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Disulfiram Implantation in Alcohol Dependency: Influence of Sociodemographic and Clinical Variables on Treatment Response

Asli Akin Aslan[1], Ozhan Yalcin[2], Zehra Arikan[3], Asli Kuruoglu[3], Behcet Cosar[3], Numan Konuk[4]

ÖZET:

Alkol bağımlılığında disülfiram implantasyonu; sosyodemografik ve klinik değişkenlerin tedavi yanıtına etkisi

Amaç: Sık görülen bir psikiyatrik bozukluk olan alkol bağımlılığı tedavisinde psikofarmakolojik, psikoterapötik ve psikososyal tedavi yöntemleri kullanılmaktadır. Alkol bağımlılığında naltrekson, akamprosat ve topiramat gibi umut vaat eden yeni psikofarmakolojik tedavi yöntemleri denenmekte ve son yıllarda bu ilaçlar ile ilgili oldukça fazla sayıda araştırma yapılmaktadır. Oldukça uzun yıllardır bilinen disülfiramın kullanımı ise gitgide azalmaktadır. 1950'li yıllardan beri kullanılan disülfiram implantasyonu ile ilgili en son araştırmalar ise 1990'lı yıllarda yapılmıştır. Bu geriye dönük çalışma ile amacımız ekonomik maliyeti oldukça düşük olan disülfiram implantasyonunun alkol bağımlılığı olan bireylerde tedavi etkinliği ve tedavi yanıtına etki eden sosyodemografik ve klinik özelliklerin etkisini incelemektir.
Yöntem: 1990 ve 2009 yılları arasında Gazi Üniversitesi Tıp Fakültesi, Gölbaşı alkol ve madde bağımlılığı yataklı servisinde yatarak tedavi görmüş, disülfiram implantasyonu uygulanmış 39 hastanın dosya ve poliklinik kartları geçmişe yönelik olarak incelenmiş ve analiz edilmiştir.
Bulgular: Disülfiram implantasyonu uygulanan tümü erkek 39 hastanın %15.4'ünde erken tam remisyon, %76.9'da kalıcı tam remisyon saptanmıştır. Hastalarda disülfiram implantasyonu sonrası ayıklık süreleri ortalaması 47 ay olarak bulunmuştur. Hiçbir hastada ciddi bir yan etki gözlenmemiştir. Evli olan, tip 1 alkolizmi olan ve duygudurum bozukluğu eş tanısı olmayan bireylerde disülfiram implantasyonu sonrası tam remisyon oranları daha yüksek olarak saptanmıştır.
Tartışma: Araştırmamızın sonuçları disülfiram implantasyonu uygulanan hastalarda uzun ayıklık süreleri ve kalıcı tam remisyon oranları yüksek olarak saptanmıştır. Klinisyenler tarafından disülfiram kullanımı, yan etkileri abartılı olarak ve gözden düşmüş bir tedavi yöntemi olarak algılansa da, disülfiram implantasyonu hem psikolojik, hem de farmakolojik caydırıcı etkisi olabilen, diğer psikofarmakolojik tedavi yöntemlerine ek olarak da uygulanabilecek, ekonomik maliyeti düşük bir tedavi yöntemidir. Son yıllarda yapılan ve oral disülfiram kullanımının alkol bağımlılığında diğer seçenekler olan akamprosat, naltrekson ve topiramat kullanımına üstün olabileceğini gösteren araştırma sonuçları ile birlikte düşünüldüğünde; disülfiramın implant formunun da bu ajanlarla etkinliğini karşılaştıran araştırmalara ihtiyaç bulunmaktadır.

Anahtar sözcükler: Alkolizm, disülfiram, bağımlılık, farmakolojik tedavi, ilaç implantları

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ABSTRACT:

Disulfiram implantation in alcohol dependency: influence of sociodemographic and clinical variables on treatment response

Objective: Psychopharmacological, psychotherapeutic and psychosocial treatment methods are being used in alcohol dependence, which is a frequently occurring psychiatric disorder. In alcohol dependence, promising treatment strategies like naltrexone, acamprosate and topiramate are being tested and numerous research studies have been conducted about these novel drugs in recent years. The administration of disulfiram, which has been used for years, appears to be decreasing. Research on disulfiram implantation, which has been used since the 1950's, had been carried out in 1990's. Our aim with this retrospective study was to investigate the contribution of low cost disulfiram implantation to the treatment of individuals with alcoholism and the influence of sociodemographic and clinical characteristics on treatment response.
Methods: Between the years 1990 and 2009, the records of 39 patients, who received disulfiram implantation and inpatient treatment for alcoholism at the clinics of alcohol and substance dependence of Gazi University Medical Faculty, in Golbasi, Ankara, were examined and analysed in detail.
Results: Of the 39 disulfiram implanted patients (all male), 15.4% had early remission and 76.9% had sustained remission. It was found that patients achieved an average of 47 months of sobriety after disulfiram implantation. None of the patients developed serious side effects. The percentage of sustained remission after disulfiram implantation was higher in married cases, individuals with type 1 alcoholism or patients, who had not been diagnosed with co-morbid affective disorders.
Conclusion: Our results showed long sobriety intervals and high sustained remission rates after disulfiram implantation. Although disulfiram treatment is perceived by clinicians as a discredited treatment option with an exaggerated side effect profile, disulfiram implantation is a low cost treatment option, which can be added to other treatment techniques because of its psychological and pharmacological deterrent effects. In conjunction with recent research showing the superiority of disulfiram over other treatment options for alcohol dependency such as acamprosate, naltrexone and topiramate, further research is needed to compare the efficacy of those agents and disülfiram implantation.

Key words: Alcoholism, disulfiram, dependency, pharmacologic therapy, drug implants

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INTRODUCTION

The overall lifetime prevalence of alcohol dependence is about 7% - 12.5% in the western population. The treatment of biological alcoholism consists of dealing with alcohol intoxication, withdrawal symptoms, neuropsychiatric disorders related to alcohol as well as the achievement and maintenance of abstinence. In the last twenty years many treatment methods have been attempted for these conditions (1).

Alcohol dependence is indicated by a decrease of control on consumption. Naturalistic and long-term follow-up studies show the recurrence of hard drinking even after decades of the abstinence (2). Relapse of hard drinking has also been demonstrated in animal studies in which long-term forced abstinence had been maintained (3). Finally, although most clinicians have suggested abstinence in the first target, there is a growing interest in reducing severe drinking for patients, whose target is not abstinence (4). Follow-up studies on alcoholism have indicated that most of patients couldn't maintain control of consumption of alcohol. (5). Although studies focusing on cognitive-behavioural therapy (CBT) have determined some positive results with self control efforts in patients with restricted alcohol problems compared to non-treatment groups, there are different views about whether this effect also could be seen in patients with alcohol dependence (2).

Various psychosocial interventions including psychotherapy have been found to be effective on the treatment of alcoholism (2). The long-term abstinence ratio has rarely exceeded 40% with these treatments (6). The effective treatment strategies are: CBT, which increases the motivation for recovery; twelve-step treatment; various therapies of family, social environment and marriage; and training for social skills. Psychodynamic therapies are less preferred (6).

After alcohol detoxification, there is no standard treatment strategy for maintenance in alcohol dependence. The usage of disulfiram in the management of alcohol dependence began in 1948 and was approved by the Food and Drug Administration (FDA) for the treatment of alcoholism in 1951. The effectiveness of this technique is limited by the patient's motivation to comply with treatment (7). Fuller et al. have showed in their study on male alcoholics that disulfiram was not found to be superior to placebo in terms of the delay to get the first alcohol or improvement in social and professional occupations. The main reason for ineffective treatment was linked to in nappropriate usage of the drug and the results of urine analysis showed that only 20% of patients were fully compliant with disulfiram treatment (10). Lundwall and Baekeland reported that only one study had adequate design criteria among more than forty studies about disulfiram, which were conducted between 1948-1971 (8). In another meta-analysis study, Garbutt and colleagues stated that, among 135 studies about the usage of oral disulfiram, only five of these studies included a control group and that the results of these studies were inconsistent with each other and were generally insufficient in terms of investigating the relapse issue. Due to these research results it has been reported that the power of disulfiram studies is low and the main methodological difficulties have been reported to be the absence of blind studies, the lack of scales assessing treatment compliance, short follow-up periods and non-random sample selection (11).

Recent open-label studies have showed that disulfiram was superior to acamprosate, naltrexone, and topiramate (12-15). Especially for individuals consuming alcohol for a long time, disulfiram has been claimed to be superior to other treatments (14).

In the studies of Petrakis and collegues, it has been determined that in alcoholic individuals with comorbid psychotic spectrum disorder, post-traumatic stress disorder or major depression, both naltrexone, and disulfiram, as well as combination therapy was superior to placebo, but that there was no significant difference between the drug groups in terms of response to treatment (16-19); however, craving scores were found to be lower with disulfiram in patients with depression (19).

In recent years, it has been discovered that disulfiram has a significant effect on noradrenaline

and dopamine pathways (20). Possibly because of these effects of disulfiram, there are growing research findings indicating that disulfiram might be used safely for alcohol dependent individuals, who have comorbidities with cocaine dependence or pathological gambling (20-23). Disulfiram also can be used safely in combination with other medications treating alcohol dependence such as acamprosate, naltrexone and topiramate and it may be effective alone for adolescents with alcohol abuse and dependence. Additionally when combined with acamprosate, a significant increase might be seen in treatment efficacy (24).

Poor adherence/compliance is a major problem with disulfiram treatment; it has been shown that most patients have left treatment within a few months (25). Therefore, disulfiram treatment is advocated to be used under supervision or adult probation. In a meta-analysis reviewing 13 controlled and 5 non-controlled studies, compared to unsupervised treatment groups and patients not taking disulfiram, disulfiram groups under supervision or probation were superior with respect to reducing alcohol intake and treatment retention (26). A recent meta-analysis published by Jorgensen and colleagues in 2011, which was based on a review of 11 studies with 1.527 patients, shows that supervised treatment with disulfiram is very effective in maintaining short-term abstinence, increases number of days to relapse and leads to a significant decline in total drinking days (27). Subdermal implantation of disulfiram, which releases the drug continuously, has been developed to improve compliance. The implantation method was used for the first time in 1955 by Marie (28). Since studies have reported longer durations of abstinence with implantation of disulfiram compared to oral disulfiram, it has been suggested that implantation of disulfiram might be preferable as a maintenance treatment method (8).

Implantation of disulfiram provides controlled release of disulfiram into the blood, which results in the disulfiram-ethanol reaction upon alcohol intake. The commonly used disulfiram implantation dose is 1 g (8).

Disulfiram inhibits the enzyme acetaldehyde dehydrogenase and leads to an increase in blood acetaldehyde levels following alcohol intake. Immediately after drinking, the disulfiram-ethanol reaction manifests itself with flushing, sweating, and mild headache. At a moderate level of intensity, the reaction causes nausea, tachycardia, palpitation, hyperventilation hypotension, and dyspnea. Vomiting, respiratory depression, cardiovascular collapse, arrhythmia, myocardial infarction, acute congestive heart failure, unconsciousness, convulsion, and death may occur in more severe disulfiram-ethanol reactions. The mild and moderate levels of reaction may occur, when the blood alcohol concentration reaches 10 mg/dL and 50 mg/dL, respectively (8). It has been suggested that the development of the disulfiram-ethanol reaction at the initiation of treatment had no effect on treatment response (9).

New findings about the clinical and sociodemographic factors that contribute to disulfiram efficacy will guide clinicians in this field. For this purpose, we have evaluated the duration of abstinence and complication rates, and have determine the relationship between these findings, sociodemographic characteristics and alcohol drinking patterns in the patients with alcohol dependence, who were hospitalized and had implanted disulfiram.

METHODS

We retrospectively examined the sociodemographic and clinical records of patients, who were hospitalized in the clinics for alcohol and substance dependence of the Gazi University Medical Faculty, Golbasi Ankara between 1990 and 2009. We investigated in patient files comprehensively and outpatient follow-up records of 39 male patients, who were given disulfiram implants during this period. Sociodemographic data, total number of hospitalizations due to alcohol problem, number of hospitalizations in this clinic, duration of dependency, age of first alcohol use (ever used), age of onset of regular alcohol use, age of perceiving and identifying alcohol as a problem, number of disulfiram implantations, abstinence duration after

implantation, cumulative abstinence duration between diagnosis of alcoholism to disulfiram implantation, comorbid psychiatric disorders, family history of psychiatric disorders and alcoholism, medical history and additional psychiatric medications used were included in the analysis.

We defined early full remission as an abstinence period of at least 1 month but less than 12 months. Patients, who did not fulfil the criteria for alcoholism after more than one year were classified as sustained full remission according to DSM-IV (29). According to clinical features, which were described by Cloninger, patients were classified as type 1 or type 2 alcoholics (30).

Data obtained from the retrospective analysis of these patient records was statistically analysed using SPSS 15.0. Descriptive statistics for continuous parameters were shown as mean (+/- standard deviation) and discontinuous parameters as percentages (%). For comparison of normally distributed continuous variables, Student's t test was used. For comparison of discrete variables, the chi-square test was used. $P<0.05$ was considered to be significant. By using Pearson's correlation analysis, we examined the relationships of clinical variables with each other. Comparison between the clinical variables of early full remission, sustained full remission and relapse groups were performed by using the ANOVA test and Tukey's post hoc test.

RESULTS

Sociodemographic Features

All of the patients were male and were living in an urban community. Thirty (76.9%) of them were married, 2 (5.1%) were single and 7 (17.9%) were divorced. Thirty-two (82.1%) patients lived in a nuclear family, 5 (12.8%) in an extended family and 2 (5.1%) lived alone. One (2.6%) of the patients was illiterate, 2 (5.1%) were literate, 1 (2.6%)had completed primary school, 12 (30.8%) had graduated from mid school, 19 (48.7%) from high school and 4 (10.3%) from university. Five (12.8%) of them had low income, 20 (51.3%) middle income and fourteen (35.9%) high income. Three (7.7%) of the patients were unemployed, 3 (7.7%) were workers, 15 (38.5%) were officers, 11 (28.2%) were self-employed and 7 (17.9%) were retired. Six (15.4%) of them had no health insurance. The mean age of the patients was 44.67±8.61 and the median age of the patients was 44.51±9.1 years.

Clinical Characteristics

Thirty-two (82.1%) of the patients had no family history of psychiatric illness, 7 (17.9%) of them had a family history of a psychiatric disorder. Seventeen (43.6%) had no family history of alcohol and/or drug dependence, 20 (51.3%) had first-degree relatives and 2 (5.1%) had second-degree relatives with a history of alcohol or drug dependency. Twenty-three (59%) of the patients had no medical illness and 16 (41%) of them had concomitant medical problems. Twenty-eight patients (71.8%) had no comorbid psychiatric disorders, 10 patients (25.6%) had major depression comorbidity and 1 patient (2.6%) had comorbid obsessive compulsive disorder.

Twelve (30.8%) of the patients were not receivin psychotropic medication, 12 (30.8%) were taking antidepressants, 7 (17.9%) oral disulfiram, 4 (10.3%) antipsychotics, 3 (7.7%) acamprosate and 1 (2.6%) was using other psychotropic drugs.

Eight (20.5%) of the patients were using disulfiram implantation for the second time. The remaining patients were implanted with disulfiram for the first time. In the cases where disulfiram implantation was done for the second time, abstinence duration after implantation was calculated with respect to the second application. All patients were smokers.

Twenty-three (59%) of the patients were classified as type 1 and 16 (41%) were classified as type 2 alcoholic. The average number of hospitalizations was 3.1±2.05, the average number of hospitalizations in our clinic was 2.33±1.44, the mean duration of the disorder was 19.13±8.44 years, the mean age of first alcohol use 16.82±4.66 years, the mean age of onset of regular use was 23.18±6.46, the mean age of perceiving and identifying alcohol

as a problem was 35.56±8.9 and the mean abstinence duration after disulfiram implantation was 47.18±40.34 months.

After implantation of disulfiram, 7.7% of the patients (n=3) experienced relapse, 15.4% (n=6) fulfilled the early full remission criteria and 76.9% of the patients (n=30) were in sustained full remission. Using the chi square test, differences in distribution emerging between groups were significant at the p<0.001 level in favour of sustained full remission.

After the first 9 months of implantation (disulfiram's active period) 84.6% of the patients (n=33) did not drink alcohol and 15.4% (n=6) of them used alcohol. According to the chi-square test, the distribution difference between the groups was significant (p <0.001).

The relapse rate in type 1 alcoholics was 4.3% and in type 2 the rate was 12.5% . Of the type 1 alcoholic patients, 4.3% were in early full remission, while in type 2 patients this rate was found to be 31.3%. Sustained full remission rates were 91.3% and 56.3% for type 1 and type 2 alcoholics, respectively. According to the chi-square test, the difference in distribution between the two groups was statistically significant (p= 0.034).

There was no statistically significant difference in the distribution between type 1 and type 2 alcoholic groups, in terms of concomitant psychiatric disorders (p= 0.620).

During the disulfiram implant treatment, 13% of the type 1 patients and 18.8% of the type 2 patients drank alcohol, a difference which was not a statistically significant (p= 0.674).

According to the Pearson's correlation analysis it was found that, the patients' mean age at the onset of regular drinking (p= 0.020, r= 0.472) and mean age of perceiving alcohol as a problem (p<0.001, r= 0.775) increased significantly with age. While the number of hospitalizations of the patients was increasing, the age of onset of regular drinking tended to decrease (p= 0.012, r=-0.398). With increasing duration of illness, the age at which the patients perceived and identified alcohol as a problem (p= 0.011, r= 0404), the number of implantations of disulfiram (p= 0.009, r= 0.412) and the duration of abstinence (p= 0.015, r = 0.386) were significantly increasing. The patients, who drank during the disulfiram implantation treatment had relapse, early full remission and sustained full remission rates of 16.7%, 66.7%, 16.7%, respectively. Non-drinkers in the first 9 months had relapse, early full remission and sustained full remission rates of 6.1%, 6.1%, 87.9%, respectively. The distribution of these values between the groups was statistically significant (p<0.001).

In those who were married, 6.7% experienced relapse, 10% experienced early full remission, 83.3% had sustained full remission. In single patients, 50% relapsed; and 50% achieved full remission. For divorced patients, 43.9% experienced early full remission and 57.1% of them fulfilled sustained full remission. The distribution of these rates between the two groups was significant (p= 0.036).

There were no significant differences between remission rates and education levels (p= 0919), income distribution (p= 0.286), occupational backgrounds (p= 0.223), presence or absence of social insurance (p= 0744), the presence or absence of family history of psychiatric illness (p= 0688), a family history of addiction (p= 0.779), presence or absence of medical illness history (p= 0.712), taking or not taking outpatient treatment (p= 0.329) and history of previous medical treatment (p= 0.184). Patients with comorbid depression compared with those without a history of comorbid depression, tended to have lower sustained full remission rates (p= 0,070).

The mean number of hospitalizations in patients with early full remission was 5.33, patients with relapse had a mean number of hospitalizations of 2.33 and in patients with sustained full remission, the mean number of hospitalizations were found to be 2.73. ANOVA analysis indicated significant statistical differences between the groups in terms of the average number of hospitalizations (p= 0.010). Tukey's post hoc analysis showed that, there was a significant difference between the early full remission and sustained full remission groups, in terms of the mean number of hospitalizations (p= 0.009).

Between the time of receiving a diagnosis of alcoholism to the time of the implantation of

disulfiram, the cumulative duration of abstinence was 56.63 months in the sustained full remission group, 16 months in patients with early full remission and 19 months in the relapse group. There were significant differences between the groups according to one way ANOVA analysis (p= 0.031). According to the t test of independent samples, between the type 1 and type 2 alcoholic groups in the terms of age, the number of hospitalizations, number of hospitalizations in our clinic, duration of disorder, age of first drinking, age at the onset of regular alcohol use, age of perceiving and identifying alcohol as a problem, number of disulfiram implantations and duration of abstinence, no significant difference was found.

DISCUSSION

In clinical practice, research findings of disulfiram's efficacy on the abstinence duration of patients are inconsistent. In addition it is known that patient compliance with disulfiram usage is weak. This lack of compliance raises questions about the usage of disulfiram in the treatment of alcohol dependence (11).

There have been few clinical studies that have properly evaluated the effectiveness of disulfiram, due to methodological limitations (11). However, owing to the positive results achieved by some patients, usage of disulfiram has been accepted in the treatment of alcohol dependence.

According to our present retrospective study, patients achieved high full remission rates and also had long mean abstinence durations after disulfiram implantation. Similarly White and O'Brien observed a three times longer abstinence duration in disulfiram implanted patients compared to a control group (31). In a study, which is one of the first controlled studies of disulfiram implantation, with a limited number of patients (10 in the study group, 7 in the control group), in the two year follow-up period compared to placebo, a longer mean abstinence duration interval was observed in the disulfiram implanted group. Not only a psychological deterrent effect but also a pharmacological deterrent effect of disulfiram implantation was pointed out, due to the development of a disulfiram-alcohol reaction (DAR) in 7 patients in the disulfiram implanted group (32). In many clinical trials, uncertainty about the bioavailability of disulfiram implantation has been reported and the psychological deterrent effect of implantation treatment has been emphasized (33-38).

There have been publications reporting no clinical efficacy, or only a psychological deterrent effect of disulfiram implantation (39). In a study conducted by Johnsen and Morland, disulfiram implantation was applied to 33 patients and placebo containing calcium phosphate was implanted in 30 patients. In the evaluation after three hundred days, no significant difference was observed in terms of mean alcohol consumption, number of days to first alcohol intake and psychosocial functionality. Decrease of alcohol consumption in both groups was linked to the psychological deterrent effect of the implantation (37). Similar results were also found in a study conducted by Wilson and colleagues, which had a similar methodology (34). In a two year follow-up study of the psychological deterrent effect, although disulfiram implantation lead to a significant increase in abstinence duration of 120 patients with chronic alcoholism, no significant correlation was determined between implanted disulfiram dose (800, 1200, 1600 mg) and treatment response (33).

Whether the psychological deterrent or pharmacological deterrent effect of disulfiram implantation reduces alcohol intake is a controversial point. Research findings about this issue are not consistent (40). In our present study, only six of the patients took alcohol and a DAR developed in all of them. Three of them took alcohol before the completion of the 9 month active phase of the implantation. The other three patients took alcohol in the 9th month and in spite of that fact, developed a DAR. Both, the alcohol intake after the 9 month active period in those aforementioned patients and prevention of alcohol intake in 84.6% of patients within the active phase of implantation, demonstrate psychogenic efficacy and development of a DAR in all patients taking alcohol, demonstrates the pharmacological efficacy of implantation.

According to Wilson, disulfiram's pharmacological deterrent effect is underestimated (40). In Johnsen and Morland's opinion, ineffective clinical research findings about disulfiram implantation might be related with lower bioavailability of disulfiram implantation compared to the oral form. Production and development of reliable controlled-release forms can be accomplished in the future (36).

The DAR associated with disulfiram implantation develops less frequently, less intensively and less severely. Some researchers have regarded this condition as an advantage for preventing serious side effects (41). Also because of that condition psychological deterrent efficacy of implantation is considered to be important. In Kingstone and Kline's opinion, disulfiram implantation may prevent alcohol consumption by the following mechanisms: 1) patients who have already accepted this procedure are highly motivated for alcohol cessation or motivation for alcohol cessation may increase after the surgical procedure, 2) palpation of the implant in the surgical area may prevent alcohol intake and improve motivation, 3) development of a pharmacological effect, 4) decrease in psychological stress due to the dissolution of fear about recurrence of alcohol consumption in patients with obsessive traits (particularly type 1 alcoholics) may reduce craving for alcohol and 5) improvement in the motivation for changing behaviours in individuals with impulsive traits (especially in type 2 alcoholics) (41). Stolpmann and Muller suggest prescribing disulfiram for prevention of relapse due to impulse control deficiencies in alcoholism (42). Although lower than type 1 alcoholics, high full remission rates (56.3%) in type 2 alcoholics, who are regarded as more impulsive, might be explained by disulfiram's deterrent effect in our study.

Disulfiram, naltrexone and acamprosate are approved treatment options for alcohol dependence. Also naltrexone and acamprosate are considered to be effective for different alcohol consumption patterns. Although naltrexone has been suggested to prevent severe relapse of alcohol intake by decreasing the rewarding effect of alcohol, in some wide scaled research this effect could not be demonstrated. Acamprosate has been suggested to reduce cravings in periods of sobriety. These medications are usually well tolerated but 10% of patients report nausea with naltrexone and diarrhea is often seen with acamprosate (24). In our present study, disulfiram-induced hepatotoxicity or other systemic side effects were not observed in any patient. In a long follow-up study with 210 patients using oral disulfiram, none of the patients discontinued treatment because of side effects but 70% of the patients discontinued medication due to a desire for alcohol or due to a feeling of recovery (43).

In recent years in consequence of usage of new drugs which lower the craving for alcohol or decrease alcohol consumption and also due to the perception of disulfiram implantation as a treatment with relatively severe side effects, the use of disulfiram has decreased. However under supervision, disulfiram is a cost-effective and efficacious treatment option. In addition, its side effects are perceived by clinicians to be very severe. Disulfiram associated deaths are rare. Disulfiram related hepatotoxicity is limited to one case out of 25000 units of disulfiram usage per year. Our findings also support disulfiram's safety, side effect profile and treatment efficacy.

In a retrospective survey research like our study covering a time as long as 12 years, compared to patients not receiving psychopharmacological treatment or compared to patients receiving psychopharmacological treatments including oral disulfiram, longer abstinence periods were determined in the disulfiram implanted patients with chronic alcoholism (47).

In studies, which were conducted by Johnsen and Morland, surgical complications were frequently observed and clinicians were warned about serious surgical complications (35,37). In our study none of the patients developed a surgical complication.

The higher sustained full remission rates found in our study in married patients (better family support), compared to divorced or single patients and higher remission rates in patients without affective disorders are consistent with scientific literature (24).

The most important limitations of this study are possible deficiencies in the recorded file data and the lack of the control group. Also the efficacy of disulfiram may have been underestimated to the inability to exclude other psychopharmacological treatments used by patients.

There are relatively few studies about disulfiram implantation and the findings are contradictory. In the future there is a need for further research about disulfiram implantation to be conducted in various populations because of the possible different pharmacodynamic and pharmacokinetic profiles of disulfiram implantation which may occur due to different pharmacogenetic traits.

Due to its low cost and cost-effectiveness, disulfiram implantation may be used effectively and safely as monotherapy or combined with acamprosate, naltrexone or topiramate in developing countries and in individuals, who have motivation for cessation of alcohol but have limited health insurance (24,27,44-46). Our study also supports this point of view. Hence there are doubts about bioavailability, production and development of more efficacious depot forms that may be beneficial for treatment (36).

The findings of our retrospective study highlight the necessity to conduct new systematic research to reevaluate disulfiram implantation as a treatment option for alcohol dependence, which is a serious public health concern.

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