



References on the Administration of Opioids Using ALZET® Osmotic Pumps

1. Apomorphine

Q4660: T. T. Yan, *et al.* Daily Injection But Not Continuous Infusion of Apomorphine Inhibits Form-Deprivation Myopia in Mice. *INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE* 2015;56(2475-2485

Agents: Apomorphine **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 1002; **Duration:** 4 weeks;

ALZET Comments: Controls received mp w/ vehicle; animal info (male, C57Bl6, 4 weeks old); functionality of mp verified by residual volume; pumps replaced every 2 weeks; comparison of injection vs mp;

Q0779: R. Sarkis, *et al.* Chronic dizocilpine or apomorphine and development of neuropathy in two rat models I: Behavioral effects and role of nucleus accumbens. *Experimental Neurology* 2011;228(1):19-29

Agents: MK-801; apomorphine HCL hemihydrate **Vehicle:** Saline; Ascorbic acid; **Route:** CSF/CNS (nucleus accumbens);

Species: Rat; **Pump:** 2002; **Duration:** Not Stated;

ALZET Comments: Controls received mp w/ vehicle; animal info (adult, female, Sprague Dawley, 200-300 g); post op. care (dexamethasone injections to prevent brain edema); behavioral testing (mechanical allodynia, Paw withdrawal latency, cold allodynia, hotplate test, spontaneous motor activity); cannula placement verified by picomicrograph of brain section; CCI, chronic constriction injury; SNI, spared nerve injury

P6896: F. Fornai, *et al.* Parkinson-like syndrome induced by continuous MPTP infusion: Convergent roles of the ubiquitin-proteasome system and alpha-synuclein. *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA* 2005;102(9):3413-3418

Agents: MPTP; L-dopa; apomorphine **Vehicle:** Not Stated; **Route:** IP; SC; **Species:** Mice; **Pump:** 2004; **Duration:** 1-28 days;

ALZET Comments: Controls received mp w/ saline; comparison of IP injections vs. mp; neurodegenerative (Parkinson's disease); L-dopa and apomorphine group had SC implanted pumps; route is unclear for the MPTP group; "Continuous MPTP infusions thus recreate a disease state that mimics human PD better than acute MPTP bolus injections." (p. 3417); MPTP group received IP pumps (2004 model), verified by e-mailing author

P5291: G. Battaglia, *et al.* Continuous subcutaneous infusion of apomorphine rescues nigro-striatal dopaminergic terminals following MPTP injection in mice. *Neuropharmacology* 2002;42(3):367-373

Agents: Apomorphine **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 28 days;

ALZET Comments: Controls received mp w/ vehicle; comparison of sc bolus injections vs. mp; 20-day stability verified by HPLC (p.368); neurodegenerative (Parkinson's disease); "The neurorescue effect of continuous subcutaneous infusion of apomorphine is particularly promising from a clinical standpoint." (p.372)

Q7707: F. Orzi, *et al.* Apomorphine as a neuroprotective drug: a study in MPTP-treated mice and potential relevance to ischemia. *Funct Neurol* 2001;16(4 Suppl):153-8

Agents: Apomorphine **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 28 days;

ALZET Comments: Dose (3.15 mg/kg/day); Controls received mp w/ vehicle; animal info (10 week old, C57, black); ischemia (Brain);

2. Buprenorphine

Q8226: M. Kongstorp, *et al.* High Accumulation of Methadone Compared with Buprenorphine in Fetal Rat Brain after Maternal Exposure. *J Pharmacol Exp Ther* 2019;371(1):130-137

Agents: Methadone or Buprenorphine **Vehicle:** Saline; **Route:** CSF/CNS; **Species:** Rat; **Pump:** 2ML4; **Duration:** 28 days;

ALZET Comments: Dose (Buprenorphine- 1 mg/kg/day or); Controls received mp w/ vehicle; animal info (Female); post op. care (Metacam); dependence;



Q8013: B. A. Griffin, *et al.* In Utero Exposure to Norbuprenorphine, a Major Metabolite of Buprenorphine, Induces Fetal Opioid Dependence and Leads to Neonatal Opioid Withdrawal Syndrome. *J Pharmacol Exp Ther* 2019;370(1):9-17
Agents: Norbuprenorphine; Morphine **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 14 days;
ALZET Comments: Dose (1,3 or 10 mg/kg/day); Controls received mp w/ vehicle; animal info (Long-Evans); dependence;

Q6540: S. L. Withey, *et al.* Effect of Tamoxifen and Brain-Penetrant Protein Kinase C and c-Jun N-Terminal Kinase Inhibitors on Tolerance to Opioid-Induced Respiratory Depression in Mice. *J Pharmacol Exp Ther* 2017;361(1):51-59
Agents: Morphine; buprenorphine; methadone **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 6 days;
ALZET Comments: Dose (45 mg/kg/d; 5 mg/kg/day; 60 mg/kg/day); Controls received mp w/ vehicle; animal info (Male CD-1 mice, approximately 30g); comparison of morphine alkaloid pellet vs mp;

Q4834: R. Hill, *et al.* Ethanol Reversal of Tolerance to the Respiratory Depressant Effects of Morphine. *Neuropsychopharmacology* 2016;41(762-773)
Agents: Buprenorphine; methadone **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 6 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, CD-1, 30g); behavioral testing (tail flick latencies, mouse locomotion); dependence; Dose (Buprenorphine 5 mg/kg/day; methadone 60 mg/kg/day);

Q4987: S. Mundt, *et al.* Analgesia in mice with experimental meningitis reduces pain without altering immune parameters. *Altx* 2015;32(3):183-189
Agents: Buprenorphine **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;
ALZET Comments: Controls received mp w/ PBS; animal info (female, C57BL6, 8 weeks old); behavioral testing (pain score); "we used subcutaneously implanted ALZET® osmotic pumps to apply the analgesic buprenorphine. We observed strongly reduced pain scores in diseased mice receiving analgesics, whereas the immune response was not altered in these mice. Hence, our study offers a new treatment option to improve wellbeing of mice used to study LCMV-induced meningitis without grossly altering immune parameters " pg 184; "In this study, we subcutaneously implanted ALZET® osmotic pumps releasing the analgesic agent buprenorphine. Continuous delivery with osmotic pumps ensures constant compound levels for maximized therapeutic efficacy and reduced adverse effects. Additionally, unnecessary stressful animal handling due to repeated injection is not required. " pg 188; Dose (0.15 mg/kg/day);

3. Butorphanol

Q5136: M. Meredith M. Clancy DVM, *et al.* Pharmacokinetics of butorphanol delivered with an osmotic pump during a seven-day period in common peafowl (*Pavo cristatus*). *American Journal of Veterinary Research* 2015;76(12):1070-1076
Agents: Butorphanol **Vehicle:** Not Stated; **Route:** SC; **Species:** Bird (peafowl); **Pump:** 2ML1; **Duration:** 7 days;
ALZET Comments: animal info: 14 healthy adult male common peafowl; functionality of mp verified by plasma levels; good methods (pg. 1071-1072); "Use of these osmotic pumps may provide options for avian analgesia." pg 1070; analgesic administration to avian species; Pharmacokinetics; Dose: 247 ug/kg/h; Resultant plasma level ((mean, 106.4 ug/L; range, 61.8 to 133.0 ug/L)); Industry authored (Wildlife Conservation Society); Interesting (Plasma concentrations of butorphanol in common peafowl were maintained at or above reported efficacious analgesic concentrations; Use of these osmotic pumps may provide options for avian analgesia) pg. 1070

Q1826: A. Mitra, *et al.* Effects of butorphanol on feeding and neuropeptide Y in the rat. *Pharmacology Biochemistry and Behavior* 2012;100(3):575-580
Agents: Butorphanol tartrate **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2ML1; **Duration:** 48 hours;
ALZET Comments: Controls received mp w/ saline; animal info (Sprague Dawley, male, 302 g); "Implantation of the pumps took less than 1 min per rat, and the length of the anesthesia was approximately 5 min per rat." pg 576; functionality of mp verified via residual volume

P9327: Y. H. Tian, *et al.* 7-nitroindazole, nitric oxide synthase inhibitor, attenuates physical dependence on Butorphanol in rat. *Synapse* 2008;62(8):582-589



Agents: Butorphanol tartrate; nitroindazole, 7- **Vehicle:** Saline; DMSO; **Route:** CSF/CNS; **Species:** Rat; **Pump:** 2001; **Duration:** 72 hours;

ALZET Comments: Enzyme inhibitor (nitric oxide synthase, NOS); animal info (male, Sprague Dawley, 250-275 g.); pump connected to catheter after 1 week recovery period; 10% DMSO used; PE60 tubing used

P7624: S. Tanaka, *et al.* Butorphanol dependence increases hippocampal kappa-opioid receptor gene expression. *Journal of Neuroscience Research* 2005;82(2):255-263

Agents: Butorphanol tartrate **Vehicle:** Saline, physiological; **Route:** CSF/CNS; **Species:** Rat; **Pump:** 2001; **Duration:** 3 days; **ALZET Comments:** Controls received mp w/ vehicle; dependence; post op. care (procaine penicillin G; animal info (male, Sprague-Dawley, 250-275 g)

P7657: S. Y. Lee, *et al.* Increases in 3H-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid AMPA receptor binding and mRNA expression of AMPA-sensitive glutamate receptor A GluR-A subunits in rats withdrawn from butorphanol. *JOURNAL OF TOXICOLOGY AND ENVIRONMENTAL HEALTH-PART A-CURRENT ISSUES* 2005;68(23-24):2163-2174

Agents: Butorphanol tartrate **Vehicle:** Not Stated; **Route:** CSF/CNS; **Species:** Rat; **Pump:** 2001; **Duration:** 3 days; **ALZET Comments:** Controls received mp w/ saline; dependence; animal info (male, Sprague-Dawley 230-250 g)

4. Dynorphin

P3465: I. H. Jonsdottir, *et al.* Chronic intracerebroventricular administration of b-endorphin augments natural killer cell cytotoxicity in rats. *Regul. Pept* 1996;62(113-118

ALZET Comments: Endorphin, B-; Enkephalin, leucine-; Enkephalin, methionine-; Dynorphin A; SC; CSF/CNS; Rat; 2001; 2ML1; 6 days; controls received saline infusion; peptides; ALZET brain infusion kit used.

P2616: D. S. Baskin, *et al.* Evaluation of delayed treatment of focal cerebral ischemia with three selective kappa-opioid agonists in cats. *Stroke* 1994;25(10):2047-2054

ALZET Comments: Dynorphin A (1-13); U-50,488; DuP E3800; SC; cat; 2ML1; 7 days; controls received mp w/ saline; no stress (see pg. 2048); ischemia (cerebral).

P1261: J. B. Long, *et al.* Neurologic deficits and neuronal injury in rats resulting from nonopioid actions of the delta opioid receptor antagonist ICI 174864. *J. Pharmacol. Exp. Ther* 1988;244(3):1169-1177

ALZET Comments: Dynorphin A (1-13); ICI-174,864; DMSO; CSF/CNS (intrathecal); Rat; 2001; 7 days; controls received mp w/saline; mp connected to catheter i.t.; DMSO is vehicle for ICI-174864; functionality of mp verified; comparison of ICV vs. i.t. injections vs. mp infusion; stability.

P0887: B. Hoskins, *et al.* Lack of effect of dynorphin on consummatory behaviors in obese and normal rats. *Life Sci* 1986;39(589-593

ALZET Comments: Dynorphin; Saline; Rat; 2002; 7 days; controls received mp w/saline; food consumption; comparison of injections vs. mp infusion; peptides.

P0591: S. Spampinato, *et al.* Characterization of dynorphin A-induced antinociception at spinal level. *Eur. J. Pharmacol* 1985;110(21-30

ALZET Comments: Dynorphin A; Calcium chloride; Magnesium chloride; Potassium chloride; Saline; CSF/CNS (intrathecal); Rat; 2001; 1 week; peptides.

5. Endorphin

Q2343: R. Dutia, *et al.* beta-Endorphin Antagonizes the Effects of alpha-MSH on Food Intake and Body Weight. *Endocrinology* 2012;153(9):4246-4255



Agents: Endorphin, beta, (1-31) **Vehicle:** Saline, sterile; **Route:** CSF/CNS; **Species:** Rat; **Pump:** 2001; 1003D; **Duration:** 3, 7 days;

ALZET Comments: Animal info (Sprague Dawley, male, 200-250 g); pumps replaced

P7890: N. Boyadjieva, *et al.* Role of beta-endorphin, corticotropin-releasing hormone, and autonomic nervous system in mediation of the effect of chronic ethanol on natural killer cell cytolytic activity. *Alcoholism Clinical and Experimental Research* 2006;30(10):1761-1767

Agents: Endorphin, B; corticotropin releasing hormone **Vehicle:** CSF, artificial; **Route:** CSF/CNS (paraventricular nucleus of hypothalamus); **Species:** Rat; **Pump:** 2002; **Duration:** 16 hours;

ALZET Comments: Controls received mp w/ vehicle; peptides; animal info (male, Fischer, 160-175g.)

P7316: M. Dokur, *et al.* Beta-endorphin modulation of interferon-gamma, perforin and granzyme B levels in splenic NK cells: Effects of ethanol. *Journal of Neuroimmunology* 2005;166(1-2):29-38

Agents: Endorphin, B- **Vehicle:** Not Stated; **Route:** CSF/CNS (paraventricular nucleus); **Species:** Rat; **Pump:** 2002; **Duration:** 18 hours;

ALZET Comments: Controls received mp w/ aCSF; immunology; peptides

P6917: M. Dokur, *et al.* Modulation of hypothalamic beta-endorphin-regulated expression of natural killer cell cytolytic activity regulatory factors by ethanol in male Fischer-344 rats. *Alcoholism Clinical and Experimental Research* 2004;28(8):1180-1186

Agents: Endorphin, beta **Vehicle:** CSF, artificial; **Route:** CSF/CNS (paraventricular nucleus); **Species:** Rat; **Pump:** 2002; **Duration:** 6 days;

ALZET Comments: Plastics One bilateral guide cannula used with a Y-connector; bilateral infusion;

P5512: C. Hill, *et al.* The effects of beta-endorphin (beta-END) on cardiovascular and behavioral dynamics in conscious rats. *Brain Research Bulletin* 2002;59(1):29-34

Agents: Endorphin, B- **Vehicle:** CSF, artificial; **Route:** CSF/CNS; **Species:** Rat; **Pump:** Not Stated; **Duration:** 12 days;

ALZET Comments: Cardiovascular

6. Enkephalin

Q3258: A. Normandin, *et al.* Spinal mu and delta Opioids Inhibit Both Thermal and Mechanical Pain in Rats. *Journal of Neuroscience* 2013;33(28):11703-11714

Agents: [D-Ala², N-Me-Phe⁴, Gly⁵-ol]-enkephalin **Vehicle:** Not Stated; **Route:** CSF/CNS (intrathecal); **Species:** Rat; mice; **Pump:** Not Stated; **Duration:** Not Stated;

ALZET Comments: animal info (rat - male, adult, Sprague Dawley, 250-300g; good methods (intrathecal catheter placement pg.11704); mice - male, adult, C57BL/6, 20-25g); No pump used, catheter only for lumbar catheterization

P7610: P. Feng, *et al.* Effects of mu, kappa or delta opioids administered by pellet or pump on oral Salmonella infection and gastrointestinal transit. *European Journal of Pharmacology* 2006;534(1-3):250-257

Agents: Morphine sulfate; enkephalin analog DPDPE; U50,488H; deltorphin II, D-ala²- **Vehicle:** Saline, pyrogen free; **Route:** SC; **Species:** Mice; **Pump:** 1003D; **Duration:** 48 hours;

ALZET Comments: Controls received mp w/ vehicle; dose-response (fig 1); comparison of pellets vs. mp; immunology; animal info (female, 6 wk old); mp primed 4 hours in 37 C saline; "morphine pellet potently exacerbated oral salmonella infection, but morphine given by pump, at doses which were immunosuppressive had a substantially lesser effect (of infection)." (p. 251). "Further, we and others have found that morphine pellets induce sepsis in mice." (p. 251)

P6537: P. J. McLaughlin, *et al.* Opioid growth factor inhibition of a human squamous cell carcinoma of the head and neck in nude mice: Dependency on the route of administration. *INTERNATIONAL JOURNAL OF ONCOLOGY* 2004;24(1):227-232

Agents: Enkephalin **Vehicle:** Saline; **Route:** SC; **Species:** Mice (nude); **Pump:** 2004; **Duration:** 28 days;



ALZET Comments: Controls received mp w/ vehicle; OGF plasma levels taken; comparison of IP and intratumoral injections vs. SC mp; adverse reaction: (see pg. 229) "within 2 days...3 minipumps containing saline were spontaneously dislodged." [possible pocket too small]; cancer (carcinoma); peptides; enkephalin was met⁻⁵ and termed OGF or opioid growth factor

P5865: S. Vonhof, *et al.* Tolerance and dependence following chronic intracerebroventricular infusions of Tyr-D-Arg(2)-Phe-Sar(4) (TAPS). *European Journal of Pharmacology* 2003;459(1):41-48

Agents: Morphine sulfate; Enkephalin analog DAMGO; Dermorphin-derived tetrapeptide (TAPS) **Vehicle:** CSF, artificial; **Route:** CSF/CNS; **Species:** Rat; **Pump:** 2001; **Duration:** 6 days;

ALZET Comments: Controls received mp w/ vehicle; comparison of bolus injections vs. chronic mp; pumps replaced on day 4 to achieve 6 days due to dead space in catheter; ALZET brain infusion kit used; tolerance; dependence; peptides; second hole with guide cannula & stylet used for bolus injections; (ALZET) cannula placement confirmed by fast green dye & the guide cannula confirmed by methylene blue; TAPS is a potent mu-opioid receptor agonist

P6116: K. Kuzume, *et al.* Sustained exogenous administration of Met(5)-enkephalin protects against infarction in vivo. *American Journal of Physiology Heart and Circulatory Physiology* 2003;285(6):H2463-H2470

Agents: Enkephalin **Vehicle:** Saline; **Route:** SC; **Species:** Rabbit; **Pump:** 2ML1; **Duration:** 24 hours;

ALZET Comments: Controls received mp w/ vehicle; cardiovascular; peptides; enkephalin was met⁻⁵

7. Etorphine

Q0665: P. A. Madia, *et al.* Dosing protocol and analgesic efficacy determine opioid tolerance in the mouse. *Psychopharmacology* 2009;207(3):413-422

Agents: Etorphine; oxycodone; hydrocodone; methadone **Vehicle:** Saline; DMSO; **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** 7 days;

ALZET Comments: Controls received placebo pellets wrapped in nylon mesh; animal info (Male, Swiss Webster, 23-30 g); tolerance; comparison of SC injections vs mp; "Higher doses of hydrocodone, oxycodone, and methadone could not be infused due to solubility issues." pg 415; 20% DMSO used; "infusion with hydrocodone or methadone produced greater tolerance than acute or intermittent treatment" pg 417

P7344: Q. Y. Zhang, *et al.* Continuous opioid agonist treatment dose-dependently regulates mu-opioid receptors and dynamin-2 in mouse spinal cord. *Synapse* 2005;56(3):123-128

Agents: Etorphine **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** 7 days;

ALZET Comments: Controls received placebo pellet; dose-response (p. 125, 126)

P7012: B. C. Yoburn, *et al.* Opioid agonist and antagonist treatment differentially regulates immunoreactive mu-opioid receptors and dynamin-2 in vivo. *European Journal of Pharmacology* 2004;498(1-3):87-96

Agents: Naloxone; etorphine hcl; morphine sulfate **Vehicle:** Saline, normal; **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** 7 days;

ALZET Comments: Controls received inert, placebo pellets or saline injections; comparison of SC injections vs. pellets vs. mp; tolerance; "Intermittent naloxone and etorphine treatment did not regulate u-opioid receptor or dynamin-2, despite the fact that the total amount of drug administered was the same as continuous treatment." (pg. 94); animal info (m, 22-30 grams)

P5492: B. A. Gomes, *et al.* mu-opioid receptor down-regulation and tolerance are not equally dependent upon G-protein signaling. *Pharmacology Biochemistry and Behavior* 2002;72(1-2):273-278

Agents: Etorphine HCl; morphine sulfate **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 3 days;

ALZET Comments: Tolerance

P4966: K. Stafford, *et al.* Mu-opioid receptor downregulation contributes to opioid tolerance in vivo. *Pharmacology Biochemistry and Behavior* 2001;69(233-237)



Agents: Etorphine hydrochloride; Morphine sulfate **Vehicle:** Saline; **Route:** SC; **Species:** mice; **Pump:** 2001; **Duration:** 7 days;

ALZET Comments: controls received placebo pellet; functionality of mp verified by analgesia "tail-flick" dose-response test; comparison of morphine pellets vs. mp; tolerance; receptor downregulation; animal info (male, swiss webster, 22-40 grams)

8. Fentanyl

Q7581: E. Nguyen, *et al.* (353) Cell-Type Specific Modulation of RBM Neurons in Nociceptive Behaviors. *The Journal of Pain* 2019;20(4):S62-S63

Agents: Fentanyl **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 28 days;

ALZET Comments: Dose (0.01 mg/kg/hr); animal info (Male, Sprague Dawley); neurodegenerative (Chronic pain);

Q6131: A. Kliewer, *et al.* Phosphorylation-deficient G-protein-biased mu-opioid receptors improve analgesia and diminish tolerance but worsen opioid side effects. *Nat Commun* 2019;10(1):367

Agents: Fentanyl citrate; morphine sulphate salt pentahydrate **Vehicle:** PBS; water, sterile; **Route:** SC; **Species:** Mice (transgenic); **Pump:** 1007D; **Duration:** 7 days;

ALZET Comments: Dose (Fentanyl (2mg/kg/day); Morphine (17 mg/kg/day)); animal info (knock-in mice with 11S/T-A mutations (Oprm1tm3.1Shlz, MGI:6117673, 11S/T-A)); behavioral testing (hot plate test; open field locomotion test); dependence; "...we used subcutaneously implanted osmotic pumps to deliver opioids at a constant rate. This approach is a powerful means of assessing both tolerance and dependence in rodents" (p.5)

Q7582: B. Hunter, *et al.* (352) Sex Differences in Sensory Processing: The Role of Stimulus Modality and Psychological Factors. *The Journal of Pain* 2019;20(4):

Agents: fentanyl **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 5 days;

ALZET Comments: Dose (0.01mg/kg/hr); Controls received mp w/ vehicle; animal info (male, Sprague-Dawley); comparison of oxycodone and morphine injection vs mp; opioids administered 1 hour, 10 days, or 28 days post-CCI (chronic constriction injury) surgery;

R0391: T. Coutant, *et al.* Advances in Therapeutics and Delayed Drug Release. *Vet Clin North Am Exot Anim Pract* 2019;22(3):501-520

Agents: Florfenicol voriconazole; fentanyl; amikacin **Vehicle:** Not Stated; **Route:** SC; in vitro; **Species:** Rat; Snake (corn, rattle); Iguana; Cat; Hamster; Gelada; Pudu; Wallaby; Monkey; Quail; Hen; **Pump:** Not Stated; **Duration:** Not Stated;

ALZET Comments: "animal info (Eastern massasauga rattlesnakes (*Sistrurus catenatus*); timber rattlesnake (*Crotalus horridus*); pudu (*Pudu puda*); wallaby (*Macropus rufogriseus*); iguanas (*Iguana iguana*); Mojave rattlesnakes (*Crotalus scutulatus*); corn snakes (*Elaphe guttata guttata*); Japanese quails (*Coturnix coturnix japonica*); hens (*Gallus domesticus*)); " Finally, the use of intracoelomic osmotic pumps was reported in iguanas (*Iguana iguana*) in a study of reproductive behavior.²⁶ No complication due to the pump placement was reported in that study." pg. 508; Advantages: Can be extracted in case of drug overdose or toxicity, Is not altered by its biological environment, Release the drug at a constant rate, Low cost, Commercially available, Release rate and operation time can be chosen; Drawbacks: Necessitate 2 light surgical procedures under anesthesia to be implanted and explanted, Can sometimes migrate in unwanted location (especially if implanted accidentally in air sacs during intracoelomic implantation) "

Q7369: J. Ball, *et al.* (351) The Opioids Oxycodone, Fentanyl, and Morphine Amplify Neuropathic when Given after Chronic Pain is Established. *The Journal of Pain* 2019;20(4):

Agents: Fentanyl **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** Pump model not stated; **Duration:** 5 days;

ALZET Comments: Dose (0.01mg/kg/hr); Controls received mp w/ vehicle; animal info (Male, Sprague-dawley); dependence;



9. Morphine

Q8250: E. M. Lefevre, *et al.* 2020;

Agents: Morphine Hydrochloride **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** 7 days;
ALZET Comments: Dose (5 mL/kg); 0.9% Saline used; Controls received mp w/ vehicle; animal info (C57BL/6J, Oprm1 KO,); dependence;

Q7580: J. V. Negrete-Diaz, *et al.* Pharmacological activation of dopamine D4 receptor modulates morphine-induced changes in the expression of GAD65/67 and GABAB receptors in the basal ganglia. *Neuropharmacology* 2019;152(22-29

Agents: PD168,077; morphine **Vehicle:** DMSO; **Route:** SC; **Species:** Rat; **Pump:** 2ML1; **Duration:** 6 days;
ALZET Comments: Dose (20 mg/kg/day- morphine, 1 mg/kg/day- PD168,077); 2% DMSO used; animal info (Male, Sprague Dawley, 250-300g); PD168,077 aka D4R agonist; dependence;

Q7004: S. Moon, *et al.* Morphine Dependence is Attenuated by Treatment of 3,4,5-Trimethoxy Cinnamic Acid in Mice and Rats. *Neurochem Res* 2019;

Agents: Morphine; Trimethoxy cinnamic acid, 3, 4, 5- **Vehicle:** Saline; **Route:** CSF/CNS (lateral ventricle); **Species:** Rat; **Pump:** 2ML1; **Duration:** 7 days;
ALZET Comments: Dose (26 nmol/10µ l/hr); Controls received mp w/ vehicle; animal info (male Sprague–Dawley rats, 220–240 g)); behavioral testing (Conditioned Place Preference Test); dependence;

Q7533: C. R. Leibrand, *et al.* HIV-1 Tat and opioids act independently to limit antiretroviral brain concentrations and reduce blood-brain barrier integrity. *J Neurovirol* 2019;

Agents: Dolutegravir, Abacavir, Lamivudine; Morphine **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** 5 days;
ALZET Comments: Dose (abacavir 2.5 mg/day (123.5 mg/kg/day), dolutegravir 0.2 mg/day (10.3 mg/kg/day), and lamivudine 1.2 mg/day (61.7 mg/kg/day); Morphine (2 mg/day)); Controls received mp w/ vehicle; animal info (Adult female mice, 70 days of age); post op. care (Bupivacaine);

Q7622: S. Kokubu, *et al.* Characterization of Analgesic Actions of the Chronic Intrathecal Infusion of H-Dmt-D-Arg-Phe-Lys-NH₂ in Rat. *Neuromodulation* 2019;

Agents: DMT-DALDA; morphine sulfate **Vehicle:** Saline; **Route:** CSF/CNS (intrathecal); **Species:** Rat; **Pump:** 2001, 2002; **Duration:** 7 days, 14 days;
ALZET Comments: Dose ((DMT-DALDA 0.3, 1, 3, or 10 pmol/µL/hour), (MS 37.5 nmol/hour)); dose-response (Figure 1a graph on page 4); Controls received mp w/ vehicle; animal info (adult, male, Sprague-Dawley, 225-300g); behavioral testing (Hargreaves-type hind paw thermal stimulator, formalin-induced flinching); DMT-DALDA (H-Dmt-D-Arg-Phe-Lys-NH₂; Dmt = 2',6'-dimethyltyrosine) is a dermorphin analogue and selective mu opioid agonist; dependence; good methods (surgical techniques and pump/catheter implantation on p.2);

10. Pentazocine

P3459: R. Bergeron, *et al.* Effect of short-term and long-term treatments with sigma ligands on the N-methyl-D-aspartate response in the CA(3) region of the rat dorsal hippocampus. *Br. J. Pharmacol* 1997;120(1351-1359

ALZET Comments: Haloperidol; JO-1784; Pentazocine; DTG; SC; Rat; 2-21 days; controls received mp w/saline; DTG is di(2-tolyl)guanidin.

P1911: A. D. Weissman, *et al.* Chronic treatment of rats with the specific sigma ligand D-pentazocine fails to modulate dopamine D2 and sigma binding in brain. *Eur. J. Pharmacol* 1991;195(163-165

ALZET Comments: Pentazocine, d-; Saline; SC; Rat; 2ML4; 4 weeks; no comment posted.

P0588: W. K. Schmidt, *et al.* Nalbuphine. *Drug Alcohol Depend* 1985;14(339-362



ALZET Comments: Ethylketocyclazocine; Heroin; Meperidine; Oxymorphone; Pentazocine; Propoxyphene; Bremazocine; Buprenorphine; Butorphanol; Methadone; Morphine; Nalbuphine; U-50,488H; SC; mice; 3 days; comparison of sc morphine pellets vs. mp infusion; comparison of agents effects; controls received unspecified placebo infusion.

11. Sufentanil

Q7464: M. A. Hurlle. Changes in the expression of G protein-coupled receptor kinases and beta-arrestin 2 in rat brain during opioid tolerance and supersensitivity. *J Neurochem* 2001;77(2):486-92

Agents: sufentanil; nimodipine **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** 10.1046/j.1471-4159.2001.00268.x;

ALZET Comments: Dose ((2 µg/h sufentanil), (1 µg/h nimodipine)); Controls received mp w/ vehicle; animal info (Male, albino Wistar, 250-300g); enzyme inhibitor ((µ-opioid agonist for sufentanil), (Ca²⁺ channel blocker for nimodipine)); dependence;

P4727: A. Diaz, *et al.* Autoradiographic mapping of m-opioid receptors during opiate tolerance and supersensitivity in the rat central nervous system. *Nauyn-Schmiedeberg's Arch Pharmacol* 2000;362(101-109

Agents: Sufentanil citrate; Nimodipine; **Vehicle:** Saline; Ethanol; Propylene glycol; Water;; **Route:** SC;; **Species:** Rat;; **Pump:** 2001;; **Duration:** 7 days;;

ALZET Comments: Controls received mp w/ vehicle; tolerance; Group 1 received sufentanil, Group 2 received sufentanil & nimodipine, Group 3 received nimodipine, Group 4 received vehicle; Nimodipine is a Ca channel blocker; sufentanil was diluted in saline; nimodipine was diluted in 10% ethanol / 20% propylene glycol / 70% water;

P4728: A. Diaz, *et al.* Opioid tolerance and supersensitivity induce regional changes in the autoradiographic density of dihydropyridine-sensitive calcium channels in the rat central nervous system. *Pain* 2000;86(227-235

Agents: Sufentanil citrate; Nimodipine; **Vehicle:** Saline; Ethanol; Propylene glycol; Water;; **Route:** SC;; **Species:** Rat;; **Pump:** 2001;; **Duration:** 7 days;;

ALZET Comments: Controls received mp w/ vehicle; tolerance; Group 1 received vehicle alone, Group 2 received chronic sufentanil, Group 3 received sufentanil & nimodipine, Group 4 received nimodipine alone; Nimodipine is a CA²⁺ antagonist opioid; sufentanil citrate was diluted in saline; nimodipine was diluted in 10% ethanol / 20% propylene glycol / 70% water

P3361: J. V. Garaulet, *et al.* Effect of chronic administration of dihydropyridine Ca²⁺ channel ligands on sufentanil-induced tolerance to u- and k- opioid agonists in the guinea pig ileum myenteric plexus. *Regul. Pept* 1996;63(1-8

Agents: Sufentanil; Nimodipine; Bay K 8644 **Vehicle:** Saline; **Route:** SC; **Species:** Guinea pig; **Pump:** 2001; **Duration:** 7 days; **ALZET Comments:** controls received mp w/saline; tolerance

R0117: C. W. Stevens. Perspectives on opioid tolerance from basic research: behavioural studies after spinal administration in rodents. *Cancer Surveys* 1994;21(25-47

Agents: Morphine; DADLE; ST-91; Sufentanil; DAMGO **Vehicle:** Not Stated; **Route:** CSF/CNS (intrathecal); **Species:** Rat; **Pump:** Not Stated; **Duration:** 7 days;

ALZET Comments: controls received mp w/ saline; cancer; peptides; tolerance; comprehensive review of mp infusion methods using y-catheter