ALCOHOL-RELATED SEIZURES AND THE KINDLING EFFECT OF REPEATED DETOXIFICATION: THE INFLUENCE OF COCAINE

DARLENE H. MOAK* and RAYMOND F. ANTON

Department of Psychiatry and Behavioral Science, Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29425, USA

(Received 17 April 1995, in revised form 25 July 1995, accepted 31 July 1995)

Abstract — The purpose of this study was to determine if individuals with concurrent alcohol and cocaine use differ in regard to seizure risk compared to individuals who abuse only alcohol, and to explore the relationship between multiple detoxifications and seizure risk in the context of concurrent cocaine use. In this study, alcoholic cocaine users had a decreased risk of seizure compared to alcoholics without cocaine use (P < 0.005). Seizures were rare in individuals who did not abuse alcohol. Alcoholic cocaine users reported a younger age at first seizure compared to alcoholics without cocaine use (P < 0.04). Alcoholic patients with seizures had significantly more previous detoxification experiences compared to matched alcoholic patients without seizures (P = 0.0001). Concurrent cocaine use did not appear to have an independent effect on the risk of seizure. The findings in this study suggest that concurrent cocaine use may accelerate the development of alcohol-related seizures in predisposed individuals but does not appear to substantially increase overall risk. Multiple previous detoxifications are associated with an increased risk of seizures in alcoholics both with and without concurrent cocaine use.

INTRODUCTION

The increasing use of cocaine continues to be an area of great concern and interest for clinicians and researchers. More recently, the combined use of alcohol and cocaine has received greater attention. Concurrent alcohol and cocaine use has been identified as the most common substance use pattern resulting in visits to emergency rooms in 27 metropolitan areas surveyed by the Drug Abuse Warning Network (National Institute on Drug Abuse, 1987).

Alcohol and cocaine used concurrently may have different effects, especially on the central nervous system, than when used alone. For instance, animal studies have linked the epileptic effects of cocaine to the serotonergic system (Ritz and George, 1993). Alcohol is known to have effects on the serotonin system as well, as indicated by both animal and human studies in which serotonin reuptake blockade is associated with decreased alcohol intake (Myers and Martin, 1973: Naranjo et al., 1984, 1987, 1990). However, alcohol has known effects on other neurochemical systems linked to seizure generation such as the γ-aminobutyrate (GABA) (Allan and Harris, 1987) and N-methyl-D-aspartate (NMDA) systems (Grant et al., 1990).

Usage patterns may vary when both drugs are abused, possibly leading to more prolonged and intense use of each (Walsh et al., 1991). Furthermore, cocaethylene, a unique metabolite of cocaine and alcohol found in people who abuse both substances, may itself have physiologic effects and exhibit neurochemical perturbations additional to those caused by the parent compounds from which it was derived. When compared to cocaine in laboratory animals, cocaethylene has caused increased activity and increased lethality (Hearn et al., 1991a; Katz et al., 1992) but has not been implicated in increased convulsions (Masur et al., 1989, Katz et al., 1992).

Seizures are well-documented and frequent sequelae of alcohol abuse. Individuals with alcohol-related seizures were approximately five times more likely to die than those individuals with seizures secondary to other aetiologies when followed for a 10-year period following the initial seizure (Piennikeroinen et al., 1992). It has been suggested that alcohol withdrawal seizures may...
be the end result of a 'kindling' process which occurs over a number of repetitive alcohol detoxifications (Ballenger and Post, 1978; Brown et al., 1988; Lechtenberg and Worner, 1990; Booth and Blow, 1993). Cocaine exhibits kindling properties in animals (Shuster et al., 1977; Stripling and Ellinwood, 1977; Post et al., 1981) and its use has been associated with seizures in humans (Pascual-Leone et al., 1990; Lowenstein et al., 1987; Mody et al., 1988), so that the combined use of the two substances might, at least theoretically, be associated with an increased risk of seizure above that of either substance alone. Also, if concurrent use of alcohol and cocaine contributed to an increased number of detoxification experiences, this might also contribute to an increased risk of seizures.

The risk of seizures with combined use of alcohol and cocaine, however, is not well-defined. Lechtenberg and Worner (1990), for instance, did not find an increased risk of seizures in 103 alcoholic inpatients who had abused cocaine, out of a total sample of 301 alcoholics. The goal of the present study was to obtain clinical information to clarify the possible effect of concurrent alcohol and cocaine use as well as repeated detoxification experiences on seizure occurrence.

METHODS

All patients admitted to a community-based detoxification unit over a 7-month period were used as the sample population. As part of routine admission procedures, information was obtained regarding alcohol consumption and use of other abused drugs, including cocaine, opiates, and benzodiazepines. Patients were also questioned about withdrawal symptoms and were specifically asked about a history of seizures. Those individuals who endorsed a past history of seizures were then administered a 12-item questionnaire by nursing staff who were completely unaware of any a priori hypotheses. The questions probed for the following historical landmarks: age at which heavy drinking began, age at first inpatient detoxification, number of inpatient detoxifications, and age at first seizure. Patients were excluded from analysis if there was a clear aetiologic factor for the seizure other than alcohol or cocaine use, such as idiopathic epilepsy with onset during childhood or reaction to a drug other than alcohol or cocaine.

A diagnosis of probable current alcohol abuse or dependence was based on quantity and frequency of alcohol use as stated at admission (>5 drinks per occasion and use of alcohol more than once per week in the month prior to admission). Individuals who met this criterion for alcohol use were then classified by positive or negative history of cocaine use. Cocaine users were also stratified as high intensity users (had used cocaine >20 times in life) and low intensity users (had used cocaine <20 times in life). The number of times that cocaine had been used by each subject was obtained from the standard intake questionnaire which probed for age of first cocaine use, frequency and quantity of cocaine use, and last cocaine use. The cut-off point of 20 lifetime usages to distinguish between high and low intensity cocaine users was chosen based on clinical experience as a representative level of use between casual (i.e. experimental) users and those who used cocaine on a more regular basis. Post-hoc analysis confirmed the statistical utility of this cut-off point, in that both 85% of all cocaine users and 85% of alcoholics who used cocaine had used >20 times in their lifetimes, a percentage that represents the median +1 SD. The patients with <20 lifetime cocaine uses are therefore the bottom 15% of users, or those individuals at least 1 SD below the population median. This would again suggest that 20 lifetime usages is a representative cut-off level between casual (i.e. experimental) and more regular cocaine use.

In order to analyse the effect of the number of inpatient detoxification experiences on seizure occurrence in a controlled fashion, a patient without a history of seizure who met the previously stated criterion for probable alcohol abuse or dependence and who matched the 'seizure history' patient for age (in most cases to within 2 years), gender, race, and category of cocaine use was selected for comparison. The number of inpatient detoxifications for the patients without a seizure history was obtained from a routine assessment performed by a clinician who was unaware of this study on the 3rd or 4th day of each patient's inpatient stay.

The relationship between the variables was examined by the χ² statistic for categorical data and the unpaired t-test or one-way analysis of variance (ANOVA) for continuous data. For the comparison of number of inpatient detoxifications
Table 1. Demographic and clinical variables of 479 consecutive admissions to an inpatient detoxification unit

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number (%)</th>
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<tbody>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>223 (47)</td>
</tr>
<tr>
<td>Black</td>
<td>256 (53)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>374 (78)</td>
</tr>
<tr>
<td>Female</td>
<td>105 (22)</td>
</tr>
<tr>
<td>Probable alcohol abuse</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>377 (79)</td>
</tr>
<tr>
<td>No</td>
<td>102 (21)</td>
</tr>
<tr>
<td>History of seizure</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>94 (20)</td>
</tr>
<tr>
<td>No</td>
<td>385 (80)</td>
</tr>
<tr>
<td>Lifetime use of cocaine</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>313 (65)</td>
</tr>
<tr>
<td>No</td>
<td>166 (35)</td>
</tr>
</tbody>
</table>

in seizure patients and matched non-seizure controls, the Wilcoxon signed-rank test was used. To assess the effect of cocaine in this comparison a two-factor ANOVA was employed.

RESULTS

Analysis of all admissions to the detoxification unit

There were 479 admissions to the detoxification unit between October 1992 and April 1993. Demographic and clinical characteristics for the total sample are shown in Table 1. Sixty-five per cent (313) had a history of cocaine use, of whom 268 (56%) had used more than 20 times. Seventy-nine per cent (377) met our definition for probable current alcohol abuse or dependence. A history of seizures was endorsed by 94 (20%) of the patients admitted over this period, only two of whom did not have probable alcohol abuse or dependence.

Alcoholic patients with a history of seizure were significantly less likely to have used cocaine ($\chi^2 = 10, P < 0.005$) than alcoholic patients who did not report a history of seizure. The cocaine use group was further stratified, by intensity of cocaine use, into those individuals who had >20 episodes of cocaine use (the ‘high cocaine intensity’ group) and those individuals who had <20 episodes of cocaine use (the ‘low cocaine intensity’ group). Both cocaine-using groups were less likely to have had a seizure than the patients who had never used cocaine (the ‘None’ group) ($\chi^2 = 11, P < 0.01$) (Fig. 1). It should be noted that the patients in both the high cocaine intensity (mean age 33.0, $F = 46.56, P < 0.001$) and the low cocaine intensity (mean age 35.9, $F = 7.02, P < 0.01$) groups were significantly younger than the patients who had never used cocaine (mean age 41.2). However, when alcoholic patients were stratified by age group in the age range in which most patients fell (20–29-year-olds, 30–39-year-olds, and 40–49-year-olds), and further classified by positive or negative history of cocaine use, alcoholics without cocaine use were still significantly more likely to have a history of seizures than those alcoholics with cocaine use ($\chi^2 = 49.69, P < 0.001$).

Clinical characteristics of seizure patients

Questionnaires were obtained from 64 (68%) of the patients who reported a history of seizures. The most common reason for not obtaining the questionnaire was that the patient was too intoxi-
icated at the time of admission and then left the treatment facility against medical advice prior to the questionnaire being given. Three of these 64 patients had a clear aetiology for their seizures other than alcohol or drug use and were excluded from analysis, leaving 61 patients in the index group of patients with alcohol- or drug-related seizures. There were 30 patients who abused alcohol only and 31 patients who also had historical cocaine use (7 in the low cocaine intensity group and 24 in the high cocaine intensity group).

Opiate abuse or dependence was present in 12 (19.7%) of the 61 patients with seizure history and was significantly associated with use of cocaine ($\chi^2 = 10, P < 0.01$). Five patients (8%) had a history of benzodiazepine abuse or dependence, and these patients were distributed equally among the high, low and no cocaine use groups.

Of the seizure patients, 92% were male, whereas 8% were female. This was very similar to the percentages seen in the alcoholic patients as a whole (82% male and 18% female). Of the seizure patients, 53% were white and 47% were black; this was similar to the distribution in the alcoholic patients as a whole, who were 50% white and 50% black.

When patients were asked with which substance their seizure was temporally associated, patients were significantly more likely to have had seizures associated with their alcohol use ($n = 45$) than with either cocaine use alone ($n = 2$) or concurrent use of both substances ($n = 8$) ($\chi^2 = 82, P < 0.05$).

Comparison of seizure patients with and without cocaine use

Data obtained from the alcohol abusing seizure patients with and without lifetime cocaine use who completed the questionnaire are shown in Tables 2 and 3. As can be seen in Table 2, any lifetime use of cocaine was significantly associated with a younger age at index admission ($t = 3.12, P < 0.002$) and a younger age at first seizure ($t = 2.29, P < 0.04$). There were no differences between the two groups in age at onset of heavy drinking, age at first inpatient detoxification, number of inpatient detoxifications, and duration of heavy drinking before first seizure. As can be seen in Table 3, when the seizure sample was divided into three groups based on intensity of cocaine use as previously described, the high intensity group, but not the low intensity group, was significantly younger than the alcohol-only group at presentation ($F = 5.57, P < 0.006$). Age at first seizure was also significantly younger for the high cocaine intensity group than for the alcohol-only group ($F = 4.73, P < 0.05$). There were no other differences between the three groups.

Comparison of alcohol-abusing patients with a history of seizure and matched alcohol-abusing patients without a history of seizure

Using a case–control matching protocol, seizure cases had significantly more inpatient detoxification experiences than non-seizure controls ($Z = -5.137, P = 0.0001$) (Fig. 2). When alcohol-abusing seizure and control non-seizure patients were stratified by history of cocaine use, both cocaine users with seizures ($Z = -4.143, P = 0.0001$) and non-cocaine users with seizures ($Z = -3.123, P = 0.0018$) had significantly more detoxification experiences than controls. The mean number of detoxifications (±SD) was $4.8 \pm 4.0$ for seizure patients with cocaine use and $4.9 \pm 5.2$ for seizure patients without cocaine use, while it was only $0.7 \pm 1.2$ for non-seizure controls with cocaine use and $1.6 \pm 2.6$ for non-seizure control patients without cocaine use. By two-factor ANOVA, there was a significant main effect for seizure on the number of detoxifications (df = 1, $F = 32, P = 0.0001$) whereas cocaine use had no effect.

DISCUSSION

The most common drug use pattern recently seen in many clinical situations is that of poly-
Table 3. Clinical variables in alcoholics with seizures by intensity of cocaine use

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intensity of cocaine use (lifetime episodes)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>None (n = 30)</td>
</tr>
<tr>
<td>Age</td>
<td>43.3 ± 8.0</td>
</tr>
<tr>
<td>Age of onset of heavy drinking</td>
<td>21.8 ± 7.7</td>
</tr>
<tr>
<td>Age at 1st detoxification</td>
<td>32.4 ± 10.1</td>
</tr>
<tr>
<td>Number of detoxifications</td>
<td>4.9 ± 5.2</td>
</tr>
<tr>
<td>Age at 1st seizure</td>
<td>35.8 ± 9.4</td>
</tr>
<tr>
<td>Years of heavy drinking before 1st seizure</td>
<td>14.2 ± 10.9</td>
</tr>
</tbody>
</table>

All values are given as means ± SD. *P < 0.05 (high vs none). **P < 0.01 (high vs none).

Fig 2 Percentage of alcoholic patients with history of seizure and matched control alcoholic patients without a history of seizure in each category of number of previous inpatient detoxifications (0-1 detoxifications, 2-3 detoxifications, and ≥4 detoxifications)

History of seizure was significantly associated with number of detoxifications by both two-factor ANOVA (F = 32, P = 0.0001) and by Wilcoxon signed-rank test (Z = −5.14, P = 0.0001) while there was no independent effect for cocaine use.

Although 92 of 102 (90%) non-alcoholic admissions were cocaine abusers, only two of these patients reported seizures. This suggests a low prevalence of seizures in cocaine-dependent inpatients who are not abusing alcohol. This is somewhat at odds with the many clinical studies citing seizures as a common cause of morbidity associated with cocaine use (Lowenstein et al., 1987; Mody et al., 1988; Pascual-Leone et al., 1990) as well as animal studies that have demonstrated...
strated 'kindling effects' of cocaine (Shuster et al., 1977; Stripling and Ellinwood, 1977; Post et al., 1981). More consistent with these reports is our finding of a younger age at first seizure for cocaine-using alcoholics compared to cocaine non-users, which suggests that cocaine might contribute in some way to earlier seizure development in predisposed individuals.

One possible explanation for these seemingly contradictory findings could be that, in individuals predisposed to seizure development, combined use of cocaine and alcohol might accelerate the development of seizures, but would not appear to increase actual seizure risk for the population in general. Perhaps synergistic effects of the two substances on neuronal cells, or even effects of the unique metabolite cocaethylene, accelerate the development of seizures in vulnerable individuals. Additionally, alcoholics who abuse cocaine might drink more alcohol, which may affect seizure risk. Walsh et al. (1991) found that alcoholics with cocaine abuse drank more alcohol per day, were drunk more frequently, and engaged in more binge drinking in the month before entering a treatment study than did alcoholics with no cocaine abuse. This increased use of alcohol with cocaine might not contribute to an overall increased risk of seizure, as indicated by our data, but might result in an earlier onset of seizures in certain individuals.

The alcoholics who abused cocaine in our sample were younger than those who did not abuse cocaine, which might have suggested that the decreased risk of seizures for this group was simply an age effect. That the younger alcoholic cocaine users had simply not been drinking for as long as the older alcoholics without cocaine use. However, the duration of heavy drinking before first seizure was similar for the alcoholic cocaine users and the cocaine non-users. It should be noted that, similar to other studies, the age at onset of heavy drinking for the cocaine-using alcoholics (19.0 years) was less than that for the alcoholics who had never used cocaine (21.8 years) although the difference was not statistically significant. When patients were stratified into three age groups (20–29-year-olds, 30–39-year-olds, and 40–49-year-olds) and then classified by presence or absence of cocaine use, alcoholics without cocaine use were still significantly more likely to have had a seizure than alcoholics who had used cocaine. Additionally, when inpatients with a history of seizure and age-matched controls without a seizure history were compared with regard to the number of inpatient detoxification experiences, cocaine did not appear to exert any independent effect on the strong relationship between seizure occurrence and number of prior detoxifications.

The role of cocaethylene in causing morbidity in cocaine and alcohol users is just now being explored. Cocaethylene has been isolated in postmortem tissues from individuals whose deaths were felt to be cocaine-related (Hearn et al., 1991b), as well as in the blood of individuals admitted to a trauma unit and seen in an emergency room (Bailey, 1995a, b). Fowler et al. (1992) compared the distribution of cocaine and cocaethylene in the baboon brain via PET scanning and, although they found a longer duration of action for cocaethylene, they did not think the difference was large enough to account for any increased toxicity for cocaethylene. As previously mentioned, although cocaethylene has been shown to cause greater locomotor activity and lethality in animal models, it has not increased the prevalence of convulsions in exposed animals. Therefore, at the present time, there is no evidence to suggest that cocaethylene is more likely to cause seizures than is cocaine.

It is interesting to speculate on the neuropharmacological mechanisms by which cocaine and alcohol might interact to affect seizure risk. Alcohol has been believed to exert its epileptic potential at least partially via the GABA–benzodiazepine–Cl complex, as demonstrated by the efficacy of the benzodiazepines in treating alcohol withdrawal seizures (Liskow and Goodwin, 1987). The NMDA receptor system is most likely involved as well (Grant et al., 1990). It is also probable that the noradrenergic system plays a facilitatory role (Nutt and Glue, 1986).

The mechanism by which cocaine causes seizures in humans is not well-defined. In studies of mice, serotonin transporters have been implicated (Sharkey et al., 1988; Ritz et al., 1992). These authors reported that serotonin reuptake inhibitors have been shown to enhance the number and severity of seizures, whereas 5-HT3 antagonists have demonstrated an opposite effect. Other studies have suggested a probable secondary role for muscarinic and sigma receptors (Sharkey et
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Based on these animal data, it would appear that cocaine mediates seizure development in a different way than alcohol. It is interesting that cocaine is more likely to be associated with seizures when smoked or injected as compared to intranasal use (Lowenstein et al., 1987; Pascual-Leone et al., 1990). This suggests that the effect of cocaine on seizure development is a more immediate one than alcohol, and dependent on the intensity of acute exposure. In contrast, seizures related to alcohol appear to depend on chronic usage which leads to physiological dependence and the appearance of withdrawal upon cessation of consumption.

In clinical studies, of 403 patients presenting to an emergency room with medical complications related to acute cocaine intoxication who had no previous history of seizure, 32 (7.9%) had suffered a seizure within 90 min of cocaine use (Pascual-Leone et al., 1990). These patients with first episode of seizure related to cocaine use were more likely to be women and to be black. Interestingly, in our sample, gender and race distributions among seizure patients and non-seizure patients were very similar. In this same population, among 71 patients with a history of seizures that were not related to cocaine use, 12 (15%) presented with a new seizure after cocaine use. Seven of these patients in fact carried a previous diagnosis of alcohol withdrawal seizures. Among 996 patients seen in an emergency room and 279 patients admitted to a hospital, 29 individuals had presented with a cocaine-induced seizure (Lowenstein et al., 1987). Seizure patients included those who had used cocaine only once and those who were chronic users. Taken together, these studies suggest that the effect of cocaine on seizure development is at least as strongly related to underlying individual vulnerability as it is to the intensity of use. It should be noted that most of our patients temporally associated their seizures with the use of alcohol rather than cocaine or concurrent use of both substances. This is in contrast to the low number of cocaine-using seizure patients who were found to have concurrent alcohol use by Pascual-Leone et al. (1990) (3% of patients who presented with their first seizure ever, 33% of patients with previous seizures).

Seizure risk in alcohol withdrawal appears to be related to the level of alcohol intake prior to seizure development and also to the number of previous treatments for alcohol withdrawal symptoms. In hospitalized individuals who had presented with a first episode of seizure, those individuals with daily alcohol intake of between 201 and 300 g had an almost 20-fold risk compared to control patients who had been admitted for reasons other than seizure (Ng et al., 1988).

Individuals with prior detoxifications are also at increased risk of seizure development. suggesting that the kindling mechanism is a basis for the development of alcohol withdrawal seizures. In a group of 25 male alcoholic inpatients who had withdrawal seizures during the index admission, 48% had had five or more previous detoxifications, compared to 12% of a matched control group of male alcoholics without seizures (Brown et al., 1987). More recently, Booth and Blow (1993) have obtained data from a sample of 6818 alcoholic men and have again shown that patients with alcohol-related seizures and withdrawal problems had more prior detoxifications. Lechtenberg and Worner (1991) also found an association between detoxification admissions and seizure prevalence, as well as a somewhat weaker association of seizures and non-detoxification hospital admissions. Our data support this relationship, in that individuals who had a history of seizures had significantly greater numbers of previous detoxification experiences than matched non-seizure control patients. quite independent of cocaine use history.

While it is quite possible that those alcoholics with a history of withdrawal seizures in this sample had a more severe drinking history than alcoholics with no history of withdrawal seizures, and that more extensive exposure to alcohol, rather than detoxification experiences, caused the development of withdrawal seizures, there is both animal and human data to support the important role of alcohol detoxification experiences in the development of withdrawal seizures. Becker and Hale (1993) have demonstrated in an animal model that those animals that are subjected to multiple withdrawals from alcohol have more severe withdrawal symptoms and more intense withdrawal seizures than animals that receive the same amount of alcohol exposure in a continuous fashion. In the study by Brown et al. (1988), the patients who experienced a seizure during hospitalization and the control group were matched for age of onset of drinking, years of
significant use, and daily amount consumed during the month prior to admission. The seizure group had significantly more prior detoxifications than the control group despite a similar alcohol use history. The retrospective nature of most human studies does not allow for a total resolution of the question of whether prior exposure to alcohol is a more important influence in the development of seizures than are prior detoxification experiences. However, the data presented here are consistent with previous human studies and animal experiments, which strongly suggest that the number of past alcohol detoxifications adds a significant risk factor to the development of alcohol withdrawal seizures.

Our examination of a large number of admissions to an in-patient detoxification unit does not demonstrate an increased risk of seizures when cocaine and alcohol use are combined. This finding is in agreement with earlier clinical studies (Lechtenberg and Worner, 1990; Ng et al., 1990). An important finding in our study is that the age at first seizure was decreased among alcoholic individuals with a history of cocaine use. We believe that this may suggest that concurrent alcohol and cocaine use can accelerate the development of seizures in individuals who are prone to develop seizures, while not increasing the overall risk of seizures among alcoholics.

It is probable that concurrent use of alcohol and cocaine will continue to be a significant clinical problem. Seizure development is a serious cause of morbidity in individuals who abuse alcohol as well as those who abuse cocaine. While it is challenging to obtain accurate histories of cocaine and alcohol use from these patients, a retrospective time-line approach and prospective longitudinal studies may further clarify the interrelationship between these two substances in influencing the development of seizures, as well as other medical and psychiatric complications. Animal studies utilizing combined exposure to alcohol and cocaine may also help to elucidate the mechanisms of seizure development. Furthermore, these studies may suggest pharmacological treatments that will decrease the risk of seizure development in substance-abusing individuals.

Acknowledgements — The authors wish to acknowledge John E. Emmel, M.D., Pamela A. Beemer, R.N., B.H.S., and Anna V. Anerum, L.P.N., for their assistance in gathering the data.

REFERENCES


Lowenstein, D. H., Massa, S. M., Rowbotham, M. C.,


