Impact of Once- Versus Twice-Daily Perphenazine Dosing on Clinical Outcomes: An Analysis of the CATIE Data

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ABSTRACT

Objective: The objective of this study was to evaluate the impact of once- versus twice-daily dosing of perphenazine, which has a plasma half-life of 8–12 hours, on clinical outcomes in patients with schizophrenia.

Method: Data from phase 1 of the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) conducted between January 2001 and December 2004 were used in this post hoc analysis. Patients with schizophrenia (*DSM-IV*) randomly allocated to treatment with perphenazine were also randomly assigned to once-daily (N = 133) or twice-daily (N = 124) dosing and followed over 18 months. Discontinuation rate and time to discontinuation were used as primary outcomes to compare the 2 groups. The following clinical outcomes were analyzed as secondary measures: *efficacy*—Positive and Negative Syndrome Scale, Clinical Global Impressions-Severity scale, Calgary Depression Scale for Schizophrenia, and Drug Attitude Inventory and *safety/tolerability*—Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, Simpson-Angus Scale, and body weight. Data on treatment-emergent adverse events, concomitant psychotropic medications, and medication adherence (pill count and clinician rating scale) were also analyzed for each group.

Results: No significant differences were found in any outcome measures between the once-daily and twice-daily dosing groups, which remained the same when using the mean dose of perphenazine as a covariate.

Conclusions: Perphenazine is routinely administered in a divided dosage regimen because of its relatively short plasma half-life. However, the present findings challenge such a strategy, suggesting that once-daily represents a viable treatment option. Results are discussed in the context of more recent evidence that challenges the need for high and continuous dopamine D_2 receptor blockade to sustain antipsychotic response.

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Plasma half-life has routinely been used to establish the dosing schedule of antipsychotics; for example, it is recommended that agents with a short plasma half-life be administered multiple times per day. This schedule holds true for perphenazine, a mid-potency conventional antipsychotic drug that recently demonstrated non-inferior effectiveness when compared to various atypical antipsychotics including risperidone, quetiapine, and ziprasidone in the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE).[1] Perphenazine has a relatively short plasma half-life of 8–12 hours,[2] leading to the recommendation that this drug should be administered 2- to 4-times daily.[3] This recommendation is in contrast to other antipsychotics, like risperidone and olanzapine, that are usually administered once daily on the basis of their longer plasma half-lives.[2]

To our knowledge, there have been 3 double-blind, randomized, controlled trials specifically examining the impact of dosing schedules for specific antipsychotics in the treatment of schizophrenia.[4–6] Nair[4] compared once-daily versus twice-daily dosing of risperidone 8 mg/d, a drug that, as noted, has a relatively long plasma half-life (ie, risperidone: up to 24 hours in poor metabolizers and, for the active metabolite 9-hydroxyrisperidone: 23 hours[2]) in 211 patients. King et al[5] compared 2 times daily versus 3 times daily dosing of quetiapine 450 mg/d, which has a short plasma half-life of 7 hours,[2] in 409 patients. Chengappa et al[6] compared once-daily versus twice-daily dosing of quetiapine 400 or 600 mg/d in 21 patients. Notably, these 3 studies failed to demonstrate any significant differences in efficacy and safety measures between the different dosing regimens, suggesting that antipsychotic drugs can be prescribed less frequently than what would be advocated based on peripheral half-lives. However, study durations of these randomized, controlled studies were as short as 4–6 weeks, which clearly limits any interpretation of results in terms of relapse prevention. In fact, these trials were not designed to assess effectiveness within the framework of longer-term maintenance treatment.

CATIE (ClinicalTrials.gov identifier NCT00014001) has proven an ideal dataset to address a number of clinically related questions given its unprecedented sample size, comprehensive psychopathological assessments, and duration of follow-up (ie, up to 18 months).[7] As part of this trial, a subgroup of patients (version 1.0 dataset) were randomly allocated to treatment with perphenazine; within this arm, they were also randomly assigned to once-daily or twice-daily dosing.[7] The purpose of the present study was to evaluate the impact of these 2 dosing regimens on clinical outcomes in patients with chronic schizophrenia.

METHOD

Study Design

The CATIE study, funded by the National Institute of Mental Health, compared the effectiveness of atypical antipsychotics and

Clinical Points

- Despite the fact that perphenazine is routinely administered in a divided dosage regimen because of its relatively short plasma half-life, no significant differences were found in discontinuation rate and time to discontinuation, or in efficacy and safety measures, between once-daily and twice-daily dosing of perphenazine in patients with schizophrenia.
- The findings suggest it may be necessary to revisit the long-standing axiom that antipsychotic dosing be established based on peripheral pharmacokinetics.

a single conventional antipsychotic, perphenazine, in patients with schizophrenia; the primary results have been detailed elsewhere.[1] Briefly, the study was performed between January 2001 and December 2004 at 57 clinical sites in the United States. Patients (N = 1,493) aged 18 to 65 years and with a *DSM-IV* diagnosis of schizophrenia, based on the Structured Clinical Interview for *DSM-IV*,[8] participated. Patients were initially randomized to olanzapine (7.5–30 mg/d), risperidone (1.5–6.0 mg/d), ziprasidone (40–160 mg/d), quetiapine (200–800 mg/d), or perphenazine (8–32 mg/d) under double-blind conditions and received treatment for up to 18 months or until treatment was discontinued for any reason (phase 1).[7]

Patients allocated to risperidone, olanzapine, and perphenazine were also randomly assigned to either a once-daily or twice-daily dosing regimen at baseline.[7] The present analysis specifically focused on perphenazine and the impact of these 2 dosing schedules on clinical outcomes, using the phase 1 data. It is of note that only patients without tardive dyskinesia were randomized to receive perphenazine; thus, no patient in the present analysis had tardive dyskinesia at baseline.

Outcome Measures

Discontinuation rate and time to discontinuation represented the primary outcome measures, and clinical outcomes could be broken down as follows: *efficacy*—Positive and Negative Syndrome Scale (PANSS),[9] Clinical Global Impressions-Severity scale (CGI-S),[10] Calgary Depression Scale for Schizophrenia (CDSS),[11] and Drug Attitude Inventory (DAI-10)[12]; *safety/tolerability*—Abnormal Involuntary Movement Scale (AIMS),[10] Barnes Akathisia Rating Scale (BARS),[13] Simpson-Angus Scale (SAS),[14] and body weight. All efficacy and safety measures other than the DAI-10 were assessed at baseline and 1, 3, 6, 9, 12, 15, and 18 months, while the DAI-10 was rated at baseline and 6, 12, and 18 months.

Both the Clinical Global Judgment of Medication Adherence[7] and proportion of capsules taken across phase 1 were used to evaluate medication adherence at every visit through phase 1. The Clinical Global Judgment of Medication Adherence is a 4-point clinician-rated scale that ranges from 1, "always/almost always (76%–100% of the time)," to 4, "never/almost never (0%–25% of the time)." Proportion of capsules taken was calculated based on pill count in the returned bottle since the previous visit.

In addition, the following information was collected: mean and modal doses across phase 1; mean dose multiplied by proportion of capsules taken across phase 1 as an actual dose taken by patients; the rates of patients who experienced treatment-emergent adverse events across phase 1; and the rates of patients who newly took concomitant psychotropic medications, time until these medications were initiated, and the duration that these medications were used across phase 1.

Table 1. Baseline Demographic and Clinical Characteristics in Once-Daily and Twice-Daily Perphenazine Dosing Groups

	Once-Daily Group (N = 133)		Twice-Daily Group (N = 124)		Group Difference,
Variable	N	%	N	%	*P*[a]
Male	97	72.9	99	79.8	.24
White	80	60.2	71	57.3	.70
Married	27	20.3	16	12.9	.13
Employed	19	14.3	20	16.4[b]	.73
Exacerbation in the preceding 3 mo	39	29.3	28	22.6	.26
Taking anticholinergic medication	22	16.5	17	13.7	.60
	Mean	SD	Mean	SD	*P*
Age (y)	40.8	10.6	39.1	11.5	.24
Duration of education (y)	12.2	2.1	12.1	2.1	.65
Duration of treatment (y)	16.4	10.7	14.6	11.3	.18
PANSS total score	74.4	18.7	74.0	17.4	.89
CGI-S score	3.92	0.99	3.98	0.95	.63
CDSS total score	4.89	4.70	4.25	4.48	.27
DAI total score	4.65	4.32	4.89	3.81	.65
AIMS total score	0.65	1.43	0.78	1.84	.51
BARS total score	0.75	1.29	0.84	1.43	.60
SAS total score	0.16	0.29	0.23	0.36	.12
Body weight (kg)	88.8	23.2	88.3	21.5	.85

[a]No significant differences between the 2 groups.
[b]This information was missing variables for 2 patients in the twice-daily group.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BARS = Barnes Akathisia Rating Scale, CDSS = Calgary Depression Scale for Schizophrenia, CGI-S = Clinical Global Impressions-Severity scale, DAI = Drug Attitude Inventory, PANSS = Positive and Negative Syndrome Scale, SAS = Simpson-Angus Scale, SD = standard deviation.

Table 2. Discontinuation Rate and Time to Discontinuation in Once-Daily and Twice-Daily Dosing Groups

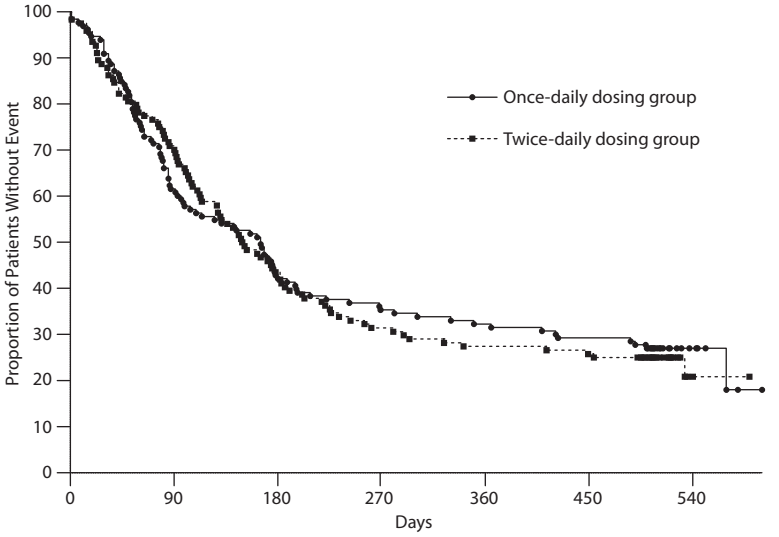
	Once-Daily Group (N = 133)		Twice-Daily Group (N = 124)		Group Difference,
Discontinuation Variable	N	%	N	%	*P*[a]
Discontinuation rate					
All cause	98	73.7	94	75.8	.77
Lack of efficacy	30	22.6	35	28.2	.32
Intolerability	20	15.0	20	16.1	.86
Patient's decision	41	30.8	36	29.0	.79
	Mean	SE	Mean	SE	*P*
Time to discontinuation (d)					
All cause	255	20	241	19	.72
Lack of efficacy	451	23	411	24	.41
Intolerability	496	21	482	22	.86
Patient's decision	413	23	405	24	.91

[a]No significant differences between the 2 groups.
Abbreviation: SE = standard error.

Statistical Analysis

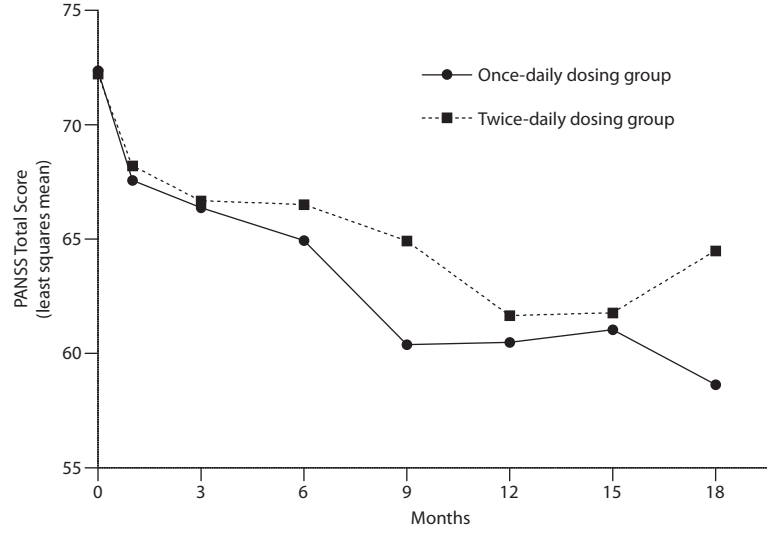
Statistical analyses were conducted using similarly constructed models, as reported in the primary CATIE publication.[1] Kaplan-Meier survival curves were used to estimate the time to discontinuation from assigned treatment. The 2 groups were compared utilizing Cox proportional-hazards regression models with adjustment for whether the patient had had an exacerbation of schizophrenia in the preceding 3 months. The scores of efficacy and safety measures over time were compared between the 2 groups employing a mixed model that included exacerbation in the preceding 3 months and baseline values as covariates, time (ie, 1, 3, 6, 9, 12, 15, and 18 months), interaction between group and time, and interaction between baseline value and time as fixed effects. Results of assessments at the end of phase 1 were assigned to the next interval to accommodate cases involving premature patient discontinuation. A 2-tailed P value of $<.05$ was considered statistically significant for all tests, and all statistical analyses were conducted using the IBM SPSS Statistics version 19 (IBM Corporation, Armonk, New York).

Figure 1. Time to All-Cause Discontinuation[a]



[a]No significant difference between the 2 groups.

Figure 2. Positive and Negative Syndrome Scale (PANSS) Total Scores Over Time[a]



[a]No significant difference between the 2 groups.

RESULTS

Baseline Demographic and Clinical Characteristics

A total of 257 patients were randomly assigned to perphenazine either once daily (N = 133) or twice daily (N = 124). Baseline demographic and clinical characteristics between 2 dosing groups are shown in Table 1; there were no significant differences in any of these variables.

Discontinuation Rate and Time to Discontinuation

Table 2 details discontinuation rates and time to discontinuation due to any cause, in addition to lack of efficacy, intolerability, and patient's decision in the once-daily and twice-daily dosing groups. There were no significant differences between the 2 groups on any of these measures. Survival curves on time to all-cause discontinuation for the 2 groups are shown in Figure 1; again, no significant difference was observed.

Efficacy and Safety Measures

Mixed-model analyses revealed no significant group-by-time interaction for the PANSS total ($P = .34$), PANSS positive ($P = .28$), PANSS negative ($P = .51$), PANSS general psychopathology subscale ($P = .62$), CGI-S ($P = .92$), CDSS total ($P = .42$), or DAI-10 total ($P = .34$) scores between the 2 groups. The PANSS total scores across time for the 2 groups are shown in Figure 2, indicating once-daily dosing was not inferior to the twice-daily dosing regimen over time throughout the study. Similarly, there was no significant group-by-time interaction for the AIMS total ($P = .32$), BARS total ($P = .27$), and SAS total ($P = .56$) scores or body weight ($P = .51$).

Medication Adherence and Perphenazine Dose

As shown in Table 3, both the Clinical Global Judgment of Medication Adherence score and proportion of capsules taken indicated good medication adherence in both groups, with no significant differences. The mean and modal doses of perphenazine, in addition to mean dose multiplied by proportion of capsules taken during phase 1, were slightly but significantly higher in the twice-daily dosing group. Accordingly, we also performed mixed-model analyses using

Table 3. Medication Adherence and Doses of Perphenazine Across Phase 1 in Once-Daily and Twice-Daily Dosing Groups

Variable	Once-Daily Group (N = 124[a]) Mean	SD	Twice-Daily Group (N = 117[b]) Mean	SD	Group Difference, P[c]
Medication adherence					
Clinical Global Judgment of Medication Adherence	1.32	0.65	1.33	0.64	.87
Proportion of capsules taken (%)	88.1	18.1	87.2	20.5	.71
Dose of perphenazine					
Mean dose (mg/d)	19.6	7.0	21.8	6.7	**.01**
Modal dose (mg/d)	19.6	8.2	22.2	7.4	**.01**
Dose × medication adherence					
Mean dose × proportion of capsules taken (mg/d)	17.2	7.5	19.3	7.8	**.04**

[a]The variables were missing for 9 patients.
[b]The variables were missing for 7 patients.
[c]Bold number: $P < .05$.
Abbreviation: SD = standard deviation.

these doses as a covariate to evaluate their impact on each outcome measure; however, no significant differences were found between the 2 groups for all outcome measures (data not shown).

Treatment-Emergent Adverse Events and Concomitant Psychotropic Medications

There were no significant differences in the rates of patients who experienced any treatment-emergent adverse event or individual adverse events categorized according to the original CATIE report[1] (ie, insomnia, hypersomnia/sleepiness, urinary hesitancy/dry mouth/constipation, decreased sex drive/arousal/ability to reach orgasm, gynecomastia/galactorrhea, menstrual irregularities, incontinence/nocturia, or orthostatic faintness) between the once-daily and twice-daily dosing groups (see Supplementary eTable 1 at PSYCHIATRIST.COM). Also, there were no significant differences in the rates of patients who newly took any concomitant psychotropic medication or specific psychotropic medication (ie, antidepressants, antiepileptics, antipsychotics, anxiolytics, hypnotics/sedatives, or lithium), or in time until these medications were initiated and the duration that these medications were used, between the 2 groups (see Supplementary eTable 2).

DISCUSSION

The present study assessed the impact of once- versus twice-daily dosing of perphenazine on clinical outcomes among patients with chronic schizophrenia. No significant differences were identified for discontinuation rate and time to discontinuation or for any efficacy and safety measures. These findings are consistent with previous studies evaluating once- versus twice-daily dosing for risperidone[4] and quetiapine[6] and in line with a further report examining a switch to once-daily dosing of a number of antipsychotics with half-lives ranging from 2.3 to 31 hours.[15]

The present results gain further support from several additional lines of investigation. Positron emission tomography (PET) has demonstrated a significant dissociation between central and peripheral pharmacokinetics for both risperidone and olanzapine; in both cases, half-life related to dopamine D_2 receptor occupancy centrally was considerably longer than plasma half-life.[16,17] This point is particularly important given that D_2 binding, an integral component of all currently available antipsychotics, represents the sine qua non of *antipsychotic* activity.[18,19] In short, the neuroimaging evidence provides compelling evidence that antipsychotic dosing should not be established by peripheral kinetics.

A second line of investigation has, as well, suggested that high and continuous D_2 occupancy is not required to maintain antipsychotic response. Studies have established that optimal antipsychotic response is achieved with D_2 occupancy exceeding a threshold of 60%–70%[20,21]; at the same time, though, there is evidence that this threshold does not need to be sustained. Neuroimaging data specific to oral antipsychotics have established that D_2 occupancy can fall below this threshold over a 24-hour interval,[22,23] while work with depot antipsychotics has confirmed this same finding when examining D_2 occupancy over the course of injections intervals.[24,25] Indeed, one PET study showed that 76–216 mg/mo of perphenazine decanoate corresponded to 66%–82% D_2 occupancy.[26] Given that 30 mg/d of oral perphenazine is equal to 210 mg/mo of depot perphenazine[27] and the mean doses of perphenazine in the 2 dosing regimen groups were approximately 20 mg/d, trough D_2 occupancy in the once-daily dosing group can be lower than the optimal range of D_2 occupancy for antipsychotic efficacy.

Building upon these findings is work that revisits current dosing recommendations from 2 perspectives. The first relates to studies directly challenging the axiom of daily oral antipsychotic dosing.[28,29] Earlier work clearly established that "intermittent" or "targeted" pharmacotherapy, allowing for extended periods without taking antipsychotics following stabilization, was associated with increased risk of relapse.[30,31] More recently, though, "extended" antipsychotic dosing has been proposed as a viable alternative; rather than allowing for prolonged periods of not taking antipsychotics, it calls for *extended* but *regular* dosing. A small pilot study indicated that stabilization could be maintained with oral antipsychotic dosing every 2 or 3 days,[32] while a larger, double-blind investigation looking at alternate-day dosing (ie, every second day) provided further support.[33] Further study is warranted, though, to establish that this strategy has advantages and is not associated with potentially adverse consequences such as increased nonadherence.

The second perspective relates to the potential for altered efficacy and tolerability in the face of continued antipsychotic exposure. To date, this work is confined to preclinical studies, but results raise important questions. As early as the 1980s, it was reported that behavioral changes (ie, locomotion) related to antipsychotic treatment diminished in the face of daily, but not alternate day, treatment,[34] suggestive of tachyphylaxis. More recently, this finding has been confirmed with other behavioral and physiological measures[35,36]; in addition, there

is evidence that continuous exposure may increase risk of adverse side effects such as tardive dyskinesia.[37,38]

This simplified dosing issue is highly relevant since previous studies have demonstrated that less frequent dosing of antipsychotics is related to better medication adherence.[39,40] However, in this study, medication adherence based on pill count or clinician rating scale did not differ between the 2 dosing regimens of perphenazine. Possible explanations for this result are 3-fold. First, the rates of medication adherence on the basis of pill count were quite high in both once-daily and twice-daily dosing groups (88% and 87%, respectively), which may have led to a ceiling effect. Second, some studies note that pill count overestimates medication adherence compared to electronic monitoring,[40–42] suggesting that pill count as measured in the current study may inflate the actual medication adherence. Finally, CATIE was a systematic randomized trial, the results of which may be different from those obtained from naturalistic observational studies. Nonetheless, many manufacturers are actually introducing longer-acting formulations of various drugs to allow for a single dosing, presumably hoping for better adherence. Adherence to antipsychotics is no doubt a key element in relapse prevention in schizophrenia, and more studies are necessary to establish how dosing simplification affects long-term outcomes such as relapse and hospitalization.

Limitations to the present study warrant comment. First, rates of treatment discontinuation by 18 months were high in both groups, greater than 70%, which must be factored into any discussion of results. Further to this point, it can be argued that even a follow-up period of 18 months is insufficient to evaluate long-term effectiveness and side effects. Second, other psychotropic medications were permitted, and it is possible that results were influenced by their concomitant use. Third, medication adherence was assessed with pill counts and a clinician rating scale, but not with a more precise method such as electronic monitoring.[39–42] Finally, it is important to keep in mind that antipsychotic dosing may be split over the course of a day for other reasons such as side effects.

In conclusion, the present findings indicate that despite a pharmacokinetic rationale supporting dosing of perphenazine at least twice daily, once-daily dosing produces similar results. It is important to underscore that we did not find once-daily dosing superior on any clinical outcome measure; rather, we simply established that once-daily dosing was not inferior to twice-daily dosing. However, patients prefer once-daily dosing to more complex schedules,[43,44] and more complex dosing regimens do adversely impact adherence.[40] Perhaps the most important take-away message from this line of investigation, though, is the need to revisit the long-standing axiom that antipsychotic dosing be established based on peripheral pharmacokinetics.

Drug names: lithium (Lithobid and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: **Impact of Once- vs Twice-Daily Perphenazine Dosing on Clinical Outcomes: An Analysis of the CATIE Data**

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List of Supplementary Material for the article

1. eTable 1 Treatment-Emergent Adverse Events in Once-Daily and Twice-Daily Dosing Groups
2. eTable 2 Newly Started Concomitant Psychotropic Medications in Once-Daily and Twice-Daily Dosing Groups

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Supplementary eTable 1. Treatment-Emergent Adverse Events[a] in Once-Daily and Twice-Daily Dosing Groups

	Once-Daily Group (N=133)		Twice-Daily Group (N=124)		Group Difference
	N	%	N	%	*P*[b]
Any treatment emergent adverse event	119	89.5	111	89.5	1.00
Insomnia	56	42.1	53	42.7	1.00
Hypersomnia/sleepiness	60	45.1	66	53.2	0.21
Urinary hesitancy/dry mouth/constipation	53	39.8	53	42.7	0.70
Decreased sex drive/arousal/ability to reach orgasm	47	35.3	38	30.6	0.43
Gynecomastia/galactorrhea	8	6.0	9	7.3	0.80
Menstrual irregularities	8	6.0	6	4.8	0.79
Incontinence/nocturia	14	10.5	11	8.9	0.68
Orthostatic faintness	36	27.1	31	25.0	0.78

[a]Adverse event was defined as treatment emergent adverse event if its severity was higher than the baseline during phase 1.
[b]No significant differences between the 2 groups

Supplementary eTable 2. Newly Started Concomitant Psychotropic Medications in Once-Daily and Twice-Daily Dosing Groups

		Once-Daily Group (N=133)		Twice-Daily Group (N=124)		Group Difference
		N or Mean	% or *SD*	N or Mean	% or *SD*	*P*
Any psychotropic medications	Rate of users	39	29.3	43	34.7	0.42
	Time to initiation (days)	103	116	88	96	0.52
	Duration of use (days)	144	166	144	181	0.99
Antidepressants	Rate of users	16	12.0	12	9.7	0.69
	Time to initiation (days)	120	123	109	84	0.79
	Duration of use (days)	142	140	110	143	0.56
Antiepileptics	Rate of users	4	3.0	5	4.0	0.74
	Time to initiation (days)	51	42	174	150	0.14
	Duration of use (days)	113	96	161	160	0.61
Antipsychotics	Rate of users	9	6.8	9	7.3	1.00
	Time to initiation (days)	99	124	142	128	0.48
	Duration of use (days)	16	31	12	10	0.70
Anxiolytics	Rate of users	21	15.8	17	13.7	0.73
	Time to initiation (days)	102	127	68	89	0.36
	Duration of use (days)	73	111	133	153	0.17
Hypnotics/sedatives	Rate of users	10	7.5	13	10.5	0.51
	Time to initiation (days)	217	157	88	100	0.03[a]
	Duration of use (days)	104	99	95	95	0.81
Lithium	Rate of users	1	0.8	2	1.6	0.61
	Time to initiation (days)	8	NA	167	105	0.43
	Duration of use (days)	187	NA	222	293	0.94

[a]No significant difference between the 2 groups after Bonferroni correction (ie, *P* value multiplied by 6)
Abbreviation: SD; Standard Deviation