Long-Term Follow-Up of Magnetic Resonance–Detectable Choline Signal Changes in the Hippocampus of Patients Treated With Electroconvulsive Therapy

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Background: In a previous proton magnetic resonance spectroscopic imaging (^{1}H MRSI) study of the hippocampus in patients receiving electroconvulsive therapy (ECT), the metabolite signals for *N*-acetylaspartate (NAA), creatine and phosphocreatine, and choline-containing compounds (Ch) were evaluated before and directly after a course of ECT. Stable metabolite signals for NAA and creatine and phosphocreatine but increasing signals from choline-containing compounds post-ECT compared with pre-ECT were found. The purpose of this investigation was to monitor the long-term course of the hippocampal metabolite signals post-ECT treatment.

Method: Twelve of 17 depressed patients (DSM-IV and ICD-10 criteria), examined while receiving ECT, were reevaluated after a minimum interval of 12 months. Data were gathered between 1997 and 2000. In all patients, ^{1}H MRSI studies of the hippocampus were performed and relative contributions of cerebrospinal fluid, gray matter, and white matter to each MRSI voxel were determined. Patients' cognitive as well as psychopathologic status was obtained.

Results: Two of the examined patients suffered a relapse. All other patients were in stable remission. No changes in hippocampal NAA signals were detected after a mean interval of 20 months (SD = 8.6) after the last ECT. The initially significant increase in the Ch signal was found to be reversed to nearly pre-ECT values.

Conclusion: The results of our long-term follow-up corroborate our original finding that ECT has no influence on NAA signals. The observed reversal of the Ch signal might reflect alterations in membrane turnover. Increased Ch signals are thought to reflect an increased membrane turnover and should reverse accordingly. This increase in membrane turnover could potentially play a role in the therapeutic effect of ECT.

(J Clin Psychiatry 2003;64:775–780)

Received May 7, 2002; accepted Jan. 3, 2003. From the Central Institute of Mental Health, Mannheim, Germany.

Presented in part at the 9th Annual Meeting of the International Society for Magnetic Resonance in Medicine, April 21–27, 2001, Glasgow, U.K.

We thank Wolfgang Weber-Fahr, Dipl.Phys., and Sigi Walter, Dipl.Phys., for help with the segmentation algorithm and data processing, Dr. Norbert Schuff for providing the spherical k-space sampling MRSI sequences, and Drs. Andrew Maudsley and Brian Soher for providing the automated spectral fitting routine supported by grant R01AG12119 from the National Institutes of Health/National Institute on Aging.

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The efficacy of electroconvulsive therapy (ECT) in the treatment of major depressive episodes is undeniable. Nevertheless, the exact nature of the therapeutic effect of ECT is unknown. The need for repeated treatment to produce any long-lasting antidepressant effect gives strong support to an involvement of long-term neuroadaptive mechanisms. In rats treated with electroconvulsive shock (ECS), an animal model of ECT in humans, changes in gene expression could be detected. Involved genes include those encoding for brain-derived neurotrophic factor (BDNF) and its receptor TrkB.[1] Repeated ECS was found to prolong the time of enhanced gene expression significantly.[1] On a cellular level, the induction of mossy fiber sprouting by ECS has been demonstrated.[2,3] Additionally, recent findings point toward a sprouting of serotonergic axons in the hippocampus after ECS.[4] In rats, increased neurogenesis in the hippocampus was shown to represent a neurobiological correlate of chronic antidepressant treatment.[5]

Among the clinical side effects of ECT are anterograde and retrograde amnesia implicating an involvement of the hippocampus.[6] The question of whether ECT-induced amnesia involves mostly personal or impersonal memory is still controversial, but recent studies suggest that the strongest effects are on impersonal memory.[7] A recent study of long-term consequences of ECT on adolescent patients could not find cognitive impairment in the long-term follow-up of ECT.[8] In fact, we are not aware of any studies showing long-term cognitive impairment following ECT.

Structural brain imaging studies and postmortem examinations did not provide evidence for ECT-associated structural brain damage.[9,10] Magnetic resonance spectroscopic imaging (MRSI) studies are considerably more sensitive than structural imaging in assessing pathologic changes in the brain even if morphologic changes are absent. Especially *N*-acetylaspartate (NAA) has been demonstrated to be a sensitive marker of neuronal function.[11] In patients with temporal lobe epilepsy, low NAA signals predict the affected side in the presurgical evaluation.[12] Therefore, we hypothesized that any serious seizure-induced neuronal malfunction would result in a decrease of the NAA signal. Depending on the nature of this malfunction, a decrease might be either immediate or delayed. In a sample of 17 patients treated with ECT, we found no immediate changes in the NAA signal corroborating that ECT does not lead to immediate neuronal loss or dysfunction.[13] However, this finding did not rule out any delayed neuronal damage, which would in turn be indicated by a delayed decrease in NAA signal.

The most striking result of our previous MRSI study of the hippocampus, though, was a significant increase in signals from choline-containing compounds (Ch) in 17 patients during and immediately after a complete course of ECT.[13] Patients' pre-ECT Ch signals were low compared with those of healthy subjects. An increased Ch signal might reflect an ECT-induced increased membrane turnover, which could be due to mossy fiber sprouting. We hypothesized that Ch signals may be related to either depressive symptoms or the processes underlying remission from depression. In the latter case, Ch signals may have decreased over time.

The purpose of the present study was to follow up the quantitative changes in Ch and NAA signals in the hippocampal region of patients who had received a course of ECT and remitted from a major depressive episode.

Table 1. Characteristics of Patients Who Were Followed Up Compared With Patients Who Could Not Be Followed Up[a]

Characteristic	Follow-Up Patients (N = 12)	Patients Not Examined (N = 5)
Age, y	63.81 (14.34)	65.42 (11.33)
Sex, F/M, N	8/4	2/3
Age at onset of depression, y	44.41 (17.19)	47.20 (12.66)
No. of episodes of depression	5.7 (6.2)	2.8 (0.8)
HAM-D score		
Pre-ECT	28.33 (4.74)	25.60 (5.81)
Post-ECT	7.58 (3.18)	6.40 (2.41)
At follow-up	6.25 (8.06)	NA
Substance or alcohol abuse, N	0	NA
Receiving medication when released from hospital, N	12	5
Tricyclic and tetracyclic antidepressants	6	3
Selective serotonin reuptake inhibitors	3	1
Monoamine oxidase inhibitors	0	0
Antipsychotics	1	1
Lithium	5	1
Carbamazepine	1	0
Valproate	3	0
Current medication use, N	10	NA
Tricyclic and tetracyclic antidepressants	4	NA
Selective serotonin reuptake inhibitors	2	NA
Monoamine oxidase inhibitors	0	NA
Antipsychotics	2	NA
Lithium	5	NA
Carbamazepine	1	NA
Valproate	4	NA
Without current medication	2	NA

[a]Data are given as mean (SD) unless otherwise noted.
Abbreviations: ECT = electroconvulsive therapy, HAM-D = Hamilton Rating Scale for Depression, NA = not applicable.

METHOD

Subjects

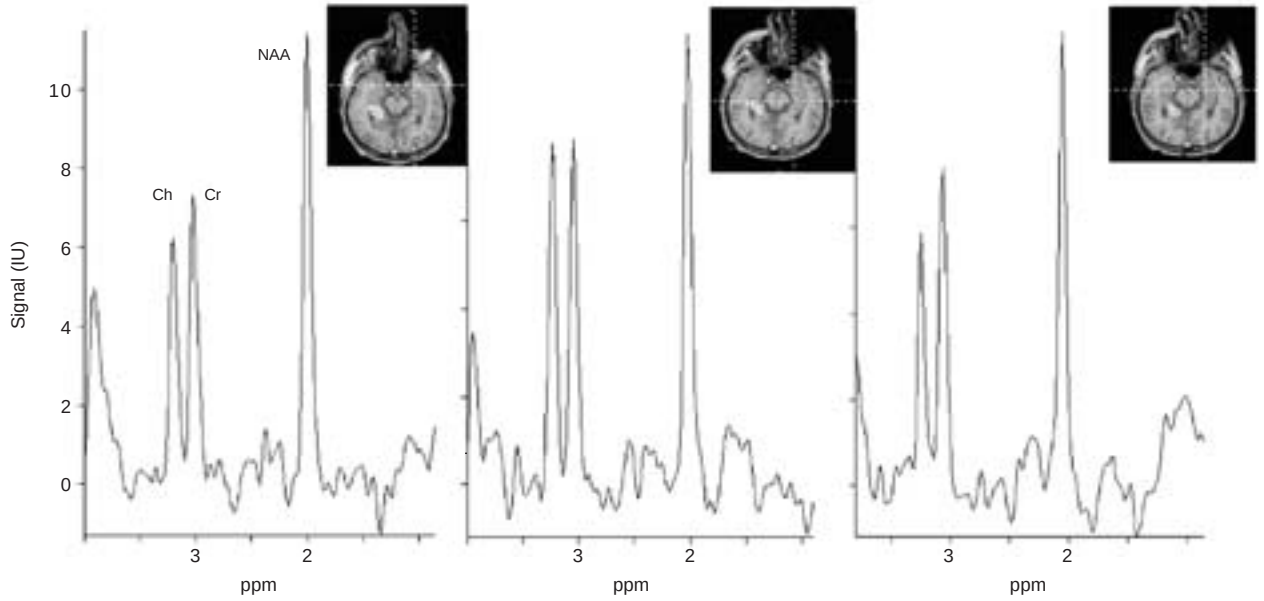
Data were gathered between 1997 and 2000. We followed a sample of 17 patients whom we had previously studied using proton (^{1}H) MRSI while they were receiving a full course of ECT at the Central Institute of Mental Health in Mannheim, Germany.[13] All patients had met DSM-IV (American Psychiatric Association, 1994) and ICD-10 (World Health Organization, 1992) criteria for a major depressive episode based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).[14] Patients were invited to participate in the examination by mail. Patients who did not respond to the mailing were contacted by telephone or through their referring physician. We were unable to contact 2 patients, who had moved away from the area. One patient who was still in remission from depressive symptoms refused participation due to his advanced age. Two patients could not be included in the ^{1}H MRSI studies because of acute depressive symptoms; 1 of the 2 was referred to another mental hospital and the other took part in the clinical examination but declined proton MRSI because of claustrophobic fears.

A summary of the subjects' clinical history is given in Table 1. All of our subjects were right-handed. The follow-up examination took place 12 to 32 months (mean ± SD = 20 ± 8.6 months) following the last ECT. Only 2 of the patients were not receiving psychopharmacologic treatment at the time of examination (see Table 1). In the initial examination, patients with a history of neurologic or psychiatric disorders other than depression had been excluded with the exception of 2 patients with a history of mild alcohol abuse who had remained abstinent. One patient had developed mild idiopathic Parkinson's disease, which was treated with bromocriptine and L-dopa.

Clinical Examination

All patients underwent a structured clinical interview to evaluate current psychiatric disease (SCID). For psy-

Figure 1. Spectra From the Right Hippocampal Region of a Patient Pre-ECT, Post-ECT, and at Follow-Up (from left to right)[a]



[a]The insets show transverse fast low-angle shot localizer images angulated parallel to the long axis of the hippocampus. The evaluated voxels are marked in the insets. The comparison of the peaks from choline-containing compounds (Ch) (at 3.2 ppm), creatine and phosphocreatine (Cr) (at 3.0 ppm), and *N*-acetylaspartate (NAA) (at 2.0 ppm) shows the marked increase in Ch post-ECT, which is reversed at follow-up.
Abbreviation: ECT = electroconvulsive therapy.

chometric assessment, the Hamilton Rating Scale for Depression (HAM-D)[15] and the Mini-Mental State Examination (MMSE)[16] were used.

MRSI Protocol

All 12 patients had given written informed consent. The entire investigation had been approved by the local ethics committee according to international standards.

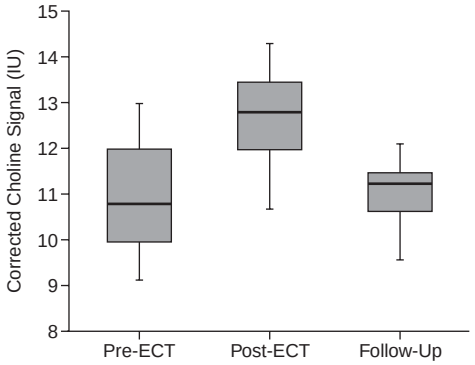
^{1}H MRSI studies were performed on a 1.5 T Siemens (Erlangen, Germany) Vision magnetic resonance imaging (MRI)/magnetic resonance spectroscopy (MRS) system equipped with a standard head coil. For MRSI localization, 2-dimensional fast low-angle shot (FLASH) images in coronal, sagittal, and oblique transverse orientation were acquired. The transverse images were angulated parallel to the long axis of the hippocampus. Point-resolved spectroscopy (PRESS) volume pre-selection was performed parallel to the transverse images and included both hippocampi.[13] Patients were carefully positioned, avoiding a sideward tilt of the head so that the MRI and MRSI volumes could be centered on the midline of both hippocampi. This procedure assures that voxels obtained from successive MRSI measures of the same subject can be selected from identical locations. Figure 1 illustrates the oblique transverse orientation of the MRI slice and MRSI volume and shows spectra from the repeated MRSI experiments in the same patient pre-ECT, post-ECT, and at follow-up. A field of view of 210 × 210 mm and a PRESS volume thickness of 15 mm were used with circular k-space sampling equivalent to a maximum of 24 × 24 phase encoding steps.[17] Other measurement parameters included reception time = 1.8 s and echo time = 135 ms, resulting in a measurement time of 13 min. The MRSI sequence was followed by a 3-dimensional (3-D) magnetization prepared rapid gradient echo data set with 154 slices and a spatial resolution of 1.05 mm covering the whole brain for tissue segmentation. Total measurement time was approximately 40 min including set-up time and acquisition of 1 MRSI data set.

MRSI Data Processing

For evaluation, voxels including primarily tissue from the hippocampal body were selected. Per–data set mean values of spectra from the left and right hippocampus are reported; added spectra are shown in Figure 1.

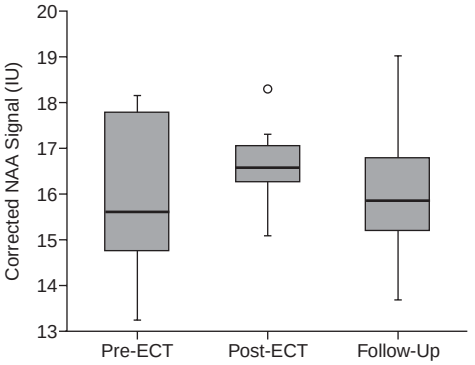
Postprocessing of the MRSI data was done with an automated spectral fitting program.[18–20] This program uses a parametric spectral model with acquisition-specific a priori information in combination with a wavelet-based, nonparametric characterization of baseline signals. A k-space apodization resulting in an effective voxel size of approximately 2.4 cm^3 and zero-filling to 32 × 32 k-space points was applied prior to the spatial Fourier transformation. Zero-filling from 512 to 1024 time domain data points and Gaussian multiplication corresponding to 0.6-Hz line broadening were carried out prior to the time-

Figure 2. Box Plots of the Corrected Signals From Choline-Containing Compounds (Ch), in IU, of the 12 Patients Examined Pre-ECT, Post-ECT, and at Follow-Up[a]



[a]The box plots show a significant increase post-ECT, which is reversed at follow-up.
Abbreviation: ECT = electroconvulsive therapy.

Figure 3. Box Plots of the Corrected *N*-Acetylaspartate (NAA) Signals, in IU, of the 12 Patients Examined Pre-ECT, Post-ECT, and at Follow-Up[a]



[a]The box plots show no significant differences in signal intensities. The small circle in the Post-ECT column designates an outlier (i.e., outside the interquartile range shown by the box).
Abbreviation: ECT = electroconvulsive therapy.

domain Fourier transformation. Spectral phasing was also performed automatically, and signals of NAA, creatine and phosphocreatine (Cr), and Ch were curve fit.

The high-resolution 3-D image data set was segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), which was achieved using a Statistical Parametric Mapping (SPM99, Wellcome Department of Cognitive Neurology, London, U.K.) routine. These data were then coregistered with the MRSI data, and 3 mean images (GM, WM, CSF) matching the size, position, and exact excitation profile of the MRSI data were created. It was assumed that CSF contains no detectable metabolite concentration[11] and only voxels containing more GM than WM and less than 25% CSF were included in the analysis. Absolute integral values of the model peaks obtained by the fitting algorithm for NAA, Cr, and Ch were then corrected for the individual point-spread-function, PRESS volume profile, chemical shift of different metabolites, and CSF content of the voxel.[21,22] Additionally, metabolite signals were corrected for differential head coil loading by multiplication with the transmitter reference voltage.[12,23] This yields a semi-quantitative measure avoiding metabolite ratios.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows release 10.0.0 (SPSS, Inc., Chicago, Ill.). A nonparametric Friedman test for 3 connected samples was applied to evaluate significant changes in metabolite signals and voxel composition over time. When significant differences between the 3 data points were found, a Wilcoxon test was applied for evaluation of the individual data pairs with significant differences. Statistical significance was evaluated at the .05 level. Data are given as mean (SD).

RESULTS

Clinical Outcome

Ten of 12 patients were in stable remission at the time of follow-up. Two had suffered a relapse of depressive symptoms. In the clinical examination performed by an experienced psychiatrist, none of the patients showed any cognitive impairment. This was confirmed by the MMSE results, which ranged between 26 and 30 points. At follow-up, the mean HAM-D score was 6.25 (8.06). The noted high SD is explained by the fact that 2 patients had relapsed with HAM-D scores of 22 and 24, respectively.

Hippocampal Metabolite Values

The nonparametric Friedman test revealed no significant differences in the tissue composition of the evaluated hippocampal voxels at the 3 timepoints of measurement. Mean contents were GM = 56.2% (3.4%), WM = 33.8% (3.0%), and CSF = 10.1% (3.0%).

During all measurements, the mean NAA signal of the 12 patients had remained within the range of repeated measurements.[24] Mean corrected NAA signals were 15.90 (1.76) IU pre-ECT, 16.57 (0.90) IU immediately post-ECT, and 16.05 (1.67) IU at follow-up. The nonparametric Friedman test revealed no significant changes in the NAA signal ($\chi^2 = 2.17$, df = 2, p = .34).

The corrected Cr signals were 10.08 (0.96) IU pre-ECT, 11.04 (1.23) IU immediately post-ECT, and 10.84 (0.99) IU at follow-up. No significant variations of the Cr signal over time were found with the nonparametric Friedman test ($\chi^2 = 2.00$, df = 2, p = .37).

The significant increase of the signals from choline-containing compounds during ECT was reversed at follow-up. The corrected Ch values were 10.94 (1.25) IU

pre-ECT, 12.62 (1.03) IU immediately post-ECT, and 11.07 (0.72) IU at follow-up. The nonparametric Friedman test revealed a significant variation of the Ch signal ($\chi^2 = 15.17$, df = 2, p = .001). Comparing Ch values before and immediately post-ECT with a Wilcoxon test revealed a highly significant increase post-ECT (Z = 3.06, p = .002) and a successive reversal comparing the values immediately post-ECT and at follow-up (Z = 3.00, p = .003), whereas no difference could be determined between Ch values pre-ECT and at follow-up (Z = 0.31, p = .75). The direction of the changes in the Ch signal were uniform in all but 1 patient. In this single patient, the Ch signal increased during the ECT treatment and remained high at follow-up. Figures 2 and 3 show box plots of Ch and NAA for all 3 timepoints.

DISCUSSION

As we had shown in our previous study,[13] Ch values in patients pre-ECT were significantly lower compared with age-matched healthy subjects and increased to normal levels post-ECT, whereas the NAA signal was stable and not different from control values. The current study yielded 2 distinct results. First, NAA remained stable not only shortly post-ECT, but also at long-term follow-up. Second, the noted increase in Ch signals from lower-than-normal levels pre-ECT to normal values immediately post-ECT reverses over time.

The observed stable NAA signal is in accordance with our hypothesis that ECT does not induce any atrophy or cell death in the hippocampus. In our previous MRSI study of healthy comparison subjects,[13] a trend but no significant age-related decrease for hippocampal NAA was found. Therefore, significant age-related decreases could be ruled out during a 20-month period. One of the major difficulties of follow-up investigations of patients treated with ECT with a focus on long-term cognitive impairment is the confounding effect attributable to the increasing prevalence of cognitive impairment with age. Within this context, Cohen et al.[8] reported that adolescents who had received ECT for severe mood disorder did not show measurable cognitive impairment at long-term follow-up. Thus our findings corroborate the hypothesis that there is no hippocampal atrophy or neuronal loss due to ECT. Although it cannot be denied that some patients report long-lasting amnestic effects, in particular concerning events during the time course of ECT, these amnestic effects of ECT are not reflected in a decrease in the NAA signal. NAA is supposed to be a very sensitive functional marker, and signal changes should be detectable even before any alterations can be seen on MRI. Therefore, we conclude that the observed amnestic effects are not attributable to detectable structural damage of hippocampal neurons or reduced neurogenesis. Furthermore, one must not exclude the increasing prevalence of cognitive impairment due to dementia as well as some evidence that cognitive impairment may be one of the long-term consequences of depressive illness itself.[25]

The most striking result of our investigations is the finding that the increase in hippocampal Ch signals to normal values post-ECT is reversed at long-term follow-up. Since NAA and Cr signals remained stable over time, a systematic bias can be ruled out as the MRSI signals of the 3 evaluated metabolites were all acquired and processed in the same manner. Most of the Ch signals arise from the phosphocholines, unless they are in lipid bilayers. As most phosphocholines are membrane bound, slight alterations in turnover may lead to a substantial increase in magnetic resonance–detectable choline-containing compounds. It has to be kept in mind that although acetylcholine is one of the choline-containing compounds contributing to the MRSI Ch signal, it accounts for less than 1% of signal intensity.[11] There is strong evidence that ECS, an animal model for ECT, induces an increased transcription of BDNF and its receptor TrkB. This gives rise not only to mossy fiber sprouting but also to sprouting of serotonergic axons in the hippocampus.[4] While sprouting of the mossy fiber pathway remains unclear in its functional consequences,[2] a sprouting of serotonergic axons may play a role in the therapeutic mechanism of ECT.

There is yet another possible implication of our findings. As low Ch signals point toward a decreased membrane turnover, the low Ch signals in depressive patients before treatment may reflect decreased neuronal plasticity, which could be a neurobiological condition underlying depression.[26] Thus, a common final pathway of all effective antidepressant treatments could be an increase in neuronal plasticity.[27] This increase could be mediated by an increased expression of cyclic adenosine monophosphate response element-binding protein and its possible targets BDNF and TrkB.[28] Since the evidence for this common pathway of antidepressant treatment is growing and this pathway may even include neurogenesis,[5] further MRSI studies in patients receiving different antidepressant treatments are needed to evaluate the hippocampal Ch signals of these patients. The interpretation of our data concerning the possible role of Ch signals as a neurobiological marker of antidepressant treatment is limited, since our sample consisted only of patients who had been treated with ECT in the past and were generally receiving psychopharmacologic treatment at follow-up.

Furthermore, the interpretation of our data is mainly based on postmortem findings in animal models. If our conclusions in humans are correct, in vivo MRS studies in animals should close this gap between ECS in animals and ECT in humans. Our MRSI results of increased Ch following ECT was recently replicated in an ECS rat model.[29] A comparison of various MRS studies in depressive patients shows a variability of the Ch signal across different brain regions. Thus, Renshaw et al.[30] found

decreased Ch/Cr ratios in the basal ganglia in comparison with control subjects, whereas Steingard et al.[31] noted increased Ch/Cr ratios in the orbitofrontal cortex in depressed adolescents and Czeh et al.[32] found reduced NAA, Cr, and Ch in an animal study of stress-induced changes. There is growing evidence that Cr is not as invariable as it was thought to be,[11,32] which limits the application of metabolite ratios considerably.

We are aware that our interpretation has to remain speculative at this time, i.e., we cannot prove that the MRSI findings are correlated with the therapeutic effect. On the other hand, we think it would be even more speculative to introduce any other explanation for the choline signal change observed after ECT since there are no signs for a toxic or damaging effect of ECT.

The advantages of a better understanding of ECT, a highly effective method of medical treatment, cannot be underestimated. By examining the mechanisms underlying antidepressant treatment, it may even be possible to find out more about the pathogenesis of the depressive disorder itself.

Drug name: carbamazepine (Carbatrol, Tegretol, and others).

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