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► To cite this version:

Brendan Le Dare, Thomas Gicquel. Therapeutic Applications of Ethanol: A Review. Journal of Pharmacy and Pharmaceutical Sciences, 2019, 22, pp.525-535. 10.18433/jpps30572 . hal-02363309

HAL Id: hal-02363309

<https://univ-rennes.hal.science/hal-02363309>

Submitted on 10 Jul 2020

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Therapeutic Applications of Ethanol: A Review

Brendan Le Daré^{1,2}, Thomas Gicquel^{1,2}

¹. Univ Rennes, INSERM, INRA, Institut NuMeCan (Nutrition, Metabolisms and Cancer) Rennes, France.

². Rennes University Hospital, Forensic Toxicology Laboratory, Rennes, France.

Received, July 31, 2019; Revised, September 17, 2019; Accepted, September 31, 2019; Published, October 3, 2019.

ABSTRACT - Purpose: To review knowledge on therapeutic uses of ethanol and the latter's effectiveness and safety profiles in a range of indications. **Methods:** MEDLINE and PubMed databases were searched for relevant peer-reviewed papers published in English between 1888 and 2018 using the following search terms: ethanol, therapeutic, alcohol withdrawal syndrome, antiseptic, antidote, methanol, ethylene glycol, neurolysis, embolization, cyst, sclerosing agent, sclerotherapy, arteriovenous malformations, ablating agent. Studies providing information about association between alcohol and therapeutic indications, or mechanistic explanation for the association were included for review. **Results:** According to the World Health Organization, approximately three millions deaths worldwide are attributable to alcohol consumption each year. However, the low-to-moderate consumption of ethanol has a number of beneficial effects (mainly on cardiovascular mortality and diabetes). Hence, ethanol has an unusual spectrum of effects that seems interesting for therapeutic purposes. Ethanol's risk-benefit ratio appears to be positive in some therapeutic indications such as antidote to methanol or ethylene glycol poisoning, neurolysis, alcohol withdrawal syndrome, or antiseptic. **Conclusion:** With the development of interventional radio technologies, and thus extremely precise access to anatomical structures, alcohol has been given new indications - particularly as an embolization, sclerosing or ablation agent. Moreover, constant progress in our knowledge of ethanol's pharmacodynamics might highlight other therapeutic indications for this compound in the future. Ethanol's low cost and wide availability make it a valuable therapeutic agent, compared with other reference treatments. Furthermore, ethanol has a long track record of safety and effectiveness in the indications mentioned above.

INTRODUCTION

On September 21st, 2018, the World Health Organization (WHO) published its "Global Status Report on Alcohol and Health". The report provides an overview of alcohol consumption and harm worldwide. The WHO estimated that in 2016, approximately 3 million deaths (mainly in men) were attributable to alcohol consumption - corresponding to one death every 10 seconds. Consequently, with a global population of nearly 7.36 billion people that year, alcohol consumption caused one in 20 deaths. Beside the deaths, alcohol consumption generated 132.6 million disability-adjusted life years; this makes alcohol the third greatest risk for disease and disability. Deaths attributable to alcohol consumption were divided into three categories by the WHO: infectious disease, non-communicable disease, and injuries. In 2016, these categories respectively accounted for 12.9%, 28.7% and 58.4% of the deaths attributable to alcohol [1]. It is interesting to note that ethanol increases the risk of infectious diseases (such as HIV/AIDS, tuberculosis and lower respiratory tract infections) by impairing immune responses [2-4]. This effect

is compounded by other factors; for example, alcohol consumption promotes unprotected sex and thus exposes users to sexually transmitted diseases. Chronic alcohol abuse is associated with poor treatment adherence and thus contributes to the development of resistance - particularly in HIV infections [4,5]. Furthermore, alcohol is a major known risk factor in different types of injury, such as road traffic injuries, drowning, burns, poisonings, and falls [6-8]. Alcohol also promotes violent attacks, homicides, and suicides [1]. Lastly, alcohol is associated with the development and/or progression of many non-communicable diseases, including cardiovascular disease, cancer, liver disease, and mental, behavioral and neurodevelopmental disorders. These diseases account for most of the deaths ascribed to alcohol [9,10]. This toxicity is directly linked to (i) ethanol's ability to distribute itself throughout all body fluids, and (ii) the toxic-generating metabolism of ethanol.

Corresponding Author: Brendan Le Daré Univ Rennes, INSERM, INRA, Institut NuMeCan (Nutrition, Metabolisms and Cancer) F-35000 Rennes, France. E-mail: brendan.le.dare@chu-rennes.fr

Interestingly, low-to-moderate alcohol consumption is associated with beneficial health effects (summarized in Table 1). The “French paradox” is founded on this phenomenon, and several meta-analyses have evidenced an inverse correlation between low-to-moderate alcohol consumption (about to one to two units per day) and mortality from cardiovascular disease [11–13]. Similarly, a meta-analysis of data from 1,902,605 participants evidenced a peak risk reduction of developing type 2 diabetes for intakes between 10 to 14 grams of alcohol (corresponding to about a single standard drink or one units) per day in women and in non-Asian populations [14]. As was seen for the cardiovascular risk, the risk of developing type 2 diabetes became higher when consumption rose above 63 grams of alcohol per day. Some studies have suggested that the effect in these moderate consumers is due to the combination of a decrease in fasting insulin concentrations with an increase in the insulin sensitivity [15]. In 2018, a meta-analysis of data on 28 million people confirmed these results and showed a beneficial effect of low-to-moderate alcohol consumption on type 2 diabetes. However, the researchers concluded that overall mortality remains unchanged, given the increase in deaths due to other causes [16]. Recent studies have

tended to show that moderate alcohol consumption has a neuroprotective action, including beneficial effects in Parkinson’s disease, Alzheimer’s disease, and dementia. Even though the underlying mechanisms have not been fully characterized, researchers suggest that ethanol has an anti-inflammatory effect and increases neuroplasticity [17–20]. Furthermore, low-to-moderate ethanol consumption has also been linked to lower pain levels in and the delayed onset of Meniere’s disease [21,22]. For several decades, several studies reported that ethanol (one to three units of alcohol per day) had beneficial effects on bone mineral density [23,24]. This is thought to be due to the higher endogenous estrogen levels induced by ethanol [25,26]. Lastly, given alcohol’s influence on the immune system (and particularly its anti-inflammatory effects), some researchers have focused on the compound’s effects on autoimmune diseases. Indeed, beneficial effects have been reported; it seems that the incidences of rheumatoid arthritis, systemic lupus erythematosus and thyroid disease (both hyperthyroidism and hypothyroidism) are inversely associated with low ethanol consumption (three to 30 units per week, depending on the study) [27–34]. The underlying mechanism has not yet been identified.

Table 1. The main beneficial effects attributable to low-to-moderate consumption of ethanol

Beneficial effect	Mechanism	References
Decreased mortality from cardiovascular diseases (French paradox)	Antioxidant effect Increase in high density lipoprotein level Reduction in low density lipoprotein level	[11–13]
Decrease in the risk of developing type 2 diabetes	Decrease in fasting insulin concentrations and lower insulin sensitivity	[14,15]
Neuroprotective effect (against Parkinson’s disease, Alzheimer’s disease, and dementia)	Anti-inflammatory effect and increased neuroplasticity	[17–20]
Osteoporosis	Ethanol-induced high levels of endogenous estrogens	[23–26]
Antalgic effects	Central Nervous System depressant effect	[21]
Delayed onset of Meniere’s disease	Unknown	[22]
Autoimmune diseases (Systemic lupus, hyperthyroidism, hypothyroidism, rheumatoid arthritis)	Unknown	[27–34]

Just as ethanol has a spectrum of harmful and beneficial effects, the compound's risk-benefit ratio appears to be favorable in some indications - making alcohol a valuable therapeutic.

In this review, MEDLINE and PubMed databases were searched for relevant papers published in English between 1888 and 2018 using the following search terms: *ethanol, therapeutic, cyst, alcohol withdrawal syndrome, antiseptic, antidote, methanol, ethylene glycol, neurolysis, embolization, sclerosing agent, ablating agent, arteriovenous malformations, sclerotherapy*. Studies providing information about association between alcohol and therapeutic indications, or mechanistic explanation for the association were included for review.

THERAPEUTIC USES OF ETHANOL

Interestingly, scientists in the late 19th century regarded alcohol as a therapeutic agent [35,36]. Their knowledge of ethanol's metabolism and toxicity was summed up by Fermie in 1894 by the nuanced phrase "It can save as well as destroy". The use of alcohol was advocated empirically in indications of insomnia, fever, and cholera [36].

In the late 19th century and early 20th century, alcohol was listed in the British Pharmacopoeia (as

spiritus vini gallici). The *Lancet* and the *British Medical Journal* respectively considered that "brandy is so universally regarded as superior to all other spirits from a medicinal point of view", [37] and "no other kind of brandy corresponds better to medical necessities than pure grape brandy" [38]. At that time, alcohol was used as a cardiac stimulant, an antipyretic, a nutritional aid, a sedative, an inhalation anesthetic, and in angina [39]. Thus, even prominent scientists, such as Pasteur, recommended the use of alcohol for health purposes (Figure 1).

In the 1920s, American physicians made great efforts to obtain the right to prescribe beer, alcohol, and other alcoholic beverages to their patients for medicinal purposes. However, the Prohibition brought in by the Eighteenth Amendment put an end to these efforts. [41].

As the pathophysiology of alcohol-related disorders became better understood and better alternatives were discovered, the therapeutic use of alcohol declined during the 20th century. In 1949, the main indication for alcohol was the prevention of delirium tremens [39]. Today, ethanol is still used in evidence-based medical practice in a number of indications (reviewed below, and summarized in Table 2).

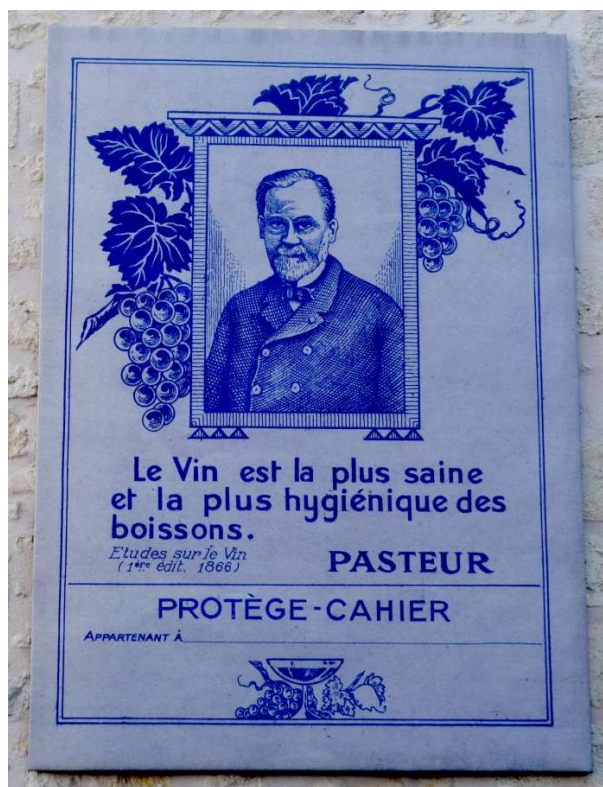


Figure 1. Promotional label of old wine brands entitled: « *Le vin est la plus saine et la plus hygiénique des boissons* » ("Wine is the healthiest and most hygienic drink"). Quotation from Pasteur's book "*Etudes sur le vin*" ("Studies on wine") from 1866 [40].

Table 2. The main therapeutic indications of ethanol

Indication	Mechanism	References
Antiseptic	Denaturation of cytoplasmic and membrane proteins Inhibition of nucleic acid and protein synthesis	[42,43]
Alcohol withdrawal syndrome	A gamma-aminobutyric acid agonist (sedation through inhibition of the central nervous system)	[44–48]
Antidote for methanol or ethylene glycol intoxication	A competitive substrate for alcohol dehydrogenase (ADH), blocking the toxic metabolism of methanol and ethylene glycol	[49–52]
Neurolysis	Nonselective destruction of nervous tissue through the precipitation of cell membrane proteins, lipid extraction, and demyelination, leading to Wallerian degeneration	[53–61]
Embolization	Induction of thrombosis by denaturing blood proteins, denuding the vascular wall of endothelial cells, precipitating the latter's protoplasm, and segmentally fracturing the vascular wall at the internal elastic lamina	[62–74]
Sclerosing agent	Herniated disks Ethanol desiccates the disk, resulting in a retraction of the aqueous nucleus and thus a reduction in intradiscal pressure Sclerotherapy of nodules Dehydration of epithelial cells and denaturation of cyst proteins, leading to obliteration of the cyst through coagulant necrosis, reactive fibrosis, and small vessel thrombosis	[75–82]
Ablating agent	Necrosis of parts of the heart area exposed to ethanol, abolishing the arrhythmic foci	[83–92]

Antiseptic

Today, the best-known use of ethanol in therapy is certainly its external use as a disinfectant antiseptic. Indeed, ethanol (along with isopropanol and n-propanol) is the alcohol most widely used as an antimicrobial disinfectant and antiseptic. Ethanol has a broad spectrum of action against vegetative bacteria, including mycobacteria (but not sporulating bacteria), viruses, and fungi [42]. Alcohol exerts its activity by denaturing membrane and cytoplasmic proteins, interfering with cell metabolism, and thus producing cell lysis. Unlike other antiseptics, ethanol's effectiveness is not correlated linearly with its concentration. The antimicrobial activity is optimal in the 60% to 90% range but falls off markedly below 50% [42].

The medical indications in this field mainly concern skin antisepsis and hard surface disinfection. Given the absence of residual action after evaporation, ethanol is usually combined with other antiseptics (e.g. chlorhexidine and povidone iodine) [43].

Fungal resistance to alcohols by phenotypic modulation has been described for many years, although the data on bacterial and viral resistance are reassuring [42]. However, some recent studies have suggested an increase in bacterial resistance to alcohols in recent years; in particular, the *Enterococcus faecium* strains isolated in hospitals after 2010 show an isopropanol tolerance threshold 10 times greater than that measured for older strains [93].

Alcohol withdrawal syndrome

In addition to ethanol's external use, this alcohol is commonly used internally in various indications. In France, ampoules of absolute ethanol are marketed under the trade name CURETHYL® for acute adjunct therapy during alcohol withdrawal management. Depending on the type of withdrawal syndrome, several ampoules are administered a day (at decreasing doses) [44].

Despite this marketing authorization and the use of ethanol in alcohol withdrawal management, the effectiveness of this procedure is subject to

debate in the literature [45,46]. Furthermore, inconsistent pharmacokinetics and a narrow therapeutic index mean that the routine use of this drug is not recommended by some researchers [45].

Hence, benzodiazepines are still considered to be the first-line treatment for alcohol withdrawal syndrome, due to their efficacy and safety profile [48]. In the event of resistance to benzodiazepines during the management of alcohol withdrawal, Dixit et al (2016) suggested a protocol using enteral ethanol. Fifty percent of the patient's estimated ethanol intake is administered as beer or vodka via a nasogastric tube every 4 to 6 hours for 24 hours, along with lorazepam. If the symptoms persisted, the ethanol dose was increased to 100% of the estimated daily intake. Treatment was continued for a minimum of three days, until the symptoms of alcohol withdrawal syndrome had disappeared, or for a maximum of seven days [47].

Ethanol as an antidote

Ethanol undergoes intense oxidative phase I metabolism by alcohol dehydrogenase (ADH) and cytochrome P450 2E1, which gives rise to acetaldehyde. The latter is a powerful toxin, and has many harmful effects. Ultimately, acetaldehyde is metabolized to acetate and thus eliminated by acetaldehyde dehydrogenase [94].

In cases of methanol or ethylene glycol intoxication, ethanol can be used as a competitive ADH substrate in order to significantly reduce the production of the toxic metabolites of methanol (i.e. formaldehyde) and ethylene glycol (i.e. glycolic acid and oxalic acid). The treatment goal is to maintain an ethanol level of between 1 and 1.5 g/L until the serum concentration of methanol or ethylene glycol has fallen to below 0.20 g/L [49,50].

Some researchers have compared the effectiveness of ethanol and fomepizole (the second reference treatment that act by inhibiting ADH) in combating methanol poisoning. Although ethanol is associated with a higher incidence of complications and adverse effects, no differences in clinical effectiveness were found - suggesting that ethanol is still useful in this indication [51]. Rietjens et al (2014) compared the respective advantages and disadvantages of fomepizole and ethanol in the treatment of ethylene glycol and methanol poisoning. Although fomepizole is easier to handle, ethanol is still used as a first-line antidote in some medical centers due to its low cost, ready availability, and familiarity for physicians [52].

Neurolysis

Ethanol is also indicated in chemical neurolysis for analgesic purposes and in the treatment of spasticity [53]. The main analgesic indications are the destruction of scar neuroma, the treatment of cancer pain (such as neuropathic pain caused by neoplastic invasion or of paraneoplastic origin), the treatment of various viral pain manifestations (such as shingles and post-herpetic neuralgia), and treatment-refractory chronic pain and sympathetically mediated pain [54–57]. Ethanol (typically in the 50%-100% range) is injected locally into the medullary, perimedullary or peripheral target nerve with electrostimulation guidance [54,58].

Ethanol produces the nonselective destruction of nervous tissue through precipitation of cell membrane proteins, lipid compound extraction, demyelination, and Wallerian degeneration. Ethanol injection reportedly produces an initial burning sensation along the nerve's path, followed by numbness in the same areas. Adverse effects include dysesthesia, hyperesthesia, cardiac rhythm disturbance, hypotension, skin and non-target-tissue necrosis, and central nervous system excitation. Furthermore, alcohol injections can also cause a disulfiram-like reaction if the patient is taking an ADH inhibitor [57]. In rare instances, celiac plexus neurolysis can result in paraplegia due to (i) diffusion of the neurolytic agent into arteries supplying the spinal cord, and (ii) the contraction of lumbar segmental arteries in response to ethanol and phenol [59].

Unfortunately, the effectiveness of chemical neurolysis has never been evaluated in a randomized, controlled trial. In 2001, Furlan et al. reviewed chemical neurolysis (using alcohol or phenol) for the treatment of neuropathic pain in a total of 66 patients [60]. The results were contrasting: 44% of the patients experienced meaningful pain relief, whereas 19% experienced non-meaningful relief. For the remaining 37%, poor outcome reporting prevented any conclusions from being drawn. Interestingly, some researchers have compared the effectiveness of alcohol neurolysis with that of other treatments in certain indications. In the case of splanchnic nerve neurolysis, Koyyalangunta et al (2016) compared ethanol and phenol in terms of effectiveness, complications, and the duration of a beneficial effect; there were no differences between these two compounds, suggesting that the choice of neurolytic medication can be based on the clinician's judgement and product availability [61].

Embolization

Absolute ethanol has been used as a chemoembolization agent for many years, due to its thrombotic effect. Furthermore, technical progress in interventional radiology has enabled highly selective access to many anatomical areas [62]. Guidelines on ethanol chemoembolization (a technique mainly used in Japan, despite its off-label status) were published in 2016 [63]. Ethanol induces thrombosis by denaturing blood proteins, denuding the vascular wall of endothelial cells, precipitating the latter's protoplasm, and segmentally fracturing the vascular wall at the internal elastic lamina [64]. A 5- to 30-minute balloon occlusion can be used to control the blood flow during the procedure [63]. Based on this observation, percutaneous alcohol injections have two main therapeutic indications: the treatment of arteriovenous malformations, and tumor embolization.

There are literature reports on the ethanol embolization of various arteriovenous malformations (in the kidneys, jaw, periorbital area, neck, ears and the hands), and posttraumatic or congenital fistulas, with good levels of efficacy and safety [62,65–69]. Although absolute (99%) ethanol was used in most cases, more dilute (50–70%) ethanol is required for the treatment of microfistulas [67]. In a retrospective study of complications in 175 ethanol embolization procedures (mainly in the limbs, pelvic cavity, and trunk), Do et al. reported an acceptable risk of adverse effects; there were 27 (15%) minor complications (skin injury and transient peripheral nerve injury) and 5 (3%) major complications (an infection, a case of acute renal failure, a permanent nerve injury in the arm, a brain infarct, and a case of focal bladder necrosis) [67].

In the field of oncology, ethanol embolization is used (alone or in combination with ethiodized oil or polyvinyl alcohol) to treat cases of hepatocellular carcinoma [70], renal angiomyolipoma, and carcinoma [71–73]. Alcohol causes cell dehydration, coagulation necrosis, intratumor arterial thrombosis, and thus tumor ischemia. However, the combination of percutaneous ethanol injections with chemoembolization in the treatment of liver metastases does not appear to prolong patient survival [74]. In a study of 83 cases of hepatobiliary cancer, Sofue et al. reported that right portal vein embolization prior to hepatic resection is safe and effective, and reduces the risk of postoperative liver failure [70]. In 1999, Kalman et al. reviewed 3225 cases of renal cell carcinoma embolization, and found a low level of evidence

among all the publications. However, complete pre-operative renal artery embolization seems to facilitate the excision of large vein-invading tumors, and palliative embolization in non-operable tumors with serious hemorrhage appears to have been successful in most cases [73]. Lastly, ethanol's properties are of value in the treatment of recurrent malignant thyroid cancers (e.g. papillary thyroid carcinoma) for which the risk of surgical complications is too high or when the patient refuses surgery [75].

Ethanol as a sclerosing agent

In the European Union, DISCOGEL® (a radiopaque gel of 96% ethanol and micronized tungsten) is marketed as a class III medical device for the treatment of certain types of herniated disk [76]. In 2018, Sayhan et al. reported that the gel provided significant, complication-free pain relief (relative to preoperative pain levels) in 33 patients with a herniated disk up to 12 months after the procedure, and was not associated with complications [76]. The device's effectiveness has been attributed to the ethanol's desiccant action, resulting in a retraction of the disk's aqueous nucleus and thus a reduction in the intradiscal pressure.

Ethanol remains the most commonly used compound for cyst sclerotherapy, due to its availability, low cost and good tolerance. The main indications are hepatic, renal and thyroid cysts [77,78]. After aspiration of the cyst content, a volume of ethanol corresponding to 50% of the aspirated cyst's volume is injected. Ethanol's sclerosing mechanism may be due to dehydration of the epithelial cell walls and the denaturation of cyst proteins. This leads to coagulant necrosis, reactive fibrosis, small vessel thrombosis, and thus obliteration of the cyst [78]. After the injection of ethanol into the cyst, the patient is turned in different directions so that the alcohol comes into contact with the whole cyst wall. After approximately 20 minutes, the alcohol is removed by aspiration. The patient is usually followed up for three months. The sclerosis can be repeated - especially if the cyst is large.

The efficacy and safety data on percutaneous ethanol sclerotherapy are reassuring. In cases of hepatic cysts, Moorthy et al. showed that this procedure was as effective as laparoscopic unroofing, and was associated with a lower incidence of complications [79]. In cases of renal cysts, Akinci et al.'s report on 98 single-session sclerotherapies evidenced an average cyst reduction of 93% at the end of the first year. Furthermore, 17.5% of the cysts had completely

disappeared, 90% of patients reported a reduction in flank pain, and 87.5% of the hypertensive patients became normotensive [80]. Lastly, ethanol sclerotherapy seems to be effective and safe in the treatment of benign cystic thyroid nodules, after the first use of percutaneous ethanol in this indication was reported by Edmonds et al. in 1987 [81]. In a prospective study of 15 patients with predominant cystic thyroid nodules, Jayesh et al. showed that injection of 95% ethanol into the cyst with ultrasound guidance was associated with complete disappearance of the cyst in four patients, and with a significant reduction ($\geq 50\%$ of initial volume) in the cyst volume in nine patients. The two patients who failed to show a significant reduction in cyst volume had nodules ≥ 20 mL. Even though no complications were attributable to ethanol injection during the study's three-months follow-up period, mild transient pain or a burning sensation at the injection site may be experienced following sclerotherapy [78]. In some cases of thyroid nodules, ethanol ablation has been coupled with radiofrequency ablation - thus increasing the procedure's effectiveness [82].

Ethanol as an ablating agent in cardiology

Although radiofrequency catheter ablation remains the primary treatment for cardiac arrhythmias, alcohol ablation of the coronary artery seems to be a valuable alternative when the first-line treatment fails [83]. The first septal branch ablation techniques in humans appeared in 1994, and were used to treat New York Heart Association Functional Classification stage III or IV obstructive hypertrophic cardiomyopathy under echocardiographic guidance [84]. The volumes of ethanol currently used (1-2 mL) are lower than those used for embolization, and are infused over 30 to 60 seconds to avoid atrioventricular block. A balloon catheter is also kept inflated for at least 5 minutes, in order to prolong contact with the alcohol [85,86].

The main indications for alcohol found in the literature are ablation of ventricular tachycardia [87-89], ventricular fibrillation [90], and atrial fibrillation [91]. The success of these procedures are attributed to necrosis of the area of the heart area exposed to ethanol, and thus abolition of the arrhythmic foci. Accordingly, ethanol ablation is an excellent treatment option for arrhythmic foci located at deep myocardial sites, and those refractory to endocardial and epicardial ablation [83]. Although complications following ethanol ablations seem to be rare, some studies have reported a risk of atrioventricular block when the septal artery is targeted - requiring permanent

pacemaker implantation in up to one third of patients [92].

CONCLUSION

Since ethanol's toxicity is closely related to its oxidative metabolism, the severity of intoxication is also closely correlated with the amount of alcohol consumed. Given that therapeutic applications of alcohol involve small amounts, the reported safety profile is good. Furthermore, the duration of exposure is relatively short, and so the chronic toxicity of ethanol reported by the WHO is not of relevance in these therapeutic settings. Ethanol's low cost and wide availability make it a valuable therapeutic agent, compared with other reference treatments. Furthermore, ethanol has a long track record of safety and effectiveness in the indications mentioned above. With the development of interventional radio technologies, and thus extremely precise access to anatomical structures, alcohol has been given new indications - particularly as an embolization, sclerosing or ablation agent. Moreover, constant progress in our knowledge of ethanol's pharmacodynamics might highlight other therapeutic indications for this compound in the future.

ACKNOWLEDGMENTS

The authors thank English language editing and review services supplied by Biotech communication SARL and Pontchaillou University Hospital (F-35000, Rennes, France).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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