Alcohol use disorders (AUDs) are among the most prevalent substance use disorders worldwide. AUDs pose a high burden both to individual with this problem and to society. Around 2 billion people consume alcoholic beverages world-wide (1,2). Alcohol consumption is responsible for approximately 3.8% of all deaths (2,3). Almost 10% of the world’s population is affected by AUDs, and the treatment of AUDs still remains a challenge (1,2,4). After suppression of the alcohol withdrawal syndrome, the primary goal in the treatment of AUDs remains complete abstinence from alcohol, even though alcohol intake reduction may also be seen as a positive result (2,4,5). In any case, a multi-professional intervention is needed to achieve these targets (1,2,4). The most common treatments for promoting abstinence, reducing alcohol intake, and preventing relapse are psychosocial interventions (i.e. cognitive behavioral therapy, motivational enhancement therapy), self-help groups (i.e. Alcoholics Anonymous), and the use of medications (1,2,4), mainly represented by anti-craving drugs.

Fewer than half of the individuals with AUDs ever get treated (6). Existing treatments of AUDs generally require total abstinence (7). Although anyone might succeed, there are a number of favorable prognostic signs. These attributes predict about a 60 percent chance for 1 or more years of abstinence (6) In another study, 12-months success rate for abstinence was reported to be 26% (7).

In treatment for AUDs, acamprosate has been found to be slightly more efficacious in promoting abstinence and naltrexone slightly more efficacious in reducing heavy drinking and craving (8), although treatment effects were found to be modest. In a systematic review a total of 85 studies, representing 18,937 subjects, were included. The evidence base for oral naltrexone (6% more days abstinent than placebo in the largest study) and topiramate (prescribed off-label) (26.2% more days abstinent than placebo in a recent study) is positive but modest. Acamprosate shows modest efficacy with recently abstinent patients, with European studies showing better results than U.S. ones. The evidence-base for disulfiram is equivocal. Depot naltrexone shows efficacy (25% greater reduction in rate of heavy drinking vs. placebo, in one of the largest studies) in a limited number of studies (8). Some studies suggest that patients do better with extensive psychosocial treatments added to medications while others show that brief support can be equally effective (9).

Despite the well-established harms caused by alcohol, treatment rates for alcohol-dependent patients are very low, whereas the abstinence goal in treating alcohol dependence has dominated the prevention and treatment of alcohol problems (10). Although alcohol
abstinence might be the optimal aim for most alcohol-dependent patients, it is not the only successful outcome (10,11).

Reduced-risk drinking (RRD), also commonly referred to as moderated drinking, asymptomatic drinking, and controlled drinking, refers to the ability of an individual who has previously exhibited out-of-control drinking to return to a decreased, or more controlled pattern of alcohol consumption (12,13). RRD is one example of a public health approach known as harm reduction. The aim of harm reduction is to reduce the negative consequences of substance use for both the client and the community by encouraging any behavioral change that reduces harm or the risk of harm (13,14).

In this kind of treatments opinion of the treatment providers is important. Although most treatment services in the USA do not accept RRD as a goal and acceptability of RRD as a goal appears to be mixed in Canada, in Australia, Britain, Norway, Switzerland and—more recently—France RRD as a goal is widely accepted by those treating AUDs (15). It has been argued that patients who reject abstinence as the treatment goal are more likely to remain engaged in treatment when they have more treatment options (10).

In the United Kingdom Alcohol Treatment Trial (UKATT), 54.3% of clients expressed a preference for abstinence and 45.7% for non-abstinence at the screening stage of the trial. The strongest predictors of goal preference were gender, drinking pattern, recent detoxification and social support for drinking (16). Clients initially stating a preference for abstinence showed a better outcome than those stating a preference for non-abstinence. This superior outcome was clearer at 3 months’ follow-up but still evident at 12 months’ follow-up. The better outcome consisted almost entirely in a greater frequency of abstinent days, with only a modest benefit in drinking intensity for goal abstainers that disappeared when baseline covariates of goal preference were controlled for. Type of successful outcome (abstinence/non-problem drinking) was related to initial goal preference, with clients preferring abstinence more likely to obtain an abstinent outcome and those preferring non-abstinence a non-problem drinking outcome. Thus, the Authors reported that the client’s personal drinking goals should be discussed in assessment at treatment entry and as a basis for negotiation (17).

Four medications are currently Food and Drug Administration (FDA)-approved in the US for the treatment of alcohol dependence: disulfiram, oral naltrexone, long-acting injectable (LAI) naltrexone, and acamprosate (18,19). These medications, other than LAI, are also approved by Turkish Ministry of Health. Unfortunately, although oral naltrexone has been licensed in Turkey, it is not on the market currently. Other medications, have also been approved for the treatment of AUDs in some European countries, e.g., sodium oxybate in Italy and baclofen in France (19). Finally, nalmefene (Selincro®) was recently approved in the European Union as the first medication directed at reduction of alcohol consumption in adult patients with alcohol dependence that have a high drinking risk level (20). In our country even more recently, the use of this medicine for the same indication has been approved by the Ministry of Health. “As needed” strategies have been proposed for harm reduction, i.e., decreasing the amount of alcohol consumed, time spent drinking and, concomitantly, recovering from the residual effects of alcohol intoxication (‘hangovers’, legal problems and problems with one’s primary support group) (19).

Most clinical research on opioid antagonists and alcohol in humans has been conducted with naltrexone, a long-acting, orally active antagonist at μ-, κ-, and δ- opioid receptors (21). Meta-analyses of controlled clinical trials of naltrexone in AUDs treatment show modest effect sizes for efficacy (0.15–0.2) in reducing heavy drinking (22). Using the Cochrane approach, Rosner et al. (23) assessed the effectiveness of naltrexone in the treatment of alcohol dependence. Based on a total of 50 RCTs with 7793 patients, naltrexone significantly reduced the risk of heavy drinking (relative risk [RR]=0.83; 95% confidence interval [CI]=0.76–0.90), the number of drinking days (mean difference [MD]=−3.89; 95% CI −5.75−−2.04), and amount of alcohol consumed (MD=−10.83; 95% CI=−19.69−−1.97), but naltrexon had no effect on total abstinence (RR=0.96; 95% CI=0.92–1.00).
Nalmefene is an opioid antagonist with highest affinity for the μ opioid receptor. It was originally used as a parenteral agent to reverse the opioid agonist effects of opioid anesthesia or in opioid overdose. Nalmefene has many similarities with naltrexone, but also some differences. The molecules are similar in structure, in that naltrexone has a ketone group at the sixth carbon, whereas nalmefene has a methylene group. Although nalmefene has a longer pharmacokinetic half-life than naltrexone following oral dosing, both naltrexone and nalmefene appear to have similarly long pharmacodynamic half-lives at the μ-opioid receptor. However, nalmefene also differs from naltrexone in two important ways. Nalmefene opioid-receptor profile is at the κ-receptor, where it is a partial agonist, whereas naltrexone is a full antagonist. Nevertheless, it is not known whether this difference in κ-opioid receptor activity between the two drugs is reflected in differences in their efficacy in reducing drinking or in differences in side effects. Naltrexone differs from nalmefene in that naltrexone carries a risk of hepatotoxicity, whereas nalmefene does not. Both medications can cause similar, less severe but more common side effects of nausea, vomiting, fatigue, and anxiety (21).

Nalmefene is a μ and δ-opioid antagonist and κ-opioid partial-agonist, which has been associated with a reduction of heavy drinking in several studies in patients with AUD. The first reported effects of nalmefene on alcohol consumption were conflicting: while one study failed to achieve a significant result (24), others reported a reduction in heavy drinking (25-27). The study that found no significant result had some limitations; participants were recently in abstinence, three different doses (5, 20 and 40 mg) were used with relatively small sample sizes in each treatment arm, rapid dose titration was used for 40 mg leading to more adverse events and short study duration (12 weeks) (24). Nevertheless, a reduction in heavy drinking has been recently confirmed by two randomized, double-blind, placebo-controlled trials (ESENSE 1 and ESENSE 2) where patients with AUD received “as-needed” (defined as self-identified high risk situations, using nalmefene when drinking is imminent or no more than 1 or 2h later after drinking) nalmefene (18mg) for 6-months (28,29). In ESENSE 1 patients taking placebo (n=289) and patients taking nalmefene (n=290) were included in the efficacy analyses. At month 6, there was a significant effect of nalmefene compared with placebo in reducing the number of heavy drinking days (-2.3 days [95% CI=-3.8 to -0.8]; p=0.0021) and total alcohol consumption (-11.0g/day [95% CI=-16.8 to-5.1]; p=0.0003). Improvements in Clinical Global Impression and liver enzymes were larger in the nalmefene group compared with placebo at week 24. Adverse events (most mild or moderate) and dropouts due to adverse events were more common with nalmefene than placebo. The number of patients with serious adverse events was similar in the two groups. In this study nalmefene provided clinical benefit, which constitutes a potential new pharmacological treatment paradigm in terms of the treatment goal and dosing regimen, and provides a method to address the unmet medical need in patients with AUD that need to reduce their alcohol consumption (28). In ESENSE 2 seven hundred and eighteen patients (placebo=360; nalmefene=358), ≥18 years of age, with a diagnosis of alcohol dependence, ≥6 heavy drinking days and an average alcohol consumption ≥ WHO (World Health Organization) medium drinking risk level in the 4 weeks preceding screening, were randomised (1:1) to 24 weeks of as-needed placebo or nalmefene 18 mg/day. The co-primary efficacy analyses showed a significantly superior effect of nalmefene compared to placebo in the change from baseline to month 6 in heavy drinking days (group difference [GD]=1.7 days/month [95% CI=-3.1; -0.4]; p=0.012) and a better but not significant effect in reducing total alcohol consumption (GD=-5.0g/day last month [95% CI=-10.6; 0.7]; p=0.088). A subgroup analysis showed that patients who did not reduce their drinking prior to randomisation benefitted more from nalmefene. Improvements in Clinical Global Impression and reductions in liver enzymes were greater in the nalmefene group than in the placebo group. Adverse events were more common with nalmefene; the incidence of adverse events leading to dropout was similar in both groups. This study provides evidence for the efficacy of nalmefene, which constitutes a new
pharmacological treatment paradigm in terms of treatment goal (reduced drinking) and dosing regimen (as-needed), in alcohol dependent patients unable to reduce alcohol consumption on their own (29).

In addition, a post-hoc analysis of these two studies, only including patients with at least a high drinking risk level (defined as ≥60g/day for men and ≥40g/day for women of alcohol intake) both at screening and randomization ("target population" which consisted of 667 patients: placebo n=332; nalmefene n=335), showed that nalmefene reduced the number of heavy drinking days (treatment difference [TD]=−3.2 days; p<0.0001) and the total alcohol consumption (TD=−14.3g/day; p<0.0001) at month 6 more significantly than placebo. Improvements in clinical status and liver parameters were greater in the nalmefene group compared with the placebo group. Adverse events and adverse events leading to dropout were more common with nalmefene than placebo. As-needed nalmefene was efficacious in reducing alcohol consumption in patients with at least a high drinking risk level at both screening and randomization, and the effect in this subgroup was larger than in the total population (30).

Nalmefene is to be taken as-needed: on each day the patient perceives a risk of drinking alcohol, one tablet (18mg) should be taken, preferably 1-2 hours prior to the anticipated time of drinking. If the patient has started drinking alcohol without taking nalmefene, the patient should take one tablet as soon as possible. The maximum dose of nalmefene is one tablet per day taken with or without food.

**CONCLUSION**

It is clear that posing abstinence as the only viable treatment goal is associated with low treatment participation and thus a large treatment gap, and with treatments that are only moderately successful (10). A sizeable fraction (20–80%) of people with alcohol dependence favour RRD over abstinence as a treatment goal, and thus complementing the current treatment system with interventions directed at RRD may reduce the treatment gap (10).

In a recent meta-analysis that included 122 RCTs and 1 cohort study (total 22,803 participants) the number need to treat (NNT) to prevent return to heavy drinking was 12 (95% CI=8-26; risk difference [RD]=−0.09; 95% CI=−0.13 to −0.04) for oral naltrexone (50mg/d). In this meta-analysis, interestingly, comparing acamprosate to naltrexone found no statistically significant difference between them for heavy drinking (RD=0.01; 95% CI=−0.05-0.06). For injectable naltrexone, meta-analyses found no association with heavy drinking (RD=−0.01; 95% CI=−0.5% to −0.56%). Finally among some medications, moderate evidence supports an association with improvement in consumption outcomes for nalmefene (heavy drinking days per month: WMD=−2.0; 95% CI=−3.0 to -1.0) and topiramate (% heavy drinking days: WMD=−9.0%; 95% CI=−15.3% to −2.7%) (31).

In a recent Cochrane review moderate-quality evidence suggested that anticonvulsants reduced heavy drinking (12 studies, 1129 participants, standardised mean difference (SMD) −0.35, 95% CI=−0.51 to −0.19). Also anticonvulsants were associated with fewer heavy drinking days (three studies, 308 participants, MD=−5.21, 95% CI=−8.58 to -1.83) (33). A recent meta-analysis that included 7 RCTs (including a total of 1,125 participants) of topiramate treatment for AUDs found that although the largest effect was on abstinence (g=0.468, p<0.01), followed by the reduction of heavy drinking (g=0.406, p<0.01) (34).

Two recent 6 month studies that evaluated the effectiveness of as-needed nalmefene suggested that compared to baseline total alcohol consumption decreased by approximately 60% and 65% respectively (28,29). This rate was 67% in other 1 year study (30). Nalmefene was safe and well-tolerated and no safety issues were raised in these studies (28-30). Thus, as-needed nalmefene provides an important new option for use in the treatment of AUDs when RRD is the goal (35). In Turkey, there are
no adequate pharmacological options for the treatment of AUDs. Nalmefene with a different mechanism of action and indication, is expected to respond to important clinical needs in the new indication areas that was not studied in the earlier clinical trials. In their review, Amsterdam and van den Brink (10) strongly recommended the development and evaluation of new psychotherapeutic and pharmacological treatments directed at RRD for patients with an AUD. One good example is topiramate, a drug that is not yet approved for use in AUDs, at a daily dose of 200mg reduced heavy drinking in problem drinkers (36). Thus, using “as needed” nalmefen (Selincro®), recently approved by the Turkish Ministry of Health, will seem to meet an important requirement in AUD’s pharmacotherapy.

REFERENCES


