



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

**Chlorpromazine**

**P2717:** P. N. M. Konings, *et al.* Chronic haloperidol and chlorpromazine treatment alters in vitro B-endorphin metabolism in rat brain. *European Journal of Pharmacology* 1990;191(115-128

**Agents:** Haloperidol; Chlorpromazine **Vehicle:** Saline, sterile; **Route:** SC; **Species:** Rat; **Pump:** 2001; 2ML1; **Duration:** 8 days;  
**ALZET Comments:** 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

**Agents:** Chlorpromazine HCl **Vehicle:** Not Stated; **Route:** IP; SC; **Species:** Mice; **Pump:** 2002; **Duration:** 7, 10 days;  
**ALZET Comments:** 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

**Agents:** Chlorpromazine; Haloperidol **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2001; 2ML1; **Duration:** 8 days;  
**ALZET Comments:** 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. *Annals of the New York Academy of Sciences* 1985;448(601-603

**Agents:** Flupenthixol, cis-; Flupenthixol, trans-; Amitriptyline; Amphetamine; Atropine; Chlorpromazine; Clozapine; Fluphenazine; Haloperidol; Morphine; Prazosin **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 2 weeks;

**ALZET Comments:** 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. *European Journal of Pharmacology* 1984;100(249-251

**Agents:** Chlorpromazine; haloperidol; phenobarbital; promethazine **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** 8 days;

**ALZET Comments:** Comparison of agents effects

**P0385:** P. Frey. Cholecystokinin octapeptide levels in rat brain are changed after subchronic neuroleptic treatment. *European Journal of Pharmacology* 1983;95(87-92

**Agents:** Chlorpromazine; Clozapine; Haloperidol **Vehicle:** HCl; Saline; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; 2ML4; **Duration:** 2, 4 weeks;

**ALZET Comments:** omparison 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

**Clozapine (2017-Present)**

**Q10342:** H. Sotoyama, *et al.* Resting-state dopaminergic cell firing in the ventral tegmental area negatively regulates affiliative social interactions in a developmental animal model of schizophrenia. *Translational Psychiatry* 2021;11(1):236

**Agents:** Clozapine-N-oxide **Vehicle:** DMSO; **Route:** SC; **Species:** Rat; **Pump:** 2002; **Duration:** 10 days; 13 days;

**ALZET Comments:** Dose: (1.5 mg/kg/day); Controls received mp w/ vehicle; animal info: EGF model rats; (postnatal week 10–12); behavioral testing: locomotion test in an open field chamber; social interaction; Clozapine-N-oxide aka (CNO); neurodegenerative



**Q9507:** P. B. Tran, *et al.* Prolonged chemogenetic inhibition of nociceptors in a murine surgical model of osteoarthritis: effects on immune responses in dorsal root ganglia. *Osteoarthritis and Cartilage* 2020;28(**Agents:** Clozapine-N-oxide **Vehicle:** Saline; **Route:** Abdomen; **Species:** Mice; **Pump:** Not Stated; **Duration:** 6 weeks;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (10-week old male NaV1.8-Pdi C57BL/6 mice); Clozapine-N-oxide aka CNO; immunology;

**Q8840:** G. A. Rodriguez, *et al.* Chemogenetic attenuation of neuronal activity in the entorhinal cortex reduces Abeta and tau pathology in the hippocampus. *PLOS Biology* 2020;18(8):e3000851

**Agents:** Clozapine-N-Oxide **Vehicle:** DMSO; **Route:** CSF/CNS; **Species:** Mice; **Pump:** 2006; **Duration:** 6 weeks;

**ALZET Comments:** Dose (1 mg/kg/day); 0.05% DMSO used; Clozapine-N-Oxide aka CNO ; neurodegenerative (Alzheimer's Disease);

**Q8862:** J. Jiang, *et al.* Activation of hypothalamic AgRP and POMC neurons evokes disparate sympathetic and cardiovascular responses. *American Journal of Physiology and Heart Circulatory Physiology* 2020;319(5):H1069-H1077

**Agents:** Clozapine-N-Oxide **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 1007D; **Duration:** Not Stated;

**ALZET Comments:** Dose (2 mg/kg/day); Controls received mp w/ vehicle; animal info (Ten- to twelve-week- old-male mice); Clozapine-N-oxide aka CNO; cardiovascular;

**Q9216:** E. A. Dulka, *et al.* Chemogenetic Suppression of GnRH Neurons during Pubertal Development Can Alter Adult GnRH Neuron Firing Rate and Reproductive Parameters in Female Mice. *eNeuro* 2020;7(3):

**Agents:** Clozapine-N-oxide **Vehicle:** DMSO; **Route:** SC; **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;

**ALZET Comments:** Dose (0.3 mg/kg); 2.75% DMSO used; Controls received mp w/ vehicle; animal info (Transgenic mice (C57Bl6/J), 2 weeks old); Clozapine-N-oxide aka CNO; dependence;

**Q9077:** B. Stutz, *et al.* Dopamine neuronal protection in the mouse Substantia nigra by GHSR is independent of electric activity. *Molecular Metabolism* 2019;24(120-138

**Agents:** Clozapine-N-oxide; Salvinorin B **Vehicle:** DMSO; Saline; **Route:** SC; **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;

**ALZET Comments:** Dose (CNO- 0.3 mg/kg or Salvinorin B- 5 mg/kg); Controls received mp w/ vehicle; animal info (); Clozapine-N-oxide aka CNO, excitatory DREADD agonist, Salvinorin B aka inhibitory DREADD agonist ; neurodegenerative (Parkinson's Disease);

**Q7611:** A. Obeidat, *et al.* Nociceptive neuroplasticity of the murine knee joint precedes severe structural joint damage in a surgical model of OA. *Osteoarthritis and Cartilage* 2019;27(**Agents:** Clozapine N-oxide **Vehicle:** Vehicle; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 6 weeks;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (10 weeks old, Male ); behavioral testing (Pressure Application Measurement, Up-Down staircase Test); Clozapine N-Oxide aka CNO; enzyme inhibitor (Nociceptor inhibitor); dependence;

**Q7989:** D. Esen-Sehir, *et al.* Establishing an effective dose for chronic intracerebroventricular administration of clozapine in mice. *Acta Neuropsychiatr* 2019;31(6):305-315

**Agents:** Clozapine **Vehicle:** Saline; **Route:** CSF/CNS (lateral ventricles); **Species:** Mice; **Pump:** 2006; **Duration:** 3 weeks;

**ALZET Comments:** Dose (0,12.5,25, or 50 ug/day); Controls received mp w/ vehicle; animal info (C57BL/6J); ALZET brain infusion kit 3 used; Brain coordinates (AP -0.5 mm, ML ± 1.4mm and DV 3mm from the skull surface); neurodegenerative ();

**Q7925:** N. D. Jayaraj, *et al.* Reducing CXCR4-mediated nociceptor hyperexcitability reverses painful diabetic neuropathy. *J Clin Invest* 2018;128(6):2205-2225

**Agents:** Clozapine-N-Oxide **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 4 weeks;

**ALZET Comments:** Dose (10 mg/kg/day); Controls received mp w/ vehicle; Clozapine-N-oxide aka CNO; diabetes;

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

**Agents:** Clozapine-N-oxide **Vehicle:** Saline; **Route:** SC; **Species:** Mice (neonate); **Pump:** 1007D; **Duration:** 7 days;

**ALZET Comments:** 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 Research* 2017;1676(77-82)

**Agents:** Haloperidol; quetiapine; aripiprazole; clozapine; olanzapine; risperidone **Vehicle:** Not Stated; **Route:** IP; **Species:** Mice; **Pump:** 1004; **Duration:** 21 days;

**ALZET Comments:** 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;

### Fluphenazine

**P0908:** P. Frey. Changes in cholecystokinin content in rat brain after subchronic treatment with neuroleptics. *Annals of the New York Academy of Sciences* 1985;448(601-603)

**Agents:** Flupenthixol, cis-; Flupenthixol, trans-; Amitriptyline; Amphetamine; Atropine; Chlorpromazine; Clozapine; Fluphenazine; Haloperidol; Morphine; Prazosin **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 2 weeks;

**ALZET Comments:** mp model not stated; comparison of sc injections vs. mp infusion; antihypertensive

### Haloperidol (2016-Present)

**Q10327:** A. Servonnet, *et al.* Dopaminergic mechanisms underlying the expression of antipsychotic-induced dopamine supersensitivity in rats. *Neuropharmacology* 2021;197(108747)

**Agents:** Haloperidol **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 17 days;

**ALZET Comments:** Dose: (0.5 mg/kg/day); Controls received mp w/o vehicle; (sham surgery) animal info: Male Sprague-Dawley rats (200–275 g); dependence;

**Q9312:** M. Kimura, *et al.* Effects of repeated electroconvulsive shocks on dopamine supersensitivity psychosis model rats. *Schizophrenia Research* 2021;228(1-6)

**Agents:** Haloperidol **Vehicle:** Glacial acetic acid; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 14 days;

**ALZET Comments:** Dose (0.75 mg/kg/day); 2% Glacial Acetic Acid used; Controls received mp w/ vehicle; animal info (twelve-week-old male Wistar rats, 240-270 g); Haloperidol aka HAL; ischemia (Schizophrenia);

**Q9311:** M. Kimura, *et al.* Reduction of dopamine and glycogen synthase kinase-3 signaling in rat striatum after continuous administration of haloperidol. *Pharmacology, Biochemistry and Behavior* 2021;202(173114)

**Agents:** Haloperidol **Vehicle:** Glacial acetic acid; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 14 days;

**ALZET Comments:** Dose (0.75 mg/kg/day); Controls received mp w/ vehicle; animal info (twelve-week-old male Wistar rats, 240-260 g); Haloperidol aka HAL; neurodegenerative (Schizophrenia);

**Q9257:** E. F. Halff, *et al.* Effects of chronic exposure to haloperidol, olanzapine or lithium on SV2A and NLGN synaptic puncta in the rat frontal cortex. *Behavioural Brain Research* 2021;405(113203)

**Agents:** Haloperidol; Lithium Chloride; Olanzapine **Vehicle:** Cyclodextrin, 2-Hydroxypropyl-B-; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 28 days;

**ALZET Comments:** Dose (0.5 mg/kg/day Haloperidol; 2 mmol/L/kg/day Lithium Chloride; 7.5 mg/kg/day Olanzapine); Controls received mp w/ vehicle; animal info (Male Sprague-Dawley rats, 220-270 g, 6-10 weeks old); Haloperidol aka HAL, Olanzapine aka OLZ, Lithium Chloride aka Li; neurodegenerative (Schizophrenia);



**Q8921:** E. C. Onwordi, *et al.* Synaptic density marker SV2A is reduced in schizophrenia patients and unaffected by antipsychotics in rats. *Nature Communications* 2020;11(1):246

**Agents:** Haloperidol; Olanzapine **Vehicle:** Cyclodextrin, B-Hydroxypropyl; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 28 days;

**ALZET Comments:** Dose (0.5 or 2 mg/kg/day ; 7.5 mg/kg/day); 20% B-Hydroxypropylcyclodextrin used; Controls received mp w/ vehicle; animal info (Male Sprague-Dawley rats, body weight 240–270 g, 6–10 weeks of age); Haloperidol aka HAL; Olanzapine aka OLZ; neurodegenerative (Schizophrenia);

**Q8240:** T. A. Lanz, *et al.* Postmortem transcriptional profiling reveals widespread increase in inflammation in schizophrenia: a comparison of prefrontal cortex, striatum, and hippocampus among matched tetrads of controls with subjects diagnosed with schizophrenia, bipolar or major depressive disorder. *Transl Psychiatry* 2019;9(1):151

**Agents:** Haloperidol or Risperidone **Vehicle:** Acetic Acid; **Route:** CSF/CNS; **Species:** Rat; **Pump:** Not stated; **Duration:** 21 days;

**ALZET Comments:** Dose (haloperidol-0.25 mg/kg/day or risperidone-5 mg/kg/day); 1% Acetic Acid used; Controls received mp w/ vehicle; animal info (2 months old, Sprague Dawley, Male); neurodegenerative (Psychiatric Disorder);

**Q7882:** T. C. Uzuneser, *et al.* Schizophrenia dimension-specific antipsychotic drug action and failure in amphetamine-sensitized psychotic-like rats. *European Neuropsychopharmacology* 2018;28(12):1382-1393

**Agents:** haloperidol **Vehicle:** water, distilled, ascorbic acid and cyclodextrin buffered; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 14 days;

**ALZET Comments:** Dose (0.05, 0.5 mg/kg/day); distilled water containing 0.3% ascorbic acid / 10% cyclodextrin used; Controls received mp w/ vehicle; animal info (male, Sprague-Dawley, 330-380 g); behavioral testing (AMPH-induced locomotion, within-session habituation, acoustic startle response, novel object recognition); HAL is an antipsychotic drug that targets the postsynaptic D2 receptors; schizophrenia induced by amphetamine-sensitization-induced psychosis model;

**Q7829:** T. Hashimoto, *et al.* Lack of dopamine supersensitivity in rats after chronic administration of blonanserin: Comparison with haloperidol. *European Journal of Pharmacology* 2018;830(26-32)

**Agents:** Haloperidol; PG-01037 dihydrochloride **Vehicle:** Acetic Acid, glacial; NaOH; Tween 80 Buffered; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 14 days;

**ALZET Comments:** Dose ((haloperidol 0.75 mg/kg/day), PG-01037 (0.6 mg/kg/day)); 2% glacial acetic acid/H<sub>2</sub>O solution (pH 3.6 w/ NaOH) with 0.5% Tween 80 used; Controls received mp w/ vehicle; animal info (7 weeks, male, Wistar); post op. care (antibiotic treatment; identity not stated); behavioral testing (Quinpirole-induced hyperlocomotion); comparison of oral administration of haloperidol vs mp; PG-01037 is a selective dopamine D3 antagonist; minipumps were removed 14 days after implantation. "In this study, we were unable to use an osmotic pump for continuous administration of blonanserin due to poor solubility in the vehicle used for haloperidol." p.31;

**Q7821:** D. Groos, *et al.* Chronic antipsychotic treatment targets GIRK current suppression, loss of long-term synaptic depression and behavioural sensitization in a mouse model of amphetamine psychosis. *J Psychopharmacol* 2018;269881118812235

**Agents:** haloperidol; olanzapine **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;

**ALZET Comments:** "Dose ((Hal 0.5 mg/kg/d), (Ola 10 mg/kg/d)); Controls received mp w/ vehicle; animal info (6-12 weeks, male, C57BL/6 or homo- and heterozygous C57Bl6-D2eGFP); behavioral testing (TruScan open field); Resultant plasma level ((Hal 5.85 ± 0.27 ng/mL), (Ola 45.93 ± 5.72 ng/mL)); haloperidol (Hal) and olanzapine (Ola) are antipsychotic drugs; "Furthermore, in animal studies, APDs were often administered with regimens that fail to achieve the high D2R occupancy (>70%) required to yield therapeutic benefits (Farde *et al.*, 1988; Kapur and Mamo, 2003; Kapur *et al.*, 2003). To overcome such limitations, we delivered haloperidol or olanzapine via implanted osmotic mini-pumps, which offers a reliable method to obtain clinically meaningful levels of D2R blockade (Amato *et al.*, 2011; Amato *et al.*, 2018; Samaha *et al.*, 2007, 2008)." pg.75 ; Vehicle control used but identity not stated. Brain concentration of agents include ((Hal 3.42 ± 0.42 ng/g), (Ola 26.32 ± 1.78 ng/g)); Therapeutic indication (chronic Hal- and Ola-treatments were able to at least partially reverse the AMPH-induced psychotic state by reversing the effects of amphetamines on reducing surface expression of GIRK channels); "



**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

**Agents:** Haloperidol, olanzapine **Vehicle:** Cyclodextrin, 2-Hydroxypropyl-B-; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 8 weeks;

**ALZET Comments:** 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

**Agents:** Haloperidol **Vehicle:** Acetic acid, water; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** Not Stated;

**ALZET Comments:** 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

**Agents:** Haloperidol-Hcl **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 2004; **Duration:** 14 days;

**ALZET Comments:** 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

**Agents:** Haloperidol **Vehicle:** Acetic acid, glacial; Water; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 14 days;

**ALZET Comments:** Dose (0.75 mg/kg/day); 2% glacial acetic acid/H<sub>2</sub>O 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 Research* 2017;1676(77-82

**Agents:** Haloperidol; quetiapine; aripiprazole; clozapine; olanzapine; risperidone **Vehicle:** Not Stated; **Route:** IP; **Species:** Mice; **Pump:** 1004; **Duration:** 21 days;

**ALZET Comments:** 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

**Agents:** Haloperidol **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2002; **Duration:** 14 days;

**ALZET Comments:** 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

**Agents:** Haloperidol **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2002; **Duration:** 14 days;

**ALZET Comments:** 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

**Agents:** Haloperidol, Olanzapine **Vehicle:** Cyclodextrin, hydroxypropyl- $\beta$ -, Ascorbic acid; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 28 days;

**ALZET Comments:** 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));

### Olanzapine (2017-Present)

**Q9257:** E. F. Halff, *et al.* Effects of chronic exposure to haloperidol, olanzapine or lithium on SV2A and NLGN synaptic puncta in the rat frontal cortex. *Behavioural Brain Research* 2021;405(113203)

**Agents:** Haloperidol; Lithium Chloride; Olanzapine **Vehicle:** Cyclodextrin, 2-Hydroxypropyl-B-; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 28 days;

**ALZET Comments:** Dose (0.5 mg/kg/day Haloperidol; 2 mmol/L/kg/day Lithium Chloride; 7.5 mg/kg/day Olanzapine); Controls received mp w/ vehicle; animal info (Male Sprague-Dawley rats, 220-270 g, 6-10 weeks old); Haloperidol aka HAL, Olanzapine aka OLZ, Lithium Chloride aka Li; neurodegenerative (Schizophrenia);

**Q8921:** E. C. Onwordi, *et al.* Synaptic density marker SV2A is reduced in schizophrenia patients and unaffected by antipsychotics in rats. *Nature Communications* 2020;11(1):246

**Agents:** Haloperidol; Olanzapine **Vehicle:** Cyclodextrin, B-Hydroxypropyl; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 28 days;

**ALZET Comments:** Dose (0.5 or 2 mg/kg/day ; 7.5 mg/kg/day); 20% B-Hydroxypropylcyclodextrin used; Controls received mp w/ vehicle; animal info (Male Sprague-Dawley rats, body weight 240–270 g, 6–10 weeks of age); Haloperidol aka HAL; Olanzapine aka OLZ; neurodegenerative (Schizophrenia);

**Q8854:** R. H. Isaacson, *et al.* Olanzapine-induced liver injury in mice: aggravation by high-fat diet and protection with sulforaphane. *Journal of Nutritional Biochemistry* 2020;81(108399)

**Agents:** Olanzapine **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 4 weeks;

**ALZET Comments:** Dose (8 mg/kg/d); Controls received mp w/ vehicle; animal info (Female C57BL/6 J mice (8 weeks old)); pumps replaced every 2 weeks; dependence;

**Q7450:** J. Cunningham, *et al.* F160. Samidorphan, an Opioid Receptor Antagonist, Mitigates Olanzapine-Induced Metabolic Dysfunction in Female Rats. *Biological Psychiatry* 2019;85(10):

**Agents:** Olanzapine, Samidorphan **Vehicle:** Not stated; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 2 days;

**ALZET Comments:** animal info (Female,); Olanzapine aka OLZ, Samidorphan aka SAM; dependence;

**Q7821:** D. Groos, *et al.* Chronic antipsychotic treatment targets GIRK current suppression, loss of long-term synaptic depression and behavioural sensitization in a mouse model of amphetamine psychosis. *J Psychopharmacol* 2018;269881118812235

**Agents:** haloperidol; olanzapine **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;

**ALZET Comments:** "Dose ((Hal 0.5 mg/kg/d), (Ola 10 mg/kg/d)); Controls received mp w/ vehicle; animal info (6-12 weeks, male, C57BL/6 or homo- and heterozygous C57Bl6-D2eGFP); behavioral testing (TruScan open field); Resultant plasma level ((Hal 5.85  $\pm$  0.27 ng/mL), (Ola 45.93  $\pm$  5.72 ng/mL)); haloperidol (Hal) and olanzapine (Ola) are antipsychotic drugs; "Furthermore, in animal studies, APDs were often administered with regimens that fail to achieve the high D2R occupancy (>70%) required to yield therapeutic benefits (Farde *et al.*, 1988; Kapur and Mamo, 2003; Kapur *et al.*, 2003). To overcome such limitations, we delivered haloperidol or olanzapine via implanted osmotic mini-pumps, which offers a reliable method to obtain clinically meaningful levels of D2R blockade (Amato *et al.*, 2011; Amato *et al.*, 2018; Samaha *et al.*, 2007, 2008)." pg.75 ; Vehicle control used but identity not stated. Brain concentration of agents include ((Hal 3.42  $\pm$  0.42 ng/g), (Ola 26.32  $\pm$  1.78 ng/g)); Therapeutic indication (chronic Hal- and Ola-treatments were able to at least partially reverse the AMPH-induced psychotic state by reversing the effects of amphetamines on reducing surface expression of GIRK channels); "



**Q7793:** E. Courty, *et al.* Antenatal antipsychotic exposure induces multigenerational and gender-specific programming of adiposity and glucose tolerance in adult mouse offspring. *Diabetes & Metabolism* 2018;44(3):281-291

**Agents:** Olanzapine **Vehicle:** DMSO; Ethanol; Propylene Glycol; **Route:** SC; **Species:** Mice; **Pump:** 1002; **Duration:** 2 weeks; **ALZET Comments:** Dose (4 mg/kg/day); Controls received mp w/ vehicle; animal info (Female, Pregnant); dependence; 42.5% DMSO, 42.5% propylene glycol and 15% ethanol used;

**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

**Agents:** Haloperidol, olanzapine **Vehicle:** Cyclodextrin, 2-Hydroxypropyl-B-; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 8 weeks;

**ALZET Comments:** 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

**Agents:** Olanzapine **Vehicle:** Lactic acid; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** Not Stated;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (Sprague Dawley , female); half-life (2.5 hours) ; Therapeutic indication (Antipsychotic drugs); Dose (6 mg/kg/day);

## Quetiapine

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

**Agents:** Haloperidol; quetiapine; aripiprazole; clozapine; olanzapine; risperidone **Route:** IP; **Species:** Mice; **Pump:** 1004; **Duration:** 21 days;

**ALZET Comments:** 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

**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.

**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

**Agents:** Olanzapine; risperidone; quetiapine fumerate **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Duration:** 28 days;

**ALZET Comments:** 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  
**Agents:** Haloperidol; olanzapine; risperidone; quetiapine; clozapine **Vehicle:** Water; acetic acid, glacial; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 7 days;

**ALZET Comments:** 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

**Agents:** Olanzapine; risperidone; quetiapine fumerate **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 28 days;

**ALZET Comments:** 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)

**Agents:** Olanzapine; Risperidone; Quetiapine fumarate **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 4 weeks;

**ALZET Comments:** controls received mp w/ vehicle; functionality of mp verified by residual volume; antipsychotic agents

### 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)

**Agents:** Remoxipride HCl **Vehicle:** Sodium chloride; **Route:** SC; **Species:** Rat; **Pump:** 2002; **Duration:** 14 days;

**ALZET Comments:** 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. *European Journal of Pharmacology* 1992;226(157-161)

**Agents:** Remoxipride HCl; Haloperidol **Vehicle:** Water; Acetic acid; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 3,14 days;

**ALZET Comments:** controls received sham operations

### Risperidone (2010-Present)

**Q8240:** T. A. Lanz, *et al.* Postmortem transcriptional profiling reveals widespread increase in inflammation in schizophrenia: a comparison of prefrontal cortex, striatum, and hippocampus among matched tetrads of controls with subjects diagnosed with schizophrenia, bipolar or major depressive disorder. *Transl Psychiatry* 2019;9(1):151

**Agents:** Haloperidol or Risperidone **Vehicle:** Acetic Acid; **Route:** CSF/CNS; **Species:** Rat; **Pump:** Not stated; **Duration:** 21 days;

**ALZET Comments:** Dose (haloperidol-0.25 mg/kg/day or risperidone-5 mg/kg/day); 1% Acetic Acid used; Controls received mp w/ vehicle; animal info (2 months old, Sprague Dawley, Male); neurodegenerative (Psychiatric Disorder);

**Q8159:** N. Amada, *et al.* Brexpiprazole has a low risk of dopamine D2 receptor sensitization and inhibits rebound phenomena related to D2 and serotonin 5-HT2A receptors in rats. *Neuropsychopharmacol Rep* 2019;39(4):279-288

**Agents:** Risperidone **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 22 days;

**ALZET Comments:** Dose (1.5 mg/kg/d); animal info (male Wistar rats, 7 weeks old); neurodegenerative (schizophrenia thought to be caused by dopamine D2 receptor sensitization);



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

**Agents:** Haloperidol; quetiapine; aripiprazole; clozapine; olanzapine; risperidone **Vehicle:** Not Stated; **Route:** IP; **Species:** Mice; **Pump:** 1004; **Duration:** 21 days;

**ALZET Comments:** 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)

**Agents:** Risperidone **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 1002; 1007D; **Duration:** 21 days;

**ALZET Comments:** 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

**Agents:** Risperidone; paliperidone **Vehicle:** Not Stated; **Route:** Intragastric; **Species:** Monkey (*macaca mulata*); **Pump:** Not Stated; **Duration:** 2 weeks;

**ALZET Comments:** 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

**Agents:** Risperidone **Vehicle:** Cyclodextrin, hydroxypropyl beta; **Route:** SC; **Species:** Rat; **Pump:** 2ML4; **Duration:** 28 days;

**ALZET Comments:** 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

### Spiiperone

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

**Agents:** Spiiperone; SCH-23390 **Vehicle:** DMSO; Water; **Route:** SC; **Species:** Rat; **Pump:** 2001; 2ML1; **Duration:** 7 days;

**ALZET Comments:** functionality of mp verified after delivery; dopamine antagonist

### 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. *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

**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

**Agents:** Dopamine, 6-hydroxy-; Haloperidol; Sulpiride **Vehicle:** Not Stated; **Route:** CSF/CNS; **Species:** Rat; **Pump:** Not Stated; **Duration:** 8 days;

**ALZET Comments:** 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

**Agents:** Dopamine HCl; Sulpiride **Vehicle:** Nitrogen; Sodium metabisulfite; **Route:** CSF/CNS (nucleus accumbens); IP; **Species:** Rat; **Pump:** Not Stated; **Duration:** 13 days;

**ALZET Comments:** 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

### Trifluoperazine

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

**Agents:** Trifluoperazine; Amphetamine sulfate, d- **Vehicle:** Saline; **Route:** CSF/CNS (corpus striatum); **Species:** Rat; **Pump:** Not Stated; **Duration:** 7 days;

**ALZET Comments:** caudate putamen