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REGULAR RESEARCH ARTICLE

A Positron Emission Tomography Study of Norepinephrine Transporter Occupancy and Its Correlation with Symptom Response in Depressed Patients Treated with Quetiapine XR

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Abstract

Background: Quetiapine is effective in treating depressive symptoms in major depressive disorder and bipolar disorder, but the mechanisms underlying its antidepressants effects are unknown. Norquetiapine, a metabolite of quetiapine, has high affinity for norepinephrine transporter, which might account for its therapeutic efficacy.
Methods: In this study, we used positron emission tomography with (S,S)-[^{11}C]O-methyl reboxetine to estimate norepinephrine transporter density and assess the relationship between norepinephrine transporter occupancy by quetiapine XR and improvement in depression in patients with major depressive disorder (n=5) and bipolar disorder (n=5). After the baseline positron emission tomography scan, patients were treated with quetiapine XR with a target dose of 150 mg in major depressive disorder and 300 mg in bipolar disorder. Patients had a second positron emission tomography scan at the end of week 2 and a final scan at week 7.
Results: Norepinephrine transporter density was significantly lower in locus ceruleus in patients compared with healthy subjects. Further, there was a significant positive correlation between quetiapine XR dose and norepinephrine transporter occupancy in locus ceruleus at week 2. The norepinephrine transporter occupancy at week 2 in hypothalamus but not in other regions predicted improvement in depression as reflected by reduction in MADRS scores from baseline to week 7. The estimated dose of quetiapine XR associated with 50% norepinephrine transporter occupancy in hypothalamus at week 2 was 256 mg and the estimated plasma levels of norquetiapine to achieve 50% norepinephrine transporter occupancy was 36.8 µg/L.
Conclusion: These data provide preliminary support for the hypothesis that norepinephrine transporter occupancy by norquetiapine may be a contributor to the antidepressant effects of quetiapine.

Keywords: major depressive disorder, bipolar disorder, quetiapine, norepinephrine transporter, positron emission tomography

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Significance Statement

The objective of this study was to examine if antidepressant effects of quetiapine could be explained by the effects of its metabolite norquetiapine on brain norepinephrine transporter (NET). To ascertain this, we used positron remission tomography brain scans to measure NET in depressed patients at baseline and at 2 and 7 weeks after treatment with quetiapine. We found that the density of NET was lower at baseline in specific regions of the brain in patients with major depressive disorder/bipolar disorder. There was a correlation between quetiapine dose and its binding to NET. Further, the NET binding of quetiapine at week 2 predicted improvement in depression at week 7. These findings lend support to the hypothesis that quetiapine may exert its antidepressant actions through its action on NET.

Introduction

The second-generation antipsychotic quetiapine has robust antidepressant effects in multiple placebo-controlled clinical trials in major depressive disorder (MDD) and bipolar disorder (BD), without clinically significant risk of inducing manic episodes in BD patients (Weisler et al., 2009; McElroy et al., 2010; Suppes et al., 2010; Young et al., 2010; Maneeton et al., 2012). However, the neurochemical mechanisms that underlie the therapeutic effects of quetiapine in improving depressive symptoms in MDD and BD remain unknown.

Norquetiapine, a metabolite of quetiapine, has high affinity for the norepinephrine transporter (NET), and it has been suggested that NET blockade by norquetiapine accounts for the antidepressant effects of quetiapine. Positron emission tomography (PET) studies in healthy volunteers suggest that NET occupancy with quetiapine 300 mg/d ranges from 15% to 54% (mean 35%) (Nyberg et al., 2013). However, many questions regarding the relationship between NET occupancy and clinical response in patients treated for depression with quetiapine remain. For example, it is unknown if NET occupancy in specific brain regions predicts therapeutic benefit, and whether a threshold fraction of NET blockade must be achieved for an antidepressant effect. The dose of quetiapine required to produce a level of NET blockade for a therapeutic effect also has not been studied. Further, it is unknown if NET density is altered in depression and if such alteration in NET has any predictive value for therapeutic effects of quetiapine and the mechanism of its antidepressant effects.

Therefore, in this study, we used PET with the ligand (S,S)-[^{11}C]O-methyl reboxetine ([^{11}C](S,S)-MRB), abbreviated as ^{11}C-MRB (Ding et al., 2003, 2010) to examine NET binding and occupancy in 10 drug-free patients with major depressive episodes (MDD, BD I, or BD II) and 9 healthy comparison subjects. After the baseline scan, patients commenced treatment with quetiapine XR, and the NET occupancy was measured at week 2 and week 7.

The primary objective of this study was to determine the relationship between NET occupancy by quetiapine XR and improvement in depressive symptoms as measured by a reduction in Montgomery Asberg Depression Rating Scale (MADRS). We hypothesized that NET occupancy at the end of week 2 will predict reduction in MADRS scores from baseline to the end of week 7 and that the NET occupancy at week 7 correlates with improvement in depressive symptoms.

The secondary objectives included:

1. To measure if NET density is altered in depression and whether such alteration predicts improvement in depression as measured by change in MADRS score from baseline to the endpoint
2. To examine the correlation between quetiapine XR dose and NET occupancy due to quetiapine XR
3. To measure the correlation between the serum levels of norquetiapine and NET occupancy at the end of week 2 and week 7.

Methods

The study was approved by the Clinical Research Ethics Board of the University of British Columbia. All participants provided written informed consent prior to commencing any study related procedures.

Subjects

Male and female patients aged 18 to 65 years who met the DSM-IV TR diagnostic criteria for MDD, BD I, or BD II and were currently experiencing a major depressive episode as determined by Structured Clinical Interview for DSM-IV were recruited. Female patients of childbearing potential were using a reliable method of contraception and had a negative urine human chorionic gonadotropin test at enrolment. All subjects had a MADRS score of ≥20 and a Young Mania Rating Scale score of ≤ 8. Patients with MDD must have failed at least one trial of an antidepressant medication at an adequate dose and for an adequate duration, in the opinion of the investigator.

Patients who posed an imminent risk of suicide or a danger to self or others in the opinion of the clinical investigator and those with a history of intolerance or lack of response to quetiapine were excluded. Subjects taking any cytochrome P450 3A4 inhibitors or inducers or those taking drugs that affect brain norepinephrine levels were also excluded. Patients with substance or alcohol dependence or medical conditions that would affect absorption, distribution, metabolism, or excretion of quetiapine XR or unstable medical conditions were excluded.

Ligand Synthesis and Imaging Protocol

All subjects completed a Magnetic Resonance Imaging (MRI) scan for exclusion of cerebral pathology and for co-registration with PET images for data analysis. ^{11}C-MRB was synthesized using the procedure previously described (Ding et al., 2003). PET images were acquired using a High Resolution Research Tomograph scanner (Siemens/CTI). After injecting ^{11}C-MRB (average injected dose of 553.41 megabecquerels) over a 60-second period with Harvard pump, dynamic PET imaging was performed for 120 minutes. Data were acquired in list mode and framed into: 4 × 60 seconds, 3 × 120 seconds, 8 × 300 seconds, and 7 × 600 seconds scans. After correction for detector normalization, random and scattered events as well as attenuation and dead time, data were reconstructed with 3DOSEM-OP, 16 subsets, 6 iterations. Reconstructed images were smoothed with an isotropic 2-mm Gaussian filter.

Quetiapine XR Treatment

Following the initial PET scans, patients commenced treatment with quetiapine XR. Patients received quetiapine XR as monotherapy or in conjunction with a stable dose of valproate or lithium for at least 4 weeks. The dose was titrated upwards to reach the target dose of 150 mg daily in people with MDD and 300 mg daily in people with BD between day 4 and 7, unless side effects precluded them from reaching the target dose. Patients who did not show at least 20% reduction in MADRS scores at week 2 had the dose of quetiapine XR increased to a maximum of 300 mg daily in people with MDD and 600 mg daily in people with BD by week 4, at the discretion of the study psychiatrist.

Patients were seen at screen and weeks 0, 1, 2, 4, 6, and 7, and during these visits all patients were assessed using standard clinical rating scales that included MADRS, Young Mania Rating Scale, and Clinical Global Impression scale. The PET scan was repeated at week 2 after patients had been taking the study medication at therapeutic doses for ≥7 days to determine the proportion of NETs blocked by quetiapine XR. The final PET scan was completed at the end of week 7 after patients had been taking the therapeutic dose of study medication for ≥21 days.

At both posttreatment scans, treatment response (≥50% improvement in baseline MADRS score) and remission (MADRS score ≤8) were assessed. A blood sample was collected at the end of week 2 and week 7 for measuring serum levels of quetiapine and norquetiapine.

Image Processing and Analysis

Statistical Parametric Mapping 8 software was used for processing PET and MR images. All PET frames for each scan for each subject were realigned to create a mean PET image for that subject. The mean PET images for the week 2 and week 7 scans for each patient were co-registered to the baseline PET scan. Each subject's MRI was co-registered to Montreal Neurological Institute (MNI) standard coordinate frame used for templates in Statistical Parametric Mapping 8 using the spatial normalization method. We then used the Atlas-based regions of interest defined in the MNI space to define the regions of interest (i.e., thalamus, hypothalamus, locus coeruleus, pontine raphe, midbrain raphe, red nucleus) as previously described (Ding et al., 2010). Then, each subject's MRI was co-registered to his/her PET and applied inverse transformation from MNI→individual MRI→PET to all regions of interest (all in one step). The PET images were smoothed using a 3-mm Gaussian filter.

The binding potential (BP_{ND}) values for NET were estimated using a Simplified Reference Tissue Model 2 (Wu and Carson, 2002). The occipital cortex was used as reference region. Since in several cases, the BP_{NDs} were too low to permit a reliable estimate of k2', we used a previously validated population-based K2' value of 0.021 (based on studies by Ding YS, Singhal T, Planeta-Wilson B, Gallezot JD, Nabulsi N, Labaree D, Ropchan J, Henry S, Williams W, Carson RE, Neumeister A, Malison RT, private communication). The resulting fits to the time activity curves were checked to ensure absence of bias. We have added this information to the manuscript.

We defined NET occupancy as the percentage change in NET binding from baseline. The NET occupancy (%) at week 2 was calculated as follows: $[(BP_{ND-BL} - BP_{ND-QTP2})/ BP_{ND-BL}] \times 100$, and for week 7, the occupancy was calculated by substituting $BP_{ND-QTP2}$ with $BP_{ND-QTP7}$.

Baseline differences between patients and controls in NET binding were computed using linear regression with and without adjustment for age and gender. Linear regression was also used to estimate the association between NET binding at baseline and the change in depression scores with MADRS. The association between quetiapine XR doses and NET occupancy was modeled using saturation binding equations. Pearson correlation was used to compute correlations between NET binding and improvement in depressive symptoms. All statistical analyses and curve-fitting were performed using R version 3.4 and GraphPad Prism version 7.03.

Results

Ten patients and 9 healthy control subjects (4 males and 5 females) completed the study. The clinical and demographic characteristics of patients are provided in Table 1. The patient group included 4 males and 6 females with a mean age of 38.3±16.14 years. Two patients had a diagnosis of BD I, 3 had BD II, and 5 had MDD. There was no significant difference in age between patients and controls ($P = .75$).

The mean (±SD) MADRS score at baseline was 29.5 ± 6.29 (MDD: 28.6 ± 7.86; BD I and BD II: 30.4 ± 5.03), indicating that patients had a moderately severe depression. The MADRS score improved to 19.3 ± 7.32 (MDD: 20.4 ± 7.83; BD I and BD II: 18.2 ± 7.5) by the end of week 2 and to 15.5 ± 11.75 (MDD: 12.2 ± 12.97; BD I and BD II: 18.8 ± 10.73) by week 7. By the end of week 7, 5 of 10 (50%) patients met criteria for response and 4 (40%) patients were in remission. Three of the 5 MDD patients

Table 1. Clinical and Demographic Characteristics of Study Patients

Patients	Age	Sex	Diagnosis	Previous mania (episodes)	Previous hypo-mania (episodes)	Previous depression (episodes)	Duration of current episode	MADRS Baseline	MADRS Week 2	MADRS Week 7
1	60	F	MDD	0	0	10	5 years	24	26	16
2	56	M	MDD	0	0	1	8 months	42	29	33
3	39	F	BD II	0	5	10	10 months	29	19	4
4	44	M	BD II	0	20	20	4 weeks	30	18	26
5	57	F	BD II	0	23	25	12 months	34	26	32
6	27	F	MDD	0	0	1	6 months	28	15	8
7	41	M	MDD	0	0	25	6 months	22	10	2
8	19	F	BD I	1	0	2	41 days	36	22	16
9	20	F	MDD	0	0	1	9 months	27	22	2
10	20	M	BD I	2	2	5	7 weeks	23	6	16

Abbreviations: BP I, Bipolar I Disorder; BP II, Bipolar II Disorder; F, female; M, male; MADRS, Montgomery Asberg Depression Rating Scale; MDD, major depressive disorder.

and one BD II patient of 3 met criteria for response and remission, while 1 of the 2 BD I patients responded by week 7. The mean quetiapine XR dose was 195 ± 83.16 (MDD: 140 ± 54.77; BD I and BD II: 250 ± 70.71) at week 2 and 280 ± 187.37 (MDD: 200 ± 106.06; BD I and BD II: 360 ± 227.48) at week 7.

The NET BP_{ND} at baseline in locus ceruleus and thalamus for patients with MDD and BD and healthy subjects is presented in Figure 1 and the means ± SD in Table 2. The NET BP_{ND} at baseline was significantly lower in locus ceruleus in patients as a group compared with healthy subjects (mean difference: 0.16, CI: 0.02, 0.30; $P < .05$), and this difference persisted when the BP_{ND} was adjusted for age and sex. The NET BP_{ND} at baseline was not different between the groups in any other brain regions. The NET BP_{ND} at baseline in patients in any brain regions did not predict improvement in depression as measured by reduction in MADRS scores at week 7.

The mean NET occupancy at week 2 for various brain regions ranged from 22.4% to 33.6% (Table 3). There was a significant curvilinear association at week 2 between quetiapine XR dose and NET occupancy in locus ceruleus ($R^2 = 0.44$, $P = .04$) and the thalamus ($R^2 = 0.26$, $P = .06$) (Figure 2). These associations did not remain significant at week 7. There was a significant negative correlation between week 7 NET binding and week 7 MADRS scores in hypothalamus ($r = -0.71$, $P = .02$) and a trend for significance in locus ceruleus ($r = -0.59$, $P = .07$) but not in other brain regions.

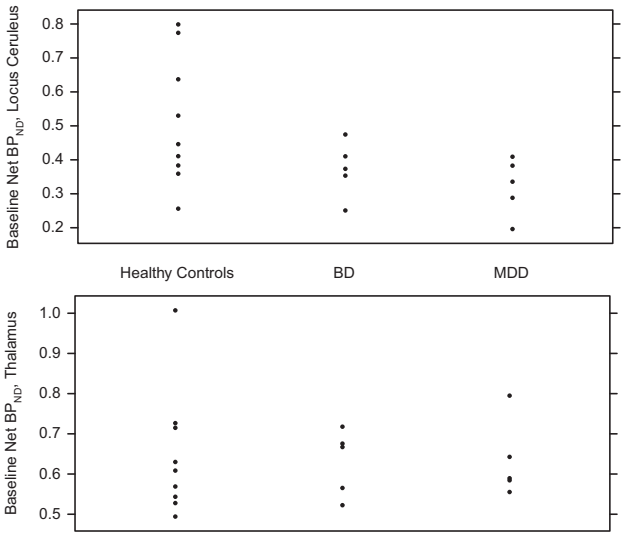

Figure 1. Baseline norepinephrine transporter (NET) binding potential (BP_{ND}) in locus ceruleus and thalamus for healthy controls (HC), patients with bipolar disorder (BD), and major depressive disorder (MDD).

Table 2. Mean (SD) NET BP_{ND} at Baseline for Patients with MDD and BD and HC

Brain Region	MDD	BD	All Patients (MDD and BD)	HC
Locus ceruleus	0.32 (0.08)	0.37 (0.08)	0.35 (0.08)	0.51 (0.19)
Thalamus	0.63 (0.10)	0.63 (0.08)	0.63 (0.08)	0.65 (0.16)
Hypothalamus	0.49 (0.05)	0.64 (0.12)	0.56 (0.12)	0.59 (0.14)
Pontine raphe	0.73 (0.19)	0.68 (0.16)	0.70 (0.16)	0.78 (0.37)
Midbrain raphe	0.62 (0.12)	0.66 (0.19)	0.64 (0.15)	0.79 (0.26)
Red nucleus	0.60 (0.14)	0.65 (0.15)	0.63 (0.14)	0.59 (0.11)

Abbreviations: BP, Bipolar Disorder; BP_{ND}, binding potential; HC, healthy controls; MDD, major depressive disorder.

The week 2 NET occupancy in hypothalamus predicted week 7 improvement in depression as reflected by reduction in MADRS scores from baseline to week 7 (β −0.28, CI −0.53, −0.04). The NET occupancy in other brain regions was not associated with improvement in depression. The estimated dose of quetiapine XR associated with 50% NET occupancy in hypothalamus at week 2 was 256 mg. The estimated plasma levels of norquetiapine associated with 50% NET occupancy in hypothalamus was 36.8 µg/L.

Discussion

This exploratory study examined NET binding in patients with a major depressive episode compared with healthy subjects, and the relationship between NET occupancy with quetiapine XR treatment and the improvement in depressive symptoms. The

Table 3. Mean NET Occupancy for Various Brain Regions in Depressed Patients (MDD and BD) at Weeks 2 and 7

Brain Region	NET Occupancy at Week 2 Mean % (SD)	NET Occupancy at Week 7 Mean % (SD)
Locus ceruleus	23.32 (22.36)	38.49 (40.17)
Thalamus	22.43 (15.77)	19.59 (14.49)
Hypothalamus	33.64 (21.42)	22.43 (31.58)
Pontine raphe	26.09 (19.45)	30.24 (23.84)
Midbrain raphe	26.31 (20.11)	10.25 (24.65)
Red nucleus	22.98 (10.73)	33.43 (14.40)

Abbreviations: BD, bipolar disorder; MDD, major depressive disorder; NET, norepinephrine transporter.

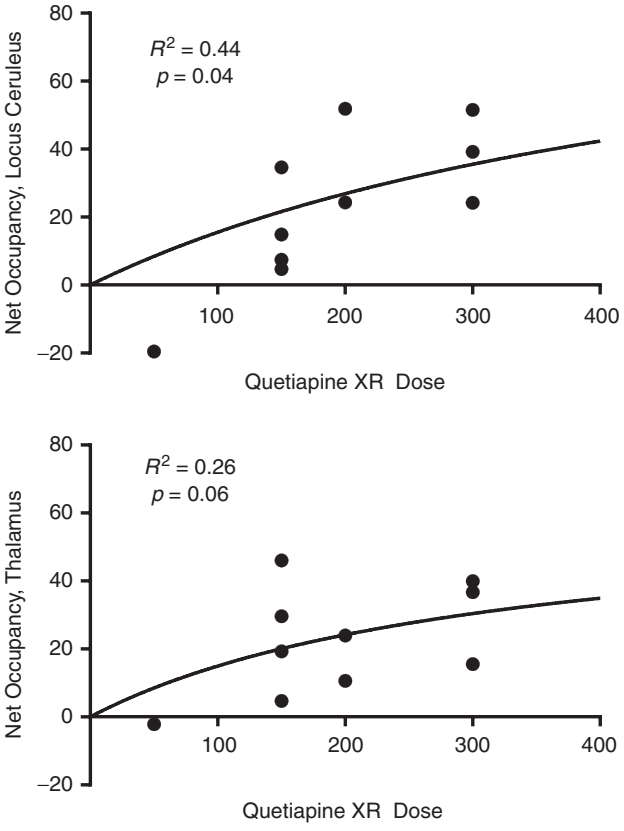

Figure 2. Relationship between norepinephrine transporter (NET) occupancy and quetiapine XR dose at week 2 in locus ceruleus and thalamus.

main findings of the study are: (1) NET binding at baseline is lower in locus ceruleus in patients compared with healthy subjects, but baseline NET binding did not predict clinical outcome with quetiapine XR; (2) quetiapine XR in clinically relevant doses is associated with NET occupancies up to 34% at the end of 2 weeks and 38% at the end of 7 weeks; (3) there was a significant correlation between quetiapine XR dose and NET occupancy at week 2 in locus ceruleus, and, furthermore, there was a trend for association between NET binding in this brain region and improvement in depressive symptoms at the end of 7 weeks; and (4) the NET occupancy at week 2 in hypothalamus but not in locus ceruleus predicted improvement in depression at the end of week 7.

The finding of a reduction in NET binding in locus ceruleus in depressed patients is consistent with the findings of a previous study that reported reduction in NET binding in midcaudal portion of the locus ceruleus in postmortem brains of depressed subjects (Klimek et al., 1997). NET binding was also reported to be reduced in locus ceruleus in a rat model of depression (Kanegawa et al., 2012). There is evidence that the density of NET is dependent on the availability of synaptic norepinephrine (Lee et al., 1983). Thus, low NET binding observed in the present study is consistent with the notion that major depression is associated with lower synaptic norepinephrine levels. Interestingly, a recent PET study in patients with MDD found no alteration in NET density in locus ceruleus and increased NET density in thalamus (Moriguchi et al., 2017). Differences in sample characteristics (e.g., inclusion of patients with BD in the current study, patients in various stages of illness vs MDD patients only in the Moriguchi et al. study) might be possible explanations for the discrepant results. Further, due to the exploratory nature of the study, we did not employ correction for multiple comparisons. Hence, the findings of the present study should be considered preliminary at best.

A previous study that assessed NET occupancy in thalamus in healthy subjects reported 19% (range 2%–36%) with 150 mg and 35% (range 15%–54%) with 300 mg of quetiapine XR (Nyberg et al., 2013). One-half of the patients enrolled in the present study had MDD, and hence the mean dose of quetiapine XR used was lower (195 mg at week 2). Thus, the NET occupancy of 22.4% to 33.6% observed in the present study in various brain regions at week 2, and 10.3 to 38.5% at week 7 is consistent with the previous data. Further, there was a correlation between NET occupancy and quetiapine XR dose at week 2 in locus ceruleus. Although previous studies have reported that >80% 5-hydroxytryptamine transporter occupancy is required for the efficacy of antidepressants (Takano et al., 2006), no such relationship has been reported for NET occupancy. Milnacipran, a serotonin norepinephrine reuptake inhibitor, has been reported to achieve 25% to 50% NET occupancy in clinically relevant doses (Nogami et al., 2013), while nortriptyline at minimum therapeutic concentration has been estimated to achieve 47% NET occupancy (Takano et al., 2014). Therefore, the NET occupancy observed with quetiapine XR in the present study is in similar range as the occupancy reported with other effective antidepressant treatments. Further, taken together, these data would suggest that the therapeutic effect with antidepressant treatments might be achieved with lower NET occupancy than what would be required to achieve this effect with 5-hydroxytryptamine transporter blockade.

The fact that the NET occupancy in hypothalamus but not in locus ceruleus at week 2 predicted improvement in depression was unexpected and surprising. However, it is important to note that this study, consistent with a previous postmortem study, showed a reduction in NET binding at baseline in patients with depression. Given that the NET binding is lower in locus ceruleus in depression, the NET occupancy in this region may not accurately represent the "real" NET occupancy with quetiapine XR. This would suggest that other brain regions that are not associated with alteration in NET in depression may be more suitable for estimating NET occupancy more accurately and to assess whether such occupancy predicts improvement in depression. In addition to NET occupancy at week 2 in hypothalamus predicting improvement, there was also a significant correlation between baseline NET binding in hypothalamus and improvement in depressive symptoms at week 7 as reflected by reduction in MADRS scores at week 7. These data taken with other findings from this study and other studies might suggest that NET occupancy with quetiapine might be relevant to antidepressant effects of this medication.

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Statement of Interest

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