References on the Administration of Anticonvulsive Agents
Using ALZET® Osmotic Pumps

1. Carbamazepine


ALZET Comments: Carbamazepine, baclofen, clomipramine; DMSO, PEG, Ethyl Alcohol, Acetone; SC; Rat; 2ML1; Controls received mp w/ vehicle; animal info (7 weeks old); dimethyl sulfoxide, propylene glycol, ethyl alcohol, and acetone at a ratio of 42:42:15:1; post op. care (morphine 5 mg/day); behavioral testing (Facial grooming); Therapeutic indication (Trigeminal neuralgia, neuropathic pain);
Dose (30 mg/day carbamazepine (the first-line drug treatment for trigeminal neuralgia), 1.06 mg/day baclofen, 4.18 mg/day clomipramine, and 5 mg/day morphine).


ALZET Comments: Carbamazepine; DMSO; propylene glycol; ethyl alcohol; acetone; SC; Rat; 2ML2; 14 days; Controls received mp w/ vehicle; functionality of mp verified by serum drug levels; 42% DMSO used; identified 3 mg/kg/day as the highest dose that could be reliably administered via minipumps over a 14-day period at 37 degrees Celsius, pg. 1969.


ALZET Comments: Carbamazepine; levetiracetam; DMSO; Propylene glycol; ethanol, saline; IP; Rat; 7 days; Controls received mp/vehicle; functionality of mp verified by drug serum levels; dose-response (text p.1428); carbamazepine was dissolved in 42.5% DMSO/42% Propylene glycol/15% ethanol. Levitiracetam was dissolved in saline; 2-day recovery period given using coiled PE-40 tubing; epilepsy; anticonvulsant.

2. Deprenyl


ALZET Comments: Clorgyline; phenelzine; deprenyl; SC; Rat; 2, 21 days; Controls received mp w/ saline; enzyme inhibitor (MAO, monoamine oxidase); animal info (adult, male, Sprague-Dawley, 160-270 g); functionality of mp verified by serum drug levels; dose-response (text p.1428); carbamazepine was dissolved in 42.5% DMSO/42% Propylene glycol/15% ethanol. Levitiracetam was dissolved in saline; 2-day recovery period given using coiled PE-40 tubing; epilepsy; anticonvulsant.


ALZET Comments: Clorgyline; Deprenyl; Saline; SC; Mice (pregnant); 2002; 2004; 6 weeks; Controls received mp w/ vehicle; teratology; enzyme inhibitors (monoamine oxidase inhibitors); 2002 pumps were replaced w/ 2004 pumps after 2 weeks to complete a 6 week infusion; agents infused singly or concomitant in the same pump.


ALZET Comments: Deprenyl, L-; Water, distilled; SC; mice; 2002; 2004; 2,4 weeks; controls received mp w/saline; functionality of mp verified by residual volume; comparison of daily i.p. injections vs. mp; good methods (p. 1588); anticonvulsant; also called selegiline.

P3400: M. C. Carrillo, et al. The optimal dosage of (-) deprenyl for increasing superoxide dismutase activities in several brain regions decreases with age in male Fischer 344 rats. Life Sci 1993;52(1925-1934

ALZET Comments: Deprenyl; Saline; SC; Rat; 3 weeks; controls received mp w/saline; dose-response.
ALZET Comments: Imipramine HCl; Desipramine HCl; Clomipramine HCl; Tranylcypromine HCl; Phenelzine sulfate; Clorgyline HCl; Deprenyl HCl; SC; Rat; 2002; 2ML4; 14,28 days; antidepressant; controls received mp with vehicle; drug concentrations determined from Greenshaw program.

ALZET Comments: Phenelzine; Tranylcypromine, 4-methoxy-; Acetylphenelzine, N2-; Tranylcypromine, 4-fluoro-; Tranylcypromine; Deprenyl; SC; IP; Rat; 28 days; antidepressant; controls received mp with vehicle; comparison of TCP and PLZ ip injections vs. mp.

ALZET Comments: Dopamine; Pargyline; Deprenyl; Lisuride; Pergolide; HCl; Sodium metabisulfite; CSF/CNS; Rat; 2001; 6,7 days; controls received mp with vehicles; replacement therapy (lesion in dopamine pathway); stability verified for 1 week by measuring dopamine concentrations and its metabolites at varying time intervals with HPLC; concomitant dopamine infusion w/ pargyline and w/ deprenyl; antihypertensive; neurodegenerative (Parkinson's disease).

ALZET Comments: Phenylethylamine HCl, 2-; Deprenyl HCl; SC; Rat; 2002; 2ML2; 28 days; Pumps replaced after 14 days; multiple pumps per animal (2); antidepressant.

ALZET Comments: Phenelzine sulfate; Phenylethylamine HCl, 2-; Deprenyl HCl; Saline; SC; Rat; 2002; 2ML2; 21, 22 days; Antidepressant; controls received mp w/ vehicle; multiple pumps per animal (2).

ALZET Comments: Deprenyl; Dopamine; Lisuride; Pargyline; Pergolide; HCl; Sodium metabisulfite; Water; CSF/CNS; Rat; 2001; 6, 7 days; mp connected to cannula; stability of DA verified in several vehicles, p 146; concomitant DA infusion with pargyline; DA infusion with deprenyl; replacement therapy (dopamine deficiency); stability verified in vitro; antihypertensive; neurodegenerative (Parkinson's disease).

ALZET Comments: Deprenyl HCl; Clonidine HCl; Clorgyline HCl; Saline; SC; Rat; 2002; 13 days; controls received mp w/vehicle; hypothalmic electrodes implanted for self-stimulation to further access agents effects; antihypertensive.

ALZET Comments: Deprenyl, 1-; Clorgyline; Saline; SC; Rat; 21-24 days; mp model not stated; comparison of ip injection vs. infusion.

3. Levetiracetam

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ALZET Comments: Levetiracetam; Saline; SC; Rat; 2ML4; 28 days; Dose (10 mg/kg/day); Controls received mp w/ vehicle; animal info (Aged, male Long-Evans rats);.

Q4492: M. Levesque, et al. The anti-ictogenic effects of levetiracetam are mirrored by interictal spiking and high-frequency oscillation changes in a model of temporal lobe epilepsy. SEIZURE-EUROPEAN JOURNAL OF EPILEPSY 2015;25(18-25

ALZET Comments: Levetiracetam; Saline; SC; Rat; 2ML2; 2 weeks; Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 250-300g); cardiovascular; “These pumps deliver a continuous dosing over 2 weeks, circumventing the need for repetitive invasive blood sampling.” pg 19;.


ALZET Comments: Levetiracetam; SB202190; BQ788; SC; Rat; 2004; 3 days; Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 7 days); pumps replaced between trials;.

Q4439: A. M. Hall, et al. Tau-Dependent Kv4.2 Depletion and Dendritic Hyperexcitability in a Mouse Model of Alzheimer’s Disease. JOURNAL OF NEUROSCIENCE 2015;35(6221-6230

ALZET Comments: Levetiracetam; Saline; SC; Mice; 2004; 28 days; Controls received mp w/ vehicle; animal info (hAPPJ20 on C57BL6J background); neurodegenerative (Alzheimer’s disease); pumps primed at 37°C for 24 hours;.


ALZET Comments: Levetiracetam; Saline; SC; Mice; 28 days; Controls received mp w/ saline; animal info (4-5 months, heterozygous hAPP transgenic and wild-type, C57NI/6J);.


ALZET Comments: Levetiracetam; Saline; SC; Rat; 4 weeks; Dose (10 mg/kg/day); Controls received mp w/ vehicle; animal info (Aged, male Long-Evans rats at 8–9 months of age);.


ALZET Comments: Levetiracetam; Saline, sterile; SC; Mice; 2004; 28 days; Control animals received mp w/ vehicle; animal info (hAPPJ20, 4-6 mo old); neurodegenerative (Alzheimer’s disease).


ALZET Comments: Levetiracetam; Saline, physiological; SC; Rat; 2ML4; 4 weeks; Controls received mp w/ vehicle; animal info (spontaneously epileptic (SER), 4 wks old); functionality of mp verified by serum levetiracetam levels.


ALZET Comments: Levetiracetam; Saline; CSF/CNS; Rat; 2004; 28 days; Controls received mp w/ vehicle; animal info (male, Sprague-Dawley, 8 wks old); 15 ul saline allowed for 3-day delayed delivery followed by 25-day levetiracetam delivery; "A preliminary study in which a mini-pump was filled with bromophenol blue instead of levetiracetam, confirmed that the pumped drug solution was constantly separated from the predrug saline for 3 days at 37 °C.” pg 196; delayed delivery;.


ALZET Comments: Levetiracetam; SC; Rat; 2ML1; 7 days; Controls received mp w/ saline; animal info (female, Sprague Dawley, 200-225 g).
ALZET Comments: Levetiracetam; Saline, normal; SC; Rat; 2ML1; 2ML2; 1, 2 weeks; Controls received no spinal cord transection; dose-response (Fig 2A); animal info (female, Sprague Dawley, 225-275 g, spinal cord transection).

ALZET Comments: Levetiracetam; Water, distilled; SC; Rat; 2ML1; 2 weeks; Functionality of mp verified; pumps replaced after 1 week; tolerance; animal info (male, Sprague Dawley, adult, 500-700 g.); "flow rate of each pump was verified after removal and corresponded to the range given by the manufacturer indicating that all minipumps functioned properly." pg. 1156.

ALZET Comments: Levetiracetam; SC; Rat; 3 weeks; 21 days; Controls received mp w/ vehicle; functionality of mp verified by drug plasma levels; dose-response (table 1, pg. 283); animal info (male, Sprague Dawley, 220-250 g.); epilepsy; "chronic treatment with levetiracetam completely inhibits the development of hippocampal hyperexcitability following pilocarpine-induced (status epilepticus)".

R0242: W. Loescher. The pharmacokinetics of antiepileptic drugs in rats: Consequences for maintaining effective drug levels during prolonged drug administration in rat models of epilepsy. Epilepsia 2007;48(7):1245-1258
ALZET Comments: Levetiracetam; phenobarbital; phenytoin; valproic acid; vigabatrin; Water, distilled; PEG 300; glycerol; PEG 400; propylene glycol; SC; IP; Rat; mice; gerbils; 2ML1; 2ML2; 1-4,2 weeks; 7 days; Comparison of IV, IP injections vs. food or water delivery vs mp; pumps replaced (every week in one set of experiments); stress/adverse reaction: (see pg. 1255); peritoneal irritation, peritonitis in some of the IP experiments); half-life (p. 1247) table 1 (18 compounds); animal info (epileptic, Sprague-Dawley, Wistar); review; see p. 1254-1255; see table 4 for advantages + disadvantages of different application routes.

ALZET Comments: Levetiracetam; Rat; 2 weeks; ALZET pumps mentioned on pg. 113.

ALZET Comments: Levetiracetam; Water, distilled; SC; Rat; 2ML1; 6 weeks; anticonvulsant; controls received mp w/ vehicle; functionality of mp verified by residual aspiration, plasma levels; pumps replaced every week; good methods (priming, filling p. 352-53); rats received 2-week saline infusion (pre-drug control period) then 2 week levetiracetam infusion then another 2-week saline infusion.

ALZET Comments: Carbamazepine; levetiracetam; DMSO; Propylene glycol; ethanol, saline; IP; Rat; 7 days; Controls received mp/ vehicle; functionality of mp verified by drug serum levels; dose-response (text p.1428); carbamazepine was dissolved in 42.5% DMSO/42% Propylene glycol/15% ethanol. Levetiracetam was dissolved in saline; 2-day recovery period given using coiled PE-40 tubing; epilepsy; anticonvulsant.

4. Phenobarbital

R0242: W. Loescher. The pharmacokinetics of antiepileptic drugs in rats: Consequences for maintaining effective drug levels during prolonged drug administration in rat models of epilepsy. Epilepsia 2007;48(7):1245-1258
**ALZET Comments**: Levetiracetam; phenobarbital; phenytoin; valproic acid; vigabatrin; Water, distilled; PEG 300; glycerol; PEG 400; propylene glycol; SC; IP; Rat; mice; gerbils; 2ML1; 2ML2; 1-4,2 weeks; 7 days; Comparison of IV, IP injections vs. food or water delivery vs mp; pumps replaced (every week in one set of experiments); stress/adverse reaction: (see pg. 1255); peritoneal irritation, peritonitis in some of the IP experiments); half-life (p. 1247) table 1 (18 compounds); animal info (epileptic, Sprague-Dawley, Wistar); review; see p. 1254-1255; see table 4 for advantages + disadvantages of different application routes.

**ALZET Comments**: Phenobarbital; SC; Rat; 2002; 8 days; Comparison of phenobarb. consumed po in drinking water vs. mp infusion; author states advantages of mp use.

**ALZET Comments**: Chlorpromazine; haloperidol; phenobarbital; promethazine; SC; Rat; 2001; 8 days; Comparison of agents effects.

**ALZET Comments**: Phenobarbital, sodium; Valproate, sodium; Water; SC; mice (pregnant); 2001; 2002; 1 and 2 weeks; no stress see p. 1580, 1582; 1-2 pumps/animal; VPA and PB used singly and in combination in mp.

**ALZET Comments**: Phenobarbital; Water; IP; Rat; 5 days; bolus injec. vs. mp infusion.

**ALZET Comments**: Phenobarbital, sodium; Propylene glycol; Water; CSF/CNS; Rat; 3 days; some groups given 6-OHDA or vehicle of ascorbic acid in Artificial CSF prior to infusion.

5. Promethazine

**ALZET Comments**: Chlorpromazine; haloperidol; phenobarbital; promethazine; SC; Rat; 2001; 8 days; Comparison of agents effects.

6. Tiagabine

**ALZET Comments**: Vigabatrin; Tiagabine; SC; Rat; 2 months; Neuroprotection; pump use mentioned on p. 147 and 155; long-term study.

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ALZET Comments: Tiagabine;; Saline;; IV (jugular);; Rat;; 2ML2;; 14 days;; Controls received mp w/ vehicle; functionality of mp verified by plasma levels; dose-response (graph p. 145); comparison of IV injections vs. mp; Tiagabine is a GABA uptake inhibitor; seizure prevention; Epilepsy.;

ALZET Comments: Tiagabine; Propylene glycol; SC; Rat; 2ML1; 7 days; functionality of mp verified by in vitro testing and residual volumes; dose-response; half-life (p. 70); compound stable for one week (see p. 78); stability.

7. Valproic Acid

ALZET Comments: Valproic acid; IR (intra-renal); Rat; 2ML2; 10 days; Dose (50mg/Kg/d); Controls received mp w/ vehicle; animal info (male Dahl salt-sensitive rats, SS-13BN);

ALZET Comments: Valproic acid; Saline; CSF/CNS (left midbrain); Mice (transgenic); 1002; 2 weeks; 4 weeks; Dose (0.25 mg/μl); Controls received mp w/ vehicle; animal info (NestinCreERT2 C57BL/6 mice); ALZET brain infusion kit 1 used; Brain coordinates (3.0 mm posterior to Bregma, 1.5 mm lateral to the midline, and 4.0 mm below the surface of the brain); neurodegenerative (Parkinson’s disease);

ALZET Comments: Valproic acid; PBS; Rat; 5 days; Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 300-400g); ischemia (cerebral); dose-response (pg 4-6); behavioral testing (modified limb-placing test); cardiovascular; bp measured using tail cuff;

Q4323: R. C. Bates, et al. Increasing pro-survival factors within whole brain tissue of Sprague Dawley rats via intracerebral administration of modified valproic acid. JOURNAL OF PHARMACOLOGICAL SCIENCES 2015;103(237 -244
ALZET Comments: Valproic Acid; SC; Rat; 2004; 28 days; Controls received mp w/ saline; animal info (Sprague-Dawley, adult male, 250-280g); ALZET brain infusion kit (1) used; behavioral testing (elevated plus maze, and open field test); wound clips used;

ALZET Comments: Valproic acid; PBS; CSF/CNS (intrathecal); Rat; 1003D; 3 days; Dose (1.5 μg VPA); Controls received mp w/ vehicle; animal info (Female adult Sprague-Dawley rats (n =41; 250 +/-30 g)); post op. care (sodium ampicillin); behavioral testing (locomotor function); enzyme inhibitor (histone deacetylase (HDAC) inhibitor); ALZET brain infusion kit 3 used; spinal cord injury;

ALZET Comments: Valproic Acid; SC; Rat; 2004; 28 days; Controls received mp w/ saline; animal info (Sprague-Dawley, adult male, 250-280g); ALZET brain infusion kit (1) used; behavioral testing (elevated plus maze, and open field maze).

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Bibliography

**ALZET Comments:** Valproic acid; PBS; SC; Mice (SCID); 2002; 14 days; Controls received mp w/vehicle; cancer (myeloma); animal info (8-10 wks old, female).

**R0242:** W. Loescher. The pharmacokinetics of antiepileptic drugs in rats: Consequences for maintaining effective drug levels during prolonged drug administration in rat models of epilepsy. Epilepsia 2007;48(7):1245-1258

**ALZET Comments:** Levetiracetam; phenobarbital; phenytoin; valproic acid; vigabatrin; Water, distilled; PEG 300; glycerol; PEG 400; propylene glycol; SC; IP; Rat; mice; gerbils; 2ML1; 2ML2; 1-4,2 weeks; 7 days; Comparison of IV, IP injections vs. food or water delivery vs mp; pumps replaced (every week in one set of experiments); stress/ adverse reaction: (see pg. 1255); peritoneal irritation, peritonitis in some of the IP experiments; half-life (p. 1247) table 1 (18 compounds); animal info (epileptic, Sprague-Dawley, Wistar); review; see p. 1254-1255; see table 4 for advantages + disadvantages of different application routes.


**ALZET Comments:** Valproic acid; Sodium chloride; SC; Mice (SCID); 2001; 14 days; Controls received no treatment; pumps replaced after 7 days; animal info (6-10 wks old, Rag 2).

**P8386:** A. Serralta, et al. Effect of intracerebroventricular continuous infusion of valproic acid versus single i.p. and i.c.v. injections in the amygdala kindling epilepsy model. Epilepsy Research 2006;70(1):15-26

**ALZET Comments:** Valproic acid; Saline; CSF/CNS; Rat; 2001; 2002; 7 days; Controls received no treatment; dose-response (fig. 1); comparison of icv, IP injections vs. mp; no stress (see pg. 22); toxicology; multiple pumps per animal (2); animal info (male, Wistar, amygdala-kindled epilepsy, 380-420g.); mp primed 1 hr. in 37.5 celsius saline; evans blue dye used to confirm cannula placement, "chronic i.c.v. VPA infusion affords protection against kindled seizures accompanied by less ataxia and sedation" (pg. 24).


**ALZET Comments:** Valproic acid; Saline, sterile physiological; SC; mice; 2001; no duration posted; functionality of mp verified by plasma levels; half-life of less than 1 hour (p. 76); 2 mps implanted concomitantly.


**ALZET Comments:** Valproic acid; SC; mice; no duration posted; comparison of iv injections vs. mp; article in Chinese w/ abstract in English.


**ALZET Comments:** Valproic acid; Sodium carbonate; Water; SC; mice (pregnant); 2001; 7 days; dose-response (text, graph); half-life; 2 pumps implanted simultaneously; functionality of mp verified by plasma levels; no stress; toxicology/teratology.


**ALZET Comments:** Antipyrine; bleomycin; dopamine HCl; melatonin; methotrexate, sodium; nicotine; prednisolone; radio-isotopes; valproic acid; $^{14}$C tracer; $^{3}$H tracer; IA; IP; SC; Mice, rabbit, Rat; no duration posted; ALZA-authored; synoptic review of mp; post op. care (antibiotic); comparison of sc injections vs. mp infusion; pulsed delivery.

**P0848:** H. Nau. Valproic acid teratogenicity in mice after various administration and phenobarbital-pretreatment regimens: the parent drug and not one of the metabolites assayed is implicated as teratogen. Fundam. Appl. Toxicol 1986;6(4):662-668

**ALZET Comments:** Valproic acid; Water; SC; mice; 1 day; teratology; states pump rate at 8 ul/hr; 2 doses of vpa infused; comparison of SC or IP injections or oral dose vs. mp infusion.

**ALZET Comments:** Aminobutyric acid, Y-acetylenic Y-; Aminoxyacetic acid; Diazepam; THIP; Valproic acid; Saline; SC; Rat; 2ML2; 2 weeks; 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.


**ALZET Comments:** Cyclophosphamide; Valproic acid; SC; mice; no duration posted; pump model not stated; review; dose-response (graph); half-life; comparison of injections vs. mp infusion; teratology.


**ALZET Comments:** Valproic acid; no duration posted; teratology; injection-infusion comparison protocol w/ VPA discussed.


**ALZET Comments:** Valproic acid; SC; Rat; 2ML2; 1, 3, or 14 days; no comment posted.


**ALZET Comments:** Valproic acid; Sodium bicarbonate; Water; SC; mice; 2001; 2002; 1 week; intermittent sc. injec. vs. mp infusion; 1 or 2 pumps/animal; comparison of human vs. animal pharmacokinetics.


**ALZET Comments:** Valproic acid; Water; SC; mice; 2001; 7 days; 1 or 2 pumps/mouse; comparison of injection vs. infusion and human vs. animal pharmacokinetics.

8. Vigabatrin


**ALZET Comments:** Vigabatrin; PBS; SC; Mice; 2002; 12 days; Dose (35, 70, and 140 mg/kg/d); Controls received mp w/ vehicle; animal info (Male C57BL/6J mice, 8-10 weeks old, 20.8-26.1 g ); post op. care (Carprofen); dependence;

Q5697: K. R. Vogel, et al. mTOR Inhibition Mitigates Molecular and Biochemical Alterations of Vigabatrin-Induced Visual Field Toxicity in Mice. Pediatr Neurol 2017;66(44-52 e1

**ALZET Comments:** Vigabatrin; PBS; SC; Mice; 2002; 14 days; Controls received mp w/ vehicle; animal info (C57BL6, 8 weeks old);

R0242: W. Loescher. The pharmacokinetics of antiepileptic drugs in rats: Consequences for maintaining effective drug levels during prolonged drug administration in rat models of epilepsy. Epilepsia 2007;48(7):1245-1258

**ALZET Comments:** Levetiracetam; phenobarbital; phenytoin; valproic acid; vigabatrin; Water, distilled; PEG 300; glycerol; PEG 400; propylene glycol; SC; IP; Rat; mice; gerbils; 2ML1; 2ML2; 1-4.2 weeks; 7 days; Comparison of IV, IP injections vs. food or water delivery vs mp; pumps replaced (every week in one set of experiments); stress/adverse reaction: (see pg. 1255); peritoneal irritation, peritonitis in some of the IP experiments); half-life (p. 1247) table 1 (18 compounds); animal
info (epileptic, Sprague-Dawley, Wistar); review; see p. 1254-1255; see table 4 for advantages + disadvantages of different application routes.


**ALZET Comments**: Vigabatrin; Tiagabine; SC; Rat; 2 months; Neuroprotection; pump use mentioned on p. 147 and 155; long-term study.

**P4904**: T. Halonen, et al. Chronic elevation of brain GABA levels beginning two days after status epilepticus does not prevent epileptogenesis in rats. Neuropharmacology 2001;40(536-550

**ALZET Comments**: Vigabatrin; Saline; SC; Rat; 2ML2; 10 weeks; controls received mp w/ vehicle; long-term study, pumps replaced every 2 weeks for 10 weeks; epilepsy; seizures.


**ALZET Comments**: Vigabatrin; Saline; SC; Rat; 2ML1; 2 months; controls received mp with vehicle; functionality of mp verified by plasma levels and residual volume; long-term study, pumps replaced every 2 weeks; enzyme inhibitor.


**ALZET Comments**: Vigabatrin; Saline; IP; hamster; 2002; 14 days; controls received mp w/saline or no treatment; comparison of injections vs. mp; GABA transaminase inhibitor.