(a) Title page

**TITLE:**

**International patent applications for non-injectable naloxone for opioid overdose reversal: Exploratory search and retrieve analysis of the Patent Scope database**

**RUNNING TITLE:**

Patent records for non-injectable naloxone

**AUTHORS’ NAMES, HIGHEST ACADEMIC QUALIFICATIONS, AFFILIATIONS:**

Rebecca McDonald, MSca,1, Øyvind Danielsson Glende, MScb,c,1, Ola Dale, MDb, d,& John Strang, MDa

a National Addiction Centre

Institute of Psychiatry, Psychology & Neuroscience, King’s College London

4 Windsor Walk

London SE5 8BB

UK

b Department of Circulation and Medical Imaging

NTNU-The Norwegian University of Science and Technology

Prinsesse Kristinas gate 3

7030 Trondheim

Norway

c Apotek 1 Nardo

Nardobakken 2

7032 Trondheim

Norway

d St. Olav’s Hospital

University Hospital of Trondheim

Prinsesse Kristinas gate 3

7030 Trondheim

Norway

1 joint first authors

**CORRESPONDING AUTHOR:**

Professor Sir John Strang

National Addiction Centre

Institute of Psychiatry, Psychology & Neuroscience, King’s College London

4 Windsor Walk

London SE5 8BB | UK

Email: john.strang@kcl.ac.uk

Phone: + 44 (0)20 7848 0438

**Word count (excluding abstract, tables, figures):** *4,520 words (excl. references)*

(b) Abstract and key words

# ABSTRACT (*250 words including headings)*

**Issues:** Non-injectable naloxone formulations are being developed for opioid overdose reversal, but only limited data have been published in the peer-reviewed domain. Through examination of a hitherto-unsearched database, we expand public knowledge of non-injectable formulations, tracing their development and novelty, with the aim to describe and compare their pharmacokinetic properties.

**Approach:** 1) The PatentScope database of the World Intellectual Property Organization was searched for relevant English-language patent applications; 2) Pharmacokinetic data were extracted, collated and analysed. 3) PubMed was searched using Boolean search query “(nasal OR intranasal OR nose OR buccal OR sublingual) AND naloxone AND pharmacokinetics”.

**Key Findings:** 522 PatentScope and 56 PubMed records were identified: 3 published international patent applications and 5 peer-reviewed papers met eligibility criteria. Pharmacokinetic data were available for intranasal, sublingual, and reference routes (intramuscular, intravenous, subcutaneous). Highly concentrated formulations (10-40mg/ml) had been developed and tested. Sublingual bioavailability was very low (F=1%; relative to intravenous). Non-concentrated intranasal spray (1mg/ml; 1ml per nostril) had low bioavailability (F=11%). For concentrated intranasal spray formulations (≥10mg/ml), bioavailability ranges were F=21-42% and FIM=26-57% (relative to intramuscular), with peak naloxone concentrations (dose-adjusted Cmax=0.8-1.7ng/ml) reached in 19-30 minutes (tmax).

**Implications:** Exploratory analysis identified intranasal bioavailability as associated positively with dose and negatively with volume.

**Conclusion:** PatentScope is a valuable data source but rarely explored. From data integration from different naloxone patent applications, we find consistent direction of development of intranasal sprays to high-concentration, low-volume formulations with bioavailability in the 20-60% range. These have potential to deliver a therapeutic dose in 0.1ml volume.

Key words:intranasal, naloxone, pharmacokinetics, opioids, drug overdose

# (c) Text

# Introduction

On November 18, 2015, the US Food and Drug Administration (FDA) gave regulatory approval for a concentrated intranasal (IN) naloxone spray by Adapt Pharma ([1](#_ENREF_1)), which constitutes the first-ever licensed non-injectable naloxone product. Regulatory approval in Canada followed in October 2016 ([2](#_ENREF_2)). The FDA and Health Canada decisions have opened up the possibility, for North America at least, of wider access to naloxone in light of the rising death toll from opioid overdoses ([3](#_ENREF_3)). At an estimated 106,000 deaths per annum ([4](#_ENREF_4)), opioid overdose deaths are also a growing international public health concern. To date, globally, no other non-injectable naloxone formulation has been licensed.

Effective non-injectable naloxone products would remove the risk of needle-stick injury in medical and community settings. Non-injectable naloxone may offer a particular implementation advantage for take-home naloxone (THN) programs, i.e. the pre-placement of naloxone kits with opioid users, families, peers, community police, and staff at treatment services, drop-in centers and hostels, where it would likely reduce regulatory obstacles and the current requirement of training laypersons in needle-and-syringe assembly and administration ([5](#_ENREF_5)). First proposed in 1996 ([6](#_ENREF_6)), THN has increasingly been introduced in the past decade, and recent WHO guidelines and a UN declaration have called for naloxone access for “anyone likely to witness an overdose” ([7](#_ENREF_7), [8](#_ENREF_8)). In response, the FDA, the US Centers for Disease Control and Prevention (CDC), National Institute on Drug Abuse (NIDA), and Office of the Assistant Secretary for Health and Human Services (HHS) sponsored a 2012 stakeholder meeting where key criteria for any novel non-injectable naloxone product were proposed ([9](#_ENREF_9), [10](#_ENREF_10)).

According to the FDA ([9](#_ENREF_9)), one or more standardized doses of a novel non-injectable naloxone formulation would need to result in plasma naloxone levels (i.e. area under the curve; *AUC*) comparable to a parenteral dose of at least 0.4mg. If the bioavailability (*F* = “absolute bioavailability”, relative to intravenous; *FIM* = “relative bioavailability”, relative to intramuscular) of the new product compared with the approved injection is low, then it is unclear if adequate efficacy can be reached. Vice versa, if the bioavailability is unexpectedly high, then this may have implications for the safety profile of the novel formulation. Furthermore, the bioavailability compared with injection would need to be reasonably constant between different individuals. In the emergency situation of opioid overdose, naloxone needs to be absorbed rapidly. Absorption would thus need to be at least as rapid as intramuscular injection, whereby onset of effect starts within 3 to 7 minutes of administration ([8](#_ENREF_8)). The key pharmacokinetic (PK) parameters for a non-injectable naloxone formulation are typically the maximum observed plasma concentration (Cmax) and the time from dosing to peak concentration (Tmax), in addition to bioavailability.

A recent systematic review ([11](#_ENREF_11)) applied the FDA criteria to the peer-reviewed literature and identified three candidate routes of administration for injection-free naloxone delivery: IN, sublingual, and buccal. However, at the time of the FDA approval of the first nasal spray, no results from clinical trials on the new nasal spray were published, and human PK data were only reported in one peer-reviewed publication for an improvised IN naloxone spray formulation (2mg/5ml), with extremely low bioavailability (F=4%) ([12](#_ENREF_12)). While improvised IN spray devices (administered by attaching a mucosal atomiser device to a pre-filled 2mg/2ml naloxone syringe) are commonly used in take-home naloxone programs in some countries (CDC) and a significant number of overdose reversals have been reported ([13](#_ENREF_13), [14](#_ENREF_14)). uncertainties regarding their efficacy have been considered and primarily concern their potential non-response rate and lack of safety data ([15-17](#_ENREF_15)).

Time lag between research and development activity in the pharmaceutical industry and the publication of relevant data in the peer-reviewed literature is not new: Indeed, more than five decades ago, the discovery and original synthesis of naloxone was first reported in a 1961 patent application ([18](#_ENREF_18)) before a conference abstract ([19](#_ENREF_19)) and a full journal article ([20](#_ENREF_20)) followed in subsequent years.

This exploratory review attempts to close the existing gap in the literature by examining published international patent applications of non-injectable naloxone formulations and contributory PK data. The aims are threefold: 1) to trace the concept and product development by route of administration; 2) to describe the non-injectable naloxone formulations for which human in vivo data are available; 3) to compare human PK data reported in the patent applications.

# Methods

A three-stage approach has been taken.

## Stage 1:

The PatentScope database of the World Intellectual Property Organization (WIPO), which contains 58 million patent documents including 3 million published international patent applications ([21](#_ENREF_21)), was searched for patent applications for non-injectable naloxone formulations. PatentScope was searched for English-language patent applications (“Language: EN”) that were registered with any international patent office (“Office(s): all”) and contained the search term “naloxone” within their First Page (default). Only patent applications for non-injectable naloxone that contained human PK data were eligible for inclusion in the analysis (Aims 2 & 3).

## Stage 2

The pharmaceutical properties of the non-injectable naloxone formulations and human PK data were extracted from patent applications and summarized. To improve comparability between formulations, dose-adjusted values per 1mg were generated.

## Stage 3

To supplement and cross-check the data obtained in Stages 1 and 2, wealsosearched PubMed for human PK data for non-injectable naloxone using the Boolean search query “(nasal OR intranasal OR nose OR buccal OR sublingual) AND naloxone AND pharmacokinetics” (see Table S1 for search protocol). These three routes of administration were chosen based on the systematic review ([11](#_ENREF_11)).

For all three stages, R.M. and Ø.D.G. conducted the PatentScope and PubMed searches, assessed retrieved records for eligibility, and extracted relevant information under supervision of the senior authors (O.D., J.S.).

\*\*\* Insert Figures 1 & 2 about here \*\*\*

# Results

## Stage 1:

A PRISMA flow diagram of the selection process of patent applications is shown in Figure 1. 522 PatentScope records were identified using the search term “naloxone” for front-page matches. At this stage, a cross-check was made for known patent applications, and it was found that no entry for the FDA-approved Adapt IN spray product had been captured. We thus additionally searched PatentScope for “Adapt OR Lightlake”-related entries. (In late 2014, Adapt Pharma had bought the global license from Lightlake Therapeutics Inc. to develop and commercialize their IN naloxone spray ([22](#_ENREF_22)).) After matching for the search term “Lightlake” (front-page search, English language, all patent offices), this additional search yielded five patent applications, which had not been captured using the search term “naloxone” because Lightlake had not included the word ‘naloxone’ on the front page. Consequently, we manually added these five Lightlake patent applications (*n.b.* in the following, we denote these as ‘Lightlake’ unless we refer directly to the licensed Adapt nasal spray product).

Of the 47 records that remained after removing 480 irrelevant records, 10 were excluded based on their abstract (e.g. active ingredient other than naloxone). The remaining 37 records were downloaded for full-text review and screened for human PK data. Of the 14 patent applications that contained relevant PK data, 11 were excluded for the following reasons: 5 reported only animal data, and 6 were duplicates (earlier or later versions of patents containing the same PK data but different patent claims or country of publication). Three published international patent applications were identified as eligible for inclusion: WO/2015/136373, WO/2015/095644, and WO/2012/156317.

A timeline of the publication of all 37 patent applications (including excluded records) is provided in Table S2 of the Online Appendix. The timeline shows that the concept of non-injectable naloxone (drops, spray, solution, suspension, ointment or gel) was first being explored at the University of Kentucky, with first animal data reported in 1982. The 1990s showed no activity for IN naloxone except for the patent application of a spray dispenser by Britannia Pharmaceuticals in 2000 (*n.b*. the same spray device as in the 2015 FDA-approved Adapt naloxone spray). In 2005, an IN naloxone powder was proposed by the Chinese PLA Academy of Military Science. The first human PK data for IN naloxone were filed by Euro-Celtique in 2012 (WO/2012/156317).

The first patent application describing the concept of sublingual or buccal naloxone was published by the Israeli company Pentach Pharmaceuticals in 2004, and patent applications covering sublingual naloxone (spray, dripping pills) by two Beijing-based companies followed in 2007 and 2011. In 2012, Euro-Celtique included sublingual PK data in its patent application on concentrate IN naloxone spray (see above). In June 2015, INSYS Pharma submitted two patent applications for sublingual naloxone spray (no PK data) and was granted FDA fast-track review later that year ([23](#_ENREF_23)).

\*\*\* Insert Table 1 about here \*\*\*

## Stage 2: Description of intranasal pharmacokinetic data

We now describe the IN PK data reported in the published international patent applications WO/2015/136373 (Lightlake Therapeutics), WO/2015/095644 (AntiOp), and WO/2012/156317 (Euro-Celtique). The pharmaceutical properties of the naloxone formulations tested by AntiOp (10mg/ml) and Lightlake (10mg/ml; 20mg/ml; 40mg/ml) are described in detail in Table S4 of the Online Appendix; Euro-Celtique only reported the concentration of their formulations (20mg/ml, 40mg/ml Naloxone HCl).

All PK data were obtained using crossover study designs, though sample sizes differed from 7 to 35 subjects per arm. For a full summary of the PK data (including reference routes), please see Table 1.

AntiOp described two studies, which are hereby referred to as ‘Trial 1 (Pilot’) and ‘Trial 2’. AntiOp tested a 10mg/ml IN formulation administered as 0.1ml into one and two nostrils, as well as 0.2ml per nostril (0.1+0.1ml with 5-minute interval). Trial 1 (Pilot) also tested non-concentrate 1mg/ml naloxone, with mucosal atomizer device (MAD) attached to a syringe, thus replicating the improvised IN naloxone distributed off-label in several countries.

Lightlake presented results from two studies: Study 1 assessed a 10mg/ml formulation, whereas Study 2 tested 20mg/ml and 40mg/ml formulations, all administered as 0.1ml into one and two nostrils (total volume: 0.2ml).

Euro-Celtique tested IN doses of 8mg (0.2ml per nostril; 20mg/ml concentration) and 16mg (0.2ml per nostril; 40mg/ml concentration). Euro-Celtique also included a sublingual arm (16mg/ml solution), but this route is not described here in detail, as its absolute bioavailability was only 1%.

For IN administration, we present F as well as FIM, as neither measure was reported across all three patent applications. (Euro-Celtique only provided F, whereas the more recent AntiOp and Lightlake patent applications reported FIM in accordance with guidance from the FDA).

*F:* For the Euro-Celtique data, we calculated F values of 22% (20mg/ml, administered as 0.2ml per nostril) and 21% (40mg/ml; 0.2ml per nostril) using AUC0-∞ data listed in the PK data appendix of the patent application. We were unable to obtain the higher F values of 32% (20mg/ml formulation) and 27% (40mg/ml) which Euro-Celtique cited in-text for lower doses (1.2 and 1.6mg, dose-adjusted from 8 and 16mg) in the body of the patent application. AntiOp only reported FIM, but included an IV reference in Trial 1 (Pilot), which allowed us to determine the following F-values for comparison: 36% (0.1ml, one nostril only) and 42% (0.1ml per nostril) for the 10mg/ml formulation, and 11% for non-concentrate naloxone (1mg/ml per nostril).

*FIM:* Lightlake achieved the highest FIM values across all three patent applications, with 0.1ml of the 10mg/ml formulation administered into both nostrils (FIM=57%). FIM was lower (48%), when the volume of the same formulation was doubled (0.2ml per nostril). For the 20mg/ml formulation, FIM was 54% (0.1ml, one nostril only) and 55% (0.1ml per nostril). The 40mg/ml formulations achieved 49% and 45% when administered into one and both nostrils, respectively. AntiOp reported the following FIM values for a 10mg/ml formulation: 34% (0.1ml, one nostril only), 31-39% (0.1ml per nostril), and 26% (0.1ml per nostril, with re-administration after 5 minutes; i.e. total volume of 0.2ml per nostril). Non-concentrate naloxone (1mg/ml per nostril) had a FIM of 10%.

*t1/2:* The terminal half-life (*t1/2*) is the time it takes for the blood concentration of a pharmacological agent to decrease by 50%, which usually translates into the loss of half of its pharmacologic activity. Euro-Celtique reported the longest terminal half-lives (t1/2) for IN administration, with 9.1 (40mg/ml) and 9.5 hours (20mg/ml), though data were only available for 4 subjects. In the AntiOp and Lightlake patent applications, t1/2 fell in the range of 1.2–2.1 hours.

*tmax:* IN tmax was 0.27 hours (i.e. 16 minutes) for non-concentrated spray (AntiOp, 1mg/ml, 1ml per nostril) and ranged from 0.31 to 0.50 hours (i.e. 19-30 minutes; AntiOp 10mg/ml, 0.1ml into one nostril and Lightlake 40mg/ml, 0.1ml into one nostril) across concentrated spray formulations.

*AUC & Cmax:* Dose-adjusted Cmax values (per mg) were highest for the Lightlake 20mg/ml formulation administered as 0.1ml per nostril (Cmax=1.66ng/ml). The same treatment arm achieved AUC0-∞=2.48ng\*h/ml. The Euro-Celtique 20mg/ml formulation reached the highest AUC0-∞ value (2.76ng\*h/ml) and a per mg Cmax of 1.60ng/ml. The 1mg/ml non-concentrate AntiOp treatment (administered as 1ml per nostril) had the lowest values (AUC0-∞=0.45ng\*h/ml; Cmax=0.27ng/ml).

*Additional exploratory analyses:* In order to examine the potential influence of spray concentration on IN absorption, we plotted AUC, Cmax, and tmax values against volume (adjusted by dose for AUC and Cmax) and dose (see Figure 3). For both AUC and Cmax, the plots indicate a positive association with dose and a negative association with volume of the IN spray. The graphs do not suggest a clear association for tmax.

\*\*\* Insert Figure 3 about here \*\*\*

## Stage 3:

The PubMed search generated 56 matches, with zero duplicates (see Figure 2 for PRISMA diagram). 46 papers were excluded based on title and abstract (no primary research data from human-subject naloxone studies).

The ten remaining records were then downloaded for full text, with five papers excluded for the following reasons: one was a review article, and four did not include naloxone PK data (see Table S3 for list of excluded studies). The remaining eligible five papers included human PK data in two papers for IN naloxone ([12](#_ENREF_12), [24](#_ENREF_24)) and three papers for sublingual naloxone ([25-27](#_ENREF_25)). None of the papers contained human PK data for buccal naloxone.

Divergent bioavailability values have been reported for IN naloxone. One healthy volunteers study (n=6) assessed a non-concentrate formulation of IN naloxone (2mg/5ml) and reported an absolute bioavailability of only 4%, which the authors attributed as possibly due to the dilute solution (and high volume) used ([12](#_ENREF_12)). Higher absorption was reported in a study ([24](#_ENREF_24)) with recreational prescription opioid users (n=10) where absolute bioavailability of IN administration of crushed buprenorphine/naloxone (4:1 ratio) of two concentrations (0.5mg, 2mg naloxone) was 24% and 30%, respectively.

Systemic uptake after sublingual naloxone administration was generally found to be low. In one healthy volunteers study, naloxone doses of 1.4mg and 2mg were administered in combination with buprenorphine, resulting in a median tmax of 0.8h and peak naloxone plasma concentrations below 0.4ng/ml for both doses ([26](#_ENREF_26)). A second study in non-dependent opioid users (n=8) ([27](#_ENREF_27)) assessed escalating naloxone doses (1mg, 2mg, 4mg) and found that dose-effect comparisons were impossible, as many naloxone plasma concentrations were below the level of quantification (0.050ng/ml). The highest individual AUC reported was 0.55ng\*h/ml.

A third study ([25](#_ENREF_25)) suggested that sublingual naloxone bioavailability is negatively associated with healthy liver functioning. A sublingual 0.5mg naloxone tablet (in combination with 2mg buprenorphine) was administered to forty-three subjects stratified by hepatic impairment (mild, moderate, or severe), HCV diagnosis without hepatic impairment, and healthy volunteers. Across all groups, the median tmax ranged from 0.8-1.1 hours, with mean t1/2 from 1.9-5.5 hours. However, the AUC0-last data revealed an approximate 3 to 14-fold increase in total naloxone exposure in subjects with moderate and severe hepatic impairment. Likewise, the naloxone Cmax was 3 to 11-times higher in subjects with hepatic impairment.

# Discussion

Human PK data for purpose-made non-injectable naloxone formulations had not been reported in peer-reviewed scientific papers at the time of the FDA-approval of the first IN naloxone spray ([28](#_ENREF_28)). However, published international patent applications by the companies AntiOp, Euro-Celtique and Lightlake contain data on concentrated sublingual and IN spray formulations in the range 10-40mg/ml. Through integration of data from WIPO PatentScope and scientific publications retrieved via PubMed, this exploratory review charts R&D activity over the past two decades (particularly 2012-present) and provides an assessment of the current status of non-injectable naloxone development relative to pre-defined regulatory criteria ([9](#_ENREF_9), [10](#_ENREF_10)).

## Statement of principal findings

Across all concentrate IN naloxone formulations, bioavailability was 21-42% relative to IV and 26-57% relative to IM. We plotted AUC0-∞-and Cmax values and found a moderately linear relationship with dose (higher dose 🡪 higher AUC0-∞, Cmax) and a negative association for volume (lower volume 🡪 higher AUC0-∞, Cmax). The highest IN bioavailability (FIM=57%) was reached when 0.1ml of a 10mg/ml formulation was administered into both nostrils. For the same formulation, FIM decreased to 48% when volume doubled to 0.2ml per nostril. Volume clearly matters. Also, dose-concentration linearity is evident. We identify the importance of (low) volume with IN bioavailability drastically lower (F=11%) when a non-concentrate formulation of 1mg/ml was administered into both nostrils. This confirms previous reports of low bioavailability (F=4%) for dilute IN spray (0.4mg/ml) ([12](#_ENREF_12)).

Sublingual naloxone administration of a concentrate solution (16mg/ml) had very low bioavailability (F=1%). This is below the range of 7-9% identified by Chiang et al. in their review of sublingual buprenorphine-naloxone formulations ([29](#_ENREF_29)). We conclude that sublingual is unlikely to be a route of administration of clinical value.

## Strengths and weaknesses of the review

This is the first review of non-injectable concentrate naloxone formulations in the peer-reviewed literature. It includes examination of public-domain information from patent applications. A core strength of this exploratory review lies in the integration of empirical evidence from PubMed and WIPO PatentScope databases, capturing both academic and pharmaceutical industry advances in the field.

The validity of our comparison of IN PK data across different patent applications is strengthened by the similarity of the IN spray formulations used. While Euro-Celtique only disclosed dose concentrations, all formulations all formulations by Lightlake and AntiOp with provided PK data are characterized by absence of absorption enhancers (which increase membrane permeation) and viscosity-increasing agents (which increase the residence time of naloxone to the nasal mucosa and thus contributes to better absorption) (see Table S4 in Online Appendix).

Potential limitations need to be considered. Firstly, not all research and development activity leads to registration of intellectual property or to journal publication, and non-significant or negative results have low likelihood of getting published.

## Secondly, our exploratory WIPO PatentScope database search was unlikely exhaustive. Considering that our search initially failed to capture the Lightlake patent applications, we cannot rule out the possibility of other false-negatives. We conducted the default “First Page” search, which identified any patent document with the search term (“naloxone”) mentioned on its cover page, generating 522 matches. Had we conducted the more comprehensive “Full Text” search (“naloxone” mentioned in any full-text patent document), PatentScope would have identified over 19,000 matches, which would have exceeded our capacity for manual screening. Compared to online literature databases such as PubMed or Embase, the functionality of the PatentScope interface is less advanced, in that users cannot export full search results to a citation manager. For every PatentScope entry, we thus had to download associated documents individually to assess eligibility for inclusion in our review. We considered supplementing our PatentScope search with additional query of all national and regional patent offices for which our PatentScope “naloxone” search had yielded relevant entries (Canada, China, European Union, Germany, Great Britain, Israel, Russia, Singapore, South Africa, United States; see Online Supplement 2). However, we concluded that this was not feasible due to their different search and output formats that are not always compatible with PatentScope: for instance, the British online database Ipsum of the UK Intellectual Property office only permits search by application or publication number (i.e. not by keyword, e.g. “naloxone”) **(**[**30**](#_ENREF_30)**)**, and the United States Patent and Trademark Office offers two separate search modes: one for patent applications (Patent Application Full-Text and Image Database, AppFT) and one for issued patents (Patent Full-Text and Image Database; PatFT) **(**[**31**](#_ENREF_31)**)**, whereas PatentScope does not provide such distinction.

The third limitation concerns the quality of the data retrieved: we did not have access to raw data, and our analysis was reliant upon summary data provided by the patent applicants. Consequently, the comparability of the PK results was limited by different analytical methods and result formats used in the individual studies included in the patent applications (e.g. bioavailability reported as F vs. FIM; central tendency expressed as mean vs. median). For instance, for no apparent reason, we were unable to replicate the F-values that Euro-Celtique cited in-text when we used the PK values listed in the data appendix. Similarly, we remain uncertain about the actual concentration of the AntiOp formulation (10mg/ml Naloxone HCl or 10mg/ml Naloxone HCl dihydrate), which could have affected calculation of dose-adjusted values in Table 1. There was also variability in the sampling periods (8-36 hours), which may have impacted AUC-dependent measures (e.g. F%, FIM%). In terms of reliability of the mean values reported in Table 1, it also needs to be borne in mind that the crossover studies (which comprised pilot and registration trials) differed substantially in sample sizes (7-35 subjects per treatment arm).

## Meaning of the review: Possible mechanisms and implications for clinicians or policymakers

These findings have multiple implications for clinicians and policymakers.

**IN naloxone:** Low spray volume and high concentrations lead to better IN naloxone absorption. Concentrated IN naloxone spray is thus a potentially valuable non-injectable formulation for opioid overdose reversal. This is likely relevant both in medical settings and in the community (THN programmes). This conclusion accords with the first FDA-approval of an IN naloxone spray product ([1](#_ENREF_1)), at 4mg/0.1ml naloxone hydrochloride (i.e. 40mg/ml concentration). However, further examination is required of the full PK curve and the resulting clinical effect since, for all doses of the 40mg/ml formulations tested (4-16mg), we found Cmax (5.34-18.3ng/ml) was much higher than for intramuscular (IM) references (Cmax=0.77-1.05ng/ml). Consequently, while clinical efficacy of concentrated IN sprays is likely, there is the risk of inducing acute opioid withdrawal in overdose victims ([32](#_ENREF_32)). A recent qualitative analysis of heroin/opioid overdose reversals found instances of apparent excessive naloxone dosing and consequent ‘over-antagonism’, sometimes triggering discharge and active further drug-seeking ([33](#_ENREF_33)). Hepatic impairment also increases naloxone bioavailability, particularly relevant when larger fractions of buccal/sublingual or IN naloxone are swallowed ([25](#_ENREF_25)), potentially causing severe distress and adverse events from naloxone over-antagonism in dependent patients.

The poor IN bioavailability of non-concentrated naloxone using the MAD device also raises important questions ([15-17](#_ENREF_15)). From a scientific perspective, how can such low absorbed doses be effective if they are indeed succeeding in reversing overdose? Also, the continued use of improvised (i.e. dilute) IN naloxone kits needs review.

**Sublingual naloxone:** In October 2015, INSYS Therapeutics announced that its sublingual naloxone spray (formulation unknown) had been granted fast-track review by the FDA. Considering the low bioavailability reported by the Euro-Celtique study, it seems unlikely that sublingual naloxone will be clinically useful.

## Unanswered questions and future research

Unanswered questions around non-injectable naloxone remain. All PK data reported in the referenced patent applications were from healthy volunteers. It remains unclear how these findings relate to the heroin/opioid users where non-response rates (i.e. response judged by ambulance personnel to need supplementary injected dose) around 18–26% have been reported for IN naloxone ([34](#_ENREF_34), [35](#_ENREF_35)).

Secondly, there are limitations in our current understanding of the pharmacokinetics and pharmacodynamics of naloxone. While this review largely focuses on the bioavailability of non-injectable naloxone relative to parenteral injection, the absolute naloxone plasma concentration range required to reverse opioid overdose remain unknown. This needs sorting. Since naloxone is a competitive antagonist, the therapeutic dose will likely differ by route of administration alongside inter-individual variability. Moreover, the naloxone dose required to reverse the effects of a specific opioid agonist will depend on the opioid agonist dose and its pharmacological properties, particularly its potency, duration of action, and receptor affinity ([36](#_ENREF_36)).

An ongoing Australian double-blinded randomised clinical trial at the Sydney Medically Supervised Injecting Centre (trial ID: ACTRN12611000852954) compares IN (0.8mg/ml) versus IM (0.8mg/ml) naloxone treatment and assesses the proportion of suspected opioid overdose cases (by treatment group) needing a second naloxone dose (both groups: 0.8mg/2ml IM) for overdose reversal. The results of this trial will likely shed light on the question of therapeutic dose.

The 2014 WHO guidelines note that a 0.4-0.8mg parenteral naloxone dose is effective in most cases to reverse opioid overdose. However, given that the duration of naloxone is shorter than that of many opioids, repeat doses of naloxone may need to be given ([37](#_ENREF_37)). The WHO guidelines advise that initial naloxone doses above 0.8mg increase the likelihood of significant withdrawal symptoms ([8](#_ENREF_8)). For any therapeutic drug, dose-related adverse effects (i.e. opioid withdrawal symptoms in the case of naloxone) often occur around Cmax ([38](#_ENREF_38)), suggesting that novel naloxone formulations with Cmax above that of a 0.8mg parenteral naloxone injection may pose elevated risk of adverse effects. Future studies should systematically monitor and assess reports of naloxone-related adverse effects (from the medical or community setting) in relation to the naloxone dose and formulation used.

Thirdly, while the PK data from the patent applications indicated a negative relationship between volume and naloxone uptake, they did not allow us to determine a cut-off for IN spray volume (volume above which naloxone is lost to pre or post-nasal drip). Definition of the maximum volume will affect repeat-administrations of IN naloxone spray. This too needs resolution.

Finally, we present a new analytical method of synthesis of public patent data from the WIPO PatentScope database. The limitations discussed above illustrate that this exploratory method will require optimization and would benefit from enhanced functionality of the PatentScope interface, so that review of a greater volume of patent documents would become manageable. A “Patent Crawler” software has been trialed as a search tool that combines analysis of medication and patent databases ([39](#_ENREF_39)). Future open-source editions of such software may potentially help academics, clinicians, and members of the general public retrieve medication-related information across patent databases and the peer-reviewed medical literature. If such open-source software becomes available, we hope that our search protocol provided in Table S1 of the Online Appendix will allow researchers to replicate our exploratory analysis with added capture capability. When replicating our search in future, researchers might also find it helpful to work together with patent experts who will be familiar with the functionality of patent databases and the legal language of (the often broad) patent claims.

In future, such syntheses would also be more valuable if data were presented uniformly: this would require investigators of non-injectable naloxone formulations (including pharmaceutical companies) to publish their data even if findings are negative (see e.g. AllTrials.net) ([40](#_ENREF_40)).

# Conclusions:

Over the past fifteen years, IN naloxone sprays have been tested in humans, but no product was licensed and commercially available until late 2015 ([1](#_ENREF_1)). With an ongoing epidemic of prescription-opioid overdose deaths alongside a more recent rapid rise in heroin deaths, an IN naloxone spray is finally available to prevent overdose deaths in opioid users - a target population vastly underserved for decades. This first licensed non-injectable naloxone marks a significant milestone towards wider naloxone access and more effective prevention of opioid overdose deaths. High-concentrate IN naloxone has good bioavailability although, thus far, formal product testing has only involved healthy volunteers. It remains possible that high-concentrate formulations may provoke naloxone over-antagonism in opioid-dependent patients. Options for dose-titration and alternative routes (e.g. buccal) also need exploration. We call for proper publication of PK data on naloxone products: only then can there be properly informed consideration of different naloxone products by the clinical, policy and scientific communities.

Table 1 | Pharmacokinetic properties of patent formulations

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |  |  | Observed values | Dose-adjusted values (permg) |
|  | Study | n | Conc.(mg/ml) | Nostrils# | Dose (mg)/ volume (ml) | F% | FIM% | tmax(h) | t1/2(h) | Cmax  (ng/ml) | AUC0-∞(ng\*h/ml) | AUC0-last(ng\*h/ml) | Cmax(ng/ml) | AUC0-∞(ng\*h/ml) | AUC0-last(ng\*h/ml) |
| **IV** | AntiOp Trial 1 | 13 | 0.4 |  | 0.4/1.0 |  |  | *0.03±0.1* | *1.28±0.2* | *3.87±2.7* | *1.67±0.5*  |  | *9.68a* | *4.18a* |  |
|  | Euro-Celtique | 11 | 1 |  | 1.0/1.0 |  |  | 0.85±1.6 | 0.89±0.1e | 17.9±29.9 | 12.6±12.4e | 10.5±7.2 | 17.9a | 12.6a | 10.5a |
| **IM** | AntiOp Trial 1 | 13 | NA |  | 1.0/NA | 106a, d |  | *0.33±0.5* | *1.41±0.3* | *2.54±1.0* | *4.43±1.2* |  | *2.54a* | *4.43a* |  |
|  | AntiOp Trial 2 | 34 | 0.4 |  | 0.4/1.0 |  |  | *0.17 (0.1, 1.0)* | 1.38±0.3 | 1.05±0.4 | 1.67±0.4 |  | 2.63a | 4.18a |  |
|  | Lightlake 1 | 14 | 0.4 |  | 0.4/1.0 |  |  | 0.34±0.1 | *1.21±0.2* | 0.77±0.2 | 1.42±0.3 | 1.38±0.3 | 1.91a | 3.55a | 3.45a |
|  | Lightlake 2 | 28 | 0.4 |  | 0.4/1.0 |  |  | *0.42 (0.1, 2.0)* | 1.19b | 0.91±0.3 | 1.83±0.4 | 1.79±0.4 | 2.26±0.7 | 4.57±1.1 | 4.48a |
| **SQ** | AntiOp Trial 1 | 13 | NA |  | 1.0/NA | 99a, d | 94a, d | *0.17±0.3* | *1.59±0.6* | *2.72±0.8* | *4.15±1.1* |  | *2.72a* | *4.15a* |  |
| **IN** | AntiOp Trial 1\* | 13 | 10 | 2 | 2.0/0.2 | 42a, d | 39a, d | *0.42±0.3* | *1.53±0.2* | *1.95±1.1* | *3.47±0.8* |  | *0.98a* | *1.74a* |  |
|  | AntiOp Trial 1\* | 13 | 10 | 1 | 1.0/0.1 | 36a, d | 34a, d | *0.50±0.2* | *1.41±0.3* | *0.84±0.5* | *1.52±0.5* |  | *0.84a* | *1.52a* |  |
|  | AntiOp Trial 1 | 7 | 1 | 2 | 2.0/2.0 | 11a, d | 10a, d | *0.27±0.1* | *1.64±0.3* | *0.53±0.2* | *0.90±0.2* |  | *0.27a* | *0.45a* |  |
|  | AntiOp Trial 2\* | 33 | 10 | 2 | 2.0/0.2 |  | 31a, d | *0.33 (0.3, 0.8)* | 1.37±0.3 | 1.78±1.0 | 2.63±1.3 |  | 0.89a | 1.32a |  |
|  | AntiOp Trial 2\* | 35 | 10 | 2+2c | 4.0/0.4 |  | 26a, d | *0.42 (0.2, 1.0)* | 1.41±0.3 | 3.06±1.6 | 4.42±2.2 |  | 0.77a | 1.11a |  |
|  | Lightlake 1 | 14 | 10 | 2 | 2.0/0.2 |  | 57 | 0.33±0.1 | 1.19±0.1 | 2.32±1.0 | 3.44±1.0 | 3.41±1.0 | 1.16a | 1.72a | 1.71 |
|  | Lightlake 1 | 14 | 10 | 2 | 4.0/0.4 |  | 48 | 0.31±0.1 | 1.22±0.1 | 4.55±2.9 | 5.68±1.6 | 5.63±1.6 | 1.14a | 1.42a | 1.41 |
|  | Lightlake 2 | 28 | 20 | 1 | 2.0/0.1 |  | 54 | *0.33 (0.3, 1.0)* | 1.70b | 3.11±1.1 | 4.86±1.5 | 4.81±1.5 | 1.56±0.6 | 2.43±0.7 | 2.41 |
|  | Lightlake 2 | 28 | 20 | 2 | 4.0/0.2 |  | 55 | *0.33 (0.1, 0.5)* | 2.09b | 6.63±2.3 | 9.91±2.7 | 9.82±2.7 | 1.66±0.6 | 2.48±0.7 | 2.46 |
|  | Lightlake 2 | 28 | 40 | 1 | 4.0/0.1 |  | 49 | *0.50 (0.2, 1.0)* | 2.00b | 5.34±2.4 | 8.87±3.3 | 8.78±3.3 | 1.34±0.6 | 2.22±0.8 | 2.20 |
|  | Lightlake 2 | 28 | 40 | 2 | 8.0/0.2 |  | 45 | *0.33 (0.2, 1.0)* | 1.91b | 10.3±4.0 | 16.1±3.8 | 15.9±3.8 | 1.29±0.5 | 2.01±0.5 | 1.99 |
|  | Euro-Celtique | 11 | 20 | 2 | 8.0/0.4 |  22)a, d |  | 0.34±0.2 | 9.48±3.9f | 12.8±4.5 | 22.0±4.2f | 20.1±4.9 | 1.60a | 2.76a | 2.51a |
|  | Euro-Celtique | 12 | 40 | 2 | 16.0/0.4 | (21)a, d |  | 0.39±0.2 | 9.09±2.7f | 18.3±7.5 | 42.8±10.6f | 32.8±10.2 | 1.14a | 2.67a | 2.05a |
| **SL** | Euro-Celtique | 11 | 16 |  | 16.0/1.0 | (1)a, d |  | 3.91±10.6 | 1.13±0.2f | 0.90±0.4 | 1.50±0.4f | 2.67±1.8 | 0.06a | 0.09a | 0.17a |
| *Annotations:* Values for tmax, Cmax, AUC, t1/2 denote mean ±SD, except for values in italics. Values in italics denote median ±SD or median (min, max). Inconsistent information between the patent and the PK data whether the formulation contained10mg/ml Naloxone HCl dihydrate or 10mg/ml Naloxone HCl. Dose-adjusted values (per mg) in table are based on Naloxone HCl. a calculated values; b harmonized mean; c re-administration after 5 minutes; d calculated F and FIM values based on AUC0-∞; e sample size = 3; f sample size = 4; NA = not available; IV = Intravenous; IM = Intramuscular; SQ = Subcutaneous; IN = Intranasal; SL = Sublingual. |



Included patents
(*n* = 3)

Manual search

*(n = 5)*

NO

Full patents retrieved

(*n* = 37)

Records identified through WIPO PatentScope search
(*n* = 522)

Irrelevant records excluded based on title

*(n = 480)*

Excluded based on abstract

*(n = 10)*

Excluded with reasons

(*n* = 11)

Duplicate *n* = 6

Animal data *n* = 5

Patents with in vivo data

(*n* = 14)

Excluded based on full patent *(n = 23)*

Contains in vivo data (e.g. PK)?

YES

Non-injectable formulation / device?

YES

NO

Records screened for abstract

(*n* = 47)

Figure 1 | PRISMA diagram of PatentScope search

Figure 2 | AUC0-∞, Cmax and tmax plotted by volume and dose

Studies screened for title and abstract

(*n* = 56)

Full papers retrieved

(*n* = 10)

Included studies
(*n* = 5)

Records identified via PubMed search
(*n* = 56)

Irrelevant records excluded based on abstract (*n* = 46)

Excluded based on paper

(*n* = 3)

No PK data *n* = 4

Review article *n* = 1

Figure 2 | PRISMA diagram of PubMed search



Included patents
(*n* = 3)

Manual search

*(n = 5)*

NO

Full patents retrieved

(*n* = 37)

Records identified through WIPO PatentScope search
(*n* = 522)

Irrelevant records excluded based on title

*(n = 480)*

Excluded based on abstract

*(n = 10)*

Excluded with reasons

(*n* = 11)

Duplicate *n* = 6

Animal data *n* = 5

Patents with in vivo data

(*n* = 14)

Excluded based on full patent *(n = 23)*

Contains in vivo data (e.g. PK)?

YES

Non-injectable formulation / device?

YES

NO

Records screened for abstract

(*n* = 47)

Figure 3 | AUC0-∞, Cmax and tmax plotted by volume and dose

(d) Acknowledgements:

The authors would like to thank Ms Carol Greaves (Patent Attorney at C.P. Greaves & Co) for her valuable comments on this manuscript.

(e) Conflict of interest:

Ø.D.G. was a Master of Science in pharmacy student at NTNU; Norwegian University of Science and Technology, during the conduct of this study. As a part of his master degree, he was involved in the conduct of a clinical trial of an intranasal naloxone formulation. Ø.D.G. is now employed as a pharmacy manager at Apotek 1 Gruppen AS

O.D. declares that his employer (NTNU; Norwegian University of Science and Technology) has a Cooperation Agreement with Den norske Eterfabrikk (DnE) Pharma to seek commercialization of an intranasal naloxone formulation developed by O.D. In this respect, NTNU and its subsidiary Technology Transfer Office and DnE-Pharma also have signed a licensing agreement. The latter regulates potential royalties for O.D. through NTNU. O.D. is engaged by DnE as Principle Investigator in a pharmacokinetic study of naloxone for which O.D. receives no personal honorarium. DnE has compensated O.D. for project-related travels from Trondheim to Oslo. O.D. is supported by the The Liaison Committee between the Central Norway Regional Health Authority and the NTNU and by The Joint Research Committee between St. Olav’s Hospital and the Faculty of Medicine, NTNU.

J.S. declares that he is a researcher and clinician who has worked with a range of types of treatment and rehabilitation service-providers. He has also worked with a range of governmental and non-governmental organisations, and with pharmaceutical companies to seek to identify new or improved treatments (including naloxone products), and from whom he and his employer (King’s College London) have received research funding, honoraria, travel costs and/or consultancy payments. J.S. has also been named in a patent application (WO/2012/156317; ‘Intranasal Pharmaceutical Dosage Forms comprising Naloxone’) filed by Euro-Celtique S.A. (an Independent Associated Company of Mundipharma Research Limited). For a fuller account of J.S.’s interests, see his personal web-page for King's College London at <http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx>. J.S. is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London.

R.M. has undertaken an unpaid student industry placement with Mundipharma Research Ltd, with focus on the analysis of naloxone nasal spray formulations. R.M. is working as a consultant for the United Nations Office on Drugs and Crime (UNODC), supporting a feasibility study of community-based opioid overdose prevention strategies in the framework of the UNODC-WHO Programme on Drug Dependence Treatment and Care (GLOK32). The views expressed in this article are those of the authors and do not necessarily reflect the position of the United Nations.

King’s College London (employer for both J.S. and R.M.) has separately applied to register intellectual property on a novel buccal naloxone formulation with which J.S. and R.M. are involved.

(f) References

1. FDA. FDA moves quickly to approve easy-to-use nasal spray to treat opioid overdose 2015 [cited 2015 November 18]. Available from: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm473505.htm>.

2. CBCnews. Health Canada OK's non-prescription nasal spray overdose antidote 2016 [cited 2016 October 5]. Available from: <http://www.cbc.ca/news/health/naloxone-nasal-spray-1.3789643>.

3. CDC. Increases in Drug and Opioid Overdose Deaths — United States, 2000–2014. Morbidity and Mortality Weekly Report (MMWR). 2016;64(50):1378-82.

4. WHO. Information sheet on opioid overdose 2014 [cited 2016 January 25]. Available from: <http://www.who.int/substance_abuse/information-sheet/en/>.

5. Compton WM, Volkow ND, Throckmorton DC, Lurie P. Expanded access to opioid overdose intervention: research, practice, and policy needs. Annals of internal medicine. 2013;158(1):65-6.

6. Strang J, Darke S, Hall W, Farrell M, Ali R. Heroin overdose: the case for take-home naloxone. BMJ: British Medical Journal. 1996;312(7044):1435.

7. UNODC/WHO. Opioid Overdose: Preventing and Reducing Opioid Overdose Mortality Vienna: United Nations; 2013 [March 10, 2016]. Available from: <http://www.unodc.org/docs/treatment/overdose.pdf>

8. WHO. Community Management of Opioid Overdose 2014 [cited 2016 January 25]. Available from: <http://apps.who.int/iris/bitstream/10665/137462/1/9789241548816_eng.pdf?ua=1&ua=1>.

9. Hertz S. Naloxone for Outpatient Use: Data Required to Support an NDA Silver Spring, MD2012 [May 30, 2014]. Available from: <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM300874.pdf>.

10. Nadel J. Clinical and Regulatory Perspectives on Naloxone Products Intended for Use in the Community 2016 [cited 2016 November 1]. Available from: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM524332.pdf>.

11. Strang J, McDonald R, Alqurshi A, Royall P, Taylor D, Forbes B. Naloxone without the needle − systematic review of candidate routes for non-injectable naloxone for opioid overdose reversal. Drug and Alcohol Dependence. In Press;<http://dx.doi.org/10.1016/j.drugalcdep.2016.02.042>.

12. Dowling J, Isbister GK, Kirkpatrick CM, Naidoo D, Graudins A. Population pharmacokinetics of intravenous, intramuscular, and intranasal naloxone in human volunteers. Therapeutic drug monitoring. 2008;30(4):490-6.

13. Walley AY, Xuan Z, Hackman HH, Quinn E, Doe-Simkins M, Sorensen-Alawad A, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. BMJ: British Medical Journal. 2013;346.

14. Madah-Amiri D, Clausen T, Lobmaier P. Rapid widespread distribution of intranasal naloxone for overdose prevention. Drug and Alcohol Dependence. 2017;173:17-23.

15. Strang J, McDonald R, Tas B, Day E. Clinical provision of improvised nasal naloxone without experimental testing and without regulatory approval: imaginative shortcut or dangerous bypass of essential safety procedures? Addiction (Abingdon, England). 2016;111(4):575-82.

16. Strang J, McDonald R. New approved nasal naloxone welcome, but unlicensed improvised naloxone spray kits remain a concern: proper scientific study must accompany innovation. Addiction (Abingdon, England). 2016;111(4):590-2.

17. Dale O. Ethical issues and stakeholders matter. Addiction. 2016;111(4):587-9.

18. Lewenstein MJ, Fishman J. Morphine derivative. US patent 3,254,088 (issued 31 May)1966.

19. Blumberg H, Dayton HB, George M, Rapaport DN. N-allylnoroxymorphine: a potent narcotic antagonist. Federation Proceedings. 1961;20:311.

20. Minakami H, Takagi H, Kobayashi S, Deguchi T, Kumakura S, Iwai I, et al. Morphine antagonistic actions of N-propargyl-14-hydroxydihydronormorphinone hydrochloride and related compounds. Life Sciences. 1962;1(10):503-7.

21. WIPO. PATENTSCOPE: Simple Search 2016. Available from: https://patentscope.wipo.int/search/en/search.jsf.

22. PRNewsWire. Lightlake Therapeutics Inc. Announces Licensing Deal with Adapt Pharma Limited Subsidiary 2014 [cited 2016 November 1]. Available from: https://http//[www.prnewswire.com/news-releases/lightlake-therapeutics-inc-announces-licensing-deal-with-adapt-pharma-limited-subsidiary-300010184.html](http://www.prnewswire.com/news-releases/lightlake-therapeutics-inc-announces-licensing-deal-with-adapt-pharma-limited-subsidiary-300010184.html).

23. FDAnews. FDA Grants Fast Track to Insys Therapeutics’ Naloxone 2015 [cited 2016 February 1]. Available from: <http://www.fdanews.com/articles/173913-fda-grants-fast-track-to-insys-therapeutics-naloxone>.

24. Middleton LS, Nuzzo PA, Lofwall MR, Moody DE, Walsh SL. The pharmacodynamic and pharmacokinetic profile of intranasal crushed buprenorphine and buprenorphine/naloxone tablets in opioid abusers. Addiction (Abingdon, England). 2011;106(8):1460-73.

25. Nasser AF, Heidbreder C, Liu Y, Fudala PJ. Pharmacokinetics of Sublingual Buprenorphine and Naloxone in Subjects with Mild to Severe Hepatic Impairment (Child-Pugh Classes A, B, and C), in Hepatitis C Virus-Seropositive Subjects, and in Healthy Volunteers. Clinical pharmacokinetics. 2015;54(8):837-49.

26. Fischer A, Jonsson M, Hjelmstrom P. Pharmaceutical and pharmacokinetic characterization of a novel sublingual buprenorphine/naloxone tablet formulation in healthy volunteers. Drug development and industrial pharmacy. 2015;41(1):79-84.

27. Harris DS, Mendelson JE, Lin ET, Upton RA, Jones RT. Pharmacokinetics and subjective effects of sublingual buprenorphine, alone or in combination with naloxone: lack of dose proportionality. Clinical pharmacokinetics. 2004;43(5):329-40.

28. Krieter P, Chiang N, Gyaw S, Skolnick P, Crystal R, Keegan F, et al. Pharmacokinetic properties and human use characteristics of an FDA approved intranasal naloxone product for the treatment of opioid overdose. Journal of clinical pharmacology. 2016;56(10):1243-53.

29. Chiang CN, Hawks RL. Pharmacokinetics of the combination tablet of buprenorphine and naloxone. Drug and alcohol dependence. 2003;70(2):S39-47.

30. IPO. Ipsum - Online Patent Information and Document Inspection Service 2016 [cited 2016 November 1]. Available from: https://[www.ipo.gov.uk/p-ipsum.htm](http://www.ipo.gov.uk/p-ipsum.htm).

31. USPTO. Search for Patents 2016 [cited 2016 November 1]. Available from: https://[www.uspto.gov/patents-application-process/search-patents#heading-1](http://www.uspto.gov/patents-application-process/search-patents#heading-1).

32. Buajordet I, Næss AC, Jacobsen D, Brørs O. Adverse events after naloxone treatment of episodes of suspected acute opioid overdose. European Journal of Emergency Medicine. 2004;11(1):19-23.

33. Neale J, Strang J. Naloxone—does over‐antagonism matter? Evidence of iatrogenic harm after emergency treatment of heroin/opioid overdose. Addiction. 2015;110(10):1644-52.

34. Kerr D, Kelly AM, Dietze P, Jolley D, Barger B. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction. 2009;104(12):2067-74.

35. Kelly AM, Kerr D, Dietze P, Patrick I, Walker T, Koutsogiannis Z. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. Medical Journal of Australia. 2005;182(1):24-7.

36. Martin WR. Drugs five years later: Naloxone. Annals of internal medicine. 1976;85(6):765-8.

37. BMJ. Best Practice: Opioid Overdose 2016 [cited 2017 April 1]. Available from: <http://bestpractice.bmj.com/best-practice/monograph/339/treatment/step-by-step.html>.

38. Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. Rand and Dale's Pharmacology. 7th ed. London: Churchill Livingstone; 2012.

39. Chorbev I, Davcev D, Boshnakoska D. Combined language processing methods and mash-up system for improving retrieval in diabetes-related patents. In: Lamas D, Buitelaar P, editors. Multidisciplinary Information Retrieval. Cham: Springer; 2014. p. 10-21.

40. Hawkes N. UK government to provide a research portal to make publicly funded research freely available to all. BMJ. 2012;344