

REVIEW

Alcohol-related chronic exocrine pancreatic insufficiency: diagnosis and therapeutic management

A proposal for treatment by the Italian Association for the Study of the Pancreas (AISP) and the Italian Society of Alcoholology (SIA)

Raffaele PEZZILLI ^{1, 2 *}, Fabio CAPUTO ^{3, 4}, Gianni TESTINO ⁵,
Valentino PATUSSI ⁶, Giovanni GRECO ⁷, Livia MACCIÒ ⁸, Maria Raffaella ROSSIN ⁹,
Davide MIONI ¹⁰, Patrizia BALBINOT ⁵, Claudia GANDIN ¹¹, Francesca ZANESINI ¹²,
Luca FRULLONI ¹³, Sarino ARICO ¹⁴, Luigi C. BOTTARO ¹⁵, Rinaldo PELLICANO ¹⁶,
Emanuele SCAFATO ¹¹, the Italian Society of Alcoholology (SIA) ‡

¹Pancreas Unit, Department of Gastroenterology, Polyclinic of Sant'Orsola, Bologna, Italy; ²Italian Association for the Study of the Pancreas, Rome, Italy; ³Department of Internal Medicine, SS. Annunziata Hospital, Cento, Ferrara, Italy; ⁴G. Fontana Center for the Study and Multidisciplinary Treatment of Alcohol Addiction, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; ⁵Regional Alcohol Center of Liguria Region, ASL3, San Martino Hospital, Genoa, Italy; ⁶Department of Alcoholology, Hospital of Florence, Florence, Italy; ⁷Department of Mental Health and Pathological Dependency, AUSL Romagna, SerT Ravenna, Ravenna, Italy; ⁸Alcohol Unit, ASL2 Savonese, Savona, Italy; ⁹ASST Fatebenefratelli, Sacco Hospital, Milan, Italy; ¹⁰Casa di Cura Parco dei Tigli, Villa Di Teolo, Padua, Italy; ¹¹National Observatory on Alcohol, National Institute of Health, Rome, Italy; ¹²Private practitioner, Genoa, Italy; ¹³Department of Medicine, Pancreas Institute, University of Verona, Verona, Italy; ¹⁴Unit of Gastroenterology, Mauriziano Hospital, Turin, Italy; ¹⁵ASL 3 Genovese, Genoa, Italy; ¹⁶Unit of Gastroenterology, Molinette Hospital, Turin, Italy

‡Members are listed at the end of the paper.

*Corresponding author: Raffaele Pezzilli, Pancreas Unit, Department of Gastroenterology, Polyclinic of Sant'Orsola, Via Albertoni 15, Bologna, Italy. E-mail: raffaele.pezzilli@aosp.bo.it

ABSTRACT

Current estimates of the prevalence of chronic pancreatitis, one of the most common causes of exocrine pancreatic insufficiency, are in the range of 3-10 per 100,000 people in many parts of the world. Alcohol consumption is a very important risk factor for exocrine pancreatic insufficiency and is involved in nearly half of all cases. The main hypothesis regarding the role of chronic alcohol consumption in pancreatitis is that there must be additional environmental or genetic risk factors involved for ongoing damage to occur. Treatment of patients with alcohol-related exocrine pancreatic insufficiency is complex, as the patient has two concomitant pathologies, alcohol-use disorder (AUD) and exocrine pancreatic insufficiency/chronic pancreatitis. Alcohol abstinence is the starting point for treatment, although even this along with the most advanced therapies allow only a slowdown in progression rather than restoration of function. This position paper of the Italian Association for the Study of the Pancreas and the Italian Society of Alcoholology provides an overview of the pathogenesis of alcohol-related pancreatitis and discuss diagnostic issues. Treatment options for both exocrine pancreatic insufficiency/chronic pancreatitis (with a focus on pancreatic enzyme replacement therapy) and AUD (acamprosate, disulfiram, oral naltrexone, long-acting injectable naltrexone, sodium oxybate, nalmefene, baclofen, and psychosocial interventions) are also reviewed.

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Alcohol is the main cause of death and disability-adjusted life-years (DALYs) in those aged <24 years, accounting for 3.8% of all deaths and 4.6% of DALYs globally.¹ The gastrointestinal, cardiovascular and nervous system are the most affected by alcohol; among gastrointestinal pathologies, alcohol-related disorders of both pancreatic acinar and ductal cells are frequent. Alcohol is a very important risk factor for exocrine pancreatic insufficiency, and is involved in about 45% of cases.² Both alcohol and smoking promote progressive overturn of parenchyma, with stimulation of pancreatic stem cells and progressive organ fibrosis. However, for severe chronic pancreatitis to develop, large quantities of ethanol are required, with one study showing development of severe chronic pancreatitis with an ethanol intake of 60-80 g/day for 12 years.³

The first study reporting the prevalence of chronic pancreatitis estimated the prevalence of this disease in the range of 3-10/100,000 people in many parts of the world.⁴ In more recent studies, prevalence has been estimated at closer to 50/100,000 people.^{5,6} The most important medical problems associated with the disease include abdominal pain, steatorrhea, diabetes mellitus and the possibility that chronic pancreatitis is a premalignant condition.^{7,8} Durbec and Sarles⁹ clearly demonstrated that alcohol is a risk factor for chronic pancreatitis and the relative risk would be multiplied by a factor of approximately 1.4 when moving from one 20-g intake to the next. Furthermore, the increase appears to be more rapid when moving from nondrinking status to that of 20 g of alcohol per day. In Western countries, alcohol is the factor most frequently associated with chronic pancreatitis; alcoholic chronic pancreatitis presents clinically in young adults 30-40 years of age, with a higher prevalence among males. The histological lesions are

chronic *ab initio* and, clinically, the disease is characterized by recurrent attacks of abdominal pain.

In Western countries, in the period from 1940 to 2003, alcohol became increasingly involved as an etiological factor for chronic pancreatitis, from involvement in 19% of cases¹⁰ to 50% of cases,¹¹ with some studies reporting alcohol involvement in as many as 80% of cases.^{9,12} The results of the studies of the Marseille group¹² regarding the etiology of chronic pancreatitis were subsequently confirmed by others in Europe,¹³⁻¹⁵ Brazil,¹⁶ Australia¹⁷ and South Africa.¹⁸ Moreover, four consecutive surveys carried out in Japan from 1970 to 1979, 1977 to 1984, in 1994, and in 1999¹⁹ showed that alcohol as an etiological factor accounted for nearly 60% of cases of chronic pancreatitis at all time points. Similar results have been subsequently confirmed by others.^{20,21} The impact of a changing lifestyle, especially in developing countries, may contribute to modification of the etiology of chronic pancreatitis. For example, alcohol consumption in developing countries has increased²² and this has changed the etiology of chronic pancreatitis in those countries, whereas in Europe and the United States of America (USA), there was a progressive reduction in alcohol consumption from 1961 to 1991.²³

Born from a collaboration between the Italian Association for the Study of the Pancreas (AISP) and the Italian Society of Alcoholology (SIA), this paper provides an overview of the pathogenesis of alcohol-related pancreatitis and discusses diagnostic issues. In particular, since many alcoholic chronic pancreatitis patients experience problems both with exocrine pancreatic insufficiency (EPI) and alcohol abuse, the therapeutic options for EPI and alcohol use disorder (AUD) are reviewed.

Alcoholic pancreatitis: acute or chronic disease?

Not all individuals with chronic alcohol consumption develop pancreatitis.²⁴ In fact, alcohol on its own is only one side of the problem. The main hypothesis for pancreatic damage with alcohol consumption identifies the potential role of additional environmental and genetic risk factors in the ongoing damage (Figure 1).^{25, 26} In individuals consuming alcohol with no pancreatic disease, alcohol may induce activation of both cellular and molecular adaptive systems that protect the pancreas from toxic effects.²⁷ Therefore, alcohol consumption may activate both damaging and protective effects, and alcohol-related acute or chronic pancreatitis is observed when the damaging effects prevail over the protective effects.²⁷ Notably, smoking²⁸ and gene mutations, such as the *N34S* mutation of the *SPINK1*-gene and cystic fibrosis transmembrane conductance regulator (*CFTR*)-gene mutations, seem to be significantly correlated with chronic alcoholic pancreatitis²⁹⁻³¹ and may facilitate the development of pancreatic diseases *via* the unfolded protein response of the endoplasmic reticulum. Finally, there are genetic polymorphisms in the *PRSS1*, chymotrypsin C-gene (*CTRC*), *SPINK1*,

carboxypeptidase A1-gene (*CPA1*), carboxyl ester lipase-gene (*CEL*) and *CFTR* genes that lead to pancreatitis due to early intrapancreatic trypsinogen activation or due to the activation of unfolded protein response.

In a large prospective study on acute pancreatitis carried out in Italy, it was found that approximately 10% of patients had pancreatitis-related to alcohol abuse³² and alcoholic pancreatitis are positively associated with the severity of the disease.³³ The question is whether the gland heals completely after the first attack of pancreatitis in alcoholics or if acute pancreatitis represents the first manifestation of chronic pancreatitis. A study conducted in European countries reported that >25% of patients studied at the first episode of acute pancreatitis had recurrent pancreatitis, of which the majority (78.8%) were young males (mean age 43 years), and alcohol was the most frequent etiological factor (57%) associated with recurrence.³⁴ However, the mortality rate was significantly lower among patients with alcoholic pancreatitis (6.9%) than among those with biliary (30%) or idiopathic pancreatitis (25%), and the majority of deaths (82.4%) occurred at the second attack of pancreatitis.³⁴ A prospective study in chronic alcoholic males with first attack of acute pancreatitis reported that 70.5% of patients had developed clinical and morphological signs of chronic pancreatitis at the 3-year follow-up.³⁵ In a study on patients with a single episode of acute pancreatitis, pancreatic insufficiency assessed using secretin cerulean test was more frequent and severe in patients with acute alcoholic pancreatitis than after biliary pancreatitis.³⁶ Another study showed that patients who underwent surgery for acute necrotic pancreatitis had both acute necrotic and chronic pancreatic lesions, and the chronic pancreatic lesions had characteristics of chronic calcifying pancreatitis consisting of perilobular and intralobular fibrosis, loss of exocrine parenchyma, dilated interlobular ducts and protein plugs within dilated ducts.³⁷ However, a prospective follow-up study reported that the number of patients with acute pancreatitis in whom chronic changes were observed increased independently of alcohol consumption.³⁸

Severe and long-lasting episodes of pain sepa-

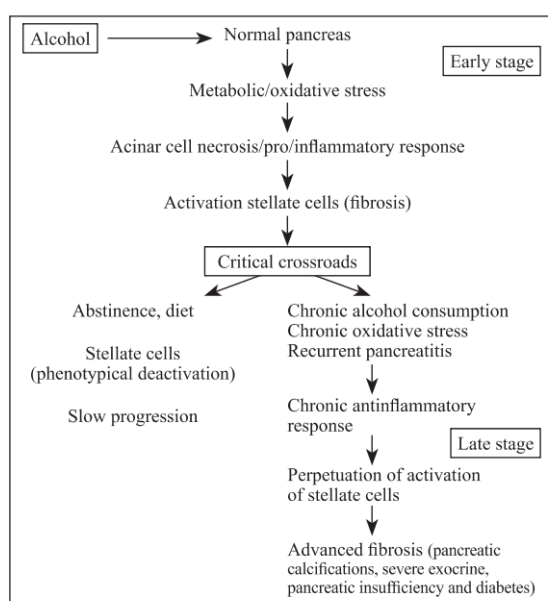


Figure 1. Pathogenesis of alcoholic pancreatitis.

rated by 1-2 month pain-free intervals are more frequent in alcoholic chronic pancreatitis and idiopathic juvenile or early-onset chronic pancreatitis.³⁹ Chronic pancreatitis is generally characterized by loss of endocrine and exocrine function with progressive fibrosis and pain.⁴⁰ Pancreatic fibrosis is induced by an injury involving interstitial mesenchymal cells, acinar cells or the duct cells, whereby the pancreatic stellate cells are transformed into myofibroblasts with excessive deposition of extracellular matrix and tissue injury.^{41, 42} It has also been reported that alcohol activates pancreatic stellate cells consequently inducing fibrosis *via* molecular mediators (transforming growth factor-beta, platelet-derived growth factor) and proinflammatory cytokines (interleukin-1, interleukin-6 and tumor necrosis factor-alpha).^{40, 43}

In conclusion, acute pancreatitis in chronic alcoholics is the first manifestation of chronic pancreatitis that becomes clinically apparent immediately or during the follow-up period. Pancreatic functional changes caused by alcohol intake progress even after cessation of alcohol use, although the progression is slower and less severe.⁴⁴

The role of antioxidants in the development of chronic pancreatitis

It has been claimed that pancreatitis develops with persistent exposure to xenobiotics⁴⁵ and that previous dietary insufficiency of micronutrients, such as methionine and ascorbic acid, facilitates pancreatitis.⁴⁶ The diversion of free radical oxidation products into the interstitium causes mast cell degranulation and leads to inflammation and fibrosis.⁴⁵ In addition, the daily exposure of acinar cells to trypsin in patients with PRSS1 or SPINK1 mutations may alter glutathione reserves, and patients with a CFTR mutation are more vulnerable to the possible coexistence of pancreatitis and intraductal calcifications when the residual CFTR protein is immobilized by electrophilic stress.⁴⁷ It has also been reported that low dietary intake of both methionine and vitamin C is associated with deficiency of selenium,⁴⁸ which may lead to the development of chronic pancreatitis by increasing the oxidant

load due to persistent exposure to environmental chemicals that induce cytochrome P-450 monooxygenases.⁴⁹

Diagnosis of chronic pancreatitis

Clinically, the early phase of chronic pancreatitis is characterized by pain or recurrent episodes of pancreatitis and complications, whereas in the advanced phase, symptoms are related to the onset of exocrine and/or endocrine insufficiency.³⁹ From a practical point of view, pain is the main feature of early chronic pancreatitis and is associated with increased serum levels of pancreatic enzymes such as amylase and/or lipase. Usually magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography, before and after secretin administration, and endoscopic ultrasonography (EUS) are the most appropriate imaging techniques to diagnose early parenchymal and ductal changes.³⁹ Advanced chronic pancreatitis can be detected by ultrasonography (US), computed tomography (CT) and/or MRI. Therefore, the choice of imaging techniques should be based on available expertise, imaging availability and the cost involved. In advanced chronic pancreatitis, EUS is a minimally invasive imaging technique and can therefore be used for tissue characterization and treatment planning.³⁹ CT, MRI or EUS are the most appropriate modalities for the assessment of most morphological complications, such as a pseudocyst, fistula, pancreatic necrosis and pancreatic fluid collections, for planning medical, endoscopic or surgical treatment.³⁹

Assessment of exocrine pancreatic function

Chronic pancreatitis is an evolving process, in which exocrine function is progressively impaired due to reduced functional capacity, leading to exocrine failure in the late phase. To detect mild or moderate exocrine pancreatic impairment, invasive tests employing a hormonal secretagogue to stimulate pancreatic secretion can be useful, but such tests are not widely available.³⁹ In addition, these tests are sensitive but

poorly specific, *i.e.* they are not diagnostic.^{50, 51} An endoscopic pancreatic test has also been proposed as an alternative tool^{52, 53} and should be applied in selected cases when the presence of clinical suspicion and minimal morphological changes can help in the diagnosis.⁵⁴ Tubeless functions tests (fecal elastase-1) can be used in the follow-up of selected patients for identifying a progressive impairment in pancreatic function by which the chronicity of the inflammatory process can be confirmed.^{55, 56} The fecal elastase-1 test does not require a timed stool collection or special diet, has a high negative predictive value for pancreatic insufficiency, and a good sensitivity in patients with moderate and severe pancreatic failure.⁵⁷

The best method reported for the diagnosis of overt steatorrhea is 72-hour fat analysis using the van de Kamer method where patients must maintain adequate dietary fat intake (100 g/day) during the 3 days of the test and the normal output is <7 g of fat per 24-hour period. Other available methods include the Sudan staining of the feces which evaluates the number and size of fat globules per high-power field with a sensitivity of 94% and a specificity of 95%,⁵⁸ and the

steatocrit, which is a quantitative measurement of fat expressed as a proportion of an entire centrifuged homogenized stool sample.⁵⁹ All these methods for determining the fecal fat excretion are unpleasant for both the patient and laboratory personnel and are not usually available in all laboratories.

In patients with steatorrhea, a checklist based on patient complaints and physical examination of the feces has been proposed and validated (Table I).⁶⁰ It has also been suggested that magnesium in combination with hemoglobin, albumin, prealbumin, retinol binding protein and glycosylated hemoglobin can be used as a primary screening tool in the evaluation of the need for pancreatic enzyme replacement therapy (PERT).⁶¹ These data need to be confirmed, but it has been noted that retinol-binding protein is not readily available in all laboratories⁶⁰ and that a magnesium level of <2.05 mg/dL along with low prealbumin and hemoglobin levels indicate the need for PERT.⁶² Finally, from an economic point of view, the cost of the set of laboratory parameters for the Italian National Health Service is € 39, compared with € 20 for the determination of fecal elastase 1 and no cost for assessing clinical parameters.⁶⁰

Data on when to assess exocrine pancreatic function in asymptomatic alcoholics are scarce, with only one main study.⁶³ This study involved 72 chronic alcoholics, 40 with chronic pancreatitis and 32 with liver cirrhosis, who underwent liver biopsy, endoscopic retrograde cholangiopancreatography and a secretin-erulein test to assess possible liver involvement in chronic pancreatitis. The authors found that 29 of the 40 patients with chronic pancreatitis had abnormal liver histology, five had micronodular cirrhosis and were older than the others, whereas no relationship was found between the degree of pancreatic impairment and the type of liver injury. In addition, five liver cirrhosis patients had an endoscopic retrograde cholangiopancreatography picture consistent with chronic pancreatitis and two were females with an alcohol intake lower than the other females. It would be interesting to evaluate exocrine pancreatic function in chronic alcoholics to determine which patients have sub-clinical chronic pancreatitis.

TABLE I.— Checklist for clinical evaluation of severe exocrine pancreatic insufficiency.

Parameters to be evaluated
<i>Patient complaints</i>
1. Increase in daily bowel movements with fatty, bulky stools that are difficult to flush away
2. It is not always a daily symptom
3. Diarrhea occurs after meals 2 to 3 times a day in individuals with a normal lipid-content diet
<i>Physical examination</i>
1. Weight loss greater than 10% with respect to a healthy weight
2. Temporal scalloping
3. Interosseous wasting
4. Lack of subcutaneous fat
5. Nail leukonychia (hypoalbuminemia)
6. Signs of liposoluble vitamin deficit:
a. ecchymoses due to clotting abnormalities in the case of vitamin K deficiency
b. ataxia and peripheral neuropathy resembling Friedreich ataxia due to vitamin E deficiency
c. abnormalities such as night blindness and xerophthalmia due to vitamin A deficiency
d. contraction or muscle spasms, osteomalacia and osteoporosis (hypocalcemia)
7. Examination of the stool: fatty, bulky stools

Pancreatic cancer in chronic alcoholic pancreatitis

Alcohol is a potent inducer of cancer and there is a strong evidence linking alcohol consumption to the increased cancer risk.⁶⁴ It is also known that recurrent acute pancreatitis can lead to glandular damage causing irreversible changes in the pancreas characteristic of chronic pancreatitis. In recent years, accumulating evidence has defined pre-existing chronic pancreatitis as a strong risk factor for the development of pancreatic cancer.⁸ Generally pancreatic cancer is not detected immediately after diagnosis of chronic pancreatitis, and, pancreatitis appearing before the diagnosis of pancreatic cancer may be due to tumor-related ductal obstruction.⁸ Although the risk of developing pancreatic cancer appears to be highest in hereditary and tropical pancreatitis, a strong link exists between chronic pancreatitis and pancreatic cancer. In fact, only around 5% of patients with chronic pancreatitis develop pancreatic cancer over a 20-year period.⁸ Early diagnosis of pancreatic cancer in chronic pancreatitis is challenging despite the availability of modern

imaging techniques, and future development of sophisticated screening procedures may render this possible until which screening for pancreatic cancer is not recommended in patients with chronic alcoholic pancreatitis.⁸

Treatment of exocrine pancreatic insufficiency

Treatment of patients with alcohol-related exocrine pancreatic insufficiency is complex as these patients suffer from two pathologies, namely AUD and exocrine pancreatic insufficiency/chronic pancreatitis (Figure 2).

Do antioxidants have a place in therapy?

Theoretically antioxidants can be beneficial in the treatment of chronic pancreatitis as they can reduce inflammation and fibrogenesis. However, micronutrient antioxidant therapy in chronic pancreatitis has not shown benefit in the ANTICIPATE study,⁶⁵ and other clinical trials on the use of antioxidant therapy in pancreatitis have also failed to establish clear evidence of clinical efficacy for the prevention of inflammation.⁶⁶ Several other substances such as flavonoids have also been evaluated, but only in experimental settings.⁶⁶ Thus, antioxidant therapy is currently not considered routinely for the treatment of pain and inflammation in chronic pancreatitis.^{67, 68}

Pancreatic enzyme replacement therapy

Patients with mild-to-moderate exocrine pancreatic insufficiency do not require PERT.³⁹ Only patients experiencing maldigestion require PERT in order to ameliorate their nutritional status.³⁹ Available formulations contain pancreatic enzymes encapsulated in microgranules or minimicrospheres with a pH-sensitive coating to prevent the release and the subsequent inactivation of enzymes by gastric acid and to ensure release of the enzymes into the intestinal lumen where the pH is higher and optimal for the digestion and absorption of food. Currently, Italian guidelines consider minimicrospheres to be an ideal pancreatic formulation.⁶⁹ The initial recommended dose of pancreatic extract is 40,000-500,00 U of lipase per meal and 25,000 U per snack, which

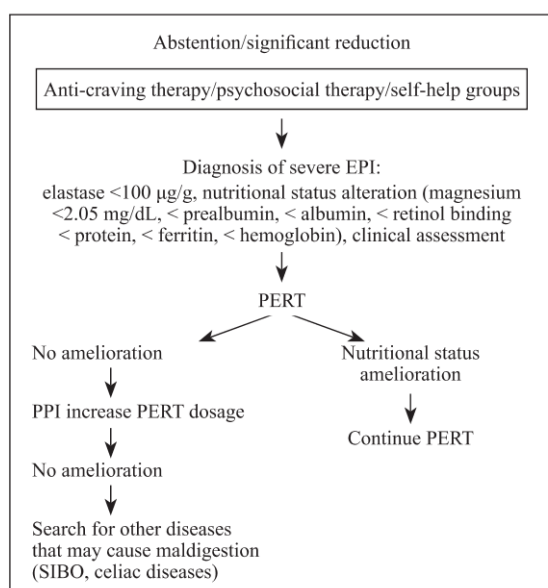


Figure 2. Exocrine pancreatic insufficiency (EPI) in subjects with harmful alcohol consumption and in alcoholic patients.

ALD: alcoholic liver disease; PERT: pancreatic enzyme replacement therapy; PPI: proton pump inhibitor; SIBO: small intestinal bacterial overgrowth.

can be progressively increased until steatorrhea sufficiently reduced and should be maintained over time.^{69, 70} A few precautions must be taken: food intake should be distributed across three main meals per day, and two or three snacks, and the pancreatic extracts must be ingested during the meals. A diet rich in fiber content is contraindicated because the fibrous material can interfere with proteolytic and amylolytic enzyme activity; acid-suppressing agents should only be utilized in patients who continue to experience symptoms of maldigestion despite administration of adequate doses of PERT.⁶⁹ Clinical assessments of patients on PERT therapy is important but continuous monitoring of fecal fat excretion may not necessary.³⁹

It should be noted that it is very difficult to completely resolve steatorrhea in severe pancreatic insufficiency; this may be due the fact that there are numerous interactions between pancreatic maldigestion, intestinal ecology and intestinal inflammation. Thus, in addition to the correction of pancreatic insufficiency using PERT and achievement of the most appropriate duodenal pH for optimal efficacy of these extracts, decontamination of the intestinal lumen and supplementation of bile acids, especially in surgical patients, should be explored in appropriate studies to evaluate how to attenuate intestinal inflammation.⁷¹ Finally, fat soluble vitamins and micronutrients, such as zinc and selenium, should be routinely assessed and administered whenever necessary.⁷²

Treatment of alcohol use disorder

The first step in the treatment of AUD is of course cessation of alcohol intake. Almost 50% of patients with AUD may develop symptoms of alcohol withdrawal which need to be treated appropriately with a pharmacological intervention; the gold standard are the benzodiazepines.⁷³ However, in some European countries, sodium oxybate and tiapride may be a further pharmacological opportunity for the treatment of the moderate form of withdrawal with the advantage to be used in the following phase of the maintenance of alcohol abstinence too.⁷³ Indeed, after the phase of detoxification, the patient must enter

in a multidisciplinary pathway for the treatment of AUD. In some cases, anti-craving therapy may be necessary.⁷⁴ Relational and psychosocial approaches must be made available to all patients with the aid of self-help groups.⁷⁵ In addition, any psychiatric comorbidity must be addressed. The European Medicines Agency (EMA) and the USA Food and Drug Administration (FDA) have approved acamprosate, disulfiram and oral naltrexone for the treatment of AUD (Table II).⁷⁴ The FDA has also approved the use of the long-acting injectable naltrexone; sodium oxybate is approved only in Austria and Italy by the national authorities (Table II).⁷⁶ The European Medicine Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) recently indicated the granting of marketing authorization for nalmefene, which is also used for the reduction of alcohol consumption (Table II).

Pharmacological intervention with approved medications

Disulfiram

Disulfiram irreversibly inhibits aldehyde-dehydrogenase, causing accumulation of acetaldehyde with ethanol intake, which can lead to "acetaldehyde syndrome" characterized by facial flushing, a purple rash over the neck and torso, tachycardia, hypertension, nausea, vomiting, diarrhea, and headaches with altered breathing. These symptoms appear 5-15 minutes after drinking alcohol and last from 30 minutes to a few hours. Awareness of the risk of acetaldehyde syndrome acts as a deterrent for alcohol consumption.⁷⁷ However, a study in alcohol dependent patients reported that experiencing the symptoms of acetaldehyde reaction at the beginning of disulfiram treatment may not lead to better treatment outcomes.⁷⁷ To ensure the correct administration of disulfiram, supervision by a carer/family member is helpful.

As matter of fact, a recent review confirmed that the effectiveness of disulfiram increases if administration is supervised by a carer able to ensure the patient's adherence⁷⁸

Disulfiram is not indicated in the presence of severe liver disease, peripheral neuropathy or optic neuritis. Moreover, disulfiram is not indicated

TABLE II.—*Drugs currently approved for the treatment of AUD: mechanism of action, clinical use, contraindications and dosages.*

Drug	Description
<i>Maintenance of complete abstinence from alcohol</i>	
Acamprosate (FDA-approved)	<ul style="list-style-type: none"> • Mechanism of action: N-methyl-D-aspartate glutamate receptor antagonist • Clinical use: anti-craving medication to be used in patients with relief craving taking into account that a reduction in the number of episodes of heavy drinking can be considered a positive result • Contraindications: severe kidney disease • Dosage: 1.3-2 g/day in 3 oral administrations for 12 months
Disulfiram (FDA-approved)	<ul style="list-style-type: none"> • Mechanism of action: aldehyde-dehydrogenase enzyme inhibitor • Clinical use: deterrent medication to be used in patients motivated to maintain complete abstinence from alcohol and in the presence of a carer/family member to be entrusted with the drug and its administration • Contraindications: cirrhosis, chronic coronary heart disease and peripheral neuropathy • Dosage: 800-1200 mg/day until the 4th day, then 400 mg/day from the 5th to the 7th day, then 200 mg/day for 5-6 months
Naltrexone (FDA-approved)	<ul style="list-style-type: none"> • Mechanism of action: μ- and κ-opioid receptor antagonist • Clinical use: anti-craving medication to be used in patients with reward craving, taking into account that a reduction in the number of episodes of heavy drinking can be considered a positive result • Contraindications: cirrhosis • Dosage: 50-100 mg/day orally, for 3-6 months or 380 mg intramuscularly (long-acting formulation) every 30 days for 6 months
Sodium oxybate (AIFA-approved)	<ul style="list-style-type: none"> • Mechanism of action: GABA_B receptors agonist • Clinical use: a) suppression alcohol withdrawal syndrome; b) anti-craving medication with alcohol-mimicking property with positive reinforcing effect to be used in patients with reward and relief craving and under the supervision of a carer/family member to be entrusted with the drug and its administration • Contraindications: poly-drug addiction and borderline personality disorders • Dosage: for the treatment of alcohol withdrawal syndrome, 50-100 mg/kg/day orally, every 4-6 hours for 7-10 days; as anti-craving, 50-75 mg/kg/day orally, every 6-8 hours for 3-12 months.
Baclofen (ANSM-approved)	<ul style="list-style-type: none"> • Mechanism of action: GABA_B receptors agonist • Clinical use: anti-craving medication to be used in patients with relief craving and alcoholic cirrhosis • Contraindications: severely impaired renal function, epilepsy (risk of lowering the seizure threshold), mood disorders (risk of manic and hypomanic episodes), suicidal ideation or suicide attempts (risk of overdose) • Dosage: 5 mg every 8 hours orally, increasing the dosage by 5-10 mg every 3 days up to a maximum of 80 mg/day divided into 3 daily doses for 1-3 months; discontinuation of the treatment should be gradual reducing the dose by 5-10 mg per week) until complete suspension
<i>Reduction of alcohol consumption in patients who have a high drinking risk level</i>	
Nalmefene (EMA-approved)	<ul style="list-style-type: none"> • Mechanism of action: μ- and δ-opioid receptor antagonist and partial agonist at κ-opioid receptors • Clinical use: to be used during a program of alcohol reduction in patients at high drinking risk level (defined as ≥ 60 g/day of pure alcohol for men and ≥ 40 g/day for women) who are currently not motivated towards reaching a complete abstinence from alcohol • Contraindications: it should be avoided in patients with alcohol withdrawal syndrome requiring pharmacological treatment (CIWA score > 10 points) and/or requiring immediate abstinence from alcohol • Dosage: 18 mg orally "as needed" for 6 months

in psychotic patients due to the risk of exacerbating symptoms of psychosis.⁷⁷ Treatment with disulfiram can only be started at 800-1200 mg/day for 3-4 days at least 12 hours after the last intake of alcohol, then reduced to 400 mg/day until the 7th day, followed by a maintenance dose of 200 mg/day for no more than 6 months; treatment can then be restarted after at least 30 days drug free.

Naltrexone

Naltrexone is a μ and κ -opioid receptor antagonist. It acts *via* reduction of dopamine release in the nucleus accumbens located in the ventral tegmental area of the limbic system.⁷⁹ Alcoholic patients who continue to drink during treatment with naltrexone thus report being

less inclined to consume large amounts of alcohol (anti-reward craving). Several double-blind controlled trials *versus* placebo have shown its efficacy, particularly when naltrexone, at doses of 50-100 mg/day, is used in combination with psycho-social treatments; indeed, medium-term treatment with naltrexone reduces relapses by 36%, and the probability of starting to drink again by 13%.⁸⁰ Furthermore, a recent review showed that naltrexone is effective in reducing the risk of binge drinking and, therefore, potentially suitable in subjects with AUD who are prone to consuming alcoholic beverages in this manner.⁷⁸

The most common adverse effects with naltrexone are headaches, nausea, dyspepsia, anorexia, anxiety and sedation. The use of a monthly 380 mg dose of intramuscular naltrexone is associated with better patient compliance.⁷⁸

Nalmefene

Nalmefene is a μ - and δ -opioid antagonist and κ -opioid partial agonist that has been reported to reduce heavy drinking in patients with AUD in several studies. Reduction in heavy drinking has been recently confirmed by two randomized, double-blind, placebo-controlled trials (ESSENCE 1 and ESSENCE 2) in which patients with AUD received nalmefene (18 mg) "as-needed" (defined as self-identified high-risk situations, using nalmefene when drinking is imminent or no more than 1 or 2 hours after drinking) for 6 months.^{81, 82} In addition, a *post-hoc* analysis of these two studies, only including patients with AUD with high-risk level of drinking (defined as ≥ 60 g/day for men and ≥ 40 g/day for women)⁸³ both at screening and randomization ("target population"), showed that nalmefene significantly reduced the number of heavy drinking days (treatment difference: -3.2 days; $P < 0.0001$) and total alcohol consumption (treatment difference: -14.3 g/day; $P < 0.0001$) at month 6 compared with placebo.⁸⁴

Finally, the authors of a recent systematic review confirmed the efficacy of nalmefene in reducing alcohol consumption highlighting, similarly to naltrexone, its effectiveness in reducing the risk of binge drinking.⁷⁸

Acamprosate

Acamprosate confers a neuroprotective effect, which can be explained through its antagonistic activity on the N-methyl-D-aspartate glutamate receptor with consequent normalization of glutamatergic hypertone, and subsequent reduction of the excessive flow of intracellular calcium ions.⁸⁵ By improving the dysphoria often found in chronic alcoholics, this mechanism indirectly causes a reduction in alcohol craving, particularly in the form of "relief" craving, with a consequent reduction in its consumption.⁸⁰ Controlled clinical trials have highlighted the efficacy of acamprosate both in reducing alcohol craving and in maintaining abstinence from alcoholic beverages. A meta-analysis of 17 controlled clinical trials including 4087 patients confirmed that acamprosate is superior to placebo in maintaining abstinence at 6 months (36.1% vs. 23.4%; $P < 0.001$). A Cochrane review reported greater efficacy with acamprosate in reducing alcohol consumption compared with placebo.⁸⁰ Furthermore, a recent systematic review confirmed the efficacy of acamprosate in reducing the number of relapses in abstinent patients, but did not show evidence of its effect in reducing the risk of binge drinking.⁷⁸

Since acamprosate is eliminated through renal excretion, it is not recommended in patients with renal failure. The main adverse effects are diarrhea, headaches and dizziness. The recommended doses and treatment duration are 1.3 g/day (weight < 60 kg) in two daily oral administrations and 2 g/day (weight > 60 kg) in three daily oral administrations, for 1 year.

Sodium oxybate

Sodium oxybate is a short-chain fatty acid, structurally similar to the inhibitory neurotransmitter γ -amino-butyric acid, which exerts an ethanol-mimicking effect on GABA_B receptors in the central nervous system.^{86, 87} In 1994, sodium oxybate was approved in Italy and Austria for the treatment of AUD,⁷⁷ and in 2002 it was approved by the FDA for the treatment of cataplexy in narcoleptic patients.⁸⁸ It has been shown that 40% to 70% of alcoholic patients receiving sodium oxybate achieve and maintain abstinence from

alcohol.⁸⁹ These favorable results have been confirmed by a recent Cochrane review highlighting that sodium oxybate is superior to naltrexone and disulfiram in maintaining alcohol abstinence, and in reducing alcohol craving.⁹⁰ Approximately 30% of patients treated with sodium oxybate experience adverse effects such as dizziness, sedation and asthenia; these adverse effects do not generally require drug discontinuation of treatment and usually disappear spontaneously with continued therapy.

The craving for and abuse of sodium oxybate is a controversial topic. Approximately 10% of patients develop a craving for the drug with very limited episodes of abuse. As highlighted in a Cochrane review,⁹⁰ only alcoholic patients with poly-drug addiction or psychiatric co-morbidities (such as Axis II borderline personality disorder) present a significant risk of developing an addiction to or abuse of sodium oxybate.^{77, 91, 92} Therefore, the risk of craving and subsequent abuse of sodium oxybate can be avoided by preliminary identification of potential abusers of sodium oxybate, in whom alternative pharmacological treatments should be considered.⁷⁷ Data from a recent randomized placebo-controlled clinical trial, showed the efficacy of granular sodium oxybate in a subgroup of AUD patients at high drinking risk (Table I); the maximum effect was obtained for the dose of 1.75 mg every 8 hours for a period of 3 months. This formulation is still being evaluated by the EMA for approval and marketing.⁹³

Thus, available data shows that sodium oxybate is effective in the treatment of AUD with an acceptable tolerability profile and mild adverse effects (<10%) that do not require treatment discontinuation.

Baclofen

Baclofen is a GABA_B receptor agonist, currently used to control spasticity. The agent's GABA_B agonist effect, mostly on the post-synaptic receptors in dopamine neurons, seems to be responsible for reduced dopamine release.⁹⁴ A recent consensus statement developed by a panel of European experts has shown that baclofen should be considered as second-line molecule in patients who have not responded to approved drugs for AUD; however, baclofen may

be considered as first-line treatment in patients with contraindications to approved medications (alcoholic cirrhosis). Furthermore, the authors stress that daily dose of baclofen should be adapted according to the patient's tolerability and response.⁹⁵ In France, the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) allowed the use of baclofen for the treatment of AUD at a maximum dosage of 80 mg/day;⁹⁶ this recommendation stems from the occurrence in recent years in France of several cases of high-dose baclofen intoxication.⁹⁷

Psychosocial interventions

Despite several psychotherapeutic hypotheses and attempts to treat AUD, none of these approaches succeeded in finding subtypes of patients who would benefit more from a differential treatment approach. In particular, the Matching Alcoholism Treatments to Client Heterogeneity (MATCH) project,⁹⁸ the comparison of the twelve-step facilitation (TSF) therapy,⁹⁹ the motivational enhancement therapy (MET),¹⁰⁰ and the cognitive-behavioral therapy (CBT)¹⁰¹ produced equally significant and sustained improvements in drinking outcomes, with little evidence that matching specific types of patients to a particular treatment improved the outcome.¹⁰² TSF therapy⁹⁹ is directed at achieving and maintaining alcohol abstinence by encouraging motivation to stop drinking, and treatment modalities are flexible and individualized to patient needs. MET¹⁰⁰ is usually a brief treatment focused on increasing patient motivation by enhancing their desire for change in behavior. CBT^{101, 103} is a psychotherapeutic approach that highlights how to recognize situations that present a risk of relapse, and to develop strategies to minimize this risk. CBT is highly structured compared with MET, although an empathic approach is encouraged in both forms of treatment. Thus, further studies identifying individualized approach to the treatment of alcoholism ("personalized medicine") seem to hold promise.¹⁰⁴

Among self-help groups, Alcoholics Anonymous (AA) is the most widespread association of patients engaged in dealing with alcohol problems, and was initiated in the USA in the 1930's.^{103, 105, 106} In addition, other mutual-help

organizations are also recognized. Among them, the socio-ecological method developed by Hudolin *et al.* in the early 1970's in Croatia has spread rapidly in Italy, reaching 2200 clubs within a few years.¹⁰⁷

Concluding remarks

Alcohol consumption is certainly the most important avoidable risk factor for the onset of exocrine pancreatic insufficiency/chronic pancreatitis. In Italy, there are about 1.5 million individuals with harmful consumption of alcohol and AUD.¹⁰⁸ It is estimated that only 10% of these individuals will develop severe disease; however, given that ethanol is particularly toxic to pancreatic tissue, it is clear that many people may have mild-to-moderate forms of exocrine pancreatic insufficiency. To date, estimation of the number of individuals with mild-to-moderate exocrine pancreatic insufficiency is not possible, as it is difficult to get an early diagnosis.

Early detection of chronic pancreatitis is necessary for both clinical and economic reasons. Early treatment can prevent or slow the cascade of events that lead to more serious forms of pancreatitis, with an undeniable improvement in quality of life¹⁰⁹ and associated significant cost savings; severe exocrine pancreatic insufficiency/chronic pancreatitis patients are a significant burden from an economic point of view in terms of both direct and indirect damage.¹¹⁰⁻¹¹² Professionals involved in the diagnosis of alcohol-related diseases should use the well-known pancreatic function test (fecal elastase-1), and the secretin-magnetic resonance cholangiopancreatography, which is also associated with excellent diagnostic results may be useful in selected cases.

Management of patients with alcohol-related exocrine pancreatic insufficiency should be done in a gastroenterological environment with professionals who possess the skills and knowledge to treat patients with AUD, and where this is not possible, a multidisciplinary approach that includes an alcoholologist is important. There is no doubt that PERT significantly improves the quality of life in patients with severe exocrine pancreatic insufficiency. Moreover, achieving alcohol abstinence is certainly the starting point

of any treatment strategy, although alcohol abstinence and drug therapies only slow the progression of pancreatitis without complete restoration of pancreatic function.

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Group name. Members of the Italian Society of Alcoholology (SIA) qualified as contributors include the following (in alphabetical order): Pierluigi ALLOSIO (Alcohol Unit, Turin, Italy), Maria Francesca AMENDOLA (Alcohol Unit, Cosenza, Italy), Cristina MENEGUZZI (Alcohol Unit, Pordenone, Italy), Vincenzo O. PALMIERI (Murri Clinic of Internal Medicine, Department of Biomedical Science and Human Oncology, University of Bari, Bari, Italy), Doda RENZETTI (Department of Internal Medicine, Mater Dei Hospital, Bari, Italy), Teo VIGNOLI (Unit of Addiction Treatment, Lugo, Ravenna, Italy) Fabio CAPUTO, Gianni TESTINO, Valentino PATUSSI, Giovanni GRECO, Livia MACCIÒ, Maria Raffaella ROSSIN, Davide MIONI, Claudia GANDIN, Sarino ARICO, and Emanuele SCAFATO, already listed in the authors' byline, also form part of the group name.

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