Pharmacological Treatment Options for Alcohol Use Disorder*

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PHARMACOLOGICAL TREATMENT OPTIONS FOR ALCOHOL USE DISORDER

Alcohol Use Disorder (AUD) and other alcohol-related health problems are a significant public health issue all over the world. The World Health Organization (WHO) reports that each year 3.3 million people lose their lives due to harmful alcohol use, with 5.9% of all deaths being related to alcohol consumption (1). It has been estimated that in 2010, the economic burden of alcohol-related costs was 155.8 billion Euro, of which 60% were connected to alcohol addiction (2).

In AUD, after the end of the withdrawal phase, when having reached a state of abstinence, the main aim is to maintain this abstinence by reducing craving and preventing relapse (3). During treatment, especially all severe cases of AUD need to be assessed from the angle of pharmacologic therapy. Drugs licensed for the treatment of AUD, worldwide as well as in Turkey, are disulfiram, acamprosate, naltrexone, and nalmefene. Long-term release naltrexone has not yet been approved in Turkey. Nalmefene, licensed in Europe and Turkey, has recently (November 2014) been approved for reducing the amount of alcohol consumed in AUD (4-6). In some European countries, baclofen and sodium oxybate have been approved (7,8). In this paper, we

assess information obtained from studies regarding drug treatments used in clinical practice today, which are summarized in Table 1. However, when examining study results for pharmacological treatments, we immediately have to remember that all of those

Table 1: Drugs used for the therapy of alcohol use disorder (AUD)

Drugs for AUD approved in Turkey

- Disulfiram
- Naltrexone
- Acamprosate
- Nalmefene

Drugs approved in some European countries

- Baclofen (Temporary recommendation of use in France)
- Sodium oxybate (Austria, Italy, and France)

Drugs at research stage for AUD

- Anticonvulsants
- Varenicline
- Ondansetron
- Dopamine receptor antagonists
- Selective serotonin reuptake inhibitors
- Memantine
- Kudzu
- CB1 receptor antagonists
- CRF1 antagonists
- Finasteride, mifepristone
- Prazosin
- Metadoxine
- Ghrelin antagonists

treatments need to be used together with psychosocial support; in particular, it should be recommended that patients be placed in a psychosocial support program suitable to them individually for the duration of therapy.

APPROVED PHARMACOTHERAPIES FOR ALCOHOL USE DISORDER

Acamprosate

Acamprosate is a synthetic glutamate N-methyl-D-aspartate (NMDA) receptor antagonist, approved by the Turkish Health Ministry in 2003 and by the FDA in 2004 (9). Acamprosate blocks the extracellular dopamine increase in the Nucleus accumbens (NAc) (10) and plays a protective role against neurotoxicity during alcohol withdrawal (11).

A number of systematic reviews and meta-analyses agree that acamprosate is effective in the prevention of relapse after detoxification (12-17). Among these studies, the National Institute for Health and Clinical Excellence (NICE) (18) found a relative risk (RR) value of 0.83 (95% confidence interval [CI]=0.77-0.88), while Rösner et al. (12) report an RR of 0.86 (95% CI=0.81-0.91). The number needed to treat was calculated as 9-11 (12,13). The rate of withdrawal from treatment because of side effects was higher in acamprosate users compared to placebo, but the difference was not statistically significant (18).

According to one meta-analysis, acamprosate is an effective drug for all AUD patients irrespective of gender, starting age, family history, presence of anxiety, and intensity of craving and dependence (19). However, there are studies showing genetic and individual characteristics playing a role in the response to acamprosate. For example, it is thought that variations in the N-methyl-D-aspartate (NMDA) mGluR5 receptor affect the response to acamprosate (20). In addition, the intronic single nucleotide polymorphism (SNP) rs13273672, coded by the GATA4 (GATA binding protein 4) gene, is reported to be related with relapse in acamprosate users (21). Furthermore, a study researching SNPs and duration of abstinence reported a correlation for GRIN2B rs2300272, rs2058878 and most strongly rs2058878 (22).

It has been reported that acamprosate is more beneficial in patients experiencing relief craving related to irregularities in the gamma-aminobutyric acid (GABA) and glutamate systems (11,23). A recent study showed that acamprosate is more effective in patients who at the beginning of treatment had a high serum level of glutamate (24). Further, it is seen that acamprosate is more effective in Lesch type I and type II alcohol dependents than in type III and type IV (25). It has been pointed out that acamprosate is beneficial especially in Lesch type I alcohol dependents, while there was no correlation between craving and acamprosate response (26).

Acamprosate is more effective in patients whose therapy goal is total abstinence than in those who aim at reducing their drinking without total abstinence (17,27). Given that drug interaction is very low, it is suitable for patients who are using further drugs for other diseases, and it can be administered to patients under opioid analgesic treatment (28). As it is excreted by the kidneys unchanged, there is no risk of hepatotoxicity, but it should not be used in patients with a high degree of kidney insufficiency (creatinine clearance <30ml/min) (29). The drug may however be used in patients with compensated cirrhosis (30).

Acamprosate is formulated in tablets of 333mg. Due to its low bioavailability, it needs to be administered in high doses (for persons below 60kg 1332mg, above 60kg 1998mg) (9,31). Most commonly observed side effects regard the gastrointestinal system. Less common are stomach ache, rash, itching, paresthesia, changes in libido, confusion, and suicidal ideation (27,37). Therapy can continue for between 3 and 12 months (18,27,33,34). The most appropriate strategy is a joint decision about the duration of therapy by doctor and patient according to the observed side effects, relapse history, and social and familial characteristics.

Naltrexone

Naltrexone is an unspecific opioid receptor antagonist. It particularly blocks the μ-opioid receptors, leading to a reduction of the increase in dopamine occurring after the use of alcohol and thus reducing its

rewarding effect (18,35). Blocking the dopaminergic effect of the endorphins secreted after alcohol use, it reduces the stimulating and positively enhancing effect of alcohol. Further, it increases the sedative effect of alcohol and reduces alcohol craving (36).

Naltrexone was approved in 1994 for use in alcohol dependence (28). The evidence for its effectiveness in AUD is of level A (31). Naltrexone reduces the relapse rate in AUD and lengthens the abstinence period. Meta-analyses show that it reduces the relative risk, compared to placebo, by 36%. On average, the number needed to treat is 7, which indicates a moderate effect size (27). Naltrexone has also been shown to reduce craving and frequency of drinking after relapse. It is more effective in reducing intensity and rate of relapse than in extending the period of abstinence (27). One meta-analysis showed that in short-term treatment (12-16 weeks) jointly with psychotherapy, 50 mg naltrexone was clinically highly beneficial in maintaining abstinence, while the safety profile was similar to that of a placebo (37).

A meta-analysis of 19 studies found that complete abstinence was reached more frequently in the naltrexone group, but the difference was not statistically significant (14). However, among the naltrexone users the period until relapse was longer, the number of drinking days, number of drinks consumed per day, total amount of alcohol consumed during the treatment, as well as the gamma-glutamyl transferase (GGT) and aspartate aminotransferase (AST) levels were lower (14).

Naltrexone is more beneficial for patients wanting to prevent relapse to heavy drinking and high alcohol intake rather than for those aiming at abstinence (17,27). Further, it was shown that naltrexone is more beneficial in patients experiencing a high level of craving during therapy (38-41), those with a family history of AUD (41-43), and for heavy drinkers (44). It is also thought that the μ-opioid receptor polymorphism affects the response to naltrexone therapy (45). In carriers of the "G" allel, it has been reported that SNP (rs179919 or A118G) on the μ-opioid receptor correlates with a better response to naltrexone (46).

It is assumed that naltrexone is more beneficial in patients experiencing "reward craving" related with the dopamine and opioid system (23). Naltrexone is more successful in Babor type-A alcohol dependents (less severe, late-onset, no family history, fewer psychiatric comorbidities) compared to type-B (47). It has been reported that patients with depression at the beginning of the therapy and Lesch type III and type IV dependents respond better to naltrexone (26). According to Cloninger's typology, early-onset type 2 alcohol dependents with more serious alcohol-related problems and comorbid psychopathologies benefit more from naltrexone than type 1 dependents (48).

For patients with comorbid opioid use disorder and AUD, naltrexone is a favorable therapeutic option in order to reduce the craving for either substance. However, for patients continuing opioid use or requiring opioid analgesic treatment, it is not a suitable drug (28). It also may not be used with acute hepatitis, liver insufficiency, or in patients with a history of hypersensitivity to naltrexone (29).

It is recommended to wait until the decline of withdrawal symptoms, 3 to 7 days after the patient had the last drink, to start naltrexone treatment (27). Recommended therapeutic dose is 50mg/day (18). While naltrexone is usually well tolerated, in 10% of the patients emesis, headache, dizziness, malaise, irritability, insomnia, or anxiety can be seen (27). More rarely, chest pain, muscle and joint pain, loss of appetite, constipation, rash, insomnia, increased thirst, depression, or delayed ejaculation can be found (29,49). While hepatotoxicity has been reported in high doses (300mg/day), this effect is rare in the recommended dose of 50mg/day (50). It is recommended to continue the drug for 3-6 months, but the best course of action is to decide about the duration of treatment jointly with the patient (18,34).

Intramuscular Naltrexone

To increase compliance and bioavailability, in 2006 the FDA approved intramuscular (IM) naltrexone, but in Turkey, this form has not yet been licensed. The FDA-licensed IM form contains 380mg and the recommended application rate is once per month (28). An open cohort study showed IM naltrexone to be useful in the first

stage treatment for maintaining abstinence (51). In addition, the rate of IM-naltrexone-users continuing the therapy was higher than among patients using oral naltrexone, acamprosate, or disulfiram (52). IM naltrexone did not reduce the risk of heavy drinking; however, it increased the total number of days of abstinence, and the number of patients remaining abstemious for 12 weeks was twice higher (53). The side effect profile of the IM form, apart from reactions to the injection, looked similar to that of the oral form (54).

Combination of Naltrexone and Acamprosate

A meta-analysis of 64 studies concluded that acamprosate is more effective in reaching abstinence and naltrexone in reducing heavy drinking and craving (17). It could be assumed that a combined use of these two drugs with their different target neurotransmitters and modes of action might be clinically more beneficial. A randomized double-blind placebo-controlled study by Kiefer et al. (55) did not find that a combined use of the two drugs produced better results in the prevention of relapse compared to the single use of naltrexone. Therefore, it has been said that naltrexone can be added to the treatment if the desired effects of acamprosate are not seen (33). The combination of the two drugs is safe, the most frequently seen side effects being diarrhea and nausea (33,56).

Even though so far there is no study investigating the safety and efficacy of a combination of acamprosate and nalmefene, given the similarity with naltrexone and the fact that the drug does not affect the liver, it can be assumed that nalmefene can be used as supplement to acamprosate when needed or on a regular basis.

Disulfiram

Disulfiram blocks the enzyme aldehyde dehydrogenase that converts acetaldehyde to acetate in the second step of alcohol metabolism. In case of alcohol intake, acetaldehyde accumulation leads to symptoms like nausea, emesis, dizziness, flushing, headache, diarrhea, shortness of breath, and cardiac arrhythmia. This effect is a deterrent for people who

know that they are bound to encounter these negative effects if they consume alcohol. Disulfiram is effective especially when taken under supervision (57,58).

As the side effects of disulfiram when taken with alcohol can be life threatening, most of the relevant studies have been carried out as open label, in which the patients and doctor knew which drug was being used. This fact reduces the reliability of the data (18).

There are studies showing that disulfiram increases the number of days to relapse compared to naltrexone, acamprosate, and topiramate (59-61). It has also been shown that disulfiram used for 12 weeks not only extends the time until first alcohol intake compared to naltrexone and acamprosate, but it also reduces the number of days of heavy drinking (62). In the meta-analysis by NICE (18), it is reported that disulfiram is not different from placebo for relapse to alcohol use, while the study by Brewer et al. (63) reports that disulfiram taken under supervision increased compliance with treatment and reduced drinking in comparison with taking disulfiram without supervision or with the control group not taking disulfiram. Another systematic review reported that disulfiram in the short term was more effective than placebo in maintaining abstinence, increasing duration till relapse and number of days drinking (64).

Because of its lower level of safety, disulfiram was suggested to be considered as a second-stage treatment (31,65) that can be used together with naltrexone or acamprosate (31). It has been reported that disulfiram used daily under supervision together with acamprosate is more effective than acamprosate on its own (66). The combination of naltrexone and disulfiram has been studied in patients with comorbid psychiatric diseases; however, for this drug combination no advantage compared to the single use of naltrexone or disulfiram was found (67-69).

Disulfiram is not a suitable option for patients with impaired judgment, high-level of impulsivity or self-harm, severe cardiac, hepatic, or respiratory problems (27). As one of the metabolites of disulfiram blocks dopamine beta-hydroxylase, which converts dopamine into norepinephrine, it can aggravate symptoms in patients with psychotic disorder (28,70).

Disulfiram is formulated in 500mg tablets, and the

recommended daily dose is 250-500mg (27). It is suggested to start disulfiram at least 24 hours after stopping alcohol consumption (18). Cross-reaction with more than 40 drugs, including benzodiazepines, isoniazid, rifampin, metronidazole, warfarin, oral hypoglycemics, phenytoin, theophylline, tricyclic antidepressants, and desipramine need to be considered (29,71). Light side effects are feeling of dizziness, headache, fatigue, acneiform eruptions, impotence, and alterations in taste sensations (29,72). More rarely seen more serious side effects are icterus, hepatitis, peripheral neuropathy, psychosis, confusion, optic neuritis, and blood dyscrasia (27,28). During disulfiram treatment, cardiac and hepatic side effects need to be closely monitored (29). It is recommended to continue the therapy for 3-6 months, but the best way is to decide about the duration of treatment with the patient, depending upon personal characteristics (18,27,34).

Nalmefene

Nalmefene is used to reduce alcohol consumption in adult alcohol addicts with a high "drinking risk level" who do not show physical withdrawal symptoms and do not require urgent withdrawal treatment. Detailed information about nalmefene can be found in the section "Reduction of heavy drinking (harm reduction)" below.

OTHER PHARMACOTHERAPIES APPROVED IN THE COUNTRIES OF THE EUROPEAN UNION

Sodium Oxybate

Sodium oxybate, a form of gamma-hydroxybutyric acid (GHB), has been approved in some countries, such as Austria, Italy, and France, for use in alcohol withdrawal and AUD (73). It is thought that sodium oxybate reacts like alcohol, reducing symptoms of craving and withdrawal (74). However, 30-40% of patients do not respond to GHB treatment (75). For this reason, in one study GHB and disulfiram were used in combination, finding that the combination therapy increased the number of days staying in treatment and

the number of days of abstinence compared to GHB therapy on its own (76). However, especially in patients with psychiatric comorbidities and other substance use disorders, sodium oxybate craving and sodium oxybate abuse were observed (77). In view of these risks, this therapy cannot be recommended commonly in the first stage of AUD treatment (78), but it is indicated for use under close supervision in patients who are able to comply with the dosage recommendations (79).

Baclofen

Baclofen is a GABA-B receptor agonist approved for the treatment of spasticity (80) with anxiolytic effect (81). In France, Baclofen has a temporary license for reduction of alcohol consumption and reaching abstinence (8).

It seems to be effective in maintaining abstinence, reducing craving (82,83), and reducing amount of alcohol and anxiety in patients who are unable to maintain abstinence (82). In a placebo-controlled double-blind study, alcohol consumption declined in each of three groups: those taking 30mg and 60mg baclofen, respectively, or placebo, but there was a significant difference between the groups (84). A placebo-controlled study by Garbutt et al. (85), while not showing a positive effect of baclofen on craving, abstinence, or amount of alcohol, demonstrated a reduction of anxiety scores. As it is known that baclofen is more effective in populations of severely addicted patients, the fact that Garbutt et al. (85) included patients at a lighter level might be related to the negative results (81). Even if results regarding the effectiveness of baclofen are mixed, it is seen as a safe drug to use in AUD patients, even with cirrhosis (78,83).

PPHARMACOTHERAPIES THAT HAVE ACHIEVED FAVORABLE RESULTS IN STUDIES BUT HAVE NOT BEEN APPROVED

Even without approval for use in AUD, some drug therapies are being used in clinical application. With an increase in studies regarding these therapies, available data are growing, and assessments of their effectiveness can be made more explicitly.

Anticonvulsants

It is assumed that **topiramate**, an AMPA-glutamate antagonist, reduces the rewarding effect of alcohol by blocking dopamine activity in the mesolimbic cortical area (86). A systematic review of seven randomized controlled studies showed that topiramate has the greatest effect on abstinence, observing a reduction in heavy drinking, while no effect on craving was found (87). A double-blind placebo-controlled study showed that topiramate reduced the amount of alcohol consumed by heavy drinkers on drinking days and the craving during the drinking period but was not effective regarding craving outside drinking periods (88). However, there are also studies that have not found topiramate to be effective in AUD (89). Topiramate has no FDA license for AUD, but the National Institute on Alcohol Abuse and Alcoholism (NIAAA) supports its use on the basis of strong evidence (50).

Gabapentin is an anticonvulsant inhibiting excitatory Ca ion channels and stimulating inhibitory GABA-B receptors (90). A systematic review reached the conclusion that gabapentin reduces heavy drinking but is not effective regarding abstinence, craving, and GGT (91). Another 12-week placebo-controlled study not included in the review, however, showed that gabapentin increased the abstinence rate and reduced heavy drinking (92). The same study showed that the positive effect of 1800mg/day gabapentin on craving, insomnia, and dysphoria was better than with 900mg/day, concluding that gabapentin, especially at a daily dose of 1800mg, could be a treatment option (92).

It has been reported that **carbamazepine** reduces the alcohol amount consumed on drinking days and extends the period to the first drink in abstinent patients (93,94). Studies with **valproate** also predict a prevention of relapse into heavy drinking and support of abstinence (95,96). It has also been seen that the use of valproate together with lithium in patients with bipolar mood disorder and AUD reduces the amount of alcohol used on drinking days (97). Soyka et al. (31) assessed these studies and proposed a level of evidence of C for carbamazepine and D for valproate. It has been reported that **oxcarbamazepine**, especially at high doses of around 1500-1800mg/day, is effective in maintaining abstinence (98). It is thought that the anticonvulsant topiramate is more beneficial in patients experiencing compulsive craving, while gabapentin is more useful in persons experiencing relief craving (99).

Varenicline

Varenicline has been licensed by the FDA for treating nicotine use disorder (100). It has been reported to have a potential for reducing the amount of alcohol used by increasing the negative effects of alcohol and reducing the rewarding effects (101) and reducing craving (102). A systematic review showed a moderate effect size of varenicline therapy (103). In 4 studies (100,104-106), a reduction of alcohol use with varenicline was observed, while in another study, a reduction of alcohol use was only reported in a group of smokers (107). In the light of these studies, we may assume that varenicline does not so much inhibit first use of alcohol but rather reduces cumulative alcohol consumption after first use (100,102,104-106).

Ondansetron

Ondansetron is a selective 5-HT3 receptor antagonist used in the treatment of nausea. Studies with ondansetron have shown a reduction in the amount of alcohol used and a longer remission in persons with early-onset AUD (108). In addition, a polymorphism in the starting region of the serotonin carrier gene has been shown to affect the response to ondansetron, and in carriers of the long LL allele, ondansetron reduced the amount of alcohol used (109). Another experimental study reported that ondansetron might reduce alcohol consumption in women with the LL 5-HTTLPR genotype, while it was not effective in women with the SS/SL 5-HTTLPR genotype (110). It has been pointed out that ondansetron is more beneficial in persons experiencing reward craving (99).

Dopamine Receptor Antagonists

It is known that the dopamine D2 receptor antagonist **haloperidol** reduces alcohol craving, the amount of alcohol used, and impulsivity (111); however, because of side effects, the use of classic antipsychotics in AUD therapy is limited (112).

In a double-blind comparative study, it has been reported that **aripiprazole** reduces craving (113). It was found to be as effective as naltrexone regarding relapse rate and number of days keeping up abstinence, but naltrexone reduced craving more than aripiprazole (114). Another randomized controlled trial did not find any difference between aripiprazole and placebo regarding number of abstinent days, rate of heavy drinking days, and period until first drinking, but it found the amount of alcohol consumed per drinking day and the severity of alcohol dependence at the end of the study to be reduced more than in the placebo group (115). It has also been shown that a 14-day use of aripiprazole reduced the response to alcohol-related stimuli in the right ventral striatum (116).

The abstinence period was longer in AUD patients who were using **quetiapine** for insomnia (117). The drug also reduced craving, total amount of alcohol used, and severity of psychiatric symptoms in patients with comorbid mood disorder and schizophrenia (118). In addition, it has been shown to reduce craving in persons with Babor type B alcohol dependence (119). Long-release form of quetiapine, however, has been found to be ineffective in the reduction of craving or prevention of heavy drinking (120).

A randomized controlled study demonstrated that a single dose of **olanzapine** reduced desire to drink and loss of control after alcohol-related stimuli (121). It was found that the use of 5mg olanzapine for 12 weeks reduced craving, while 2.5mg olanzapine reduced the number of drinking days and increased the control over alcohol drinking (122). In persons who were homozygous or heterozygous with seven or more repeats of the DRD4 repeat allele, olanzapine reduced alcohol consumption and craving, whereas in patients with a shorter allele, no benefit of olanzapine was found (123).

Finally, even if data regarding dopamine receptor antagonists are not entirely consistent, it can be said that these substances can be beneficial especially in AUD patients with comorbid psychiatric conditions (112).

Selective Serotonin Reuptake Inhibitors

Selective Serotonin Reuptake Inhibitors (SSRI) are used frequently in AUD patients to reduce signs of depression and anxiety. While the first studies showed that the SSRI **fluoxetine** reduced craving and heavy drinking (124), a later placebo-controlled study demonstrated that in patients without depression, fluoxetine had no effect on drinking (125). Another study showed that fluoxetine reduced craving but had no effect on drinking (127). It has been shown that **sertraline** is beneficial for Babor type B alcohol dependents (125,127). An experimental study found that sertraline reduced alcohol consumption in women with an SS/SL 5-HTTLPR genotype but was not useful in women with an LL 5-HTTLPR genotype (110). A randomized controlled trial found **fluvoxamine** ineffective regarding alcohol-related therapeutic aims (128).

It has been found that SSRI are more beneficial in persons experiencing obsessive craving (99). However, SSRI are not recommended as first-stage agents in AUD, but in case of additional depression or anxiety disorder, their usefulness has been established (71).

Kudzu

Kudzu is a plant used in Chinese herbal medicine; while its mode of action is not entirely known, it is thought to be operating through the aldehyde dehydrogenase of monoamine oxidase-acetaldehyde pathways (129). It causes a rapid fall in blood alcohol level after alcohol use, greater access to alcohol for the central nervous system, and an increase of alcohol-related reward from the first drink (130). In a double-blind, placebo-controlled 4-week study, kudzu reduced the amount of alcohol used in heavy drinkers (131). There are also studies showing that after 7 days of using kudzu, the amount of alcohol used in a laboratory setting is reduced (132,133).

Other Therapies

CRF antagonists and drugs affecting neuropeptide Y are still under investigation in AUD therapy (78). In particular, it has been shown that CRF-1 antagonists may have positive effects in anxious alcoholics (134). The steroid secretion inhibitor **finasteride** and the progesterone antagonist **mifepristone** reduced alcohol consumption in animal models (135). Additionally, in humans, the use of finasteride reduced alcohol consumption (136), and mifepristone reduced the amount of alcohol used in the short term (137).

The alpha-1 adrenergic antagonist prazosin has been reported to reduce the quantity of alcohol used after exposure to stress and to decrease anxiety (138) and, according to a different study, craving (139). It is believed that prazosin is effective especially in the presence of post-traumatic stress disorder comorbidity (140,141).

Metadoxine (pyridoxine-L-2-pyrrolidone-5-carboxylate) accelerates the urinary excretion of ethanol and acetaldehyde (142) and can lead to a reduction of certain biological indicators of alcohol-related liver damage (143). It has been shown that metadoxine users remain longer in therapy and abstinence periods are longer (144).

In animal models, **CB1 receptor antagonists** reduced the rewarding effect of alcohol and the amount consumed (145). However, studies with humans usually produced negative results (146,147). Considering the hyperglutamatergic state seen in AUD, it was thought that the NMDA receptor antagonist **memantine** could be useful (50); however, in comparison with placebo, memantine showed no advantage (148-150). Based on studies showing that basal ghrelin levels are correlated with alcohol craving (151), research about the uses of **ghrelin antagonists** in AUD therapy is still ongoing (50).

REDUCTION OF HEAVY DRINKING (HARM REDUCTION)

The logic of a strategy of harm reduction is based on the expectation that even a small reduction in the quantity of alcohol used will reduce the disease burden (152) and with the patient's self-selected treatment goal the treatment outcome will be better (153). It is reported that 78.1% of persons abusing alcohol or being dependent to alcohol are not seeking any kind of therapy (154,155). One of the reasons for avoiding therapy is that some people may want to reduce the amount of alcohol used but are not inclined towards total abstinence (156). To choose harm reduction as a treatment goal can be a important step that may lead to an internalization of consuming less alcohol, possibly leading towards total abstinence (157).

One of the aims of a harm reduction strategy is to reduce heavy drinking. The WHO reports a global rate of 16% for heavy drinking, whereas in Turkey the rate is 0.2% (158). However, the scales used for the concept of heavy drinking differ between various studies. The National Institute on Alcohol Abuse and Alcoholism, NIAAA defines as heavy drinking if women consume more than 4 standard units in a single session and men more than 5 standard units (159). The WHO proposes a measure of more than 60gr (7.5 standard units) ethanol intake for men and more than 40gr (5 standard units) for women to be considered as heavy drinking (160). The Centers for Disease Control and Prevention define the weekly consumption of over 14 standard units by men and over 7 standard units by women as heavy drinking (161), while the Substance Abuse and Mental Health Services (SAMSHA) define as heavy drinking if someone in the previous 30 days consumed 5 or more units in one session on 5 or more days (28).

Nalmefene

Nalmefene was the first drug licensed for reduction of alcohol consumption (162). In the European Union, it is approved for AUD, while in the United States of America approval has not yet been granted (50). In Turkey, it was licensed for use in AUD in November 2014.

Nalmefene is an opioid receptor antagonist like naltrexone. In contrast to naltrexone, it has a partially agonistic characteristic at the kappa-opioid receptor, the dose-dependent hepatotoxicity is lower than that of naltrexone (50), and the bioavailability is higher (163).

Two double-blind placebo-controlled studies with nalmefene have shown that the drug reduces heavy

drinking and prevents relapse to heavy drinking (164,165). Another double-blind placebo-controlled study reported that nalmefene is effective and safe for reducing heavy drinking and in addition leads to a reduction of liver enzymes (166). In one study, administration of nalmefene alongside motivational therapy was not found to be superior to placebo (167). Reasons for this result may be that the participants during the study were in an abstinent period, 3 different dosage patterns were applied (5mg, 20mg, and 40mg); the number of participants in each group was low and the monitoring period was short, and because of a rapid dose titration, there may have been an increase in side effects (167).

In three randomized controlled trials carried out recently (ESENSE 1, ESENSE 2, SENSE), the patients were advised to use nalmefene "as needed", when they felt at risk, and this treatment strategy was applied jointly with the "BRENDA" psychosocial support program. The result of these studies indicated that nalmefene reduced the number of days with heavy drinking as well as the total amount of alcohol consumed, and it also helped improve liver enzyme levels (168-170). In a post-hoc analysis of two of these studies (168,169), it was seen that nalmefene used in the 6th month reduced the amount of alcohol and the number of drinking days (171), and the effect was greater in the group of patients whose alcohol intake had not yet been reduced at the beginning of the treatment (171). Further, it has been reported that nalmefene reduces craving after the first alcohol intake in alcohol dependents who are not seeking treatment (35).

Nalmefene is formulated in 18mg tablets. In all studies, it was found to be safe and well tolerated (164,166,168,169,171,172). There is no difference between regular and intermittent use of nalmefene regarding toleration and safety (173). Most commonly found side effects are nausea, fatigue, headache, insomnia, and a feeling of hangover (167,168), but most of the side effects occur at the beginning of treatment and are temporary (173). No recommendation for the required duration of the nalmefene treatment could be found. Given that at the end of the 1-year SENSE study (170), nalmefene was shown to reduce alcohol amount and number of heavy drinking days we may assume that nalmefene is effective for at least 1 year.

In the light of these studies, it can be assumed that nalmefene is beneficial for reducing the disease load caused by AUD and to close the therapy gap. It seems that nalmefene, in concert with continuous psychosocial support, is an effective treatment strategy for alcohol dependents and high-risk alcohol users who have no physical withdrawal symptoms and do not require urgent withdrawal treatment for the reduction of alcohol use (174). It has also been pointed out that the combination of nalmefene and psychosocial support offers positive outcomes in a cost-benefit analysis as an advantageous and appropriate treatment from the perspective of public health (175).

The only pharmacotherapy approved for the reduction of alcohol use is nalmefene. Thus, it is the drug to be used for the treatment goal of reducing heavy drinking. Considering the importance of harm reduction strategy, role of other drugs, some with approval for AUD and some without, in heavy drinking have been studied. For those drug therapies, below we are assessing data regarding their effectiveness in reducing heavy drinking. However, in order to be able to assess the effectiveness of those therapies in harm reduction strategy, more studies are required.

Naltrexone

Naltrexone is more effective in reducing heavy drinking and reaching controlled drinking than in maintaining abstinence (33). In one meta-analysis, with naltrexone 38% less relapse into heavy drinking was reported (14). Based on 20 randomized controlled studies, it was reported that naltrexone reduces the risk of heavy drinking (RR=0.83, 95% CI=0.76-0.90), number of days drinking (mean difference [MD]=3.89, 95% CI=-5.75--2.04), and amount of alcohol used (MD=-10.83; 95% CI=-19.69--1.97) (176). The effect of naltrexone in reducing heavy drinking in AUD is at a moderate level (0.15-0.20) (85). It has also been found that naltrexone has a significant positive effect regarding relapse into heavy drinking, and it also reduced the number of units consumed on days drinking and the

number of days with heavy drinking (18). It was also found to be effective in patients using the drug "as needed" when experiencing intensive craving, extending a reduced alcohol intake (177-179).

With extended release naltrexone, the number of days with heavy drinking dropped over 6 months (4). Used together with low-intensity psychotherapy, 380mg IM naltrexone achieved a 25% reduction of heavy drinking compared to placebo, whereas at a dose of 190mg no significant difference was reported (54).

Acamprosate

Acamprosate, which is basically effective in maintaining abstinence, has been found by some meta-analyses to reduce patients' heavy drinking (18,180,181). In a recent meta-analysis based on 122 randomized controlled studies and one cohort study, interestingly no difference was found between acamprosate and naltrexone in preventing heavy drinking (182).

Other Therapies

It has been said that **baclofen**, by reducing the positive reward effect, makes people use alcohol in lower doses (183). One small study (82) also shows that baclofen can effectively lead to abstinence and, in those where it does not, reduce the amount of alcohol used. **Anticonvulsants** also reduce heavy drinking

and the number of days with heavy drinking (89). In one placebo-controlled study (184) and in meta-analyses, it has been seen that **topiramate** reduces heavy drinking (87-182). It has also been reported that being homozygous for the rs2832407 C allele coding for the GluK1 subunit of the glutamate kainate receptor leads to a better response to topiramate in heavy drinkers (185). **Gabapentin** increases the abstinence rate and reduces heavy drinking (92). A study comparing a combination of gabapentin and naltrexone with naltrexone only found that the combination of two drugs, compared to naltrexone only and placebo, extended the period until heavy drinking and reduced the number of days with heavy drinking and the amount of alcohol used on days with drinking; in addition, gabapentin is reported to have a positive effect on sleep (186). A small study with **aripiprazole** showed a significant reduction in the number of days with heavy drinking compared to placebo (116).

Considering the chronic course and the disease load caused by AUD, its therapy has a great significance. Drug treatments aimed at preventing relapses are successful in some patients but not in others. Therefore, on the one hand research into new therapies continues, while on the other hand the great issue is personalization of treatment, to understand which drug is most effective in what type of patient. As the researches in this area increase, more useful evidence based medicines can be introduced to patients.

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