Antipsychotic dosing in preclinical models is often unrepresentative of the clinical condition – a suggested solution based on *in vivo* occupancy.

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Running title: **Dosing of Antipsychotics in Animal Models**

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List of Abbreviations:

C.L.: confidence limits

 i.v.: intravenous

s.c.: subcutaneous

SEM: standard error of the mean.

ABSTRACT

What is the appropriate dose of an antipsychotic in an animal model? The literature reveals no standard rationale across studies. This study was designed to use *in vivo* dopamine D_2 receptor occupancy as a cross-species principle for deriving clinically-comparable doses for animal models. The relationship between dose, plasma levels and *in-vivo* dopamine D_2 receptor occupancy was established in rats for a range of doses administered as a single dose or multiple doses [daily injections or osmotic minipump infusions] for five of the most commonly used antipsychotics. As a single dose, haloperidol 0.04-0.08mg/kg, clozapine 5-15mg/kg, olanzapine 1-2mg/kg, risperidone 0.5-1mg/kg and quetiapine 10-25mg/kg – reached clinically-comparable occupancies. However, when these "optimal" single doses were administered as multiple doses, either by injection or by a mini-pump, it led to no or inappropriately low trough (24 hour) occupancies. This discrepancy arises because the half-life of antipsychotics in rodents is 4-6 times faster than in humans. Only when doses *five* times higher than the optimal single dose were administered by pump were clinically-comparable occupancies obtained (e.g. haloperidol 0.25mg/kg/d; olanzapine 7.5mg/kg/d). This could not be achieved for clozapine or quetiapine due to solubility and administration constraints. The study provides a rationale as well as clinically-comparable dosing regimens for animal studies and raises questions about the inferences drawn from previous studies which have used doses unrepresentative of the clinical situation.

A search of the Medline database for the terms "antipsychotic or neuroleptic" and "human" reveals 38,000 articles since the 1960's. When the term human is replaced with "animal", the search returns an almost equal number of articles, 34,000 articles. Studies of antipsychotics in animal models are almost as important a scientific enterprise as their study in humans (Lipska and Weinberger, 2000). In humans, the antipsychotics are effective in treating psychosis in a very narrow therapeutic dose range – a dose range that can be determined only in careful clinical trials of psychosis. Since psychosis per se cannot be modeled or measured in animals, what is the representative dose of antipsychotics in animal models?

A sampling of published papers shows three different approaches to this question (Kapur et al., 2000a). Most commonly, the dose of an antipsychotic is listed in the methods section without any justification for the particular choice. Less commonly, authors refer to previous papers (which may have been as arbitrary in their choice) as their reason to choose a particular dose. Least commonly, one finds a reasoned discussion of the choice of dose or finds a complete dose-response experiment. Thus, despite the critical importance of dosing, most of the studies in the literature have neglected this issue, leading in some instances to confounding and misleading conclusions (Kapur et al., 2000a).

Determination of the correct antipsychotic dose in animals is complicated by several factors. First, the symptoms that these drugs treat in patients – delusions and

hallucinations, cannot be modeled by themselves in animals (Lipska and Weinberger, 2000). What is used instead are a series of paradigms with predictive-validity (e.g. amphetamine-induced hyperlocomotion, stereotypy, sensorimotor gating etc.) (Arnt et al., 1997). However, just because an antipsychotic "works" in one of these predictive models, it does not mean that the dose at which it does so is representative of the clinical condition. Secondly, most of the currently popular atypical antipsychotics block multiple receptors with affinities varying by two orders of magnitude (Schotte et al., 1996). A classic example is clozapine which blocks more than a dozen different receptors with affinities ranging from <1 nM to >100 nM. As a result of this non-specificity, when used at different doses, the drug produces a very different pharmacodynamic profile. Finally, antipsychotics in the clinical situation are used under multiple-dosing conditions. Whereas the half-life of these antipsychotics in humans is usually 12-24 hours, their half-life in rodents tends to be 2-4 hours. Thus if the human practice of once-a-day or twice-a-day dosing is emulated in rodents, the rat receives a dose only once every four to eight half-lives. As a result, while a steady state in humans leads to a substantial presence of the drug at the active site throughout the 24 hours, in rats the drug is almost completely eliminated at trough.

Given that a true anti-"psychotic" effect cannot be achieved in an animal, how does one choose representative doses for animal studies? Perhaps the most valid approach is to find doses which produce patient-equivalent effects on a critical target within the brains of experimental animals. This is now possible for most antipsychotics. With the advent of PET and SPECT imaging, it has been possible to measure the effects of most

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antipsychotics on dopamine D_2 receptors in vivo, in patients, at clinically relevant doses in the "therapeutic window" (Kapur and Remington, 2001). These findings are now well replicated across different laboratories, seem to correlate with clinical efficacy and side-effects, and also help understand clinical differences between the available antipsychotics (Kapur et al., 1999; Nyberg and Farde, 2000; Bressan et al., 2001). We do not wish to suggest that action at D_2 receptors is the exclusive or central mechanism of action of these antipsychotics. However, it does provide an empirical and plausible marker which can be measured reliably and analogously in both species, and thus provides one basis for choosing clinically-comparable doses of drugs for studies in animal models.

To obtain such clinically-comparable doses for five of the most common antipsychotics in use currently (haloperidol, risperidone, olanzapine, quetiapine, clozapine), we chose to measure their dopamine D_2 receptor occupancy using a validated method of calculating in-vivo receptor occupancy which is similar to that used in clinical studies. Once the clinically-comparable single doses were identified, we carried out studies using multiple-dosing regimens, by daily injections or continuous-infusion pumps, to obtain the clinically-comparable doses for multiple-dosing studies.

Methods

Animals

Male Sprague Dawley rats (Charles River, Montréal, Canada) with initial body weight of 250-275g were used. All animals were housed two per cage with food and water available ad libitum.

Drugs

Haloperidol (Sabex INC, Boucherville, QC, Canada) and risperidone (Sigma-Aldrich Inc, St. Louis, Missouri) were dissolved in distilled water while olanzapine (gift from Eli Lilly, Indianapolis, IN, USA), quetiapine (gift from AstraZeneca, Mississauga, ON, Canada) and clozapine (ANAWA Trading AS, Wangen, Zurich) were dissolved in 1-2% glacial acetic acid in distilled water. All drugs were administered subcutaneously. [^{3}H]-raclopride (NEN Life Sciences, Boston, MA, USA) was used as the radioligand for occupancy studies and given intravenously via the tail.

Single Dose Conditions

Animals (n=150) were allocated to one of five drug conditions, and then further subdivided to one of five or six doses per drug or corresponding vehicle – haloperidol (0.025-1 mg/kg), clozapine (2.5-60 mg/kg), olanzapine (0.1-2 mg/kg), risperidone (0.05-2 mg/kg) and quetiapine (5-100mg/kg). Rats that received a subcutaneous injection of haloperidol, olanzapine or risperidone were sacrificed two hours post-drug administration (Campbell et al., 1980; Schotte et al., 1996). Those rats that received clozapine or quetiapine were sacrificed one hour post-drug administration since these drugs have been shown to have peak effects in the brain earlier than the other antipsychotics (Burki, 1986; Saller and Salama, 1993). It should be pointed out that the "peak" times were chosen

based on previous studies relating to pharmacokinetics and functional effects and therefore should be regarded as approximations as opposed to definitive periods of maximal occupancy.

Ten minutes prior to sacrifice, the animals were tested for catalepsy. Animals were placed on an inclined (60°) grid and observed by a rater blind to the treatment-assignment status of the animals. To establish a reliable baseline, the first 30 s were excluded from the actual rating time. The time the rat remained in the same position was then measured for a maximum of 2.5 min. The catalepsy was scored from 0-5 according to the time (square root transformation) the animal remained immobile (min): $0 = 0$-0.08, $1 = 0.09$-0.35, $2 = 0.36$-0.80, $3 = 0.81$-1.42, $4 = 1.43$-2.24, $5 = \geq 2.25$ min. An animal was considered cataleptic with a score greater than or equal to 2.

Multiple-Dosing Conditions

Animals (n=144) were allocated to one of five antipsychotic drug groups to receive daily doses of antipsychotic either by subcutaneous injection or by ALZET osmotic minipump at a rate of 5.0μl/hr (model 2M2, DURECT Corp., Cupertino, CA, USA) for seven days. Since the half-life of all antipsychotics is of the order of 2-4 hours, seven days is more than sufficient to obtain steady-state kinetics. All animals underwent surgery for implantation of a minipump or sham procedures. The rats were anaesthetized with 1-2% isoflurane and pumps were inserted into the subcutaneous space through a small incision on the back. All animals with drug-releasing minipumps received a daily injection of vehicle, while those that had undergone sham surgery received a daily injection of drug. The doses chosen for this multiple-dosing experiment were based on the dose which gave rise to clinically-comparable D_2 occupancy under acute conditions and, where feasible,

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five-times this dose. While this was possible for haloperidol and olanzapine, we were not able to do it for risperidone due to non-availablity of sufficient quantities of the compound. With clozapine and quetiapine we ran into a dissolution/tolerability problem. To administer the five-times-single dose required concentrations in excess of 100 mg/ml of drug in solution to be administered via the ALZET pump. While such concentrations could be achieved by lowering the pH of the solvent into the range of 2-3, these low pH solutions led to tolerability problems when implanted subcutaneously for long periods of time. Thus, animals received pump delivery or daily injections of haloperidol 0.05 or 0.25 mg/kg, olanzapine 1.5 or 7.5mg/kg, risperidone 1mg/kg, quetiapine 10 or 25 mg/kg or clozapine 7.5 or 15 mg/kg. Corresponding controls received sham surgery and daily vehicle injections. The experimental design is summarized in Figure 1.

D_2 Occupancy Measurement

On the day of occupancy determination, the animals receiving daily injections of antipsychotic for seven days were further split into two groups to examine the trough and peak occupancy levels. Animals that were assigned to the "trough" group were sacrificed at the time that they would have usually received their next injection (i.e. 24 hours after last injection), while the animals in the "peak" group received a final injection on the seventh day and were sacrificed one (clozapine and quetiapine groups) or two hours (haloperidol, olanzapine, risperidone groups) after drug administration.

Thirty minutes prior to sacrifice all animals received an i.v. injection of [³H]-raclopride (7.5µCi/rat; in a volume of 0.4 mL of 0.9% NaCl solution) via the lateral tail vein. Animals were sacrificed by decapitation, plasma was collected and stored at -80°C until

drug levels could be assayed. The brains were immediately removed and striata and cerebellum were rapidly dissected. The cerebellum was homogenized with a small spatula and ~1/3 (50-100mg) of this was sampled. The left and right striata were pooled into a single sample (~60 mg). Tissue samples were collected in previously weighed 20mL glass scintillation vials. The vials were then weighed with tissue and 2 mL of Solvable™ (Canberra Packard, Canada) was added. The vials were kept on an automated shaking-tray and gently agitated for 24 hours at room temperature. Thereafter 5 mL of Aquasure™ (Canberra Packard, Canada) scintillation fluid was added and allowed to mix for another 24 hours. [^{3}H]-raclopride radioactivity was determined by liquid scintillation spectrometry using a Beckman LS5000 CE liquid scintillation counting system. Striatal and cerebellar counts were obtained and expressed as disintegrations per minute/milligram (DPM/mg).

The D_2 receptor binding potential (D_2BP) was obtained for each of the animals as

(Striatum DPM/mg – Cerebellum DPM/mg) /(Cerebellum DPM/mg). The receptor occupancy in each rat was then determined with reference to the D_2BP in the control group using the same formula as used in human studies (Farde et al., 1988; Kapur et al., 1999): %Occupancy = $100 \times (D_2BP_{control} - D_2BP_{indiv} / D_2BP_{control})$. For further details on the protocol for receptor occupancy assessment and its validation vs. ^{11}C-raclopride see Wadenberg et al. (Wadenberg et al.).

Drug plasma level measurement

Plasma obtained from animals at the time of sacrifice for the occupancy studies detailed above was stored for analysis for drug levels. In general, drug levels were quantified

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using a liquid-liquid extraction to prepare the specimen for analysis. The samples obtained from liquid-extraction were separated using liquid chromatography and then introduced into the mass spectrometer using electrospray ionization (LC-MSD) implemented using a HP 1100 LC-DAD-MSD system controlled by HP LC-MSD Chemstation software (Hewlett-Packard Company, USA). As applied to haloperidol, the method has a lower limit of quantitation of 1 nmol/L and a linearity limit of 212 nmol/L with CV ranging from 3-10% across the dose range. Clozapine is detected with a lower limit of quantitation of 10 nmol/L and a linearity limit of 6100 nmol/L with CV ranging from 2-7% across the dose range. Risperidone is quantified with a lower limit of 1 nmol/L and a linearity limit of 7200 nmol/L with CV ranging from 2-7% across the dose range. Olanzapine was quantified with a lower limit of 5 nmol/L and a linearity limit of 800nmol/L with CV ranging from 2-10% across the dose range. Quetiapine levels were quanitified with lower limit of 3 nmol/L and a linearity limit of 2265 nmol/L with quality control samples within ±10%.

Results

In single dose models, the doses that were required to achieve 50% D_2 receptor occupancy (ED50%) are listed in Table 2. Based on these data, the estimated doses that would approximate the clinically-comparable D_2 receptor occupancy are: haloperidol 0.04-0.08 mg/kg/sc, olanzapine 1-2mg/kg/sc, risperidone 0.5-1mg/kg/sc, quetiapine 10-25mg/kg/sc, clozapine 5-15 mg/kg/sc (Table 2 & Figure 2).

The same doses administered repeatedly by injection, achieved peak occupancy similar to human levels, but the trough occupancy at the end of the day was minimal and not at all

comparable to what is seen in patients (Figure 3). If the single therapeutic dose was administered daily via mini-pump, the occupancies were stable through the day, but the average occupancies were much lower than clinically-comparable therapeutic levels (Figure 3 for details). When administered by pump, a dose approximately five times higher than the single doses achieved stable therapeutic occupancies comparable to that seen in humans (Figure 3, Table 3) – 0.25mg/kg haloperidol, 7.5mg/kg olanzapine. We were unable to examine the doses for quetiapine and clozapine five times higher than the representative single dose as it was not feasible to dissolve these concentrations without making the solutions too acidic for prolonged administration (for 100mg/kg/day, concentration required would be approximately 292mg/ml).

Drug plasma levels reflected the same overall pattern as the occupancy data (Table 3). With the injection approach, the peak levels were very high, often multiple times higher than that seen in clinical conditions. However, this was accompanied by nearly undetectable trough levels, multiply lower than that seen in patients. When the 'optimal' single dose was administered as a continuous infusion, the levels were often undetectable or unrepresentatively low (see Table 3 for details). Only when the drug was administered with a pump, at levels five times the representative single-dose, were the levels close to that seen in clinical conditions at steady state.

Discussion

There are few studies that have systematically addressed the issue of antipsychotic dosing in animal models previously. While *none* have examined the issue of multiple-dosing, two studies have systematically determined dopamine D_2 occupancy with single doses (Schotte et al., 1996; Zhang and Bymaster, 1999). Both of these studies find the same relative pattern of D_2 occupancy as us: the potency for D_2 occupancy is haloperidol > risperidone/olanzapine >> clozapine $\geq$ quetiapine. However, the dose of haloperidol required to produce 75% D_2 occupancy in our study is 0.06 mg/kg while it is 0.36 mg/kg in Zhang et al. and 0.6 mg/kg in Schotte et al. – a difference of an order of magnitude. We believe that our estimates are more representative of the human condition because the method used (raclopride iv injection and in-vivo competition) are identical to those used in humans (Kapur et al., 1999; Kapur et al., 2000c; Nyberg and Farde, 2000; Bressan et al., 2001). In contrast, Schotte et al. used ex-vivo autoradiography approach – an approach shown to be less sensitive due to the dissociation of antipsychotic in the incubation bath (Kapur et al., 2001). Bymaster et al. injected the radiotracer subcutaneously, a route that does not establish equilibrium conditions in the short period of time (30 minutes) and is likely to under-estimate occupancy (Olsson and Farde, 2001).

A simple approach using just the same mg/kg dose in animals and humans would not work well (Tables 1 and 3). For example, in patients at steady-state a dose of 0.2 mg/kg/d olanzapine provides plasma levels in the range of 50 nM and a receptor occupancy of about 70%. Such a dose in the rats would provide neither adequate plasma levels nor significant occupancy. On the other hand in rats 7.5 mg/kg/d which leads to 430 nM in the plasma is what leads to 70% occupancy. Such a dose in humans would be

decidedly supra-therapeutic and perhaps even toxic. Thus, differences in absorption, distribution, metabolism/excretion and perhaps brain-penetration preclude the use of simple dose or plasma level parity as an effective means to obtain valid and representative antipsychotic doses in animals.

Most importantly even if one uses the dose that provides comparable single-dose effects, it does not lead to clinically-comparable occupancies with multiple-dosing. The half-life of the drugs are on average 4-6 times faster in rodents than they are in humans: haloperidol (rodent 1.5 hrs vs. human 12-36 hrs, (Cheng and Paalzow, 1992; Bezchlibnyk-Butler and Jeffries, 1999)); risperidone (rodent 1 hr vs. human 20-24 hrs; (van Beijsterveldt et al., 1994; Bezchlibnyk-Butler and Jeffries, 1999)); olanzapine (rodent 2.5 hrs vs. human 21-54 hrs; (Aravagiri et al., 1997; Bezchlibnyk-Butler and Jeffries, 1999)); quetiapine (rodent 0.5 hrs vs. human 6-7 hrs;(Saller and Salama, 1993; Bezchlibnyk-Butler and Jeffries, 1999)); and clozapine (rodent 1.5 hrs vs. human 5-16 hrs; (Baldessarini et al., 1993; Bezchlibnyk-Butler and Jeffries, 1999)). For a certain peak concentration (occupancy), the trough is inversely proportional to the exponent of the half-life of the drug (Rowland and Tozer, 1995). Since animals have a 4-6 times shorter half-life, it is only to be expected that for similar peak levels/occupancies, the animals would show significantly lower trough levels/occupancies than those seen in humans.

Thus if one wishes to capture the same pattern of diurnal occupancies as in patients, a single daily injection cannot suffice. Since the human dosing intervals are of the order of one half-life, to obtain similar peak/trough effects as in humans, the drugs would have to be administered to animals in 6-8 equally spaced injections through the

day. Since this is not a practical approach, we examined if administering the drug through the pump may more closely approximate the human occupancies. However, if just the optimal single dose was just administered via the pump through the day the occupancy level was much lower (and in several cases undetectable) than those associated with routine clinical treatment (Table 3). The ratio of the maintenance daily dose vs. the single loading dose to obtain a certain plasma level is inversely proportional to the plasma half life (Rowland and Tozer, 1995) – this may explain why the average maintenance dose required is about 5 to 6 times the single dose.

Based on the foregoing considerations, we propose that the doses presented in Table 2 form a reasonably valid approximation of the clinical situation in single-dose rat models. Insofar as multiple-dosing dosing is concerned, we propose that only administration by pump (or administration more than four times a day) can provide clinical-like occupancies for haloperidol, olanzapine and risperidone. Due to sheer administration limitations it is hard to achieve clinically-comparable effects for quetiapine and clozapine, and indeed none of the previous preclinical studies may have achieved them. We are only aware of one study that expressly addressed this issue through the use of repeated-dosing via the addition of clozapine to drinking-water (Schmitt et al., 1999). In this study 40 mg/kg/day were delivered via drinking-water yet the serum concentrations for clozapine were only 22 ng/ml (whereas clinically-comparable concentrations are in the range of 350 ng/ml 12 hours after last dose) – thus pointing to the limitation of this method of delivery, even though the nominal dose may seem reasonably high. Therefore multiple-dosing studies of quetiapine and clozapine

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should be interpreted with caution – especially as far as they claim to be a representative model for the clinical condition.

Limitations of our data as well as its implications are outlined next. First, we observed that animals treated with 10 mg/kg/day quetiapine multiple-dosing using the daily injection approach showed no detectable D_2 occupancy even at peak (Table 3). This is a surprising finding given that when a single injection of the same dose is administered, it leads to 50% occupancy at peak. Furthermore, this dose showed a plasma level consistent with expectation (469 nmol/L), and the next higher dose (25 mg/kg/day) showed occupancy (78%) and plasma levels (913 nmol/L) also consistent with expectation. While it is conceivable that multiple-dosing may lead to changes in disposition which may account for this, a more likely explanation is that this represents experimental error.

In a strict sense, the doses proposed here (Table 2) are only valid for the species studied (young Sprague-Dawley male rats) and the route of administration (subcutaneous). One would have to be cautious in extrapolating across species and strains since pharmacokinetic differences are noted between them. Furthermore, one would have to be cautious in extrapolating across routes (s.c. vs. oral or i.p.) as different first-pass and other metabolic considerations could change these optimal doses. Nonetheless, the general approach outlined here could be used for deriving the right estimates for these different strains and routes of administration. A limitation to this method of deriving optimal pre-clinical dosing of antipsychotics is that it is (and will be) relevant only for the current generation of atypical and typical antipsychotics which have a significant level of D_2 occupancy in patients. As new drugs are developed, which

totally avoid the D_2 receptors, obviously such an approach would not work. However, one could hope that once such new targets are developed, similar equivalent occupancy studies could be done across humans and animals to confirm the valid doses. Finally, we do not see the restricted optimal ranges we provide in Table 2 as a substitute for doing complete dose-response relationship studies. The ideal way to understand the findings in animal models still remains the complete dose-response relationship study, however the ranges presented here will be important in interpreting the dose-response relationships into a clinical context.

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Footnotes

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Figure Legends

Figure 1: Flow chart depicting the experimental design for the multiple-dosing condition.

Figure 2: Relationship between drug dose and D2 receptor occupancy after single-dose subcutaneous administration. Shaded box depicts the occupancy range that corresponds to clinically-comparable conditions. (A) Haloperidol; (B) Olanzapine; (C) Risperidone; (D) Quetiapine; (E) Clozapine.

Figure 3: D2 Occupancy levels produced by daily injections (at trough or peak) or osmotic mini-pump. Intermittent daily injection does not result in sustained clinically relevant D2 occupancy. D2 occupancy comparable to the clinical condition is achieved with the mini-pump at approximately 5x the clinically-comparable single dose. Shaded box depicts the occupancy range that corresponds to clinically comparable conditions. (A) Haloperidol; (B) Olanzapine; (C) Risperidone; (D) Quetiapine; (E) Clozapine.

Table 1: Usual clinical dosing parameters. Compiled from the following sources:

(Bezchlibnyk-Butler and Jeffries, 1999; Kapur et al., 1999; Kapur et al., 2000b; Kapur et

al., 2000c; Tauscher and Kapur, 2001; Citrome and Volavka, 2002).

Drug	Usual Clinical Dose (mg/d)	Daily Dose for a 65 kg man (mg/kg/day/po)	Peak %D_2 Occupancy In Patients	Plasma Levels* (nmol/L) at steady state
Haloperidol	2 – 4	0.05	65-80%	5-10
Olanzapine	10-20	0.20	65-80%	40-80
Risperidone	2-6	0.06	65-80%	25-50
Quetiapine	300 – 600	7.0	30-60%	550-1100
Clozapine	300 – 500	6.0	45-65%	1050

*The plasma levels noted here are those observed at the usual clinical doses, but, have
not been all independently tested for being "optimal."

Table 2: Dose required for 50% D_2 occupancy and to achieve clinically-comparable

occupancy levels under SINGLE DOSE conditions.

Drug	%D_2 Occupancy In Patients	Dose (mg/kg/sc) for 50% D_2 Occupancy In Rats	Dose (mg/kg/sc) for Clinically-Comparable D_2 Occupancy
Haloperidol	65-80%	0.02 (0.016-0.024)	0.04-0.08
Olanzapine	65-80%	0.57 (0.42-0.72)	1-2
Risperidone	65-80%	0.32 (0.16-0.48)	0.5-1
Quetiapine	30-60%	11.81 (8.59-15.03)	10-20
Clozapine	45-65%	7.26 (2.24-12.27)	5-15

Table 3: Relationship between dose, mode of administration (injection vs. minipump), D_2 occupancy and plasma levels at different doses of antipsychotics with MULITPLE DOSE administration.

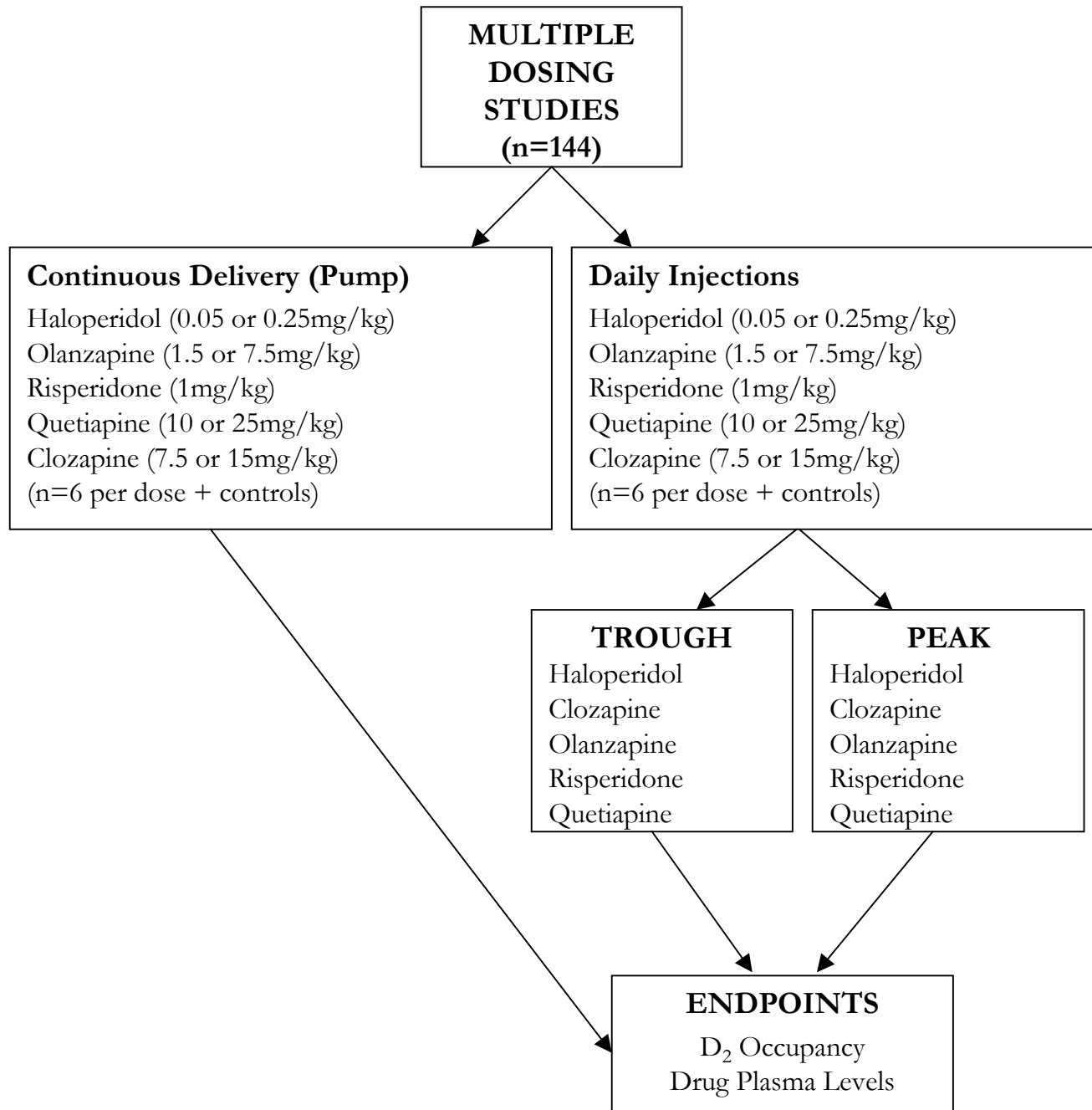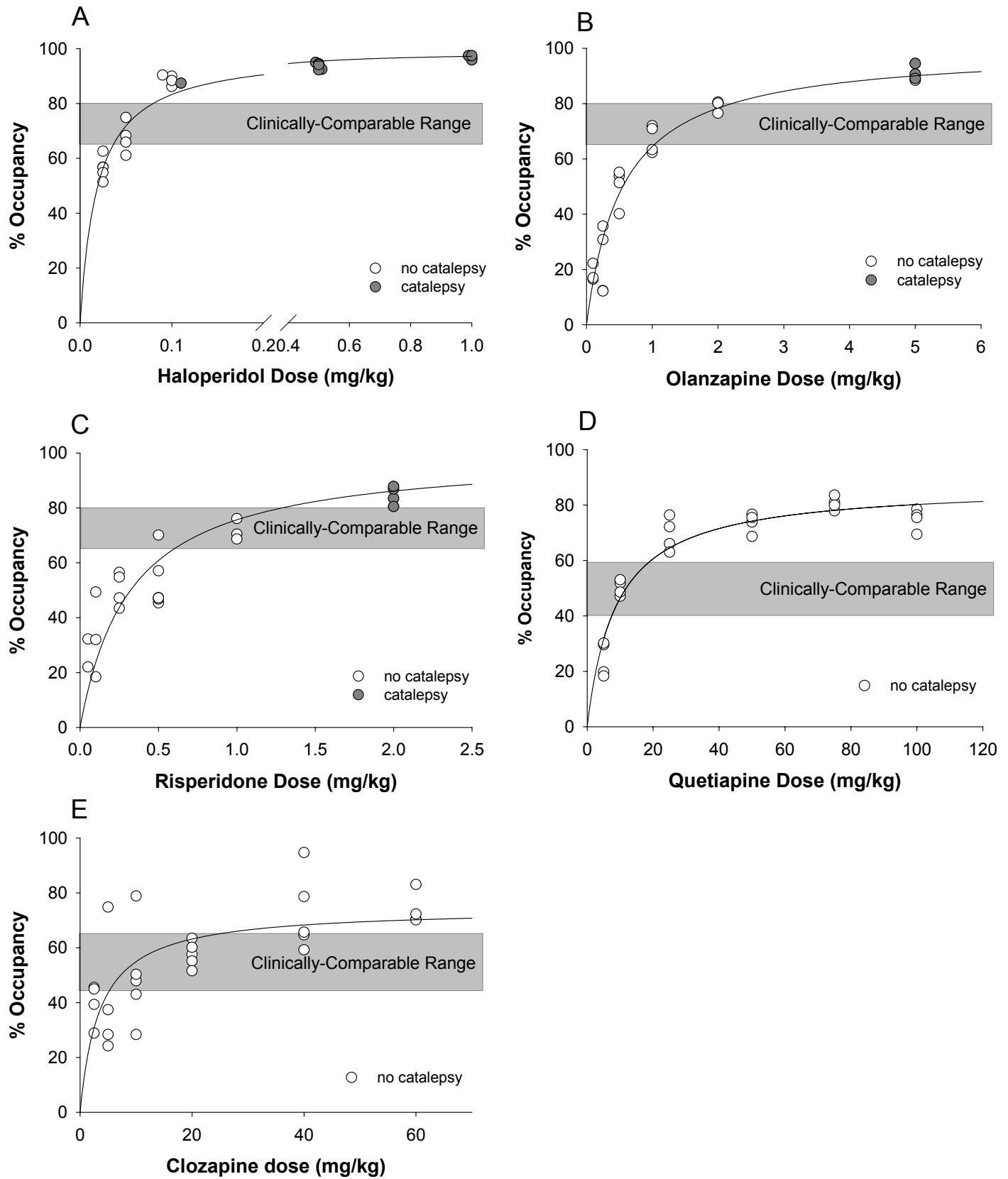| Drug Group	Delivery Condition	D_2 Occupancy (mean $\pm$ SD)	Plasma levels (mean $\pm$ SD) (nmol/L)
Haloperidol 0.05mg/kg	Injection – TROUGH	19 $\pm$ 31	<1
	Injection – PEAK	74 $\pm$ 7	1.57 $\pm$ 0.42
	Mini-pump	41 $\pm$ 16	<1
Haloperidol 0.25mg/kg	Injection – TROUGH	5 $\pm$ 2	<1
	Injection – PEAK	92 $\pm$ 1	11 $\pm$ 2.08
	Mini-pump	69 $\pm$ 14	2.40 $\pm$ 1.01
Olanzapine 1.5mg/kg	Injection – TROUGH	16 $\pm$ 24	6.67 + 2.89
	Injection – PEAK	74 $\pm$ 7	251 $\pm$ 88.39
	Mini-pump	38 $\pm$ 16	130.83 $\pm$ 118.90
Olanzapine 7.5mg/kg	Injection – TROUGH	59 $\pm$ 4	<5
	Injection – PEAK	92 $\pm$ 1	3124.33 $\pm$ 823.29
	Mini-pump	75 $\pm$ 7	434.33 $\pm$ 291.19
Risperidone 1mg/kg	Injection – TROUGH	*ND	<1
	Injection – PEAK	61 $\pm$ 3	99.97 $\pm$ 33.77
	Mini-pump	31 $\pm$ 9	39.36 $\pm$ 24.36
Quetiapine 10mg/kg	Injection – TROUGH	*ND	4.56 $\pm$ 2.71
	Injection – PEAK	*ND	469.00 $\pm$ 18.96
	Mini-pump	7 $\pm$ 10	108.20 $\pm$ 31.88
Quetiapine 25mg/kg	Injection – TROUGH	*ND	9.56 $\pm$ 7.8
	Injection – PEAK	69 $\pm$ 10	913.01 $\pm$ 223.5
	Mini-pump	25 $\pm$ 23	78.79 $\pm$ 12.33
Clozapine 7.5mg/kg	Injection – TROUGH	*ND	13 $\pm$ 3
	Injection – PEAK	29 $\pm$ 15	1240 $\pm$ 438.42
	Mini-pump	2 $\pm$ 22	98 $\pm$ 128.83
Clozapine 15mg/kg	Injection – TROUGH	0.2 $\pm$ 20	15 $\pm$ 6.35
	Injection – PEAK	60 $\pm$ 12	2969 $\pm$ 809.60
	Mini-pump	*ND	98 $\pm$ 45.30

*ND – No Detectable Occupancy
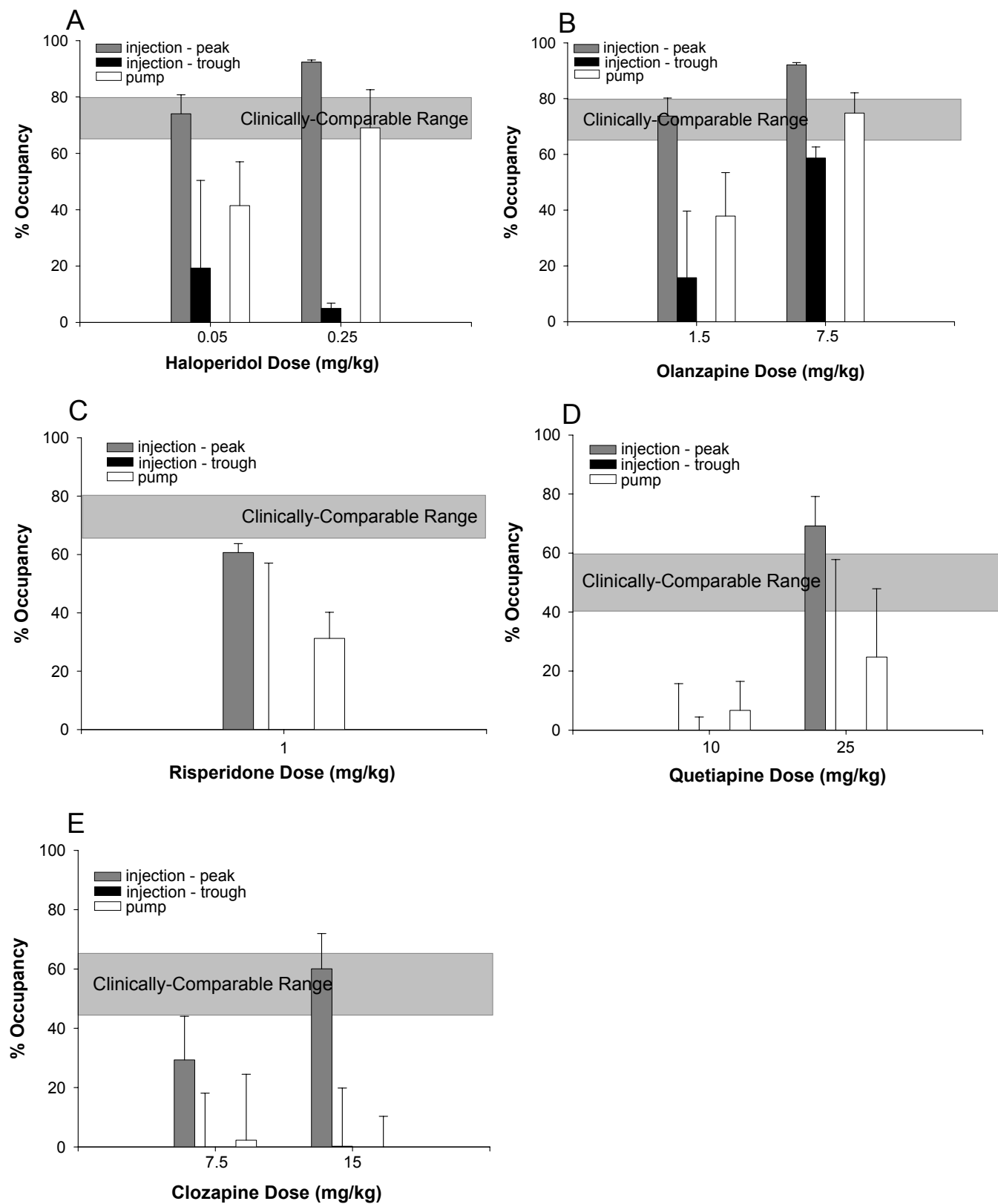
Figure 1

Figure 2

Figure 3