

Short-term Treatment of Cocaine and/or Methamphetamine Abuse With Vigabatrin

Ocular Safety Pilot Results

Robert D. Fechtner, MD; Albert S. Khouri, MD; Emilia Figueroa, MD; Marina Ramirez, MD; Martha Federico, LSW; Stephen L. Dewey, PhD; Jonathan D. Brodie, MD, PhD

Objective: To evaluate the ocular safety of short-term use of vigabatrin to treat cocaine and/or methamphetamine addiction.

Methods: Individuals who were actively using cocaine and/or methamphetamine were eligible for enrollment. Enrolled subjects were scheduled for comprehensive eye examinations at the beginning and end of the study. Visual field testing was performed at baseline and 1 week, 4 weeks, 8 weeks, and 1 month or more after discontinuing vigabatrin. Twenty-eight subjects received at least 1 dose of vigabatrin; however, only 20 subjects continued beyond the initial escalating vigabatrin dose phase to the treatment phase. Of these 20 subjects, 18 completed the study with full follow-up. Visual fields were evaluated subjectively by 2 glaucoma specialists and analyzed objectively for group and individual changes in quadrant mean sensitivity. The objective analysis was also repeated for superior field quadrants after excluding the uppermost peripheral points to minimize the eyelid effect.

The main outcome measures were change of visual field, visual acuity, and ocular adverse effects.

Results: Vigabatrin seemed to help treat cocaine and/or methamphetamine addiction. Of 18 subjects, 16 had negative test results for cocaine and methamphetamine use during the last 6 weeks of the trial. No ocular adverse events were detected. The subjective evaluation did not reveal visual field constriction in any of the 18 evaluable participants. Objective group and individual analyses for quadrant mean sensitivity did not show any change from baseline in any quadrant. No changes in visual acuity were noted.

Conclusions: In this short-term pilot study, vigabatrin seemed to help treat cocaine and/or methamphetamine abuse. There was no evidence of ocular or visual field adverse effects.

Arch Ophthalmol. 2006;124:1257-1262

Author Affiliations: Institute of Ophthalmology and Visual Science, University of Medicine and Dentistry of New Jersey–New Jersey Medical School, Newark (Drs Fechtner and Khouri); Codet Aris Vision Institute, Tijuana, Mexico (Drs Figueroa and Ramirez and Ms Federico); Department of Psychiatry, NYU School of Medicine, New York (Drs Dewey and Brodie); and Chemistry Department, Brookhaven National Laboratory, Upton, NY (Dr Dewey).

THE CLINICAL USE OF VIGABATRIN has been limited because of an association with the development of visual field defects.^{1,2} Vigabatrin (γ -vinyl-GABA [γ -vinyl- γ -aminobutyric acid]) is indicated for the long-term treatment of epilepsy in combination with other antiepileptic drugs, mostly for patients who have resistant partial epilepsy with or without secondary generalization (ie, vigabatrin is indicated where other appropriate drug combinations have proved inadequate or have not been tolerated). Vigabatrin is also used as monotherapy in the treatment of infantile spasms.

Vigabatrin is effective, but clinicians are reluctant to prescribe it because of the visual field defects it can cause. The exact pathophysiological mechanism of vigabatrin-associated visual field defects remains unclear. Interindividual susceptibility suggests that a possible idiosyncratic drug reaction may underlie the pathogenesis of observed visual

field loss.² The observed visual field defects in various studies tended to behave differently. Although some studies³ suggested that visual field loss was irreversible, a few^{1,4} reported an improvement in visual field loss on discontinuation of vigabatrin. Other studies^{2,5} found no correlation between treatment duration or cumulative dosage and visual field loss. While there are conflicting reports as to whether emergent defects are stable³ or reversible,⁶ to our knowledge, there is not a single report of progression following vigabatrin discontinuation.

Because vigabatrin is typically used to treat chronic conditions such as epilepsy, long-term safety remains a concern. However, short-term use of vigabatrin has not been well studied because of its indication for the treatment of chronic disease.

A new and promising short-term use of vigabatrin has recently been described. Short-term use of vigabatrin seems to be effective in the treatment of cocaine and/or methamphetamine dependence.⁷ In the

Table 1. Study Flow Chart*

Procedure	Visit 1 (Baseline), Day -30 to 0	Visit 2 (Initial), Week 1	Visit 3 (Interim), Week 4	Visit 4 (Final), Week 8	Visit 5 (Follow-up), Week 12	End Point Testing†
Best-corrected Snellen visual acuity determination	X	X	X	X	X	X
Visual field determination						
Peripheral (both eyes)‡	X (2 fields at baseline)§	X	X	X	X	X
Central (1 eye)	X				X	X
Fundus examination¶	X				X	X

*X denotes that the procedure was performed at that time point; no entry indicates that the procedure was not performed at that time point.

†If the Humphrey field analyzer (HFA) 60-4 test result changed, end point testing was performed.

‡The HFA 60-4 test was used.

§The HFA 120-point screening test was used if the subject had not had an HFA examination before.

||The HFA 24-2 test was used on the eye with the better best-corrected visual acuity or, if the best-corrected visual acuity was equal, on the right eye.

¶Must be performed last if dilation is required.

present study, 16 of 18 subjects had negative test results for cocaine and methamphetamine abuse during the last 6 weeks. This group of subjects had a mean daily reported use of nearly 1 g of methamphetamine or cocaine for 12 years, and no subject acknowledged a history of more than several consecutive days drug free in the year preceding enrollment in the study.

Vigabatrin, an irreversible inhibitor of GABA transaminase, attenuates the rapid elevation in nucleus accumbens dopamine level that characterizes the neurochemical response to cocaine, methamphetamine, and other drugs of abuse.^{8,9} In contrast with its long-term use as an antiepileptic drug, vigabatrin for drug dependence was used for a relatively short period (9 weeks) in this pilot study. This dosing regimen may not carry the same risk of visual field loss as does long-term use in combination with other drugs for epilepsy.

Because long-term vigabatrin use is associated with visual field loss, the subjects in this pilot study of vigabatrin treatment of methamphetamine and/or cocaine dependence underwent ocular safety monitoring and frequent automated visual field testing. We report herein the monitoring strategy developed and the results of the ocular safety analysis.

METHODS

All enrolled subjects were recruited by word of mouth and provided signed informed consent. The protocol for this study was reviewed and approved in Mexico by the Comision Federal para la Proteccion Contra Riesgos Sanitarios (reference No. 03320100101) following review by the staff of the director de Evaluacion de Medicamentos, according to the standards of the Declaration of Helsinki, as currently modified. Institutional review board committee approval (University of Medicine and Dentistry of New Jersey, Newark) was obtained for the review and analysis of all visual safety data.

Subjects who met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*¹⁰ criteria for methamphetamine and/or cocaine dependence and who were eligible to begin vigabatrin treatment provided a complete preadmission history and underwent a physical examination. Subjects underwent a complete ophthalmic evaluation by an ophthalmologist (E.F.) at baseline and on completion of the study. This included an

evaluation of best-corrected visual acuity (using the Snellen chart) and slitlamp and dilated fundus examinations. Visual acuity was determined before any other visual field testing at each visit. Visual acuity was tested with best refraction.

Automated visual field testing with the Humphrey field analyzer (HFA) was performed at baseline before starting vigabatrin treatment. To ensure the reliability of visual field testing, all subjects underwent at least 1 visual field test before baseline. For training purposes, a 120° screening visual field test was performed. Practice fields were marked as “practice” and not used in the analysis of data.

To monitor for visual field defects, testing was performed at baseline and then repeated after 1, 4, and 8 weeks of treatment with vigabatrin. Subjects were retested 4 weeks (or more) after cessation of vigabatrin treatment. Study fields were tested with HFA 60-4 to test the peripheral field. Every subject had 2 sets of reliable fields at baseline for both eyes before starting the study medication (visit 1). The 2 baseline fields were obtained on the same day or on different days. To probe for the emergence of any detectable central visual field threshold changes, each subject also had a central field test (HFA 24-2) performed in 1 eye (either the eye with the better best-corrected visual acuity or, if equal, the right eye) at baseline and again on the last exit visit.

Vigabatrin administration was initiated according to protocol at 500 mg twice daily for 3 days, then 1.5 g/d for the next 4 days and 2.0 g/d for the next week. On day 15, subjects were given 3.0 g/d; that dose was maintained for the next 28 days. Then, subjects were tapered off medication over the next 3 weeks. Completers received a cumulative dose of 137.0 g of vigabatrin.

Once receiving treatment with vigabatrin, subjects returned for follow-up at 1 week (visit 2), 4 weeks (visit 3), and 8 weeks (visit 4) of therapy. During each of those visits, best-corrected visual acuity was measured and HFA 60-4 testing was performed on both eyes. Visual field test results were evaluated by an ophthalmologist (E.F.) at each study visit and compared with the baseline fields. If a subject showed a change in visual field at visits 2, 3, or 4, the protocol required confirmation and discontinuation of the study drug.

Once treatment was completed, subjects returned for their exit visit 1 month (longer for some) after discontinuing vigabatrin. On their exit visit (visit 5), best-corrected visual acuity was determined and slitlamp and dilated fundus examinations were performed. Peripheral visual field testing (with HFA 60-4) was performed on both eyes, and central testing (with HFA 24-2) was performed in 1 eye (**Table 1**).

For this study, we had to develop an analysis algorithm for the HFA 60-4 tests. Although there is abundant information about assessing change in central visual field (HFA 24-2 and 30-2 tests) using threshold automated achromatic perimetry, there is little information on and no software for performing similar analysis in the peripheral field. The effects of cocaine and/or methamphetamine on visual field performance are similarly undefined. The study population actively abusing drugs does not correspond to any available normative database. Nevertheless, these subjects were able to provide reliable visual fields.

To best analyze our data, we established a baseline for each subject and then developed subjective and objective analysis strategies. The subjective analysis was performed by 2 glaucoma specialists (R.D.F. and A.S.K.) with experience in visual field evaluation and pathological patterns. Each test was evaluated separately for defects and reliability. Reliability criteria (fixation losses, false positives, and false negatives) below 20% were considered indicative of adequate performance. Final visual field test results were then compared with their respective baseline results, and a clinical impression of clinically significant change or no change was assigned.

The objective analysis was performed for the whole group and for individual subjects by quadrant. For the group objective analysis, total sensitivity (sum of thresholds) per quadrant for right and left eyes was the unit of analysis. The quadrant mean sensitivity, standard deviation, and root mean square error/mean as a measure of variability for the 2 baseline peripheral fields were calculated for both eyes. The 8 quadrant total sensitivities at the end of the study were then compared with the corresponding baseline totals. Because of frequent upper eyelid artifact, the superior field quadrants were also analyzed after adjusting the total sensitivity per quadrant by excluding the uppermost peripheral tested points most likely to be influenced by eyelid position (**Figure**).

For the individual objective analysis, the calculated quadrant means and standard deviations for the study population at baseline, in each of the 8 quadrants, were used to establish the estimated variability. Deciding on the best criteria for objective analysis was particularly challenging because of the known inherent variability in peripheral field sensitivity¹¹ and the lack of published standards for the analysis of peripheral visual fields. A significant change was defined as any quadrant total sensitivity in a patient that decreased by greater than 2 SDs.

RESULTS

No subjects were excluded for ocular abnormalities. Although there were high dropout rates at the screening phase (42 subjects were screened for the study, but 14 did not return to start vigabatrin treatment), most subjects who continued beyond the initial escalating dose phase completed the study; retention was excellent in subjects exposed to more than a few doses of vigabatrin. In total, 28 subjects received at least 1 dose of vigabatrin; however, only 20 subjects continued beyond the initial escalating vigabatrin dose phase. Two of those subjects were lost to follow-up. Eighteen subjects completed the study (17 men and 1 woman; average age, 33 years), with an exit examination at the visit 4 weeks or beyond (visit 5) following cessation of vigabatrin treatment.

No changes in visual acuity, slitlamp biomicroscopy, or retinal examination results were noted throughout the study. No subjects had to discontinue the study

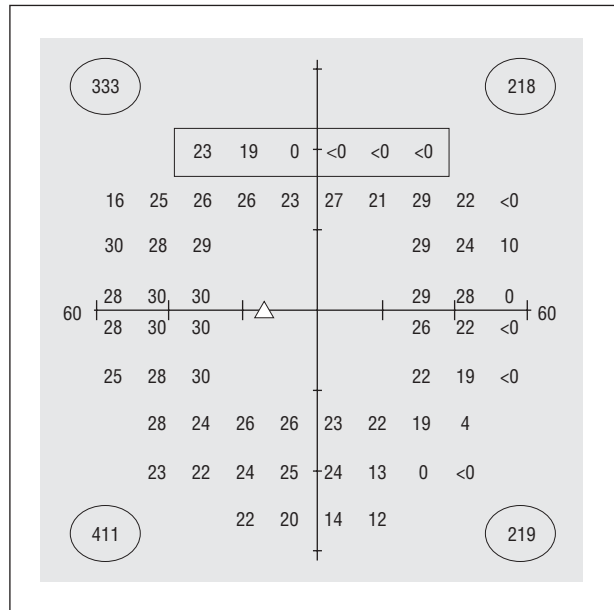


Figure. Illustration of the 60-4 threshold plot of the visual field analyzer (Humphrey field analyzer) (the open triangle is part of the standard printout and indicates the location of the optic nerve). All data points are given in decibels. The quadrant total sensitivities used in the analysis are in ovals; the censored superior points in the rectangular box were excluded in the subanalysis.

medication during the protocol because of visual field change. Among the 18 subjects who completed the study, none showed a change in the central or peripheral field warranting cessation of the drug. In addition, for the 28 subjects for whom at least 1 visual field while receiving treatment was available, there were no abnormalities detected.

Subjective evaluation of baseline peripheral visual field examination results showed variability, which was expected for peripheral locations and inexperienced visual field test takers. Far peripheral defects at baseline were more commonly present in the superior and nasal quadrants, but did not progress during the study. Seven subjects had fields that were unequivocally stable from baseline through the end of the study. Eleven subjects required retesting at study exit. These subjects most typically showed a depressed sensitivity in the far superior and/or nasal visual field region. Five had a superior-nasal peripheral depression, 5 had a superior depression only, and 1 had a nasal depression only. All returned according to protocol to be retested for confirmation of a possible change in their peripheral visual field. On retesting, all returned to the baseline condition. During retesting, special attention was paid to eliminating upper eyelid artifact and head turn (nasal) artifact. No defects were noted on the central HFA 24-2 visual field test results at baseline or at exit.

Thus, our subjective interpretation of peripheral and central fields yielded no change from baseline for any of the 18 subjects.

For the study group as a whole, changes in quadrant total sensitivities were analyzed for both eyes and showed no significant decrease in any quadrant of either eye (**Table 2**). For superior quadrants, group objective analyses were repeated after excluding the outermost supe-

Table 2. Group Objective Visual Field Quadrant Sensitivity Analysis Before and After Treatment

Quadrant	Sensitivity Before Treatment, Mean (SD), dB	RMSE/Mean, %	Sensitivity After Treatment, Mean (SD), dB	Mean Change, %	P Value
Right Eye					
I/N	310.2 (66.0)	24	334.0 (45.7)	11.6	.09
I/T	418.8 (44.5)	15	435.9 (25.8)	5.3	.11
S/N	278.6 (47.4)	15	293.4 (44.5)	7.4	.13
S/T	335.9 (45.1)	11	341.9 (28.7)	3.3	.36
Left Eye					
I/N	302.8 (46.7)	16	322.8 (61.9)	6.8	.06
I/T	426.3 (28.3)	6	428.5 (30.4)	0.7	.67
S/N	269.9 (59.6)	20	266.9 (45.4)	-3.5	.62
S/T	335.8 (36.8)	14	343.7 (31.2)	3.1	.26

Abbreviations: I/N, inferonasal; I/T, inferotemporal; RMSE, root mean square error; S/N, superonasal; S/T, superotemporal.

Table 3. Group Objective Visual Field Quadrant Sensitivity Analysis With Censored Superior Points Before and After Treatment

Quadrant	Sensitivity Before Treatment, Mean (SD), dB	RMSE/Mean, %	Sensitivity After Treatment, Mean (SD), dB	Mean Change, %	P Value
Right Eye					
S/N	231.6 (33.7)	15	248.1 (27.3)	9	.05
S/T	285.8 (30.2)	9	295.2 (13.4)	5	.17
Left Eye					
S/N	229.0 (45.6)	18	232.2 (24.6)	5	.35
S/T	284.8 (25.4)	10	293.1 (16.8)	3	.08

Abbreviations: See Table 2.

rior points. No significant changes in total sensitivity were noted (**Table 3**).

Because the group analysis would not identify individuals with visual field change, individual objective analysis was also performed. None of the subjects showed a negative change in quadrant sensitivity that exceeded 2 SDs for that specific quadrant. In fact, 3 subjects showed an improvement in quadrant mean sensitivity of greater than 2 SDs.

A post hoc power calculation showed that the 18 subjects were enough to rule out (reject) a mean 0.5 root mean square error decrease or worse at $P < .05$ for all visual field quadrants.

COMMENT

The short-term use of vigabatrin seems promising for treating cocaine and methamphetamine abuse. No visual field defects developed with short-term use in this pilot study. No changes in acuity and no ocular adverse effects were encountered. The long-term use of vigabatrin for the treatment of patients with epilepsy has been associated with the development of visual field defects. Most published studies^{2,6,12} have used Goldmann kinetic perimetry to screen and observe vigabatrin-treated patients.

Automated achromatic perimetry with various testing strategies has been used to study small groups of pa-

tients treated with vigabatrin. In 1 study¹³ of 32 patients who had taken vigabatrin for at least 3 years, visual field testing with HFA revealed bilateral abnormalities in 19 (59%) of the patients compared with 0 of the 120 drug-free control subjects. The program used for testing in this study was the Humphrey 120-point, suprathreshold, 3-zone static perimetry test.¹³ In another previous report,¹⁴ 33 sequential patients who began receiving vigabatrin were referred for ophthalmologic evaluation, including visual field testing with HFA 30-2 and Esterman or Octopus 32. Twenty-nine patients were able to complete testing. Of these patients, only 32% showed no visual field constriction (68% had slight to severe visual field constriction).¹⁴ In another report¹⁵ of visual field testing with HFA 30-2 in 15 children receiving long-term vigabatrin therapy, visual field defects were observed in 3 (20%). These were described as bilateral, symmetric, nasal defects.

In this study, we used achromatic automated threshold perimetry to 60°. We selected HFA 60-4 because it provides full-threshold testing. Although this program is associated with high variability, we believed it would provide data for more robust analyses than a screening program (such as the 120-point screening test). Our rationale is that for future clinical trials, a standardized method would need to be developed and significant new visual field defects would be detectable with this

protocol. While we cannot be certain that there were no extremely peripheral changes beyond the limits of the HFA 60-4 test, we would have expected to be able to detect vigabatrin-associated visual field loss with this strategy. In marked contrast with the reports previously described, none of our subjects developed confirmable visual field loss. In addition, we used the HFA 24-2 test in 1 eye of each subject to probe for subtle central defects. Our rationale was that the availability of normative data for central testing might allow for the detection of central depressions. There were none.

The subjective evaluation showed that most of the observed field defects in our study were peripheral in the superior and nasal quadrants, and were mostly due to the eyelid, eyebrow, or nose obscuring parts of the peripheral fields. Facial anatomy can obscure the test object in peripheral visual field programs. A drooping upper eyelid or an incorrect head position during the visual field test may produce such artifacts. Nasal peripheral visual field defects were also predominant in previously reported studies.¹⁶ With proper patient instruction and head positioning, these defects were not reproduced in any of the 11 patients exhibiting them. In no subjects were concentric peripheral defects observed. The pattern of peripheral superior and nasal defects observed in the 11 subjects was not consistent with the concentric pattern of field loss attributed to vigabatrin in other studies. More importantly, the defects were not reproduced, and the fields returned to baseline status on retesting. We believe that there was testing artifact from the eyebrow and nose.

We performed group and individual objective analyses of the peripheral fields. In the group analysis, the total sensitivity in all quadrants for both eyes did not diminish during the study. Actually, all of the observed change was in the positive direction, with improvement in total quadrant scores. It may be that improved test performance and patient cooperation have contributed to the improved peripheral field scores. It is also likely that once patients were abstinent from drug abuse, they performed better on visual field testing. To reduce any possible confounding effects of our subjects becoming better test takers by training and being free from drug abuse, we did not use training fields in the analysis, and all tests analyzed had good reliability variables. Whether the subjects' abstinence from cocaine and/or methamphetamine affected their measured visual field sensitivity remains unknown.

One concern with the study population was dropouts. Most of the subjects who began receiving vigabatrin had visual field data available for safety analysis. Many subjects (n=42) were screened for the study but never started receiving the study drug. This is not surprising given the population of active substance abusers. Of those subjects motivated enough to complete the dose escalation phase, retention was excellent (18 [90%] of 20 subjects). The cumulative maximum vigabatrin dose received among completers in the study was 137 g, less than 10% of the lifetime exposure at which there seems to be an increase in the incidence of visual field abnormalities. In 1 study,¹⁷ subjects who had taken a total dose of 1500 g or more of vigabatrin

for epilepsy treatment were at risk of developing significant visual field defects.

Vigabatrin-associated visual field loss was thought to affect males more severely than females.² Of the 18 subjects who completed this study, 17 were males. One might expect our population to be at higher risk for vigabatrin-associated field loss, but we do not believe we studied a uniquely low-risk population.

Digital imaging technologies and fundus photography can identify retinal nerve fiber layer attenuation in subjects receiving long-term vigabatrin treatment of epilepsy.^{18,19} The sensitivity of these imaging modalities in the detection of structural abnormalities after short-term vigabatrin exposure is still unknown. Such tests may provide additional means of monitoring for ocular safety in future studies.

We have established an ocular safety protocol that was clinically practical in the study of vigabatrin for cocaine and/or methamphetamine abuse. Study subjects were able to perform reliable automated threshold perimetry. The absence of any detectable ocular adverse effects or changes in visual field with this relatively low-dose and short-term regimen of vigabatrin is promising with regard to its safety in the short-term treatment of drug abuse.

We recognize the limitations of this pilot trial because it was a nonrandomized open-label study without a control group. Our findings suggest that there can be further study of vigabatrin for the treatment of drug abuse without undue concern about ocular safety and with proper rigorous monitoring of the visual field. Furthermore, in this challenging population, subjects were able to perform visual field testing reliably enough to allow meaningful ocular safety monitoring. Considering the significant morbidity associated with cocaine or methamphetamine abuse, vigabatrin seems promising and worthy of further study.

Submitted for Publication: November 17, 2005; final revision received March 28, 2006; accepted April 3, 2006.

Correspondence: Robert D. Fechtner, MD, Institute of Ophthalmology and Visual Science, University of Medicine and Dentistry of New Jersey—New Jersey Medical School, 90 Bergen St, Suite 6100, Newark, NJ 07103 (Fechtner@umdnj.edu).

Financial Disclosure: None reported.

Funding/Support: This study was supported in part by Research to Prevent Blindness and by a grant (for the clinical trial on which the analysis is performed) from Catalyst Pharmaceutical Research LLC.

Acknowledgment: We thank Jeff Gornbein, DrPH, of the Statistical/Biomathematical Consulting Clinic, Department of Biomathematics, David Geffen School of Medicine at UCLA.

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