

Actigraphic measurement of the effects of single-dose haloperidol and olanzapine on spontaneous motor activity in normal subjects

Michael Kiang, MD; Z. Jeff Daskalakis, MD, PhD; Bruce K. Christensen, PhD;
Gary Remington, MD, PhD; Shitij Kapur, MD, PhD

Schizophrenia Division, Centre for Addiction and Mental Health; Department of Psychiatry, University of Toronto, Toronto, Ont.

Objective: To quantitatively examine the effects of haloperidol and olanzapine on spontaneous motor activity in normal subjects. **Design:** Randomized, double-blind, placebo-controlled medication study. **Participants:** Normal volunteers ($n = 30$). **Interventions:** Subjects received 1 dose of either haloperidol 2 mg ($n = 9$), olanzapine 10 mg ($n = 10$) or placebo ($n = 10$) and were admitted to hospital for the next 24 hours. **Outcome measures:** Subjects wore an actigraphic monitor, which recorded movement in 15-second epochs. The Simpson–Angus Extrapyramidal Side Effect Scale (SAS) and the Barnes Akathisia Scale (BAS) were administered before and 7 and 24 hours after medication was given. **Results:** Compared with placebo, total motor activity was decreased by 41% with olanzapine ($p = 0.004$) and by 12% with haloperidol (NS). There were significantly more epochs with zero movement with olanzapine than with haloperidol or placebo. For non-zero epochs, the mean activity count and the distribution of activity counts did not differ significantly among groups. There were no positive findings on the SAS or the BAS. **Conclusions:** Olanzapine decreased total motor activity by increasing the amount of time during which subjects were immobile, rather than by affecting the magnitude of movement during periods in which there was activity. This effect occurred at a dose of olanzapine low enough not to cause clinically observed extrapyramidal side effects. Our results suggest that actigraphy is useful as a sensitive, noninvasive tool for measuring the effect of antipsychotics on spontaneous motor activity.

Objectif : Examiner quantitativement les effets de l'halopéridol et de l'olanzapine sur l'activité motrice spontanée de sujets normaux. **Conception :** Étude sur les médicaments contrôlée par placebo, à double insu et randomisée. **Participants :** Volontaires normaux ($n = 30$). **Interventions :** Les sujets ont reçu soit 2 mg d'halopéridol ($n = 9$), soit 10 mg d'olanzapine ($n = 10$), soit un placebo ($n = 10$) et ont été hospitalisés pendant les 24 heures suivantes. **Mesures de résultats :** Les sujets ont porté un actigraphe, qui enregistrait les mouvements par période de 15 secondes. L'échelle des effets secondaires extrapyramidaux de Simpson-Angus (SAS) et l'échelle d'acathisie de Barnes (BAS) ont été appliquées avant la prise des médicaments, ainsi que 7 heures et 24 heures après l'administration. **Résultats :** Comparativement au placebo, l'olanzapine et l'halopéridol ont entraîné une diminution de l'activité motrice totale s'établissant à

Correspondence to: Dr. Shitij Kapur, Schizophrenia/PET Centre, Centre for Addiction and Mental Health, 250 College St., Toronto ON M5T 1R8; fax 416 260-4164; skapur@camhpet.on.ca

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41 % ($p = 0,004$) et à 12 % (NS) respectivement. On a compté beaucoup plus de périodes sans mouvement chez les sujets ayant reçu de l'olanzapine que chez ceux ayant reçu de l'halopéridol ou un placebo. En ce qui concerne les périodes au cours desquelles il y a eu des mouvements, on n'a pas observé de différence considérable entre les groupes au chapitre de la moyenne du résultat relatif aux activités et de la répartition des résultats relatifs aux activités. L'application des échelles SAS et BAS n'a pas produit de résultats positifs. **Conclusions** : L'administration de l'olanzapine a diminué l'activité motrice totale. Cette diminution tenait à l'accroissement du nombre de périodes au cours desquelles les sujets étaient immobiles plutôt qu'à un effet du médicament sur l'amplitude du mouvement pendant les périodes d'activité. L'effet a été produit par l'administration d'une dose d'olanzapine suffisamment faible pour ne pas causer d'effets secondaires extrapyramidaux observables sur le plan clinique. Nos résultats indiquent que l'actigraphie est utile comme outil non effractif précis de mesure de l'effet des neuroleptiques sur l'activité motrice spontanée.

Introduction

One of the hallmarks of antipsychotic agents is their propensity to decrease spontaneous locomotor activity in rodents.¹⁻³ This finding has been reported with both typical and atypical antipsychotics. The principal mechanism of therapeutic action of both typical and atypical antipsychotics is thought to be their blockade of dopamine D₂ receptors, although atypical antipsychotics are defined by their lower propensity for causing extrapyramidal side effects.⁴ At sufficiently high doses, all antipsychotics cause catalepsy (defined as delayed or absent correction of an abnormal posture)⁵ and decreased treadmill locomotion in rodents.⁶ The effect on spontaneous motor activity, however, is seen at doses lower than those that cause catalepsy or decreased treadmill locomotion.^{2,6} Thus, it has been postulated that these effects of antipsychotics are mediated by different mechanisms, with extrapyramidal side effects resulting from blockade of nigrostriatal dopamine D₂ receptors and spontaneous locomotor activity being inhibited by D₂ receptor blockade in the nucleus accumbens of the limbic forebrain.⁶⁻⁸

In humans, although it is well known that antipsychotics cause extrapyramidal side effects, there has been little study of whether they also decrease spontaneous motor activity. When patients receiving antipsychotics were compared with normal control subjects, "normal purposeless movements," defined as "restlessness, fidgeting and shifting of posture," were found to be significantly less numerous in patients than in controls.⁹ To our knowledge, there have been no other attempts in the human literature to compare spontaneous motor activity in patients taking and not taking antipsychotics. In a double-blind crossover study, Crowley and Hyding-Macdonald⁷ compared activity in patients with schizophrenia who were taking different antipsychotics

— thioridazine or thiothixene. They pointed out the importance of making the distinction in patients, like in animals, between decreased spontaneous activity in the absence of motor impairment and hypokinesia caused by antipsychotic-induced parkinsonism. Spontaneous locomotion was found to be greater in patients taking thioridazine than in those taking thiothixene, even though parkinsonian scores were equal.

The purpose of this study was to quantify the effect of antipsychotics on spontaneous motor activity in humans. To eliminate any confounding effect of psychiatric illness, we chose to measure this in normal subjects. We measured motor activity in a placebo-controlled design, after a single dose of antipsychotic low enough to be unlikely to cause significant extrapyramidal side effects.¹⁰ Motor activity was measured by actigraphy; the subject wore an actometer (or activity monitor), a small device that contains an accelerometer which serially records the amount of motion it has undergone. This type of device has been used in quantifying movement in patients with schizophrenia, including those with antipsychotic-induced akathisia,^{7,11-14} as well as in other neuropsychiatric illnesses.¹⁵⁻¹⁸ One treatment group received a typical antipsychotic (haloperidol) and the other, an atypical antipsychotic (olanzapine). Given that both agents are known to block dopamine D₂ receptors, we wished to test the hypothesis that the antipsychotics would decrease total spontaneous motor activity, even at a dose too low to cause extrapyramidal side effects. We also wished to investigate whether antipsychotics would change the profile of motor activity (i.e., the relative frequency of different amounts of movement).

Methods

Thirty healthy subjects volunteered to participate in the

study. The mean age was 28.6 years (standard deviation [SD] 9.3, range 18–55 yr). Twelve (40%) were women. On the basis of a screening interview, all subjects were found to be free of medical or neurologic illness, and on the basis of results of the Structured Clinical Interview for DSM-IV (SCID-I) all were free of any DSM-IV Axis I diagnoses.¹⁹ Subjects gave informed written consent and were paid for their participation. The study was approved by the ethics review board at the Centre for Addiction and Mental Health.

Medications

This was a double-blind, placebo-controlled, between-subjects design. Subjects were randomly assigned to 1 of 3 groups and received a single oral dose of either haloperidol (2 mg), olanzapine (10 mg) or placebo at 9:30 am on the day of the study. These doses of haloperidol and olanzapine were chosen because they have been shown to produce an equivalent level of dopamine D₂ receptor occupancy but are below the threshold for causing extrapyramidal symptoms.¹⁰ They also are considered equivalent doses clinically, based on the ratio of comparable daily doses of the 2 medications.²⁰

Actigraphic recordings and analysis

Subjects wore an activity monitor (Actiwatch-16, Mini Mitter Company, Bend, Ore.) on their dominant wrist for 24 hours after receiving the study medication. During this period, they were admitted to an inpatient ward. All subjects were assigned to the same room during their respective admissions. There were no other restrictions on subjects' activity.

The Actiwatch uses an omnidirectional accelerometer to sample acceleration 32 times per second with a sensitivity threshold of 0.05 g. This information is digitally integrated by the activity monitor to obtain counts of total activity for 15-second epochs throughout the monitoring period. After the monitoring period, the data were downloaded from the watch to a computer for further analysis. For each subject, data consisted of 5760 consecutive activity counts, corresponding to each of the 15-second epochs over the 24 hours.

A bar chart of activity counts for each epoch in the 24-hour period was plotted for each subject and was visually inspected for plausibility. Epochs were classified as either "zero epochs" if they contained no movement (i.e., their activity count was 0), or "non-zero

epochs" if they contained any movement (i.e., activity count was greater than 0). For each subject, the data were analyzed to determine total movement over 24 hours, number of zero epochs and mean activity count for all non-zero epochs. The means of these variables for the 3 treatment groups were compared using a 1-way analysis of variance (ANOVA).

In addition, for each subject, a percentage distribution for the activity count in non-zero epochs was derived. This was done by sorting non-zero epochs into bins based on the total activity count of the epoch. Thus, the percentage of non-zero epochs whose activity counts ranged from 1 to 50, from 51 to 100, and so on, were respectively calculated. This yielded a histogram representing the number of epochs in each bin. An inverse regression model was fit to this histogram, yielding the equation $y = B/x + c$, where x is the upper limit activity count of the bin, y is the percentage of epochs in the bin and B and c are constants. For the total group of subjects, an analysis of covariance was performed, with y as the outcome variable, treatment group as the nominal independent variable and $1/x$ as the ratio independent variable. This was performed to determine whether the distribution of activity counts differed with treatment group.

Extrapyramidal side-effect rating scales

To rule out antipsychotic-induced parkinsonism and akathisia, the Simpson–Angus Extrapyramidal Side Effect Scale (SAS)²¹ and the Barnes Akathisia Scale (BAS)²² were administered to subjects before they received the medication and 7 hours and 24 hours after they received it.

Results

On visual inspection, bar charts of the actigraphic recordings appeared plausible except for 1 subject in the haloperidol group for whom the recording was incomplete; data for this subject were excluded from further analysis. For the 3 treatment groups, the mean values for the 24-hour monitoring period for total movement, number of zero epochs and mean activity count for all non-zero epochs are shown in Fig. 1. The distribution of each of these 3 variables did not depart significantly from normality for any of the 3 treatment groups, as determined by the Shapiro–Wilk test (haloperidol $W = 0.95$, $p = 0.72$; olanzapine $W = 0.89$,

$p = 0.15$; placebo $W = 0.94$, $p = 0.55$). Also, for each variable, Levene's test showed equality of variances among the 3 treatment groups ($F = 0.13$, $p = 0.88$). One-way ANOVA demonstrated a statistically significant group effect on total movement ($F = 6.88$, $p = 0.004$) and on number of zero epochs ($F = 14.39$, $p < 0.001$). Post-hoc between-group comparisons, with Tukey's honestly significant difference correction for multiple comparisons, showed a significant difference in total movement between the olanzapine and haloperidol groups ($p = 0.046$) and between olanzapine and placebo ($p = 0.004$), but not between haloperidol and placebo ($p = 0.60$). Total movement was 41% lower with olanzapine than with placebo and was 12% lower with haloperidol than with placebo, although the latter difference was not statistically significant. There was a significant difference in the number of zero epochs between olanzapine and haloperidol ($p = 0.001$) and between olanzapine and placebo ($p < 0.001$), but not between haloperidol and placebo ($p = 0.66$). There was no significant difference among groups on mean activity count for all non-zero epochs ($F = 0.22$, $p = 0.80$).

For non-zero epochs, the overall distribution of activity counts for the 3 groups is shown in Fig. 2. For the total group of subjects, the best fit to the regression model $y = B/x + c$, (where x is the upper limit activity count of the bin and y is the percentage of epochs in the bin) accounted for 99.1% of the variance. Analysis of covariance showed a bin effect ($F = 6271.8$, $p < 0.0001$) but no treatment group effect ($F < 0.001$, $p > 0.999$), suggesting the distributions were virtually identical among groups.

None of the subjects received a score above 0 on the SAS or on the BAS at any of the 3 times they were tested.

Discussion

Our results showed that a single dose of olanzapine in normal subjects led to a significant decrease in total motor activity, compared with either haloperidol or placebo. Total activity was decreased 41% with olanzapine compared with placebo. Our use of normal subjects to preclude confounding effects of illness implies that this was an intrinsic effect of the medication. Total

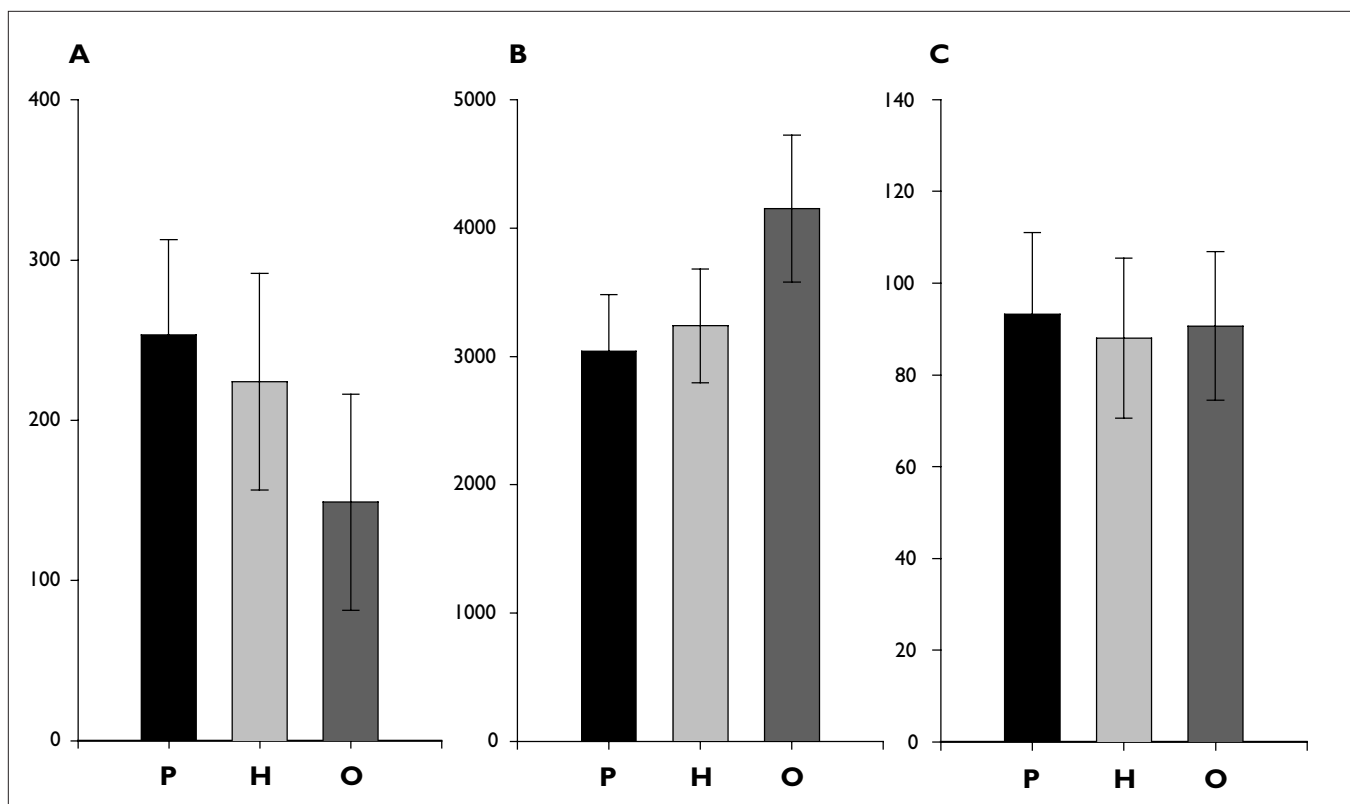


Fig. 1: Twenty-four-hour values for total activity (A), number of zero epochs (B) and mean activity count for all non-zero epochs (C). Group means are shown, with bars representing standard error of the mean. P = placebo; H = haloperidol; O = olanzapine.

activity was decreased 12% with haloperidol compared with placebo, but the difference was not statistically significant.

The decrease in motor activity with olanzapine was explained exclusively by an increase in the periods of time when there was no activity (i.e., when subjects were immobile). In contrast, we found no difference between the 3 groups in the relative amount of activity during the periods that subjects were moving (i.e., for non-zero epochs, the mean activity count per epoch and mathematical descriptors of the distribution of epochs by magnitude of activity count for each group were indistinguishable). This finding, along with the absence of positive findings on the SAS, suggests that olanzapine increased periods of immobility but did not change the magnitude of movements that were made, as might be expected with antipsychotic-induced parkinsonism. Although to our knowledge the profile of movements has not been documented in Parkinson's disease or parkinsonism, one might expect that if such motor impairment was present, there would be a skew

toward a greater relative frequency of low-magnitude movements.

The decreased motor activity caused by olanzapine in the absence of extrapyramidal side effects is consistent with rodent studies in which antipsychotics, including olanzapine,²³ decreased motor activity at doses lower than those that cause catalepsy or decreased treadmill locomotion (signs thought to correspond with extrapyramidal side effects in humans).²⁶ It has thus been postulated that the decreased spontaneous motor activity and extrapyramidal side effects caused by antipsychotics are mediated by different mechanisms. According to this theory, the former is caused by blockade of mesolimbic dopaminergic D₂ receptors in the nucleus accumbens and the latter by blockade of the nigrostriatal dopaminergic pathway.^{6-8,23}

Our finding that haloperidol did not significantly decrease motor activity seemed inconsistent with this theory, as well as with reports that haloperidol decreases spontaneous motor activity in rodents.^{2,24,25} As we found motor activity to be 12% less in the

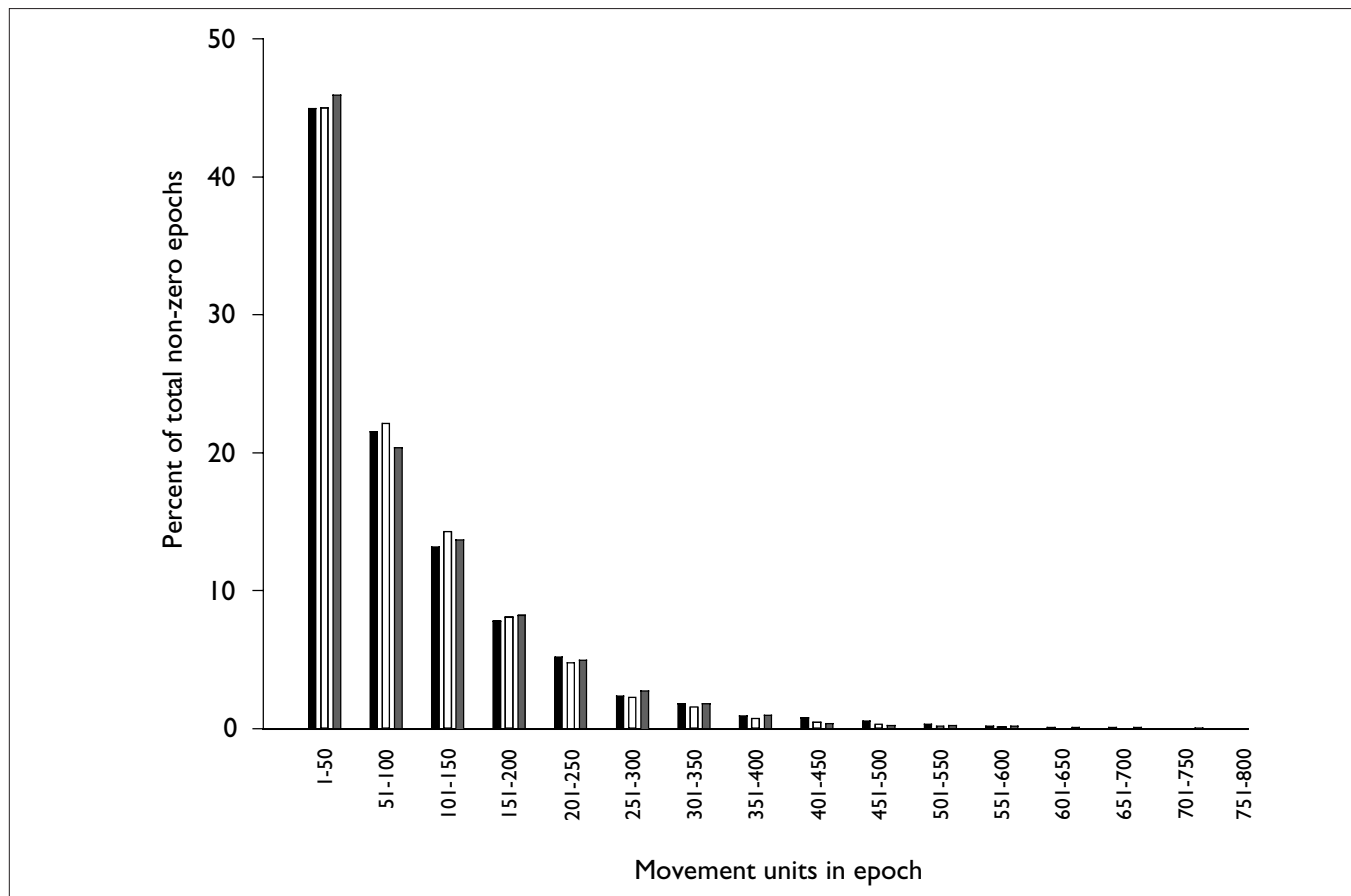


Fig. 2: Percent distribution of non-zero epochs according to activity count per epoch.

haloperidol group than in controls, a possible explanation is that this reflected a true drug effect, but that our sample was not large enough for it to be statistically significant. Assuming the true difference in activity between haloperidol and placebo was of the magnitude that we found, a sample size of 29 for each group would have been necessary to detect a difference between these 2 means at a statistical significance of 0.05 with 80% power.²⁶

There have been no animal studies that have directly compared the effects of haloperidol and olanzapine on spontaneous locomotor activity and could thus serve as a comparison for our result. Simon et al²⁵ compared haloperidol with clozapine, which like olanzapine has a relatively high affinity for serotonergic 5-HT₂ receptors and histaminergic H1 receptors and a low affinity for dopaminergic D₂ receptors.²⁷ They found a dose-dependent effect of the drugs on motor activity in mice, with both haloperidol (0.3 mg/kg) and clozapine (3.6 mg/kg) decreasing motor activity by a similar amount. Human data, however, imply that these doses of the 2 drugs are not equivalent. For example, the recommended therapeutic dose for haloperidol is 3–20 mg/d²⁷ versus 200–400 mg/d for clozapine.²⁸ In a PET receptor study of patients, 200–400 mg/d of clozapine produced a lower occupancy of D₂ receptors than 8 mg/d of haloperidol.²⁹ This suggests that in the study by Simon et al,²⁵ an equivalent dose of clozapine would have been substantially higher and might have decreased motor activity more, which would be consistent with our finding that olanzapine decreased motor activity more than an equivalent dose of haloperidol.

In our subjects, olanzapine might have caused longer periods of immobility by inducing more somnolence, for instance, through its greater affinity than haloperidol for histamine H1 receptors.^{30,31} Clinically, however, it has been shown that olanzapine at 7.5–12.5 mg/d, a dose similar to the one we used, did not cause more subjective somnolence than placebo.³² A limitation of our study was that it was not possible to definitely determine whether the immobility in the olanzapine group reflected an increase in time asleep or an increase in the time individuals were awake and immobile. Future studies that also include objective sleep monitoring could help elucidate the extent to which a differential reduction of motor activity by different antipsychotics is accounted for by their relative sedative effects.

To our knowledge, this is the first study to show

quantitatively that antipsychotic medication can decrease spontaneous motor activity in humans. These data were obtained in healthy subjects and, therefore, may not generalize to patients with schizophrenia or other illnesses because of the possible interaction with illness-induced motor alteration.

Although the decrease in motor activity with haloperidol did not reach statistical significance, our results provide tentative support for the postulate, based on animal research, that decreased motor activity is an intrinsic effect common to all antipsychotics as a result of D₂ receptor blockade. Additional actigraphic studies, using a wider range of antipsychotics and dosages and larger samples, are needed to confirm this and to determine whether various antipsychotics have different effects on spontaneous motor activity.

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