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SULPIRIDE PSYCHOPHARMACOTHERAPY IN PATIENTS WITH ALCOHOL ADDICTION AND DEPRESSION COMORBIDITY

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SUMMARY – Depression is quite common in the early stage of treatment for alcohol addiction. The patient's awareness of his difficult situation may be one of the reasons for depression. Furthermore, depression can develop as the result of depressive disorders that are primarily or secondarily associated with alcohol addiction. Antidepressive therapy is usually initiated after a two-week detoxification procedure. Only exceptionally it may start earlier in case of severe depressive disorder. The administration of sulpiride from the very beginning of treatment yields favorable results because of the wide range of its action, especially antidepressive effects. The effect of sulpiride therapy was investigated in 20 alcoholics suffering from minor to moderate depressive disorders. The patients were administered 50 mg sulpiride capsules three times a day. Control group included 20 patients who received placebo. Both the study and control group patients underwent psychotherapeutic methods usually conducted in a sociotherapeutic community. The severity of depressive disorder was measured by use of Hamilton's and Beck's scale before, and then at 2, 4 and 6 weeks from the beginning of treatment. Also, the patients were clinically observed during the psychotherapeutic procedures and other activities performed in the therapeutic community. Study results confirmed the efficacy of sulpiride in the management of depressive alcohol addiction in alcoholics. The sulpiride dose of 150 mg/day showed a rapid antidepressive effect. Accordingly, sulpiride was confirmed to play an important role in the rational use of psychopharmacotherapy in patients with alcohol addiction in a sociotherapeutic community.

Key words: *Alcoholism, drug therapy; Depressive disorder, drug therapy; Sulpiride, therapeutic use*

Introduction

Both depressive disorders and alcoholism are very common psychiatric diseases. Their comorbidity is also very frequent, however, there is a surprising lack of dual diagnoses[1]. The prevalence of depressive disorders and of alcoholism in the general population ranges from 3.6% to 6.8%, and from 3.5% to 4.0%, respectively, whereas the prevalence of depressive disorders in alcoholics is from 24% to 57%[2]. It is difficult to make clear distinction between depressive disorder and depressive behavior in healthy persons, and even more so in alcoholics. The patients themselves, their environment and the clinicians often fail to recognize a depressive disorder due to physical symptoms and the fact that some depressions are 'masked' or have a 'creeping' character. Alcoholism itself masks other psychological disorders and especially depression, as the symptoms of both disorders are similar because of a number of vegetative symptoms present in both disorders, thus hampering the diagnosis of a depressive disorder. These symptoms include inappetence, insomnia, decrease in bioenergy potential, difficulties in reasoning and concentration, poor memory, decreased libido, feeling of guilt, etc. The depression in alcoholics, be it a primary or secondary or concurrent disorder with alcoholism, is a serious problem and treatment for both disorders is required.

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However, it is important to distinguish between depressive disorders and a feeling of sadness, which sometimes develops in the early abstinence phase and can be caused by the patient's understanding of his/her situation. This can be clinically relevant to avoid unnecessary antidepressant therapy.

Alcoholics with depressive disorders should be treated with appropriate psychopharmacotherapy, generally introduced after two weeks of abstinence when the withdrawal symptoms disappear. Antidepressants may be introduced earlier in patients with less pronounced withdrawal symptoms but showing the symptoms of depression, in order to ensure faster therapeutic effects through patients' participation in the psychotherapeutic work.

The diagnosis of depressive disorders in alcoholics is largely dependent on the psychiatric approach of the institution conducting the treatment. Substance abuse centers often expect a lower rate of depressive disorders and often tend to underdiagnose them, whereas psychiatric hospitals are frequently focused on depression and treat alcoholism as a secondary disorder. Differences in the clinical work of various institutions call for adjustment and standardization of research methods.

Pharmacological studies of the association between depression and alcoholism often exclude patients with depression if there is a high risk of suicide or severe physical impairment.

Important characteristics of alcoholics with depression are symptoms related to low serotoninergic function. There is a higher adrenergic, noradrenergic and dopaminergic action in alcoholism and abstinence syndrome[3-5]. The major concern in this study was the higher dopaminergic action, as sulpiride the effects of which in the treatment of alcoholics with depression were evaluated, influences dopaminergic D2 and D3 receptors[6,7].

Neurotransmission action in alcoholics and effects of sulpiride

The amines acting as neurotransmitters are norepinephrine, epinephrine, dopamine, serotonin and histamine. Dopamine, norepinephrine and epinephrine are catecholamines used together in the biosynthesis pathway. The pathway starts with tyrosine amino acid, which is changed into L-dopa and then into dopamine, which is the end of the pathway for dopaminergic neurons. Noradrenergic neurons have one additional enzyme that changes dopamine into norepinephrine. Other cells add methyl group to form epinephrine[3,6].

The neurons containing high levels of dopamine are located in mesencephalon, and some of their axons reach telencephalon and possibly take part in emotional reactions. Other dopaminergic axons end in corpus striatum and are thought to play an important role in complex movement control.

Dopaminergic pathways are used in a number of brain functions, e.g., motor control, autoimmune and endocrine functions, mental and emotional reactions, etc. In alcoholics, during longstanding intoxication and in early abstinence, the functioning of the neurotransmitting systems is altered, i.e. there is a higher level of synaptic activity. Laboratory tests show an increase in dopamine and norepinephrine as well as a decrease in serotonin[4,5]. Higher dopamine levels cause changes in the brain function and can lead to hallucinations and delirium[6].

As all neurotransmitting systems are inter-related, the changes contributing to depression can hardly be attributed to one of them. Instead, it is more productive to view them as a dynamic process in which one of the pathways can initiate changes that in turn cause complex actions and adaptation of other systems.

It can be assumed that the decrease in dopamine can indirectly, through adaptation and balancing in neurotransmitters induce serotonin increase and consequently mood improvement, although this explanation should be considered a simplification.

Sulpiride

Sulpiride is a wide-range antipsychotic with a specific effect on D2 and D3 dopamine receptors[7,8]. Strictly speaking, it is not considered an antidepressant although its antidepressant effect has been clinically confirmed in doses of up to 300 and even 600 mg. Higher doses of 800 to 1600 mg have shown good antipsychotic effects. It is also indicated in neurotic states, central and peripheral vertigo, and psychosomatic disorders[9,10].

The aim of the present study was to confirm the efficacy of sulpiride in the early treatment of patients with comorbidity of alcohol addiction and major depressive disorders.

Subjects and Methods

Subjects

The patients included in the study exhibited mild to moderate depressive symptoms (N=40). They all were male and without a suicidal risk. The exclusion criteria

were serious hepatic, renal or cardiac disease, and mental retardation. The patients were not taking any psychoactive drugs before the study. The study was conducted during the daily treatment program for alcohol addiction at the University Department of Psychiatry, Sestre milosrdnice University Hospital, Zagreb. Study subjects were divided into two groups of 20 subjects. One group received sulpiride therapy (50 mg) 3x1 capsule daily. The other, control group received no medication but vitamins as placebo.

Methods

The trial was designed as an open study. A psychiatrist performed a structured clinical interview and made the diagnosis based on DSM-IV criteria for alcohol addiction[11,12]. The grade of depression was measured by Hamilton's and Beck's depression inventory scales. CAGE questionnaire was used for its simplicity and reliability. Assessment of the depressive behavior scales was done before, and then at 2, 4 and 6 weeks of treatment. All study subjects were administered psychotherapy, both individualized and in a group setting. Statistical analysis was done by the χ^2-test.

Results

Data on the Beck's self-assessment scale pointed to a faster decrease of depression in the sulpiride treated group, however, between group differences were not statistically significant. On days 15, 30 and 45 of treatment, data on the Hamilton's scale showed the presence of depressive disorder in 40% and 90%, 30% and 50%, and 20% and 30% of the experimental group and control group, respectively. Obviously, there was a faster reduction of depression in the experimental group at all points of measurement. The between group difference was statistically significant on day 15 of treatment (χ^2-test, $p<0.05$) (Table 1).

Clinical observation revealed the experimental group patients to have more easily and readily adapted to the therapeutic process, and to be more cooperative in the psychotherapeutic work due to faster reduction of anxiety and depressive mood. On clinical observation, less desire to start drinking was also recorded, although there were no recidivists in either group during the study period.

In spite of the encouraging effects observed, this preliminary study included a small number of patients and will be continued at a larger scale to provide more reliable data.

Discussion

Studies of the effects of sulpiride in the treatment of alcoholics are very rare, probably due to the fact that it has not been registered in the United States. In some countries (e.g., United Kingdom) sulpiride is more often prescribed as an antipsychotic, whereas in others it is more commonly used as an antidepressant (e.g., Germany). Most of the available studies were experimental and carried out on rats and mice[13]. It is important to note an experimental study of the sulpiride effect on D2 receptor blocking, which showed a small but statistically significant reduction in alcohol requirement in mice[14].

The wide indications for the use of sulpiride in the treatment of complex disorders in alcoholism include its favorable effect in dysphoric-depressive mood, fast decline of emotional outbursts, antiemetic effect, improved appetite, and effect on vegetative symptoms[15-17].

It should also be emphasized that the effects of sulpiride are noticeable soon upon therapy introduction. Furthermore, it is well tolerated, can be combined with other drugs, and can be administered in patients with mild liver

Table 1. Comparison of sulpiride and placebo in the treatment of depressive symptoms in patients with alcohol addiction according to days of treatment

	1. Day		15. Day		30. Day		45. Day	
	+	–	+	–	+	–	+	–
Sulpride	20	0	12	8	6	14	4	16
%	100	0	60	40	30	70	20	80
Placebo	20	0	18	2	10	10	6	14
%	100	0	90	10	50	50	30	70

χ^2-test=18.76; Df=3; p=8.97E-05* (*p<0.05)
+ depressive disorder present, – depressive disorder absent
Comparison for each examination by Poisson distribution method: day 1, p=1; day 15, p=7.744; day 30, p=0.073; day 45, p=0.329

dysfunction, which has a high prevalence among alcoholics. Small doses (50 mg/day) of sulpiride have an agonistic effect, as reported in recent studies of negative symptoms in schizophrenia, chronic depression and dysthymia[6]. These results have paved the way to the research into the effect of small doses of sulpiride in treating depression in severe alcoholism with minus symptoms and inhibited depression, in the early period of abstinence. Large doses of 800-1600 mg have a good antipsychotic effect and can be used in treating alcohol delirium.

In the present study sulpiride was assumed to act on the reduction of abstinence symptoms and anxiety and indirectly reducing the desire to drink in the early stages of alcoholic treatment. Our results confirmed the efficacy of sulpiride psychopharmacotherapy on depressive syndrome in patients with alcohol addiction in the first six weeks of abstinence. A faster decrease in the level of depression was observed in the group of patients administered sulpiride. These patients were more readily included in the complex treatment program and were more accessible to psychotherapeutic work. This fast therapeutic process is highly relevant in the light of limitations imposed on the duration of inpatient treatment program as well as of the cost-benefit aspect of treatment.

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Sažetak

PSIHOFARMAKOTERAPIJA SULPIRIDOM U BOLESNIKA S OVISNOŠĆU O ALKOHOLU I DEPRESIJOM

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U početnoj fazi liječenja u alkoholičara se često očituje depresivno raspoloženje. Ono može biti posljedica uvida u problematičnu situaciju u kojoj se alkoholičar nalazi ili se radi o depresivnom poremećaju primarno ili sekundarno vezanom uz alkoholizam. Uvođenje ciljane antidepresivne terapije prakticira se nakon dvotjednog detoksikacijskog postupka, a iznimno kod jasno izraženih slika i ranije. Primjena sulpirida u početku liječenja alkoholizma daje pozitivne rezultate zbog njegovog širokog raspona, između ostalog i antidepresivnog, djelovanja. Ispitivalo se je djelovanje sulpirida u skupini od 20 bolesnika s lakšim i srednje teškim depresivnim poremećajem liječenih u Dnevnoj bolnici za alkoholizam na Klinici za psihijatriju, alkoholizam i druge ovisnosti Kliničke bolnice "Sestre milosrdnice" u Zagrebu. Ispitanici su primali 3x1 kapsulu od 50 miligrama sulpirida, dok je 20 bolesnika u kontrolnoj skupini primalo placebo. Obje su skupine podvrgnute individualnim i grupnim psihoterapijskim metodama u okviru socioterapijske zajednice. Razina depresivnog poremećaja ispitivana je Hamiltonovom i Beckovom ljestvicom koja je primijenjena pri dolasku na liječenje, te nakon dva, četiri i šest tjedana liječenja. Bolesnici su i klinički promatrani tijekom psihoterapijskih postupaka i ostalih aktivnosti koje se provode u terapijskoj zajednici. U radu je potvrđena djelotvornost sulpirida u dozi od 150 mg/dan u liječenju depresivnih poremećaja alkoholičara kroz njegov brz antidepresivni učinak, te je istaknuta njegova uloga u racionalnoj psihofarmakoterapiji alkoholičara u socioterapijskoj zajednici.

Ključne riječi: *Alkoholizam, terapija lijekovima; Depresivni poremećaj, terapija lijekovima; Sulpirid, terapijska primjena*