# **CONTINUING MEDICAL EDUCATION**

# Alcohol Dependence and Harmful Use of Alcohol

**Diagnosis and Treatment Options** 

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# **SUMMARY**

Background: In Germany today, there are more than 1.8 million persons who are dependent on alcohol, and 1.6 million persons whose use of alcohol is harmful. The many complications of alcohol use are both mental and physical—in particular, gastrointestinal and neurological. Yet more than 80% of persons whose alcohol use is problematic still receive no treatment for their harmful use or dependence, despite contact with the health-care system.

<u>Methods:</u> This article is a selective review of the pertinent literature, including guidelines, meta-analyses, and Cochrane Reviews.

<u>Results:</u> The treatment is divided into an early interventional and motivational phase, qualified withdrawal, long-term cessation therapy, and a stabilization phase. Pharmacotherapy with acamprosate or naltrexone increases the rate of abstinence (number needed to treat: 12 and 20, respectively). If a patient lacks the motivation to abstain from alcohol entirely, reduced consumption can be agreed upon as a goal of treatment. 85% of patients relapse if no further treatment is given after initial detoxification.

<u>Conclusion:</u> What is needed in routine medical practice is practical diagnostic evaluation followed by individually tailored treatment, based on the severity of the condition, the development of the patient's motivation to be treated, and the local treatment options (e.g., outpatient addiction clinics, counseling centers, or day clinics).

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G erman society is permissive with respect to the drinking of alcohol: it is a part of the local culture that is accepted in many different kinds of social events, sometimes even as a ritualized tradition. High per capita alcohol consumption and the early onset of regular or episodic intensive drinking among young people in Germany are the consequence and lead to high alcohol-related morbidity and mortality (e1).

The German S3 treatment guidelines (1) contain a comprehensive set of recommendations for the treatment of alcohol-related disorders. For this review, we searched the literature on the basis of the S3 guidelines, supplemented by the most recent clinical trials and reviews related to the main therapeutic recommendations of the guidelines.

#### Learning goals

Readers of this article should gain knowledge of

- the impact of alcohol consumption on health,
- strategies for diagnosing and addressing harmful alcohol consumption, and
- measures for the acute and postacute treatment of harmful alcohol use and alcohol dependence.

# The epidemiology of alcohol consumption in Germany

Per capita alcohol consumption in Germany has remained for several years at the high level of just under 10 liters of pure ethanol per year (e1). Healthendangering alcohol consumption affects 14% of the adult population aged 19 to 64, or about 7.4 million people. It is estimated that 3.1% of the population meet the diagnostic criteria for harmful alcohol use (4.7% of men and 1.5% of women), while 3.4% of persons aged 19 to 64 (4.8% of men and 2.0% of women; about 1.8

#### **Alcohol-related morbidity and mortality**

Alcohol-related morbidity and mortality are high in Germany. The harmful use of alcohol accounts for about 10% of overall mortality.

# BOX 1

# The diagnostic criteria for alcohol dependence, according to the ICD-10 (F10.2) (e9)

Three or more of the following should be present together for at least one month, or else repeatedly during a one-year period:

- A strong desire or sense of compulsion to take the psychoactive substance (alcohol)
- Difficulties in controlling substance-taking behavior in terms of its onset, termination, or levels of use
- A physiological withdrawal state when substance use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms
- Evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses
- Progressive neglect of alternative pleasures or interests because of psychoactive substance use
- Persistient substance use despite clear evidence of overtly harmful consequences (mental and/or physical)

million people) meet the criteria for alcohol dependence (4.8% of men and 2.0% of women) (e2).

#### Alcohol consumption and its consequences

About 74 000 persons die as a result of alcohol consumption in Germany each year, accounting for about 10% of overall mortality (e3). The harmful effects of regular alcohol consumption on multiple organ systems have been repeatedly demonstrated. Alcohol use increases the risk of diseases of the oral cavity, esophagus, stomach, intestines, pancreas, and liver by promoting carcinogenesis and affecting inflammatory processes (2). It can also lead to cardiovascular problems such as heart failure, arrhythmia, arterial hypertension, and alcoholic cardiomyopathy, as well as hematopoietic disorders (3). Meanwhile, the widespread notion that low-level alcohol use is good for the heart can no longer be sustained now that the pertinent epidemiologic studies have been re-analyzed (4).

The harmful effect on the fetus of maternal alcohol consumption during gestation has been known for

many years. Fetal alcohol spectrum disorder (FASD) is seen in about 4000 newborn babies in Germany every year. These children suffer long-term damage, with abnormal behavior, impaired cognition, high psychiatric comorbidity, learning disorders, and developmental disorders (5).

In 2012, German hospitals recorded having treated 345 000 patients with an alcohol-related disorder (F10x) coded among their diagnoses (6). Alcohol use increases risks in many different branches of medicine (7), e.g., the risk of surgical complications, the risk of undesired drug interactions, or the risk of a worse outcome from an infectious disease. Even so, the vast majority of patients treated in and outside hospitals for the physical effects of alcohol use receive no specific treatment for their drinking problem.

The motivation to drink less, and the opportunity to treat harmful alcohol use and alcohol dependence, often arise not only from the medical consequences of excessive drinking, but also from its social side effects (loss of driver's license, disruption of marriage or other relationship, loss of job). The annual cost to the nation of problematic alcohol consumption have been estimated at 25.4 billion euros (e4). Thus, alcohol use is one of the main avoidable risk factors for disease and premature death, as well as a major source of healthcare costs and social problems (crimes committed under the influence of alcohol, alcohol-related traffic accidents, etc.).

#### When is alcohol use a health problem?

Mild, occasional alcohol consumption is considered unproblematic for health. The quantity of alcohol consumed determines the risk: the German Drug Abuse Center (*Deutsche Hauptstelle für Suchtfragen*, DHS) sets a daily average threshold value of 12 g of pure alcohol for women and 24 g of pure alcohol for men. At least two alcohol-free days per week are recommended (e5). On the basis of these values, one can derive overall threshold values for per annum consumption of 4.4 liters for women and 8.8 liters for men. Yet the average individual consumption of alcohol in Germany is well above this recommended threshold, at 9.7 liters per year.

When the health risks of alcohol use are considered, it should also be borne in mind that regular alcohol use often accompanies regular tobacco smoking—a further major risk factor for impaired health whose effects in combination with alcohol are

#### **Thresholds crossed in Germany**

Mean per capita alcohol consumption in Germany exceeds the thresholds for low-risk use.

#### How the will to change arises

The motivation to cut down on drinking often arises not only from the medical consequences of excessive drinking, but also from its social side effects (loss of driver's license, disruption of marriage or other relationship, loss of job). not merely additive, but in some cases actually multiplicative. About 80% of persons undergoing inpatient treatment who use alcohol regularly also smoke cigarettes every day, and, conversely, persons dependent on cigarette smoking are about twice as likely to develop an alcohol-related disorder as the non-nicotine-dependent general population (8, e6, e7).

## Psychological and neurobiological fundamentals

Alcohol use is socially accepted and ritualized in Germany. Aside from social reinforcement, the psychotropic effects of alcohol are a further major motivation for its use. Alcohol improves mood in the short term, helps the drinker overcome social anxiety and insecurity, and creates distance to current negative emotions. In the long term, however, the effect of alcohol on the serotonergic and dopaminergic systems increases the risk of a depressive disorder (9, 10).

Like other addicting substances, alcohol causes dopaminergic stimulation in the nucleus accumbens, which rewards alcohol use (9).

Alcohol use is promoted not only by operant conditioning processes, i.e., the pleasant effects of consumption as a reward, but also by classical (Pavlovian) conditioning processes, i.e., the association of previously neutral stimuli in drinking situations with the generation and induction of the desire for alcohol, leading to habitual use. The frequent coupling of alcohol with pleasant situations, mood elevation, disinhibition, and the suppression of negative affects all increase the likelihood of regular drinking.

Alcohol is a drug that directly induces neural adaptation processes which, in turn, partly counteract the effects of alcohol and contribute to the development of tolerance. If the individual then suddenly stops using alcohol, an imbalance arises between the (missing) alcohol-induced sedation and the (persistent) counter-regulatory excitation, leading to withdrawal phenomena. The autonomic manifestations of alcohol in particular—diaphoresis, tremor, tachycardia, hypertension, psychoautonomic irritability—may lead the individual to start drinking again, even if he or she would prefer to abstain, and even before the full delirium tremens syndrome arises (e8).

## BOX 2

# The diagnostic criteria for harmful alcohol use, according to the ICD-10 (F10.1) (e9)

- There is clear evidence that substance use is largely or wholly responsible for mental and/or physical harm, including impaired judgment or abnormal behavior, that can cause impairment or adverse consequences in interpersonal relationships.
- The nature of the harm caused by the substance should be clearly specifiable and describable.
- The pattern of harmful use has been present for at least one month or repeatedly over the past twelve months.
- The diagnostic criteria for another mental or behavioral disorder caused by the same substance are not simultaneously satisfied (with the possible exception of acute intoxication, F10.0).

Problematic alcohol use has a high comorbidity with other types of mental illness, including depressive disorders, anxiety disorders, attention deficit–hyperactivity disorder, and personality disorders that involve emotional instability (dissocial or avoidant personality disorder), as well as alcohol-induced aggressiveness (11, 12).

#### **Diagnostic classification**

In the International Classification of Diseases (ICD-10) (e9), the harmful use of alcohol (*Box 2*) and alcohol dependence (*Box 1*) are coded as F10.1 and F10.2, respectively. The former diagnosis requires the presence of some type of harm consequent to alcohol use, while the latter requires at least three of six criteria for dependence to have been simultaneously met in the past 12 months. The core elements of a diagnosis of dependence are tolerance, desire for alcohol, impaired self-control, and the appearance of withdrawal phenomena.

# International debate on the concept of addiction

The American Psychiatric Association released the fifth edition of its Diagnostic and Statistical Manual of Psychiatric Diseases (DSM-5) in May 2013 (e10). The category of substance-related disorders was renamed

# **Reasons for frequent relapses**

Relapses after detoxification treatment are common because of habits, conditioning, and the functionality of alcohol use, as well as the appearance of withdrawal phenomena.

# High comorbidity with other mental illnesses, including:

depressive and anxiety disorders, attention deficit-hyperactivity disorder, personality disorders, and alcohol-induced aggressiveness.

#### BOX 3

# DSM-5 diagnostic criteria for alcohol-related disorder (e10)\*

- Alcohol is often taken in larger amounts or over a longer period than was intended.
- There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
- A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
- Craving, or a strong desire or urge to use alcohol.
- Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
- Continued alcohol use despite persistent or recurrent social or interpersonal problems caused or exacerbated by alcohol.
- Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
- Recurrent alcohol use in situations in which it is physically hazardous.
- Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
- Tolerance, i.e., either a need for markedly increased amounts of alcohol to achieve intoxication or desired effect, or else a
  markedly diminished effect with continued use of the same amount of alcohol.
- Withdrawal, as manifested by either the characteristic withdrawal syndrome for alcohol or by the repeated use of alcohol (or a closely related substance, such as a benzodiazepine) to relieve or avoid withdrawal symptoms.

\*(2 or 3 criteria, mild disorder; 4 or 5 criteria., moderate disorder; 6 or more criteria, severe disorder.)

"addiction and related disorders." The previous subclassification of substance-related disorders as abuse, harmful use, or dependence was abandoned in favor of a new, unitary nosological entity (*Box 3*).

It is not yet clear whether or to what extent this reconceptualization of the concept of addiction will find its way into the upcoming ICD-11. The current subclassification into harmful alcohol use and alcohol dependence will likely be kept. The new DSM-5 concept does have some generally recognized advantages, however; in particular, its dimensional approach accords well with the empirical finding that the criteria for alcohol dependence and abuse lie on a continuum of severity.

The DSM-5 classification has been criticized, however, for softening the diagnosis of alcohol dependence, whose clinical definition was well delimited until now, with the addition of relatively vague criteria for harmful use (e11). For example, repetitive use leading to neglect of responsibilities at work, in school, or at home, repetitive use despite interpersonal problems, and marked expenditure of time in order to obtain alcohol can all be either present or absent in particular cases depending on social norms and prescriptions. In a place where alcohol consumption is generally forbidden, even moderate consumption can become associated with one or more of the above problems and end up meriting the diagnosis of a substance-related disorder (e11). It is for this reason that some experts advocate the retention of the diagnosis "alcohol dependence."

#### Diagnostic testing, laboratory findings, psychometric evaluation instruments, and self-assessment scales

Typical effects of alcohol use that are found on physical examination (polyneuropathy, fetor alcoholicus, rhinophyma, spider nevi, altered facial appearance, and many more) and laboratory biomarkers of alcohol use are clues to the physician that the patient is using alcohol problematically. The most sensitive laboratory test is the gamma-GT concentration; an elevated mean red-cell volume (MCV) is also suggestive but may be

# ICD-10

In the International Classification of Diseases (ICD-10), alcohol dependence and the harmful use of alcohol are coded separately.

## DSM-5

In contrast, the American classification system (DSM-5) employs a dimensional concept, according to which alcohol abuse and alcohol dependence belong to the same disease entity. influenced by a nutritional deficiency or other clinical factors. An elevation of the carbohydrate-deficient transferrin (CDT) concentration is correlated with chronic alcohol use; it normalizes within a few weeks if the patient becomes abstinent. GOT and GPT (respectively, ASAT and ALAT) and tests for other substances such as methanol, acetone, or cholesterol ester transfer protein are less specific. For clinical use, gamma-GT, MCV, and CDT are the simplest and most reliable tests. The combined measurement of gamma-GT and CDT seems to be the most sensitive and specific test available (13).

The fact that alcohol has been consumed in the past three to four days can be confirmed by detection of the direct ethanol metabolite ethyl glucuronide (or ethyl sulfate, EtS), which is present for several days in the urine and even longer (up to three months) in hair (14). The sensitivity and specificity of various laboratory tests are shown in the *Table*.

We recommend the use of objective laboratory tests in combination with screening instruments. Selfadministered questionnaires such as AUDIT (the Alcohol Use Disorder Identification Test [e12]) and AUDIT-C (*Box 4*) (e13, 15) are useful complementary aids to diagnosis, both in the hospital and in general practice.

The diagnosis can only be definitively established by the operationalized clinical criteria of the ICD-10 (*Box* 1 and 2), of which three out of six must have been simultaneously met in the past 12 months.

#### The treatment of alcohol dependence

The treatment of alcohol dependence is divided into an early interventional and motivational phase (in a family-practice setting or an outpatient addiction clinic), acute treatment (detoxification or "qualified withdrawal"), cessation therapy (in a specialized center), and a stabilization phase.

The evidence base for pharmacotherapy now permits robust conclusions to be drawn regarding efficacy (1, 15). The efficacy of motivating techniques, targeted early intervention, and some types of pharmacotherapy is also well documented (1).

Early intervention for counseling and motivating the patient to be treated, primarily through motivational discussion, is often carried out in the primary-care setting or in psychosocial counseling facilities, but can just as well take place (depending on the circumstances) in the workplace, or in relation to other social

#### TABLE

The sensitivity and specificity of biomarkers for alcohol use (from reference 13)

Marker	Sensitivity	Specificity
GOT	15–69%	low
GPT	18–58%	low
Gamma-GT	34–85%	11–95%
CDT	39–94%	82–100%
MCV	34-89%	26–95%

consequences of alcohol use. The goals of early intervention are to make the patient aware of the alcohol problem and desirous of changing his or her behavior, and to give him or her access to treatment. The most important element is the establishment of an empathetic doctor-patient relationship (16).

Detoxification is carried out in patients suffering from alcohol withdrawal with the objective of preventing the severe manifestations and complications of alcohol withdrawal, including delirium tremens, Wernicke encephalopathy, a grand mal seizure, and central pontine myelinolysis. The risk of complications implies that this should be done in an inpatient setting. When the treatment also includes concomitant motivational psycho-educative measures, it is called "qualified withdrawal"; the duration of treatment is generally three weeks (15). Qualified withdrawal treatment is most commonly administered on a psychiatric inpatient ward or a specialized medical ward for addiction, but it can also be given in an outpatient setting or in a day clinic if severe withdrawal phenomena are not expected to arise.

#### Detoxification

Withdrawal seizures and delirium tremens are the most serious manifestations of alcohol withdrawal. Untreated delirium tremens carries a mortality of 5% to 15% (17, 18), and the likelihood of an epileptic seizure during alcohol withdrawal is about 10% (18, 19).

Treatment schemes for withdrawal syndromes involve the initiation of pharmacotherapy with clomethiazole or a benzodiazepine (lorazepam, diazepam, oxazepam, or chlordiazepoxide) in a manner depending on the severity

# **Psychometric evaluation instruments**

Further aids to diagnosis, aside from the diagnostic criteria of the ICD-10, include psychometric self-assessment instruments (AUDIT, AUDIT-C) and alcohol-specific laboratory tests (GGT, MCV, CDT and EtG).

#### **Qualified withdrawal treatment**

Qualified withdrawal consists of psycho-educative measures to promote insight into the condition, motivational interventions, and, if needed, medical treatment of the alcohol withdrawal syndrome.

#### BOX 4

# AUDIT-C (15)\*

How often do you drink alcohol?	Points
Never	0
About once per month	1
2-4 times per month	2
2–3 times per week	3
4 or more times per week	4

On a day when you drink alcohol, how many drinks do you typically consume?

51 5	
1 or 2	0
3 or 4	1
5 or 6	2
7 or 8	3
10 or more	4

How often do you consume more than six alcoholic drinks on a single day?

Never	0
Less than once per month	1
Once per month	2
Once per week	3
Every day or almost every day	4

\* One alcoholic drink is defined as 330 ml of beer, 250 ml of wine or sparkling wine, or 20 ml of liquor. A score of 4 or more for women, or 5 or more for men, arouses suspicion of an alcohol-related disorder.

of the withdrawal phenomena (19, 20); in general, the doses of these drugs can then be reduced over 7 days. Benzodiazepines should be given in 2 to 4 doses per day; clomethiazole should be given at closely spaced intervals (every 2 hours) because of its short half-life. Carbamazepine and oxcarbazepine can alternatively be used to treat alcohol withdrawal syndrome (1, 15).

#### The elements of qualified withdrawal

Qualified withdrawal involves not only preventing the serious complications of alcohol withdrawal but also motivating the patient for stable, long-term abstinence, with therapeutic support if necessary and with integration into the German nationwide addiction aid and self-help system. Psycho-education mainly consists of informing the patient about the conditions that promote alcohol dependence and enabling him or her to consider rationally the advantages and disadvantages of abstinence, as opposed to continued alcohol use, with the aid of motivational discussion techniques (e14). This can be enhanced by the integration of family members and the addition of elements from social competence training, relaxation therapy, ergotherapy, and physiotherapy.

## **After detoxification**

About 85% of alcohol-dependent patients who undergo detoxification without any further treatment suffer a relapse (21, 22). The main goal of postacute treatment is to increase the chance of long-term abstinence. Short-term detoxification makes sense only if followed by postacute treatment, which can be delivered in an outpatient or day-clinic setting or on an addiction-specific inpatient rehabilitation ward. The treatment generally consists of psychotherapy (often behavior therapy), including elements of social competence training, stress management training, stimulus exposure techniques, relapse prevention, and relapse management, as well as the reinforcement of self-control, re-establishment of social resources, occupational measures, and job searching to promote personal participation. The behavior-therapeutic techniques developed in the 1970s for alcohol-specific psychotherapy have been extended and supplemented in recent years with cognitive behavioral elements (22). The efficacy of individual methods is well established, particularly motivational training, cognitive behaviortherapeutic training, abstinence training, social competence training, exposure techniques, and communitybased reinforcement models.

There have not, however, been any reported clinical trials of the common type of postacute treatment (22).

These patients' rehabilitation, post-rehabilitative care, and reintegration into the workplace and into a stable familial and social environment should always be accompanied by participation in a self-help group and continuing care by the family physician, with regular abstinence checks, updating of coping skills for problematic situations, and effective relapse management (1, 22).

# The long-term pharmacotherapy of alcohol dependence

So-called anti-craving drugs can support abstinence. They must be integrated into an overall treatment plan as a complement to other, behavioral strategies to treat

# **Detoxification**

Withdrawal seizures and delirium tremens are the most serious complications of alcohol withdrawal.

# The need for further treatment

About 85% of alcohol-dependent patients who undergo detoxification without any further treatment suffer a relapse. addiction. The needed motivational support can be provided in regularly occurring discussions in an outpatient addiction clinic or in the general practitioner's office.

The approved drugs of this type in Germany are acamprosate and naltrexone, an opioid antagonist. Metaanalyses have shown both to be effective for relapse prevention (23, 24), with a number needed to treat (NNT) of about 12 and about 20, respectively (25, 26).

Disulfiram was once used in Germany for aversive therapy but is no longer approved and has become practically unavailable. Nonetheless, the efficacy of aversive therapy with disulfiram is well documented, above all in combination with frequent psychotherapy (27–29). The mechanism of action of disulfiram is the irreversible inhibition of aldehyde dehydrogenase, leading to the accumulation of toxic acetaldehyde and, in turn, to facial erythema, tachycardia, urinary urgency, nausea, and headache whenever the patient drinks alcohol.

A further substance that has not yet been approved for this indication is baclofen, a  $GABA_B$  agonist (30). It can only be used off label at present.

#### **Reduced drinking: pro and con**

Reduced drinking as a strategy (previously known as "controlled drinking") remains a highly contentious matter (31, e15, e16).

Multiple studies (32, 33, e17) have shown that reduced drinking is a feasible goal, at least when the patient is in the early phase of dependence and has only a small number of alcohol-related problems. Patients treated with this goal in mind were able to achieve stable drinking patterns for 6 or 12 months (depending on the study). There is, however, no way to determine what percentage of patients might continue to be stably reduced drinkers over the long term after such treatment, because the studies generally yielded no information about outcomes beyond the mid-range follow-up interval in the groups of patients who reduced their drinking, became abstinent, or kept on drinking as before (34). In any case, 10–30% of patients achieve abstinence during or after participation in a drinking reduction program (e15).

A few studies (35) have shown that drinking reduction works, but that patients whose goal it is to quit drinking achieve better results than those whose goal is merely to drink less—better results, that is, with respect to both abstinence and reduced drinking. On the other hand, certain groups of patients are often left out of consideration when the results of abstinence-oriented programs are evaluated, including those who engage in risky alcohol use, those who are severely dependent and drink constantly, and homeless alcoholics. There are some studies aiming to show that managed access to alcohol as a means of damage control for chronically homeless alcohol-dependent persons can improve their quality of life and lessen uncontrolled drinking behavior (36, 37). Moreover, the reduction of daily alcohol intake often enables patients to reach an agreement with their therapists on new treatment goals (38). Reduced-drinking programs include not only pharmacological support, but also behaviorally oriented recommendations on how to deal with alcohol use or the desire to drink (36). Nonetheless. despite the documented advantages of the reduced-drinking approach, one must take care, when implementing it in practice, not to offer it as an alternative to abstinence for patients who are likely to benefit from abstinence therapy, which current evidence supports as the safest, most effective form of treatment. Possible indications for reduced drinking as a treatment goal include harmful alcohol use without dependence, a lack of motivation for abstinence, or multiple, failed professionally supported attempts at abstinence and a lack of motivation to make a further attempt.

There has been renewed discussion of the possibility of stably reducing alcohol consumption without eliminating it since the recent demonstration that nalmefen, an opioid modulator ( $\mu$ - and  $\delta$ -receptor agonist and partial  $\kappa$ -receptor agonist), is effective for this purpose. Three recent studies and an earlier one from Finland have shown that even the groups treated with counseling and placebo were able to lessen the amount they drank by about 60% for six and twelve months, with a moderate and significant additional effect for nalmefen (39). The advocates of the reduced-drinking approach saw this as strong empiric support for their concept. It should be emphasized, however, that this type of treatment is restricted to persons without any known physical manifestations of alcohol withdrawal who do not require immediate detoxification. Nalmefen should only be given in combination with psychosocial support. Moreover, the treatment should only be started in persons whose alcohol consumption is still at a high-risk level 14 days after initial examination. Nalmefen can only be prescribed for three months, or, in justified exceptional cases, for six months at most. According to the German Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA), nalmefen confers no additional benefit beyond naltrexone for the same indications (40).

# **Relapse prevention**

The approved drugs for relapse prevention in Germany are acamprosate and naltrexone, an opioid antagonist.

## **Drinking reduction programs**

If abstinence-oriented treatment is not possible, there are alternative therapeutic approaches involving the controlled reduction of alcohol use.

#### **Conformity with guidelines**

The current S3 guidelines for the treatment of alcohol and tobacco dependence were published and released on the Internet on 30 January 2015 (1, 15). They contain treatment recommendations accompanied by extensive explanatory text and supported by references to the literature.

#### **Conflict of interest statement**

Prof. Batra has received third-party funding from Alkermes for participating in a multicenter trial.

Dr. Müller has received research support and payment for preparing scientific meetings from Lundbeck.

Prof. Mann has served as a paid consultant for Lundbeck, from which he has also received reimbursement of meeting participation fees, travel and accommodation expenses, payment for preparing continuing medical education events and for authorship of a publication with a topic related to that of this article, and financial support for a research project that he initiated.

Prof. Heinz states that he has no conflict of interest

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#### REFERENCES

- 1. Mann K, E, Batra A: S3-Leitlinie Screening, Diagnose und Behandlung alkoholbezogener Störungen. Heidelberg: Springer 2015.
- Rocco A, Compare D, Angrisani D, Sanduzzi Zamparelli M, Nardone G: Alcoholic disease: liver and beyond. World J Gastroenterol 2014, 20: 14652–9.
- Mukamal KJ, Jadhav PP, D'Agostino RB, et al.: Alcohol consumption and hemostatic factors: analysis of the Framingham Offspring cohort. Circulation 2001, 104: 1367–73.
- Knott CS, Coombs N, Stamatakis E, Biddulph JP: All cause mortality and the case for age specific alcohol consumption guidelines: pooled analyses of up to 10 population based cohorts. BMJ 2015; 350: h 384.
- Landgraf MN, Nothaber M, Kopp IB, Heinen F: Clinical practice guideline: The diagnosis of fetal alcohol syndrome. Dtsch Arztebl Int 2013; 110: 703–10.
- Statistisches Bundesamt: www.destatis.de/DE/ZahlenFakten/ GesellschaftStaat/Gesundheit/Krankenhaeuser/Tabellen/Diagnosenlnsgesamt.html;jsessionid=BC1BFC5DDBFD7
   48FC963F019695C9656. cae3 (last accessed on 13 November 2015).
- Nath B, Li Y, Carroll JE, Szabo G, Tseng JF, Shah SA: Alcohol exposure as a risk factor for adverse outcomes in elective surgery. J Gastrointest Surg 2010; 14: 1732–41.
- Rüther T, Bobes J, De Hert M, et al.: EPA guidance on tobacco dependence and strategies for smoking cessation in people with mental illness. Eur Psychiatry 2014; 29: 65–82.

#### **Stably reduced drinking**

Renewed discussion of the stabe reduction (but not elimination) of alcohol consumption has followed the recent demonstration that nalmefen, an opioid modulator, is effective for this purpose.

- Di Chiara G, Imperato A: Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci USA. 1988; 85: 5274–8.
- Duncan J, Johnson S, Ou XM: Monoamine oxidases in major depressive disorder and alcoholism. Drug Discov Ther 2012; 6: 112–22.
- Ho PS, Shih MC, Ma KH, et al.: Availability of the serotonin transporter in patients with alcohol dependence. World J Biol Psychiatry 2011; 12: 134–42.
- Heinz AJ, Beck A, Meyer-Lindenberg A, Sterzer P, Heinz A: Cognitive and neurobiological mechanisms of alcohol-related aggression. Nature Reviews Neuroscience 2011; 12: 400–13.
- Hannuksela ML, Liisanantti MK, Nissinen AET, Savolainen MJT: Biochemical markers of alcoholism. Clin Chem Lab Med 2007; 45: 953–61.
- Aradottir S, Asanovska G, Gjerss S, Hansson P, Alling C: Phosphatidylethanol (PEth) concentrations in blood are correlated to reported alcohol intake in alcohol-dependent patients. Alcohol and alcoholism 2006; 41: 431–7.
- 15. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V.: Alkoholbezogene Störungen: Screening, Diagnose und Behandlung. AWMF S3 Leitlinie. www.awmf.org/ uploads/tx\_szleitlinien/076–001I\_S3-Leitlinie\_Alkohol\_2015–04.html (last accessed on 13 November 2015).
- Norcross JC, Wampold BE: Evidence-based therapy relationships: research conclusions and clinical practices. Psychotherapy (Chic) 2011; 48: 98–102.
- Erwin WE, Williams DB, Speir WA: Delirium tremens. South Med J 1998; 91: 425–32.
- Zilker T: Alkoholentzugssyndrom und Delirium tremens. MMW 1999; 141: 26–30.
- Hillborn M, Pieninkeroinen I, Leone M: Seizures in alcoholdependent patients: epidemiology, pathophysiology and management. CNS Drugs 2003; 17:1013–30.
- Lutz U, Batra A: Diagnostik und Therapie des Alkoholentzugssyndroms: Fokus auf Delirium tremens und Entzugskrampfanfall. Psych Praxis 2010; 37: 271–8.
- 21. Boothby LA, Doering RL: Acamprosate for the treatment of alcohol dependence. Clin Ther 2005; 27: 695–14.
- Walter M, Dürsteler KM, Petitjean SA, Wiesbeck GA, Euler S, Sollberger D: Psychosocial treatment of addictive disorders—an overview of psychotherapeutic options and their efficacy. Fortschr Neurol Psychiatr 2015; 83: 201–10.
- Mann K, Lehert P, Morgan MY: The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis. Alcohol Clin Exp Res 2004; 28: 51–63.
- Rösner S, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisurapanont M, Soyka M: Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev 2010; (12): CD001867.
- Jonas DE, Arnick HR, Feltner C, et al.: Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA. 2014; 311: 1889–900.
- Mann K, Leménager T, Hoffmann S, et al.: Results of a double-blind placebo controlled pharmacotherapy trial in alcoholism conducted in Germany and comparison with the US COMBINE study. Addict Biol 2013; 18: 937–46.

- Krampe H, Ehrenreich H: Supervised disulfiram as adjunct to psychotherapy in alcoholism treatment. Curr Pharm Des 2010; 16: 2076–90.
- Niederhofer H, Staffen W: Comparison of disulfiram and placebo in treatment of alcohol dependence of adolescents. Drug Alcohol Rev 2003; 22: 295–7.
- Krampe H, Stawicki S, Wagner T: Follow-up of 180 alcoholic patients for up to 7 years after outpatient treatment: impact of alcohol deterrents on outcome. Alcohol Clin Exp Res 2006; 30: 86–95.
- Müller CA, Geisel O, Pelz P: High-dose baclofen for the treatment of alcohol dependence (BACLAD study): A randomized, placebocontrolled trial. Eur Neuropsychopharmacol 2015; 8: 1167–77.
- Körkel J: Kontrolliertes Trinken bei Alkoholkonsumstörungen: Eine systematische Übersicht. Sucht 2015; 6: 147–74.
- Feuerlein W, Küfner HA: prospective multicenter study of in-patient treatment for alcoholics: 18– and 48-month follow-up (Munich Evaluation for Alcoholism Treatment, MEAT). Eur Arch Psychiatry Neurol Sci 1989; 239: 144–57.
- Mann K, Schäfer DR, Längle G, Ackermann K, Croissant B: The long-term course of alcoholism, 5, 10 and 16 years after treatment. Addiction 2005; 100: 797–805.
- 34. Gual A, Bravo F, Lligoña A, Colom J: Treatment for alcohol dependence in Catalonia: health outcomes and stability of drinking patterns over 20 years in 850 patients. Alcohol and alcoholism 2009; 44: 409–15.
- Adamson SJ, Heather N, Morton V, Raistrick D: Initial preference for drinking goal in the treatment of alcohol problems: II. Treatment outcomes. Alcohol Alcohol 2010; 45: 136–42.
- Collins SE, Malone DK, Clifasefi SL: Housing retention in single-site housing first for chronically homeless individuals with severe alcohol problems. Am J Public Health 2013; 103: 269–74.
- Collins SE, Clifasefi SL, Dana EA, et al.: Where harm reduction meets housing first: exploring alcohol's role in a project-based housing first setting. Int J Drug Policy 2012; 23: 111–9.
- Collins SE, Grazioli VS, Torres NI, et al.: Qualitatively and quantitatively evaluating harm-reduction goal setting among chronically homeless individuals with alcohol dependence. Addict Behav 2015; 45: 184–90.
- 39. van den Brink W, Sørensen P, Torup L, Mann K, Gual A: Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: A 1-year, randomised controlled study. J Psychopharmacol 2014; 28: 733–44.
- G-BA: https:// www.g-ba.de/downloads/39–261–2179/ 2015–02–19\_AM-RL-XII\_Nalmefen\_2014–09–01-D-127\_BAnz.pdf (last accessed on 12 February 2016).

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Supplementary material: For eReferences please refer to:: www.aerzteblatt-international.de/ref1716

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Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the most appropriate answer.

## **Question 1**

How many adults in Germany meet the diagnostic criteria for alcohol dependence?

- a) 0.8 million b) 1.8 million
- D) 1.8 MIIIO
- c) 2.8 million
- d) 3.8 million e) 4.8 million

# **Question 2**

# What combination of laboratory tests seems to be most sensitive and specific for chronic alcohol use?

- a) Blood gas analysis and creatinine kinase concentration
- b) Carbon monoxide concentration in exhaled air and fasting blood sugar
- c) Red blood cell concentration and urinary urea concentration
- d) Methanol and acetone concentrations
- e) Gamma-GT and carbohydrate-deficient transferrin concentrations

## **Question 3**

# What drugs are approved in Germany for the purpose of keeping alcohol-dependent patients abstinent?

- a) Acamprosate and naltrexone
- b) Nalmefen and baclofen
- c) Clomethiazol and disulfiram
- d) Lorazepam and diazepam
- e) Oxazepam and chlordiazepoxide

## **Question 4**

# Which of the following is a recommended element of qualified detoxification?

- a) Fasting
- b) Psychotherapy based on depth psychology
- c) Motivational discussions
- d) Creative therapy
- e) Biographical history

## **Question 5**

Which of the following is included in the DSM-5 as one of the 11 diagnostic criteria for an alcohol-related disorder?

- a) The diagnostic criteria for another mental or behavioral disorder caused by the same substance are not simultaneously satisfied.
- b) Craving, i.e., a strong desire for alcohol, is present.
- c) Excessive alcohol use has been present for at least one month or repeatedly over the past year.
- d) Abnormal behavior is present that can lead to impairment or negative consequences in interpersonal relationships.
- e) Clear evidence indicates that substance use is responsible for the disorder.

# **Question 6**

# What is the neuropsychological explanation for the development of alcohol dependency?

- a) Like other addictive substances, alcohol promotes the release of dopamine in the brain's "reward system" (including the nucleus accumbens); this, in turn, rewards alcohol consumption, in a vicious cycle.
- b) Chronic alcohol use lessens the sensitivity of  $\mathsf{GABA}_{\mathsf{B}}$  receptors.
- c) Because of a genetic difference in persons prone to alcoholism, there is an increased neuronal calcium inflow through the open ion channels of NMDA receptors.
- d) Increased histone modification in the DRD3 genes of the striatum leads to chronification of the disorder.
- e) Alcohol promotes the expression of acetylcholine receptors, leading to tolerance.

# **Question 7**

# What are the most serious complications of alcohol withdrawal?

- a) Seizures and delirium tremens
- b) Tremor and hyperhidrosis
- c) Insomnia and restless legs syndrome
- d) Pruritus and ulceration
- e) Sleep apnea and visual loss

## **Question 8**

What percentage of alcohol-dependent patients relapse if given no further treatment beyond detoxification?

- a) 55%
- b) 65%
- c) 75%
- d) 85%
- e) 95%

# **Question 9**

#### Which of the following may be an indication for "reduced drinking"?

- a) Harmful alcohol use with demonstrated dependence
- b) Multiple failed professionally supported attempts to abstain
- c) High motivation for abstinence
- d) Stable social predictors
- e) Lack of a self-help group nearby

## **Question 10**

# What is the approximate per capita consumption of pure alcohol in Germany?

a) 6 L/year b) 8 L/year c) 10 L/year d) 12 L/year Additional material to:

Alcohol Dependence and Harmful Use of Alcohol Diagnosis and Treatment Options

by Anil Batra, Christian A. Müller, Karl Mann, and Andreas Heinz

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#### eREFERENCES

- e1. Gaertner B, Freyer-Adam J, Meyer C, John U: Alkohol Zahlen und Fakten zum Konsum. In: DHS (eds): Jahrbuch Sucht 2015, Lengerich: Pabst 2015.
- e2. Pabst A, Kraus L, Matos EGD, Piontek D: Substanzkonsum und substanzbezogene Störungen in Deutschland im Jahr 2012. In: DHS (eds): Jahrbuch Sucht 2013, Lengerich: Pabst 2013.
- John U, Hanke M: Alcohol-attributable mortality in a high per capita consumption country Germany. Alcohol Alcoholism 2002, 37; 581–5.
- e4. Effertz T: Die volkswirtschaftlichen Kosten gefährlicher Konsumgüter – Eine theoretische und empirische Analyse für Deutschland am Beispiel Alkohol, Tabak und Adipositas. Frankfurt am Main: Peter Lang Verlag 2015.
- e5. Seitz HK, Bühringer G, Mann K: Grenzwerte für den Konsum alkoholhaltiger Getränke. In: DHS (eds): Jahrbuch Sucht 2008, Geesthacht: Neuland Verlagsgesellschaft mbH 2009.
- e6. DiFranza JR, Guerrera MP. Alcoholism and smoking. J Stud Alcohol. 1990; 51: 130–5.
- e7. Breslau N, Kilbey MM, Andreski P: DSM-III-R nicotine dependence in young adults: prevalence, correlates and associated psychiatric disorders. Addiction. 1994; 89: 743–54.
- e8. Heinz A, Batra A, Scherbaum N, Gouzoulis-Mayfrank E: Neurobiologie der Abhängigkeit: Grundlagen und Konsequenzen für Diagnose und Therapie von Suchterkrankungen. Stuttgart: Kohlhammer 2012.
- e9. Simms G0. ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Bertrams 1992.
- e10. Falkai P, Wittchen HU, Döpfner M: Diagnostisches und Statistisches Manual Psychischer Störungen – DSM-5. Göttingen: Hogrefe 2014.
- e11. Maier W, Falkai P, Heinz A: Stellungnahme der Deutschen Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde (DGPPN) Wann wird seelisches Leiden zur Krankheit? Zur Diskussion um das angekündigte Diagnosesystem DSM-V. www.dgppn.de/fileadmin/user\_upload/\_medien/down load/pdf/stellungnahmen/2013/DGPPN-Stellungnahme\_DSM-5\_Final.pdf (last accessed on 1 December 2015).
- e12. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG: The Alcohol Use Disorders Identification Test (AUDIT): Guidelines for use in primary care. Geneva: World Health Organization 2001.
- e13. Levola J, Aalto M: Screening for at-risk drinking in a population reporting symptoms of depression: A validation of the AUDIT, AUDIT-C, and AUDIT-3. Alcohol Clin Exp Res 2015; 39: 1186–92.
- e14. Miller WR, Rollnick S: Motivierende Gesprächsführung. Freiburg im Breisgau: Lambertus-Verlag (3<sup>rd</sup> eds) 2015.
- e15. Körkel J: Kontrolliertes Trinken: Vom Abstinenzfundamentalismus zur bedarfsgerechten Behandlungsoptimierung. Sucht aktuell 2001; 8: 16–23.
- e16. Stellungnahme der fünf Selbsthilfe- und Abstinenzverbände zum Ambulanten Gruppenprogramm zum kontrollierten Trinken (AkT). Sucht 46, 457–8.
- e17. Mann K, Batra A: Community based management of alcohol dependent patients. Evaluation of a combined inpatient and ambulatory treatment concept. Psychiatr Prax 1993; 20: 102–5.