



References on the Administration of Benzodiazepines
Using ALZET® Osmotic Pumps

Adinazolam

P0433: A. Turmel, *et al.* Sensitization of rat forebrain neurons to serotonin by adinazolam, an antidepressant triazolobenzodiazepine. *European Journal of Pharmacology* 1984;99(241-244

Agents: Adinazolam; Diazepam **Vehicle:** Benzyl alcohol; Ethanol; Propylene glycol; Sodium benzoate; Water; **Route:** IP; **Species:** Rat; **Pump:** 2002; **Duration:** 5 and 14 days;

ALZET Comments: comparison of adinazolam. iv injec vs. mp infusion; comparison of agents effects; adinazolam. used with water vehicle, Diaz. with combination vehicle

Alprazolam

Q9313: A. Kiryk, *et al.* IntelliCage as a tool for measuring mouse behavior - 20 years perspective. *Behavioural Brain Research* 2020;388(112620

Agents: Alprazolam **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 1 day;

ALZET Comments: Controls received mp w/ vehicle; animal info (female C57BL/6 mice); toxicology;

Q8585: A. Kiryk, *et al.* IntelliCage as a tool for measuring mouse behavior - 20 years perspective. *Behav Brain Res* 2020;388(112620

Agents: Alprazolam **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not stated; **Duration:** 1 day;

ALZET Comments: Controls received mp w/ vehicle; animal info (female C57BL/6 mice); toxicology;

Q5063: N. Ito, *et al.* Contribution of protein binding, lipid partitioning, and asymmetrical transport to drug transfer into milk in mouse versus human. *Pharm Res* 2013;30(9):2410-22

Agents: acetaminophen, cephalothin sodium salt, clindamycin hydrochloride, disopyramide phosphate salt, labetalol hydrochloride, nitrofurantoin +-propranolol hydrochloride, terbutaline hemisulfate salt, verapamil hydrochloride, Acyclovir, alprazolam, atenolol, anhydrous caffeine, cefotaxime sodium salt, cephapirin sodium salt, diltiazem hydrochloride, metronidazole, nitrazepam, prednisolone, 6-propyl-2-thiouracil, trazadone hydrochloride, chloramphenicol, cimetidine, theophylline, fluconazole, metoprolol, mirtazapine, praziquantel, quetiapine fumarate, triprolidine hydrochloride, metformin, moclobemide. **Vehicle:** DMSO; water; **Route:** IP; **Species:** mice; **Pump:** 1003D; **Duration:** Not Stated;

ALZET Comments: animal info: lactating mice, postnatal age of 14 days; functionality of mp verified by measurement of drug concentration in milk and plasma; mp were used to infuse study lactational drug transfer.

P3498: V. A.-M. I. Tanay, *et al.* Chronic administration of antipanic drugs alters rat brainstem GABA-A receptor subunit mRNA levels. *Neuropharmacology* 1996;35(9/10):1475-1482

Agents: Phenelzine; alprazolam; imipramine; buspirone **Vehicle:** Water, sterile; DMSO; propylene glycol; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 21 days;

ALZET Comments: Antidepressant; controls received mp w/ vehicle; pumps were turned in subcutaneous pocket to avoid fibrous tissue outgrowth

P3673: J. J. Byrnes, *et al.* Chronic benzodiazepine administration. *Psychopharmacology* 1993;111(91-95

Agents: Alprazolam; Lorazepam **Vehicle:** PEG 400; **Route:** SC; **Species:** mice; **Pump:** 2001; 2002; **Duration:** 7, 8, or 14 days;

ALZET Comments: controls received vehicle; tolerance

P2332: G. B. Kaplan, *et al.* Effects of benzodiazepine administration on A1 adenosine receptor binding in-vivo and ex-vivo. *J. Pharm. Pharmacol* 1992;44(700-703

Agents: Alprazolam; Lorazepam **Vehicle:** PEG 400; **Route:** IP; **Species:** mice; **Pump:** 2001; **Duration:** 6 days;

ALZET Comments: controls received mp w/ vehicle



P3033: J.-L. Moreau, *et al.* Physical dependence induced in DBA/2J mice by benzodiazepine receptor full agonists, but not by the partial agonist Ro 16-6028. *European Journal of Pharmacology* 1990;190(269-273)
Agents: Triazolam; Alprazolam; Diazepam **Vehicle:** Propylene glycol; **Route:** SC; **Species:** mice; **Pump:** 2001; **Duration:** 7 days;
ALZET Comments: controls received mp with vehicle; functionality of mp verified by receptor binding study; comparison of oral alprazolam vs. mp; ". . .the use of implantable minipumps. . .permitted. . .development of behavioral tolerance associated with downregulation of benzodiazepine receptor binding and GABA receptor function. . ."; dependence

P1779: L. G. Miller, *et al.* Chronic benzodiazepine administration. IV. Rapid development of tolerance and receptor downregulation associated with alprazolam administration. *Biochemical Pharmacology* 1989;38(21):3773-3777
Agents: Alprazolam **Vehicle:** PEG 400; **Route:** SC; **Species:** mice; **Pump:** 2001; 2002; **Duration:** 14 days;
ALZET Comments: functionality of mp verified by measuring plasma levels; tolerance

P1396: J. Bell, *et al.* Increased central nonadrenergic activity during benzodiazepine withdrawal: an electrophysiological study. *Neuropharmacology* 1988;27(11):1187-1190
Agents: Alprazolam; Lorazepam **Vehicle:** Ethanol; Propylene glycol; Saline; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 12 days;
ALZET Comments: no comment posted

Chlordiazepoxide

Q5755: C. Brouillard, *et al.* Long-lasting bradypnea induced by repeated social defeat. *American Journal of Physiology Regulatory, Integrative, and Comparable Physiology* 2016;311(2):R352-64
Agents: Chlordiazepoxide **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2ML1; **Duration:** 5 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (weight: 290-310g); behavioral testing (Social defeat); chlordiazepoxide is a benzodiazepine receptor agonist; Days infused (D5 – D+10) (Housing: individual cages post. Op.) ; Therapeutic indication (Anxiety); Dose (10 mg/kg*day);

Q2541: C. Sevoz-Couche, *et al.* Involvement of the dorsomedial hypothalamus and the nucleus tractus solitarii in chronic cardiovascular changes associated with anxiety in rats. *JOURNAL OF PHYSIOLOGY-LONDON* 2013;591(7):1871-1887
Agents: Chlordiazepoxide **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2ML1; **Duration:** 6 days;
ALZET Comments: Control animals received mp w/ vehicle; animal info (Sprague Dawley, male, 250-300 g)

R0297: A. de Mooij-van Malsen, *et al.* Cross-species behavioural genetics: A starting point for unravelling the neurobiology of human psychiatric disorders. *PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY* 2011;35(6):1383-1390
Agents: Chlordiazepoxide **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 1 week;
ALZET Comments: Animal info (C57BL/6J)

P9959: C. H. Vinkers, *et al.* The rapid hydrolysis of chlordiazepoxide to demoxepam may affect the outcome of chronic osmotic minipump studies. *Psychopharmacology* 2010;208(4):555-562
Agents: Chlordiazepoxide **Vehicle:** Not Stated; **Route:** In vitro; **Species:** Not Stated; **Pump:** Not Stated; **Duration:** Not Stated;
ALZET Comments: "When the cumulative CDP concentration over time was corrected for its hydrolysis, drug release from the minipumps followed the theoretical release profile over time (white symbols), suggesting that CDP hydrolysis completely accounted for the declined CDP release over time." pg 558; "In general, the use of osmotic minipumps presents a valid and attractive alternative to the labor-intensive daily injections. However, the issue of drug stability and release should always be carefully investigated before initiating chronic minipump experiments." pg 562

Q0421: C. Rivat, *et al.* Chronic stress induces transient spinal neuroinflammation, triggering sensory hypersensitivity and long-lasting anxiety-induced hyperalgesia. *Pain* 2010;150(2):358-368
Agents: CI-988; chlordiazepoxide; Acetylsalicylic acid **Vehicle:** DMSO; saline; **Route:** SC; CSF/CNS (intrathecal); **Species:** Rat; **Pump:** 2ML1; 2001; 2002; **Duration:** 14 days;
ALZET Comments: Controls received mp w/ vehicle; animal info (Male, Sprague-Dawley, 300-325 g, 8 wks old; ALZET intrathecal catheter used (0007740); behavioral testing (elevated plus-maze)



P9610: C. H. K. West, *et al.* Antidepressant drugs with differing pharmacological actions decrease activity of locus coeruleus neurons. INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY 2009;12(5):627-641

Agents: Desipramine; mirtazapine; chlorpheniramine; Paroxetine; scopolamine; amphetamine; escitalopram; chlordiazepoxide
Vehicle: Not Stated; **Route:** SC; IP; **Species:** Rat; **Pump:** 2ML2; **Duration:** 14, 21 days;

ALZET Comments: Controls received mp w/vehicle; dose-response (Fig 2-5); pumps replaced on day 14; good methods pg 629; animal info (male, Sprague Dawley, 5-7 mo old, 550-700g); "Importantly, use of minipumps also eliminates the need for repeated handling and injection of animals to administer the drug chronically." pg. 628; IP catheter used

P9061: M. J. H. Kas, *et al.* Differential genetic regulation of motor activity and anxiety-related behaviors in mice using an automated home cage task. Behavioral Neuroscience 2008;122(4):769-776

Agents: Chlordiazepoxide **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;

ALZET Comments: Controls received mp w/ saline; animal info (C57BL/6J, male); chlordiazepoxide is an anxiolytic

P7318: J. Andre, *et al.* Involvement of cholecystokinergic systems in anxiety-induced hyperalgesia in male rats: Behavioral and biochemical studies. Journal of Neuroscience 2005;25(35):7896-7904

Agents: Chlordiazepoxide **Vehicle:** Water, distilled; **Route:** SC; **Species:** Rat; **Pump:** 2ML1; **Duration:** 4-7 days;

ALZET Comments: Controls received mp w/ saline

P4378: D. J. Cash, *et al.* Desensitization of a g-aminobutyric acid type A receptor in rat is increased by chronic treatment with chlordiazepoxide: a molecular mechanism of dependence. Journal of Pharmacology and Experimental Therapeutics 1997;283(2):704-711

Agents: Chlordiazepoxide; **Vehicle:** Not Stated; **Route:** SC;; **Species:** Rat;; **Pump:** Not Stated; **Duration:** 15 days;;

ALZET Comments: controls received mp with vehicle; tolerance; dependence; chlordiazepoxide is a tranquilizer; rats were 6-8 weeks old;

Clonazepam

P3556: M. I. Arnot, *et al.* Dimethyl sulfoxide/propylene glycol is a suitable solvent for the delivery of diazepam from osmotic minipumps. J. Pharm. & Tox. Meth 1996;36(29-31

Agents: Diazepam; Clonazepam; flumazenil **Vehicle:** DMSO; Propylene glycol; Tetraglycol; ³H tracer; Radio-isotopes; **Route:** in vitro (egg); **Species:** Not Stated; **Pump:** 2ML4; **Duration:** no duration posted;

ALZET Comments: no comment posted

P3305: L. Lima, *et al.* Serotonin turnover rate, [3H] paroxetine binding sites, and 5-HT1A receptors in the hippocampus of rats subchronically treated with clonazepam. Neuropharmacology 1995;34(10):1327-1333

Agents: Clonazepam **Vehicle:** PEG; **Route:** CSF/CNS (dorsal raphe nucleus); **Species:** Rat; **Pump:** Not Stated; **Duration:** 10 days;

ALZET Comments: comparison of IP injections vs. mp

P2654: K. Brodin, *et al.* Clomipramine and clonazepam increase cholecystokinin levels in rat ventral tegmental area and limbic regions. European Journal of Pharmacology 1994;263(175-180

Agents: Nortriptyline; Amitriptyline; Clomipramine; Alaproclate; Clonazepam **Vehicle:** Alcohol; Saline; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 14 days;

ALZET Comments: antidepressant; controls received mp w/ vehicle; functionality of mp verified by plasma levels; dose-response (Table 1; pg. 177); enzyme inhibitor; clonazepam is a benzodiazepene; the others are monoamine uptake inhibitors

P1650: L. G. Miller, *et al.* Chronic benzodiazepine administration. VI. a partial agonist produces behavioral effects without tolerance or receptor alterations. J. Pharmacol. Exp. Ther 1990;254(1):33-36

Agents: Clonazepam; RO-16-6028 **Vehicle:** PEG 400; **Route:** SC; **Species:** mice; **Pump:** Not Stated; **Duration:** 14 days;

ALZET Comments: functionality of mp verified by tissue levels; dose-response (graph); tolerance/dependence



Diazepam

Q7673: L. E. Villasana, *et al.* Diazepam Inhibits Post-Traumatic Neurogenesis and Blocks Aberrant Dendritic Development. *J Neurotrauma* 2019;36(16):2454-2467

Agents: Diazepam **Vehicle:** DMSO, Propylene Glycol; **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** 7 days;
ALZET Comments: Dose (15 mg/kg/day); 1:1 DMSO:Propylene glycol used; Controls received mp w/ vehicle; animal info (Male and female C57Bl/6J wild-type mice); Therapeutic indication (traumatic brain injury);

Q7777: M. C. D. Bridi, *et al.* Two distinct mechanisms for experience-dependent homeostasis. *Nat Neurosci* 2018;21(6):843-850

Agents: Diazepam; Ro 25-6981 **Vehicle:** Saline; Propylene Glycol; DMSO; **Route:** CSF/CNS (left lateral ventricle); SC; **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;
ALZET Comments: Dose (2 mg/mL Diazepam; 30mg/kg/day Ro 25-6981); 50% Propylene glycol, 50% saline used for Diazepam and 20% DMSO, 80% Saline for Ro 25-6981; Controls received mp w/ vehicle; animal info (C57BL/6, Pv-cre); post op. care (Meloxicam); enzyme inhibitor (Ro 25-6981 is a GluN2B-specific antagonist); Dental cement used; dependence;

Q2140: C. H. Vinkers, *et al.* GABA-A Receptor alpha Subunits Differentially Contribute to Diazepam Tolerance after Chronic Treatment. *PLoS One* 2012;7(8):U614-U624

Agents: Diazepam; zolpidem; TPA023; bretazenil **Vehicle:** PEG 400; alcohol; water, distilled; **Route:** SC; **Species:** Mice; **Pump:** 2004; **Duration:** 4 weeks;
ALZET Comments: Controls received mp w/ vehicle; animal info (129 Sv/Ev Tac, 10-12 wks old); 95% PEG 400 used; 2.5% alcohol used; stress/adverse effects "severe hypothermia likely explains the death of seven animal's postsurgically..." pg 9; TPA023 is an alpha 2/3 selective GABAa receptor positive allosteric modulator

Q1966: M. Spolidoro, *et al.* Food restriction enhances visual cortex plasticity in adulthood. *Nature Communications* 2011;2(:):U210-U217

Agents: Diazepam; mercaptopropionic acid **Vehicle:** Propylene glycol; **Route:** CSF/CNS (visual cortex); **Species:** Rat; **Pump:** 2002; **Duration:** Not Stated;
ALZET Comments: Animal info (Long Evans hooded, P60-P90, male, female); 50% propylene glycol used

P9449: E. A. Stone, *et al.* Evaluation of the repeated open-space swim model of depression in the mouse. *Pharmacology Biochemistry and Behavior* 2008;91(1):190-195

Agents: Imipramine HCl, desmethyl; diazepam; fluoxetine; haloperidol **Vehicle:** Saline; DMSO; water; **Route:** SC; **Species:** Mice; **Pump:** 1002; **Duration:** 14 days;
ALZET Comments: Controls received mp w/either saline, 25, 50% or 100% DMSO; half-life (p. 191); animal info (male, Swiss Webster, 8-10 wks old); behavioral testing (swimming behavior, tail-suspension test, sucrose suspension test); "since drugs have relatively short half-lives in mice, to more closely mimic the human condition in which blood levels are maintained for prolonged periods, all agents were administered by osmotic minipump." (p. 191); all mice were housed singly for the duration of the experiment (3 weeks). Dose: desmethylimipramine in saline (10-11.5 mg/kg/d) in a 35-40 g mouse, fluoxetine dissolved at the same concentration in 50% DMSO; halodoperidol dissolved in 25%DMSO at 0.3-0.34 mg/kg/day (2 mg/ml) and diazepam in 100% DMSO at 1-1.1 mg/kg/day (6.66 mg/ml).

P8816: A. M. Depino, *et al.* GABA homeostasis contributes to the developmental programming of anxiety-related behavior. *Brain Research* 2008;1210(189-199

Agents: Diazepam **Vehicle:** DMSO; Propylene glycol; **Route:** SC; **Species:** Mice; Mice (neonate); **Pump:** 1002; 2002; **Duration:** 14 days;
ALZET Comments: Controls received mp w/ vehicle; dose-response (Fig. 1); no stress (see pg. 193); post op. care (flumazenil); animal info (C57BL/6 x 129/SvJ, male, 14 days old, 60 days old); 50% DMSO used; behavioral testing (maze); wound clips used; 50% propylene glycol used

P5972: T. K. Hensch, *et al.* Columnar architecture sculpted by GABA circuits in developing cat visual cortex. *Science* 2004;303(5664):1678-1681

Agents: Diazepam **Vehicle:** Propylene Glycol; **Route:** CSF/CNS (visual cortex); **Species:** Cat (kitten); **Pump:** 2004; 2ML4; **Duration:** 4 weeks;
ALZET Comments: Diazepam is a benzodiazepine agonist



Q7335: M. I. Arnot, *et al.* GABAA Receptor Gene Expression in Rat Cortex: Differential Effects of Two Chronic Diazepam Treatment Regimes. *Journal of Neuroscience Research* 2001;64(617-625

Agents: Diazepam **Vehicle:** DMSO, propylene glycol; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 14 days;
ALZET Comments: Dose (15 mg/kg/day); 50% DMSO, 50% PG used; Controls received mp w/ vehicle; animal info (Male, Sprague–Dawley, 180–200 g); comparison of single daily injection vs mp; " Osmotic minipumps in vitro deliver diazepam at a relatively constant rate when 50% DMSO/50% PG is used as the vehicle (Arnot et al.,1996). Further, HPLC analysis of cortical tissue obtained from animals receiving diazepam via osmotic minipumps indicates that steady-state levels are achieved at 48 hr post implantation (159.2+/-14.7 ng/g) with the concentration (n = 3) at the 24-hr time point being 92.2 +/- 8.1 ng/g. A single daily sc injection (15 mg/kg diazepam; n = 3) resulted in an initial increase in diazepam levels in the cortex to a maximum concentration occurring 2 hr after injection (398.2 +/- 30.6 ng/g), followed by a decline to the limit of detection 24-hr post injection (33.8 +/- 2.4 ng/g)." pg.620; "Recently, we performed a behavioral comparison of animals receiving diazepam via daily injection demonstrating increased anxiety levels in the social interaction test relative to diazepam pump infused animals (Fernandes et al.,1999)." pg.624; "pumps were turned every second day" p.618

P5275: M. Fagiolini, *et al.* Inhibitory threshold for critical-period activation in primary visual cortex. *Nature* 2000;404(6774): 183-186

Agents: Diazepam **Vehicle:** Propylene glycol; **Route:** CSF/CNS (visual cortex); **Species:** Mice; **Pump:** 1007D; **Duration:** 4 days;
ALZET Comments: Controls received mp w/ vehicle; comparison of icv injections vs. mp; 50% propylene glycol used

P7957: T. K. Hensch, *et al.* Local GABA Circuit Control of Experience-Dependent Plasticity in Developing Visual Cortex. *ScienceDynamics* 1997;210(53

Agents: Tetrodotoxin; diazepam **Vehicle:** Propylene glycol; **Route:** CSF/CNS (visual cortex); **Species:** Mice; **Pump:** 1007D;
Duration: 1 week;

ALZET Comments: Controls received mp w/ vehicle; half-life (p. 1508), rapid breakdown (diazepam); monocular deprivation, localization of cannula delivery confirmed with dye

P3556: M. I. Arnot, *et al.* Dimethyl sulfoxide/propylene glycol is a suitable solvent for the delivery of diazepam from osmotic minipumps. *J. Pharm. & Tox. Meth* 1996;36(29-31

Agents: Diazepam; Clonazepam; flumazenil **Vehicle:** DMSO; Propylene glycol; Tetraglycol; ³H tracer; Radio-isotopes; **Route:** in vitro (egg); **Species:** Not Stated; **Pump:** 2ML4; **Duration:** no duration posted;

ALZET Comments: no comment posted

P3118: C. D. Torchin, *et al.* A system for testing the development and reversal of anticonvulsant tolerance to benzodiazepines in mice. *Epilepsy Research* 1993;16(27-35

Agents: Diazepam; flumazenil; flunitrazepam; ZK-93426 **Vehicle:** Tetraglycol; **Route:** SC; **Species:** mice; **Pump:** 2001; **Duration:** no duration posted;

ALZET Comments: controls received mp with vehicle; tolerance; tetraglycol chosen as solvent because PEG, propylene glycol, tween, DMSO, saline, moleculsol, and methyl cellulose did not maintain benzodiazepines in solution or proconvulsant activity was seen (see pg. 30); flumazenil is RO-15-1788; infusion delayed in some animals by using saline-filled catheter tubing; some animals received benzodiazepine + antagonist concomitantly

P2618: K. Rasmussen, *et al.* The CCK-B antagonist LY288513 blocks effects of diazepam withdrawal on auditory startle. *NeuroReport* 1993;5(2):154-156

Agents: Diazepam **Vehicle:** Water; Tween 80; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 12 days;

ALZET Comments: no comment posted

P3033: J.-L. Moreau, *et al.* Physical dependence induced in DBA/2J mice by benzodiazepine receptor full agonists, but not by the partial agonist Ro 16-6028. *European Journal of Pharmacology* 1990;190(269-273

Agents: Triazolam; Alprazolam; Diazepam **Vehicle:** Propylene glycol; **Route:** SC; **Species:** mice; **Pump:** 2001; **Duration:** 7 days;

ALZET Comments: controls received mp with vehicle; functionality of mp verified by receptor binding study; comparison of oral alprazolam vs. mp; ". . .the use of implantable minipumps. . .permitted. . .development of behavioral tolerance associated with downregulation of benzodiazepine receptor binding and GABA receptor function. . ."; dependence



P1392: M. Hawkins, *et al.* Desensitization of adenosine A2 receptors in the striatum of the rat following chronic treatment with diazepam. *Neuropharmacology* 1988;27(11):1131-1140

Agents: Diazepam **Vehicle:** Propylene glycol; Water;; **Route:** SC; **Species:** Rat; **Pump:** 2ML1; **Duration:** 7 days;
ALZET Comments: functionality of mp verified by sectioning; neuroscience

P0886: W. Loscher. Development of tolerance to the anticonvulsant effect of GABAmimetic drugs in genetically epilepsy-prone gerbils. *Pharmacol. Biochem. Behav* 1986;24(1007-1013

Agents: Aminobutyric acid, γ -acetylenic γ -; Aminoxyacetic acid; Diazepam; THIP; Valproic acid **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 2 weeks;
ALZET Comments: controls received mp w/saline; diazepam too unstable to be used in mp; epilepsy; functionality of mp verified after 14 day exper. period - all 50 mps worked accurately; stability of VPA, THIP, GAG and AOAA

P0433: A. Turmel, *et al.* Sensitization of rat forebrain neurons to serotonin by adinazolam, an antidepressant triazolobenzodiazepine. *European Journal of Pharmacology* 1984;99(241-244

Agents: Adinazolam; Diazepam **Vehicle:** Benzyl alcohol; Ethanol; Propylene glycol; Sodium benzoate; Water; **Route:** IP; **Species:** Rat; **Pump:** 2002; **Duration:** 5 and 14 days;
ALZET Comments: comparison of adinazolam. iv injec vs. mp infusion; comparison of agents effects; adinazolam. used with water vehicle, Diaz. with combination vehicle

Lorazepam

P8188: J. M. Fahey, *et al.* The effect of chronic lorazepam administration in aging mice. *Brain Research* 2006;1118(13-24

Agents: Lorazepam **Vehicle:** PEG 400; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 1, 14 days;
ALZET Comments: Controls received mp w/ vehicle; functionality of mp verified by lorazepam plasma concentrations; tolerance; animal info (male, CD-1, 2-3 months old, 10-12 months old, 22-24 months old)

P4914: J. M. Fahey, *et al.* Pharmacodynamic and receptor binding changes during chronic lorazepam administration. *Pharmacology Biochemistry and Behavior* 2001;69(1-8

Agents: Lorazepam **Vehicle:** PEG 400; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 1,14 days;
ALZET Comments: Controls received mp w/ vehicle; plasma lorazepam levels; brains examined postmortem for membrane binding; lorazepam is a benzodiazepine with anxiolytic and anti-insomnia properties;

P4593: M. H. J. Tehrani, *et al.* Sequestration of g-Aminobutyric acid_A receptors on clathrin-coated vesicles during chronic benzodiazepine administration in vivo;. *The Journal of Pharmacology and Experimental Therapeutics* 1997;283(1):384-390

Agents: Lorazepam **Vehicle:** PEG 400; **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** 7 days;
ALZET Comments: ontrols received mp w/vehicle; tolerance

P3328: M. Mortensen, *et al.* The effect of lorazepam tolerance and withdrawal on metabotropic glutamate receptor function. *J. Pharmacol. Exp. Ther* 1995;274(1):155-163

Agents: Lorazepam **Vehicle:** PEG 400; **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** 7 days;
ALZET Comments: Tolerance

P3673: J. J. Byrnes, *et al.* Chronic benzodiazepine administration. *Psychopharmacology* 1993;111(91-95

Agents: Alprazolam; Lorazepam **Vehicle:** PEG 400; **Route:** SC; **Species:** Mice; **Pump:** 2001; 2002; **Duration:** 7, 8, or 14 days;
ALZET Comments: Controls received vehicle; tolerance

P2501: L. G. Miller, *et al.* Chronic benzodiazepine administration. x. concurrent administration of the peripheral-type benzodiazepine ligand PK11195 attenuates chronic effects of lorazepam. *J. Pharmacol. Exp. Ther* 1992;261(1):285-289

Agents: Lorazepam; PK 11195 **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** Not Stated;
ALZET Comments: Controls received mp w/ vehicle; tolerance; Lorazepam and PK11195 infused separately and together; PK11195 is a peripheral-type site ligand; pumps chosen because they produce "constant plasma and brain concentrations".



P2332: G. B. Kaplan, *et al.* Effects of benzodiazepine administration on A1 adenosine receptor binding in-vivo and ex-vivo. *J. Pharm. Pharmacol* 1992;44(700-703

Agents: Alprazolam; Lorazepam **Vehicle:** PEG 400; **Route:** IP; **Species:** Mice; **Pump:** 2001; **Duration:** 6 days;
ALZET Comments: Controls received mp w/ vehicle

P2610: A. M. Allan, *et al.* Effects of lorazepam tolerance and withdrawal on GABA receptor operated chloride channels in mice selected for differences in ethanol withdrawal severity. *Life Sci* 1992;51(12):931-943

Agents: Lorazepam **Vehicle:** PEG 400; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 7 days;
ALZET Comments: Controls received mp w/ vehicle; tolerance

P2080: A. M. Allan, *et al.* Effects of lorazepam tolerance and withdrawal on GABA-A receptor-operated chloride channels. *J. Pharmacol. Exp. Ther* 1992;261(2):395-402

Agents: Lorazepam **Vehicle:** PEG 400; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 7 days;
ALZET Comments: Tolerance

P2362: L. Miller, *et al.* Prenatal benzodiazepine administration, II. lorazepam exposure is associated with decreases in [35S]TBPS binding but not benzodiazepine binding. *Pharmacol. Biochem. Behav* 1991;40(429-432

Agents: Lorazepam **Vehicle:** PEG 400; **Route:** SC; **Species:** Mice (pregnant); **Pump:** 2001; **Duration:** 7 days;
ALZET Comments: Teratology

P1591: A. Schatzki, *et al.* Lorazepam discontinuation promotes 'inverse agonist' effects of benzodiazepines. *British Journal of Pharmacology* 1989;98(451-454

Agents: Lorazepam **Vehicle:** PEG 400; **Route:** SC; **Species:** Mice; **Pump:** 2001; 2002; **Duration:** 7 days;
ALZET Comments: no comment posted

P1290: L. G. Miller, *et al.* Chronic benzodiazepine administration II: discontinuation syndrome is associated with upregulation of gamma-aminobutyric acid receptor complex binding and function. *J. Pharmacol. Exp. Ther* 1988;246(1):177-182

Agents: Lorazepam **Vehicle:** PEG 400; **Route:** SC; **Species:** Mice; **Pump:** 2001; **Duration:** 7 days;
ALZET Comments: tolerance; functionality of mp verified by plasma, brain levels

P1319: L. G. Miller, *et al.* Chronic benzodiazepine administration. 1. tolerance is associated with benzodiazepine receptor downregulation and decreased gamma-aminobutyric acid receptor function. *J. Pharmacol. Exp. Ther* 1988;246(1):170-176

Agents: Lorazepam **Vehicle:** PEG 400; **Route:** SC; **Species:** Mice; **Pump:** 2001; 2002; **Duration:** 14 days;
ALZET Comments: Dose-response (graph, text); tolerance; functionality of mp verified by plasma levels

P1396: J. Bell, *et al.* Increased central nonadrenergic activity during benzodiazepine withdrawal: an electrophysiological study. *Neuropharmacology* 1988;27(11):1187-1190

Agents: Alprazolam; Lorazepam **Vehicle:** Ethanol; PEG; Saline; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 12 days;
ALZET Comments: no comment posted

Triazolam

P2656: C. Cohen, *et al.* Tolerance, cross-tolerance and dependence measured by operant responding in rats treated with triazolam via osmotic pumps. *Psychopharmacology* 1994;115(86-94

Agents: Triazolam **Vehicle:** Propylene glycol; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 14 days;
ALZET Comments: controls received mp w/ vehicle; tolerance; dependence

P2115: L.-W. Zhou, *et al.* Triazolam blocks the initial rotational effects of quinpirole but permits the later developing reduction of dopamine D2-mediated rotational behavior and dopamine D2 receptors. *European Journal of Pharmacology* 1992;218(219-227

Agents: Quinpirole HCl; Sulpiride; Triazolam **Vehicle:** Ascorbic acid; DMSO; **Route:** SC; **Species:** mice; **Pump:** 2001; **Duration:** 6 days;
ALZET Comments: Quinpirole is a dopamine agonist; antidepressant; stability verified in vitro for 7 days



P3033: J.-L. Moreau, *et al.* Physical dependence induced in DBA/2J mice by benzodiazepine receptor full agonists, but not by the partial agonist Ro 16-6028. *European Journal of Pharmacology* 1990;190(269-273)

Agents: Triazolam; Alprazolam; Diazepam **Vehicle:** Propylene glycol; **Route:** SC; **Species:** mice; **Pump:** 2001; **Duration:** 7 days; **ALZET Comments:** controls received mp with vehicle; functionality of mp verified by receptor binding study; comparison of oral alprazolam vs. mp; ". . .the use of implantable minipumps. . .permitted. . .development of behavioral tolerance associated with downregulation of benzodiazepine receptor binding and GABA receptor function. . ."; dependence