



References on the Administration of Antipsychotics Using ALZET® Osmotic Pumps

1. Chlorpromazine

P2717: P. N. M. Konings, *et al.* Chronic haloperidol and chlorpromazine treatment alters in vitro B-endorphin metabolism in rat brain. *Eur. J. Pharmacol* 1990;191(115-128)

ALZET Comments: Haloperidol; Chlorpromazine; Saline, sterile; SC; Rat; 2001; 2ML1; 8 days; controls received mp w/ vehicle.

P1348: T. N. Myschuk, *et al.* Long term (1 week) tranquilization of mice using Alzet(R) mini-osmotic pumps. *Can. Lab Anim. Sci. News* 1987;20(1):18-20

ALZET Comments: Chlorpromazine HCl; IP; SC; mice; 2002; 7, 10 days; complications with sc delivery; no stress/stress.

P1137: T. P. Davis, *et al.* Neuroleptic drug treatment alters in vitro central neurotensin metabolism. *Psychoneuroendocrinology* 1987;12(4):253-260

ALZET Comments: Chlorpromazine; Haloperidol; SC; Rat; 2001; 2ML1; 8 days; controls received sham op; concomitant infusion of agents; comparison of agents effects; functionality of mp verified by gravimetric analyses.

P0908: P. Frey. Changes in cholecystokinin content in rat brain after subchronic treatment with neuroleptics. *Ann. N. Y. Acad. Sci* 1985;448(601-603)

ALZET Comments: Flupenthixol, cis-; Flupenthixol, trans-; Amitriptyline; Amphetamine; Atropine; Chlorpromazine; Clozapine; Fluphenazine; Haloperidol; Morphine; Prazosin; SC; Rat; 2 weeks; mp model not stated; comparison of sc injections vs. mp infusion; antihypertensive.

P0447: T. P. Davis, *et al.* Centrally acting drugs alter in vitro B-endorphin processing in the rat. *Eur. J. Pharmacol* 1984;100(249-251)

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

P0385: P. Frey. Cholecystokinin octapeptide levels in rat brain are changed after subchronic neuroleptic treatment. *Eur. J. Pharmacol* 1983;95(87-92)

ALZET Comments: Chlorpromazine; Clozapine; Haloperidol; HCl; Saline; SC; Rat; 2ML2; 2ML4; 2 and 4 weeks; comparison of single injec vs. infusion; comparison of agents effects; Hal. given for 2 & 4 weeks, Chlor. & Cloz. for 2 weeks; saline & HCl vehicle used w/Cloz., others used saline only; stability of Hal., Chlor. & Cloz. by TLC.

2. Clozapine

Q5793: F. Donato, *et al.* Stellate cells drive maturation of the entorhinal-hippocampal circuit. *Science* 2017;355(6330):

ALZET Comments: Clozapine-N-oxide; Saline; SC; Mice (neonate); 1007D; 7 days; Controls received mp w/ vehicle; animal info (11-14 days); clozapine-N-oxide (CNO)

Therapeutic indication (learning and memory); Dose (1 mg/kg);.

Q6104: K. Chikama, *et al.* Chronic atypical antipsychotics, but not haloperidol, increase neurogenesis in the hippocampus of adult mouse. *Brain Res* 2017;1676(77-82)

ALZET Comments: Haloperidol; quetiapine; aripiprazole; clozapine; olanzapine; risperidone; IP; Mice; 1004; 21 days; Dose (haloperidol 1 mg/kg/d, quetiapine 20 mg/kg/d, aripiprazole 3 mg/kg/d, clozapine 20 mg/kg/d, olanzapine 2 mg/kg/d, risperidone 0.5 mg/kg/d); Controls received mp w/ vehicle; "It is known that osmotic pumps serve some preferable aspect such as to reduce stress to the animals, minimize unwanted experimental variables, and hold the drug concentration constant" pg. 80;.



Q5965: X. Mason. Neural Circuit Mechanisms Underlying the Exacerbation of Alzheimer's Disease by Chronic Stress. Doctoral dissertation, Harvard Medical School 2015;

ALZET Comments: Clozapine-N-oxide; Saline, sterile; SC; Mice; 2004; 28 days; animal info (Adult male Swiss Webster mice); neurodegenerative (Alzheimer's disease);.

Q3806: P. M. Anderson, *et al.* Chronic administration of antipsychotics attenuates ongoing and ketamine-induced increases in cortical gamma oscillations. INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY 2014;17(1895-1904

ALZET Comments: Haloperidol; clozapine; LY379268; Saline; acetic acid; water, sterile; SC; Rat; 2ML4; 28 days; Controls received mp w/ vehicle; animal info (male, Wistar, 10-12 weeks old, 250-350g); functionality of mp verified by residual volume; behavioral testing (locomotor activity); LY379268 is a metabotropic glutamate 2/3 receptor agonist (mGluR 2/3);.

Q6778: K. E. Stevens, *et al.* Intermittent versus continuous central administration of clozapine in DBA/2 mice, improvement in sensory inhibition deficits. Schizophr Res 2013;149(1-3):121-6

ALZET Comments: Clozapine; Saline; CSF/CNS (lateral ventricle); Mice; 1002; 24 hours; Dose (0, 3, 7.5, 15 or 30 µg/day); Controls received mp w/ vehicle; animal info (DBA/2 mice (20–25 g)); comparison of once-per-day injection vs mp; ALZET brain infusion kit 3 used; Brain coordinates ([0.9 mm anterior to bregma, 0.1 mm lateral to midline and –2.0 mm from the brain surface); cyanoacrylate adhesive;.

Q1815: L. J. Steward, *et al.* Chronic phencyclidine (PCP)-induced modulation of muscarinic receptor mRNAs in rat brain : Impact of antipsychotic drug treatment. Neuropharmacology 2012;62(3):1554-1563

ALZET Comments: Clozapine; haloperidol; Acetic acid; saline; water; SC; Rat; 2ML4; Animal info (Hooded Long Evans, 186-248 g); pump functionally verified via residual volume.

Q1814: N. Amitai, *et al.* Repeated phencyclidine administration alters glutamate release and decreases GABA markers in the prefrontal cortex of rats. Neuropharmacology 2012;62(3):1422-1431

ALZET Comments: Clozapine; HCl; saline; SC; Rat; 2ML1; 14 days; Controls received mp w/ vehicle; animal info (Wistar, male, 300 g); pumps replaced after 7 days; "The limited solubility of clozapine at the concentration that was required to deliver 4 mg/kg/day in the maximal volume that could be contained in the minipumps prevented the use of a single 14 day osmotic minipump; thus, two successive 7 day minipumps were used" pg 1423; wound clips used; post op. care (antibacterial ointment) pg 1423.

Q0666: D. M. Thomson, *et al.* Dissociation of acute and chronic intermittent phencyclidine-induced performance deficits in the 5-choice serial reaction time task: influence of clozapine. Psychopharmacology 2011;213(4):681-695

ALZET Comments: Clozapine; Acetic acid, glacial; water, sterile; SC; Rat; 2ML4; 28 days; Controls received mp w/ vehicle; animal info (male, hooded, Long-Evans, 333 g).

P9474: N. Amitai, *et al.* Clozapine attenuates disruptions in response inhibition and task efficiency induced by repeated phencyclidine administration in the intracranial self-stimulation procedure. European Journal of Pharmacology 2009;602(1):78-84

ALZET Comments: Clozapine; Hydrochloric acid; saline; SC; Rat; 2ML1; 14 days; Controls received mp w/ vehicle; pumps replaced after 7 days; post op. care (antibacterial ointment on incision area); animal info (Wistar rats, 300 g.); antipsychotic; subsequent pump implanted contralateral to the first minipump.

P6686: S. Semenova, *et al.* Clozapine treatment attenuated somatic and affective signs of nicotine and amphetamine withdrawal in subsets of rats exhibiting hyposensitivity to the initial effects of clozapine. Biological Psychiatry 2003;54(11):1249-1264

ALZET Comments: Nicotine tartrate; amphetamine; clozapine; HCL; saline; SC; Rat; 2ML1; 7,14 days; Controls received mp w/ vehicle; pumps replaced every 7 days for the 14 day study infusing clozapine; dependence; "in this experiment involving three pump implantations each pump was placed in a different part of the rats' body (left or right side of the back of the animal or at the shoulder area)." p. 1252; behavioral study.



P6169: S. Kapur, *et al.* Antipsychotic Dosing in Preclinical Models is Often Unrepresentative of the Clinical Condition: A Suggested Solution Based on in Vivo Occupancy. *Journal of Pharmacology and Experimental Therapeutics* 2003;305(2):625-631

ALZET Comments: Haloperidol; olanzapine; risperidone; quetiapine; clozapine; Water; acetic acid, glacial; SC; Rat; 2ML2; 7 days; Plasma levels taken; dose-response (p. 629); comparison of daily injections vs. chronic mp; half-life (p. 626) 2-4 hours; haloperidol and risperidone were dissolved in distilled water; olanzapine, quetiapine and clozapine were dissolved in 1% to 2% acetic acid; great dose information; "we propose that only administration by pump (or administration more than four times a day[injections]) can provide clinical-like occupancies for haloperidol, olanzapine, and risperidone." p. 630.

P6201: S. M. Cochran, *et al.* Induction of metabolic hypofunction and neurochemical deficits after chronic intermittent exposure to phencyclidine: Differential modulation by antipsychotic drugs. *Neuropsychopharmacology* 2003;28(2):265-275

ALZET Comments: Clozapine; haloperidol; Acetic acid, glacial; water; SC; Rat; 2ML4; 21 days; Controls received mp w/ vehicle.

P8874: D. J. Abrams, *et al.* An initial animal proof-of-concept study for central administration of clozapine to schizophrenia patients. *SCHIZOPHRENIA RESEARCH* 1999;112(1091):86-96

ALZET Comments: Clozapine; Cyclodextrin, hydroxypropyl, beta; CSF/CNS; Rat; 28 days; Controls received mp w/ saline; ALZET brain infusion kit used; animal info (male, Sprague Dawley, 250-300g.); Schizophrenia.

P2833: K. M. Merchant, *et al.* Effects of chronic haloperidol and clozapine treatment on neurotensin and c-fos mRNA in rat neostriatal subregions. *J. Pharmacol. Exp. Ther* 1994;271(1):460-471

ALZET Comments: Haloperidol; Clozapine; SC; Rat; 2ML2; 28 days; controls received mp with saline; pumps replaced at 14 days.

P1706: R. E. See, *et al.* Comparison of chronic administration of haloperidol and the atypical neuroleptics, clozapine and raclopride, in an animal model of tardive dyskinesia. *Eur. J. Pharmacol* 1990;181(175-186)

ALZET Comments: Clozapine; Haloperidol; Raclopride; Acetic acid, glacial; HCl; Sodium hydroxide; Water; SC; Rat; 2ML4; 28 days; controls received an empty plastic pellet of identical size.

P0908: P. Frey. Changes in cholecystokinin content in rat brain after subchronic treatment with neuroleptics. *Ann. N. Y. Acad. Sci* 1985;448(601-603)

ALZET Comments: Flupenthixol, cis-; Flupenthixol, trans-; Amitriptyline; Amphetamine; Atropine; Chlorpromazine; Clozapine; Fluphenazine; Haloperidol; Morphine; Prazosin; SC; Rat; 2 weeks; mp model not stated; comparison of sc injections vs. mp infusion; antihypertensive.

P0385: P. Frey. Cholecystokinin octapeptide levels in rat brain are changed after subchronic neuroleptic treatment. *Eur. J. Pharmacol* 1983;95(87-92)

ALZET Comments: Chlorpromazine; Clozapine; Haloperidol; HCl; Saline; SC; Rat; 2ML2; 2ML4; 2 and 4 weeks; comparison of single injec vs. infusion; comparison of agents effects; Hal. given for 2 & 4 weeks, Chlor. & Cloz. for 2 weeks; saline & HCl vehicle used w/Cloz., others used saline only; stability of Hal., Chlor. & Cloz. by TLC.

3. Fluphenazine

P0908: P. Frey. Changes in cholecystokinin content in rat brain after subchronic treatment with neuroleptics. *Ann. N. Y. Acad. Sci* 1985;448(601-603)

ALZET Comments: Flupenthixol, cis-; Flupenthixol, trans-; Amitriptyline; Amphetamine; Atropine; Chlorpromazine; Clozapine; Fluphenazine; Haloperidol; Morphine; Prazosin; SC; Rat; 2 weeks; mp model not stated; comparison of sc injections vs. mp infusion; antihypertensive.



4. Haloperidol

Q7103: A. Calevro, *et al.* Effects of chronic antipsychotic drug exposure on the expression of Translocator Protein and inflammatory markers in rat adipose tissue. *Psychoneuroendocrinology* 2018;95(28-33)

ALZET Comments: Haloperidol, olanzapine; Cyclodextrin, 2-Hydroxypropyl-B-; SC; Rat; 2ML4; 8 weeks; Dose (Haloperidol-2mg/ kg/ day, Olanzapine-10 mg/kg/ day); Controls received mp w/ vehicle; animal info (10-week old, male, Sprague-Dawley, 240–250 g); pumps replaced every 4 weeks; long-term study; dependence;.

Q5973: A. Servonnet, *et al.* Neurotensin in the nucleus accumbens reverses dopamine supersensitivity evoked by antipsychotic treatment. *Neuropharmacology* 2017;123(10-21)

ALZET Comments: Haloperidol; Acetic acid, water; SC; Rat; 2ML2; Controls received mp w/ vehicle; animal info (200-225 g); Mp vs. intermittent administration by injection; Therapeutic indication (Anti-psychosis); Dose (0.5 mg/kg);.

Q5738: L. E. Sebel, *et al.* Haloperidol Selectively Remodels Striatal Indirect Pathway Circuits. *Neuropsychopharmacology* 2017;42(4):963-973

ALZET Comments: Haloperidol-Hcl; Saline; SC; Mice; 2004; 14 days; Controls received mp w/ vehicle; animal info (hemizygous bacterial artificial chromosome (BAC) transgenic mice (p28-p38) expressing eGFP under either *Drd1a* or *Drd2* control); Therapeutic indication (Schizophrenia); Dose (0.25 mg/kg/day);.

Q6192: Y. Oda, *et al.* Alterations in glutamatergic signaling in the brain of dopamine supersensitivity psychosis and non-supersensitivity psychosis model rats. *Psychopharmacology (Berl)* 2017;234(20):3027-3036

ALZET Comments: Haloperidol; Acetic acid, glacial; Water; SC; Rat; 2ML2; 14 days; Dose (0.75 mg/kg/day); 2% glacial acetic acid/H₂O solution (pH adjusted to 3.8 with NaOH); Controls received mp w/ vehicle; animal info (Eleven-week-old male Wistar rats weighing 240–270 g); Therapeutic indication (dopamine supersensitivity psychosis);.

Q6104: K. Chikama, *et al.* Chronic atypical antipsychotics, but not haloperidol, increase neurogenesis in the hippocampus of adult mouse. *Brain Res* 2017;1676(77-82)

ALZET Comments: Haloperidol; quetiapine; aripiprazole; clozapine; olanzapine; risperidone; IP; Mice; 1004; 21 days; Dose (haloperidol 1 mg/kg/d, quetiapine 20 mg/kg/d, aripiprazole 3 mg/kg/d, clozapine 20 mg/kg/d, olanzapine 2 mg/kg/d, risperidone 0.5 mg/kg/d); Controls received mp w/ vehicle; “It is known that osmotic pumps serve some preferable aspect such as to reduce stress to the animals, minimize unwanted experimental variables, and hold the drug concentration constant” pg. 80;.

Q6316: A. Almey, *et al.* Interactions between estradiol and haloperidol on perseveration and reversal learning in amphetamine-sensitized female rats. *Horm Behav* 2017;89(113-120)

ALZET Comments: Haloperidol; Saline; SC; Rat; 2002; 14 days; Dose (0.25 mg/day, 0.13 mg/day); Controls received mp w/ vehicle; animal info (female Sprague-Dawley rats); behavioral testing (Locomotor activity boxes); Haloperidol aka HAL;.

Q5414: D. Madularu, *et al.* High estrogen and chronic haloperidol lead to greater amphetamine-induced BOLD activation in awake, amphetamine-sensitized female rats. *Horm Behav* 2016;82(56-63)

ALZET Comments: Haloperidol; Saline; SC; Rat; 2002; 14 days; Controls received mp w/ vehicle; Animal info (OVX Sprague Dawley rats, 200-250 g, 2 months old); post op. care (Anafen analgesic 0.1 mL/rat, and local antibiotic ointment); replacement therapy (estrogen replacement); MRI compatible PEEK tubing used; Dose (0.25 mg/kg/day); Therapeutic indication (Schizophrenia);.

Q6020: W. R. Crum, *et al.* Chronic exposure to haloperidol and olanzapine leads to common and divergent shape changes in the rat hippocampus in the absence of grey-matter volume loss. *Psychol Med* 2016;46(15):3081-3093

ALZET Comments: Haloperidol, Olanzapine; Cyclodextrin, hydroxypropyl-β-, Ascorbic acid; SC; Rat; 2ML4; 28 days; Controls received mp w/vehicle; animal info (10 weeks old) pumps replaced every 4 weeks; Therapeutic indication (Learning and memory, hippocampus, antipsychotic); Dose (HAL (2 mg/kg perday), or OLZ (10 mg/kg perday);.



Q5240: Y. Oda, *et al.* G protein-coupled receptor kinase 6/beta-arrestin 2 system in a rat model of dopamine supersensitivity psychosis. *J Psychopharmacol* 2015;29(12):1308-13

ALZET Comments: Haloperidol; Acetic acid, glacial; water; SC; Rat; 2ML2; 14 days; Controls received mp w/ vehicle; animal info (Eleven-week-old male Wistar rats, 240–260 g); functionality of mp verified by ELIZA testing; 2% acetic acid used; good methods (pg 1309); stress/adverse reaction: “One animal did not recover from pump-implanting surgery and was excluded from analysis” (see pg. 1310); behavioral testing (MAP-induced locomotion test); Vehicle pH adjusted to 3.6-3.8 with NaOH; 9mm wound clips used; Dose (0.75 mg/kg/d);.

Q5037: D. Madularu, *et al.* Changes in brain volume in response to estradiol levels, amphetamine sensitization and haloperidol treatment in awake female rats. *Brain Res* 2015;1618(100-10)

ALZET Comments: Haloperidol; SC; Rat; 2002; 14 days; Controls received sham surgery; animal info (female, Sprague Dawley, 200-250g 2-3 months old, OVX); post op. care (Anafen 0.1 mL/rat; antibiotic ointment); MRI; PEEK; Dose (0.25 mg/kg/day);.

Q5144: C. El Hage, *et al.* Antipsychotic treatment leading to dopamine supersensitivity persistently alters nucleus accumbens function. *Neuropharmacology* 2015;99(715-25)

ALZET Comments: Haloperidol; Olanzapine; Acetic acid; water; SC; Rat; 2ML2; 15 days; 17 days; Controls received sham surgery; animal info: Male Sprague-Dawley rats; %0.5 or %2 of acetic acid; behavioral testing (trained to associate the delivery of 100 ml water (the unconditioned stimulus; UCS) into a receptacle with a light/tone conditioned stimulus (CS)); Dose: 0.5 mg/kg/day (haloperidol); 10 mg/kg/day (olanzapine).

Q5134: A. Charron, *et al.* 5-HT₂ receptors modulate the expression of antipsychotic-induced dopamine supersensitivity. *Eur Neuropsychopharmacol* 2015;25(12):2381-93

ALZET Comments: Haloperidol; Acetic acid, glacial; water; SC; Rat; 2ML2; 15, 17 days; Controls received sham surgery consisting of an incision and sutures; animal info: Male Sprague-Dawley rats 200–225g; water (pH 5) used; half-life (p. 2383), 1.5 hours; models the kinetics of standard antipsychotic treatment in patients; Dose: 0.5 mg/ kg/day.

Q3580: S. Natesan, *et al.* Effect of chronic antipsychotic treatment on striatal phosphodiesterase 10A levels: a [(11C)]MP-10 PET rodent imaging study with ex vivo confirmation. *TRANSLATIONAL PSYCHIATRY* 2014;4(U4-U10)

ALZET Comments: Haloperidol; Cyclodextrin, 2-hydroxypropyl-b-; Ascorbic acid; SC; Rat; 2ML4; 3 weeks; Controls received mp w/ vehicle; animal info (male, Sprague Dalwy, 308-456g); functionality of mp verified by plasma; 20% B-hydroxypropylcyclodextrin used; behavioral testing (chewing movements); "Daily intraperitoneal injections in rodents lead to plasma levels that dip to a negligible level during a 24-h period as most antipsychotics have a half-life of 2-4 h in rodents, whereas the half-life of most antipsychotics in humans is usually 12-24 h.14 Hence, the present study was designed taking into consideration a delivery method (subcutaneous mini-osmotic pumps) that maintained constant plasma levels to evaluate the effect of chronic antipsychotic treatment on striatal PDE10A levels in rodents" pg 1;

Q3306: D. Madularu, *et al.* Estrogen potentiates the behavioral and nucleus accumbens dopamine response to continuous haloperidol treatment in female rats. *European Journal of Neuroscience* 2014;39(2):257-265

ALZET Comments: Haloperidol; Saline; SC; Rat; 2002; 12 days; Animal info (female, Sprague Dawley, ovariectomized); behavioral testing (motor activity); replacement therapy (ovariectomized); pump removed after 12 days;

Q3884: J. Gao, *et al.* Differential effects of intermittent versus continuous haloperidol treatment throughout adolescence on haloperidol sensitization and social behavior in adulthood. *PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY* 2014;54(67-75)

ALZET Comments: Haloperidol; Water, sterile; SC; Rat; 2ML4; 28 days; Controls received mp w/ vehicle; animal info (male, Sprague Dawley, PND44-71); comparison of injection vs mp; post op. care (incision cleaned with 75% ethanol); behavioral testing (two-way avoidance conditioning apparatus; locomotor activity monitoring apparatus; avoidance training); dependence; used 9mm wound clips; pumps wiped with 75% ethanol; pumps removed after 28 days;

Q3290: M. Cazorla, *et al.* Dopamine D2 Receptors Regulate the Anatomical and Functional Balance of Basal Ganglia Circuitry. *Neuron* 2014;81(1):153-164



ALZET Comments: Haloperidol; Lactic acid; sodium hydroxide; SC; Mice (transgenic); 2002; 14 days; Controls received mp w/ vehicle; animal info (male, D2R-OE, adult); behavioral testing (open field, locomotor activity);.

Q3806: P. M. Anderson, *et al.* Chronic administration of antipsychotics attenuates ongoing and ketamine-induced increases in cortical gamma oscillations. *INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY* 2014;17(1895-1904

ALZET Comments: Haloperidol; clozapine; LY379268; Saline; acetic acid; water, sterile; SC; Rat; 2ML4; 28 days; Controls received mp w/ vehicle; animal info (male, Wistar, 10-12 weeks old, 250-350g); functionality of mp verified by residual volume; behavioral testing (locomotor activity); LY379268 is a metabotropic glutamate 2/3 receptor agonist (mGluR 2/3);.

5. Olanzapine

Q7103: A. Calevro, *et al.* Effects of chronic antipsychotic drug exposure on the expression of Translocator Protein and inflammatory markers in rat adipose tissue. *Psychoneuroendocrinology* 2018;95(28-33

ALZET Comments: Haloperidol, olanzapine; Cyclodextrin, 2-Hydroxypropyl-B-; SC; Rat; 2ML4; 8 weeks; Dose (Haloperidol-2mg/ kg/ day, Olanzapine-10 mg/kg/ day); Controls received mp w/ vehicle; animal info (10-week old, male, Sprague-Dawley, 240–250 g); pumps replaced every 4 weeks; long-term study; dependence;.

Q5988: A. Stefanidis, *et al.* Prevention of the adverse effects of olanzapine on lipid metabolism with the antiepileptic zonisamide. *Neuropharmacology* 2017;123(55-66

ALZET Comments: Olanzapine; Lactic acid; SC; Rat; 2ML2; Controls received mp w/ vehicle; animal info (Sprague Dawley , female); half-life (2.5 hours) ; Therapeutic indication (Antipsychotic drugs); Dose (6 mg/kg/day);.

Q6104: K. Chikama, *et al.* Chronic atypical antipsychotics, but not haloperidol, increase neurogenesis in the hippocampus of adult mouse. *Brain Res* 2017;1676(77-82

ALZET Comments: Haloperidol; quetiapine; aripiprazole; clozapine; olanzapine; risperidone; IP; Mice; 1004; 21 days; Dose (haloperidol 1 mg/kg/d, quetiapine 20 mg/kg/d, aripiprazole 3 mg/kg/d, clozapine 20 mg/kg/d, olanzapine 2 mg/kg/d, risperidone 0.5 mg/kg/d); Controls received mp w/ vehicle; “It is known that osmotic pumps serve some preferable aspect such as to reduce stress to the animals, minimize unwanted experimental variables, and hold the drug concentration constant” pg. 80;.

Q6020: W. R. Crum, *et al.* Chronic exposure to haloperidol and olanzapine leads to common and divergent shape changes in the rat hippocampus in the absence of grey-matter volume loss. *Psychol Med* 2016;46(15):3081-3093

ALZET Comments: Haloperidol, Olanzapine; Cyclodextrin, hydroxypropyl-β-, Ascorbic acid; SC; Rat; 2ML4; 28 days; Controls received mp w/vehicle; animal info (10 weeks old) pumps replaced every 4 weeks; Therapeutic indication (Learning and memory, hippocampus, antipsychotic); Dose (HAL (2 mg/kg perday), or OLZ (10 mg/kg perday);.

Q5144: C. El Hage, *et al.* Antipsychotic treatment leading to dopamine supersensitivity persistently alters nucleus accumbens function. *Neuropharmacology* 2015;99(715-25

ALZET Comments: Haloperidol; Olanzapine; Acetic acid; water; SC; Rat; 2ML2; 15 days; 17 days; Controls received sham surgery; animal info: Male Sprague-Dawley rats; %0.5 or %2 of acetic acid; behavioral testing (trained to associate the delivery of 100 ml water (the unconditioned stimulus; UCS) into a receptacle with a light/tone conditioned stimulus (CS)); Dose: 0.5 mg/kg/day (haloperidol); 10 mg/kg/day (olanzapine).

Q2974: R. H. Schmidt, *et al.* Olanzapine Activates Hepatic Mammalian Target of Rapamycin: New Mechanistic Insight into Metabolic Dysregulation with Atypical Antipsychotic Drugs. *Journal of Pharmacology and Experimental Therapeutics* 2013;347(1):126-135

ALZET Comments: Olanzapine; Saline; SC; Mice; 28 days; Animal info (female, C57Bl/6J, 8 wks old); functionality of mp verified by (oral glucose test); pumps replaced every (2 weeks); post op care (anesthetized with ketamine/xylazine (100/15 mg/kg/ip); antipsychotic.



Q2678: V. Mondelli, *et al.* Haloperidol and olanzapine mediate metabolic abnormalities through different molecular pathways. *TRANSLATIONAL PSYCHIATRY* 2013;3(;):U25-U31

ALZET Comments: Haloperidol; olanzapine; SC; Rat; 2ML4; 8 weeks; Control animals received mp w/ vehicle; animal info (Sprague Dawley, male, 9 wks old, 240-250 g); pumps replaced after 28 days; long-term study.

Q6727: S. Mann, *et al.* Chronic olanzapine administration in rats: effect of route of administration on weight, food intake and body composition. *Pharmacol Biochem Behav* 2013;103(4):717-22

ALZET Comments: Olanzapine; Acetic acid; sodium hydroxide; SC; Rat; 2ML2; 14 days; Dose (7.5 mg/kg/day); 2% acetic acid solution, buffered with 1 N NaOH used; Controls received mp w/ vehicle; animal info (Forty-eight female Sprague–Dawley rats weighing 200–225 g); comparison of IP and SC injections vs mp;

Q2891: A. M. Bedard, *et al.* Prior Haloperidol, but not Olanzapine, Exposure Augments the Pursuit of Reward Cues: Implications for Substance Abuse in Schizophrenia. *SCHIZOPHRENIA BULLETIN* 2013;39(3):692-702

ALZET Comments: Haloperidol; olanzapine; Acetic acid; water, distilled; SC; Rat; 2ML2; 19 Days; Animal info (male, sprague-dawley, 200-225g); half-life (24hr, haloperidol); behavioral testing (lever pressing).

Q1378: A. C. Vernon, *et al.* Effect of Chronic Antipsychotic Treatment on Brain Structure: A Serial Magnetic Resonance Imaging Study with Ex Vivo and Postmortem Confirmation. *Biological Psychiatry* 2011;69(10):936-944

ALZET Comments: Haloperidol; olanzapine; Cyclodextrin, beta-hydroxypropyl; SC; Rat; 2ML4; 8 weeks; Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 240-250 g, 9 wks old); pumps replaced after 28 days; half-life 2.5 hours (p. 937); "MRI-safe" pumps; 20% cyclodextrin used; long-term study.

Q1960: G. Remington, *et al.* Modeling chronic olanzapine exposure using Pharmacological limitations. *Pharmacology Biochemistry and Behavior* 2011;100(1):86-89

ALZET Comments: Olanzapine; Acetic acid, glacial; water, sterile; In vitro; 2ML4; Controls received vehicle; drug levels verified using a liquid-liquid extraction and liquid chromatography; "We suggest that olanzapine administration via (ALZET pumps) represents a viable option for (sub)chronic exposure with the caveats that a) duration be confined to 2 weeks..., and b) consideration be given to strategies in dissolving olanzapine that diminish the risk of oxidation." pg 89; "we strongly agree with van der Zwaal and colleagues (2008) that the issue of drug degradation is not specific to olanzapine, and that it is imperative to establish whether compounds being considered for minipump administration are capable of remaining stable in solution at body temperature."

P9790: M. J. A. Joosen, *et al.* Long-term cognitive deficits accompanied by reduced neurogenesis after soman poisoning. *Neurotoxicology* 2009;30(1):72-80

ALZET Comments: Olanzapine; Acetic acid, glacial; SC; Rat; 2ML4; 4 weeks; Functionality of mp verified by residual volume; animal info (male, Sprague Dawley); stability verified for 4 weeks by electrospray MS/MS.

Q0631: R. Coccorello, *et al.* 30 Days of Continuous Olanzapine Infusion Determines Energy Imbalance, Glucose Intolerance, Insulin Resistance, and Dyslipidemia in Mice. *Journal of Clinical Psychopharmacology* 2009;29(6):576-583

ALZET Comments: Olanzapine; Acetic acid; saline, isotonic; sodium hydroxide; SC; Mice; 2004; 30 days; Controls received mp w/ vehicle; animal info (CD-1, 11 wks old, female); functionality of mp verified by residual volume; "Although (degradation of AAP agents in mini-pump reservoir over time) is a serious concern, significant increases of body weight and food intake were found in female rats33Y35 and mice14 under constant OL infusion via implanted mini-pumps" pg 582.

P9276: N. M. Wallingford, *et al.* Zonisamide prevents olanzapine-associated hyperphagia, weight gain, and elevated blood glucose in rats. *Neuropsychopharmacology* 2008;33(12):2922-2933

ALZET Comments: Olanzapine; Lactic acid; SC; Rat; 2ML2; 12, 14 days; Controls received mp w/ vehicle; comparison of SC injections vs. mp; no stress (see pg. 2923); animal info (female, Sprague Dawley, 230-275 g.); "Mini-pumps were used to chronically deliver OLZ in order to minimize stress-related changes in food intake and body weight associated with daily handling and intraperitoneal (IP) injection." (p. 2923).



P9724: E. M. van der Zwaal, *et al.* Olanzapine-induced weight gain: Chronic infusion using osmotic minipumps does not result in stable plasma levels due to degradation of olanzapine in solution. *European Journal of Pharmacology* 2008;585(1):130-136

ALZET Comments: Olanzapine; Acetic acid, glacial; saline; hydrochloric acid; water, distilled; SC; Rat; 2ML4; 4 weeks; Controls received mp w/vehicle; comparison of SC injections vs. mp; half-life (p.130) "2-5 h in rats"; animal info (male, Wistar); "...at the end of the study, we noticed a strong discoloration of the solution remaining in the minipumps of the olanzapine-treated rats (from bright orange to dark green), as well as a dark precipitate in the pumps interior, which was most notable in the highest dose group" pg 132; "...this suggests that lower plasma levels of olanzapine occur over time only when osmotic minipumps are used and not with daily s.c. injections." pg 135; "Only drugs that are (relatively) stable in a solution at body temperature will result in truly constant drug delivery from an osmotic minipump and, therefore, enable accurate and reliable experimental results." pg 136.

P9427: K. Lykkegaard, *et al.* The once-daily human GLP-1 analog, liraglutide, reduces olanzapine-induced weight gain and glucose intolerance. *SCHIZOPHRENIA RESEARCH* 2008;103(1-3):94-103

ALZET Comments: Olanzapine; PBS; NaOH; lactic acid; SC; Rat; 2ML4; 28 days; Controls received mp w/ vehicle; stress/adverse reaction: (see pg. 96) 6 animals out of 40 developed local irritation/wounds at implantation site; post op. care (carprofen); animal info (male, Sprague Dawley, 240 g.); "we used continuous subcutaneous administration of olanzapine via osmotic minipumps in order to obtain a steady-state of olanzapine with no sedation. The result of this... is an animal model that mimics the side effect profile encountered in schizophrenic patients treated with olanzapine. This may be a valuable, rapid, and inexpensive model for screening." (p. 100).

P9396: A. F. Chintoh, *et al.* Insulin resistance following continuous, chronic olanzapine treatment: An animal model. *SCHIZOPHRENIA RESEARCH* 2008;104(1-3):23-30

ALZET Comments: Olanzapine; Acetic acid; SC; Rat; 2ML4; 4 weeks; Controls received no treatment; dose-response (fig. 2); animal info (male, Sprague Dawley, 225-275 g.); "The choice of administration by osmotic pump acknowledged the rapid metabolism of antipsychotics reported in rodents... and an effort to more closely approximate the human condition by providing sustained exposure." (p. 24); behavioral testing (locomotor activity).

P8434: A. N. Samaha, *et al.* "Breakthrough" dopamine supersensitivity during ongoing antipsychotic treatment leads to treatment failure over time. *Journal of Neuroscience* 2007;27(11):2979-2986

ALZET Comments: Haloperidol; olanzapine; Acetic acid, glacial; water; NaOH; SC; Rat; 2ML2; 2,12,13 days; Controls received mp w/ vehicle; dose-response (fig. 4); comparison of SC injections vs. mp; half-life (p. 2985), 24 hours in humans, 1.4 hours in rats; tolerance; animal info (male, Sprague-Dawley, 225-250 grams); "Animal studies that use a mode of drug administration that more closely mimics clinical antipsychotic treatment (i.e., relatively continuous treatment) might be more informative about the true effects of these drugs in humans." (p. 2985).

P8543: K. Rasmussen, *et al.* The orexin-1 receptor antagonist SB-334867 blocks the effects of antipsychotics on the activity of A9 and A10 dopamine neurons: Implications for antipsychotic therapy. *Neuropsychopharmacology* 2007;32(4):786-792

ALZET Comments: Olanzapine; haloperidol; Water, distilled; sodium hydroxide; lactic acid; SC; Rat; 2ML2; 21 days; Controls received mp w/ vehicle; pumps replaced after 2 weeks; animal info (male, Sprague-Dawley, 280-330 grams).

6. Quetiapine

Q6104: K. Chikama, *et al.* Chronic atypical antipsychotics, but not haloperidol, increase neurogenesis in the hippocampus of adult mouse. *Brain Res* 2017;1676(77-82)

ALZET Comments: Haloperidol; quetiapine; aripiprazole; clozapine; olanzapine; risperidone; IP; Mice; 1004; 21 days; Dose (haloperidol 1 mg/kg/d, quetiapine 20 mg/kg/d, aripiprazole 3 mg/kg/d, clozapine 20 mg/kg/d, olanzapine 2 mg/kg/d, risperidone 0.5 mg/kg/d); Controls received mp w/ vehicle; "It is known that osmotic pumps serve some preferable aspect such as to reduce stress to the animals, minimize unwanted experimental variables, and hold the drug concentration constant" pg. 80;.



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

ALZET Comments: 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.; DMSO; water; IP; mice; 1003D; 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.

P5912: F. I. Tarazi, *et al.* Long-term effects of olanzapine, risperidone, and quetiapine on ionotropic glutamate receptor types: Implications for antipsychotic drug treatment. *Journal of Pharmacology and Experimental Therapeutics* 2003;306(3):1145-1151

ALZET Comments: Olanzapine; risperidone; quetiapine fumarate; SC; Rat; 28 days; Functionality of mp verified by residual volume; antipsychotic drugs.

P6169: S. Kapur, *et al.* Antipsychotic Dosing in Preclinical Models is Often Unrepresentative of the Clinical Condition: A Suggested Solution Based on in Vivo Occupancy. *Journal of Pharmacology and Experimental Therapeutics* 2003;305(2):625-631

ALZET Comments: Haloperidol; olanzapine; risperidone; quetiapine; clozapine; Water; acetic acid, glacial; SC; Rat; 2ML2; 7 days; Plasma levels taken; dose-response (p. 629); comparison of daily injections vs. chronic mp; half-life (p. 626) 2-4 hours; haloperidol and risperidone were dissolved in distilled water; olanzapine, quetiapine and clozapine were dissolved in 1% to 2% acetic acid; great dose information; "we propose that only administration by pump (or administration more than four times a day[injections]) can provide clinical-like occupancies for haloperidol, olanzapine, and risperidone." p. 630.

P5866: F. I. Tarazi, *et al.* Long-term effects of newer antipsychotic drugs on neuronal nitric oxide synthase in rat brain. *NITRIC OXIDE-BIOLOGY AND CHEMISTRY* 2002;7(4):297-300

ALZET Comments: Olanzapine; risperidone; quetiapine fumarate; SC; Rat; 28 days; Controls received mp w/ vehicle; antipsychotic agents.

P5122: F. I. Tarazi, *et al.* Long-term effects of olanzapine, risperidone, and quetiapine on serotonin 1A, 2A and 2C receptors in rat forebrain regions. *Psychopharmacology* 2002;161(263-270

ALZET Comments: Olanzapine; Risperidone; Quetiapine fumarate; SC; Rat; 4 weeks; controls received mp w/ vehicle; functionality of mp verified by residual volume; antipsychotic agents.

7. Remoxipride

P2736: J. Georgieva, *et al.* Neurochemical effects of prolonged treatment with remoxipride as assessed by intracerebral microdialysis in freely moving rats. *Prog. Neuro-Psychopharmacol. Biol. Psychiat* 1994;18(1187-1201

ALZET Comments: Remoxipride HCl; Sodium chloride; SC; Rat; 2002; 14 days; controls received sodium chloride; functionality of mp verified by checking blood levels of drug and determining residual drug amount; comparison of sc injections vs mp; remoxipride is an antipsychotic drug.

P2204: H. Ericson, *et al.* Subchronic treatment of rats with remoxipride fails to modify sigma binding sites in the brain. *Eur. J. Pharmacol. - Mol. Pharmacol. Sect* 1992;226(157-161

ALZET Comments: Remoxipride HCl; Haloperidol; Water; Acetic acid; SC; Rat; 3,14 days; controls received sham operations.

8. Risperidone



Q6104: K. Chikama, *et al.* Chronic atypical antipsychotics, but not haloperidol, increase neurogenesis in the hippocampus of adult mouse. *Brain Res* 2017;1676(77-82

ALZET Comments: Haloperidol; quetiapine; aripiprazole; clozapine; olanzapine; risperidone; IP; Mice; 1004; 21 days; Dose (haloperidol 1 mg/kg/d, quetiapine 20 mg/kg/d, aripiprazole 3 mg/kg/d, clozapine 20 mg/kg/d, olanzapine 2 mg/kg/d, risperidone 0.5 mg/kg/d); Controls received mp w/ vehicle; "It is known that osmotic pumps serve some preferable aspect such as to reduce stress to the animals, minimize unwanted experimental variables, and hold the drug concentration constant" pg. 80;.

Q5070: B. L. Teng, *et al.* Reversal of social deficits by subchronic oxytocin in two autism mouse models. *Neuropharmacology* 2016;105(61-71

ALZET Comments: Risperidone; SC; Mice; 1002; 1007D; 21 days; Controls received mp w/ vehicle; animal info (C58/J); pumps replaced every 14 days; behavioral testing (chamber choice task; acoustic startle test; marble burying assay); "This pump replacement allowed dosage to be adjusted for increased body weight during the chronic risperidone treatment." pg 62-63; Dose (2 mg/kg/day); used clozapine slow-release pellets because of drug solubility for osmotic minipumps (pg.62);.

Q1929: E. C. Muly, *et al.* Relationship between Dose, Drug Levels, and D2 Receptor Occupancy for the Atypical Antipsychotics Risperidone and Paliperidone. *Journal of Pharmacology and Experimental Therapeutics* 2012;341(1):81-89

ALZET Comments: Risperidone; paliperidone; Intragastric; Monkey (macaca mulata); 2 weeks; Animal info (male, Rhesus, 4.2-6.3 years old); pumps replaced; 2-week pump replaced with 4-week pump containing saline for a washout period. 4-week pump was then replaced with 2-week pump to continue dosing.

Q1321: A. Secher, *et al.* Risperidone Treatment Increases CB(1) Receptor Binding in Rat Brain. *Neuroendocrinology* 2010;91(2):155-168

ALZET Comments: Risperidone; Cyclodextrin, hydroxypropyl beta; SC; Rat; 2ML4; 28 days; Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 180-200 g); post op. care (Baytril); stress/adverse reaction: "infections" (see pg. 156); 20% cyclodextrin used; "We chose to administer risperidone through osmotic minipumps to ensure steady-state plasma levels and avoid plasma fluctuations observed with drug injections." pg 156.

P8027: E. O'Brien, *et al.* Effects of chronic risperidone treatment on the striatal protein profiles in rats. *Brain Research* 2006;1113(24-32

ALZET Comments: Risperidone; Water, sterile; acetic acid; sodium hydroxide; SC; Rat; 2ML4; 28 days; Controls received mp w/ vehicle; animal info (Sprague-Dawley, male, 357 grams; 11 weeks old); behavioral study.

P8279: E. J. D. Lin, *et al.* Distinct endocrine effects of chronic haloperidol or risperidone administration in male rats. *Neuropharmacology* 2006;51(7-8):1129-1136

ALZET Comments: Haloperidol; risperidone; Acetic acid; SC; Rat; 2ML4; 28 days; Controls received mp w/ vehicle; no stress (see pg. 1131); half-life (p. 1131) 4-6 times shorter in rodents than in humans; post op. care (bupivacaine); animal info (male, Sprague-Dawley, 9-10 weeks old, 280-430 grams); "This dosing regimen also takes into consideration the reported 4-6 times shorter half-life of antipsychotic drugs in rodents than humans and highlights the advantage of using minipumps in the present study for continuous drug administration to achieve receptor occupancies comparable to clinical use in humans." (p. 1131).

P5912: F. I. Tarazi, *et al.* Long-term effects of olanzapine, risperidone, and quetiapine on ionotropic glutamate receptor types: Implications for antipsychotic drug treatment. *Journal of Pharmacology and Experimental Therapeutics* 2003;306(3):1145-1151

ALZET Comments: Olanzapine; risperidone; quetiapine fumerate; SC; Rat; 28 days; Functionality of mp verified by residual volume; antipsychotic drugs.

P6169: S. Kapur, *et al.* Antipsychotic Dosing in Preclinical Models is Often Unrepresentative of the Clinical Condition: A Suggested Solution Based on in Vivo Occupancy. *Journal of Pharmacology and Experimental Therapeutics* 2003;305(2):625-631



ALZET Comments: Haloperidol; olanzapine; risperidone; quetiapine; clozapine; Water; acetic acid, glacial; SC; Rat; 2ML2; 7 days; Plasma levels taken; dose-response (p. 629); comparison of daily injections vs. chronic mp; half-life (p. 626) 2-4 hours; haloperidol and risperidone were dissolved in distilled water; olanzapine, quetiapine and clozapine were dissolved in 1% to 2% acetic acid; great dose information; "we propose that only administration by pump (or administration more than four times a day[injections]) can provide clinical-like occupancies for haloperidol, olanzapine, and risperidone." p. 630.

P5866: F. I. Tarazi, *et al.* Long-term effects of newer antipsychotic drugs on neuronal nitric oxide synthase in rat brain. NITRIC OXIDE-BIOLOGY AND CHEMISTRY 2002;7(4):297-300

ALZET Comments: Olanzapine; risperidone; quetiapine fumarate; SC; Rat; 28 days; Controls received mp w/ vehicle; antipsychotic agents.

P5122: F. I. Tarazi, *et al.* Long-term effects of olanzapine, risperidone, and quetiapine on serotonin 1A, 2A and 2C receptors in rat forebrain regions. Psychopharmacology 2002;161(263-270

ALZET Comments: Olanzapine; Risperidone; Quetiapine fumarate; SC; Rat; 4 weeks; controls received mp w/ vehicle; functionality of mp verified by residual volume; antipsychotic agents.

9. Spiperone

P1288: T. S. Shippenberg, *et al.* Motivational effects of opioids; influence of D-1 versus D-2 receptors antagonists. Eur. J. Pharmacol 1988;151(233-242

ALZET Comments: Spiperone; SCH-23390; DMSO; Water; SC; Rat; 2001; 2ML1; 7 days; functionality of mp verified after delivery; dopamine antagonist.

10. Sulpiride

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. Eur. J. Pharmacol 1992;218(219-227

ALZET Comments: Quinpirole HCl; Sulpiride; Triazolam; Ascorbic acid; DMSO; SC; mice; 2001; 6 days; Quinpirole is a dopamine agonist; antidepressant; stability verified in vitro for 7 days.

P1444: H. Ueda. Time course study of changes in the activity of rats during intraventricular infusion of 6-hydroxydopamine, haloperidol and sulpiride: a study of the relationship between an origin of the negative symptoms in schizophrenia and catecholamines. J. Iwate Med. Assoc 1988;40(3):385-398

ALZET Comments: Dopamine, 6-hydroxy-; Haloperidol; Sulpiride; CSF/CNS; Rat; 8 days; Japanese, English abstract.

P0630: B. Costall, *et al.* The continuity of dopamine receptor antagonism can dictate the long-term behavioural consequences of a mesolimbic infusion of dopamine. Neuropharmacology 1985;2(3):193-197

ALZET Comments: Dopamine HCl; Sulpiride; Nitrogen; Sodium metabisulfite; CSF/CNS (nucleus accumbens); IP; Rat; 13 days; mp model not stated; comparison of Sulp ip injec vs. mp infusion; 2 mp/rat - bilateral infusion; mp primed overnight; vehicles listed used w/DOP; concomitant Sulp admin. ip.

11. Trifluoperazine

P0144: G. G. Dougherty Jr, *et al.* Amphetamine behavioral toxicity: rotational behavior after chronic intrastriatal infusion. Biol. Psychiatry 1981;16(5):479-488

ALZET Comments: Trifluoperazine; Amphetamine sulfate, d-; Saline; CSF/CNS (corpus striatum); Rat; 7 days; caudate putamen.

