



## 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

**ALZET Comments:** Apomorphine; SC; Mice; 1002; 4 weeks; 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

**ALZET Comments:** MK-801; apomorphine HCL hemihydrate; Saline; Ascorbic acid; CSF/CNS (nucleus accumbens); Rat; 2002; 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

**ALZET Comments:** MPTP; L-dopa; apomorphine; IP; SC; Mice; 2004; 1-28 days; 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

**ALZET Comments:** Apomorphine; Saline; SC; Mice; 28 days; 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).

**P3178:** T. Vander Borgh, *et al.* The vesicular monoamine transporter is not regulated by dopaminergic drug treatments. *Eur. J. Pharmacol* 1995;294(577-583

**ALZET Comments:** Apomorphine; L-DOPA methyl ester; Benserazide; Tetrabenazine; Ascorbic acid; Propylene glycol; SC; Rat; 2ML2; 2 weeks; controls received mp with propylene glycol; 2 mps used to deliver apomorphine.

**P1345:** M. Tanaka, *et al.* Dopaminergic activity and met-enkephaline levels in the rat striatum after continuous treatment with various dopaminergic agents. *Neuroscience* 1988;14(114-116

**ALZET Comments:** Apomorphine; Haloperidol; Methamphetamine; SC; Rat; 2 weeks; japanese with english abstract.

**P1339:** M. A. Lyerly, *et al.* The deafferentation syndrome in the rat: effects of intraventricular apomorphine. *Exp. Neurol* 1988;100(188-202

**ALZET Comments:** Apomorphine; Ascorbic acid; water; CSF/CNS; Rat; 2002; 2 weeks; mp connected to cannula; stress/adverse reaction (pg 198).

**P1291:** C. A. Altar, *et al.* Dopamine release and metabolism after chronic delivery of selective or nonselective dopamine autoreceptor agonists. *Mol. Pharmacol* 1988;33(690-695

**ALZET Comments:** CGS-15855A; Apomorphine; Dopamine, antagonists; Ascorbic acid; Saline; SC; Rat; 2ML2; 2, 14 days; comparison of ip injections vs. mp infusion; functionality of mp verified by serum, brain levels; stability verified at 14 days by HPLC.



**P0595:** S. George, *et al.* Met-enkephalin concentrations in striatum respond reciprocally to alterations in dopamine neurotransmission. *Peptides* 1987;8(3):487-492

**ALZET Comments:** Apomorphine; FK-33824; Haloperidol; Naloxone; Ethanol; Tartaric acid; Water; SC; Rat; 5, 9 days; mp model not stated; controls received mp w/ unspecified vehicle or were sham-operated; agents infused separately w/ appropriate vehicle; comparison of sc inject. vs. mp infusion.

**P0860:** J. D. Winkler, *et al.* Reversal of supersensitive apomorphine-induced rotational behavior in mice by continuous exposure to apomorphine. *J. Pharmacol. Exp. Ther* 1986;238(1):242-247

**ALZET Comments:** Apomorphine; Ascorbic acid; DMSO; SC; mice; 2002; 8-10 days; controls rec'd mp w/ vehicle; 6-OHDA unilateral lesions of the nigrostriatal dopaminergic neurons; no stress (see p. 243).

**P0704:** M. Robin, *et al.* Effect of chronic apomorphine on the development of denervation supersensitivity. *Pharmacol. Biochem. Behav* 1985;22(5):47-55

**ALZET Comments:** Apomorphine HCl; Ascorbic acid; Water; SC; Rat; 2ML1; 5 and 15 days; pump replaced on 8th day; pumps replaced w/ pumps previously incubated in saline.

**P0197:** F. Porreca, *et al.* Differentiation of apomorphine from bromocriptine, piribidel and TRH by chronic administration in rats. *Psychopharmacology* 1982;76(70-74)

**ALZET Comments:** Apomorphine HCl; Saline; SC; Rat; 2001; no duration posted; comparison of agents effects.

## 2. Buprenorphine

**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

**ALZET Comments:** Morphine; buprenorphine; methadone; Saline; SC; Mice; 6 days; 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(7):762-773

**ALZET Comments:** Buprenorphine; methadone; Saline; SC; Mice; 6 days; 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

**ALZET Comments:** Buprenorphine; SC; Mice; 1007D; 7 days; 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);.

**Q0846:** R. S. Yamdeu, *et al.* p38 Mitogen-activated Protein Kinase Activation by Nerve Growth Factor in Primary Sensory Neurons Upregulates  $\mu$ -Opioid Receptors to Enhance Opioid Responsiveness Toward Better Pain Control. *Anesthesiology* 2011;114(1):150-161



**ALZET Comments:** Fentanyl propionanilide; buprenorphine hydrochloride; Saline, isotonic; CSF/CNS (intrathecal); Rat; 96 hours; Controls received mp w/ vehicle; animal info (male Wistar, 200-250 g); pain.

**P9868:** M. S. Virk, *et al.* Buprenorphine Is a Weak Partial Agonist That Inhibits Opioid Receptor Desensitization. *Journal of Neuroscience* 2009;29(22):7341-7348

**ALZET Comments:** Buprenorphine; DMSO; water; Rat; 2ML1; Controls received mp w/ vehicle; functionality of mp verified by plasma drug levels; animal info (male, Sprague Dawley, 150-200 g.); 40% DMSO used; "the osmotic minipump delivered buprenorphine efficiently and predictably" pg. 7342.

**P9326:** F. M. Placenza, *et al.* Effects of chronic buprenorphine treatment on levels of nucleus accumbens glutamate and on the expression of cocaine-induced behavioral sensitization in rats. *Psychopharmacology* 2008;200(3):347-355

**ALZET Comments:** Buprenorphine; SC; Rat; 2ML2; Controls received sham surgery; animal info (male, Long-Evans, 350-375 g.).

**P8265:** R. E. Sorge, *et al.* The effects of long-term chronic buprenorphine treatment on the locomotor and nucleus accumbens dopamine response to acute heroin and cocaine in rats. *Pharmacology Biochemistry and Behavior* 2006;84(2):300-305

**ALZET Comments:** Buprenorphine HCL; SC; Rat; 2ML2; 14, 28 days; Controls received sham surgery; dose-response (fig. 2); pumps replaced after 14 days; half-life (pg. 300) long half-life; tolerance; animal info (male, Long-Evans, 325-350g.).

**P8264:** R. E. Sorge, *et al.* The effects of chronic buprenorphine on intake of heroin and cocaine in rats and its effects on nucleus accumbens dopamine levels during self-administration. *Psychopharmacology* 2006;188(1):28-41

**ALZET Comments:** Buprenorphine; SC; Rat; 2ML2; 28 days; Controls received sham surgery; functionality of mp verified by plasma buprenorphine levels; dose-response (fig. 1); pumps replaced after 14 days; no stress (see pg. 29); dependence; animal info (male, Long-Evans, 300-350g.).

**P7423:** R. E. Sorge, *et al.* Rats maintained chronically on buprenorphine show reduced heroin and cocaine seeking in tests of extinction and drug-induced reinstatement. *Neuropsychopharmacology* 2005;30(9):1681-1692

**ALZET Comments:** Buprenorphine; CSF/CNS (nucleus accumbens); Rat; 2ML2; Controls received incision and pocket, no pump; dependence; post op. care (antibiotic injection); animal info (male, long-evans, 350-375 g); Plastics One 20G cannula used.

**P6955:** J. Patenaude, *et al.* Burn injury induces a change in T cell homeostasis affecting preferentially CD4<sup>+</sup> T cells. *Journal of Leukocyte Biology* 2005;77(2):141-150

**ALZET Comments:** Buprenorphine; Mice; 1,5,10 days;

**P7403:** M. D'Elia, *et al.* Corticosterone binding globulin regulation and thymus changes after thermal injury in mice.

*AMERICAN JOURNAL OF PHYSIOLOGY-ENDOCRINOLOGY AND METABOLISM* 2005;288(5):E852-E860

**ALZET Comments:** Buprenorphine; SC; Mice; 12 hours; Pain treatment.

### 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

**ALZET Comments:** Butorphanol; SC; Bird (peafowl); 2ML1; 7 days; 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

**ALZET Comments:** Butorphanol tartrate; SC; Rat; 2ML1; 48 hours; 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

**ALZET Comments:** Butorphanol tartrate; nitroindazole, 7-; Saline; DMSO; CSF/CNS; Rat; 2001; 72 hours; 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

**ALZET Comments:** Butorphanol tartrate; Saline, physiological; CSF/CNS; Rat; 2001; 3 days; 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

**ALZET Comments:** Butorphanol tartrate; CSF/CNS; Rat; 2001; 3 days; Controls received mp w/ saline; dependence; animal info (male, Sprague-Dawley 230-250 g).

**P7059:** S. Y. Kim, *et al.* Proteomic analysis of phosphotyrosyl proteins in the rat brain: Effect of butorphanol dependence. *Journal of Neuroscience Research* 2004;77(6):867-877

**ALZET Comments:** Butorphanol tartrate; CSF/CNS; Rat; 2001; 72 hours; Controls received mp w/ saline; functionality of mp verified by residual drug volume; dependence; post op. care (procaine penicillin G); stadol; mp primed overnight at 35 degree C in sterile saline.

**P6118:** D. S. Kim, *et al.* Changes of the level of G protein alpha-subunit mRNA by tolerance to and withdrawal from butorphanol. *Neurochemical Research* 2003;28(12):1771-1778

**ALZET Comments:** Butorphanol; Saline; CSF/CNS; Rat; 2001; 3 days; Controls received mp w/ vehicle; tolerance; guide cannula used (10mm); solution was filter sterilized.

**P5962:** L. W. Fan, *et al.* Changes in the brain kappa-opioid receptor levels of rats in withdrawal from physical dependence upon butorphanol. *Neuroscience* 2003;121(4):1063-1074

**ALZET Comments:** Butorphanol; morphine; Saline, sterile; CSF/CNS; Rat; 2001; 72 hours; Controls received mp w/ vehicle; dependence; post op. care (penicillin, 0.5% sensorcaine in wound site); guide cannula with stylet was used; dental cement used to adhere cannula to skull; protective aluminum cap was placed around the cannula; tygon tubing was used; solutions were filter sterilized during filling of the pumps; brain diagram (p. 1066).

**P5479:** S. Sinchaisuk, *et al.* Focal kappa-opioid receptor-mediated dependence and withdrawal in the nucleus paragigantocellularis. *Pharmacology Biochemistry and Behavior* 2002;74(1):241-252

**ALZET Comments:** Morphine sulfate; butorphanol tartrate; CSF/CNS; Rat; 2001; 3 days; Controls received mp w/ saline; dependence; minipumps were inserted 6-10 days after guide cannula implantation; stylet used.

**P5743:** S. Y. Jang, *et al.* The bindings of [3H]muscimol and [3H]flunitrazepam are elevated in discrete brain regions of butorphanol-withdrawal rats. *Neurochem Res* 2002;27(9):939-946

**ALZET Comments:** Butorphanol; CSF/CNS; Rat; 2001; 3 days; Controls received mp w/ saline; tolerance; dependence.

**P6208:** L. W. Fan, *et al.* Withdrawal from dependence upon butorphanol uniquely increases kappa1-opioid receptor binding in the rat brain. *Brain Research Bulletin* 2002;58(2):149-160



**ALZET Comments:** Butorphanol tartrate; morphine; Saline, sterile physiological; CSF/CNS; Rat; 2001; 72 hours; Controls received mp w/ vehicle; functionality of mp verified by residual drug volume; good methods (p. 150); dependence; post op. care (sensorcaine, procaine penicillin G); guide cannula & stylet used; dental cement secured cannula.

**P6207:** L. W. Fan, *et al.* Butorphanol dependence and withdrawal decrease hippocampal K-2-opioid receptor binding. *Brain Research* 2002;958(2):277-290

**ALZET Comments:** Butorphanol tartrate; Saline, sterile physiological; CSF/CNS; Rat; 2001; 72 hours; Controls received mp w/ vehicle; functionality of mp verified by residual volume; good methods (p. 279); dependence; post op. care (sensorcaine, procaine penicillin).

**P5000:** S. Tokuyama, *et al.* Further evidence for a role of NMDA receptors in the locus coeruleus in the expression of withdrawal syndrome from opioids. *NEUROCHEMISTRY INTERNATIONAL* 2001;39(103-109)

**ALZET Comments:** Morphine; Butorphanol; Saline; CSF/CNS; Rat; 2001; 3 days; controls received mp w/ vehicle; good methods (p. 104-105); dependence; opioid agonists; cannula placement assessed by the presence of CSF in the guide cannula; stylets used to maintain cannula patency during 1-week recovery period;

**P5245:** S. Tokuyama, *et al.* A protein kinase inhibitor, H-7, blocks naloxone-precipitated changes in dopamine and its metabolites in the brains of opioid-dependent rats. *Brain Res Bull* 2000;52(5):363-369

**ALZET Comments:** Morphine; Butorphanol; H7; Saline; CSF/CNS; Rat; 2001; 3 days; Controls received mp w/ vehicle; enzyme inhibitor; dependence; H7 is a protein kinase C inhibitor; tygon tubing used; one week recovery period; guide cannula with stylet used to ensure patency; concomitant infusion of H7 and opioids performed by mixing agents in the same pump.

#### 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.



**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

**ALZET Comments:** Dynorphin A(1-8); Bestatin; Captopril; Dynorphin A; Enkephalin agonist DADL; Fentanyl; Thiorphan; Saline; SC; vas deferens; Mice; 2001; 2ML1; no duration posted; Comparison of agents effects; 2ML1 pump used w/ captopril, thiorphan, and bestatin; DADL & FEN admin. sc; peptides; antihypertensive.

**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

**ALZET Comments:** Dynorphin (1-13); Morphine sulfate; SC; Rat; 2001; 2 days; 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. *Nature* 1984;312(5994):551-552

**ALZET Comments:** Enkephalin, Leu-; dynorphin; dynorphin (3-13); Saline; SC; Cat; 2ML1; 7 days; 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 subtypes (isoreceptors) of multiple opiate receptors in the mouse vas deferens. *Eur. J. Pharmacol* 1981;76(61-66)

**ALZET Comments:** Endorphin, a-neo-; DsThr; Dynorphin; Enkephalin analog DADLE; FK-33824; MR-2034; MRZ; Normorphine; Sufentanil; Water; SC; mice; 2001; 6 days; peptides; MRZ is 5,9-dimethyl,2'S-5,9-dimethyl-2'-hydroxy-2-(2-methoxy-propyl)-6,7-benzomorphan, a kappa opioid agonist.

## 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

**ALZET Comments:** Endorphin, beta, (1-31); Saline, sterile; CSF/CNS; Rat; 2001; 1003D; 3, 7 days; 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

**ALZET Comments:** Endorphin, B; corticotropin releasing hormone; CSF, artificial; CSF/CNS (paraventricular nucleus of hypothalamus); Rat; 2002; 16 hours; 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

**ALZET Comments:** Endorphin, B-; CSF/CNS (paraventricular nucleus); Rat; 2002; 18 hours; 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

**ALZET Comments:** Endorphin, beta; CSF, artificial; CSF/CNS (paraventricular nucleus); Rat; 2002; 6 days; 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

**ALZET Comments:** Endorphin, B-; CSF, artificial; CSF/CNS; Rat; 12 days; 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

**ALZET Comments:** Endorphin, B-; CSF, artificial; CSF/CNS (paraventricular nucleus of hypothalamus); Rat; 2002; 16 hours; Controls received mp w/ vehicle; peptides; mp connected w/ two infusion cannulae using a Y-connector.

**Q6818:** N. Boyadjieva, *et al.* Chronic Ethanol Inhibits NK Cell Cytolytic Activity: Role of Opioid Peptide  $\beta$ -Endorphin. The Journal of Immunology 2001;167(10):5645-5652

**ALZET Comments:**  $\beta$ -endorphin; naltrexone; CSF, artificial; CSF/CNS (bilateral paraventricular nuclei); Rat; 2002; 4 hours; 16 hours; Dose (100 ng of  $\beta$ -EP/0.5  $\mu$ l/h); Controls received mp w/ vehicle; animal info (Male Fischer-344 rats of 150–175 g body weight); naltrexone is an opiate antagonist; Brain coordinates (1.8 mm behind bregma, 1.5 mm lateral to the midline, and 7.7 mm below the skull surface); bilateral cannula used: The osmotic pump was implanted was connected with two infusion cannulae (bilateral guide cannula) using a Y-connector;.

**P5752:** N. Boyadjieva, *et al.* Chronic ethanol inhibits NK cell cytolytic activity: role of opioid peptide beta-endorphin. J Immunol 2001;167(10):5645-5652

**ALZET Comments:** Endorphin, B-; Naltrexone; CSF, artificial; CSF/CNS (paraventricular nucleus); Rat; 2002; 4,16 hours; Controls received mp w/ vehicle; naltrexone is an opiate antagonist; used a Y-connector to connect pump with a bilateral cannula; bilateral infusion;.

**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.

**P3710:** S. M. Tolpygo, *et al.* Comparative analysis of effects from prolonged peripheral and intracerebral exposure to B-endorphin. Bul. Exp. Biol. and Med 1995;120(1):1079-1082

**ALZET Comments:** Endorphin, B-; Saline, physiological; SC; CSF/CNS; Rat; 2001; 7 days; controls received mp w/ saline; peptides.

## 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

**ALZET Comments:** [D-Ala<sup>2</sup>, N-Me-Phe<sup>4</sup>, Gly<sup>5</sup>-ol]-enkephalin; CSF/CNS (intrathecal); Rat; mice; 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

**ALZET Comments:** Morphine sulfate; enkephalin analog DPDPE; U50,488H; deltorphin II, D-ala<sup>2</sup>-; Saline, pyrogen free; SC; Mice; 1003D; 48 hours; 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

**ALZET Comments:** Enkephalin; Saline; SC; Mice (nude); 2004; 28 days; 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-<sup>5</sup> 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

**ALZET Comments:** Morphine sulfate; Enkephalin analog DAMGO; Dermorphin-derived tetrapeptide (TAPS); CSF, artificial; CSF/CNS; Rat; 2001; 6 days; 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

**ALZET Comments:** Enkephalin; Saline; SC; Rabbit; 2ML1; 24 hours; Controls received mp w/ vehicle; cardiovascular; peptides; enkephalin was met<sup>-5</sup>.

**P4965:** Z. Vertes, *et al.* Epidermal growth factor influenced by opioid peptides in immature rat uterus. *Journal of Endocrinological Investigation* 2000;23(502-508)

**ALZET Comments:** Enkephalin analog; Naloxone; Saline; IP; Rat; 1003D; 1-3 days; 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.

**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.

**P3476:** D. P. Menard, *et al.* Alteration of calcitonin gene related peptide and its receptor binding sites during the development of tolerance to mu and delta opioids. *Can. J. Physiol. Pharmacol* 1995;73(1089-1095)

**ALZET Comments:** Morphine sulfate; Naltrexone; Enkephalin; U-50,488H; Saline; CSF/CNS (intrathecal); Rat; 2001; 7 days; tolerance.

**P2919:** T. Rubino, *et al.* Effect of chronic exposure to naltrexone and opioid selective agonists on G protein mRNA levels in the rat nervous system. *Mol. Brain Research* 1994;23(333-337)

**ALZET Comments:** Naltrexone; DAGO; Enkephalin analog DADLE; DPDPE; U-50,488H; SC; CSF/CNS; Rat; 2001; 7 days; DAGO is a mu-opioid agonist; DPDPE is a delta-opioid agonist.

**P2513:** R. U. Chukwuocha, *et al.* The in vivo effects of opioid peptides on the murine immune response. *Int. J. Immunopharmac* 1994;16(3):205-215

**ALZET Comments:** Enkephalin; PBS; mice; 1003D; no duration posted; no stress (see pg. 207); immunology; agents are met-enkephalin, DTLET, FK 33-824; pump implantation has no significant effect on humoral immune response as compared with sham-op and untreated animals (p. 208).

**P3137:** Y. Takano, *et al.* Chronic spinal infusion of dexmedetomidine, ST-91 and clonidine: spinal alpha2 adrenoceptor subtypes and intrinsic activity. *J. Pharmacol. Exp. Ther* 1993;264(1):327-335

**ALZET Comments:** Dexmedetomidine; Clonidine; Enkephalin analog ST-91; Saline; CSF/CNS (intrathecal); Rat; 2001; 7 days; controls received mp with vehicle; tolerance; externalized loop of tubing allowed cessation of flow; dose-response (pg. 330); antihypertensive.

**P2630:** C. W. Stevens, *et al.* Studies of morphine and D-ala2-D-leu5-enkephalin (DADLE) cross-tolerance after continuous intrathecal infusion in the rat. *Anesthesiology* 1992;76(4):596-603

**ALZET Comments:** Morphine sulfate; Enkephalin analog DADLE; Saline; CSF/CNS (intrathecal); Rat; 2001; 7 days; controls received mp w/ vehicle; dose-response (pg.600); stability of morphine in spinal cord assessed; tolerance; "cont. spinal





infusion, in contrast to . . . avoids the peak and trough or exponentially decreasing concentration of tolerogen and the receptor during exposure period";  $\gamma$ -catheter used for intrathecal infusion.

**R0132:** T. L. Yaksh. Tolerance: factors involved in changes in the dose-effect relationship with chronic drug exposure. In 'Towards a new pharmacotherapy of pain', A. I. Basbaum & J. -M. Besson (eds), John Wiley & Sons Ltd 1991;  
**ALZET Comments:** Morphine; Sufentanil; Enkephalin; Saline; IV; CSF/CNS (intrathecal); CSF/CNS; Rat; 7 days; controls received mp w/vehicle; dose-response (p. 163); tolerance; pain; reference of mp pump study on pp. 162-164.

## 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

**ALZET Comments:** Etorphine; oxycodone; hydrocodone; methadone; Saline; DMSO; SC; Mice; 2001; 7 days; 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

**ALZET Comments:** Etorphine; Saline; SC; Mice; 2001; 7 days; 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

**ALZET Comments:** Naloxone; etorphine hcl; morphine sulfate; Saline, normal; SC; Mice; 2001; 7 days; 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

**ALZET Comments:** Etorphine HCl; morphine sulfate; Saline; SC; Mice; 3 days; Tolerance.

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

**ALZET Comments:** Etorphine hydrochloride; Morphine sulfate; Saline; SC; mice; 2001; 7 days; 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)

**ALZET Comments:** Etorphine; Morphine;; SC;; mice;; 2001;; 2, 3 days;; 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;.

**P4229:** F. Sehba, *et al.* In vivo homologous regulation of m-opioid receptor gene expression in the mouse. *Eur. J. Pharmacol* 1997;339(33-41)

**ALZET Comments:** Etorphine HCl; Saline; SC; mice; 2001; 7 days; controls received inert placebo pellet; dose-response (p. 35-38); tolerance.

**P3345:** A. Duttaroy, *et al.* The effect of intrinsic efficacy on opioid tolerance. *Anesthesiology* 1995;82(1226-1236)



**ALZET Comments:** Morphine sulfate; Fentanyl; Etorphine; Saline; SC; mice; 2001; 2002; 7 days; 72 hrs; controls received inert placebos; comparison of SC injections vs. mp; tolerance; "Intrinsic efficacy appears to induce tolerance more significantly after continuous administration than after intermittent administration." p.1235.

**P3058:** B. C. Yoburn, *et al.* Opioid antagonist-induced receptor upregulation: effects of concurrent agonist administration. *Brain Res. Bull* 1994;33(2):237-240

**ALZET Comments:** Naloxone; Fentanyl citrate; Etorphine HCl; NaCl; SC; mice; 2001; 2002; 7-8 days; controls received placebo pellets.

**P3060:** B. C. Yoburn, *et al.* Opioid receptor regulation in mice. *J. Pharmacol. Exp. Ther* 1993;265(1):314-320

**ALZET Comments:** Etorphine HCl; Fentanyl citrate; Naloxone HCl; NaCl; SC; mice; 2001; 2002; 7-8 Days; controls received placebo pellets; dose-response; comparison of sc fentanyl injections vs. mp; good methods; tolerance.

## 8. Fentanyl

**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

**ALZET Comments:** Fentanyl citrate; morphine sulphate salt pentahydrate; PBS; water, sterile; SC; Mice (transgenic); 1007D; 7 days; Dose (Fentanyl (2mg/kg/day); Morphine (17 mg/kg/day)); animal info (knock-in mice with 11S/T-A mutations (Opr1tm3.1Shlz, 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).

**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

**ALZET Comments:** VRP26, Fentanyl; Saline; SC; mice; 1007D; 7 days; 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

**ALZET Comments:** Fentanyl; Saline; SC; Rat; 2ML4; 28 days; 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  $\mu$ -Opioid Receptors to Enhance Opioid Responsiveness Toward Better Pain Control. *Anesthesiology* 2011;114(1):150-161

**ALZET Comments:** Fentanyl propionanilide; buprenorphine hydrochloride; Saline, isotonic; CSF/CNS (intrathecal); Rat; 96 hours; 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

**ALZET Comments:** Morphine; methadone; fentanyl; oxycodone; Water, sterile, distilled; SC; Mice; 7 days; 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



**ALZET Comments:** Fentanyl; SC; Rat; 2ML4; 4 weeks; 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).

**Q0820:** H. Zheng, *et al.* &mu;-Opioid Receptor Agonists Differentially Regulate the Expression of miR-190 and NeuroD. MOLECULAR PHARMACOLOGY 2010;77(1):102-109

**ALZET Comments:** Morphine; fentanyl; Mice; 1003D; 3 days; Controls received mp w/ saline; animal info (CD1 (ICR), 6-8 wks old).

**Q0727:** A. R. Waxman, *et al.* Acute and chronic fentanyl administration causes hyperalgesia independently of opioid receptor activity in mice. Neuroscience Letters 2009;462(1):68-72

**ALZET Comments:** Fentanyl; Saline; SC; Mice; 2001; 6 days; Controls received mp w/ vehicle; animal info (adult, male, CD-1); comparison of SC injections vs. mp; "Although acute fentanyl injection (0.25 mg/kg) caused hyperalgesia within 15 min, hyperalgesia was not similarly evident on infusion Day 1 even though pumps were filled with a fentanyl dose (10mg/kg/24 h) that dispenses ~0.42 mg/kg/h, almost double the dose given by bolus injection." pg 71.

**Q0264:** J. M. Sykes, *et al.* Evaluation of an osmotic pump for fentanyl administration in cats as a model for nondomestic felids. American Journal of Veterinary Research 2009;70(8):950-955

**ALZET Comments:** Fentanyl; Saline, sterile; SC; Cat (felid); 2ML1; 96 hours; Animal info (spayed, female, 56 months old, 4.5 kg); functionality of mp verified by residual volume; comparison of transdermal patch vs. SC mp; no stress see pg 952; "if fentanyl is "to be used for nondomestic cats, then the faster elimination of fentanyl after removal of a delivery device is an important advantage of the osmotic pump versus the transdermal patch" pg 953; "Compared with a transdermal patch, an osmotic pump provides several pharmacokinetic advantages for fentanyl administration in cats." pg 954.

**P9594:** S. Sirohi, *et al.* The Relative Potency of Inverse Opioid Agonists and a Neutral Opioid Antagonist in Precipitated Withdrawal and Antagonism of Analgesia and Toxicity. Journal of Pharmacology and Experimental Therapeutics 2009;330(2):513-519

**ALZET Comments:** Fentanyl; SC; Mice; 2001; 72 hours; Dependence; animal info (Swiss-Webster, 25-33g).

**P9445:** S. Sirohi, *et al.* The analgesic efficacy of fentanyl: Relationship to tolerance and mu-opioid receptor regulation. Pharmacology Biochemistry and Behavior 2008;91(1):115-120

**ALZET Comments:** Fentanyl hydrochloride; Saline; SC; Mice; 7 days; Controls received placebo pellets; dose-response (fig. 3); comparison of SC injections vs. mp; tolerance; animal info (male, Swiss Webster, 23-35 g.).

**P9308:** J. Liu, *et al.* Effects of fentanyl dose and exposure duration on the affective and somatic signs of fentanyl withdrawal in rats. Neuropharmacology 2008;55(5):812-818

**ALZET Comments:** Fentanyl citrate; Saline, physiological; SC; Rat; 2ML2; 14 days; Controls received mp w/ vehicle; functionality of mp verified by plasma fentanyl levels; dose-responses (fig. 1); dependence; animal info (male, Wistar, 300-350 g.).

**P9157:** C. Goicoechea, *et al.* Analgesic activity and pharmacological characterization of N-[1-phenylpyrazol-3-yl]-N-[1-(2-phenethyl)-4-piperidyl] propenamide, a new opioid agonist acting peripherally. European Journal of Pharmacology 2008;595(1-3):22-29

**ALZET Comments:** Fentanyl; IQMF-4; SC; Mice; 2001; 7 days; Controls received mp w/ saline; tolerance; animal info (male, CD1, 25-30 g.); IQMF-4 also known as N-[1-phenylpyrazol-3-yl]-N-[1-(2-phenethyl)-4-piperidyl] propenamide, is a fentanyl analog; behavioral testing (nociceptive response).

## 9. Morphine

**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;



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

**ALZET Comments:** Fentanyl citrate; morphine sulphate salt pentahydrate; PBS; water, sterile; SC; Mice (transgenic); 1007D; 7 days; 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).

**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

**ALZET Comments:** Morphine sulfate, Nicotine bitartrate; Saline, isotonic; SC; Rat; 2ML1; 7 days; 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;.

**Q7153:** T. Lilius, *et al.* Ketamine and norketamine attenuate oxycodone tolerance markedly less than that of morphine: from behaviour to drug availability. *Br J Anaesth* 2018;120(4):818-826

**ALZET Comments:** Morphine, oxycodone; Sterile water; SC; Rats; 2ML1; 7 days; Dose (oxycodone 3.6 mg day<sup>-1</sup>); (morphine 40 mg ml<sup>-1</sup>); animal info (Male Sprague-Dawley rats); behavioral testing (tail-flick, hot-plate tests); Toxicology (tolerance);.

**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;

**ALZET Comments:** Morphine; Saline; CSF/CNS (intrathecal); Rat; 7 days; Dose (15  $\mu$ g/h); Controls received mp w/ vehicle; animal info (27 Male Wistar rats (350 400 g), each rat (with 12 weeks of age)); neurodegenerative ();.

**Q7171:** S. Arttamangkul, *et al.* Cellular tolerance at the micro-opioid receptor is phosphorylation dependent. *Elife*

2018;7(**ALZET Comments:** Morphine sulfate; Water; SC; Rat; 2ML1; 7 days; Dose (80mg/kg/day); animal info (5-6 Weeks); tolerance;.

**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

**ALZET Comments:** Morphine; buprenorphine; methadone; Saline; SC; Mice; 6 days; 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;.

**Q5887:** A. Rivera, *et al.* Dopamine D4 receptor stimulation prevents nigrostriatal dopamine pathway activation by morphine: relevance for drug addiction. *Addict Biol* 2017;22(5):1232-1245

**ALZET Comments:** Morphine; PD168,077; DMSO; NaCl; SC; Rat; 2ML1; 6 days; animal info (male, Sprague Dawley, 225-250g); 2% DMSO used; behavioral testing (withdrawal behavior; tail-flick test); dependence; Dose (Morphine 20 mg/kg/day; PD168,077 1 or 3 mg/kg/day);.

**Q6065:** V. D. McLane, *et al.* Long-term morphine delivery via slow release morphine pellets or osmotic pumps: Plasma concentration, analgesia, and naloxone-precipitated withdrawal. *Life Sci* 2017;185(1-7

**ALZET Comments:** Morphine; Saline; SC; Mice; 2001; 7 days; Dose (64 mg/mL); animal info (8 week old C57BL/6NCR mice); comparison of pellets vs mp; Resultant plasma level (Fig. 1, Pg 3); dependence;.

**Q6212:** A. Lyndon, *et al.* Risk to heroin users of polydrug use of pregabalin or gabapentin. *Addiction* 2017;112(9):1580-1589

**ALZET Comments:** Morphine; SC; Mice; 6 days; Dose (45 mg/kg/day); animal info (Male CD-1 mice weighing 30 g); comparison of sc pellet vs mp; tolerance;.



**Q6304:** A. Kaneguchi, *et al.* Nociception contributes to the formation of myogenic contracture in the early phase of adjuvant-induced arthritis in a rat knee. *J Orthop Res* 2017;35(7):1404-1413

**ALZET Comments:** Morphine hydrochloride; SC; Rat; 2ML1; 5 days; Dose (41–48 mg/kg/day); animal info (8-week-old male Wistar rats weighing 200–240 g); Therapeutic indication (Knee arthritis);.

**Q5745:** K. Gong, *et al.* Sustained Morphine Administration Induces TRPM8-Dependent Cold Hyperalgesia. *J Pain* 2017;18(2):212-221

**ALZET Comments:** Morphine; Saline; SC; Rat, Mice; 2ML1, 1007D; 7 days; Controls received mp w/ vehicle; animal info (180-200 g) ; functionality of mp verified by residual volume; behavioral testing (Cold plate assay); Therapeutic indication (Analgesic, Opioid); Dose (15 mg/mL);.

**Q5812:** M. Flinspach, *et al.* Insensitivity to pain induced by a potent selective closed-state Nav1.7 inhibitor. *Sci Rep* 2017;7(39662)

**ALZET Comments:** JNJ63955918, Morphine; Saline; CSF/CNS (intrathecal); Rat; 2002, 2001; 14 days, 2 weeks; Controls received mp w/ vehicle; animal info (250-300g) behavioral testing (Hargreaves test, hotplate test, tail-flick test, formalin flinching); JNJ63955918 is a tarantula venom-derived peptide (a potent, highly selective, closed-state Nav1.7 blocking peptide) ; Therapeutic indication (Pain, analgesia, electrophysiology);.

**Q5511:** J. Zhao, *et al.* Thalidomide Promotes Morphine Efficacy and Prevents Morphine-Induced Tolerance in Rats with Diabetic Neuropathy. *Neurochem Res* 2016;41(12):3171-3180

**ALZET Comments:** Morphine; Saline; SC; Rat; 2ML2; 14 days; Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 180-200g);behavioral testing (von Frey testing; hind paw withdrawal); dependence; Dose (2 mg/kg/day);.

**Q5105:** J. E. Zadina, *et al.* Endomorphin analog analgesics with reduced abuse liability, respiratory depression, motor impairment, tolerance, and glial activation relative to morphine. *Neuropharmacology* 2016;105(215-27)

**ALZET Comments:** Morphine; endomorphine analog; Saline; CSF/CNS (intrathecal); Rat; 2001; 7 days; Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 250-400g); half-life (p. 219); behavioral testing (tail flick test; rotarod testing); stability verified by (internal testing; stability >1 year at 37C); pumps primed in 37C saline for 16 hours; used PE-8 IT catheter; Dose (2 ug/hr morphine; 0.056-0.075 ug/hr analog);.

**Q5502:** T. Yayeh, *et al.* Morphine dependence is attenuated by red ginseng extract and ginsenosides Rh2, Rg3, and compound K. *J Ginseng Res* 2016;40(4):445-452

**ALZET Comments:** Ginsenoside, Rg3; ginsenoside, Rh; compound K; morphine; Saline; CSF/CNS; Rat; 2ML1; 7 days; Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 220-240g); behavioral testing (conditioned place preference; escaping behavior); dependence; cyanoacrylate wound closure; Dose (morphine 26nmol/10ul/hr, ginsenoside 10 ug/ul/h); Brain coordinates (L: 1.3 mm; AeP: e0.5 mm; and DeV: e4.3 mm);.

**Q5076:** R. Y. Tsai, *et al.* Resveratrol reverses morphine-induced neuroinflammation in morphine-tolerant rats by reversal HDAC1 expression. *J Formos Med Assoc* 2016;115(6):445-54

**ALZET Comments:** Morphine; CSF/CNS (intrathecal); Rat; 120 hours; Controls received mp w/ saline; animal info (male, Wistar); behavioral testing (tail-flick); Dose (15 ug/h);.

**Q5165:** P. Nardelli, *et al.* Reduced motor neuron excitability is an important contributor to weakness in a rat model of sepsis. *Exp Neurol* 2016;282(1-8)

**ALZET Comments:** Oxymorphone; IP; Rat; 5 days; post op. care (buprenorphine SC 0.12 mg/kg; 5 ml SC saline; Baytril SC 10 mg/kg Q12H); used 2ML size; pumps used for continuous pain relief in rat sepsis model; Dose (30 ug/kg/h);.

**Q6574:** J. S. Kim, *et al.* Anti-opioid Effects of RFRP-3 on Magnocellular Neuron Activity in Morphine-naïve and Morphinetreated Female Rats. *Endocrinology* 2016;157(10):4003-4011



**ALZET Comments:** Morphine; Saline; Rat; 2002; 10.1210/en.2016-1374; Dose (10 mg/kg/day); Controls received mp w/ vehicle; animal info (Female adult freely-cycling Sprague-Dawley rats weighing ~280 g); dependence.

**Q5359:** K. Gong, *et al.* GluN2B N-methyl-D-aspartate receptor and excitatory amino acid transporter 3 are upregulated in primary sensory neurons after 7 days of morphine administration in rats: implication for opiate-induced hyperalgesia. *Pain* 2016;157(1):147-58

**ALZET Comments:** Morphine; Ro 25-6981; Saline; SC; Rat; 2ML1; 1 week; Controls received mp w/ vehicle; animal info (Male Sprague-dawley rats, 220-250 g); functionality of mp verified by behavioral tests; good methods (pg. 148); post op. care (opiate administration using pumps); behavioral testing (Hargreaves plantar test); Dependence/tolerance induced; Opiate use; Dose ( 15 mg/ml Morphine, 5 mg/kg Ro 25-6981);

**Q5804:** K. A. Eddinger, *et al.* Intrathecal Catheterization and Drug Delivery in Guinea Pigs: A Small-animal Model for Morphine-evoked Granuloma Formation. *Anesthesiology* 2016;125(2):378-94

**ALZET Comments:** Morphine; Saline; SC; Guinea pig; 2002; 14 days, 2 weeks; Controls received mp w/ vehicle; good methods (catheter construction pg. 379);

stress/adverse reaction: Note that these animals were receiving infusion through in-house/Non-Alzet catheters (see pg. 385 Therapeutic indication (Granuloma); Dose (0.25, 2.5, 8, or 25 mg/ml);

## 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

**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

**ALZET Comments:** Sufentanil citrate; Nimodipine;; Saline; Ethanol; Propylene glycol; Water;; SC;; Rat;; 2001;; 7 days;; 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

**ALZET Comments:** Sufentanil citrate; Nimodipine;; Saline; Ethanol; Propylene glycol; Water;; SC;; Rat;; 2001;; 7 days;; 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<sup>2+</sup> 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 Ca<sup>2+</sup> channel ligands on sufentanil-induced tolerance to  $\mu$ - and  $\kappa$ - opioid agonists in the guinea pig ileum myenteric plexus. *Regul. Pept* 1996;63(1-8)

**ALZET Comments:** Sufentanil; Nimodipine; Bay K 8644; Saline; SC; Guinea pig; 2001; 7 days; 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)

**ALZET Comments:** Morphine; DADLE; ST-91; Sufentanil; DAMGO; CSF/CNS (intrathecal); Rat; 7 days; controls received mp w/ saline; cancer; peptides; tolerance; comprehensive review of mp infusion methods using y-catheter.

**P4187:** J. V. Garaulet, *et al.* Cross-tolerance between  $\mu$ - and  $\kappa$ -opioid agonists in the guinea pig ileum myenteric plexus. *J. Pharmacol. Exp. Ther* 1994;269(3):993-999

**ALZET Comments:** Sufentanil; Saline, sterile; SC; Guinea pig; 2001; 7 days; controls received mp w/vehicle; tolerance.

**R0132:** T. L. Yaksh. Tolerance: factors involved in changes in the dose-effect relationship with chronic drug exposure. In 'Towards a new pharmacotherapy of pain', A. I. Basbaum & J. -M. Besson (eds), John Wiley & Sons Ltd 1991;

**ALZET Comments:** Morphine; Sufentanil; Enkephalin; Saline; IV; CSF/CNS (intrathecal); CSF/CNS; Rat; 7 days; controls received mp w/vehicle; dose-response (p. 163); tolerance; pain; reference of mp pump study on pp. 162-164.

**P2081:** M. Sosnowski, *et al.* Differential cross-tolerance between intrathecal morphine and sufentanil in the rat. *Anesthesiology* 1990;73(1141-1147)

**ALZET Comments:** Morphine sulfate; Sufentanil citrate; Saline; CSF/CNS (intrathecal); Rat; 2001; 7 days; dose-response; tolerance; PE10 heat fused to PE60; externalized loop of catheter permitted cessation of infusion without pump removal.

**P1273:** C. W. Stevens, *et al.* Time course characteristics of tolerance development to continuously infused antinociceptive agents in rats spinal cord. *J. Pharmacol. Exp. Ther* 1989;251(1):216-223

**ALZET Comments:** Enkephalin analog ST-91; Enkephalin analog DADLE; Enkephalin analog DAMGO; Morphine; Sufentanil; Saline; CSF/CNS (intrathecal); Rat; 2001; 7 days; no comment posted.

**P1612:** C. W. Stevens, *et al.* Magnitude of opioid dependence after continuous intrathecal infusion of  $\mu$  and  $\delta$ -selective opioids in the rat. *Eur. J. Pharmacol* 1989;166(467-472)

**ALZET Comments:** Sufentanil citrate; Enkephalin analog DADLE; Enkephalin analog DAMGO; Morphine; Saline; CSF/CNS (intrathecal); Rat; 2001; 7 days; tissue infusion; dose-response; peptides; tolerance, dependence.

**P1560:** C. Stevens, *et al.* Potency of infused spinal antinociceptive agents is inversely related to magnitude of tolerance after continuous infusion. *J. Pharmacol. Exp. Ther* 1989;250(1):1-8

**ALZET Comments:** Enkephalin analog DADLE; Enkephalin analog DAMGO; Enkephalin analog ST-91; Morphine sulfate; Sufentanil citrate; Saline; CSF/CNS (intrathecal); Rat; 2001; 7 days; mp connected to Y-catheter; dose-response; peptides.

**P1529:** F. J. Ayesta, *et al.* Tolerance to respiratory actions of sufentanil: functional tolerance and route-dependent differential tolerance. *J. Pharmacol. Exp. Ther* 1989;250(1):371-378

**ALZET Comments:** Sufentanil citrate;; Saline; SC; Rat; 2001; 7 days; controls received mp w/ saline; comparison of sc, iv & icv injections; tolerance; agent  $\mu$  opioid receptor agonist; pumps left in longer than 7 days; "possibility that the minipump implanting process could influence the results was eliminated . . . no difference . . . in nonimplanted and implanted rats." (p. 372).