Comorbidity of alcohol dependence with other psychiatric disorders. Part II. Pathogenesis and treatment

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Summary

Co-occurrence of alcohol dependence with other mental disorders is very common, being important cause of diagnostic and therapeutic difficulties. There is a lack of systemic solutions in mental health care dedicated to the patients with dual diagnosis. The literature on the topic of treatment of patients with dual diagnosis is limited. While comorbidity of alcohol dependence with mental disorders is prevalent, there is rising interest among researchers on that issue. In this paper we present current hypotheses on pathogenesis of dual diagnosis as well as recommendations for its treatment. The role of disturbances in functioning of hypothalamic-pituitary – adrenal axis in pathogenesis of co-occurrence of alcohol dependence with anxiety and affective disorders is presented. Researchers studying dual diagnosis underline the fact that simultaneous treatment of alcohol dependence and co-occurring psychiatric disorders increases the chance to improve patients’ functioning. Inappropriate treatment without complete management of all existing problems may make full recovery impossible.

Key words: alcohol dependence, mental disorders, dual diagnosis, treatment, pathophysiology
Introduction

Dual diagnosis is a condition when psychiatric disorder is accompanied by substance dependence. This “double disorder” implicates serious difficulties in diagnosing and treatment. According to Anthenelli, Modesto-Lowe and Kranzler alcohol use disorders can potentiate or mimic almost all psychopathological symptoms [1, 2]. Health service systems around the world have major difficulties with providing treatment to patients with dual diagnosis. The significance of accurate diagnosis and initiation of appropriate treatment is crucial in these patients, because it is estimated that more than 30% of patients with psychiatric disorder meet criteria for substance abuse or dependence, including alcohol [3].

It is often difficult to distinguish between primary symptoms and those induced by alcohol use. The most reliable sign for symptoms secondary to alcohol use is when they withdraw without pharmacotherapy after a couple of weeks of abstinence [1, 4–6]. On the other hand, many alcohol-dependent individuals suffer from other psychiatric conditions [7]. This comorbidity brings other problems. The presence of some psychopathological symptoms among addicts decreases the effectiveness of pharmacotherapy [8]; in addition, substance abuse or dependence complicates the course, treatment and worsen the prognosis of coexisting psychiatric condition [3, 9].

Making the appropriate diagnosis of both substance use disorder and co-occurring psychiatric disorder is crucial to plan and to manage effective treatment. Substance use, including alcohol is rather norm than exception in the population of psychiatric patients [7]. However, main reasons why patients with dual diagnosis request medical advice are usually psychopathological symptoms and not the fact of excessive alcohol consumption [4, 10].

The pathomechanism of coexistence between alcohol use disorder and other psychiatric conditions

There are several concepts explaining the pathomechanism of substance use development among patients with psychiatric disorders and development of psychiatric disorders among alcohol abusers or addicts. One of them is a disturbance of biological response to stress. This theory implies the disturbance of mutual functional connections between the limbic system, hypothalamus, pituitary gland and suprarenal glands. There are many studies on prevalence of psychiatric disorders in the population of alcohol dependent patients as well as on prevalence of alcohol use disorder among patients with other psychiatric conditions. Much research has been performed to explain and find a primary condition in patients with dual diagnosis. Several differences can be found in the sequence of manifestation of psychiatric disorders regarding the gender of patients [11].
Some studies were conducted to establish the role of hypothalamic-pituitary-adrenal (HPA) axis and its reaction to stress in this group of patients. It was shown that traumatic situations and alcohol consumption lead to similar hormonal response [12, 13]. It was also noticed that response to stressing situations is similar among patients with depressive disorders, posttraumatic stress disorder and alcohol dependence.

**Theories of pathophysiological background of dual diagnosis**

Under physiological conditions stress is causing several signals to be reached by hypothalamus from various parts of the limbic system. Key neurotransmitters to lead these signals are serotonin and noradrenalin. This causes release of corticoliberin (CRH), which stimulates pituitary gland to release corticotrophin (ACTH), and thus promoting cortisol production in suprarenal glands. In healthy subjects, when HPA axis is working normally, cortisol is inhibiting release of CRH and ACTH as a feedback loop [14].

Besides the HPA axis in the CNS, another source of CRH (extrahypothalamic CRH – eCRH) has been found. This is so called Extended Amygdala (AE) consisting of: amygdalar nucleus, portion of the amygdale and substantia in nominate ventral to the globus pallidus and putamen, the portion of nucleus accumbens, and stria terminalis. There is a hypothesis formulated in 2005 that the most important interactions between brain reward centre and stress mediating structures are taking place in AE [15]. AE is responsible for controlling sympathetic and behavioural response of organism to stress stimuli [16]. This structure is strategic in explaining the effect of ethanol on neurobiological responses to stress. It was found that alcohol intoxication provokes AE to release eCRH, which activates whole HPA axis – ACTH release in pituitary gland and cortisol release in suprarenal glands [12, 13]. This is explaining one of the mechanisms that are responsible for increasing the level of stress hormones due to alcohol consumption. Progressive adaptation of CNS secondary to excessive release of the hormones is one of the key components in development of addiction [17]. Stopping alcohol consumption and the development of withdrawal syndrome is associated with another, large increase in the secretion of CRH in the brain, and then increase of serum ACTH level [18]. Behavioural manifestation of these neuroendocrine processes are emergence of anxiety and depressed mood, which was proved by blocking the action of CRH and thus decreasing above withdrawal symptoms [16]. The dexamethasone inhibition test showed no pathology in alcohol-dependent patients [11]. There is a gap in the literature concerning results of dexamethasone inhibition test in patients with depressive disorder. According to Koob and LeMoal, during the course of addiction gradual adaptation and allostasis arises. A new, inappropriate balance is created in the reward centre, and brain reaction to stress is disturbed [15, 19]. This phenomenon results in greater vulnerability of alcohol dependent patients to stress situation [19],...
which promotes relapse in difficult situations [13, 20]. Fortunately, with maintaining absolute abstinence HPA axis is coming back to normal [13, 20].

Depressive disorder as well as alcohol abuse and dependence have the source in difficult and stressing events. The same mechanism is responsible for development of PTSD, and traumatic experience is a condition essential to diagnose PTSD. Koob and LeMoal [19] pointed out that chronic stress accompanied by elevation of CRH, ACTH and cortisol leads to the lesion of particular brain structures including hippocampus. Cognitive impairment is accompanied with suppression of the HPN axis [21]. Developing neural adaptation and pathological stress response lead to anxiety disorders and cardiovascular diseases, which are strongly linked to alcohol abuse. Shivani showed that up to 80% of patients with alcohol dependence reported symptoms of depression, and 40% of them suffered at least once from a major depressive episode [22]. It is known that 40–60% of patients with depression have elevated cortisol level [23]. Lack of inhibition with dexamethasone is the marker of disturbance in HPA axis. Inappropriate results of dexamethasone suppression test are present among 40–65% of those patients. In healthy subjects dexamethasone inhibits ACTH release in pituitary gland and decreases cortisol levels. Lack of this reaction in alcohol-dependent patients is associated with more severe course of dependence and higher risk for relapse. Furthermore, patients with depression have excessive reaction of pituitary gland for stimulation with CRH [24]. Exorbitant release of ACTH after CRH administration is present even in 80% of patients with depression [25]. Discrepancy in cortisol levels among subjects with depression (elevated) and PTSD (decreased) with elevated CRH level may be a valuable tool to distinguish these two disorders.

Studies in a group of patients with PTSD showed decreased levels of ACTH and cortisol. Levels of hormones were correlated with duration, severity and recurrence of traumatizing events [23, 25], while CRH level was elevated in PTSD patients [26]. Both patients with PTSD secondary to one traumatizing event and those with PTSD secondary to repeated trauma have lower cortisol levels in comparison with healthy subjects, including those who suffered from traumatizing events, but did not revealed PTSD symptoms [23]. Decreased reaction to CRH and secondary reduced cortisol level may be reasons for alcohol use. Intoxication with ethanol, as described above, stimulates HPA axis and increases cortisol production in suprarenal glands. Alcohol ingestion seems to correct insufficient HPA axis and to cause transient improvement in patients’ mood [27]. However, when alcohol dependence is present in PTSD patients, the results of standard PTSD treatment, both pharmacological and psychotherapy, are worse. Brady et al. found that pituitary response to physical stress was similar among alcohol dependent subjects during abstinence, patients with PTSD and patients with both disorders [28, 29]. All subjects responded with lower ACTH release along with aggravated subjective feeling of discomfort. It was also found that the lower ACTH level was found among alcohol-dependent patients, the higher was risk for relapse.
Comorbidity of alcohol dependence with other psychiatric disorders. Part II

during stressing period in life. This correlation was not found among patients with coexisting alcohol dependence and PTSD. The nature of this phenomenon is not clear. Junghanns et al. suggest considering weakened ACTH release in stress as a marker of relapse risk in alcohol-dependent individuals [20].

Several studies were conducted to explain pathophysiology of discrepancies in epidemiology and clinical course of depression, anxiety disorder and alcohol dependence in respect of gender. It was found that observed discrepancies begin in puberty when sex hormones are released in increased amounts [30, 31]. It is believed that estrogens can bind to various types of receptors (ER, estrogen receptors) in CNS. Estrogens stimulate CRH release in hypothalamus, while vasopressin release is inhibited [32]. Changes in estrogen level are one of the reasons for different response to stress according to menstrual cycle. Estrogens influence also level of cortisol binding protein, which changes level of free cortisol in blood. When level of cortisol binding proteins decreases fraction of free cortisol, which is directly responsible for metabolic effects, increases. Observed changes in cortisol activity according to estrogens level is one of the explanations for variable response to stress in different moments of menstrual cycle. The same results have estrogens used as oral contraception [33]. Observed variations in release and activity of stress hormones make interpretation of studies on gender response to stress harder. It was also found that sex hormones influence on production, reuptake and metabolism of serotonin [34].

Further studies were taken to explore gender-related differences in alcohol dependence and PTSD. Direct effect of ethanol on HPA axis has been studied. Ethanol administered to laboratory animals caused increased release of ACTH; release was higher among females [35, 36]. This may explain why the risk for developing PTSD and depression after traumatizing stimuli is different among women – because of different functioning of HPA axis and different CRH release from extended amygdala [11, 28–30]. The animal model can explain differences observed in humans.

Treatment of patients with dual diagnosis

Access to psychiatric treatment for patients with dual diagnosis

Only 120,000 to 130,000 of nearly 800,000 alcohol dependents individuals start addiction treatment in Poland. This means that only one out of seven alcohol-dependent subjects begins therapy, not necessarily completing the program. Patients with alcohol dependence are the least likely treatment submitting group out of patients with mental disorders. The European Study of the Epidemiology of Mental Disorders of 2004 showed that only 8% of patients with alcohol use disorders were seeking medical advice or any form of treatment [37].

It was found that if other mental disorder coexists with alcohol dependence the probability of seeking medical advice is more than three times higher [38]. Unfortu-
nately, seeking for advice is not followed by more efficient treatment and by complex treatment. One of reasons for this fact is that patients with dual diagnosis often drop out from treatment programs. This may indicate difficulties with functioning inside treatment programs and the healthcare system. Despite the fact that patients with dual diagnosis more often visit specialists, got less benefit from treatment and frequently terminate it early [39]. The effectiveness of treatment depends on a time when it was started. When treatment is started on early stages of dependence, the effectiveness is better, patients suffer fewer complications and costs for health care system are reduced [39–41].

There are only a few treatment programs in Poland dedicated directly to alcohol dependent patients with other psychiatric disorders. In many regions of Poland, it is difficult to refer a patient to a clinic, in which both alcohol dependence and coexisting psychiatric disorders could be treated. Only few reports on effectiveness of dual diagnosis treatment program exist, while large group of this patients require such programs. Alcohol dependence cause large costs, and is one of the heaviest economic burdens among medical conditions [40]. In Poland, retail of alcoholic beverages brought to the budget around 16 to 18 billion PLN in 2011, while costs generated by alcohol abuse and dependence are estimated to reach 45 billion PLN per year. These costs cover expenses related to treatment programs, work absence, paid sick leaves, social benefits, law problems and traffic accidents [42].

Pharmacotherapy of patients with dual diagnosis

In most clinical trials assessing effectiveness of treatment for alcohol dependence researchers did not take into consideration dual diagnoses. Increasing popularity of this area brought many interesting facts regarding treatment of this specific, very demanding group of patients. Recent years of clinical research gave possibility to estimate potential efficacy of combined therapy for alcohol dependence and coexisting psychiatric disorder. Some very specific problems of dual diagnosis patients entering treatment programs were identified. Various authors underline issues with group therapy, where usually equal requirements are formulated both to patients with isolated addiction and to patients with dual diagnosis. Depressed mood and psychomotor retardation impair functioning and progress during group therapy. Both positive and negative symptoms in patients with schizophrenia also make therapeutic process less effective in groups where most patients are individuals with dependence only. Impairment of cognitive functions and disorganized thinking are strong barriers in seeking help among patients with dual diagnosis. Isolation in a therapeutic group decreases motivation to treatment [9]. Effective treatment of a comorbid disorder improves effectiveness of addiction therapy [9].
Pharmacotherapy of alcohol dependence in patients with dual diagnosis

Several medicines were investigated as adjuncts to psychotherapy for treatment of alcohol dependence. Effectiveness of disulfiram, acamprosate and naltrexone in reduction of risk of relapse and promotion of abstinence were studied. Nalmefene was investigated as an agent used to reduce amount of alcohol consumed, in a paradigm of harm reduction. Nalmefene is a drug used as a part of new strategy of treatment proposed to patients who are not interested in or cannot maintain abstinence.

Disulfiram is used in treatment of alcohol dependence for more than 50 years [43]. It blocks aldehyde dehydrogenase – the enzyme that takes part in ethanol metabolism. Inhibition of metabolism at this level leads to accumulation of acetaldehyde causing such symptoms as nausea, vomiting, headaches, vertigo and red flushes. Patients taking disulfiram maintain abstinence because they are afraid of these symptoms. A multicenter trial performed in the United States showed that disulfiram is equal to placebo. The key in disulfiram treatment is patient’s attitude towards treatment, level of motivation to treatment, and compliance with therapist. There is subpopulation of patients for whom alcohol craving along with a fear of intoxication due to disulfiram brings motivation to quit medication and continue drinking [44]. Next interventions were taken to increase effectiveness of disulfiram. It was more effective when taken under supervision, administered by close relatives and there was a written contract to take drug according to doctor's prescription [45–47]. After controversial observations made in 60s and 70s suggesting that disulfiram may exacerbate depression, mania and psychosis [48], a research study on patients with dual diagnosis was performed. The final conclusion was that dose of 250 to 500 milligrams per day do not worsen co-occurring disorders and disulfiram may be safely prescribed to patients with dual diagnosis [49]. Disulfiram may give small elevation of serum concentration of antipsychotic agents and antidepressants, which is usually clinically irrelevant [48]. Current recommendations suggest caution when disulfiram is prescribed to patients on antipsychotic medication and antidepressants.

Naltrexone is antagonist of opioid receptors. Its effects are based on antagonizing effect of endogenous opioid release after ethanol intake. Randomized, double blinded trials on 70 [50], 97 [51], and 131 alcohol-dependent patients were conducted to assess effectiveness of naltrexone [52]. It was found that naltrexone used as an adjunct to psychotherapy reduced craving, decreased amount of daily alcohol consumed, reduced drinking days, reduced heavy drinking days and risk of relapse. Naltrexone reduced alcohol craving and limited positive feedback for drinking. Stimulation of reward centre was decreased by naltrexone. This caused tested individuals to be less willing for the next drink and the risk for heavy drinking was reduced [50–52]. Another trial did not find naltrexone to be effective in treatment of alcohol dependence [53]. Other research investigated naltrexone treatment in alcohol-dependent patients with schizophrenia. Naltrexone did not exacerbate symptoms of schizophrenia and did...
not deteriorate course of the disorder [54]. There was no difference in adverse effects caused by naltrexone administration between patients with alcohol dependence only and population with dual diagnosis [55]. Patients with co-occurring bipolar disorder, schizophrenia and schizoaffective disorder responded to naltrexone treatment by reducing alcohol consumption and decreasing rates of dropouts from therapeutic programs [56]. Published data is promising, but further studies are needed.

The mechanism of action of acamprosate is probably based on the impact on glutamatergic NMDA receptors. Its effectiveness in maintaining abstinence confirmed in Multicentre European research using a placebo [57]. Authors of reports also postulate that acamprosate relieves withdrawal symptoms [57].

Multicenter European trials ESENSE I, ESENSE II and SENSE showed that nalmefene reduced amount of ethanol consumed in patients with alcohol dependence. To these trials high percentage of patients was recruited, for whom it was the very first treatment, what indicates a big need for treatment in this group of alcoholics. Investigated patients reduced alcohol consumed during administration of nalmefene and continued to drink less during the period of observation without taking nalmefene. It was found that patients treated with nalmefene had less heavy drinking days ( > 60 gram per day – man, and > 40 gram per day – woman). Nalmefene was superior to placebo [58].

Pharmacological treatment of alcohol-dependent patients becomes individualized. Dividing this highly heterogenous group of patient into subgroups (e.g. according to Lesch, Cloninger, Babor typologies) gives a chance to find specific patients who may benefit from particular treatment. It is possible that confusing results of trials are strongly due to the heterogeneity of enrolled patients. In the Lesch typology proposed certain medicines characterized by the highest proven efficacy in the treatment of different groups with similar characteristics [8]. To prevent relapse, LAT I patients should be offered disulfiramor acamprosate as an adjunct to psychotherapy. For LAT II patients, acamprosate and antidepressants are suggested; moclobemide and trazodone are also agents with proved effectiveness. It may be interesting that authors of LAT do not encourage LAT II patients to attend Anonymous Alcoholics meetings.

Patients classified as LAT III should be treated with naltrexone supported by psychotherapy. Best results in relapse prevention described at LAT IV patients are also reached with naltrexone (table 1). Because of limited space, psychotherapy, which is still a basis of treatment for alcohol dependence, will be not discussed.
Table 1. **Pharmacological methods recommended for relapse prevention in Lesch types of alcohol dependence.**

<table>
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<tr>
<th>Lesch type (LAT)</th>
<th>Pharmacological methods recommended for relapse prevention</th>
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<tr>
<td><strong>Type I (LAT I) – “Allergymodel”</strong>&lt;br&gt;high component of physical addiction&lt;br&gt;alcohol consumption is the way to avoid or to mitigate alcohol withdrawal symptoms&lt;br&gt;characteristic sequence of clinical history: harmful drinking and continue through abuse into fully developed alcohol addiction</td>
<td>Disulfiram&lt;br&gt;Acamprosate</td>
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<td><strong>Type II (LAT II) – “Conflict Resolution and Anxiety Model”</strong>&lt;br&gt;alcohol is a way of problem and conflicts solving&lt;br&gt;frequent with low self-esteem, dominated by life partners, having difficulties to articulate personal needs&lt;br&gt;alcohol consumption makes dependents offensive&lt;br&gt;aggressive and auto aggressive behaviour are common</td>
<td>Acamprosate&lt;br&gt;Antidepressants (efficacy of moclobemide and trazodone was confirmed)</td>
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<tr>
<td><strong>Type III (LAT III) – “Depressive Model”</strong>&lt;br&gt;this group uses alcohol as mood enhancer and to relieve sleep problems&lt;br&gt;after short period of recovery, depression and anxiety relapse&lt;br&gt;more frequent in women&lt;br&gt;frequent co-occurrence with depression and addiction&lt;br&gt;auto-aggressive and aggressive behaviours, emotional liability present&lt;br&gt;treatment for affective disorder is essential</td>
<td>Naltrexone</td>
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<td><strong>Type IV (LAT IV) – “Conditioning Model”</strong>&lt;br&gt;CNS lesions appearing in childhood as a result of adverse impacts during development are believed to be crucial for the progress of addiction&lt;br&gt;excessive impulsivity and behavioural disorders are observed in adolescence&lt;br&gt;no criticism for addiction&lt;br&gt;patients follow the pressure of environment to drink&lt;br&gt;due to primary CNS lesion patients are vulnerable to alcohol toxicity&lt;br&gt; frequent seizures&lt;br&gt;cognitive impairment is enhanced by alcohol&lt;br&gt;higher percentage of males comparing to general population of alcohol addicts</td>
<td>Naltrexone</td>
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Pharmacotherapy of coexisting psychiatric disorders in alcohol-dependent patients

**Antidepressant treatment.** Despite many research programs describing co-occurrence of depression with alcohol dependence, it is still difficult to manage this group of patients. Symptoms of these two medical conditions are overlapping and neurobiological background is partially common [59]. Because of that, treatment of depression in alcohol-dependent patients is challenging. The decision about medication should always be carefully considered. Potential interaction of antidepressants and alcohol is feared phenomenon. Risk for such situation is important step in planning therapy and advising a patient. Tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI) are best studied. The effectiveness of TCA in treating symptoms of depression was proved, but no effect on decreasing amount of alcohol consumed in this group was found [60]. Because of narrow therapeutic window, this group of antidepressants is not recommended for patients with dual diagnosis [60].

SSRIs are recommended as the first line treatment [61]. SSRIs are safe and well tolerated agents, which may be used safely in alcohol-dependent patients. Efficacy and toleration of tianeptine and fluvoxamine were compared in randomized, controlled trial among polish alcohol dependent patients with depression. Both drugs appeared effective, however tianeptine was better tolerated, with lower drop-out rate in comparison to fluvoxamine [62].

SSRI were found effective in treating symptoms of depression and in reducing amount of consumed alcohol in depressed individuals [63, 64]. Based on this observation it was postulated that SSRI decrease consumption of alcohol among patients with isolated addiction. Unfortunately, it has not been proven [65]. Pettinati et al. suggest that SSRIs may be effective in depression and drinking reduction only in some selected subpopulations of alcohol-dependent patients [66]. This group of drugs was also found to be effective in treatment of PTSD and decreasing ethanol consumption in dual diagnosis patients [67].

**Anxiolytic treatment.** Anxiety disorders in patients with dual diagnosis are treated mainly with SSRIs. There are no appropriately conducted trials to establish effectiveness and safety of SSRIs among alcohol-dependent patients with anxiety disorder. Benzodiazepines are highly effective in short-time treatment of anxiety, but use of benzodiazepines is strongly restricted and remains controversial in a group of already addicted. Alcohol-dependent individuals treated with benzodiazepines may develop cross-dependence, which complicates course of dependence and jeopardize treatment. Furthermore, benzodiazepines cause cognitive impairment and other neurological symptoms resulting from alcohol toxicity. Buspirone was found to be ineffective in treatment of anxiety disorder among alcohol dependent patients. Pilot study showed effectiveness, but this was no proved later. No clear evidence exists that buspirone may reduce alcohol consumption and anxiety symptoms [68].
**Antipsychotic treatment.** No guidelines supported by large trials concerning antipsychotic treatment among alcohol-dependent individuals exist. There are some data supporting the opinion that atypical antipsychotic drugs should be used first. These drugs have unique ability to decrease negative symptoms due to increasing dopaminergic transmission in mesocortical tracts by acting on serotonin system. Because alcohol is used to self-medicate negative symptoms by patients with dual diagnosis, atypical antipsychotics seem to be the best option. Clozapine was found to ameliorate psychotic symptoms and significantly reduced amount of alcohol consumed by dual diagnosis patients, probably through serotonergic transmission [69]. This effect was also found for quetiapine, but not for risperidone or olanzapine [70]. When choosing antipsychotic treatment several factors must be taken into consideration. For example, high risk for withdrawal seizures suggests treatment with risperidone rather than clozapine.

**Mood stabilizers.** Research on treatment with lithium among individuals with alcohol dependence and bipolar disorder showed limited efficacy [71]. It may be explained e.g. by course of bipolar disorder among addicts which is characterized by faster change of phases and more frequent occurrence of mixed episodes. Many adverse effect, narrow therapeutic range and need of blood level monitoring result in difficulties of lithium therapy among individuals with dual diagnosis [72].

It was found that patients treated with lithium because of depression decreased amount of consumed alcohol comparing to placebo group, while no reduction of depressive symptoms was observed [71]. Lithium was also investigated as treatment limiting alcohol consumption among addicts without diagnosed depression with similar results – lithium limited alcohol consumption. Further trials on lithium in relapse reduction showed no unequivocal results [71].

Because of faster phase change as well as more frequent presence of mixed episodes valproate was investigated and showed efficacy in reduction of affective disorders relapse among alcohol addicts [72]. Liver enzymes elevation in alcohol addicted patients treated with valproate was finally recognized as clinically irrelevant, despite fear at the beginning concerning possible accumulation of hepatotoxicity induced with alcohol and valproate and some clinical report on fatal liver injury [73].

Double blinded study with placebo showed that valproate reduced alcohol consumption among individuals with both bipolar and alcohol dependence disorder. Interestingly efficacy of treatment correlated with serum levels of valproate. Also level of gamma-glutamyl transpeptidase (GGTP) was reduced in the group receiving valproate comparing to placebo [74]. Study by Bonnet et al. showed valproate and topiramate to be effective in reducing of alcohol consumption among patients with coexisting bipolar disorder [75].

Carbamazepine is sometimes used to treat alcohol withdrawal syndrome in patients with coexisting bipolar disorder, although benzodiazepines are the first line of
treatment in such clinical situation. Some evidence was found that patients receiving carbamazepine to treat withdrawals maintained abstinence longer and consumed less alcohol during twelve days observation period [76]. Long time observation (120 days) of patients prescribed with carbamazepine to reduce relapse risk showed significantly longer time of abstinence. It was found that patients from carbamazepine group returned to drinking later than individuals from placebo group. Unfortunately in one-year observation time this results were found to be insignificant [77]. No final conclusion can be made when evaluating carbamazepine as treatment to limit relapse reduction in patients with alcohol dependence and bipolar disorder.

Small number of papers concerning efficacy of atypical antipsychotic drugs in dual diagnose patients can be found. Randomized controlled trial in a group of patients with bipolar disorder and alcohol dependence showed no reduction of both craving and alcohol consumption [78]. Other trial showed olanzapine to be effective in craving reduction but without influence on alcohol induced reward [79].

**Recapitulation**

The treatment of patients with alcohol dependence accompanied by other psychiatric disorders is complicated by organizational difficulties and by frequent lack of patients’ compliance [80] and poor social functioning [81]. Lack of spontaneous disclosing coexisting problems by patients is also significant issue in the clinical practice. Creating friendly atmosphere and commitment gives a chance for honest communication with a patient, which can lead to thorough psychiatric assessment and get a full clinical picture. All researchers studying dual diagnosis underline the fact that simultaneous treatment of alcohol dependence and co-occurring psychiatric disorders increases a chance to improve patients’ functioning. Inappropriate treatment without complete management of all existing problems may make full recovery impossible. In Poland, where alcohol abuse is a serious issue, dual diagnosis may be expected even in higher percentage of patients comparing to the Western Europe. Authors hope that as number of patients with dual diagnosis increasing, development of clinics running dedicated programs is only a matter of time. Kandel proposed independent treatment programs for patients with dual diagnosis. He suggested separated treatment setting with cooperation with previous therapeutic community, but dedicated to that type of patients [82].

**References**


11. Anthenelli RM. *Sex differences in the stress hormone response to the combined dexamethasone-corticotropin-releasing hormone (Dex-CRH) stimulation test*. San Diego, California: Alcohol Stress Interest Group, 32nd Annual Scientific Meeting of the Research Society on Alcoholism; 2009.


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