PRIOR CLINICAL STUDIES DEMONSTRATING THE EFFICACY OF INHALED OPIOIDS

EXECUTIVE SUMMARY

In this document we collected 11 clinical studies which as early as 1990 were able to demonstrate the efficacy of generic and proprietary-formulation inhaled opioids. The stage of trials we found were:

Pivotal	3
Pilot	2
Phase III	2
Phase II	2
Phase I	2

These clinical studies demonstrate that:

- a generic medical nebulizer[1] (one not specifically designed for opioid inhalation, eg the AeroEclipse[2]) will vaporize and administer the most popular opioids (methadone and fentanyl) with faster onset and similar efficacy as IV administration, with greater safety and fewer side effects.[3]
- the brand and model of nebulizer is relatively unimportant – they all work[4]. The brand is only important if one wants to consider relative efficiency raising serum level concentrations of the opioid used

[1] Nebulizer general information: https://www.sciencedirect.com/topics/medicine-and-dentistry/nebulizer
[2] https://www.monaghanmed.com/AeroEclipse-II-BAN
[3] We expect we would be able to demonstrate similar results with other opioid medications having similar molecular weights and lipophilicity, because these are the primary factors which determine bioavailability of proteins by intratracheal instillation and aerosol delivery, as documented in PUBMED study 16113455
[4] https://healthdocbox.com/77366071-Asthma/Breath-actuated-nebulizer-confidence-in-aerosol-delivery.html

Also included in this summary is documentation on routes of FDA approval for inhalers which show that that:

- when a nebulizer is not packaged with medication, then phase I, II and III clinical trials are not needed nor used; instead two much smaller and less expensive studies called *pilot* (<30 patients) and *pivotal* (<300 patients) are used
- a 510(k) PMA is most commonly used route for nebulizer approval, and takes approximately 6 months, provided the nebulizer mechanical design is similar to already-approved models

DEVICE STUDIES DEMONSTRATING EFFICACY OF INHALED OPIOIDS[5]

The following studies apply to all devices which are designed in general to nebulize medications. They test route-of-administration without regard to nebulizer model or manufacturer. When taken as a whole they demonstrate that the specific brand or design of nebulizer is unimportant. These following studies are not divided into clinical trial phases – when a device is not packaged with a medication then clinical study phases are not used – but instead device studies are used,[6] divided into pilot (<30 subjects) and pivotal studies (>30 subjects.)

Overall summary and conclusions of the following studies:

- a nebulizer not specifically designed for opioid inhalation is able to vaporize and administer opioids with faster onset and similar efficacy as IV administration, with greater safety and fewer side effects.
- the brand and model of nebulizer is unimportant

[5] Details for all following studies are available by following the links to PUBMED or ClinicalTrials.gov. Note that PUBMED contains the summary of the study and with results, while Clinictrials.gov is a relatively new site which contains additional trial details but only contains results if they have been manually submitted, so for the most part this site does not yet contain the results of the studies even though results may have been published.

[6] Medical Device Clinical Trials – How Do They Compare with Drug Trials?

PIVOTAL DEVICE STUDIES (>30 PATIENTS)

PMID: 26143313

EFFICACY AND SAFETY OF NEBULIZED MORPHINE GIVEN AT 2 DIFFERENT DOSES COMPARED TO IV TITRATED MORPHINE IN TRAUMA PAIN

Non-device specific (generic medical nebulizer) study.

CONCLUSIONS:

Nebulized morphine using boluses of 10 mg has similar efficacy and better safety than IV titrated morphine in patients with severe posttraumatic pain. Increasing nebulized boluses to 20 mg increases the effectiveness without increasing side effects.

Study Size:	300 patients
Study Year:	2015
Study Type:	prospective, randomized, controlled double-blind clinical trial
Drug:	Morphine
ClinicalTrials.gov	NCT02200185

PMID: 25027194

NEBULIZED FENTANYL VS INTRAVENOUS MORPHINE FOR ED PATIENTS WITH ACUTE LIMB PAIN: A RANDOMIZED CLINICAL TRIAL

Non-device specific (generic medical nebulizer) study.

CONCLUSION:

This study suggests that nebulized fentanyl is a rapid, safe, and effective method for temporary control of acute limb pain in emergency department patients.

Study Size:	47 patients
Year published	2014
Study type:	placebo-controlled, double-blind randomized clinical trial.
Drug:	Fentanyl

PMID: 17898251

RANDOMIZED CLINICAL TRIAL OF NEBULIZED FENTANYL CITRATE VERSUS I.V. FENTANYL CITRATE IN CHILDREN PRESENTING TO THE EMERGENCY DEPARTMENT WITH ACUTE PAIN

Non-device specific (generic medical nebulizer) study.

CONCLUSIONS:

Nebulized fentanyl citrate 3 microg/kg through a breath-actuated nebulizer appears to be a feasible alternative to IV fentanyl citrate for a variety of painful conditions in patients older than 3 years.

Study size:	41 patients
Year published:	2007
Study type:	randomized controlled trial
Drug:	Fentanyl citrate

PILOT DEVICE STUDIES (<=30 PATIENTS)

PMID: 15963870

NEBULIZED VERSUS SUBCUTANEOUS MORPHINE FOR PATIENTS WITH CANCER DYSPNEA: A PRELIMINARY STUDY

Non-device specific (generic medical nebulizer) study.

CONCLUSIONS:

Nebulized morphine offered dyspnea relief similar to that of SC morphine. Larger randomized controlled trials in patients with both continuous dyspnea and earlier stages of dyspnea are justified.

Study size: 11 patients

Year published: 2005

Study type: blinded

Drug: Morphine

PMID: 8866928

SYSTEMIC ABSORPTION OF NEBULIZED MORPHINE COMPARED WITH ORAL MORPHINE IN HEALTHY SUBJECTS.

Non-device specific (generic medical nebulizer) study.

CONCLUSIONS:

Nebulization is a rapid method of administering morphine.

Study size: 11 patients

Year published: 1996

Study type: not specified

Drug: Morphine sulphate

DRUG OR DRUG+DEVICE STUDIES DEMONSTRATING EFFICACY OF INHALED OPIOIDS[7]

Some pharmaceutical companies (eg YM BioSciences) have developed inhaled formulations of opioids (eg AeroLEF – liposomal encapsulated fentanyl) and some device manufactures (eg Aradigm) have designed inhalers (eg AERx) specifically to administer opioids. Possible motivations for an opioid-specific formulation or inhaler:

- to capitalize on a market opportunity for inhaled opioids with demonstrated efficacy, safety, convenience and patient comfort over pills and IV
- to create a market opportunity for a proprietary opioid formulation and/or delivery system
- to create an initial product and thereby enter into the vast and relatively untapped inhaled-medications market using a formulation and/or device which is easily demonstrated to be as or more efficacious and safer than IV and pills

Possible reasons that such formulations and/or devices are not yet on the market:

- companies have not been able to demonstrate an advantage to the formulation or inhaler which justifies and overcomes the added cost of the formulation or device over IV and pills. Aradigm has published a statement to this effect in clinical trial NCT00348712:
    - *The decision to discontinue the development of AERx® is not due to any safety concerns. An analysis concluded that fast-acting inhaled insulin in the form it is known today, is unlikely to offer significant clinical or convenience benefits over injections of modern insulin with pen devices.*

PHASE III TRIALS

[7] Details for all following studies are available by following the links to PUBMED or ClinicalTrials.gov. Note that PUBMED contains the summary of the study and with results, while Clinictrials.gov is a relatively new site which contains additional trial details but only contains results if they have been manually submitted, so for the most part this site does not yet contain the results of the studies even though results may have been published.

STUDY NCT03580187

NEBULIZED MORPHINE IN CHEST TRAUMA PATIENTS: A PROSPECTIVE STUDY

Study Type:	Phase III[8] Interventional (Clinical Trial)
Study size:	75 participants
Masking:	None (Open Label)
Publication Year:	2018
Drug:	morphine sulfate diluted in saline solution

STUDY NCT01123551

NEBULIZED MORPHINE VERSUS INTRAVENOUS MORPHINE IN THE MANAGEMENT OF POST TRAUMATIC PAIN IN EMERGENCY DEPARTMENT (ED)

Conclusion[9]

This study suggests that nebulized fentanyl is a rapid, safe, and effective method for temporary control of acute limb pain in emergency department patients.

Study Type:	Phase III[10] Interventional (Clinical Trial)

[8] https://clinicaltrials.gov/ct2/show/study/NCT01123551
[9] https://www.ajemjournal.com/article/S0735-6757(14)00420-3/fulltext
[10] https://clinicaltrials.gov/ct2/show/study/NCT01123551

Study size:	200 participants[11]
Allocation:	Controlled randomized, placebo, parallel assignment[12]
Masking:	Quadruple
Publication Year:	2014
Drug:	morphine sulfate[13] diluted in saline solution

PHASE II TRIALS

STUDY NCT00020618

INHALED MORPHINE COMPARED WITH MORPHINE BY MOUTH IN TREATING CANCER PATIENTS WITH BREAKTHROUGH PAIN

Aradigm Phase II official study for the AERx device.

Product:	Aradigm's AERx
Study size:	50 patients
Year published:	2004
Study Type:	Randomized, Multicenter, Crossover Phase II Clinical Trial

[11] https://clinicaltrials.gov/ct2/show/study/NCT01123551
[12] A parallel study is a type of clinical study where two groups of treatments, A and B, are given so that one group receives only A while another group receives only B. Other names for this type of study include "between patient" and "non-crossover"
[13] https://clinicaltrials.gov/ct2/show/study/NCT01123551

Drug: Morphine sulfate

STUDY NCT00286065

STUDY TO DETERMINE EFFICACY AND SAFETY OF INHALED AEROLEF IN THE TREATMENT OF ACUTE POST-OP PAIN IN ADULT PATIENTS UNDERGOING ELECTIVE ORTHOPEDIC SURGERY

Results:

This was a two-part study. The drug completed the Phase IIa trial and cleared for initiation of a randomized Phase IIb trial,[14] and Phase IIb trial met primary endpoint in patients with post-surgical pain.[15]

Study Type:	Two-part Interventional (Clinical Trial)
Enrollment:	123 participants
Allocation:	Randomized
Intervention Model:	Factorial Assignment[16]
Masking:	Double
Year Published:	2006
Other Study ID Numbers:	DLXLEF-AP4

[14] https://www.sec.gov/Archives/edgar/data/1178347/000114420406004032/v034388_ex99-1.htm
[15] Published in Biospace https://www.biospace.com/article/releases/ym-biosciences-reports-aerolef-tm-randomized-phase-iib-trial-meets-primary-endpoint-in-patients-with-post-surgical-pain-/
[16] Factorial assignment. A type of intervention model describing a clinical trial in which groups of participants receive one of several combinations of interventions. For example, two-by-two factorial assignment involves four groups of participants.

STUDY NCT00791804

A PHASE II STUDY EVALUATING INHALED AEROLEF (LIPOSOME-ENCAPSULATED FENTANYL 500MCG/ML) FOR POST-OPERATIVE PAIN IN ADULTS AFTER ACL KNEE SURGERY

Conclusions[17]: effective analgesia was achieved within minutes following the voluntary cessation of inhaled dosing.

Product:	YM BioSciences's AeroLEF formulation
Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	19 participants
Allocation:	Non-Randomized
Intervention Model:	Single Group Assignment
Masking:	None (Open Label)
Year published:	2004

[17] Conclusion opublished in American Society of Anesthesiologists (ASA) Journal: http://www.asaabstracts.com/strands/asaabstracts/abstract.htm?year=2004&index=3&absnum=2102

PHASE 1 TRIALS

STUDY NCT00794209[18]

PHASE LB, FIVE PERIOD CROSSOVER, OPEN-LABEL STUDY EVALUATING A SINGLE DOSE ADMINISTRATION OF 3ML OR 5ML OF INHALED AEROLEF (LIPOSOME-ENCAPSULATED FENTANYL 500 MCG/ML), DELIVERED BY UP TO FOUR AEROSOL DELIVERY DEVICES IN HEALTHY SUBJECTS

Study Type : Interventional (Phase I Clinical Trial)

Actual Enrollment : 9 participants

Intervention Model: Crossover Assignment

Masking: None (Open Label)

Drug: AeroLEF (liposomal fentanyl citrate)

Study Start Date : March 2003

Actual Primary Completion Date : May 2003

Actual Study Completion Date : May 2003

STUDY NCT00709254

[18] This study is interesting because it is the only one we found which names the nebulizer brand used. They used 4 brands to compare efficacy: Opti- Maersk Mist 750E, Allegiance Misty-Neb, PARI LC-Plus and Trudell AeroEclipse..

STUDY OF SINGLE AND MULTIPLE DOSES OF INHALED AEROLEF (LIPOSOME-ENCAPSULATED FENTANYL)IN HEALTHY SUBJECTS (LEF-2495)

Study Type: Interventional (Phase I Clinical Trial)

Actual Enrollment : 12 participants

Allocation: Randomized

Intervention Model: Crossover Assignment

Masking: None (Open Label)

Primary Purpose: Treatment

Official Title: Phase I, 3-Period, Fasting, Bioavailability, Safety Assessment and PK Study Evaluating Single Dose Administration of i.v. Fentanyl (200 µg) and Single and Multiple Doses of 3 mL of Inhaled AeroLEF (Liposome-Encapsulated Fentanyl 500 µg/mL) Administered in Normal Healthy Subjects

Study Start Date : December 2001

Actual Primary Completion Date : January 2002

Actual Study Completion Date : January 2002

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Morphine Inhalation by Cancer Patients: A Comparison of Different Nebulization Techniques Using Pharmacokinetic, Spirometric, and Gasometric Parameters

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MORPHINE INHALATION BY CANCER PATIENTS: A COMPARISON OF DIFFERENT NEBULIZATION TECHNIQUES USING PHARMACOKINETIC, SPIROMETRIC, AND GASOMETRIC PARAMETERS

(BCTS-S) and the Bronchial Control Treatment System-Micro Cirrus (BCTS-MC). The first method delivers relatively large aerosol particles (2–5 μm) preferentially to the bronchial tree and trachea. In the BCTS-MC method, small aerosol particles (0.5–2 μm) mostly reach the alveoli. Ten patients with cancer were randomly assigned to either the BCTS-S or BCTS-MC inhalation of 5 mg morphine HCl. Patients using the BCTS-S method inhaled a morphine dose in 6.6±2 minutes, whereas with the BCTS-MC method, the inhalation time was 28.8±8 minutes. The areas under the curve of morphine and glucuronides were several times higher after BCTS-S than after BCTS-MC. The proportion of morphine-3-glucuronide to morphine-6-glucuronide (M6) was, on average, close to one for both methods. From the same amount of morphine in the BCTS-S method, five times more M6 was produced. In both methods, the time to maximum concentration for morphine metabolites was 20–40 minutes, much shorter than expected from oral, intranasal, or intravenous administration. The study shows that the method of inhalation may have a profound effect on the pharmacokinetics of morphine.

STUDY 12960555 (PUBMED)

ANALGESIC EFFICACY OF INHALED MORPHINE IN PATIENTS AFTER BUNIONECTOMY SURGERY

CONCLUSIONS:

Comparable analgesic efficacy was demonstrated between a carefully matched dose of inhaled and intravenous morphine in a postsurgical pain model.

Device:	Aradigm AERx
Study size:	89
Year published:	2003
Drug:	Morphine

STUDY 15366326 (PUBMED)

SAFETY AND PHARMACOKINETICS OF INHALED MORPHINE DELIVERED USING THE AERX SYSTEM IN PATIENTS WITH MODERATE-TO-SEVERE ASTHMA

CONCLUSIONS:

Inhaled morphine using the AERx System was absorbed rapidly and demonstrated dose-dependent plasma concentrations. It was well-tolerated and did not cause clinically significant bronchoconstriction in most subjects with moderate-to-severe asthma.

Device:	Aradigm AERx
Study size:	20
Study type:	placebo, single-blind crossover study
Year published:	2004
Drug:	Morphine