# Less Is More: Antipsychotic Drug Effects Are Greater with Transient Rather Than Continuous Delivery

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**Background:** Most studies on the effects of antipsychotics focus on achieving threshold levels of the drug. The speed and frequency with which drug concentrations reach threshold levels and rise and fall within the day are generally ignored. Based on prior data, we predicted that variations in the within-day kinetics of antipsychotic drug delivery would produce different outcomes, even if we held achieved dose, route, and total duration of treatment constant.

**Methods:** We compared the effects of within-day continuous (via minipump) versus transient (via subcutaneous injection) haloperidol treatment ($n = 4–9$/condition/experiment) at doses that yield equivalent peak levels of striatal D2 receptor occupancy (~74%).

**Results:** Over time, transient haloperidol gained efficacy, while continuous haloperidol lost efficacy in two animal models of antipsychotic-like effects (the suppression of amphetamine-induced locomotion and conditioned avoidance responding). This was related to the fact that continuous treatment led to a greater increase in striatal D2 receptor numbers—particularly D2 receptors in a high-affinity state for dopamine—relative to transient treatment and produced behavioral dopamine supersensitivity (as indicated by an enhanced locomotor response to amphetamine following antipsychotic treatment cessation). Treatment kinetics also influenced the postsynaptic response to haloperidol. Transient treatment increased striatal c-fos messenger RNA (mRNA) expression, while continuous treatment did not.

**Conclusions:** Relative to continuous antipsychotic exposure, within-day transient exposure is more efficacious behaviorally and is associated with a distinct molecular and gene expression profile. Thus, differences in the within-day kinetics of antipsychotic treatment can have different efficacy, and the potential clinical implications of this should be explored further.

**Key Words:** Antipsychotics, conditioned avoidance, D2 receptors, dopamine, kinetics, supersensitivity

In the study of drug action, considerable attention is given to drug dose and the crossing of certain "threshold" levels of receptor occupancy (1). The kinetics of drug delivery are often regarded as secondary, simply a means to provide target levels of drug and receptor occupancy. This assumption is likely wrong. Independent of current drug levels, drug kinetics (i.e., the speed with which drug levels rise and the number of times they rise and fall in the day) are just as important in determining outcome. For example, withdrawal from continuous (via osmotic minipump) rather than transient (via daily subcutaneous injection) raclopride treatment more readily induces tolerance to the motor suppressant effects of raclopride and locomotor supersensitivity to amphetamine, even when transient treatment leads to markedly higher peak levels of striatal D2 receptor blockade (2). Similarly, continuous haloperidol or olanzapine treatment (via minipump) increases the likelihood of vacuous chewing movements (an animal model of tardive dyskinesia) relative to transient treatment (via subcutaneous injection), even when the latter leads to higher peak levels of D2 blockade (3,4,5).

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These and other findings (6-8) suggest that some of the antidopaminergic effects of antipsychotics are determined as much by the kinetics of receptor occupancy as by the peak levels of drug or receptor occupancy achieved. However, several issues confound the interpretation of these studies. First, the kinetics of drug delivery are confounded with dose in some studies (8) and duration of treatment in others (6). Second, most studies have investigated the effects of drug delivery kinetics on the period following withdrawal from antipsychotics (2,7,8). The more relevant clinical question concerns the effects of drug delivery kinetics while the drug is being taken, not after. To our knowledge, only Carey and DeVeaugh-Geiss (6) and Turrone *et al.* (3,4) measured antipsychotic effects without an overt withdrawal period. However, both measured indices of motor side effects rather than antipsychotic efficacy (spontaneous locomotion and extrapyramidal side effects, respectively). Thus, it remains to be determined whether the kinetics of antipsychotic treatment can influence antipsychotic efficacy.

In the current studies, therefore, we asked a simple question: If one holds the achieved dose, route, and total duration of antipsychotic drug treatment constant but varies the within-day kinetics of treatment, can one get differential drug effects? We found this to be the case. Remarkably, within-day transient antipsychotic treatment was much more effective than continuous treatment, even when we tested a 10 fold lower dose. We then investigated potential mechanisms and found that the kinetics of antipsychotic treatment influence 1) the number and sensitivity of striatal D2 receptors, and 2) the postsynaptic response to antipsychotic, as measured by induction of messenger RNA (mRNA) for the immediate early gene c-fos.

## Methods and Materials

Male Sprague Dawley rats (Charles River Laboratories, Montreal, PQ, Canada) weighing 225 g to 250 g were housed two per cage in a climate-controlled colony room with a 12-hour reverse

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light/dark cycle (lights off at 8:00 AM). Food and water were available ad libitum. All testing was conducted during the dark phase of the animals' circadian cycle and was in compliance with the institute's animal care committee.

### Drugs

Haloperidol (HAL; .05 or .5 mg/kg/day via minipump or .05 mg/kg/day via subcutaneous [SC] injection) (Sabex Inc., Boucherville, PQ, Canada) was dissolved in a .5% glacial acetic acid/water ($H_2O$) solution (pH adjusted to ~5 with sodium hydroxide [NaOH]) for treatment via minipump (Alzet model 2ML2, 19-day drug delivery according to the manufacturer, Durect Corporation, Cupertino, California) and was dissolved in 20 mmol/L phosphate buffered saline (PBS) for treatment via subcutaneous injection. D-amphetamine sulfate (AMPH; 1.5 mg/kg) (US Pharmacopoeia, Rockville, Maryland) was dissolved in .9% saline and given SC (1 mL/kg).

### Rationale for Doses and Modes of Haloperidol Administration

The goal of the present set of experiments was to examine the contributions of the kinetics of antipsychotic drug delivery (i.e., maintaining continuous versus transiently high levels of drug within the day) to the neurobehavioural response to antipsychotic using equivalent and clinically representative doses. Positron-emission tomography (PET) studies in humans suggest that therapeutically efficacious doses of antipsychotic that do not also significantly increase the risk of motor side effects yield between 65% and 80% striatal D2 receptor occupancy (9-11). Similarly, doses of antipsychotic that disrupt conditioned avoidance responding (a widely used index of antipsychotic-like efficacy in animals) in animals without inducing catalepsy (a model of extrapyramidal side effects [EPS]) also occupy between 70% and 80% striatal D2 receptors (12,13).

In rats, HAL treatment via minipump leads to continuously high levels of D2 receptor occupancy (14,15), whereas HAL given via SC injection leads to only transiently high occupancy, which is greatly reduced 24 hours after injection (14). Therefore, we varied the kinetics of antipsychotic treatment by administering HAL via osmotic minipump or SC injection. To hold achieved dose/peak levels of D2 receptor occupancy constant, we selected doses that would achieve equivalent and therapeutically meaningful peak levels of striatal D2 receptor blockade under the two treatment conditions. Thus, we administered .5 mg/kg/day HAL via minipump (73% ± 14 SD striatal D2 receptor occupancy) (A-N. Samaha, PhD; G.E. Reckless, B.Sc; S. Kapur, MD, PhD; unpublished observations; February 16, 2006) and .05 mg/kg/day via SC injection (74% ± 7 SD striatal D2 receptor occupancy 2 hours postinjection and 19% ± 31 SD striatal D2 receptor occupancy 24 hours postinjection) (14). We also included a group of rats treated with .05 mg/kg/day HAL via minipump (41% ± 16 SD striatal D2 receptor occupancy) (14) to examine the effects of drug delivery kinetics while holding dose constant. Thus, four groups were generated: two groups receiving .05 mg/kg HAL either via daily SC injection (HAL-TRANS) or minipump (HAL-.05 CONT), a group receiving .5 mg/kg via minipump (HAL-.5 CONT), and a vehicle control group (VEH).

### Treatment

Under 1.5% isoflurane anesthesia, HAL-.5 CONT and HAL-.05 CONT rats were implanted with minipumps containing HAL as described previously (15). The HAL-TRANS and VEH animals received sham surgery, which consisted of an incision that was then closed with wound clips. Starting 1 day later, animals in the HAL-TRANS group were injected with HAL once a day. All remaining animals were injected with VEH once a day. Thus, all animals were subjected to equivalent surgical, handling, and injection procedures.

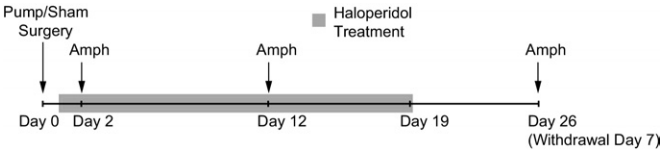



**Figure 1.** Graphical depiction of the sequence of treatment and testing for Experiment 1, where the effects of HAL on amphetamine-induced locomotion were assessed on the 2nd and 12th days of neuroleptic treatment as well as on the 7th day following neuroleptic cessation. HAL, haloperidol.

### Experiment 1: Behavioral Sensitivity to AMPH as a Function of Mode of HAL Administration

In Experiment 1, we assessed the effects of the mode of HAL treatment on the locomotor response to AMPH over time.

**Apparatus.** The locomotor response to AMPH (1.5 mg/kg, SC) was assessed in clear Plexiglas cages (27 × 48 × 20 cm) as described previously (15).

**Groups and Procedures.** As illustrated in Figure 1, AMPH-induced locomotion was assessed on the 2nd and 12th days of treatment in independent groups of animals ($n$ = 8/group/day). The animals that were tested on day 12 continued to receive neuroleptic or VEH treatment for an additional 7 days (until day 19, at which time the minipumps in the HAL-CONT groups were empty of drug solution) and their locomotor response to AMPH was again assessed on the seventh day following HAL treatment cessation (day 26). On test days, animals were brought to the locomotor activity room and animals in the HAL-TRANS group were injected (SC) with HAL and animals in the other groups received VEH injections. The animals were then placed in the locomotor activity cages and locomotor activity was monitored for 30 min. Animals were then injected with AMPH and locomotor activity was recorded for 60 min.

### Experiment 2: Conditioned Avoidance Responding

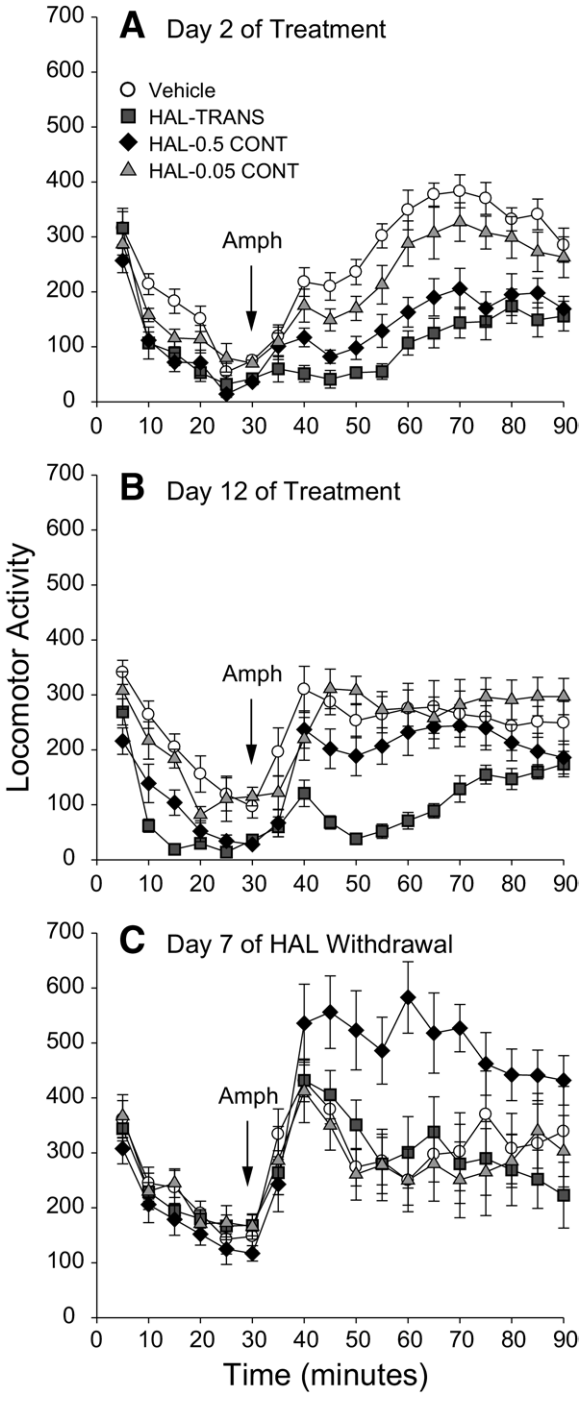
In Experiment 2, we monitored the effects of the mode of HAL treatment on the avoidance response to a conditioned aversive stimulus over time.

**Procedures.** Rats were trained and tested in two-way active avoidance shuttle boxes as described previously (15). Each conditioned stimulus presentation was immediately followed by foot shock. Movement to the other compartment during the 10 sec conditioned stimulus presentation was recorded as "avoidance." Spontaneous movement to the other compartment was recorded as "crossover." Fifty-four naïve rats were trained once a day for a total of 9 days. Animals that reached a training criterion of ≥80% avoidance on days 8 and 9 (36 out of 54 rats) were randomly assigned to the HAL-TRANS, HAL-.05 CONT, HAL-.5 CONT, or VEH condition ($n$ = 9 per group). Starting on day 3 of treatment, the same animals were tested for conditioned avoidance responding (CAR) once a day for 5 consecutive days (i.e., until day 7 of treatment) and then on days 10, 12, 14, and 16 of treatment using the same procedures as during training, including presentation of the foot shock. Testing was conducted 1 hour after VEH or HAL injections. On days when no testing occurred, animals were injected in their home cages.

### Experiment 3: D2 Receptor Binding Capacity and Guanine Nucleotide-Sensitive $D2^{High}$ Receptors

In Experiment 3, we quantified changes in the density of striatal D2 receptors and D2 receptors in a high-affinity state for dopamine ($D2^{High}$) as a function of HAL treatment kinetics. Because administration of .05 mg/kg/day HAL via minipump (HAL-.05 CONT) had no effect in either Experiment 1 or 2, this experimental group was not included in either Experiment 3 or 4.

**Procedures.** On the 12th day of treatment, rats from the HAL-TRANS, HAL-.5 CONT, and VEH groups were sacrificed by carbon dioxide ($CO_2$) narcosis 4 hours after their injection and their striata were dissected and stored at −70°C until use. The $D2^{High}$ states were measured using [$^3$H](+)PHNO, a D2 agonist, using procedures described in Samaha *et al.* (15).




### Experiment 4: C-fos mRNA Expression

In Experiment 4, we examined the effects of HAL treatment kinetics on the postsynaptic response to the antipsychotic using the immediate early gene c-fos. This study was conducted using a subset of the rats that had been tested in Experiment 2.

**Procedures.** On the 17th day of treatment, rats in the HAL-TRANS group were injected with HAL and rats in the HAL-.5 CONT and VEH groups were injected with VEH in their home cages. Thus, injection and handling procedures were equivalent across groups prior to collection of the brains for c-fos mRNA measurement. Ninety minutes following the injection, animals were sacrificed by live decapitation. Their brains were removed, frozen rapidly in isopentane on dry ice, and stored at −80°C until processing.

**In Situ Hybridization.** The in situ hybridization and quantification procedures are described in Supplement 1. C-fos mRNA levels were quantified in the anterior cingulate, prelimbic, infralimbic, and somatosensory cortices; the nucleus accumbens core and shell; and four subdivisions of the caudate-putamen (dorsomedial [DM], dorsolateral [DL], ventromedial [VM], and ventrolateral [VL] quadrants). Anatomical regions were identified according to the atlas of Paxinos and Watson (16). Sections were analyzed without awareness of group membership.

## Results

### Experiment 1: Effects of the kinetics of HAL Treatment on Behavioral Sensitivity to AMPH Over Time

In Experiment 1, we examined the effects of the kinetics of chronic antipsychotic drug administration (achieved by administering HAL via minipump or daily SC injection) on the suppression of AMPH-induced locomotion over time. The locomotor response to AMPH in the HAL-.05 CONT rats was not different from control animals at any time point tested. Early in treatment (day 2; Figure 2A), AMPH-induced locomotion was suppressed in both the HAL-.5 CONT and HAL-TRANS groups to a similar degree. With continued treatment (day 12; Figure 2B), suppression of AMPH-induced locomotion was maintained in the HAL-TRANS group (59% suppression relative to vehicle control animals, ±4 SEM) but not in the HAL-.5 CONT group. On the seventh day of HAL withdrawal (Figure 2C), HAL-.5 CONT animals displayed a potentiated locomotor response to AMPH relative to control animals (55% greater locomotion ± 14.9 SEM),

**Figure 2.** The effects of chronic and continuous (HAL-.05 CONT and HAL-.5 CONT; .05 or .5 mg/kg/day, respectively) versus chronic and transient (HAL-TRANS; .05 mg/kg/injection) haloperidol treatment on the locomotor response to amphetamine (1.5 mg/kg/injection) on the 2nd **(A)** and 12th **(B)** days of neuroleptic treatment and on the 7th day following neuroleptic cessation **(C)**. *n*'s = 8 per condition. The locomotor response to amphetamine in the HAL-.05 CONT group was not different from the vehicle group at any time point tested (all *p*'s > .05). In **(A)**, the locomotor response to amphetamine is suppressed in both the HAL-.5 CONT and HAL-TRANS groups relative to the vehicle group [one-way ANOVA on total locomotion from minutes 40 to 90, followed by Tukey's multiple comparison tests; $F(3) = 14.8$, all *p*'s < .05]. In **(B)**, the locomotor response to amphetamine is suppressed in the HAL-TRANS group but not the HAL-.5 CONT group relative to vehicle [$F(3) = 8.2$, all *p*'s < .05]. In **(C)**, the locomotor response to amphetamine is greater in the HAL-.5 CONT group relative to the vehicle [$F(3) = 3.77$], HAL-.05 CONT, and HAL-TRANS groups (all *p*'s < .05). ANOVA, analysis of variance; HAL-.05 CONT, group receiving .05 mg/kg haloperidol via minipump; HAL-.5 CONT, group receiving .5 mg/kg haloperidol via minipump; HAL-TRANS, group receiving .05 mg/kg haloperidol via daily subcutaneous injection.

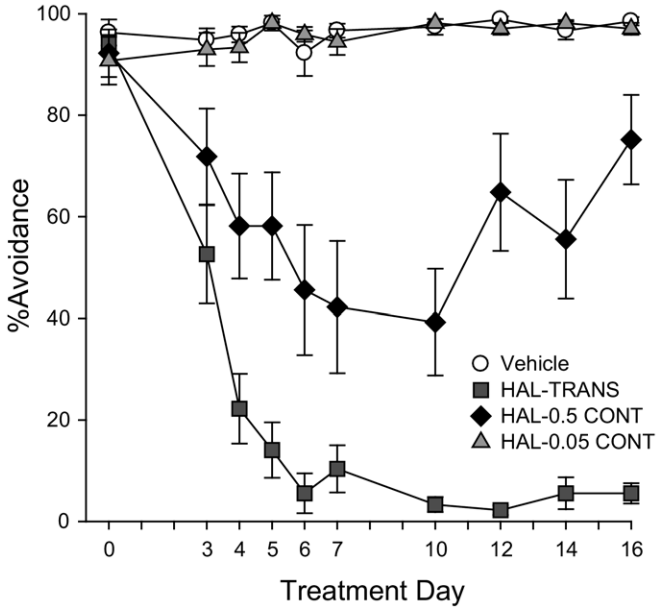



**Figure 3.** The effects of chronic and continuous (HAL-CONT; .05 or .5 mg/kg/day) versus chronic and transient (HAL-TRANS; .05 mg/kg/injection) haloperidol treatment on conditioned avoidance responding over time. *n's* = 9 per condition. In the first days of testing, avoidance responding is suppressed in both the HAL-TRANS and HAL-.5 CONT groups relative to predrug (day 0) and vehicle control levels [two-way ANOVAs, main effect of group; HAL-TRANS vs. VEH, $F(1,16) = 538.7$; HAL-.5 CONT vs. VEH, $F(1,16) = 16.7$, *p's* < .001) and suppression is greater in the HAL-TRANS group [$F(1,16) = 17.7$, $p < .001$]. Over time, the disruption of avoidance responding lessened in the HAL-.5 CONT group [group by day interaction from day 10 to 16, $F(1,3) = 8.9$, $p < .0001$] but is maintained in the HAL-TRANS group. The HAL-.05 CONT group is not different from the vehicle group at any time point tested ($p > .05$). ANOVA, analysis of variance; HAL-.05 CONT, group receiving .05 mg/kg haloperidol via minipump; HAL-.5 CONT, group receiving .5 mg/kg haloperidol via minipump; HAL-TRANS, group receiving .05 mg/kg haloperidol via daily subcutaneous injection; VEH, vehicle control group.

HAL-.05 CONT (68% greater locomotion ± 16.1 SEM), and HAL-TRANS animals (61% greater locomotion ± 15.4 SEM). The HAL-TRANS animals were not different from control animals. Thus, the HAL-.5 CONT group but not the HAL-TRANS group developed dopamine supersensitivity.

### Experiment 2: Effects of the Kinetics of HAL Treatment on Conditioned Avoidance Responding

In Experiment 2, we measured the effects of the kinetics of chronic antipsychotic drug treatment on the avoidance response to an aversive conditioned stimulus over time. There was no effect of HAL in the HAL-.05 CONT rats at any time point tested (Figure 3). Conditioned avoidance responding was initially suppressed in both the HAL-TRANS and HAL-.5 CONT groups relative to predrug (day 0) and control levels and suppression was greater in the HAL-TRANS group. In the HAL-.5 CONT group, CAR suppression peaked on the 10th day of treatment (60% suppression of CAR compared with control animals, ± 10.8 SEM) but diminished over time, such that by the last day of testing CAR was only suppressed by 24% (± 9 SEM). In the HAL-TRANS group, CAR suppression peaked on the 12th day of treatment (98% ± 1.2 SEM) and did not diminish thereafter. There was no effect of treatment condition on spontaneous movement between compartments during testing (crossovers) on any testing day (data not shown). Thus, the effects of treatment condition on CAR over time are unlikely to be due to impaired movement.

### Experiment 3: Effects of the Kinetics of HAL Treatment on Striatal D2 Receptor Bmax and Guanine Nucleotide-Sensitive $D2^{High}$ States

In Experiment 3, we measured changes in striatal D2 receptor number and sensitivity on the 12th day of ongoing treatment with HAL via minipump or SC injection. The D2 receptor Bmax was increased by 112% (± 14.2 SEM) in the HAL-.5 CONT group compared with vehicle (Figure 4A). Although D2 receptor density in the HAL-TRANS group was 45% (± 16.3 SEM) higher than that seen in the VEH group, this difference did not reach statistical significance.

The kinetics of antipsychotic treatment also influenced striatal $D2^{High}$ density (Figure 4B). Compared with VEH animals, both the HAL-TRANS and HAL-.5 CONT groups had elevated levels of $D2^{High}$ sites (168% elevation ± 61 SEM and 490% elevation ± 19 SEM, respectively). However, this increase was greater in the HAL-.5 CONT group relative to the HAL-TRANS group.

### Experiment 4: Effects of the Kinetics of HAL Treatment on c-fos mRNA Expression

As illustrated in Figure 5, c-fos mRNA levels were greater in the HAL-TRANS group relative to either the HAL-.5 CONT or VEH groups in all subdivisions of the caudate-putamen with the exception of the VM subdivision, where no comparisons were significant. There was no effect of HAL treatment mode on c-fos mRNA levels in the anterior cingulate, prelimbic, infralimbic, or somatosensory cortices or in the nucleus accumbens core and shell (in this latter region, c-fos mRNA expression was greater

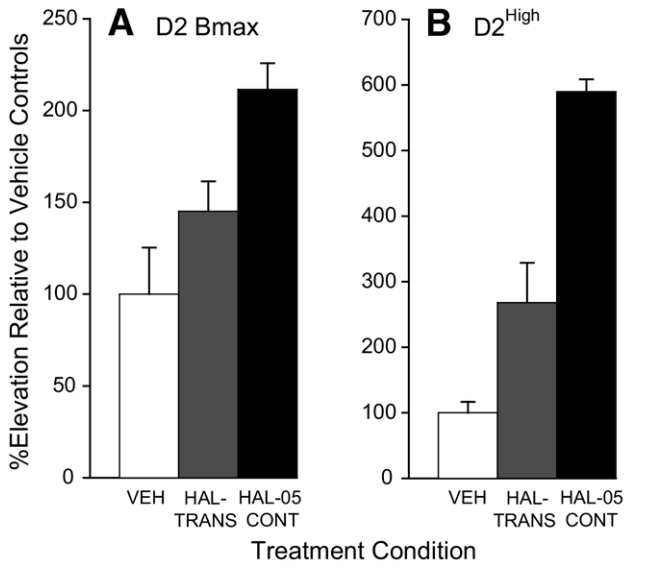



**Figure 4.** The effects of chronic and continuous (HAL-.5 CONT; .5 mg/kg/day) versus chronic and transient (.05 mg/kg/injection; HAL-TRANS) haloperidol treatment on striatal dopamine D2 receptor binding **(A)** and D2 High density **(B)**. *n's* = 9 per condition. Relative to vehicle levels, D2 receptor Bmax is significantly elevated in the HAL-.5 CONT group **(A)** [one-way ANOVA followed by Tukey's multiple comparison test; $F(2) = 7.1$, all *p's* < .05] but not the HAL-TRANS group. Relative to vehicle levels, $D2^{High}$ density is elevated in both the HAL-TRANS and HAL-.5 CONT groups [one-way ANOVA followed by Tukey's multiple comparison tests; $F(2) = 27.3$, all *p's* < .05), but this elevation is greater in the HAL-.5 CONT group relative to the HAL-TRANS group ($p < .05$). ANOVA, analysis of variance; HAL-.5 CONT, group receiving .5 mg/kg haloperidol via minipump; HAL-TRANS, group receiving .05 mg/kg haloperidol via daily subcutaneous injection.

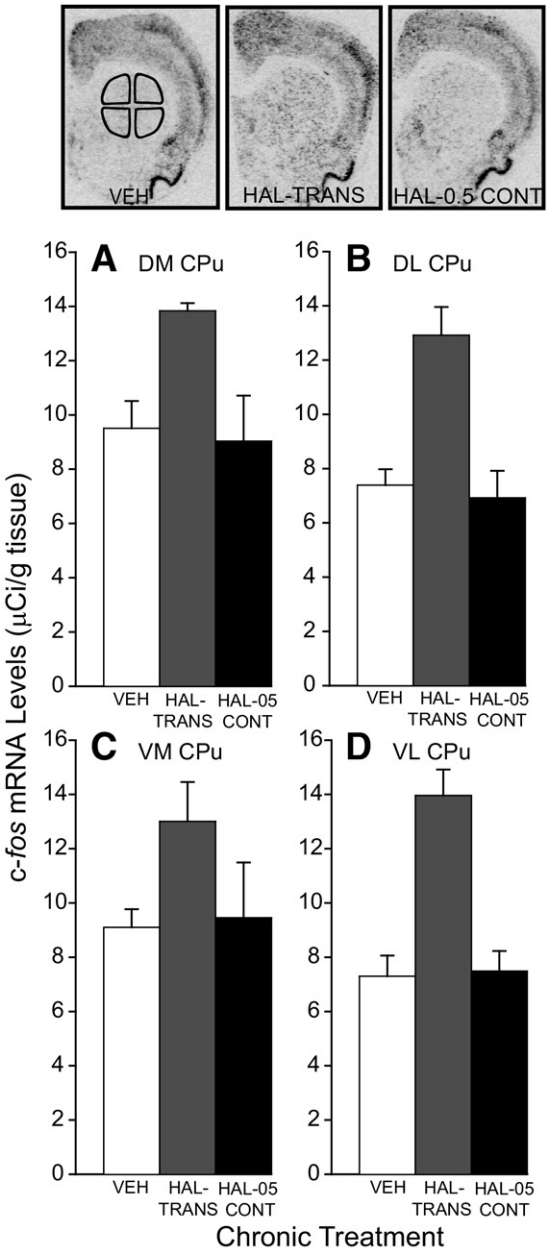



**Figure 5.** The effects of chronic and continuous (HAL-.5 CONT; .5 mg/kg/day) versus chronic and transient (HAL-TRANS; .05 mg/kg/injection) haloperidol treatment on c-fos mRNA expression in the **(A)** dorsomedial (DM), **(B)** dorsolateral (DL), **(C)** ventromedial (VM), and ventrolateral **(D)** (VL) quadrants of the caudate-putamen (CPu). Also included are representative densitograms illustrating c-fos mRNA density in the three treatment groups and an illustration of how the CPu was subdivided for quantification. *n*'s = 4 per condition. c-fos mRNA levels were elevated in the HAL-TRANS group compared with either the HAL-.5 CONT or VEH groups in all subdivisions of the CPu [one-way ANOVA followed by Tukey's multiple comparison tests; DM, $F(2) = 7.9$; DL, $F(2) = 14.62$, VL, $F(2) = 19.28$; all $p$'s $< .05$] with the exception of the VM CPu, where no comparisons were statistically significant. ANOVA, analysis of variance; CPu, caudate-putamen; DL, dorsolateral; DM, dorsomdial; HAL-.5 CONT, group receiving .5 mg/kg haloperidol via minipump; HAL-TRANS, group receiving .05 mg/kg haloperidol via daily subcutaneous injection; mRNA, messenger RNA; VEH, vehicle control group; VL, ventrolateral; VM, ventromedial.

in the HAL-.5 CONT than in the HAL-TRANS condition; however, neither group was different from vehicle control animals; Table 1).

## Discussion

We show here that chronic treatment with an antipsychotic, using the same achieved dose and route of administration but different treatment kinetics (i.e., within-day continuous versus transient), leads to tolerance to ongoing antipsychotic treatment in one case and progressively increasing efficacy in the other. Transient treatment was more effective than continuous treatment even when a 10-fold lower dose was administered using the transient mode, thus producing greater efficacy with lesser drug. This difference in efficacy was observed using two commonly used convergent (one behavioral and one pharmacological) models of antipsychotic-like efficacy in animals, the conditioned avoidance responding and amphetamine-induced locomotion tests, respectively. Within-day transient and continuous antipsychotic treatment led to different outcomes in spite of equivalent peak levels of striatal dopamine D2 receptor occupancy. This suggests that a within-day rise and fall in antipsychotic drug levels preserves/enhances the efficacy of ongoing treatment relative to continuously high levels of antipsychotic.

Disruption of amphetamine-induced locomotion is not a property that is exclusive to antipsychotic compounds. However, it is a reliable and commonly used test to assess the antidopaminergic efficacy of antipsychotics (17,18). As regards antipsychotic-induced disruption of conditioned avoidance responding, it is not completely clear how the avoidance response to an aversive stimulus (an adaptive response) in rats might relate to psychosis in humans (19). Nonetheless, from an empirical perspective, the conditioned avoidance responding model shows very high predictive validity for antipsychotic activity (20). All clinically effective antipsychotics selectively disrupt conditioned avoidance responding at doses that do not alter unconditioned escape responses, and antipsychotic effects in this test are positively correlated with clinical antipsychotic potency (21–23). In the present studies, transient treatment was superior to continuous treatment in these two widely used and validated animal models of antipsychotic-like efficacy, and the effects were robust and consistent across paradigms and across independent groups of animals. Nevertheless, it is possible that these models are not complete predictors of antipsychotic-like efficacy, and future studies might extend the current findings to other behavioral paradigms such as prepulse inhibition, latent inhibition, and/or phencyclidine (PCP)-induced or apomorphine-induced psychomotor activation.

We have shown previously that the loss of efficacy that occurs during continuous antipsychotic treatment is linked to increases in the density of striatal D2 receptors and D2 receptors in a high-affinity state for dopamine (15). We replicate and extend these findings here by showing that compared with continuous antipsychotic treatment, transient treatment does not significantly alter D2 Bmax (although there was a trend toward an increase) and leads to a smaller elevation in $D2^{High}$ density. These results suggest that if the kinetics of treatment lead to a certain threshold level of D2 and $D2^{High}$ upregulation, dopamine supersensitivity and a loss of antipsychotic efficacy will be observed. However, behavioral dopamine supersensitivity can be dissociated from changes in D2 receptor number (15,24,25). In contrast, dopamine supersensitivity induced by a variety of genetic, pharmacological, and environmental manipulations is consistently linked to elevations in striatal $D2^{High}$ levels (15,26,27).

Changes in the proportion of $D2^{High}$ receptors in striatal cells might lead to changes in intracellular function. Chronic exposure to transient haloperidol (via daily systemic injection) induces

**Table 1.** The Effects of Chronic and Continuous Versus Chronic and Transient Haloperidol Treatment on c-fos mRNA Expression in the Anterior Cingulate, Prelimbic, Infralimbic, and Somatosensory Cortices and the Nucleus Accumbens Core and Shell

| | AC Cortex | PL Cortex | IL Cortex | SS Cortex | NAcc Core | NAcc Shell |
|---|---|---|---|---|---|---|
| VEH | 26.1 ± 2.3 | 25.4 ± 2.4 | 18.6 ± 1.9 | 16.7 ± 1.9 | 10.3 ± 1.5 | 8.0 ± .6 |
| HAL-.5 CONT | 23.7 ± 2.8 | 23.3 ± 4.2 | 16.4 ± 3.4 | 19.2 ± 1.8 | 9.5 ± .1 | 12.1 ± 1.4[a] |
| HAL-TRANS | 29.3 ± 2.0 | 25.6 ± 1.5 | 17.6 ± .9 | 16.6 ± 3.8 | 9.9 ± 1.6 | 6.3 ± .7 |

Values = mean ± SEM.
HAL-.5 CONT: .5 mg/kg/day.
HAL-TRANS: .05 mg/kg/injection.
*n*'s = 4 per condition.
AC, anterior cingulate; HAL-.5 CONT, group receiving chronic and continuous treatment of .5 mg/kg haloperidol via minipump; HAL-TRANS, group receiving chronic and transient treatment of .05 mg/kg haloperidol via daily subcutaneous injection; IL, infralimbic; mRNA, messenger RNA; NAcc, nucleus accumbens; PL, prelimbic; SS, somatosensory; VEH, vehicle control group.
[a]>HAL-TRANS.

mRNA expression of the immediate early gene c-fos in several brain regions, including the caudate-putamen (though c-fos levels are lower than those seen when the neuroleptic is given for the first time) (28–31). We show here that transient but not continuous haloperidol treatment increases striatal c-fos mRNA expression. This finding is in contrast to the effect on $D2^{High}$ levels, but it is consistent with the effects on behavior, where transient but not continuous treatment increased antipsychotic efficacy over time. It has been suggested that antipsychotic-induced elevations in Fos activity might be associated with greater propensity for extrapyramidal side effects (32). However, we measured catalepsy (an animal model of EPS) on days 2 and 12 of haloperidol treatment and no catalepsy was found in any group (data not shown). This is consistent with findings that haloperidol doses <.1 mg/kg via SC injection do not produce catalepsy (21) and that striatal Fos activation and EPS liability can be dissociated (13,32,33). Although the mechanisms by which haloperidol increases striatal c-fos mRNA levels remain to be identified, acute haloperidol treatment increases striatal dopamine levels (34–36) and this might contribute to c-fos mRNA induction. However, chronic haloperidol treatment (either via minipump, the drinking water, or daily SC injection) decreases striatal dopamine levels (15,37–41), suggesting that nondopaminergic mechanisms might be involved. One candidate is glutamate, which remains elevated in the striatum during chronic haloperidol treatment (42–44) and is involved in antipsychotic-induced striatal c-fos expression (45–47). Whatever the underlying mechanisms, the positive correlation between c-fos mRNA expression and antipsychotic efficacy suggests that gene regulation might be a step in a chain of intracellular events that contribute to and/or maintain antipsychotic efficacy over time.

Why might continuous but not transient antipsychotic treatment promote a loss of antipsychotic efficacy over time? One possibility is that by disrupting normal dopamine function on a continual basis, continuous antipsychotic exposure elicits compensatory responses, including an upregulation of $D2^{High}$ receptors, which lead to dopamine supersenstivity. This, in turn, would overwhelm the antidopaminergic effects of ongoing antipsychotic treatment. In contrast, when dopamine antagonism is high for only part of the day, the dopamine signaling that occurs in between dopamine blockade peaks might be sufficient to prevent such compensatory changes from occurring and even evoke sensitizing neuroadaptations that gradually enhance antipsychotic efficacy. Indeed, more than 25 years ago, Post (48) emphasized the importance of the kinetics of stimulation by drugs or other stimuli in "... determining the direction and magnitude of adaptive response following repeated presentation." In support of this, intermittent psychostimulant drug exposure leads to psychomotor sensitization while continuous exposure leads to tolerance (49–54). In the 6-hydroxydopamine lesion model of Parkinson's disease, intermittent levodopa treatment preferentially induces sensitization of rotational behavior compared with continuous treatment (55–57). Finally, even very small differences in the kinetics of drug delivery can have large effects on the neurobehavioral response to addictive drugs (58–61). Thus, the kinetics of drug delivery are important in considering the effects of many drugs, in many contexts, and certainly within the dopamine system.

The current findings challenge the assumption that high levels of antipsychotic/D2 receptor occupancy need to be maintained continuously to maintain efficacy. How do these findings fit with clinical data on intermittent medication? Intermittent medication strategies have often resulted in increased relapse rates in patients (62–68). However, intermittent treatment is often achieved by alternating between periods of treatment and relatively long drug-free periods (lasting up to months). So, while there can be little doubt that there must be a "breakpoint" where if occupancy has been low enough for long enough efficacy will be lost, it might also be the case that continuous occupancy (due to its induction of dopamine supersensitivity) is less than optimal. It is possible that intermittent administration with shorter interdosing intervals (as modeled here with daily subcutaneous injections) might be more effective. This possibility has been examined in a recent study that has demonstrated that dosing every 2 to 3 days might be sufficient to maintain antipsychotic efficacy in patients with schizophrenia (69). Taken in the context of these recent clinical findings, our results suggest that transient but regular antipsychotic treatment approaches need to be investigated further. However, it is important to note that the possibility that continuous treatment (e.g., via depot antipsychotic) might induce some neuroadaptations that could be of benefit to some patients cannot be ruled out completely.

One potential limitation of the present findings is that the efficacy of transient haloperidol treatment was assessed at a single time point following neuroleptic administration (a time point when peak drug levels were expected to occur). Thus, we do not know whether transient antipsychotic treatment would maintain its superiority over continuous treatment at times of the day when transient drug levels are not at their peak. However, 48 hours after the last transient antipsychotic exposure (via SC injection), clozapine and haloperidol maintain their antipsychotic-like efficacy in rats (70). In addition, as mentioned above, clinical findings show that antipsychotics remain efficacious when given every 3 days as compared with daily (69) and that

some antipsychotics such as quetiapine are clinically efficacious in spite of only transient striatal D2 receptor blockade (71). Taken together, these findings suggest that upon an initial exposure to antipsychotic, a chain of intracellular events is initiated that will perpetuate the antipsychotic's effects well beyond its presence at the receptor. In other words, it might not be necessary for antipsychotic drugs to remain bound to their receptors 24 hours, every day of the week to be efficacious. In fact, the present findings suggest that if antipsychotics remain bound to their binding sites for a long period of time (and it remains to be determined how long this must be) neuroadaptations are evoked that counter the antipsychotic's effects over time. This plasticity might include elevations in the number and sensitivity of D2 receptors as well as changes in gene regulation.

In summary, our findings show that 1) continuous antipsychotic treatment promotes the development of dopamine supersensitivity and functional tolerance during ongoing treatment; and 2) this can be prevented if antipsychotic treatment is transient, such that normal receptor signaling is periodically restored. The challenge now is to identify the neurobiological processes involved and determine whether the present findings extend to other antipsychotics. These findings along with others showing that continuous receptor occupancy by antipsychotic is not necessary to maintain efficacy (69–71) suggest that one might be able to increase efficacy and potentially reduce side effects by maintaining transiently rather than continuously high brain levels of antipsychotic—a possibility that can be investigated clinically.

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