v. 2, n. 29, 2022

International Journal of Health Science

PHARMACOLOGICAL ASPECTS OF ETHANOL AND DRUG TREATMENT FOR CHRONIC ETHYLISM

Láysa Minelle Machado Duarte
Centro Universitário Uni LS
Brasília-DF
http://lattes.cnpq.br/3238085976305528

Michelle Assis de Oliveira
Centro Universitário Uni LS
Brasília-DF
http://lattes.cnpq.br/3702748665060916

Débora Santos Lula Barros
Centro Universitário Uni LS
Brasília-DF
http://lattes.cnpq.br/1459897614268075

Abstract: Ethanol in the form of an alcoholic beverage is the most consumed psychoactive substance worldwide, considered a potent depressant of the central nervous system, the drink is directly linked to a high rate of mortality and morbidities, which affect not only the individual but also the society in which it is inserted. In view of the seriousness of the problem that is alcoholism, the present research was carried out on the pharmacological aspects of ethanol and drug treatment for chronic alcoholism. An integrative review of the scientific literature was carried out with a database consisting of articles, monographs, dissertations and theses on the subject. In view of this, it appears that ethanol is a substance subject to dependence and when ingested in an abusive and chronic way it can lead to a series of complications in the body that correspond to more than 60 types of diseases, making evident the need for an effective treatment for this problem. The drugs used in the treatment of chronic alcoholism still present a series of reactions and contraindications, limiting their use, which imposes the need for the search, research and development of new pharmacological treatment options.
Keywords: Alcohol. Alcoholism. Alcoholism.

INTRODUCTION

Ethanol has been used in the form of an alcoholic beverage since prehistoric times. Its use began with the fermented drink, containing low alcohol content, where beers and wine were produced, present from the tables of powerful and rich people, to religious rituals and ceremonies. Around the 11th century, the Arabs in their stills developed the distilled beverage, containing a high alcohol content (LAPA, 1989; MELONI E LARANJEIRA, 2004). Today, alcohol is considered the most consumed psychoactive substance in the world, it has great acceptance, a symbol of joy and celebrations and its use is encouraged by the major media (REIS et al. 2014).

Apparently harmless, the act of drinking can become a problem both for the individual and his family, as well as for society, because it is a substance subject to dependence. Drunkenness begins when the amount of ethanol exceeds 50mg per 100 ml of blood, as alcohol intake increases, the effects of the substance become greater, developing resistance and dependence in the long term. The term chronic alcoholism is used to describe alcohol dependence, a serious public health problem, since, associated with its use, we have more than 60 types of diseases, from liver cirrhosis, various types of cancers, cardiovascular problems, disorders mental health and traffic accidents. Its medium and long-term use can bring a series of physical, mental and social complications (DUAILIBI and LARANJEIRA, 2007; COSTA, 2020).

According to the World Health Organization (WHO) about two billion people consume alcohol worldwide, whether in social drinking or as dependents, in 2005 the II Household Survey on the Use of Psychotropic Drugs in Brazil was carried out, indicating that 12, 3% of people surveyed, aged between 12 and 65 years, meet criteria for alcohol dependence and about 75% have drunk at least once in their lives, the data also indicate that alcohol consumption is increasingly precocious, including among children and adolescents (CHAGAS, 2014).

Considering that the chronic and abusive consumption of ethanol is linked to serious health problems and significantly associated with causes of morbidity and mortality worldwide, it is necessary to search for forms of treatment that are effective and lasting in order to minimize risks and rehabilitate substance dependents. The present study aimed to review in the scientific literature the pharmacological aspects of ethanol and

the forms of drug treatment for chronic alcoholism.

MATERIALS AND METHODS

For the development of the present study, an integrative review of the scientific literature was carried out, with the objective of gathering, synthesizing, organizing, and debating the investigated topic. The construction process of this research was based on different topics, in order to provide a more comprehensive understanding of the subject in question (BOTELHO; CUNHA; MACEDO, 2011).

Seeking to clarify the problem of this study, the research was carried out with the aim of expanding knowledge, providing the necessary basis for understanding and discussion on the subject.

Therefore, this review was carried out by searching the following databases: Scielo, BVS, Scholar Google, Portal CAPES and PAHO. These sites were chosen because they have scientific and reputable recognition in the area of health knowledge. To search for articles, the terms were used: alcohol, alcoholism, dependence, withdrawal syndrome and treatment of chronic alcoholism.

The inclusion criteria consisted of articles, monographs, dissertations and theses written in Portuguese, English and Spanish, available for access and published in the last 15 years. Files that for some reason did not fit the proposed objective and theme were excluded.

RESULTS AND DISCUSSONS

ETHANOL FROM A PHARMACOLOGICAL POINT OF VIEW

Ethyl alcohol, also known as ethanol, is a liquid, volatile, colorless substance with a strong odor and burning taste, with high water solubility and rapid absorption. It has a molecular structure CH3CH2OH, with a molecular weight of 46.07 g/mol. It is formed from the fermentation of sugar in products such as ripe fruit. Alcohol can be ingested both in the forms of fermented beverages (wine and beer with an alcohol content between 3.5 and 15%) as well as in distilled beverages containing a higher alcohol content (up to 60% in some drinks), we also find ethanol used as fuel in vehicles, antiseptic and universal solvent, its boiling point is 78.5ºC (GOODMAN & GILMAN, 2012; REIS et al., 2014).

Because ethanol is highly soluble in water, it reaches plasma levels in a short time, about 30 minutes may be enough for total absorption, when consumed in an empty state (KATZUNG et al, 2014; FIGUEIRA and JUNIOR, 2021). From the moment it comes into contact with the oral cavity, ethanol begins to be absorbed, the stomach and intestine are responsible for completing this process, soon after it will be distributed throughout the body mass, becoming present in greater amounts in the blood, brain, heart, lungs, liver, pancreas and kidneys respectively. Women, due to their lower body mass, tend to have higher blood concentrations and higher alcohol content compared to men. Due to its wide distribution and reaching the lungs, alcohol detection can be done through devices such as a breathalyzer (GOODMAN & GILMAN, 2012; KATZUNG et al, 2014).

The liver is the organ responsible for metabolizing about 90% of all alcohol ingested, the rest will be eliminated through sweat, lungs, urine and tears. The process carried out by the liver will be the hepatic oxidation, through the action of the enzyme alcohol dehydrogenase (ADH) that will convert alcohol into acetaldehyde, a substance highly toxic to the human body. Acetaldehyde, in turn, will undergo the action of the aldehyde dehydrogenase enzyme and

will be converted into acetate, the alcohol metabolism process will form Nicotinamide Adenine Dinucleotide (NADH), which in turn, if produced in excess, generates metabolic disorders such as lactic acidosis, decreased uric acid eliminated by urine and hypoglycemia (ISAYAMA, 2008; REIS et al. 2014).

Ethanol, despite its stimulating or euphoric effect, acts as a potent Central Nervous System (CNS) depressant. 2012). Ethanol affects all neurochemical systems in the brain, stimulates the release of dopamine, alters the reward system, and the communication between neurons. When it enters the brain, alcohol connects to both gamma-aminobutyric acid (GABA) receptors, responsible for inhibiting neurons, and glutamate receptors, which have an excitatory action. At GABAA receptors, ethanol binds and induces the inhibitory action of neurons, whereas at glutamate receptors, it prevents the excitatory effect from occurring (FUNCHS and WANNMACHER, 2015; CHAGAS, 2014; COSTA, 2020).

The effects caused by the ingestion of the substance range from euphoria, anxiety relief, disinhibition, impairment of judgment, decision making, slurred speech, ataxia, and with increased consumption, sedation, CNS depression can occur, in more severe cases, respiratory depression, coma and death. With frequent consumption, the user can become resistant, tolerant or insensitive to alcohol, this tolerance leads the individual to ingest larger and more frequent doses to achieve the same results as before (CHAGAS, 2014; FEITOSA, 2014).

CAS(mg/dL)[1]	Clinical Effect
50-100	Sedation, subjectively "high", slower reaction times
100-200	Impaired motor function, slurred speech, ataxia
200-300	emesis, stupor
300-400	With the
>400	Respiratory depression, death

Table 1 - Effects of alcohol on various blood concentrations.

Source: KATZUNG et al, 2014.

ALCOHOL WITHDRAWAL SYNDROME AND THE USE OF BENZODIAZEPINES

The alcohol-dependent individual, also called chronic alcoholic, when trying to abstain from the consumption of the substance abruptly, may present the Alcohol Withdrawal Syndrome (ASA), characterized by signs and symptoms such as anxiety, motor agitation, insomnia, changes in mood, tremors, nausea, vomiting, tachycardia, elevated blood pressure and reduced seizure threshold. SAA is responsible for a significant increase in morbidity and mortality associated with alcohol consumption. The first symptoms appear within 6 hours after stopping drinking, in less severe cases most of the symptoms disappear within one to two days, in more complex cases convulsions or hallucinations may occur in the first five days of abstinence. Anxiety and insomnia symptoms can remain indefinitely (FIGUEIRA E JUNIOR, 2021, DUAILIBI and LARANJEIRA, 2007).

Occasionally, in older users who have maintained a chronic, high and daily intake of alcohol for years, Delirium Tremens (DT) occurs, considered the worst of the complications in the mental health status of the alcoholic patient, as it presents a risk of mortality and in most cases, full recovery does not occur. DT can be installed in 24

to 72 hours of abstinence and can last for a week or extend for several months, the main characteristics are clouding of consciousness, confusion and hallucinations, a series of serious complications such as seizures, heart and respiratory failure, cerebral and pulmonary edema and various physiological disorders (KATZUNG et al, 2014; FIGUEIRA E JUNIOR, 2021).

The pharmacological treatment of SAA is of paramount importance to achieve the recovery of the chronic alcoholic patient. It is necessary to carry out the balance of electrolytes and deficit of vitamins and minerals, thiamine therapy is recommended in all cases of AAS, in order to prevent the development of Wernicke-Korsakoff syndrome. The drug approach includes benzodiazepines as the main class chosen for the treatment of withdrawal, since these drugs replace alcohol in GABA receptors, minimizing the increase in neuron excitability generated by glutamatergic increase (GOODMAN & GILMAN, 2012; KATZUNG et al, 2014).

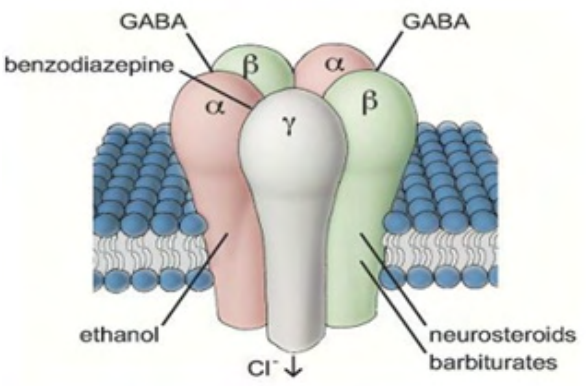

Figure 1 - Structure of the GABA receptor.

Source: AMARAL E MACHADO, 2012.

The most used benzodiazepine for SAA is Diazepam, in more severe patients, the administration is preferably given intravenously, in less severe cases, the drug can be administered orally. The disadvantage of diazepam is its slow metabolism and elimination, which can generate an accumulation of its metabolites, especially in patients with hepatic complications, for these, the most indicated drugs are lorazepam and oxazepam, both have a short half-life and are converted into inactive water-soluble metabolites, facilitating excretion. A gradual reduction in benzodiazepine intake must occur in a programmed way, as soon as the normalization of NS and especially sleep are reestablished (AMARAL AND MACHADO, 2012; COSTA, 2020; KATZUNG et al, 2014).

PHARMACOLOGICAL TREATMENT FOR CHRONIC ALCOHOLISM

Although treating alcohol dependence is a multidisciplinary task, pharmacological treatment plays an important role in the patient's recovery, helping to reduce the symptoms of SAA, maintaining abstinence and reducing the desire for drinking, increasing adherence to treatment and minimizing the relapses. For a long time, pharmacological interventions were limited to the treatment of SAA and to the use of disulfiram, considered the main anti-alcohol drug for producing an aversion to drink. In recent years, drugs such as naltrexone and acamprosate have been approved by the Food and Drug Administration (FDA) to treat alcohol dependence. In Brazil, the National Health Surveillance Agency (ANVISA) only approves the use of disulfiram and naltrexone. The European Medicines Agency, in turn, has not yet approved the use of long-acting naltrexone (CHAGAS, 2014; FEITOSA, 2014).

Disulfiram

Tetraethylthiuram disulfide – disulfiram (DSF) was approved by the FDA in 1951 as the first drug used to treat chronic alcoholism. It has an aversive effect on alcohol by altering the way the substance is metabolized in the body. Drug therapy with the DSF becomes successful when the patient accepts the treatment and

understands the drug's mechanisms of action, in addition to maintaining abstinence and joining an alcohol dependence treatment and social rehabilitation program such as Alcoholics Anonymous (AA).) (COSTA, 2014; FIGUEIRA E JUNIOR, 2021). The mechanism of action of DSF occurs through the irreversible inhibition of the ADH enzyme, indispensable in the metabolism of alcohol when it is in the acetaldehyde stage (FEITOSA, 2014).

If alcohol is ingested in association with the DSF drug, there will be an accumulation of acetaldehyde, which, as it is a substance toxic to the human body, will result in the ethanol-disulfiram reaction, which consists of a series of unwanted effects considered to be of intense intensity. moderate, such as the flushing, headache, nausea and vomiting, sweating, low blood pressure, and mental confusion. The symptoms described can appear in less than 30 minutes after the concomitant ingestion of the two substances and can last for hours. In more severe cases, symptoms can evolve, causing arrhythmia, unconsciousness, convulsions, respiratory depression, myocardial infarction, acute congestive heart failure and, in the worst case, death (CASTRO AND BALTIERI, 2004; REIS et al., 2014).

The ethanol-disulfiram reaction can have adverse effects even when contact occurs topically or with the ingestion of minimal amounts, such as alcohol present in foods with vinegar, for example. The use of cosmetics must also be done with caution, since we can find the substance in products such as aftershave lotions, colognes, deodorants, antiseptics, among others. It is important to warn the patient that all sources of alcohol must be avoided during treatment and up to two weeks after stopping DSF intake, the time necessary for the body to completely eliminate the substance (FIGUEIRA E JUNIOR, 2021).

Abstinence of at least 12 hours is recommended to start using DSF, in order to achieve a good response to treatment. The initial dosage will be 500mg/day lasting one to two weeks, after this period, the maintenance dose is 250mg/day, which may vary between 125mg/day and 500mg/day, depending on the patient and their clinical history. (COSTA, 2020). It is worth mentioning that the DSF does not have a significant reduction in the desire for alcohol, for this reason the patient must remain motivated to remain in treatment, counting on a support network and specialized supervision (CHAGAS, 2014).

Although Disulfiram is a well-tolerated medication, some side effects apart from ethanol-disulfiram reactions can be listed. Hepatitis is described as a rare adverse event, but it can occur, especially after the first two months of taking the drug. It is vitally important to monitor liver functions periodically, it is recommended to perform exams every 15 days during the initial two months of treatment and after this period, exams can occur on a quarterly basis. Associated with the use of the drug, reactions such as drowsiness, fatigue, erectile dysfunction and, less frequently, neuropathies, dermatological problems, psychiatric and gastrointestinal disorders have been described (CASTRO AND BALTIERI, 2004; FEITOSA, 2014).

DSF is contraindicated in patients with hypersensitivity to disulfiram or other components of the formula, hypersensitivity to latex, pesticides or fungicides, liver failure or cirrhosis, diabetes mellitus, epilepsy, renal failure, cardiac complications, the elderly and in pregnant women the DSF presents a risk of abnormalities congenital. The drug must not be used for treatment without the patient's consent, since it is contraindicated in concomitant use with alcohol (FEITOSA 2014; FIGUEIRA E JUNIOR, 2021).

Naltrexone

Naltrexone (NTX) in oral form was approved in 1994 by the FDA as a potent and promising tool to treat alcoholism. The drug has a competitive antagonist action to opioid receptors in the human body, considerably reducing the pleasurable and rewarding sensation acquired when ingesting the alcoholic beverage. NTX proved to be effective in inhibiting the desire for alcohol consumption and reducing relapses. Considered the first drug approved for the treatment of alcohol dependence since disulfiram, presenting an innovative proposal, and with a different treatment perspective, since it is not considered an aversive drug. In 2006, the FDA approved the use of NTX for injectable and prolonged-release applications (CASTRO and BALTIERI, 2004; FEITOSA 2014).

The pharmacotherapeutic indication of NTX consists of the daily intake of 25mg/day during the first week of treatment, in order to minimize the occurrence of adverse events, subsequently, the recommendation is 50mg/day. The treatment must be maintained for at least 12 weeks (CASTRO and BALTIERI, 2004). NTX with extended release must be administered by injection and intramuscularly once a month, with doses of 380 mg/month, this form of administration aims to minimize the problems of non-adherence to treatment (FEITOSA, 2014). It is worth mentioning that even in the face of the correct pharmacotherapy, there may be non-adherence to treatment, since there is a variation in the alcoholic population, with different endophenotypes, generating different responses to treatment with NTX (CHAGAS, 2014).

The use of NTX is contraindicated in cases of allergy or hypersensitivity to naltrexone or any of the components of the formula, hepatitis or liver cirrhosis, association with opioid analgesics such as morphine and its derivatives, opioid dependence, in cases of acute opioid withdrawal syndrome, pregnant women must not use the substance without medical knowledge and monitoring. Drug treatment with NTX must start only after a period of abstinence from opioids of at least 7 - 10 days, avoiding symptoms similar to SAA. Adverse effects related to the drug are nausea, anorexia, gastrointestinal discomfort, headache, dizziness, fatigue and anxiety. NTX can cause hepatotoxicity, for this reason it is important to monitor the serum levels of liver enzymes periodically and in cases of changes it is recommended to suspend treatment (CASTRO AND BALTIERI, 2004; COSTA, 2020).

Acamprosate

In 2004, the FDA approved the use of calcium acetylhomotaurinate - acamprosate (ACA) to treat chronic alcoholism. The drug has the potential to reduce the desire to drink alcohol. Although there is no exact knowledge of its mechanism of action, studies show that ACA acts directly on the CNS, as a glutamate antagonist and GABA agonist, returning the stabilization previously altered by the abusive and chronic consumption of alcohol, inhibiting the compensatory system and hyperarousal., in addition to reducing the desire to drink. It is not an aversive drug (FEITOSA 2014).

ACA must be administered to patients with a body weight greater than 60 kg, the recommended dosage is three daily tablets of 333.3 mg/dose, before meals, the dose can be adjusted according to the patient's body weight and may be higher. or less. The treatment time must be between 6 and 12 months (CHAGAS, 2014). ACA is slowly absorbed and bioavailability is low and can be reduced to zero if administered with food. The elimination of the drug occurs through the urine and about 90% is excreted in full,

which makes it contraindicated for patients suffering from renal failure. There are no studies that prove the safety of the drug in pregnant women. The most common adverse effects are gastrointestinal disorders (nausea, vomiting and diarrhea), skin disorders (rash), intoxication, mental confusion and drowsiness (CASTRO AND BALTIERI, 2004; KATZUNG et al, 2014).

FINAL CONSIDERATIONS

The present research brings to evidence how the abusive and chronic consumption of ethanol is alarming and it is a public health problem, since it compromises the life and health of the alcoholic individual, his family and society as a whole, being a cause of morbidity and mortality worldwide. Therefore, it is necessary to understand the pharmacology of ethanol and chronic alcoholism, since it is a serious disease and its treatment cannot be limited to the patient's wishes, denoting the need for pharmacotherapy, so that it can be done. possible to overcome SAA, patient rehabilitation and elimination of relapses.

The search in the scientific literature showed how deficient is the treatment consisting only of a trio of drugs (disulfiram, naltrexone and acamprosate), which are effective only for a part of the population for which they are intended, in addition to presenting a series of adverse events and contraindications., making it unfeasible or compromising treatment adherence for many patients. It is concluded that although there are drugs available for alcoholism, it is necessary to research and develop new drug alternatives in order to help patients in the rehabilitation and control of the disease.

REFERENCES

AMARAL, B. D. A.; MACHADO, K. L.: **Benzodiazepínicos: Uso Crônico E Dependência.** 30 f. Monografia (Especialização em farmacologia), UNIFIL -Centro Universitário Filadélfia, Londrina, 2012.

BOTELHO, L. L. R.; CUNHA, C. C. A.; MACEDO, M.: **O método da revisão integrativa nos estudos organizacionais**. Gestão e Sociedade, v. 5, n. 11, p. 121-136, Maio-Agosto, 2011.

BRASIL, Ministério da Saúde: **Nota Técnica N° 100/2012 naltrexona, 2015** https://www.gov.br/saude/pt-br/composicao/conjur/demandas-judiciais/notas-tecnicas/notas-tecnicas-medicamentos/notas-tecnicas/n/naltrexona-atualizada-em-23-11-2015.pdf Acesso em março de 2022.

BRASIL, Ministério da Saúde: **II Levantamento Domiciliar Sobre o Uso de Drogas Psicotrópicas no Brasil: Estudo Envolvendo as 108 Maiores Cidades do País.** 2005 / São Paulo : CEBRID - Centro Brasileiro de Informação sobre Drogas Psicotrópicas: UNIFESP - Universidade Federal de São Paulo, 2006. https://www.cebrid.com.br/wp-content/uploads/2014/10/II-Levantamento-Domiciliar-sobre-o-Uso-de-Drogas-Psicotr%C3%B3picas-no-Brasil.pdf acesso em março de 2022.

BRASIL, (Ministério da Saúde. Secretaria Executiva. Coordenação Nacional de DST/Aids.): **A Política do Ministério da Saúde para ateņão integral a usuários de álcool e outras drogas / Ministério da Saúde, Secretaria Executiva, Coordenação Nacional de DST e Aids**. – Brasília: Ministério da Saúde, 2004. https://www.unodc.org/documents/brazil/polit_ms_acool_e_drogas.pdf acesso em março de 2022.

CASTANHA, A. R.; ARAUJO, L. F.: **Álcool e agentes comunitários de saúde: um estudo das representações sociais.** Psico-USF, v. 11, n. 1, p. 85-94, jan./jun. 2006.

CASTRO, L. A.; BALTIERI, D. A.: **Tratamento farmacológico da dependência do álcool**. Rev Bras Psiquiatr, n. 26, p. 43-46, 2004.

CASTRO, L. A.; LARANJEIRA, R.: **Ensaio clínico duplo-cego randomizado e placebocontrolado com naltrexona e intervenção breve no tratamento ambulatorial da dependência de álcool**. Journal Bras Psiquiatr, v. 58, n. 2, p. 79-85, 2009.

CHAGAS, M. S. A.: **Tratamento Farmacológico Da Síndrome Da Dependência Do Álcool.** Monografia (Curso de Graduação em Farmácia) – Centro de Educação e Saúde / UFCG, 2015.

COSTA, F. L.: **Tratamento Medicamentoso Para O Alcoolismo.** Artigo (Graduação em Farmácia) Universidade de Uberaba, Minas Gerais, 2020.

CPPAS, Comissão Permanente de Protocolos de Atenção à Saúde da SES-DF: **Uso do Dissulfiram e Naltrexona no Tratamento Da Dependência De Álcool**. https://www.saude.df.gov.br/documents/37101/183291/Protocolo-Uso-do-Dissulfiram-e-Naltrexona-no-Tratamento-da-Depend%C3%AAncia-de-%C3%81lcool.pdf/68957f10-da61-c6e3-5ba1-3d8ed9d3cc4a?t=1648938710912 acesso em abril 2022.

DUAILIBI, S.; LARANJEIRA, R.: **Políticas Públicas Relacionadas ás Bebidas Alcoólicas**. Revista Saúde Pública. São Paulo, vol.41, n.5, p. 839-848. Ago./ 2007.

FEITOSA, N. C.: **Uso do dissulfiram na dependência de álcool**: uma revisão. 2014. 63 f. Dissertação (Graduação em Farmácia) – Universidade de Brasília, Brasília, 2014

FIGUEIRA, B. G.; JUNIOR, V. A. S.: **A importância da terapia medicamentosa com dissufiram associado ao alcoolismo – Uma revisão da literatura.** Revista Ibero-Americana de Humanidades, Ciências e Educação. São Paulo, v.7.n.10. out. 2021. ISSN - 2675 – 3375.

FUCHS, F.D.; WANNMACHER, L.: **Farmacologia Clínica. Fundamentos da terapêutica racional**. 4.ed Rio de Janeiro: Guanabara Koogan, 2015. 1284p.

GOODMAN & GILMAN: **As bases farmacológicas da terapêutica.** 12ª Edição. Porto Alegre (RS): Mc Graw Hill/Artmed, 2012.

ISAYAMA, R. N.: **Efeitos Do Etanol Na Formação Do Sistema Gabaérgico Telencefálico.** Rio de Janeiro: UFRJ, PCM / ICB, 2008. xvi, 113p.

KATZUNG, B.G.; MASTERS, S. B.; TREVOR, A. J.: **Farmacologia Básica e Clínica.** 12ª edição. Rio de Janeiro. McGraw-Hill, 2014. 1228 p.

LAPA, A.: **Estudo Clínico do Alcoolismo**. Brasília: S&S 1998.

LARANJEIRA et al.: **I Levantamento Nacional sobre os padrões de consumo de álcool na população brasileira**. Brasília: SENAD, 2007.

LARANJEIRA, R.; NICASTRI, S.; JERÔNIMO, C.; MARQUES, A. C.: **Consenso Sobre a Síndrome de Abstinência do Álcool (SAA) e o seu Tratamento**. Revista Brasileira de Psiquiatria. São Paulo, vol. 22, n.2, p. 62-71.2000.

MELONIA, J. N.; LARANJEIRA, R.: **Custo Social E De Saúde Do Consumo Do Álcool.** Rev Bras Psiquiatr 2004;26(Supl I):07-10.

OMS, Organização Mundial da Saúde. **Relatório sobre a Saúde no Mundo 2001 – Saúde Mental: Nova Concepção, Nova Esperança.** OMS, Genebra, 2001. https://www.nescon.medicina.ufmg.br/biblioteca/imagem/0205.pdf acesso em abril de 2022.

OPAS, Organização Pan- Americana da Saúde.: **Folha Informativa – Álcool.** 2019. Disponível em: https://www.paho.org/pt/topicos/alcool#:~:text=O%20consumo%20de%20%C3%A1lcool%20por,e%20complica%C3%A7%C3%B5es%20no%20parto%20prematuro.&text=Em%20todo%20o%20mundo%2C%203,de%20200%20doen%C3%A7as%20e%20les%C3%B5es.. Acesso em: abril 2022.

REIS, G. A.; GÓIS, H. R.; ALVES, M. S.; PARTATA, A. K.: **Alcoolismo e seu tratamento.** Revista Científica do ITPAC, Araguaína, v. 7, n.2, Abr., 2014.