Recent References on the Administration of Opioids
Using ALZET® Osmotic Pumps

Apomorphine (2001-Present)

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);

Buprenorphine (2017-Present)

Q9504: E. A. Townsend, *et al.* A drug-vs-food "choice" self-administration procedure in rats to investigate pharmacological and environmental mechanisms of substance use disorders. Journal of Neuroscience Methods 2021;354(109110
Agents: Buprenorphine **Vehicle:** Ethanol; DMSO; Sterile water; **Route:** SC; **Species:** Rat; **Pump:** 2001; 2ML1; **Duration:** 1 week;
ALZET Comments: Dose (0.01; 0.032 mg/kg/h); 15% ethanol, 20% DMSO, 65% sterile water used; Controls received mp w/ vehicle; animal info (Sprague-Dawley female rats, 240− 260 g, ~12 weeks old and male rats, 290− 310 g, ~11 weeks old);

Q9318: H. J. Kulbeth, *et al.* Automated quantification of opioid withdrawal in neonatal rat pups using Ethovision(R) XT software. Neurotoxicology and Teratology 2021;84(106959
Agents: Buprenorphine, nor-; Morphine **Vehicle:** DMSO; PEG 400; Saline, Sterile; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **ALZET Comments:** Dose (15 or 20 mg/kg/day Morphine; 0.3, 1.0, 3.0, or 10 mg/kg/day norbupernorphine); Controls received mp w/ vehicle; animal info (timed-pregnant Long-Evans rats); norbuprenorphine aka NorBUP; dependence;

Q9147: A. Bakhti-Suroosh, *et al.* A buprenorphine-validated rat model of opioid use disorder optimized to study sex differences in vulnerability to relapse. Psychopharmacology (Berl) 2021;238(4):1029-1046
Agents: Buprenorphine **Vehicle:** Water; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 14 days;
ALZET Comments: Dose (3 mg/kg/day); Controls received mp w/ vehicle; animal info (sexually mature male and female Sprague-Dawley rats, 370 g (male) and 270 g (female)); dependence;

Q8788: M. Kongstorp, *et al.* Prenatal exposure to methadone or buprenorphine impairs cognitive performance in young adult rats. Drug and Alcohol Dependence 2020;212(108008
Agents: Methadone HCl; Buprenorphine HCl **Vehicle:** Water, Sterile; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 5 days;
ALZET Comments: Dose (8 mg/kg/day methadone; 0.8 mg/kg/day buprenorphine); Controls received mp w/ vehicle; animal info (Female (346.9 ± 8.1 g, n = 55) and male (12 weeks, n = 28) Sprague-Dawley rats); behavioral testing (novel object recognition test, simultaneous brightness discrimination test, Morris water maze test); dependence;

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; Buprenorphine **Vehicle:** Saline; **Route:** CSF/CNS; **Species:** Rat; **Pump:** 2ML4; **Duration:** 28 days;
ALZET Comments: Dose (Buprenorphine- 1 mg/kg/day or Methadone 10mg/kg/day); 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;

Butorphanol (2005-Present)

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; “Use of these osmotic pumps may provide options for avian analgesia.” Dose: 247 ug/kg/h); Resultant plasma level ((mean, 106.4 ug/L; range, 61.8 to 133.0 ug/L));

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)

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
Agents: Endorphin, B-; Enkephalin, leucine-; Enkephalin, methionine-; Dynorphin A **Vehicle:** Not Stated; **Route:** SC; CSF/CNS;
Species: Rat; **Pump:** 2001; 2ML1; **Duration:** 6 days;
ALZET Comments: 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
Agents: Dynorphin A (1-13); U-50,488; DuP E3800 **Route:** SC; **Species:** Cat; **Pump:** 2ML1; **Duration:** 7 days;
ALZET Comments: 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
Agents: Dynorphin A (1-13); ICI-174,864 **Vehicle:** DMSO; **Route:** CSF/CNS (intrathecal); **Species:** Rat; **Pump:** 2001; **Duration:** 7 days;
ALZET Comments: 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
Agents: Dynorphin **Vehicle:** Saline; **Route:** Not Stated; **Species:** Rat; **Pump:** 2002; **Duration:** 7 days;
ALZET Comments: 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. European Journal of Pharmacology 1985;110(21-30
Agents: Dynorphin A **Vehicle:** Calcium chloride; Magnesium chloride; Potassium chloride; Saline; **Route:** CSF/CNS (intrathecal);
Species: Rat; **Pump:** 2001; **Duration:** 1 week;
ALZET Comments: peptides

P0482: R. Schulz, *et al.* Receptor preference of dynorphin A fragments in the mouse vas deferens determined by different techniques. J. Pharmacol. Exp. Ther 1984;230(1):200-204
Agents: Dynorphin A(1-8); Bestatin; Captopril; Dynorphin A; Enkephalin agonist DADL; Fentanyl; Thiorphan **Vehicle:** Saline;
Route: SC; vas deferens; **Species:** Mice; **Pump:** 2001; 2ML1; **Duration:** Not Stated;
ALZET Comments: Comparison of agents effects; 2ML1 pump used w/ captopril, thiorphan, and bestatin; DADL & FEN admin.

P0454: J. G. Kiang, *et al.* Sensitivity to morphine-evoked bradycardia in rats is modified by dynorphin (1-13), leu- and met-enkephalin. J. Pharmacol. Exp. Ther 1984;229(2):469-473
Agents: Dynorphin (1-13); Morphine sulfate **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** 2 days;
ALZET Comments: comparison of agents effects; agents given by mp alone and in combination; peptides

P8160: D. S. Baskin*, et al.* Dynorphin (1-13) improves survival in cats with focal cerebral ischaemia. Letters to Nature 1984;312(5994):551-552
Agents: Enkephalin, Leu-; Dynorphin; Dynorphin (3-13) **Vehicle:** Saline; **Route:** SC; **Species:** Cat; **Pump:** 2ML1; **Duration:** 7 days;
ALZET Comments: Controls received mp w/ vehicle; peptides; post op. care (penicillin E, lactated ringer's solution); ischemia (cerebral); animal info (adult, male, MCAO)

P0173: R. Schulz*, et al.* Are there sybtypes (isoreceptors) of multiple opiate receptors in the mouse vas deferens. European Journal of Pharmacology 1981;76(61-66
Agents: Endorphin, a-neo-; DsThr; Dynorphin; Enkephalin analog DADLE; FK-33824; MR-2034; MRZ; Normorphine; Sufentanil
Vehicle: Water; **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** 6 days;
ALZET Comments: Peptides; MRZ is 5,9-dimethyl,2'S-5,9-dimethyl-2'-hydroxy-2-(2-methoxy-propyl)-6,7-benzomorphan

Endorphin (2002-Present)

Q8920: T. Okano*, et al.* Beta-Endorphin Mediates the Development and Instability of Atherosclerotic Plaques. International Journal of Endocrinology 2020;2020(4139093
Agents: B-Endorphin **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 1002; **Duration:** 4 weeks;
ALZET Comments: Controls received mp w/ vehicle; animal info (male spontaneously hyperlipidemic Apoe−/− mice, 13 weeks of age); pumps replaced every 2 weeks; Blood pressure measured via tail-cuff method;91.4 mmHg - 92.1 mmHg; Resultant plasma level (294.3 mg/dL Glucose); peptides; dependence;

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- **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

P6696: N. I. Boyadjieva, *et al.* beta-endorphin modulation of lymphocyte proliferation: Effects of ethanol. Alcoholism Clinical and Experimental Research 2002;26(11):1719-1727
Agents: Endorphin, B- **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; mp connected w/ two infusion cannulae using a Y-connector

Enkephalin (2000-Present)

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;
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 catherization

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 immunosuppresive 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;; pumps replaced on day 4 to achieve 6 days due to dead space in catheter; 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}

P4965: Z. Vertes, *et al.* Epidermal growth factor influenced by opioid peptides in immature rat uterus. Journal of Endocrinological Investigation 2000;23(502-508
Agents: Enkephalin analog; Naloxone **Vehicle:** Saline; **Route:** IP; **Species:** Rat; **Pump:** 1003D; **Duration:** 1,3 days;
ALZET Comments: Controls received mp w/ vehicle; functionality of mp verified by aspirating remaining contents; peptides; Enkephalin analog ENK was (D-Met2-Pro5)enkephalinamide, inhibits epidermal growth factor

Etorphine (2002-Present)

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:** DMSO; Saline; **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)

P4674: J. Shen, *et al.* Role of cAMP-dependent protein kinase (PKA) in opioid agonist-induced m-opioid receptor downregulation and tolerance in mice. Synapse 2000;38(322-327
Agents: Etorphine; Morphine **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** 2,3 days;
ALZET Comments: Controls received inert placebo pellet; opioid agonists; etorphine infused for 2 days; morphine infused for 3 days; morphine pellets also used in mp/morphine implanted mice;

Fentanyl (2011-Present)

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.

Q7582: B. Hunter, *et al.* (352) Sex Differences in Sensory Processing: The Role of Stimulus Modality ad 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)

Q8735: S. M. Green-Fulgham, *et al.* Oxycodone, fentanyl, and morphine amplify established neuropathic pain in male rats. Pain 2019;160(11):2634-2640
Agents: Fentanyl **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** 5 days;
ALZET Comments: Dose (0.01 mg/kg/hr); Controls received mp w/ vehicle; animal info (Male, Sprague Dawley, 10 weeks old);

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: Florfenicoll 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 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 accidently 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;

Q5277: J. P. Anand, *et al.* The behavioral effects of a mixed efficacy antinociceptive peptide, VRP26, following chronic administration in mice. Psychopharmacology (Berl) 2016;233(13):2479-87
Agents: VRP26, Fentanyl **Vehicle:** Saline; **Route:** SC; **Species:** mice; **Pump:** 1007D; **Duration:** 7 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (Male, female C57BL/6 wild-type, homozygous MOR knockout; 20-30 g, 8-16 wks); functionality of mp verified by in vitro testing (pg. 2481); dose-response (pg 2481); good methods (pg 2481); behavioral testing (tail suspension test, conditioned place preference and locomotor activities); behavioral testing (tail suspension test, conditioned place preference and locomotor activities); peptides; Primed for 4 hours, 37 degree Saline; antinociceptive peptide; Dose (0.3 mg/kg/day fentanyl or 10 mg/kg/day VRP26);

Q3568: J. D. Mitzelfelt, *et al.* Thermal sensitivity across ages and during chronic fentanyl administration in rats. Psychopharmacology 2014;231(1):75-84
Agents: Fentanyl **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 28 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (male, Fischer 344 x Brown Norway, 16, 20 and 24 months old); behavioral testing (temperature preference/heat and cold sensitivity, locomotor activity); Pumps removed after 4 weeks;

Q0846: R. S. Yamdeu*, et al.* p38 Mitogen-activated Protein Kinase Activation by Nerve Growth Factor in Primary Sensory Neurons Upregulates μ-Opioid Receptors to Enhance Opioid Responsiveness Toward Better Pain Control. Anesthesiology 2011;114(1):150-161
Agents: Fentanyl propionanilide; buprenorphine hydrochloride **Vehicle:** Saline, isotonic; **Route:** CSF/CNS (intrathecal); **Species:** Rat; **Pump:** Not Stated; **Duration:** 96 hours;
ALZET Comments: Controls received mp w/ vehicle; animal info (male Wistar, 200-250 g); pain

Q0735: K. M. Raehal*, et al.* The role of beta-arrestin2 in the severity of antinociceptive tolerance and physical dependence induced by different opioid pain therapeutics. Neuropharmacology 2011;60(1):58-65
Agents: Morphine; Methadone; Fentanyl; Oxycodone **Vehicle:** Water, distilled; **Route:** SC; **Species:** Mice; **Duration:** 7 days;
ALZET Comments: Animal info (male, WT, barr2-KO); dependence; wound clips used

Q0785: J. D. Mitzelfelt*, et al.* Effects of chronic fentanyl administration on physical performance of aged rats. Experimental Gerontology 2011;46(1):65-72
Agents: Fentanyl **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 4 weeks;
ALZET Comments: Controls received mp w/ saline; animal info (male, Fisher 344 x Brown Norway, 12, 24, 30 mo old); behavioral testing (open field activity, grip strength, rotarod)

Morphine (2018-Present)

Q10447: J. A. Blakeley-Ruiz*, et al.* Morphine and high-fat diet differentially alter the gut microbiota composition and metabolic function in lean versus obese mice. ISME Communications 2022;2(1):
Agents: Morphine sulfate **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 2 weeks;
ALZET Comments: Dose (10 mg/kg/day); Controls received mp w/ vehicle; animal info (18 total; Control group fed standard mouse diet; 2nd group w/ diet-induced obesity by eating 60% fat diet; 3rd group fed standard diet yet obese due to spontaneous mutation of leptin receptor); immunology; "This study shows that an antinociceptive dose of morphine administered continuously for two weeks via a subcutaneous osmotic pump altered the composition of the gut microbiota in mice."

Q10661: A. Rivera*, et al.* Dopamine D(4) Receptor Is a Regulator of Morphine-Induced Plasticity in the Rat Dorsal Striatum. Cells 2021;11(1):
Agents: Morphine; PD168077 **Vehicle:** DMSO; Saline; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 7 days; 14 days;
ALZET Comments: Dose: (morphine 20 mg/kg/d; PD168077 1 mg/kg/d); 2% DMSO, 0.9% NaCl vehicle used; animal info (1-2 months old; Male Sprague Dawley); post op. care: animals kept warm on heating pad; dependence

Q10641: F. Pantouli*, et al.* Comparison of Morphine, Oxycodone and the Biased MOR Agonist SR-17018 For Tolerance and Efficacy in Mouse Models of Pain. Neuropharmacology 2021;185(108439
Agents: Morphine **Vehicle:** Saline; **Route:** Not Stated; **Species:** Mice; **Pump:** 2001; **Duration:** 6 days;
ALZET Comments: Controls received mp w/ vehicle; animal info: C57BL/6J mice 10–20 weeks of age (23–32 g)dependence; pain

Q9368: F. Meng*, et al.* Naloxone Facilitates Contextual Learning and Memory in a Receptor-Independent and Tet1-Dependent Manner. Cellular and Molecular Neurobiology 2021;41(5):1031-1038
Agents: Naloxone; Morphine **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** 7 days;
ALZET Comments: Dose (); animal info (Male mice, 2-3 months old); behavioral testing (Morris Water Maze Test); dependence;

Q9318: H. J. Kulbeth*, et al.* Automated quantification of opioid withdrawal in neonatal rat pups using Ethovision(R) XT software. Neurotoxicology and Teratology 2021;84(106959
Agents: Buprenorphine, nor-; Morphine **Vehicle:** DMSO; PEG 400; Saline, Sterile; **Route:** SC; **Species:** Rat; **Pump:** 2ML2;
ALZET Comments: Dose (15 or 20 mg/kg/day Morphine; 0.3, 1.0, 3.0, or 10 mg/kg/day norbuprenorphine); Controls received mp w/ vehicle; animal info (timed-pregnant Long-Evans rats); norbuprenorphine aka NorBUP; dependence;

Q9432: H. M. Rodgers*, et al.* Dopamine D1 or D3 receptor modulators prevent morphine tolerance and reduce opioid withdrawal symptoms. Pharmacology, Biochemistry and Behavior 2020;194(172935
Agents: Morphine; SCH 39166; Pramipexole **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 1002; 2002; **Duration:** 14 days;
ALZET Comments: Dose (2 mg/kg); Controls received mp w/ vehicle; animal info (female, Long- Evans rats, weighing 200–225 g); behavioral testing (Withdrawal testing); Multiple pumps per animal (2 or 3); dependence;

Q9796: E. M. Lefevre*, et al.* Interruption of continuous opioid exposure exacerbates drug-evoked adaptations in the mesolimbic dopamine system. Neuropsychopharmacology 2020;45(11):1781-1792
Agents: Morphine hydrochloride **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump: Duration:** 7 days;
ALZET Comments: Dose (5 mL/kg); 0.9% Saline used; Controls received mp w/ vehicle; animal info (C57BL/6J); dependence;

Q8759: T. W. Grim*, et al.* A G protein signaling-biased agonist at the mu-opioid receptor reverses morphine tolerance while preventing morphine withdrawal. Neuropsychopharmacology 2020;45(2):416-425
Agents: Morphine **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** Not Stated;
ALZET Comments: Dose (24 or 48 mg/kg/day); Controls received mp w/ vehicle; animal info (C57BL6, 10-20 weeks old);

Q8430: W. D. Cornwell*, et al.* Tobacco smoke and morphine alter peripheral and CNS inflammation following HIV infection in a humanized mouse model. Sci Rep 2020;10(1):13977
Agents: Morphine **Vehicle:** Not stated; **Route:** Not stated; **Species:** Mice; **Pump:** Not stated; **Duration:** 28 days;
ALZET Comments: Dose (1 mg/kg/day); dependence;

Q8413: I. J. Chen*, et al.* The Circadian Hormone Melatonin Inhibits Morphine-Induced Tolerance and Inflammation via the Activation of Antioxidative Enzymes. Antioxidants (Basel) 2020;9(9):
Agents: Morphine **Vehicle:** DMSO; Saline; **Route:** CSF/CNS (intrathecal); **Species:** Rat; **Pump:** Not stated; **Duration:** 10 days;
ALZET Comments: 0.9% Saline used; Controls received mp w/ vehicle; animal info (adult male wistar rats, 300-350 g); behavioral testing (Nociceptive Test); 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); animal info (Male SD 200-300g);

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; **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);

Q8596: T. Kanemasa*, et al.* Pharmacologic effects of naldemedine, a peripherally acting mu-opioid receptor antagonist, in in vitro and in vivo models of opioid-induced constipation. Neurogastroenterology & Motility 2019;31(5):e13563
Agents: Morphine HCl **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2ML1; **Duration:** 5 days;
ALZET Comments: Dose (6 mg/kg); Controls received mp w/ vehicle; animal info (6-week-old Jcl Wistar male rats);

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;

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)

Q8205: R. Hill, *et al.* Prolonged ethanol administration prevents the development of tolerance to morphine-induced respiratory depression. Drug Alcohol Depend 2019;205(107674
Agents: Morphine **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not stated; **Duration:** 16 days;
ALZET Comments: Dose (45 mg/kg/day); Controls received mp w/ vehicle; animal info (Male CD-1 mice, approximately 30);

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;

Q9050: S. Arttamangkul, *et al.* Separation of Acute Desensitization and Long-Term Tolerance of micro-Opioid Receptors Is Determined by the Degree of C-Terminal Phosphorylation. Molecular Pharmacology 2019;96(4):505-514
Agents: Morphine Sulfate **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2ML1; **Duration:** Not Stated;
ALZET Comments: animal info (5-6 weeks old, Sprague Dawley, 180-300 g); dependence;

Q7301: C. P. Schaefer, *et al.* Chronic morphine exposure potentiates p-glycoprotein trafficking from nuclear reservoirs in cortical rat brain microvessels. PLoS One 2018;13(2):e0192340
Agents: Morphine sulfate **Vehicle:** saline; **Route:** SC; **Species:** Rat; **Pump:** pump model not stated; **Duration:** 6 days;
ALZET Comments: Dose (5 mg/kg/day); 0.9% saline used; Controls received mp w/ vehicle; animal info (female, Sprague-Dawley,175–200 g); behavioral testing (von Frey test, Hargreaves method); functionality of mp verified by weighing (empty, after filling, after priming, after removal); dependence;

Q8143: K. M. Nation, *et al.* Lateralized kappa opioid receptor signaling from the amygdala central nucleus promotes stress-induced functional pain. Pain 2018;159(5):919-928
Agents: Morphine Sulfate **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** 7 days;
ALZET Comments: Dose (7.68 mg/kg/day); 0.9% Saline used; Controls received mp w/ vehicle; animal info (Male, Sprague Dawley, 175-200 g); post op. care (Gentamycin); neurodegenerative (Functional Pain Syndrome);

Q8126: L. Micheli, *et al.* Involvement of the N/OFQ-NOP system in rat morphine antinociceptive tolerance: Are astrocytes the crossroad? Eur J Pharmacol 2018;823(79-86
Agents: Nociceptin/orphanin FQ; Morphine **Vehicle:** Not stated; **Route:** CSF/CNS (intrathecal); **Species:** Rat; **Pump:** 1002; **Duration:** 10 days;
ALZET Comments: Dose (1 and 3 nmol/h); animal info (Male, Sprague-Dawley, Wistar,); behavioral testing (Paw Pressure Test, Rota-rod Test); Nociceptin/orphanin FQ aka (N/OFQ) ; dependence;

Q6963: D. H. Malin, *et al.* A subtype-specific neuropeptide FF receptor antagonist attenuates morphine and nicotine withdrawal syndrome in the rat. Neurosci Lett 2018;684(98-103
Agents: Morphine sulfate, Nicotine bitartrate **Vehicle:** Saline, isotonic; **Route:** SC; **Species:** Rat; **Pump:** 2ML1; **Duration:** 7 days;
ALZET Comments: Dose (morphine at 0.3 and 0.6 mg/kg/hr, nicotine at 9 mg/kg/day); Controls received mp w/ vehicle; animal info (male Sprague-Dawley rats averaging 234 g); dependence;

Q8086: T. O. Lilius, *et al.* Interactions of (2S,6S;2R,6R)-Hydroxynorketamine, a Secondary Metabolite of (R,S)-Ketamine, with Morphine. Basic Clin Pharmacol Toxicol 2018;122(5):481-488
Agents: Morphine **Vehicle:** Not stated; **Route:** SC; **Species:** Rat; **Pump:** 2ML1; **Duration:** 6 days;
ALZET Comments: Dose (9.6 mg/day); animal info (Sprague Dawley, Male, 200-250 g); dependence;

Q7153: T. Lilius, *et al.* Ketamine and norketamine attenuate oxycodone tolerance markedly less than that of morphine: from behaviour to drug availability. British Journal of Cancer 2018;120(4):818-826
Agents: Morphine, oxycodone **Vehicle:** Sterile water; **Route:** SC; **Species:** Rats; **Pump:** 2ML1; **Duration:** 7 days;
ALZET Comments: Dose (oxycodone 3.6 mg day-1); (morphine 40 mg ml-1);animal info (Male Sprague-Dawley rats); behavioral testing (tail-flick, hot-plate tests); Toxicology (tolerance);

Q8073: E. S. Levitt, *et al.* Desensitization and Tolerance of Mu Opioid Receptors on Pontine Kolliker-Fuse Neurons. Mol Pharmacol 2018;93(1):8-13
Agents: Morphine Sulfate **Vehicle:** Not stated; **Route:** SC; **Species:** Rat; **Pump:** 2ML1; **Duration:** 7 days;
ALZET Comments: Dose (50 mg/kg/day); animal info (Male, Sprague Dawley, 4-7 weeks old); dependence;

Q3539: Y. C. Cheng, *et al.* Melatonin regulation of transcription in the reversal of morphine tolerance: Microarray analysis of differential gene expression. Int J Mol Med 2018;
Agents: Morphine **Vehicle:** Saline; **Route:** CSF/CNS (intrathecal); **Species:** Rat; **Pump:** Not Stated; **Duration:** 7 days;
ALZET Comments: Dose (15 µg/h); Controls received mp w/ vehicle; animal info (27 Male Wistar rats (350 400 g), each rat (with 12 weeks of age)); neurodegenerative ();

Q10120: E. Brolin, *et al.* Chronic administration of morphine using mini-osmotic pumps affects spatial memory in the male rat. Pharmacology, Biochemistry and Behavior 2018;167(1-8
Agents: Morphine hydrochloride **Vehicle:** DMSO; Saline; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 28 days;
ALZET Comments: Dose (17.5 mg/kg/day); 2% DMSO used; Controls received mp w/ vehicle; animal info (male Sprague Dawley); 8 wks old; behavioral testing (Tail flick, Morris water maze); Multiple pumps per animal (2); good methods (see pg 5);

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. British Journal of Pharmacology 1997;120(1351-1359
Agents: Haloperidol; JO-1784; Pentazocine; DTG **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Duration:** 2,21 days;
ALZET Comments: 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. European Journal of Pharmacology 1991;195(163-165
Agents: Pentazocine, d- **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 4 weeks;
ALZET Comments: no comment posted

P0588: W. K. Schmidt, *et al.* Nalbuphine. Drug and Alcohol Dependence 1985;14(339-362
Agents: Ethylketocyclazocine; Heroin; Meperidine; Oxymorphone; Pentazocine; Propoxyphene; Bremazocine; Buprenorphine; Butorphanol; Methadone; Morphine; Nalbuphine; U-50,488H; **Route:** SC; **Species:** Mice; **Duration:** 3 days;
ALZET Comments: Comparison of sc morphine pellets vs. mp infusion; comparison of agents effects; controls received unspecified placebo infusion

Sufentanil (2000-Present)

Q7464: M. A. Hurle. 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;
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 ((mu-opioid agonist for sufentanil), (Ca2+ channel blocker for nimodipine));

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 CA^{2+} antagonist opioid; sufentanil citrate was diluted in saline; nimodipine was diluted in 10% ethanol / 20% propylene glycol / 70% water