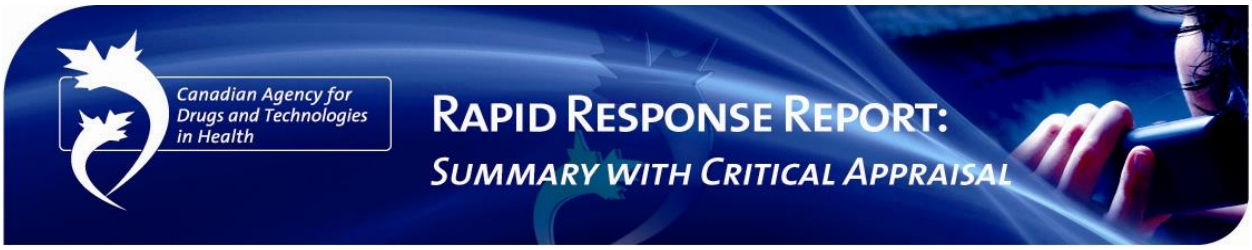

TITLE: Crushed Buprenorphine or Buprenorphine-Naloxone for Opioid Dependency: A Review of the Clinical Effectiveness and Guidelines

DATE: 18 July 2016

CONTEXT AND POLICY ISSUES

Opioid dependence is a chronic condition and can negatively impact the individual and society.[1] If untreated, it may result in increased mortality, increased risk of blood borne virus transmission through drug injections, loss of productivity, poor social functioning, and criminal activities and associated criminal justice expenditures.[1] Treatment involves a multidisciplinary approach including medications for opioid substitution and psychosocial interventions.[1] Buprenorphine is a μ-opioid receptor partial agonist and a κ-opioid receptor antagonist[2] and has been used alone or in combination with naloxone (a μ-opioid receptor antagonist) for treatment of opioid dependency. Buprenorphine reduces cravings in patients who are dependent on full μ-opioid agonists. The addition of naloxone to buprenorphine is intended to reduce abuse potential as it precipitates withdrawal symptoms when taken parenterally but has limited bioavailability and minimal systemic effects when taken sublingually.[3] Sublingual buprenorphine and buprenorphine-naloxone combination formulations have been recommended for office-based opioid dependence treatment.[3] These agents are associated with abuse potential including misuse and diversion (i.e. selling, trading, sharing or giving away the medication to unintended recipients).[4] Crushing of these buprenorphine tablets before administering to the individual has been suggested as a method of preventing diversion.[1,2] There is uncertainty around the effects of crushing. One report[1] has mentioned that crushing did not alter the serum buprenorphine levels, absorption time or withdrawal symptoms, and another report[5] has mentioned that crushing could impact the bioavailability of the drug and consequently its clinical benefit.

The purpose of this report is to review the clinical effectiveness and safety of sublingual crushed buprenorphine or crushed buprenorphine-naloxone for treating opioid dependency, compared to the uncrushed products, and to review the evidence-based guidelines regarding the administration of crushed buprenorphine or crushed buprenorphine-naloxone.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of sublingual crushed buprenorphine for treating opioid dependency?

2. What is the clinical effectiveness and safety of sublingual crushed buprenorphine-naloxone for treating opioid dependency?

3. What are the evidence-based guidelines regarding the administration of crushed buprenorphine or crushed buprenorphine-naloxone for the treatment of opioid dependency?

KEY FINDINGS

A single crossover RCT with 16 patients showed that there were no statistically significant differences with respect to opioid withdrawal or opioid craving between treatments with the whole buprenorphine tablet or the crushed tablet. The number of patients experiencing adverse events was higher in the crushed tablet group compared to the whole tablet group however there were no serious adverse events reported in either group. There was no information identified regarding the effectiveness of the crushed tablet in resolving misuse and diversion issues. No relevant studies comparing sublingual administration of crushed buprenorphine-naloxone with uncrushed buprenorphine or uncrushed buprenorphine-naloxone tablets or buprenorphine-naloxone film for the treatment of opioid dependency were identified. No evidence based guidelines on the use of crushed buprenorphine or crushed buprenorphine-naloxone were identified.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2006 and June 17, 2016

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer performed the first level screening of citations (titles and abstracts) and selected the potentially relevant citations. Full-text articles of these citations were retrieved and a second reviewer assessed these articles for final selection. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Adults with opioid dependency
Intervention	Sublingual administration of crushed buprenorphine (e.g. Subutex) or buprenorphine-naloxone combination tablets (e.g. Suboxone)
Comparator	Buprenorphine or buprenorphine-naloxone combination tablets, uncrushed Buprenorphine-naloxone film
Outcomes	Clinical effectiveness, safety (including potential for misuse, abuse, or diversion), evidence-based guidelines
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCT), observational studies, and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2006. Guidelines with unclear methodology were excluded.

Critical Appraisal of Individual Studies

The included randomized controlled trial was critically appraised using the Downs and Black checklist.[6] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 239 citations were identified in the literature search. Following screening of titles and abstracts, 235 citations were excluded and four potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, three publications were excluded for various reasons, while one publication met the inclusion criteria and was included in this report. This was a RCT with crossover design. No relevant health technology assessments, systematic reviews, meta-analyses, observational studies, or evidence-based guidelines were identified. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest that did not meet the selection criteria are provided in Appendix 6.

Summary of Study Characteristics

Characteristics of the included RCT are summarized below and details are available in Appendix 2, Table A1.

One relevant RCT was identified.[2] It was published in 2010 from Finland. It was a double-blind, randomized, crossover trial with 16 patients and compared crushed and uncrushed buprenorphine tablets. Patients were randomized into two groups: Group A and Group B. Group

A received three whole active tablets (BW) and three crushed placebo tablets (PC) (i.e. 3xBW + 3xPC) at visit 1 and the reverse regimen (i.e. 3xPW + 3xBC, PW = whole placebo tablet and BC = crushed active tablet) at visit 2. Each tablet was 8 mg. Group B received (3xPW + 3xBC) at visit 1 and the reverse regimen (3xBW + 3xPC) at visit 2. There was a 6-day interval between the two visits. During this interval the patients had their normal daily buprenorphine dose (i.e. 3xBW daily). The mean age of the patients was 28 years and the proportion of males was 62.5%. The primary outcome was pharmacokinetic parameters and secondary outcomes included dissolution time, opioid withdrawal and craving, and adverse events.

Summary of Critical Appraisal

Critical appraisal of the included RCT is summarized below and details are available in Appendix 3, Tables A2.

In the included RCT,[2] the objectives and inclusion and exclusion criteria were stated. Patient characteristics, interventions, and outcomes were described. Randomization seemed to be appropriate. The study was double blinded. Sample size determinations were not presented, so it is unclear whether the study had adequate power to detect a clinically meaningful difference between groups. Conflict of interest disclosures were not mentioned. Generalizability was limited as the study was conducted in a population of 16 patients in Finland.

Summary of Findings

What is the clinical effectiveness *and safety of sublingual crushed buprenorphine for treating opioid dependency?*

Findings are summarized below and details are provided in Appendix 4, Tables A3

One crossover RCT[2] showed that there were no statistically significant difference ($P = 0.95$) between crushed and whole buprenorphine tablet groups, with respect to opioid withdrawal as determined using the Short Opiate Withdrawal Scale (SOWS). Also there was no statistically significant difference ($P = 0.2$) between the two groups, in opioid craving as determined using the Visual Analog Scale (VAS). The dissolution time (i.e. the time that elapsed between placing the tablet in the patients mouth and the point at which the tablet is no longer visible) was not statistically significantly different between whole and crushed tablets ($P = 0.75$).The differences in pharmacokinetic parameters between crushed and whole tablets of buprenorphine were not statistically significant (*P* values not reported.)

Four patients receiving intact tablets reported adverse events (fatigue and dysphoria) and eight patients receiving crushed tables reported adverse events (pollakiuria, fatigue, headache, strange feeling, craving and pain). Serious adverse events were not reported in any of the two groups.

What is the clinical effectiveness *and safety of sublingual crushed buprenorphine-naloxone for treating opioid dependency?*

No relevant studies comparing sublingual administration of crushed buprenorphine-naloxone with uncrushed buprenorphine or uncrushed buprenorphine-naloxone tablets or buprenorphine-naloxone film for the treatment of opioid dependency were identified.

What are the evidence-based guidelines regarding the administration of crushed buprenorphine or buprenorphine-naloxone for the treatment of opioid dependency?

No evidence-based guidelines regarding the administration of crushed buprenorphine or crushed buprenorphine-naloxene for the treatment of opioid dependency were identified

Limitations

There is limited relevant information available for buprenorphine and no relevant information identified for buprenorphine-naloxone. The findings for buprenorphine are from a single, small (N = 16) study and need to be interpreted with caution.

Information on the comparative effects of whole tablets and crushed tablets with respect to misuse or diversion was not available. No studies comparing crushed buprenorphine or crushed buprenorphine-naloxone with buprenorphine-naloxone film were identified.

No evidence based guidelines on the use of crushed buprenorphine or crushed buprenorphine-naloxone were identified.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

One relevant RCT with crossover design was identified.[2] No relevant health technology assessments, systematic reviews, meta-analyses, observational studies, or evidence-based guidelines were identified.

The included RCT showed that there were no statistically significant differences with respect to opioid withdrawal or opioid craving between treatments with the whole buprenorphine tablet or the crushed tablet. The number of patients experiencing adverse events was higher in the crushed tablet group compared to the whole tablet group. There were no serious adverse events reported in either group. With the limited information available, definitive conclusions are not possible.

There was no information identified regarding the effectiveness of the crushed tablet in resolving misuse and diversion issues.

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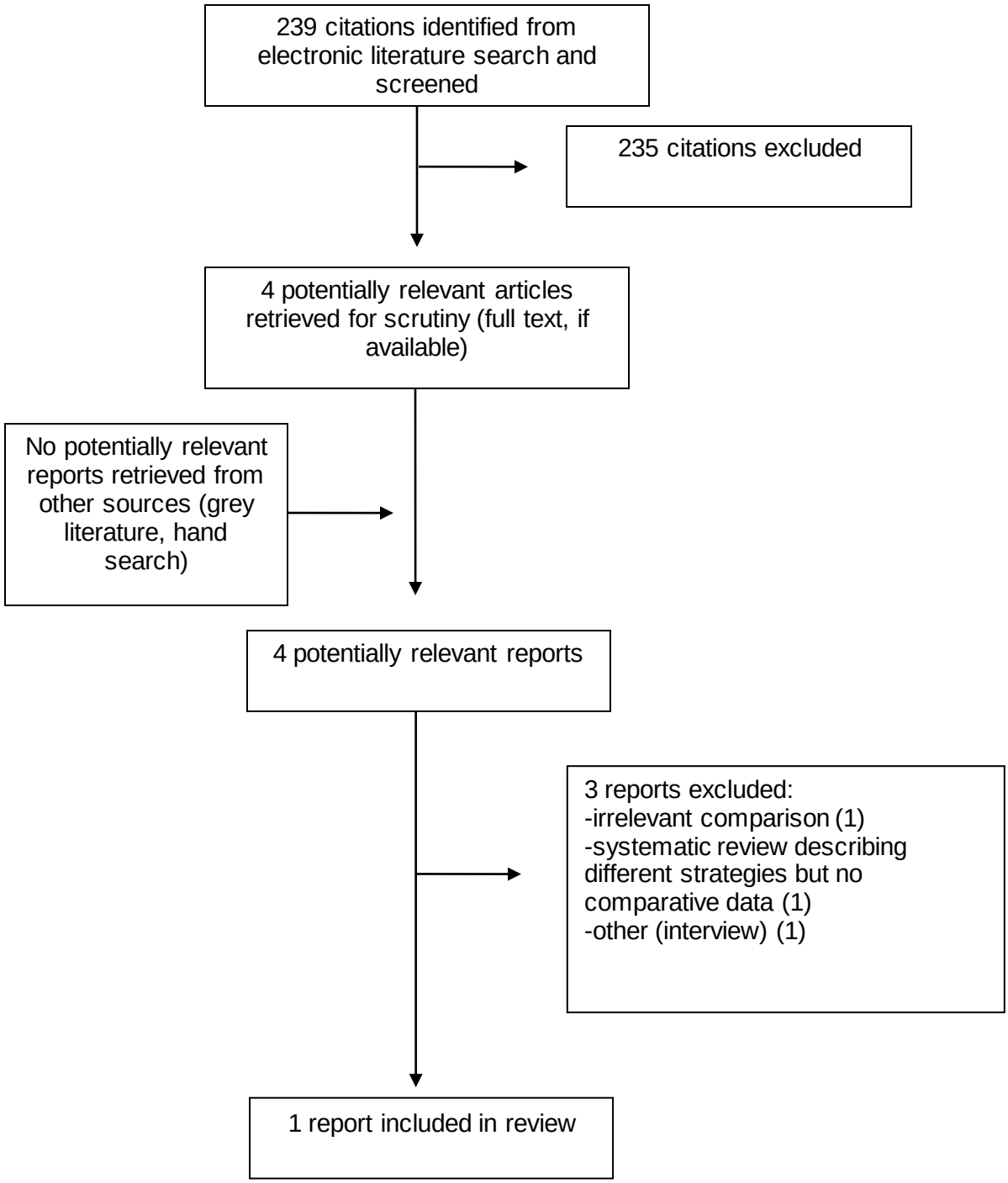
ABBREVIATIONS

AUC	area under the curve
mg	milligram
ml	millilitre
ng	nanogram
RCT	randomized controlled trial
SOWS	Short Opiate Withdrawal Scale
VAS	Visual Analog Scale

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Comparison	Clinical Outcomes
Randomized controlled trials				
Simojoki,[2] 2010, Finland	Double-blind, double-dummy, cross-over RCT Mainly out-patient and conducted at 3 centers	Adults with opioid dependency N = 16 (13 had been in a opioid maintenance program and 3 had received supervised buprenorphine [24 mg] daily for 2 weeks prior to the study) Mean age (years): 28 Male (%): 62.5 Opioid dependency (years): 7.6	Two groups compared. Group A: Three 8-mg active tablets (whole) and three 8-mg placebo tablet (crushed) at Visit 1 and reverse regimen at Visit 2 Group B: Three 8-mg placebo tablets (whole) and three 8-mg active tablet (crushed) at Visit 1 and reverse regimen at Visit 2 There was a 6 day interval between the two study visits. During this interval the patients had their normal daily buprenorphine dose (i.e.three 8 mg tablets daily)	Primary outcome: Pharmacokinetics Secondary outcomes: dissolution time, opioid withdrawal, opioid craving, and adverse events. Outcomes were measured up to 24 hours after administration of study intervention

RCT = randomized controlled trial,

APPENDIX 3: Critical Appraisal of Included Publications

Table A2: Strengths and Limitations of Randomized Controlled Trial using Downs and Black Checklist[6]

Strengths	Limitations
Simojoki,[2] 2010, Finland	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described. • Randomized using Vassar statistics randomizer • Double-blind (neither study doctor or patient were aware of the treatment regimen) • One patient (6%) discontinued after the first day of the study and was excluded from the analysis. • *P*-values were provided in most instances	• Sample size calculation was not provided • Conflict of interested disclosures were not reported • Generalizability is limited to a small population (N = 16) in Finland

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A3: Summary of Findings of Included Clinical Studies

Main Study Findings and Author's Conclusions

Randomized controlled trial

Simojoki,[2] 2010, Finland

Main Findings:

Only findings relevant for this report is presented here

Comparison of scores with buprenorphine crushed and buprenorphine whole

Outcome	Time point (hour)	Scores		*P* value
		Crushed	Whole	
Opioid withdrawal (measured using SOWS)	0	9 ± 7	12 ± 1	0.20
	5	7 ± 7	6 ± 6	0.32
	24	9 ± 9	10 ± 10	0.95
Opioid craving (measured using VAS)	0	3.9 ± 3.7	5 ± 4	0.1
	5	3.3 ± 3.4	1.2 ± 2.1	0.1
	24	3.4 ± 4	4.3 ± 4.2	0.2

SOWS = Short Opiate Withdrawal Scale, VAS = Visual Analog Scale

Time to dissolution:

Time to dissolution was 16.53 minutes for the crushed buprenorphine tablet and 16.63 minutes for the whole tablet (*P* = 0.75)

Pharmacokinetic parameters for buprenorphine crushed and buprenorphine whole

Parameter	Crushed	Whole	*P* value
AUC_{0-24}	98.16 ± 39.61	108.0 ± 65.91	NS
T_{max}, hour	1.44 ± 0.60	1.68 ± 0.36	NS
C_{max}, ng/ml	9.73 ± 3.41	9.59 ± 3.83	NS
C_{min}, ng/ml	3.48 ± 3.24	2.94 ± 1.55	NS

AUC_{0-24} = area under the curve between 0 to 24 hour, C = concentration of buprenorphine in serum, T_{max} = time to peak buprenorphine serum level,

Adverse events

Whole tablet group: Four patients reported adverse events (fatigue and dysphoria)

Crushed tablet group: Eight patients reported adverse events (pollakiuria, fatigue, headache, strange feeling, craving and pain)

No serious adverse events were reported in either group.

Authors' Conclusions:

"The results presented here indicate that the crushing of the active medication did not alter serum levels of buprenorphine and demonstrated no clinically significant impact when compared to administration of the whole tablet. This finding suggests that the crushing of Subutex [buprenorphine] tablets may be a suitable alternative in settings where there is a high risk of buprenorphine diversion, such as in prisons, without concerns about a reduction in medication efficacy." Page 90

APPENDIX 6: Additional References of Potential Interest

Guidelines (unclear methodology)

Queensland opioid treatment program: clinical guidelines 2012 [Internet]. Brisbane (AU): Queensland Health; 2012. [cited 2016 Jul 8]. Available from: https://www.health.qld.gov.au/publications/clinical-practice/guidelines-procedures/medicines/drugs-of-dependence/qotp-clinical-guidelines.pdf

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