

## Bright Light Therapy for Negative Symptoms in Schizophrenia: A Pilot Study

**Sir:** Negative symptoms like blunted affect, lack of spontaneity, and emotional and social withdrawal are disabling conditions for many schizophrenic patients. Pharmacologic strategies alone are frequently insufficient in the treatment of negative symptoms. New treatment approaches are therefore required. Bright light therapy is the treatment of choice for seasonal depression, but is now also shown to be efficacious in nonseasonal depression.<sup>1</sup> Until now, no studies of bright light therapy in schizophrenic patients have been published. This is the first study to evaluate the safety and tolerability of bright light therapy in patients diagnosed with the residual subtype of schizophrenia.

**Method.** Ten patients (8 men and 2 women) with a diagnosis of schizophrenia (DSM-IV criteria) were included in the study, which was conducted from January 2001 to October 2003. At study entry, the mean age of all patients was 41.8 years. Inclusion criteria were residual subtype of schizophrenia (295.6) and stable antipsychotic medication treatment for at least 4 weeks. Antidepressants were not allowed, and any medication inducing photosensitivity was an exclusion criterion. All patients signed informed consent statements before they were enrolled in the study, and the study was approved by the local human subjects research committee.

Bright light therapy with 10,000 lux (Chronolux CL-100; Samarit; Aachen, Germany) was applied 1 hour daily, 5 days a week, for 4 weeks. All patients were evaluated with the Positive and Negative Syndrome Scale (PANSS),<sup>2</sup> a visual analog scale (VAS) for mood and a VAS for drive (ranging from 0 mm [absolute best mood or drive] to 100 mm [absolute worst mood or drive]), the Clinical Global Impressions scale (CGI),<sup>3</sup> and the Hamilton Rating Scale for Depression (17 items).<sup>4</sup> Measurements were conducted by blinded raters at the screening visit and at weeks 1, 2, and 4, and follow-up examinations were conducted at weeks 8 and 12.

Statistical analyses were conducted using SPSS, Version 12 (SPSS Inc.; Chicago, Ill.). The effect of light therapy on the time course of the outcome variables listed above was tested with the Friedman test, as the assumption of normality was not met. Post hoc comparisons between individual time points were performed using the Wilcoxon test. During the treatment period (weeks 1-4), patients were analyzed by an intent-to-treat method, replacing missing data by the last-observation-carried-forward method.

**Results.** Nine patients concluded 4 weeks of treatment, and 1 patient discontinued after 2 weeks for personal reasons. None of the 10 patients showed exacerbated psychotic symptoms or had to be withdrawn from the study due to increasing positive symptomatology. Scores on the PANSS subscales for positive and general psychopathology did not change significantly over time. However, the negative scale score improved significantly over time (overall  $p = .001$ , baseline vs. 2 weeks:  $p = .037$ , baseline vs. 4 weeks:  $p = .014$ ), and, at a trend level, improvement continued until week 12 ( $p = .085$ ). In addition, the VAS score for drive decreased significantly over time, indicating improvement in drive (overall  $p = .028$ , baseline vs. 4 weeks:  $p = .021$ ), but continuation of this effect up to week 12 could not be proved ( $p = .138$ ). Scores on the VAS for mood, Hamilton Rating Scale for Depression (17 items), and CGI remained unchanged.

Bright light therapy was safe in our patients and did not result in psychotic exacerbation, as seen in the unchanged positive scores on the PANSS. The subjective improvement in drive was statistically significant after 4 weeks, but did not persist after discontinuation of bright light therapy.

Evidence for efficacy is limited by the small study population, no comparison to a control group, and the open design of the trial. Nevertheless, there was significant improvement in negative score on the PANSS, giving hope for some biological treatment efficacy of bright light therapy in schizophrenic patients with a residual subtype. Future studies are necessary to prove these encouraging results.

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## Dosing of Divalproex Extended Release

**Sir:** I read with great interest the article by Bowden et al.<sup>1</sup> in the October 2006 issue of the *Journal*. This important study establishes the efficacy and safety of using divalproex sodium extended release (ER), a relatively new formulation of divalproex sodium, for treating acute mania. In that study, divalproex ER was initiated using a dose of 25 mg/kg rounded up to the nearest 500 mg. Three days later, the dose was increased by 500 mg for all patients. The first measurement of plasma valproate levels was taken on day 5 of treatment. Bowden et al. do not provide a rationale for this dosing schedule.

On our inpatient service, the Neuropsychiatry and Behavioral Medicine Unit at the University of California, San Diego Medical Center, we have been utilizing divalproex ER as the mood stabilizer of choice for approximately the last 5 years. Prior to the availability of the extended release formulation, the divalproex delayed release (DR) formulation had been the most widely prescribed mood stabilizer on our service. It was customary on our service to initiate divalproex DR at 20 to 30 mg/kg/day, which is higher than the labeled recommended

starting dose of 750 mg/day in divided doses. Our practice was based upon studies that have demonstrated that rapid oral titration of divalproex DR using an initial dose of 20 to 30 mg/kg/day is well tolerated and has therapeutic advantages by rapidly achieving therapeutic-range plasma levels of valproate in patients with acute mania.<sup>2-6</sup>

The availability of the ER formulation of divalproex in 2000 (initially for the indication of prophylaxis of migraine headache) offered a potential pharmacokinetic advantage over the DR formulation that was particularly relevant for rapid oral loading. Plasma peaks of valproate are reduced in the ER formulation relative to the DR formulation, and this is likely to reduce side effects during rapid oral loading. On the basis of this advantage, divalproex ER began to replace the DR formulation on our service soon after its appearance on the market. In the absence of published rapid oral loading protocols for the ER formulation, my colleagues and I adopted, by consensus, a practice of initiating divalproex ER with a 30-mg/kg/day dose and taking blood levels on day 3 of treatment. This practice was based on our evaluation of the pharmacokinetics of the ER formulation relative to the DR formulation, including the fact that the ER formulation has somewhat lower bioavailability than divalproex DR.<sup>7</sup>

Our experience over the past 5 years using this rapid oral loading regimen has been overwhelmingly positive, and it remains the standard approach for initiating divalproex treatment on our inpatient service, which treats a large number of acutely manic patients. Patients, in our experience, generally tolerate this rapid loading regimen very well, and plasma levels in the high therapeutic range are usually achieved on day 3 without a need to adjust the initiating dose in most cases. In fact, a retrospective chart review of a small sample of patients who were treated using this regimen was published by us.<sup>8</sup> This analysis demonstrated that approximately 80% of patients started with 30 mg/kg/day had plasma valproate levels on day 3 that were in the therapeutic range of 50 to 120 µg/mL. The average plasma level in this sample was 93.2 µg/mL on day 3, a highly desirable, high-therapeutic plasma level for this acutely ill population and very similar to the final therapeutic level achieved in the Bowden et al. study on day 5 (95.9 µg/mL) after a single forced adjustment in dose and subsequent optional ones. In our analysis, most patients had received concomitant psychotropic drugs, including antipsychotics and benzodiazepines. Despite this, only 14% of patients experienced any side effects, and in only half of these patients was the side effect deemed significant enough to warrant a medication adjustment.

Rapid oral loading regimens are a widely used strategy for enhancing the therapeutic use of divalproex DR in patients with acute mania. Similarly, rapid loading regimens are likely to enhance the therapeutic benefits of divalproex ER now that it has been approved for treatment of this condition. This is an area that would benefit from further research. Our extensive experience with rapid oral loading of divalproex ER leads us to believe that adoption of a loading strategy of 30 mg/kg/day would achieve even greater benefits than demonstrated for this drug in the Bowden et al. study by allowing most acutely manic patients to achieve desirable therapeutic plasma levels by day 3 of treatment or sooner and obviating the need to increase doses further, as was the practice in the Bowden et al. study.

*Dr. Feifel has received grant/research support from Abbott.*

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#### Dr. Bowden Replies

**Sir:** Dr. Feifel's observational information on the effectiveness of a loading dose strategy for divalproex ER adds a pragmatic extension to our recent publication. The one caveat we would add is that dosing practices that may be well tolerated in acutely manic, hospitalized patients may be less well tolerated in less severely ill outpatients, likely consequent to lower levels of increased activation.

*The article discussed here was supported by Abbott.*

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#### Eosinophilia Indicating Subclinical Clozapine-Induced Pericarditis

**Sir:** Literature on clozapine-induced pericarditis (CIP) is very rare. CIP usually presents as a very acute clinical picture with polyserositis or pericardial tamponade. We report on a schizophrenic patient with eosinophilia who developed CIP with no further clinical signs, obvious laboratory abnormalities, or pathologic electrocardiogram (ECG) alterations that could be clearly attributed to cardiac disease.

**Case report.** Mr. A, a 22 year-old white man, was referred to our hospital in 2005 with a 6-month history of sustained psychotic and severe negative symptoms in the course of DSM-IV-diagnosed paranoid schizophrenia. Physical examination and ECG findings were within normal limits. Laboratory assessment showed no abnormalities, apart from mild eosinophilia (5%–7% of white blood cells [WBCs]) due to treatment with olanzapine.

We first added aripiprazole to olanzapine but obtained no relevant clinical improvement during 6 weeks of combined treatment. We tapered olanzapine during a 2-week period and,

1 week after first reduction of olanzapine dosage, started clozapine, which was titrated to a dose of 350 mg/day while maintaining aripiprazole treatment. Three weeks after commencing clozapine treatment, eosinophils increased to 21% of WBCs. WBCs, temperature, blood pressure, and pulse rate were within normal limits, but serum C-reactive protein (CRP) was slightly elevated (10.5 mg/L; normal range, < 3 mg/L). At this time, the patient reported recovery from flu-like symptoms and mild diarrhea, which had started approximately 2 weeks after initiation of clozapine. We attributed these findings to some unspecific gastrointestinal infection rather than cardiac disease because the patient's girlfriend had suffered from the same symptoms. Furthermore, by the time pericarditis was later diagnosed, these symptoms had already resolved and CRP was within the normal range.

Although the patient denied any cardiac complaints, we conducted an ECG and measured levels of creatin phosphokinase-MB, troponin T, and aspartate aminotransferase. The ECG showed mild sinus tachycardia (103 b.p.m.) but no other abnormalities. Despite daily regular pulse measurement, sinus tachycardia could not be replicated. Levels of enzymes indicative of heart affection were within normal limits. Stool probes were negative for parasites, and an acute infection with enterovirus could be ruled out with polymerase chain reaction. Because of persistent eosinophilia up to 27% of WBCs 5 weeks after starting clozapine treatment, we performed a cardiac ultrasound, which revealed a normal ejection fraction but pericardial effusion of 5 to 7 mm with an area of slightly swollen perimyocardial tissue over the right ventricle. Twenty-four-hour ECG showed sinus rhythm with 79 to 151 b.p.m. (101 b.p.m. on average) but without any dangerous arrhythmia.

A rheumatologic workup for systemic lupus erythematoses and other autoimmune diseases was negative except for an elevated level of immunoglobulin E (IgE) (52 kU/L; normal range, up to 20 kU/L). We tapered clozapine within 1 week and introduced perazine instead. Six days after clozapine had been stopped, the ECG findings were within normal limits with 68 b.p.m. and cardiac ultrasound showed significant reduction of pericardial effusion (1–2 mm). After another 5 days, eosinophils reduced to 5% of WBCs. Findings of the last cardiac ultrasound conducted 4 weeks after clozapine discontinuation were within normal limits. Eosinophils and IgE dropped to within the normal range another 5 weeks later, and the patient exhibited no cardiopulmonary problems or pathologic ECG alterations.

Eosinophilia after clozapine initiation was the only finding that prompted us to perform a cardiac ultrasound, which revealed pericarditis. According to the literature, eosinophilia occurs in 0.2% to 62% of all clozapine-treated patients.<sup>1,2</sup> Some authors have reported a predictive value for subsequent agranulocytosis.<sup>3</sup> However, the clinical relevance of clozapine-associated eosinophilia remains controversial, and its degree varies intraindividually depending on the day of treatment.<sup>1,2</sup> Eosinophilia usually develops 3 to 5 weeks after clozapine initiation, disappears spontaneously after another 4 weeks, and may reach more than 50% of WBCs.<sup>2</sup>

Relevant mechanisms of clozapine-related cardiac complications are still unclear, but an IgE-mediated acute hypersensitivity is discussed.<sup>4</sup> This hypothesis is supported by an elevated IgE level and peripheral eosinophilia in our patient, who lacks any other history of allergic diseases.

This case suggests that eosinophilia might predict subclinical but nevertheless potentially fatal cardiac diseases in clozapine-treated patients. Screening guidelines to monitor patients for clozapine-associated cardiac side effects are lacking

at present.<sup>5</sup> On the basis of this case report and recent literature, we recommend an ECG, measurement of creatine phosphokinase-MB and troponin T, and a cardiac ultrasound not only for patients with symptoms of cardiopulmonary disease (tachycardia, chest pain, dyspnea), but also for those who develop, alone or in combination, fever, flu-like symptoms, or eosinophilia.<sup>5</sup>

*The authors report no financial affiliation or other relationship relevant to the subject of this letter.*

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## Quetiapine in Patients With Tourette's Disorder: An Open-Label, Flexible-Dose Study

**Sir:** Tourette's disorder (TD), or Gilles de la Tourette's syndrome, is a neuropsychiatric disorder, usually starting in early childhood, characterized by multiple motor and vocal tics.

Although the etiology of TD remains largely unknown, it has been hypothesized that overactivity or hypersensitivity of the D<sub>2</sub> receptors in the striatum plays a role.<sup>1</sup> This hypothesis is consistent with the proved effectiveness of central D<sub>2</sub>-blocking agents like haloperidol and pimozide that decrease the intensity and frequency of tics in approximately 70% of the patients. However, high D<sub>2</sub>-receptor binding affinity is also responsible for the frequent occurrence of undesirable extrapyramidal side effects (EPS), resulting in up to 70% of the patients' stopping these drugs within 1 year of treatment. The most important side effects include tremor, akinesia, rigidity, akathisia, dystonia, and dyskinesia.

These disadvantages form reasons to continue the search for psychopharmacologic drugs better tolerated, encouraging interest in the effect of new psychopharmacologic drugs such as the atypical antipsychotic drugs, defined as agents with lower D<sub>2</sub> binding affinity or faster D<sub>2</sub>-receptor dissociation properties.<sup>2</sup> The efficacy of the atypical antipsychotic drug quetiapine, a drug with predominantly  $\alpha_1$ -adrenergic, 5-HT<sub>2A</sub>, and histaminergic properties, has not been systematically investigated in adults with TD, although 2 case reports are available, 1 concerning a TD patient with concomitant mania who was stabilized on 600 mg/day<sup>3</sup> and 1 pertaining to a 19-year-old female patient with tic disorder in whom tics disappeared after 4 weeks of

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treatment with quetiapine (200 mg/day).<sup>4</sup> Further, in children with TD, the effectiveness of quetiapine appeared to be promising: 2 successful case reports<sup>5,6</sup> and 1 open-label trial<sup>7</sup> have been published thus far. This 8-week open-label trial with quetiapine (mean dose: 72.9 mg/day), including 12 children with TD, reported a significant tic reduction, ranging from 30% to 100%, as measured with the Yale Global Tic Severity Scale (YGTSS).<sup>8</sup> Three children complained of sedation in the first week of treatment, but this side effect was neither severe nor persistent, and it disappeared at the second week.

These encouraging effects in children inspired us to perform the current open-label study, aiming at evaluating the short-term efficacy and tolerability of quetiapine in adults.

**Method.** All drug-free adult patients with TD as the main diagnosis who visited the anxiety outpatient clinic of GGZ Buitendamstel consecutively between June 2003 and June 2004 were invited to participate in the present study. Diagnosis of TD was determined by D.C.C. according to DSM-IV<sup>9</sup> criteria and with the aid of the YGTSS,<sup>8</sup> and the Diagnostic Confidence Index (DCI).<sup>10</sup> Excluded were patients with mental retardation, neurologic disorders other than TD, major depressive disorder, alcohol abuse or dependence, and psychosis. Patients who had received pharmacotherapy for TD in the 3 months preceding the study were excluded as well.

Patients were treated for 12 weeks (6 consultations) with quetiapine in flexible doses between 50 to 600 mg per day. The mean dosage of quetiapine was 205.8 mg/day after 12 weeks (SD = 138.0 mg, range = 50–600 mg/day). No cognitive-behavioral treatment for TD was provided.

Measurements assessing presence and severity of tics were taken at baseline and posttest by an independent assessor using the ordinal scales of the YGTSS, which rate number, frequency, intensity, complexity, interference, and overall impairment due to tics; motor and vocal tics are rated separately on these scales. Side effects were scored at each session by the treating clinician, using the Fawcett Side Effect Scale.<sup>11</sup>

Baseline and posttest scores were compared with paired *t* tests. Both completer and intention-to-treat (ITT) analyses were carried out. In addition, Cohen's *d* was used to calculate the effect size between baseline and posttest by subtracting the posttest score from the baseline score and then dividing the difference by the pooled standard deviation.

**Results.** Twelve patients, all men, meeting the inclusion and exclusion criteria gave written informed consent, after explanation of the full study procedures, and the study was approved by the institutional review board at GGZ Buitendamstel. Mean age of patients was 38 years (SD = 12 years, range = 20–52 years). Mean age at onset of tics was 8 years (SD = 2 years, range = 5–11 years). The mean YGTSS motor and vocal tic severity score at baseline was 23.6 (SD = 11.8; range = 8–42), with a mean YGTSS impairment score of 4.4 (SD = 1.8; range = 1–8), thus representing a group with moderate severity.

Three patients dropped out of the study prematurely because of side effects: somnolence (N = 3), tiredness (N = 3), and headache (N = 2), leaving 9 completers.

The mean completer posttest YGTSS total motor and tic severity score was 18.0 (SD = 8.3), while the mean completer posttest YGTSS impairment score was 2.0 (SD = 1.2). On the YGTSS motor and vocal tic severity score, no significant effect was found in the completer and ITT analyses (both analyses: *t* = 1.9, *p* = .08; completer sample effect size Cohen's *d* = 0.6).

On the YGTSS impairment score, a significant severity reduction was found, both in the completer and ITT analyses (completer analysis: *t* = 5.1, *p* = .001; ITT analysis: *t* = 3.8, *p* = .003; completer sample effect size Cohen's *d* = 1.49).

To investigate whether the more severely affected subjects might have benefited more from treatment than the less severely affected patients, the high and low scorers on YGTSS tic severity (i.e., tic severity scores > 20 vs. scores ≤ 20) and high and low scorers on tic impairment (i.e., scores > 5 vs. scores ≤ 5) were subsequently analyzed with paired samples *t* tests. We found that those patients scoring in the > 20 range showed a significant reduction in tics at posttest (in both the completer and ITT analyses *t* = 4.0; *p* = .02), whereas patients in the < 20 range did not improve significantly (*t* = -0.2; *p* = .82). Analyses on those persons scoring low and high on impairment showed that both groups improved significantly (*t* = 3.6, *p* = .02 and *t* = 4.9, *p* = .04, respectively). No significant dose-effect relationships were detected.

In the completer sample, the most commonly reported side effects seriously interfering with daily functioning were somnolence (N = 8), tiredness (N = 5), headache (N = 3), anxiety (N = 3), akathisia (N = 3), and dizziness (N = 3).

This study is the first open-label study reporting on the efficacy and tolerability of quetiapine in adults with TD. The independent YGTSS ratings indicated a significant effect on both tic reduction in the high-scoring subsample and a reduction in tic impairment in the entire study group, with clinically significant effect sizes. However, quetiapine was not well-tolerated; 3 of 12 included patients dropped out prematurely because of side effects. Further, 8 of 9 patients completing the study complained of somnolence interfering with daily functioning.

Although one should interpret these results with caution, these results are in line with the reported effect of quetiapine in children.<sup>7</sup> Possibly, the lack of effect found in patients at the lower scoring range of tic severity might partly be explained by the narrow margin in which persons should improve, and consequently an inability of the YGTSS to pick up subtle improvements. However, we cannot exclude the possibility that quetiapine is ineffective in patients in the mild-to-moderate range of TD. This result is of interest in light of the comparison with clozapine, the model atypical antipsychotic drug with similarly low D<sub>2</sub>-binding capacity, which has shown little effect in tic treatment.<sup>12</sup> Possibly, this difference in effect between quetiapine and clozapine is explained by differences in 5-HT binding capacity between the 2 drugs.

In conclusion, these findings are moderately encouraging, although, due to the small sample size and the uncontrolled character of the study, not conclusive. Therefore, future studies, including study subjects at the severe end of the TD spectrum and using a controlled design, seem to be of particular interest.

*The authors report no financial affiliation or other relationship relevant to the subject of this letter.*

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## REFERENCE

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## Dr. Bhat Replies

**Sir:** I would like to thank Dr. Green for his insightful and well-articulated comments in response to my column.

I am a psychiatrist as well as an internist, and I would like to reassure Dr. Green that I am not the least bit biased against psychiatry. I practice evidence-based psychiatry in an academic setting, and I recommend and prescribe psychotropics just as any sensible psychiatrist would.

In the story, the psychiatrist prescribes antidepressants, but then considers the possibility, however remote, that suffering was intrinsic to the Buddha's quest for enlightenment. As Dr. Green implies, there is no conclusive evidence for or against the existentialist perspective that suffering can precipitate and perpetuate a search for meaning and therefore, ultimately, enhance one's life.

Through the story, I wished to underline the fact that our decisions to treat are made after a careful consideration of not just pharmacologic and diagnostic issues but also psychological, social, philosophical, and spiritual ones. In treating a hypothetical young man with a similar presentation to Buddha's life story, the psychiatrist ponders the very same principles that our detractors accuse us of ignoring—of autonomy and independence, context and meaning of the symptom, and patient-centered treatment.

I want to thank Dr. Green for providing me an opportunity to place the column in proper perspective.

*Dr. Bhat reports no financial or other relationship relevant to the subject of this letter.*

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## If Buddha Were in Treatment

**Sir:** This letter is in response to "The Death of a Buddha" (A PSYCHIATRIST'S DIARY, October 2006).<sup>1</sup> Shyam K. Bhat, M.D., wrote a very thought-provoking column that I enjoyed. I noticed that he is from the Department of Internal Medicine at Southern Illinois University School of Medicine, so I am not sure if his perspective is as a psychiatrist or internist. It sounded a little biased against psychiatry as is often the case when psychiatry is viewed from the perspective of other specialties.

My patients often share a similar viewpoint or concern that psychotropic medication will so alter their mental state that they will no longer be able to express opinions or viewpoints on the world or follow a calling like Buddha did. This is not only false and without any scientific proof, but also furthers the stigma that is often attached to psychiatric treatment. If Buddha had really been in treatment for depression and had been given an SSRI centuries ago, I think his depression (if he even had depression) would most likely improve, but his desire to gain enlightenment, understand human suffering, and continue seeing the world as he did would remain as it was, without any blunting of will or drive. He just might have done it with a lighter mood. Psychotropics tend to be given this perceived power and dramatic capability to alter people's core personality and being, by some, that they just do not have.

*Dr. Green has been a consultant for and received honoraria from GlaxoSmithKline.*

## Correction

In the article "Alternative Treatments for Depression: Empirical Support and Relevance to Women" by Rachel Manber, Ph.D., et al. (July 2002 issue, pp. 628–640), Dr. Morris' middle initial was incorrect in the byline. The author's correct name is Margaret E. Morris. The online version of the article has been corrected.