"Extended" Antipsychotic Dosing in the Maintenance Treatment of Schizophrenia: A Double-Blind, Placebo-Controlled Trial

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Objective: In the treatment of schizophrenia, all currently available oral antipsychotics are administered at least once daily, with strict adherence strongly encouraged to minimize risk of relapse. Based on a better understanding of the brain kinetics of antipsychotics, we have proposed a variation of this approach, "extended" dosing, which allows for intermittent but regular dosing.

Method: We carried out a randomized, double-blind, placebo-controlled trial evaluating 35 individuals with *DSM-IV*–defined schizophrenia who had been stabilized on antipsychotic therapy. Over a 6-month interval, 18 subjects received their medication as usual (daily), while 17 received their antipsychotic therapy every second day (extended). Outcome measures included clinical scales to assess symptoms (Brief Psychiatric Rating Scale [the primary outcome measure], Calgary Depression Scale), illness severity (Clinical Global Impressions-Severity of Illness scale), and relapse (ie, rehospitalization) rates. Side effects were also assessed, including movement disorders (Barnes Akathisia Scale, Simpson-Angus Scale, Abnormal Involuntary Movement Scale) and weight. The study was conducted from February 2003 to July 2007.

Results: Individuals in the extended dosing group were not at greater risk of symptom exacerbation, relapse, or rehospitalization; indeed, more rehospitalizations occurred in those receiving regular dosing. At the same time, though, there was no indication that side effects were significantly reduced in the extended dosing group.

Conclusions: These results challenge the long-standing dogma that oral antipsychotics must be administered daily in stabilized patients with schizophrenia. Further studies with larger samples are needed to replicate these findings, as well as to elucidate whether postulated clinical advantages can be established and determined to outweigh potential risks.

Trial Registration: clinicaltrials.gov Identifier: NCT00431574

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Discontinuing antipsychotic medication during the ongoing treatment of schizophrenia has been clearly linked to increased relapse rates[1–4]; for example, these are 25% to 30% higher in individuals who discontinue treatment in the first year following hospital discharge.[3] Thus, ensuring ongoing compliance is considered critical to any treatment program's success.[5]

This said, we actually know very little regarding the daily administration of antipsychotic medications. Prescribing patterns have historically been guided by peripheral pharmacokinetic factors (eg, plasma half-life, steady-state levels),[6–9] and all of the oral antipsychotics that are currently available clinically are administered at least once daily. In the past, there has been interest in "intermittent" or "targeted" antipsychotic therapy, which allowed for relatively lengthy intervals off antipsychotic treatment and readministration based on identification of prodromal symptoms suggestive of decompensation.[6–13] Enthusiasm for this approach was tempered, though, with reports of poorer outcomes in studies employing such a strategy (Table 1).[14–20]

However, several more recent lines of investigation support a reexamination of this notion. While dopamine D_2 blockade continues to represent the sine qua non of antipsychotic activity,[21] the nature of this role has been refined. At a molecular level, the rapid dissociation model confirmed that even drugs with very transient binding to the D_2 receptor (eg, quetiapine, clozapine) demonstrate antipsychotic efficacy clinically.[22–24] In addition, animal work involving behavioral models of antipsychotic efficacy (ie, conditioned avoidance responding, amphetamine-induced locomotion) has provided evidence that transient antipsychotic exposure circumvents changes at the level of the D_2 receptor associated with continuous treatment that may compromise response over time.[25,26] Systemically, neuroimaging data have established that optimal clinical response occurs when D_2 occupancy exceeds 60% to 70% for many antipsychotics,[27,28] especially drugs like haloperidol and risperidone; however, it has also been demonstrated that response can be maintained at lower occupancies.[29,30] Taken together, this evidence confirms a central role for D_2 occupancy in the

Table 1. Characteristics of 5 Trials Involving Targeted or Intermittent Antipsychotic Treatment in Schizophrenia

Study	Design	Sample	Outcome
Carpenter et al, 1987[11,a]	Open 2-Year follow-up	Schizophrenia, outpatients (N = 42) Continuous (n = 21) Targeted + psychosocial intervention (n = 21)	Dropouts: continuous 42.9% vs targeted 33.3% Targeted: antipsychotic-free 68.8% of time No difference in hospitalizations, psychopathology, or level of functioning
Carpenter et al, 1990[14]	Single-blind 2-Year follow-up	Schizophrenia, stabilized (N = 116) Continuous (n = 59) Targeted (n = 57)	Dropouts: continuous 18.6% vs targeted 50.9% Targeted: antipsychotic-free 48% of time Targeted: increased rates of decompensation and hospitalization (53% vs 36%) + decreased employment
Herz et al, 1991[17,b]	Double-blind 2-Year follow-up	Schizophrenia/schizoaffective, stabilized (N = 101) Continuous (n = 51) Intermittent (n = 50)	Dropouts: continuous 25.5% vs targeted 62% Intermittent: antipsychotic-free 73% of the time Targeted: increased relapse rates (16% vs 30%); no difference in side effects
Jolley et al, 1990[19,c]	Double-blind 2-Year follow-up	Schizophrenia, stabilized (N = 54) Continuous (n = 27) Intermittent (n = 27)	Dropouts: continuous 7.4% vs intermittent 11.1% Intermittent: mean total antipsychotic dose 18.4% of continuous group Targeted: increased relapse rates (50% vs 12%); decreased extrapyramidal symptoms and tardive dyskinesia (30% vs 44%)
Pietzcker et al, 1993[20]	Open 2-Year follow-up Intermittent subdivided (early intervention with prodromal symptoms; crisis intervention with relapse)	Schizophrenia, stabilized (N = 364) Continuous (n = 122) Intermittent: Early intervention (n = 127) Crisis intervention (n = 115)	Dropouts: continuous 42.6% vs early intervention 59.8% vs crisis intervention 67% Intermittent: approximately 50% cumulative antipsychotic dosage Intermittent: increased dropouts, relapse rates (continuous 23% vs early intervention 49% vs crisis intervention 63%), and rehospitalization (continuous 24% vs early intervention 37% vs crisis intervention 43%)

[a]Preliminary data.[10,12]
[b]Preliminary data.[16]
[c]Preliminary data.[18]

action of antipsychotics, but also indicates that *sustained* D_2 occupancy 24 hours daily is not necessary.

These advances in our understanding led us to postulate that intermittent, but regular, antipsychotic exposure may provide clinical benefits comparable to daily dosing in maintenance therapy, and in so doing decrease overall antipsychotic exposure. An earlier open pilot study[31] by our group further supported this principle, indicating no increase in relapse rates in a small number of individuals who, during maintenance treatment for schizophrenia, were instructed to take their antipsychotic every second day over a 3-month interval, followed thereafter by a 3-month period in which the antipsychotic was administered every 3 days. We chose to call this strategy "extended" versus intermittent dosing to underscore the need for regular antipsychotic administration, contrasted with the prolonged gaps permitted in early trials of intermittent pharmacotherapy.

Armed with what we saw as a tenable rationale and these preliminary data, we undertook a larger, double-blind trial to establish whether extended antipsychotic dosing is viable in the maintenance treatment of schizophrenia. This line of investigation is very much in keeping with a recent review of intermittent dosing and its conclusion that "initial studies should examine clinically stabilized patients to establish whether intermittent dosing maintains remission to the same degree as traditional schedules of dosing."[32(p216)]

METHOD

Setting and Sample Selection

The study was undertaken at the Centre for Addiction and Mental Health, Toronto, Ontario, Canada. Eligible subjects were recruited from the outpatient population of the Schizophrenia Program, which offers both acute inpatient and ongoing outpatient care to over 4,000 individuals. Written, informed consent was obtained for all those who participated following approval of the protocol and its documentation by the University of Toronto Human Subjects Review Committee. The study was conducted from February 2003 to July 2007 and was registered with ClinicalTrials.gov (NCT00431574).

The study was restricted to subjects meeting the following criteria: (1) *DSM-IV* diagnosis of schizophrenia based on clinical interview, collaborative history, and chart review; (2) capacity to provide written, informed consent; (3) stabilized as outpatients with a single, oral antipsychotic (with the exception of clozapine and quetiapine) ≥ 3 months;

(4) no exposure to a depot antipsychotic ≥ 1 year; (5) no current diagnosis of substance abuse according to *DSM-IV* criteria; and (6) evidence of adherence with current antipsychotic treatment. With regard to criterion 3, patients receiving clozapine and quetiapine were excluded as there is theoretical and anecdotal evidence that abrupt discontinuation of these drugs, possibly related to their rapid k_{off}, may result in an increased risk of symptom exacerbation.[33,34] Clozapine was also excluded because of the differences required in monitoring individuals on this medication (ie, more frequent visits, routine bloodwork) and concerns that this could influence outcome. With regard to criterion 6, patients were deemed adherent with antipsychotic treatment if their clinicians and case managers rated this to be ≥ 80%.

Study Design and Interventions

Those individuals who met the aforementioned criteria were maintained on their same antipsychotic and randomly assigned (1:1 ratio) to 1 of 2 treatment arms: (1) treatment as usual (TAU) or (2) the same daily dose administered every other day. To maintain a double-blind design, pharmacy.ca (Toronto, Ontario, Canada; a company specializing in the preparation of drugs for experimental trials) was employed to provide, on an individualized basis, all antipsychotics at the appropriate dose and placebo when necessary in matching gelatin capsules. Thus, from the individual subject's position, antipsychotic medication continued according to the same daily schedule as before the protocol commenced. Other psychotropic medications prescribed prior to the study were permitted, with any changes in dosing during the course of the study documented.

Outcome Measures

Study duration was 6 months with scheduled visits every 2 weeks, at which time scales were completed and study medication dispensed. Blister packs were prepared for the study medication, and adherence (≥ 80%) was monitored through pill counts at regularly scheduled visits. Plasma antipsychotic and prolactin levels were drawn at 3 and 6 months, or upon premature study discontinuation if possible. Administered scales were chosen to assess symptoms as well as side effects and included the following: Brief Psychiatric Rating Scale (BPRS),[35] Clinical Global Impressions-Severity of Illness scale (CGI-S),[36] Calgary Depression Scale,[37] Barnes Akathisia Scale,[38] Simpson-Angus Rating Scale for extrapyramidal symptoms,[39] Abnormal Involuntary Movement Scale (AIMS) for tardive movements,[36] and Drug Attitude Inventory for subjective response.[40]

Statistics

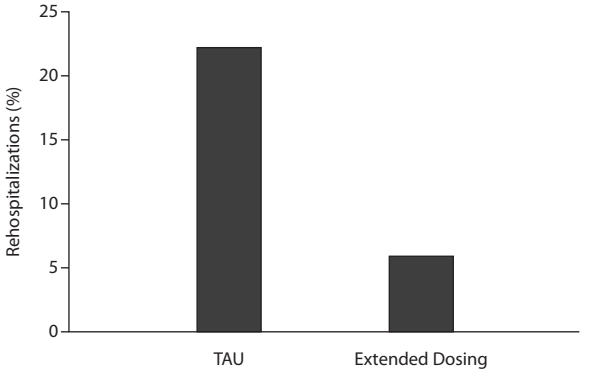
All subjects who completed at least 1 follow-up visit were included in the data analyses, which were carried out using the Statistical Package for Social Sciences (SPSS) for Windows, Version 16 (SPSS Inc; Chicago, Illinois). Our primary hypothesis was that total BPRS scores would not significantly differ over the course of the trial between the extended dosing group and TAU.

Table 2. Baseline Comparison of Regular Dosing (n = 18) and Extended Dosing (n = 17) Groups on Demographic and Clinical Measures[a]

Measure	Regular Dosing	Alternate-Day Dosing	*t* (2-tailed)[b]	*P*
Gender, male/female, n	10/8	11/6	…	.73[c]
Age, y	37.1 (14.6)	39.8 (11.5)	2.40	.55
Weight, lb	190.3 (50.9)	184.4 (50.0)	−0.30	.77
BPRS				
Total	25.2 (4.2)	25.6 (5.7)	2.40	.81
Thought disorder	7.6 (2.8)	9.4 (4.2)	1.29	.21
Withdrawal-retardation	7.8 (2.1)	7.6 (1.7)	−0.35	.73
Anxiety-depression	9.6 (3.4)	9.1 (3.2)	−0.34	.74
Hostility-suspiciousness	4.2 (0.6)	5.2 (1.5)	2.45	.25
Activation	3.8 (2.3)	3.1 (0.3)	−1.15	.28
CGI-S	2.9 (1.0)	2.8 (0.7)	−0.61	.55
Calgary Depression Scale	2.33 (3.1)	1.9 (2.5)	−0.43	.67
Barnes Akathisia Scale	0.42 (0.7)	0.5 (1.2)	0.22	.83
Simpson-Angus Rating Scale	1.0 (1.0)	0.9 (1.0)	−0.35	.70
AIMS	0.33 (0.8)	0.0 (0.0)	1.74	.09

[a]Values expressed as mean (SD) unless otherwise specified.
[b]*df* = 33.
[c]Fisher test, 2-tailed.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale.

Figure 1. Rehospitalization Rates During the Study and the Following Month for the Treatment as Usual (TAU; 4/18 subjects, 22.2%) and Extended Dosing (1/17 subjects, 5.9%) Groups



Demographic and clinical details of the study population were examined using *t* tests or Fisher exact test. We were also interested in comparing whether differences existed between those who completed the 6-month trial and partial completers. Analysis of variance, using polynomial contrasts, evaluated interactions between linear trend of time and group.

RESULTS

Subject Characteristics

A total of 38 subjects consented to the study (BPRS score range, 18–39), although 3 individuals withdrew consent

Table 3. Baseline Comparison of Those Completing the Study (n = 26) and Partial Completers (n = 9) on Clinical Measures[a]

Measure	Completers	Partial Completers	*t* (2-tailed)[b]	*P*
Gender, male/female, n	12/14	8/1	…	.05[c]
Age	39.9 (14.6)	34.2 (9.0)	1.12	.27
Weight, lb	182.8 (43.6)	203.5 (68.4)	−0.89	.38
BPRS				
Total	25.4 (5.0)	22.9 (3.4)	−1.42	.17
Thought disorder	8.6 (3.7)	6.6 (0.7)	−2.65	.01
Withdrawal	7.7 (1.9)	8.6 (2.5)	1.09	.28
Anxiety-depression	9.4 (3.2)	8.0 (2.5)	−1.13	.27
Hostility	4.7 (1.2)	4.4 (0.9)	−0.63	.53
Activation	3.4 (1.6)	3.0 (0.0)	−0.80	.43
CGI-S	2.9 (0.9)	2.7 (0.7)	0.75	.46
Calgary Depression Scale	2.1 (2.8)	1.2 (1.6)	−0.87	.39
Barnes Akathisia Scale	0.5 (1.0)	0.3 (0.7)	−0.37	.71
Simpson-Angus Rating Scale	0.9 (1.0)	1.2 (1.3)	0.71	.48

[a]Values expressed as mean (SD) unless otherwise specified.
[b]*df* = 23.
[c]Fisher test, 2-tailed.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale.

Table 4. Trends Across Time and Interactions With Group for Clinical Measures (n = 21–24)[a]

Measure	Baseline, Mean (SD)	Week 24, Mean (SD)	Linear Trend		Linear Trend × Group	
			F[b]	*P*	F[b]	*P*
BPRS						
Total	25.6 (4.9)	24.1 (4.4)	6.39	.02	< 1.0	.43
Thought disorder	8.8 (3.8)	9.0 (3.6)	< 1.0	.34	< 1.0	.51
Withdrawal-retardation	7.6 (1.8)	6.8 (1.6)	6.72	.02	2.18	.15
Anxiety-depression	9.4 (3.3)	8.1 (2.4)	12.18	.00	< 1.0	.75
Hostility-suspiciousness	4.8 (1.3)	4.5 (1.1)	3.53	.08	1.29	.27
Activation	3.4 (1.6)	3.2 (0.8)	4.74	.04	2.67	.12
CGI-S	0.8 (0.6)	0.7 (0.6)	< 1.0	.89	1.52	.23
Calgary Depression Scale	2.3 (2.9)	0.8 (2.0)	9.71	.01	< 1.0	1.0
Barnes Akathisia Scale	0.4 (0.7)	0.2 (0.5)	< 1.0	.49	3.62	.07
Simpson-Angus Rating Scale	1.0 (1.1)	0.4 (0.8)	8.77	.01	< 1.0	.85

[a]Ns vary across measures.
[b]*df* = 1.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale.

before the first follow-up visit. In each of these cases, there was no indication, subjective or objective, of symptom deterioration. Of the remaining 35 subjects, 18 were assigned to TAU (risperidone, n = 8; olanzapine, n = 8; loxapine, n = 2), while 17 received their same daily antipsychotic dose but every other day, that is, extended dosing (risperidone, n = 6; olanzapine, n = 11). Demographic and clinical details of the study population, with the use of *t* tests or Fisher exact test as required, indicated no significant difference at baseline on any of the identified outcome measures (Table 2).

Twenty-six individuals completed the 6-month trial, with an additional 9 partial completers. Of the latter, 4 withdrew consent, and 5 were withdrawn by the investigator. Among the 4 individuals withdrawing consent, 1 (who was in the TAU condition) was hospitalized within a month of study completion. Of the 5 subjects withdrawn by the investigator, 1 failed to attend regularly scheduled visits (BPRS improvement of 11% at endpoint). The remaining 4, all but 1 of whom were in the TAU condition, were readmitted to the hospital (Figure 1).

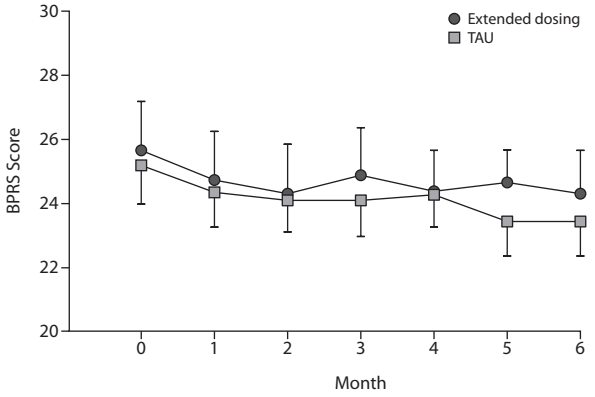
As well as hospitalization, we chose to look at relapse, operationally defined as a 20% increase in symptoms. We were specifically interested in overall symptoms (ie, BPRS total), as well as the subscale scores for thought disorder and hostility-suspiciousness given that these may be most sensitive to changes in antipsychotic dosing. Relapse rates for each of the measures were as follows: BPRS total: TAU = 3/18 (16.67%) vs extended dosing = 4/17 (23.52%), $P = .61$, NS; BPRS thought disorder: TAU = 5/18 (27.78%) vs extended dosing = 5/17 (29.41%), $P = .91$, NS; BPRS hostility-suspiciousness: TAU = 3/18 (16.67%) vs extended dosing = 2/17 (11.77%), $P = .68$, NS. Thus, there was no indication that extended dosing was associated with increased relapse rates in terms of either total psychopathology or psychotic symptoms.

Further comparisons between groups on baseline measures generally showed no differences at onset between completers and partial completers (Table 3). Of note, women were more likely to complete the trial than men (93.3% vs 60.0%, $P = .04$), while partial completers had slightly lower scores on the BPRS thought disorder subscale (Table 3). The Levene test of homogeneity of variance also found the partial completers to be significantly more homogeneous on this measure than completers ($F = 10.51$, $P = .003$); as a result, the means of the 2 groups on that measure were compared with a *t* test that did not assume homogeneity of variance. Mean CGI-S scores were significantly higher at baseline in men versus women (3.15 vs 2.17, $t_{33} = -2.44$, $P = .02$), which may have, at least in part, contributed to the lower rate of completion among men. However, there were no significant differences between men and women on total BPRS (24.85 vs 24.67) or BPRS thought disorder (7.70 vs 8.53) or hostility/suspiciousness (4.60 vs 4.73) subscales at baseline.

Clinical Outcome and Side Effects

Analysis of variance that used polynomial contrasts found no significant interactions between linear trend of time and group (Table 4), indicating consistent changes in mean outcomes across the trial were approximately the same for both groups. This is clearly evident, for example, in examining changes in total BPRS scores, the primary outcome measure (Figure 2). Although it might be argued that there was inadequate power to afford adequate tests of the interactions, the finding that *P* values were so consistently large suggests that low power was probably not a good explanation for these null results. Averaging scores across groups revealed that patients improved modestly over the course of the 24-week trial on most of the outcomes examined (main effects of time shown in Table 4), possibly reflecting the added structure and contact accompanying the study. No significant differences were noted between groups for depression, akathisia,

Figure 2. Change in Mean (± SD) Total BPRS Scores for the Extended Dosing Group (n = 14) Versus the Treatment as Usual (TAU) Group (n = 12) in Those Completing the 6-Month Trial



Abbreviation: BPRS = Brief Psychiatric Rating Scale.

or extrapyramidal symptoms (EPS), and there was a mild reduction in weight for both groups (TAU 2.7% vs extended dosing 1.7%) that was not significantly different.

Certain measures examined are not included in Tables 3 and 4 as statistical analysis of data obtained with them were not amenable to classical statistical procedures. On the AIMS, for example, the extended dosing group had a mean score of 0.00 (SD = 0.00) at all times, while the TAU sample had a mean of 0.33 (SD = 0.78) at all times.

A similar pattern of essentially no change over time for either group emerged on the CGI-S. The extended dosing group had a mean CGI-S score of 2.75 (SD = 0.75) in all but 1 week; at week 12, the mean was negligibly higher at 2.83 (SD = 0.84). For the TAU sample, the mean CGI-S score was 3.08 (SD = 1.16) in all but 1 week (ie, week 12; mean = 3.25, SD = 1.14).

DISCUSSION

The negative impact of antipsychotic nonadherence on outcome in schizophrenia has been well established,[5,41] leading clinicians to stress the importance of taking the medication daily and not missing doses. While we do not disagree with the need for regular dosing, we wanted to examine whether this means daily administration. The present data, representing a double-blind study comparing daily with alternate day (extended) dosing, suggest this may not be necessary in the maintenance treatment of individuals with schizophrenia who have been stabilized. In summary, over 6 months there was no evidence that those in the extended dosing group showed any greater risk of symptom exacerbation, relapse, or rehospitalization versus those in the TAU group. These findings are in keeping with earlier pilot data by our group.[31]

Our results are at odds with a number of previous studies evaluating "intermittent" antipsychotic therapy,[14–20] but this may not be so surprising. This earlier work accommodated prolonged intervals without medication (eg, months), depending on medication reinstatement at the earliest sign of prodromal symptoms, a strategy that is nonspecific at best and very possibly too late in reversing a clinical deterioration already in motion. Our use of "extended" dosing was based on several more recent lines of investigation indicating that while D_2 occupancy is critical for antipsychotic efficacy, this does not need to be sustained.[21–24,30] To this end, we advocated regular dosing and in this study confined the interval to 48 hours. Of note, a study[42] that allowed for weekly 2-day holidays over 6 weeks in patients with stabilized schizophrenia receiving oral haloperidol also failed to find an increased risk of clinical deterioration. While our pilot data extended this interval in a very small group to 72 hours,[31] what constitutes a "safe" window remains unclear. Along similar lines, in a 54-week, double-blind study[43] involving the depot antipsychotic fluphenazine decanoate, extending the injection interval from 2 to 6 weeks did not increase relapse risk. More recently, we have also reported a similar strategy with long-acting injectable risperidone, extending the injection interval from 2 to 4 weeks over a 48-week follow-up period. D_2 occupancy levels were evaluated during the last 4 days of the injection interval, and despite 4 of 7 subjects having levels below 60%, there was no indication of clinical deterioration.[30] Given that psychosis is very likely mediated by a number of biologic and psychological factors,[44–46] it is also possible that this window may be subject to both interindividual and intraindividual variability. Further, it remains to be seen if there are differences between antipsychotics; the present sample, incorporating individuals receiving both conventional and second-generation antipsychotics, was too small to systematically evaluate interdrug differences. Further, we did not have subjects receiving aripiprazole or ziprasidone, and we chose not to include individuals receiving clozapine or quetiapine, as there is at least theoretical concern that risk of relapse may be greater with discontinuation of antipsychotics characterized by rapid dissociation from the D_2 receptor.[33,34] Whether risk of relapse would increase with extended dosing based on this, or other pharmacologic or clinical differences, remains unclear.

Any interpretation of the present findings must be weighed in the context of the study's limitations. Most notable is the relatively small sample size; we hypothesized that extended dosing would not increase risk of clinical deterioration, but to capture a 20% difference in outcome between treatment groups would require a sample of approximately 40 subjects per group ($\alpha = .05$, $\beta = .80$, 1-tailed). As pointed out, though, the consistently large *P* values offer at least indirect evidence that lack of statistical power may not be a plausible explanation for the lack of difference between groups in outcomes. However, lack of power may explain our failure to confirm predictions that extended dosing would result in fewer side effects versus TAU. Our primary measure of compliance was pill count, with an established threshold of ≥ 80%. Previous work by our group has, in fact, demonstrated that pill count may be the best proxy clinicians have for assessing adherence, but this does not speak to patterns of adherence (eg, missing sporadic single doses versus multiple doses in sequence),

and what constitutes a reliable threshold for antipsychotic adherence has yet to be established.[47] The present study was confined to a 6-month interval and therefore cannot speak to the possibility of increased risk over time.

Decreased antipsychotic exposure, whether in the form of lower doses and/or intermittent dosing, has been driven by concerns regarding the short- and long-term side effects of these medications. While the logic seems intuitively straightforward, identification of clear benefits has not been so clear. Of the past studies employing a targeted strategy, 1 reported decreased EPS with this approach,[18,19] although this was not the case in others.[16,17,20,43] Moreover, differences were not found for tardive dyskinesia,[16–20,43] global side effects, subjective well-being, psychosocial functioning, or social integration.[16,17,20,43] In our study, diminished depression scores were not detected, as was hypothesized, although it may be that more discrete measures are necessary to elucidate possible changes in antipsychotic-related dysphoria per se. The use of lower antipsychotic doses and newer antipsychotics may well account for the inability to detect decreased EPS, supported by the very low EPS scores seen at baseline in this sample. In terms of other side effects, we were unable to detect notable changes in weight in those who received a 50% decrease in antipsychotic exposure over 6 months. Specifically, both TAU and extended dosing showed a very small reduction over the study's course, 2.7% and 1.7%, respectively. Such results remind us that side effects may not be dose-dependent, at least in a linear fashion, and that measures such as weight gain may be multifactorial in origin.

These limiting factors, in conjunction with other practical concerns, emphasize the need for caution in immediately translating our results to clinical practice. It cannot be ignored, for example, that taking medication on alternate days may actually be more difficult than a routine of daily dosing. We would argue, though, that the evidence calls into question the long-established notion of daily antipsychotic dosing, occasionally multiple times daily, based on older concepts such as peripheral pharmacokinetics, plasma half-life, and steady-state levels. At least in individuals who have been stabilized, this may not be necessary, although in point of fact this question remains as valid in acute psychosis. We highlight that the requirement here was stabilization, not minimal or absent symptoms. This was also the case in the 1 other report that employed a clearly circumscribed, relatively brief drug-free interval (ie, 2-day drug holidays weekly) and found no clinical deterioration.[42]

Evidence convincingly argues against intermittent or targeted antipsychotic therapy. However, such a strategy is notably different from our proposed notion of extended antipsychotic dosing, which instead advocates regular, but not necessarily daily, ongoing treatment. Extended dosing draws support from advances in our understanding of antipsychotic action, particularly with respect to D_2 binding, and the results of this double-blind study add to earlier positive findings from an open trial.

What are the implications of this work? Perhaps most importantly, it encourages us to critically reexamine the long-established clinical axiom that individuals with schizophrenia must receive oral antipsychotic treatment daily to remain stabilized. While this could be true for some individuals, we are reminded that schizophrenia is heterogeneous and that there may be at least a subgroup that can do as well, or even better, with extended but regular dosing. Future work would benefit from (1) replicating the present findings, (2) examining whether postulated clinical advantages can be established and determined to outweigh potential risks, and (3) pursuing markers by which clinicians could identify potential candidates for extended dosing. From a mechanistic standpoint, a fundamental question centers on how long (or how often) the D_2 receptor needs to be blocked to effect clinical response. That transient D_2 binding can be as effective is in line with the position that sustained D_2 occupancy is not necessary to set in motion the cascade of biochemical events downstream that translate to clinical response. From another perspective, does continuous blockade invoke changes that could be detrimental, and what is the nature of these changes? Preclinical work involving animal models of antipsychotic activity has identified loss of efficacy in conjunction with continuous treatment and linked this, in part, to increased density of striatal D_2 receptors and D_2 receptors in a high-affinity state for dopamine.[25,26] Expanding this work to humans, using in vivo imaging techniques, will be critical. The possibility of diminished response over time with continuous antipsychotic exposure raises the issue of tolerance, an issue that has been raised clinically vis-à-vis antipsychotics in the past[48–50]; to date, though, the field has not ascribed antipsychotic tolerance to chronic exposure.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), loxapine (Loxitane and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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