological Society and The Royal College of Psychiatrists; 2008. 271 p. [cited 2011 Aug 11]. (National clinical practice guideline number 52). Available from: <http://www.nice.org.uk/nicemedia/live/11813/35999/35999.pdf>
2. American Society of Addiction Medicine. Public Policy Statement on Rapid and Ultra Rapid Opioid Detoxification [Internet]. Chevy Chase (MD): The Society; 2005. [cited 2011 Aug 15]. Available from: <http://www.asam.org/1ROD-UROD%20-%20REV%20OF%20ADUSA%204-051.pdf>
3. O'Shea J, Law F, Melichar J. Opioid dependence. Clin Evid [Internet]. 2009 [cited 2011 Aug 11];40. Available from: <http://clinicalevidence.bmj.com/ceweb/conditions/meh/1015/1015-get.pdf>
4. Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, Jones K, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. N Engl J Med [Internet]. 2003 Sep 4 [cited 2011 Aug 10];349(10):949-58. Available from: <http://www.nejm.org/doi/pdf/10.1056/NEJMoa022164>
5. Popova S, Rehm J, Fischer B. An overview of illegal opioid use and health services utilization in Canada. Public Health. 2006 Apr;120(4):320-8.
6. Drug monograph. Suboxone™ buprenorphine HCl - naloxene HCl dihydrate. 2011 [cited 2011 Aug 25]. In: e-CPS [database on the Internet]. Ottawa: Canadian Pharmacists Association. Available from: <http://www.e-therapeutics.ca/>
7. Orman JS, Keating GM. Spotlight on buprenorphine/naloxone in the treatment of opioid dependence. CNS Drugs. 2009 Oct 1;23(10):899-902.
8. Common Drug Review. Buprenorphine/Naloxone (Suboxone - Schering-Plough Canada Inc.). CEDAC final recommendation and reasons for recommendation [Internet]. Canadian Agency for Drugs and Technologies in Health; 2011. 2 p. [cited 2011 Aug 11]. Available from: [http://www.cadth.ca/media/cdr/complete/cdr\\_complete\\_Suboxone\\_September-24-2008.pdf](http://www.cadth.ca/media/cdr/complete/cdr_complete_Suboxone_September-24-2008.pdf)
9. Methodology checklist 2: randomized controlled trials [Internet]. In: SIGN 50: a guideline developer's handbook. Edinburgh: Scottish Intercollegiate Guidelines Network; 2008 [cited 2011 Jul 12]. Available from: <http://www.sign.ac.uk/guidelines/fulltext/50/checklist2.html>.
10. Woody GE, Poole SA, Subramaniam G, Dugosh K, Bogenschutz M, Abbott P, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. JAMA [Internet]. 2008 Nov 5 [cited 2011 Aug 10];300(17):2003-11. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2610690/pdf/nihms78835.pdf>
11. Ling W, Amass L, Shoptaw S, Annon JJ, Hillhouse M, Babcock D, et al. A multi-center randomized trial of buprenorphine-naloxone versus clonidine for opioid detoxification: findings from the National Institute on Drug Abuse Clinical Trials Network. Addiction [Internet]. 2005 Aug [cited 2011 Aug 10];100(8):1090-100. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1480367/pdf/nihms4540.pdf>

APPENDIX 1: Selection of Included Studies

