Low Risk of Development of Substance Dependence for Barbiturates and Clobazam Prescribed as Antiepileptic Drugs: Results from a Questionnaire Study

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Keywords

Addiction; Antiepileptic drugs (AED); Barbiturates; Clobazam; Dependence; Epilepsy; Outcome expectation.

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doi: 10.1111/j.1755-5949.2008.00073.x

There is no systematical research about the topic of dependence on antiepileptic drugs (AED) for patients with epilepsy, despite the fact that barbiturates and benzodiazepines comprise a potential risk of dependence. We hypothesize that there is no psychological substance dependence for patients with epilepsy, possibly because of their outcome expectations. The aim of the study was to examine these patients in terms of substance dependence. One hundred inpatients at the Lake Constance Epilepsy Center were asked about their experiences with AED in terms of dependence in a structured interview. We registered general statements about dependence of AED, markers for substance dependence, and outcome expectations. About 50% of the patients reported withdrawal symptoms and the development of tolerance, but less than 10% noticed loss of control and craving. Withdrawal symptoms and development of tolerance were significantly lower in a group of patients without barbiturates or clobazam versus patients with barbiturates or/and clobazam. There was no significant difference between these two groups in psychological criteria of dependence, that is, loss of control and craving. Outcome expectations of AED were clearly related to the efficacy against seizures, and only to a small amount to psychotropic effects. The study demonstrates that physiological variables of dependence are present more in patients with epilepsy with a permanent intake of barbiturates or clobazam, but psychological variables of dependence are rarely present in epileptic patients, with or without an intake of barbiturates and clobazam. These results confirm our hypothesis that substance dependence is not a major problem in benzodiazepines and barbiturates in patients with epilepsy. Outcome expectations seem to be related mainly to the anticonvulsant and not the psychotropic effect. This might be the reason for the absence of dependence.

Introduction

The topic of dependence on barbiturates and benzodiazepines in patients with epilepsy has not been studied systematically, despite the fact that these substances are generally able to induce a state of dependence. Salzman [1] stated a difference between addiction and dependence, whereby both include physical states and possible psychological components, but only addiction implies nonmedical use and definite use for pleasurable purposes. Therefore, dependence does not necessarily imply addic-

tion. Since in patients with epilepsy drug use is primarily for medical reasons, we prefer the term dependence over addiction in the present work.

In patients with epilepsy, in their relatives and their physicians, rumination about the question of dependence from antiepileptic drugs (AED) is a topic of interest [2–4]. On the other hand, refusal of AED in patients with epilepsy seems to be much higher than a dependence-related positive attitude [5]. Gostomzyk and Heller [6] stated that the development of substance dependence seems to be inexistent in patients with epilepsy, when

the psychotropic effect of the substance is not the reason for the intake. We suggested that this is due to outcome expectations about medication in patients with epilepsy [7,8]. Outcome expectations are a person's estimates about certain outcomes associated with behavior [9]. Cognitive factors, like outcome expectations about the presence or absence of emotional states, are considered to be an important factor in the development of dependence [10]. Generally, positive expectancies about drug effects are able to predict the use of drugs [11]. Also, studies assessing self-efficacy beliefs and outcome expectations among adults with epilepsy showed that these patients are substantially more adherent to strict medication regimen than to health-enhancing lifestyle behaviors [12]. We hypothesize that in substances taken as AED, outcome expectations of patients with epilepsy comprise the efficacy against seizures and not the presence of positive, or the absence of negative psychotropic state. Therefore, psychological variables of dependence, such as craving and loss of control, should not be an important issue in chronic users of benzodiazepines, barbiturates, or other substances, when taken to fight epilepsy. Physiological variables of dependence, that is, the development of tolerance to the anticonvulsant effect and withdrawal symptoms in patients with epilepsy, on the other hand, have been published extensively [13,14].

In the present study, we examined patients with epilepsy in terms of physiological and psychological substance dependence from AED, with a main focus on barbiturates and clobazam.

Methods

Subject Characteristics and Research Design

Adult patients with epilepsy consecutively admitted to the Lake Constance Epilepsy Center in Weissenau, Germany, were included in the study and interviewed on a voluntary basis about their history of medication with an emphasis on dependence. Experiences with AED and attitudes towards AED in patients' history were requested in a structured interview from July 1999 to February 2002. The study was a cross-sectional survey about patients' history of their former and current AED intake. Inclusion criteria to the study were a confirmed diagnosis of epilepsy, a general intake of AED for at least 1 year, and the ability of the person to remember all AED taken in the past. We considered only AED that were taken continuously at least over a 4-week period, as this is considered to be the minimum time where psychological or physiological dependence (especially in barbiturates and benzodiazepines) can take place [15–17]. Psychosocial variables of patients were not recorded systematically and

therefore patients with specific risk factors for dependence could not be excluded from the study. A total of 118 patients with epilepsy were asked to volunteer for the study, with 100 (85%) patients agreeing to participate. In the study period of 2.5 years, 460 patients were admitted with a confirmed diagnosis of epilepsy. Only 118 could be asked to participate since most patients had to be excluded because they could not remember their complete history of AED. Additionally, duration of hospitalization was very short in some cases leading to the inability to be interviewed in a timely manner.

The sample was divided into two groups after the interview in order to test the hypothesis. The objective was to determine whether there is a difference in dependence markers in patients with epilepsy when permanent AED intake includes barbiturates or/and clobazam or not. Barbiturates and benzodiazepines are seen to be especially relevant for the development of dependence. From the spectrum of benzodiazepines, only clobazam was included in the study because clobazam is understood to be more tolerated. Sedative and behavioral side effects seem to be less distinct in comparison to other classical benzodiazepines; especially clonazepam. It is therefore considered as an AED for permanent use [18–20]. The study group was therefore divided into a "high-risk group for dependence" for patients with a history of barbiturates or/and clobazam intake (55 patients) and a "low-risk group" without a history of barbiturates or/and clobazam intake (45 patients). Patients' compliance was checked by asking them in the interview. Subjectively, all patients declared that they had a regular intake of the prescribed AED in the past and present.

The study was approved by the ethics committee of the department of psychiatry of the hospital in Weissenau, Germany.

Interview

We examined patients' experiences and attitudes towards AED in a structured interview [21]. All medication used as anticonvulsants was taken into account, when the intake was permanent (at least over a 4-week period). In the first part of the interview, patient's general statements about dependence of AED were registered. We wanted to know whether the topic of dependence from AED is central for patients with epilepsy. The questions concerned patients' rumination about the problem of possible development of dependence and statements of their relatives and their physicians about this. In the second part of the interview, substance dependence was registered in terms of the markers according to ICD-10 criteria (WHO), which is the standard classification system in German hospitals. The criteria comprised

physiological and psychological variables of dependence. The psychological markers of dependence included the persistent desire to consume the substance ("craving") or compulsive drug-taking behavior and unsuccessful efforts to cut down or control substance use. In the interview, loss of control was defined as a higher intake or an earlier and additional intake of AED than prescribed. Craving was defined as a persistent desire to consume AED. The physiological criteria of dependence comprised questions about the development of tolerance and physiological withdrawal symptoms after discontinuation of AED. Another important marker of substance dependence according to ICD-10, and therefore a question in our interview was the potential reduction of important social, occupational, or recreational activities due to substance use. Markers of physiological dependence, such as withdrawal symptoms and the development of tolerance, were also part of the interview. One question was, if there were any physical withdrawal symptoms after discontinuation of a substance. The "development of tolerance" was surveyed with the question, if the physician did increase AED after a longer time of efficacy and with the question about the direct loss of efficacy. The last section of the interview comprised questions about patient's outcome expectations of AED. The interview question was whether

antiepileptic medication best helps against seizures, sleep disorders, anxiety/nervousness, pain, tremor, sweating, or was generally not helpful; patients could check multiple answers. Duration of the complete interview was 30 to 60 minutes.

Statistical Analysis

In order to avoid making assumptions about the distribution of the outcome parameters, we used nonparametric Fisher's exact test (one tailed) to test for significance in differences between groups for the diagnostic markers and outcome expectations. Differences in demographic and clinical data were analyzed with Mann-Whitney *U*-tests and also Fisher's exact test.

Results

Demographic and Clinical Characteristics of the Study Group

Patients' characteristics are demonstrated in table 1. In most patients, the course of the epilepsy was long and chronic. Fifty-five patients had a history of medication with clobazam or/and barbiturates (phenobarbital or

Table 1 Demographic and clinical characteristics of study group

Demographic and clinical characteristics of patients	All patients n = 100	Low-risk group ^a n = 45	High-risk group ^b n = 55	Significance
Gender: female/male	58/42	26/19	32/23	<i>P</i> = 0.56
Still initial AED in monotherapy	6	6	0	<i>P</i> = 0.007
CBZ and VPA and PHT in drug history ^c	42	11	31	<i>P</i> = 0.001
LTG in drug history ^c	55	18	37	<i>P</i> = 0.006
TPM in drug history ^c	24	5	19	<i>P</i> = 0.005
GBP in drug history ^c	22	3	19	<i>P</i> = 0.000
Drug-resistance	90	35	55	<i>P</i> = 0.001
Age: mean, SD	42.7 (14.2)	38.3 (14.7)	46.2 (13.0)	<i>P</i> = 0.004
range	17–78	17–67	24–78	
Duration of epilepsy: mean, SD	23.7 (16.1)	15.4 (15.4)	30.4 (13.3)	<i>P</i> = 0.000
range	1–67	1–67	2–61	
Diagnosis:				
Partial (ICD-10 G40.2)	93	41	52	
Generalized (G40.3)	3	2	1	
Unclear focal or generalized (G40.8)	2	1	1	
Epilepsy not specified (G40.9)	2	1	1	
Etiology:				
Symptomatic	56	25	31	
Cryptogenic	41	18	23	
Idiopathic	3	2	1	

^aLow-risk group: patients without barbiturates and without clobazam intake; n = 45.

^bHigh-risk group: patients with barbiturates or/and clobazam intake; n = 55.

^cCBZ = carbamazepine; VPA = valproic acid; PHT = phenytoin; LTG = lamotrigine; TPM = topiramate; GBP = gabapentin.

primidone). These patients were considered the high-risk group for dependence. Patients in this group were significantly older and had a longer duration of epilepsy. A total of 90% of the whole sample was considered to be drug-resistant, defined as an intake of two AED in monotherapy or combination without seizure freedom or without good tolerability [21]. Forty-two patients had a history of AED-treatment with at least carbamazepine, valproic acid, and also phenytoin, significantly more patients of them were also in the high-risk group. Only six patients still took their initial antiepileptic medication as monotherapy. These patients were all in the low-risk group. Also, in the high-risk group there were significantly more patients with a drug history of lamotrigine, topiramate, or gabapentin. Forty-two patients of the sample were male, 58 female. Most patients had a diagnosis of partial epilepsy with symptomatic or cryptogenic etiology.

Diagnostic Markers for Substance Dependence

The two psychological criteria of dependence included craving and loss of control. Less than 10% of the interviewed patients met these criteria of psychological dependence. Only 3% of the patients reported some form of craving. Loss of control was reported in about 7% of the interviewed patients. Another important criterion comprised social implications. As much as 26% of the interviewed patients stated the reduction of important social, occupational, or recreational activities due to the use of AED. This relatively high percentage was due to adverse events from AED, like tiredness and dizziness, and was, therefore, not considered dependence related. None of the patients gave other reasons for reduction of activities of daily living. Markers of physiological dependence, such as withdrawal symptoms and the development of tolerance, were also part of the interview. In 90 patients, at

least one AED was withdrawn, and 48% of them stated at least mild withdrawal symptoms in one of the substances. About 44% of all patients noticed the development of tolerance to the anticonvulsant effect in at least one of the AED. Detailed results of dependence related markers for the sample are listed in table 2.

The sample was divided into 2 groups to evaluate whether there is a difference in dependence markers in patients with epilepsy when AED intake includes barbiturates or/and clobazam. As also seen in table 2, there is a significant difference between the two groups in terms of their markers for physical dependence. The high risk for dependence group reported a significantly higher rate of withdrawal symptoms (Fisher's exact test, one-tailed; $P = 0.01$) and the development of tolerance in terms of efficacy loss (Fisher's exact test, one-tailed; $P = 0.05$) or in terms of dosage increase (Fisher's exact test, one-tailed; $P = 0.04$). No other marker reached the significant level.

In a general paragraph of the interview, we wanted to know whether the topic of dependence from AED is central for patients with epilepsy. About 35% of the patients stated they ruminate often about the problem of dependence from their antiepileptic medication. A total of 29% of the patients reported that their physicians at home did stress the possible problem with dependence from AED. Of them, 16% indicated that their relatives and close friends noted a problem with dependence in AED.

Outcome Expectations

The topic of drug dependence can be connected with the topic of outcome expectations. In the interview, patients' possible reasons for drug intake were registered. In substances taken as AED, possible outcome expectations comprised the efficacy against seizures as well as changes in psychotropic states such as help against sleep

Table 2 Diagnostic markers for substance dependence, percentage of patients affirming the statement in the interview, and differences between groups

Patients' statements about markers of substance dependence	% of all patients	Low-risk group ^a (%)	High-risk group ^b (%)	Significance
Persistent desire to consume the substance (craving)	3	0	5	$P = 0.12$
Higher intake of AED than prescribed (loss of control)	7	9	4	$P = 0.25$
Earlier and additional intake of AED than prescribed (loss of control)	4	2	6	$P = 0.38$
Reduction of social, occupational or recreational activities due to substance use	26	24	27	$P = 0.46$
Physical withdrawal symptoms	48	38	55	$P = 0.01$
Loss of efficacy (development of tolerance)	48	38	56	$P = 0.05$
Medical intended increase of dosage after time (development of tolerance)	44	33	53	$P = 0.04$

^aLow-risk group: patients without barbiturates and without clobazam intake; $n = 45$.

^bHigh-risk group: patients with barbiturates or/and clobazam intake; $n = 55$.

Figure 1 Outcome expectations of AED for high and low risk group, multiple answers possible (Question: AED helps against. . .).

Table 3 Differences between groups in outcome expectations

Patients' statements about outcome expectations of AED	Low-risk group ^a (%)	High-risk group ^b (%)	Significance
Exclusively psychotropic outcome expectations	9	5.5	$P = 0.39$
Seizure connected and psychotropic outcome expectations	15.5	29	$P = 0.08$

^aLow-risk group: patients without barbiturates and without clobazam intake; $n = 45$.

^bHigh-risk group: patients with barbiturates or/and clobazam intake; $n = 55$.

disorders, anxiety, nervousness, pain, tremor, and sweating. In all patients of the sample, AED were prescribed against seizures. Nevertheless, only 77% of our sample of patients with epilepsy subjectively expected their AED to help against seizures. In 13% of the patients, medication was considered to help additionally or exclusively against anxiety and nervousness. Ten percent (10 patients) named sleep disorders as an additional reason to take AED. Other additional reasons for drug intake were: pain 3%, tremor 3%, and sweating 2%. Overall, 15% of the patients rated their medication as not helpful in any of the symptoms. This high percentage is likely due to the fact that most patients in our sample are considered drug refractory, where no AED can clearly be related to seizure reduction. In sum, more than 90% of our patients connected AED use with the consisting or missing anti-convulsant effect. In figure 1, the results of possible outcome expectations are illustrated separately for the high and low-risk group of the sample. Only 8% of the sample

(eight patients) had an outcome expectation exclusively to psychotropic effects. Six of these patients' medication was subjectively taken against anxiety and nervousness, but only one of the six patients named clobazam as the effective substance, two patients considered their medication as helpful exclusively against sleep disorders, while one patient named barbiturates. This means that in sum 26% of the sample had an additional or exclusive intake of AED for psychotropic reasons, but clobazam or barbiturates are barely connected to an expected psychotropic outcome. Table 3 depicts the differences in outcome expectations in the high- and low-risk groups. There is no significant difference between the two groups for exclusive psychotropic outcome expectations. When examining both psychotropic and seizure connected outcome expectations, there is a marginal significant effect between the groups (Fisher's exact test, one-tailed; $P = .08$). Patients in the high-risk group seem to realize the additional psychotropic effect of their medication.

Discussion

The results confirm our hypothesis, that substance dependence is not a major problem in patients with epilepsy, even when AED intake includes benzodiazepines and barbiturates. In conformity with the literature [22,23], this study demonstrated that physiological variables of dependence, that is, loss of efficacy and withdrawal symptoms, are present in almost half of the sample, but psychological variables, that is, craving and loss of control, in less than 10%. About 45% of all patients noticed the development of tolerance to the anticonvulsant effect in at least one of the AED and 48% stated physical withdrawal symptoms.

When splitting the sample in a group with high risk for dependence, containing patients with an intake of barbiturates or/and clobazam, and a group with low risk for dependence, with no intake of barbiturates or/and clobazam, interesting differences emerge. Only physiological variables of dependence reach significance in differentiating the groups, with a significant higher rate of physiological dependence markers in the high-risk group. Craving and loss of control is not existent in the low-risk group, but also barely in the so-called high-risk group with a permanent intake of clobazam or/and barbiturates. Psychological variables of dependence seem only barely existent in chronic users of barbiturates or clobazam, when taken as AED.

Outcome expectations about AED intake in patients with epilepsy are mostly related to seizure reduction and seizure activity. Over 90% of our patients connect AED use with the consisting or missing anticonvulsant effect. Nevertheless, a quarter of the sample relates AED with changes in psychotropic states, but clobazam or barbiturates are considered to be psychotropic effective for only a very small amount of patients, also all other AED were seen as effective. This means, clobazam and barbiturates are seen to have a similar profile in psychological dependence as all other AED, in patients with epilepsy. Between the high- and low-risk groups, there are no significant differences in outcome expectation, when psychotropic effects are considered exclusively. For the combination of antiepileptic and psychotropic outcome expectations, there is a marginal difference between the two groups. The high-risk group tends to realize that there might be additional psychotropic effects in barbiturates and clobazam. But these are not the reason for the intake of the drug.

In conclusion, the results are consistent with our hypothesis that substance dependence is not a common problem in patients with epilepsy, even when AED intake includes clobazam and barbiturates. Outcome expectations may not have incentive properties of positive psy-

chotropic states and, therefore, in patients with epilepsy psychological criteria of dependence, that is, craving and loss of control are only existent to a very small amount. But even when patients continue to take barbiturates or benzodiazepines to avoid discontinuation symptoms, this is not evidence of addiction or of dependence [24].

In this studied sample, the high percentage of drug resistance could be attributed to the fact that most patients had different clinical profiles with chronic epilepsy and the symptomatic and cryptogenic etiologies complicate their condition, which is the reason why they have been admitted to an epilepsy center. Especially in the high-risk group, the course of epilepsy is long and seizure control was less successful. Patients were also older and had therefore rather older AED regimen, inclusive barbiturates or clobazam. Even if this group of patients has a significant different profile in clinical characteristics, dependence related markers are not different between the groups. For that group of epilepsy patients, barbiturates and clobazam are still possible treatment options, even though there are a number of new AED with probably better profiles of adverse effects.

Results show that dependence from AED is indeed an important and interesting topic for patients with epilepsy. Patients seem to ruminate about this question. In our interview, as much as 35% reported that this is a question for patients with epilepsy. Even families and physicians of the patients think about the difficulty of getting dependent from AED, especially from barbiturates and benzodiazepines. In our experience, physicians' focus on dependence is mainly on benzodiazepines, which is sometimes exaggerated, and especially for clobazam. On the other hand, in barbiturates, the topic of dependence is disregarded in some cases. In sum, the quantity of about 25% seems to be suitable for our sample and fits to patients' tendency to ruminate about the topic. Patients and their relatives share a common interest to know whether their medication leads to the development of addiction or dependence. And rumination about the topic of dependence from AED is a problem in the treatment of epilepsy, because this may influence compliance to medication. This problem is of course not specific for patients with epilepsy.

One of the limitations of the study is the fact that we did not measure compliance objectively, so we are not sure whether drug intake of the studied sample was constant. This might have affected our results as well as the fact that psychosocial factors of the sample were not recorded and controlled for, which might be a confounding variable for the results. Because of the small sample size, possible gender differences in dependence criteria and in outcome expectations were not considered. In a further study with a greater sample size, it is important

to address this point because it is well known that drug dependency is more frequent in women [17]. Also, pharmacokinetic interactions of the administered AED were not recorded, as we did not measure the serum concentration of the AED on a regular base. In case of clobazam this should be insignificant, in case of phenobarbital a decrease of the serum concentration by enzyme inducing drugs, and a significant increase by valproic acid has to be considered [14]. In our opinion, this limitation does not influence the result of the study essentially. On the other hand, it should be taken into account that the development or nondevelopment of dependence from clobazam and barbiturates may have been influenced by the simultaneous intake of other anticonvulsants. Several anticonvulsants, for example, carbamazepine, lamotrigine, topiramate, gabapentin, or valproic acid are used in the treatment of alcohol dependence [25, 26] as well as in the treatment of drug dependence [27–29]. In our study, the combined intake of different AED may have softened the effect of development of dependence. Research in this area would be interesting, but is hard to perform since monotherapy with clobazam or barbiturates can be studied only exceptionally.

Also, information about the development of dependence on barbiturates and benzodiazepines in other neurological diseases is still unknown, such as essential tremor (primidone, benzodiazepines) or muscular pain in patients with disorders of the spine (benzodiazepines like tetrazepam). The product information of Musaril®/tetrazepam warns patients of the risk of physical and psychological dependence, but also no studies about the topic of dependence are available.

No previous studies addressed the topic of dependence from antiepileptic medications in patients with epilepsy and there were no reported studies about the psychological and physiological properties of barbiturates and benzodiazepines in epilepsy. This has been attributed to the various confounding variables that interfere with proper analysis and interpretation of data. According to this, there are limited notifications about a topic, which is present at least since the introduction of phenobarbital in 1912. With regard to the fact that in our study 35% of the patients and 16% of their relatives stated to ruminate about the problem of dependence on AED, we considered it as a necessity to approach this problem despite of the confounding variables and the lack of objective measures in our survey. Other factors that may be important for developing dependence or addiction (for example, psychosocial markers) were not included in our study because that would have gone beyond our primary scope of interest. To improve knowledge for clinical practice, controlled studies on the risk of dependence with benzodiazepines and barbiturates are needed. Although

many new anticonvulsants are available, both groups of conventional drugs, clobazam, and barbiturates are still in use worldwide.

Conflict of Interest

The authors declare no conflict of interest.

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