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Clinical Staging of Alcohol Use Disorder: Proposal of a New Stratified Approach

Staging of Alcohol Use Disorder

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ABSTRACT

Introduction: Clinical staging is widely applied in various fields of Medicine. Staging makes it possible to constitute early diagnoses and interventions, improving prognosis and preventing disease progression. In relation to Alcohol Use Disorder (AUD), staging is still an underdeveloped subject in the scientific literature. The treatment of AUD is effective for a minority of patients, requiring more targeted interventions individually. This study aims to propose a staging model for AUD that establishes key factors related to the progression of the disorder.

Method: Non-systematic review of the literature on Pubmed/Medline database focusing on articles about AUD and that present a stratified classification and treatment outcomes for that subpopulation through the progression of the disease.

Results: The model proposed includes stages 0 (latent), I A, I B, II A, II B, III A, III B and IV.

Discussion: This study can be used as a basis for a myriad of other reviews with the aim of validating a staging model in AUD. We recommend a systematic review study to validate the model suggested in this study and correlate clinical aspects with neurobiological aspects and the effectiveness of certain treatments.

Conclusion: This work shows that, based on the stratified classification of response to treatment, it is possible to suggest a staging model for AUD. Furthermore, the stages can be subdivided based on different clinical characteristics, risk factors, prognosis and management.

Keywords: alcoholism; prognosis; disease progression

INTRODUCTION

Alcohol Use Disorder

Alcohol use disorder (AUD) is a public health matter that may still grow in the next few years. The pattern of alcohol use varies according to the country, but an increase in alcohol consumption is expected in high population countries like Brazil, Mexico and the United States.[1] Moreover, AUD is also prevalent. Research in the United States evaluated the prevalence of DSM-5 AUD and found a 12 month prevalence of 13,9%, and a lifetime prevalence of 29,1%.[2]

According to the National Institute of Alcohol Abuse and Alcoholism (NIAAA), the high risk alcohol consumption includes binge drinking and heavy drinking. These patterns of use increase the risk of harmful consequences, like alcohol use disorder. Binge drinking corresponds to 5 or more standard doses for males and 4 or more standard doses for females in a period of 2 hours. Heavy drinking is the consumption of 5 or more doses in a day or more than 14 doses in a week for males; for females, heavy drinking corresponds to the consumption of 4 or more doses in a day or more than 7 doses in a week.[3]

A widely used instrument is the CAGE questionnaire (*Cut Down/ Annoyed/ Guilty/ Eye-opener Questionnaire).* It was created in 1968, and consists of a brief evaluation of alcohol consumption based on 4 questions. If 2 answers are positive, the probability of alcohol use disorder increases.[4] It is also important to cite the *Alcohol Use Disorders Identification Test* (AUDIT), which was developed by the World Health Organization (WHO). The AUDIT consists of 10 questions concerning recent alcohol use, alcohol

dependence symptoms and alcohol-related problems. Each response has a score ranging from 0 to 4 and the scores should be added to form a total score. Total scores of 8 or more suggest hazardous and harmful alcohol use.[5]

In the DSM-IV TR, there was a difference between alcohol abuse and alcohol dependence. On the other hand, the DSM-5 considered alcohol abuse a mild alcohol use disorder.[6] Currently, the alcohol use disorder diagnosis is based on DSM-5 or the eleventh revision of the International Classification of Diseases (ICD-11).

Alcohol use disorder is a complex condition affected by multiple factors, both biological and psychosocial. The genetic influence in alcohol use disorder can be represented by the existence of genes involved in alcoholism, like ADH1B and ALDH2 [7] and the expression of characteristics that increase the risk of the disorder, like impulsiveness and negative affectivity.[8]

The interaction between genetic and environmental factors can lead to the development of alcohol use disorder. In this sense, adolescence is a crucial period, as social relations and conduct disorders at this age seem to affect the pattern of alcohol consumption.[8] The age of first alcohol use has been studied as a predictor for a future diagnosis of dependence.[9] Stress, dysfunctional family environments and traumatic events are risk factors of developing alcohol use disorder.[10] Moreover, the comorbidity with mental disorders increases the risk of alcohol use disorder.[11]

Alcohol consumption can have many clinical and social consequences.[1] Some motor and cognitive deficits may be reversible with abstinence.[12] In addition to clinical consequences, like brain damage due to vitamin deficiencies[13], there is the high prevalence of alcohol use in individuals involved in car accidents.[1]

The available treatments for alcohol use disorder benefit a minority of patients, possibly due to the heterogeneity of diagnostic categories.[14] Patients present high rates of relapse after a year of treatment.[15] The co-occurrence of psychiatric comorbidities, the lack of family support and poverty are predictors of relapse and poor treatment compliance.[16]

Staging

Staging is a classification made according to severity of the disease and it is widely used, like in the areas of cardiology and oncology.[17,18] On the other hand, this subject is not so present in psychiatric clinical practice as in research. In this area, treatments

on stages tend to consider the clinical course, cognition, functionality and biomarkers.[19]

Staging aims to direct the treatment according to the severity and phase of the disorder. In severe diseases, including alcohol use disorder, theoretical models that categorize patients according to the severity and progression of the disorder are useful for the approach. The staging of a pathology contributes to guide a more specific treatment, differentiate an early clinical phenomenon from a severe one, improve prognosis by preventing the progression to advanced stages of the disease and allowing an early intervention.[20,21]

Although the classification of the severity of alcohol use disorder is not well defined in scientific literature, some studies seek to develop a possible staging for this disorder. The development of alcohol use disorder in 3 stages was proposed in 1995: alcohol abuse, with legal and interpersonal damage; dependence, with tolerance and abstinence; and adaptation to disease, with a reduction of activities due to substance use.[22] Subsequently, 4 stages were proposed: abuse, harmful consequences, adaptation to disease and physiological dependence.[23]

George Koob and Nora Volkow described the addiction model in three stages according to the affect neuronal circuitries: compulsion/intoxication, involving the basal ganglia, comprising the reward system and the incentive salience; negative affect (dysphoria)/abstinence, involving the extended amygdala and habenula; and anticipation/worry, involving the prefrontal cortex. Changes of molecular genetic mediation and epigenetics in these circuitries increase the risk of developing substance use disorder in individuals with previous vulnerabilities and also increase their susceptibility to environmental risk factors.[24]

The MATCH project was a randomized clinical trial about treatment of alcohol use disorder coordinated by NIAAA. Patients were randomized to cognitive behavioral therapy (CBT) (12 sessions) *versus* motivational therapy (4 sessions), motivational therapy *versus* 12 steps (12 sessions) and CBT *versus* 12 steps.[25] Patients with more anger had a better response to treatment with motivational therapy in the 3-year follow-up. Patients with severe alcohol use disorder had better results with 12 steps, while patients with mild alcohol use disorder had a better response with CBT.[26]

Studies with predictors of different outcomes of treatment in long-term care institutions suggest that this approach can be better for patients with a more severe pathology, low social stability and low social competence. However, there is not strong

empirical evidence for these data. On the other hand, patients with mild to moderate alcohol problems and social stability seem to benefit more from brief interventions. The American Society of Addiction Medicine (ASAM) developed a classification of patients in 5 levels of care: early intervention, outpatient care, intensive outpatient care, residential and inpatient with pharmacological treatment. In order to suit patients to the level of care, rates of severity in 6 dimensions are used: potential of abstinence; biomedical conditions; behavioral and emotional issues; readiness for treatment; potential of relapse and living in a recovery environment ("sober house"). There is limited support for the predictive validity of these criteria. An alternative idea is that severe cases may be conducted by case management and that harm reduction strategies can also be useful in this context.[27] The most consistent predictors of outcome of treatment were severity of dependence, classification of psychopathology, self-efficacy related to alcohol, motivation to change and treatment purpose.[28]

There is a gap in the literature of models of classification of alcohol use disorder in stages. Initially, models were based on symptoms and did not point to a therapeutic intervention;[22,23] AUDIT aimed to indicate interventions[5], but without altering the clinical course of the disease. The model based on neural circuitry[24] focused only on neurobiological aspects and not on treatments. Studies that evaluated the effectiveness of treatments for alcohol use disorder according to the characteristics of patients, like Project MATCH, did not have a satisfactory result to change clinical practice.

As staging leads to a better management of cases in many areas of Medicine, the formulation of a clinical staging for alcohol use disorder may contribute to an earlier and more suitable treatment according to the stage of the disorder and, consequently, improve prognosis.

METHOD

Once the project was submitted and approved by Centro de Ensino e Pesquisa - HCPA and Plataforma Brasil, a narrative review of literature was conducted on Pubmed. The search included articles in English with the terms "Alcohol Abstinence"[Mesh]) OR "Binge Drinking"[Mesh]) OR "Alcohol-Induced Disorders, Nervous System"[Mesh]) OR "Alcohol Drinking"[Mesh]) OR "Alcohol-Related Disorders"[Mesh]) OR "Alcoholism"[Mesh]. The filters used were *humans* and *clinical trials.*

After the search on the database, two tables were created: “included” and “excluded”. In the table “included” were the articles that presented an intervention for the treatment of alcohol use disorder and the description of the response of the population studied to the intervention. In the table “excluded” were the articles that did not present the requirements cited above.

In the table “included”, there were four columns: name of the article, population studied, intervention and whether the intervention was efficacious or not. By analyzing the populations of these selected articles, a division in 8 subpopulations was proposed: stage 0/ latent - individuals with risk factors for alcohol use disorder (family history of alcohol use disorder, personality traits for alcohol use disorder, social vulnerability, offending conduct related to alcohol use and mental disorder); stage Ia - mild alcohol use disorder without social or clinical harm or high risk alcohol use; stage Ib - Ia and psychiatric comorbidities (other than severe mental disorders - schizophrenia and other psychotic disorders, bipolar disorder, dementia, personality disorders and addictive disorders, other than tobacco use); stage IIa - alcohol use disorder with mild social or clinical harm with or without psychiatric comorbidities and without alcohol withdrawal syndrome; stage IIb - IIa and mild to moderate alcohol withdrawal syndrome; stage IIIa - alcohol use disorder with severe social or clinical harm due to alcohol use, with or without severe psychiatric comorbidities and with or without mild to moderate alcohol withdrawal syndrome; stage IIIb - IIIa and severe alcohol withdrawal syndrome; and stage IV - alcohol use disorder without response to treatment/ resistant and/or presence of Korsakoff syndrome. This division was established based on the characteristics of the samples used on the selected clinical trials and on previously known data about alcohol use disorder progression. The definition of alcohol use disorder staging was based on these subpopulations, resulting in the 8 stages cited above.

After the first search on PubMed, other searches about alcohol use disorder and treatment were realized. These searches included articles in English that evaluated interventions with proven effectiveness for specific phases of alcohol use disorder.

Moreover, the articles that presented severe alcohol withdrawal syndrome without severe social or clinical harm were considered as stage IIIb. On the other hand, the articles with mild to moderate alcohol withdrawal syndrome without reporting of social or clinical harm were considered as stage IIb.

The features, prognosis and management of each subpopulation were described in each stage. During the production of this review, group meetings were held to propose the cutoffs of each stage according to scientific literature.

It is essential to point out that family therapy, contingency management and motivational interviewing were not included in management of staging because they are not related to the progression of the disease, although they have proven effectiveness for alcohol use disorder. Moreover, the pharmacological treatments supported by scientific evidence for alcohol use disorder, like disulfiram, acamprosate and naltrexone, were not included on the model because they do not help to distinguish between one stage and another.

RESULTS

The stages are synthesized in the following table and described below (Table 1).

Table 1.

	Characteristics	**Prognosis**	**Management**
Stage 0/ latent	*Risk factors for AUD (at least 1)* *•Family history of AUD* *•Personality traces presenting risk of AUD* *•Social vulnerability* *•Infringing conduct related to alcohol use* *•Presence of mental disorders*	*•Favorable*	*•Psychoeducation* *•Prevention programs for the community* *•Treatment of mental disorders*
Stage IA	*•Mild AUD without social and clinical harm, or* *•High risk consumption*	*•Favorable* *•Reversible*	*•Brief intervention* *•CBT*
Stage IB	*•I a, and* *•Psychiatric comorbidity (except for severe psychiatric disorders)**	*•Favorable* *•Reversible*	*•Interventions from I a* *•Treatment of psychic comorbidity*

Stage IIA	*•AUD with mild social and/or clinical harm with or without psychiatric comorbidity (except for severe psychiatric disorders)** *•No AWS*	*•Favorable •Reversible*	*•AA •CBT •Treatment of psychiatric comorbidity*
Stage IIB	*•II a and •Mild to moderate AWS*	*•Favorable or unfavorable •Reversible or irreversible*	*•IIa interventions •Outpatient or hospitalization management for AWS*
Stage IIIA	•AUD with severe s*ocial and clinical harm resulting from the use of alcohol*** *with or without psychiatric comorbidity, with or without mild to moderate AWS*	*•Favorable or unfavorable •Reversible or irreversible*	*•Interventions from I a •Treatment of psychic comorbidity*
Stage IIIB	*•III a and •Severe AWS*	*•Favorable or unfavorable •Reversible or irreversible*	*•II b interventions •Hospitalization with management for severe AWS*
Stage **IV**	*•AUD without response to treatment/ resistant and/or •Korsakoff Syndrome*	•Unfav*orable •Irreversible*	*•Permanent internment in a home*

- **Stage 0/ Latent:** This stage comprises individuals that have risk factors to develop AUD as to have specific traits of personality such as anxiety sensitivity, novelty seeking, negative thoughts and impulsivity;[29,30] social vulnerability;[31] offending conduct related to alcohol;[32,33] familial history of AUD[34] and the presence of mental illness.[35] This stage has a favorable prognosis.[36] The

indicated interventions are psychoeducation, prevention programs for the community and the treatment of the psychiatric comorbidity.[11,31,37,38]

- **Stage I A:** This stage comprises individuals that have high risk alcohol consumption and mild AUD without social and clinical complications due to alcohol use.[39-45] This stage has a favorable prognosis and is reversible.[36] The indicated interventions are cognitive behavioral therapy (CBT)[46] and brief interventions.[47]
- **Stage I B:** This stage comprises individuals that have high risk alcohol consumption and mild AUD without social and clinical complications due to alcohol use and the presence of mental disorders - except severe mental disorders, such as schizophrenia and other psychotic disorders, dementia, personality disorders and addictive disorders - except tobacco use disorder.[48,49] This stage has a favorable prognosis and is reversible.[36] The indicated interventions are cognitive behavioral therapy (CBT)[46,48], brief interventions[47] and the treatment of psychiatric comorbidity.[49]
- **Stage II A:** This stage comprises individuals that have AUD with mild social and/ or clinical complications and with or without the presence of mental disorders - except severe mental disorders - without alcohol withdrawal syndrome (AWS).[50,51] This stage has a favorable prognosis and is reversible [36]. The indicated interventions are CBT[46,48], Alcoholics Anonymous (AA)[52,53] and the treatment of psychiatric comorbidity.[49]
- **Stage II B:** This stage comprises individuals that have AUD with mild social and/ or clinical complications and with or without the presence of mental disorders - except severe mental disorders - with mild alcohol withdrawal syndrome (AWS).[54] This stage has a favorable prognosis and is reversible.[36] The indicated interventions are CBT[46], Alcoholics Anonymous (AA)[52,53], the treatment of the psychiatric comorbidity[49] and out-patient or in-patient mild AWS treatment.[55]
- **Stage III A:** This stage comprises individuals that have AUD with severe social and/ or clinical complications and with or without the presence of severe mental disorders[56] with or without mild to moderate alcohol withdrawal syndrome (AWS).[54] This stage has a favorable or unfavorable prognosis and it has a reversible or irreversible course.[36] The indicated interventions are CBT[46], Alcoholics Anonymous (AA)[52,53], the treatment of the psychiatric comorbidity[49]

and out-patient or in-patient mild to moderate AWS treatment[55], day medical center[57] and liaison psychiatry.[55]

Examples of severe social complications: homelessness[58], domestic violence[59], divorce, no relationship with sons and unemployment.[60] Examples of severe clinical complications: traumatic brain injury (TBI)[61] and facial lesions.[62]

- **Stage III B:** This stage comprises individuals that have AUD with severe social and/ or clinical complications and with or without the presence of severe mental disorders[56] with severe alcohol withdrawal syndrome (AWS).[54] This stage has a favorable or unfavorable prognosis and it has a reversible or irreversible course.[36] The indicated interventions are CBT[46], Alcoholics Anonymous (AA)[52,53], the treatment of the psychiatric comorbidity[49] and in-patient severe AWS treatment[63,64], day medical center[57] and liaison psychiatry.[65]
- **Stage IV:** This stage comprises individuals that have AUD with severe social and/ or clinical complications, Korsakoff syndrome, and with or without the presence of severe mental disorders with severe AWS. This stage has a favorable or unfavorable prognosis and it has a reversible or irreversible course.[36] The indicated interventions are CBT[46], Alcoholics Anonymous (AA)[52,53], the treatment of the psychiatric comorbidity[49] and severe AWS treatment[55], day medical center[57] and liaison psychiatry.[55]

DISCUSSION

The aim of the study was to propose a model of clinical staging of alcohol use disorder. The model was designed to allow modifications and improvements.

The cutoffs between each stage are hypotheses without enough evidence. This is in line with the First International Consensus of transdiagnostic clinical staging in youth's mental health, which highlights a need to establish what is a significant change or a threshold to deterioration that could be considered a cutoff of a stage. As the progression of disease is related to severity, recurrence, persistence of symptoms and functioning[66], all of these factors should be evaluated when establishing a cutoff between stages.

It is important to highlight that the concept of transition from one stage to another is a probability and not an inevitable occurrence[66], and can vary according to biopsychosocial features of risk to develop alcohol use disorder, level of evidence,

duration and compliance with treatment. It is well established in literature that an individual with a family history of alcohol use disorder is more vulnerable to develop the disease.[34] The clinical trajectory of this individual can vary according to biological, psychological and social aspects. Factors like personality traits of risk to substance use disorder[29,30], social vulnerability[31], mental disorder[11] and family history of alcohol use disorder[34] make this individual more prone to alcohol use disorder. For this reason, avoiding the development of alcohol use disorder by treating mental disorders[11] and promoting psychoeducation[37,38] is essential. On the other hand, individuals without a family history can benefit from primary prevention programs to the community.

In order to develop this proposal of staging, the authors searched for models of other mental disorders, like the one for bipolar disorder. However, some adaptations were made because of particularities of alcohol use disorder. The progression of alcohol use disorder can be considered different from the progression of bipolar disorder. Bipolar disorder can begin in initial stages or in a more advanced course[36,67], while alcohol use disorder tends to evolve in a more predictable and linear way. Therefore, after conducting the initial search in Pubmed, the authors selected articles that presented an intervention for alcohol use disorder treatment and the response of the population to the intervention. Articles that did not describe the characteristics of the population and did not specify the severity of alcohol use disorder were added to stage Ia, which includes the majority of patients with alcohol use disorder. Participants with alcohol abuse were classified in the same stage according to DSM-5, where mild alcohol use disorder comprises patients with alcohol abuse according to the criteria of DSM-IV.

Although family therapy, contingency management and motivational interview were not included in staging, they are indicated in the presence of family conflicts (family therapy) and in the motivational stage (contingency management and motivational interview). Moreover, pharmacological interventions for alcohol use disorder were not included in the model because they do not contribute to differentiating one stage from another. On the other hand, in bipolar disorder some medications will have a better response in specific stages, like lithium in initial stages.[36]

We can point out the following limitations in this study, which presents selection bias as it is a narrative review, and a systematic review of the existing literature on the topic is not carried out. Furthermore, biomarkers, changes in neuropsychological aspects and neuroimaging were not evaluated and included in the

model since it was not the scope of this study to carry out a neurobiological and neuropsychological analysis. As several studies did not specify the characteristics of the population with AUD, this also ended up limiting the classification in the model. Furthermore, different instruments and references were observed to classify binge drinking and the diagnosis of AUD, which is another limitation for data analysis.

This study proposes a new way of developing the AUD staging model, using the response to treatment as a starting point to differentiate the stages and carry out the search for creating the model. The aim of identifying subgroups in a heterogeneous disorder is related to aspects of personalized Psychiatry. This concept proposes that the combination of genetic and environmental information can help identify populations with distinct patterns of prognosis and response to treatment. The term "precision Psychiatry" seems to be preferred in biological research.[68–70] It is expected that the advance of technology may accelerate the development of personalized Psychiatry.[71]

We consider that this study can be used as a basis for a myriad of other reviews with the aim of validating a staging model in AUD and, thus, be of clinical use. We recommend a systematic review study to validate the model suggested in this study and correlate clinical aspects with neurobiological aspects and the effectiveness or otherwise of certain treatments as suggested in another study.[67]

Although risk and protective factors are important aspects to consider in the development of AUD, we cannot predict its progression due to complex epigenetic factors.[67] In this case, for future perspectives, studies with new methodologies, for example machine learning, could evaluate and predict such issues. The machine learning method has been used more frequently in research in the area of mental health, including substance use disorders. A recent study used machine learning models to identify high-risk alcohol consumption patterns among doctors and medical students. In conclusion, it was found that variables such as tobacco and marijuana use, family income, marital status, sexual orientation and physical activity were the most relevant for the models studied. Studies using this methodology propose new tools for identifying individuals at different stages of alcohol consumption, enabling the development of new preventive and treatment strategies in the future.[72]

CONCLUSION

This work shows that, based on the stratified classification of response to treatment, it is possible to suggest a staging model for AUD. Furthermore, the stages can be subdivided based on different clinical characteristics, risk factors, prognosis and management. These aspects allow a better understanding of the severity of AUD, its evolution and reversibility throughout the progression of the disease. Furthermore, this study shows that we can target more specific treatment according to the patient's clinical characteristics.

Although AUD staging is still an incipient topic, which requires further studies to evaluate and validate its use in clinical practice, this proposed model is a first step to serve as a basis for future work. Therefore, it is essential that more studies are carried out on this topic so that the patient can have a better prognosis, quality of life and cost-benefit of the indicated treatment.

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The authors declare they have no conflict of interest.

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