# A Pilot Study of Quetiapine Treatment of Aggression Due to Traumatic Brain Injury

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*In a 6-week open-label, flexible dose pilot study of quetiapine for treatment of aggression secondary to traumatic brain injury (TBI), seven subjects who were at least 3-months post-injury were enrolled. The Overt Aggression Scale – Modified (OAS-M) and Clinical Global Impression (CGI) were primary outcome measures. Administration of quetiapine at doses of 25 to 300mg daily was efficacious and well-tolerated in reducing irritability and aggression resulting from TBI, with an associated improvement in cognitive functioning.*

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Traumatic brain injury accounts for approximately one million emergency room visits and 500,000 hospitalizations in the United States each year.[1] Agitation and aggression complicate the postinjury recovery of up to 71% of traumatic brain injury (TBI) patients[2] and can lead to substantial psychosocial impairment and a failure to access or benefit from neurorehabilitation services.[3] Atypical antipsychotic agents have demonstrated efficacy in the reduction of impulsive aggression in schizophrenia and other conditions.[4–6] This prospective, open-label study was designed to provide preliminary data on the efficacy and tolerability of quetiapine in the treatment of TBI-induced aggression.

## METHOD

This 6-week, flexible-dose, open-label study was approved by the Institutional Review Board of the Robert Wood Johnson Medical School. Subjects were required to be at least 3 months post-injury, medically stable, and residing in a noninstitutional setting. Irritability and aggression, or a score of at least 15 on the Overt Aggression Scale Modified for Outpatients (OAS-M),[7] must have started after the index injury and persisted for a minimum of 1 month prior to screening. Subjects with a preinjury history of recurrent impulsive aggression, a preinjury diagnosis of schizophrenia, bipolar disorder, or attention deficit hyperactivity disorder, were excluded. Drug or alcohol abuse within 1 month of screening, or concomitant use of antipsychotics, lithium, or psychostimulants, were additional exclusionary criteria. Subjects were permitted to remain on antidepressants, benzodiazepines, or anticonvulsants if the doses had not been adjusted for 2 months prior to enrollment and aggression persisted.

The primary efficacy measures were the OAS-M and the Clinical Global Impression (CGI). A secondary outcome measure was the Neurobehavioral Functioning Inventory (NFI).[8] Tolerability measures included the Simpson-Angus Scale, Barnes Akathisia Rating Scale, Abnormal Involuntary Movements Scale, and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).[9] We administered a regimen of quetiapine, 50–100mg daily in bedtime doses for the first week, then titrated every 3 to 4 days as tolerated in single doses to a maximum of 800mg daily by the end of the third week. This was followed by a maintenance phase of 3 weeks during which the dose could be adjusted based on clinical need and tolerability.

Statistical analysis for outcome variables consisted of paired t tests. In cases where data were missing, a last observation carried forward (LOCF) analysis was used.

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## RESULTS

### Subject Characteristics

Subjects included four men and three women, mean age = 48.9 years (SD = 2.4), with a mean time since injury of 23.1 months (SD = 15.9). All subjects had sustained closed head injuries. Two of the subjects had severe injuries that resulted in a coma (5 and 20 days, respectively) and intracranial hemorrhage. Of these, only one had residual neurological impairment. None of the subjects developed postinjury seizure disorders. All subjects scored at or below the 25th percentile on baseline RBANS assessment, with a mean total scale score of 75.4 (SD = 14.1), corresponding to the 5th percentile.

### Outcome Measures

Quetiapine dose ranged from 25 to 300mg daily, with a mean of 110.7mg (SD = 93.4). Subjects experienced a mean reduction in OAS score of 84.5% ($p = 0.002$). The CGI severity scale improved from a mean of 4.14 (SD = 0.38) to 2.29 (SD = 1.11) ($p = 0.002$). Final assessments on the NFI were not completed in two subjects. LOCF analysis demonstrated significant improvements in the Aggression subscale ($p = 0.036$).

Sedation was reported in three (42.8%) patients. In two cases it resolved by Week 3; in one case it did not resolve until Week 6. No discontinuations were attributed to sedation. The Simpson Angus Scale and Barnes Akathisia Scale revealed mild extrapyramidal side effects and akathisia in one subject. There were no treatment-emergent impairments in cognitive functioning. Overall scale scores on the RBANS indicated a mean improvement of 8.02% ($p = 0.027$).

## DISCUSSION

Neurobehavioral complications of TBI are a significant source of distress and dysfunction in patients and caregivers alike. Traditional antipsychotic agents such as haloperidol and chlorpromazine have been used to successfully control such agitation.[10] However, side effects of cognitive impairment and extrapyramidal side effects complicate the use of such medications in the TBI population.[11,12] Quetiapine is well tolerated and effective in reducing aggression in nonpsychotic syndromes, such as pervasive developmental disorder[13] and Alzheimer's disease.[5] In this study, the administration of quetiapine in doses of 25mg to 300mg daily was well-tolerated and led to significant reductions in aggression and irritability. The use of atypical antipsychotics in post-TBI psychiatric disorders has been limited to treatment of post-TBI psychosis[14,15] and post-TBI delirium with delusions.[16,17] This is the first prospective study of an atypical antipsychotic medication used to treat aggression following TBI in postacute patients.

Cognitive function was not only preserved, but actually improved slightly in the study cohort. Practice effect is an unlikely cause due to the fact that subjects took different versions of the RBANS at baseline and endpoint. While treatment of schizophrenia with atypical antipsychotics has led to improved cognitive performance in some studies,[18–20] these studies generally involved either head to head or crossover designs using conventional antipsychotics as the control or baseline treatment. As a result, no conclusions can be drawn regarding any direct effect of these medications on cognition in treatment-naïve patients. One possible explanation for the improvements may be that a reduction in psychiatric symptom intensity reduced the distracting effects of these symptoms on cognitive test performance. Anxiety and depression were not specifically monitored in this protocol, but these are known to affect neuropsychological test performance.[21,22] The clinical relevance of the observed cognitive improvement has not been established, since performance on neuropsychological testing has not reliably correlated with functional improvements.[23,24]

This study is limited by its open-label noncontrolled design, although the robust response suggests a real therapeutic benefit from treatment. The small sample size also limits the generalizability of findings. The dosage of quetiapine was very low and never achieved the minimal labeled threshold of 400mg daily, although treatment response was substantial even at such low doses. Larger, double-blind studies are warranted to further elucidate the efficacy and tolerability of psychotropic medications in the treatment of TBI-related agitation and aggression.

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