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Is AUD the same for everyone? The different typologies of AUD patients

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ABSTRACT

Alcohol dependence and related disabilities are a large burden for the population. Problems in families, working places and severe medical symptoms are often caused by alcoholism.

Most of these patients never reach a specialized, high-quality treatment program. They get no specific withdrawal treatment, no specific psychosocial help, and only 3-5% get anticraving medications.

One of the main causes of this situation is that the diagnosis according to ICD and DSM is too broad and does not give sufficient information for the right treatment program.

Therefore, we need a more specific diagnostic procedure. Subgroups of alcohol dependence should be able to offer better motivational and treatment programs.

In this article, the history of subgroups will be presented, as well as the modern developments of subgroups. Today, the minimal standard for subgroups, defined in different ways in different countries, will be shown. The Lesch typology is one of these approaches, using these instruments (www.lat.online.at). The results of its use in basic and clinical research show the importance of these subgroups.

KEYWORDS

ALCOHOL DEPENDENCE

SUBGROUPS

BASIC RESEARCH

THERAPY

INTRODUCTION

1) Diagnosis in Psychiatry

Psychiatric symptoms are caused by significantly different biological, psychological and social dimensions, and the multidimensional approach is everywhere accepted. Since 150 years, France started, and nowadays, the World Health Organisation defines international classificatory systems for psychiatric disorders. The 10th revision (ICD-10) has become important for a better comparison of the frequency of disturbances between countries and cultures. It is also used for payoff for the National Insurances. It does not correspond to long-term courses and does not give enough information for the necessary therapies. Therefore, the 11th revised version has been undertaken. These facts have already been delineated in the German version introduction by the authors H. Dilling, W. Mombour, and MH. Schmidt: "ICD-10 is only a descriptive diagnostic procedure, and it relates to only one part, though to an important one, for the nosological understanding([1]). Important aspects of psychopathology, psychodynamics and psychophysiology should be regarded. Especially the individual and personal biographic developmental facts should not be neglected (WHO 1993). Also, personal future perspectives play an important role[2].

ICD-11 focuses, besides on the severity degree, also on the long-term course[3]. This represents a major improvement. DSM 5 converged to ICD-11 because it newly included craving as a central symptom. DSM 5 defined 3 severity degrees. Moderate and severe correspond in ICD-11 to the term dependence. Therapy research according to DSM-IV and ICD-10 showed very divergent results[4,5]. Therefore, as we know from research

and clinical work, it is necessary to define subgroups of dependent patients for more sufficient therapy[6,7]. The new ICD-11 and DSM 5 systems are better than ICD-10 or DSM 5 but still too general, though the new focus on the severity degree and the long-term illness course has to be mentioned as advancement[8,9]. According to substance and behaviour, 19 groups are formed, but important therapy-relevant factors are still missing, like biography, vulnerabilities, etc.[1,3,10,11]. Alcohol dependence is caused by bio-, psycho-, and social disturbances in different severities, as shown in Figure 1.

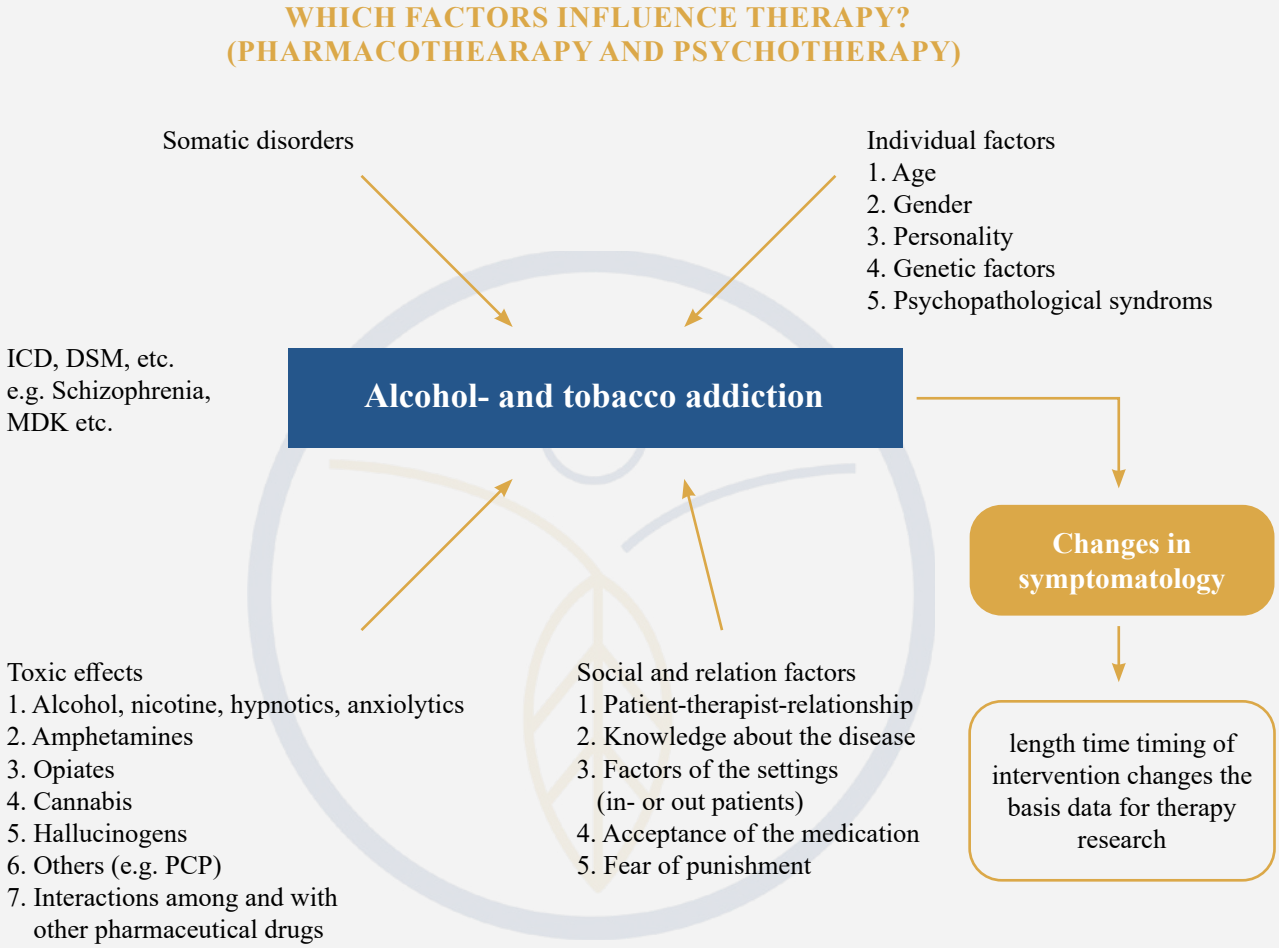


Figure 1. Influencers for therapy are multi-factorial (modified from Lesch OM, et al, 1990, 2010).

2) ICD-10 Dependence Syndrome

A cluster of behavioural, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persistent use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increase tolerance and sometimes a physical withdrawal state.

The dependence syndrome may be present for a specific psychoactive substance (e.g., tobacco, alcohol or diazepam), for a class of substances (e.g., opioid drugs), or for a wider range of pharmacologically different psychoactive substances.

Diagnostic criteria

Three or more of the following manifestations should have occurred together for at least one month or, if they have persisted for periods of less than one month, then they should have occurred together repeatedly within a twelve-month period.

1. A strong desire or sense of compulsion to take the substance.
2. Impaired capacity to control substance-taking behaviour in terms of onset, termination or level of use, as evidenced by the substance often being taken in larger amounts or over a longer period than intended, or any unsuccessful effort, or persistent desire, to cut down or control substance use.

3. A physiological withdrawal state (see F1x.3 and F1x.4) when substance use is reduced or ceased, as evidenced by the characteristic withdrawal syndrome for the substance, or use of the same (or closely %) substance with the intention of relieving or avoiding withdrawal symptoms.
4. Evidence of tolerance to the effects of the substance, such that there is a need for markedly increased amounts of the substance to achieve intoxication or desired effect, or that there is a markedly diminished effect with continued use of the same amount of the substance.
5. Preoccupation with substance use, as manifested by important alternative pleasures or interests being given up or reduced because of substance use or a great deal of time being spent in activities necessary to obtain the substance, take the substance, or recover from its effects.
6. Persisting with substance use despite clear evidence of harmful consequences (see ICD-10 F1x.1), as evidenced by continued use when the person was actually aware of or could be expected to have been aware of the nature and extent of harm.

a) Subgroups according to ICD-10
Course specifiers
- Currently abstinent
- Early remission
- Partial remission
- Full remission
- Currently abstinent but in a protected environment (e.g., in a hospital, in a therapeutic community, in prison, etc.)
- Currently on a clinically supervised maintenance or replacement regime [controlled dependence]
- Currently abstinent but receiving treatment with aversive or blocking drugs (e.g., naltrexone or disulfiram)
- Currently using the substance [active dependence]
- Without physical features
- With physical features

b) Subgroups of dependence according to DSM-IV
1. With Physical Dependence. This specifier should be used when Substance Dependence is accompanied by evidence of tolerance (Criterion 1) or withdrawal (Criterion 2).
2. Without Physical Dependence. This specifier should be used when there is no evidence of tolerance (Criterion 1) with withdrawal (Criterion 2). In these individuals, Substance Dependence is characterized by a pattern of compulsive use (at least three items from Criteria 3-7).

These 2 subgroups are nearly not used in clinical trials, but a lot of other subgroups are developed.

3) Historical Important Subgroups
a) Typology according to Jellinek[12]
The drinking behaviour-based typology, according to Jellinek12, which has established itself internationally due to its simplicity, was neither able to support basis research, nor provide information for therapy. Yet this typology was very important for the development of diagnostic methods and especially for the WHO in defining dependence and abuse. Yet this typology is not mentioned by any recognized journal nor is it documented in any therapy study.
b) Typology according to Foucault
The French school, which has clearly always taken considerably more account of the aetiology and course of mental disorders than the German-speaking psychiatric schools, developed by Foucault M[13], a typology that pays special attention to aetiology and sequelae[14]. The type "alcoolite" shows gender differences (about 60% of male and 5% of female alcohol dependents). The type "alcoolose" is marked by psychological disorders, often displays an episodic intoxicating drinking behaviour and can be found in type III, according to Lesch. Independent of drinking behaviour, the type "soma-alcoolose" often shows somatic symptoms, like severe polyneuropathy or real epilepsies, and it is very similar to Lesch's type IV.
Multivariate and multidimensional typologies (e.g., Bleuler M, 1983[15]; Morey LC und Blashfield RK, 1981[16]; Rounsaville BJ et al, 1987[17]; Tarter REH et al, 1977[18] have led to research tools that are suitable for defining different groups of alcohol dependents, but further studies about basis research and therapy of these subgroups are still needed.
c) Subgroups according to the Addiction Severity Index (ASI)
In 2003, Van den Brink suggested at a consensus conference of the ECNP in Nizza that all therapy studies on addictive diseases and, of course, alcohol addiction should use the ASI to ensure that the studies' results from different countries are more comparable. A German language validated version has already been published[19,20].

4) Important Subgroups for Research and Practice
a) Two-cluster-solutions
1. **Schuckit's typology**
   In 1985, Schuckit differentiated between primary and secondary alcoholics. Primary alcoholics don't show any mental disorders before the onset of alcohol abuse, whereas secondary alcoholics show

psychological disorders before the onset of alcohol addiction. Secondary alcoholics tried to "treat" these disorders by using alcohol as a form of self-therapy. Regarding this process, Schuckit MA showed that the regression of psychical symptoms like those in anxiety or depression occurs in many patients even without a specific therapy within 14 to 21 days only of absolute abstinence[21,22].

2. **Cloninger's typology**
As a result of genetic studies, in 1981 Borland MS, et al[23] and Cloninger CR, et al[24] differentiated between two types of alcoholics. Type I, according to Cloninger, is characterized by varying alcohol abuse (sometimes occasional, sometimes heavy). Their fathers don't show any delinquent behaviour, and they belong to the upper classes. One of the biological parents is often alcohol dependent. Type I dependents, according to Cloninger, have lesser alcohol-related social problems with less frequent in-patient admittances, and the onset of alcohol dependence occurs after the age of 25. The dependents are easily influenced by their environment ("high reward dependence"), very careful and often react with avoidance behaviour ("high harm avoidance"). They are very reluctant to put themselves in risk situations ("low novelty situations")[25]. Cloninger type II patients often have more alcoholics in their family next to their alcohol-dependent father/mother. Type II alcohol dependents, according to Cloninger, grow up in very difficult social conditions, and aggression and violence are frequent factors in these families. The patients can also turn aggressive for minor reasons or no reason at all. They often take other drugs, and the addiction process starts before the age of 25. According to Cloninger's personality dimensions, they can be characterized by a high readiness to enter risk situations ("high novelty seeking"), a love of unstable life situations ("low harm avoidance") and act like they are very independent from their environment ("low reward dependence"). These types are biologically validated (type II shows a high MAO-activity) and the classification has been used by researchers in therapy studies, which showed that Acamprosate and Topiramate show different effects in Cloninger's types (Kiefer F et al, 2005 and Johnson B et al, 2004). Cloninger types are continuously used for genetic studies. Type II patients, according to Cloninger, show higher heritability than type I patients. Furthermore, type II patients are more frequently admitted into in-patient clinics and suffer from severe mental problems. Cloninger's typology has also been included in several pharmaceutical relapse studies, in which type II clearly shows better results about anti-craving substances. Naltrexone reduces relapses in type II[26]. Ondansetron also showed better results in type II27. This data shows that the biological mechanisms of craving are heterogenic in type II, and this is in line with Lesch's typology, as type IV shows an early onset of addiction and is defined by severe psychiatric and neurological complications.

3. **Typology according to Babor**
In 1992, Babor TF examined 321 female and male alcohol dependents during their in-patient admission[28]. 17 categories were used for a multidimensional classification, and he recorded premorbid risk factors, abuse of alcohol, the use of other addictive substances, chronifications in the process and alcohol-related sequelae[28]. Similar to Cloninger's type, type A, according to Babor, shows symptoms such as a late onset of dependence, few problems during childhood and less psychopathological symptoms. Type B, according to Babor, has a high prevalence of infantile behaviour disorders and multiple alcoholic members in the family; early manifestation of alcohol addiction symptoms in the individual's life and acute life stress factors can be observed. This group of dependents requires lengthier treatment and individuals have often been in in-patient care. The symptoms are very similar to Cloninger's type II. Other authors (e.g., Brown J et al[29]; Del Boca FK[30], Del Boca FK and Hesselbrock MN[31,32] were able to verify these syndromes in their patients, according to Babor A and Babor B. Babor's typology has also been included in therapy studies in which SSRIs lead to an improvement of the process, especially in type B[33]. Only recently, Johnson showed that Ondansetron significantly reduces the relapse rate, especially in "early onset" dependents and in Babor type B. Since 1992, primarily the team around Schuckit MA has continued to research Babor's typology[21,22], whereas other researchers were not able to match some cases with the typologies according to Babor and Cloninger, so that the two-cluster solution was described as not satisfactory by some authors[34,35].

b) The four-cluster solutions

1. **Del Bocca and Hesselbrock's typology[34]**
Several studies have found that two-group solutions seldom fully capture the clinical entity or adequately classify general population samples. The variability in the number of subtypes could be a consequence of the data reduction technique used (e.g., cluster analysis, factor analysis) since most are not governed by

prescribed rules. Further, the final solution could also be influenced by a variety of factors, including sample characteristics and sample size, availability of clinical information and the theory underlying the original analysis. Depending upon the variables of interest and the number of subjects examined, more recent studies typically identify 3-5 subtypes. The indeterminate nature of cluster-derived typologies (and a limit of the statistical procedure) is best exemplified by a re-analysis of the Babor et al data by Del Boca and Hesselbrock[31] (1996). Their results showed four clusters as functional solutions that distinguished alcohol-dependent persons along gender and several clinically important dimensions.

Cluster Low Risk/Low Severity (LR/LS)

The largest subtype, containing approximately one-third of the cases (39% of females and 29% of males) was characterized as relatively low risk and low severity, while 22% of females and 22% of males were classified as high risk and high severity. The low risk/low severity (LR/LS) groups were characterized as having a mild form of alcohol dependence, with a late onset of alcoholism, low alcohol involvement, with no alcoholic family members or co-morbid psychopathology.

Cluster High Risk/High Severity (HR/HS)

In contrast, the High Risk/High Severity (HR/HS) group was characterized as having a severe form of alcohol dependence, an early onset of alcohol use and dependence, a positive family history of alcoholism, high alcohol involvement, behaviour problems, polydrug use, depression and antisocial personality disorder. There were no gender differences in terms of the proportions or characteristics of subjects among both mild and severe forms of alcohol dependence.

Two other identified clusters can be characterized as moderate forms of alcohol dependence and were labelled as Internalizing and Externalizing groups. Gender-specific differences were found for both groups.

Cluster Internalizing type

The Internalizing type included a higher proportion of women (32%) than men (11%). This group was characterized as depressed, anxious, and having severe alcohol dependence. They also reported medical and/or physical problems resulting from chronic alcohol use, but a moderate family history of alcoholism risk.

Cluster Externalizing type

The Externalizing subtype was predominantly male (38% of men and 7% of women) and was characterized as having a moderate alcoholism family history risk, high levels of alcohol use, social consequences and antisocial personality, but no depression or anxiety disorders.

While many studies of alcoholic typologies do not have long-term follow-up or treatment outcome data, subjects in the Del Boca and Hesselbrock's study completed one and three-year follow-up interviews. In addition, 25-year mortality data have also been obtained. At the one-year follow-up, the majority of men in the Externalizing, High Risk/High Severity and Internalizing clusters relapsed to regular drinking and/or sought treatment of alcohol problems (86%, 74%, and 72%, respectively) while a little over half (56%) of men in the Low Risk/Low Severity group reported regular drinking and/or seeking treatment. Among women, five of six who were classified as Externalizers relapsed to regular drinking or received treatment. The remaining subtypes of women fared better; the rates of relapse to regular drinking or treatment ranged from 52% to 57% of women in the other three clusters.

At the three-year post-discharge follow-up, a similar trend continued to be found. Both the High Risk/High Severity group and the External group continued to report high rates of relapse to drinking for both the men and women, while the men, regardless of their cluster assignment, tended to report higher rates of relapse than the women. Nearly 4 out of 5 men in the HR/HS group and the Externalizing group continued to relapse to regular drinking or receiving treatment, as compared to approximately half of the men in the LR/LS and the Internalizing groups. There were no differences in the rates of relapse among women by cluster subgroups. Regardless of their cluster assignment, approximately half of the women were either abstinent or engaged only in occasional drinking at the three-year follow-up. However, the number of women in each cluster was small, and these findings should be interpreted with caution.

A 25-year post-treatment follow-up of this sample was made through a search of the Social Security Death Index records, death certificates and autopsy results. An overall crude death rate as of December 2005 was 45.7% for men and 41.7% for women. The crude death rate was highest among the "Low Risk/Low Severity" (53.0%) and "Internalizing" (55.6%) clusters for men and Low Risk/Low Severity cluster for women. Both men and women in the High Risk/High Severity cluster had the lowest crude death rates (29.4 and 21.1%, respectively). These crude death rates are reflective of the discrepancy in the different clusters' ages at the time of their admission to the treatment centre (baseline). The average age of the HR/HS group was youngest at admission, 27.7

years old, followed by the Externalizing and Internalizing groups (40.5 yrs. and 40.0 yrs., respectively), with LR/LS group being the oldest (44.7 years). Consequently, the age of death for the HR/HS group was youngest, 49.5 yrs for men and 47.8 yrs for women, followed by the Externalizing group (58.6 yrs. for men and 53.8 yrs. for women). The LR/LS group had the oldest age of death (62.8 for men and 60.2 for women). The available death certificates were reviewed by two physicians and classified into three categories: (1) definitely related to alcohol, (2) definitely not related to alcohol, (3) cannot be determined. The two reviewers were mostly in agreement, but in a few cases, a third person was asked to review the certificates and discuss his reviews with the other two to determine the appropriate category. Among those subjects whose deaths could be determined, 6 of 7 HR/HS men's deaths were alcohol-related. Approximately half of the Externalizing and LR/LS men's deaths were related to alcohol, while less than half of the Internalizing group deaths were related to the use of alcohol. There were no statistically significant differences in alcohol-related deaths by cluster among women. Approximately 50% of all deaths were related to alcohol among all clusters, but the number of women whose cause of death could be determined was too small for meaningful analysis (the number ranged 0 to 6).

We were able to determine the manner of death for 117 subjects. Most subjects died of natural causes (86% for men and 80% for women). The suicide rate was higher among women than men (17% vs. 8%), while accidental death was slightly higher among men than women (6% vs. 3%). Among the 7 men who committed suicide, three men each were from the Externalizer and Internalizer groups, while one man was from LR/LS subgroup. Among the 5 women who committed suicide, three were from the Internalizer group and two from the LR/LS groups. To adjust for the variation in age among the four cluster groups, a standard mortality ratio (SMR) was calculated for each cluster by gender using the State of Connecticut mortality table for 1980 to 2005. Overall, the SMR was quite high, with the rate for women being much higher than that of men (5.41 (CF 3.77-7.52) for women vs. 2.82 (CF 2.30-3.43) for men). The SMR was highest among High Risk/High Severity group men and women (4.72 for men and 6.60 for women). The SMR was also high among men in the Externalizing group (3.18 (2.27-4.33)), while the SMR for both Low Risk/Low Severity and the Internalizing clusters were similar and the lowest (2.42 and 2.09). Unlike the men, the SMR was also high among Low Risk/Low Severity and Internalizing cluster women. However, the results for women could be biased since the number of women in each cluster was very small.

As expected, the grouping of alcohol-dependent persons into more homogeneous clusters provided important information regarding the long-term course of alcohol dependence among treated persons. The High Risk, High Severity group was particularly associated with early onset alcohol dependence, severe multiple addictions, psychiatric co-morbidity at baseline, one-year and three-year follow-ups, and impacted on long-term survival. These findings again demonstrate the potential clinical importance of grouping patients into homogeneous clusters since different clusters/typologies do present with different clinical symptom profiles and have different short and long-term prognoses, and such different types of alcoholics also require different treatment plans.

2. **Windle and Scheidt's typology**

   These authors also identified four clusters of addiction by using a similar method of data collection as the one used by Babor. They defined a mild progression with multiple addictive drugs and compared this to an alcohol addiction with a depressive symptomatic and a chronic progression with an antisocial personality disorder[36].

   Cluster 1

   The mild progression showed less infantile behavioural disorders and a later onset of alcohol addiction with this group drinking less than the other group. Additionally, withdrawal syndromes occurred.

   Cluster 2

   In cluster 2, the highest concomitant use of other addictive drugs, especially benzodiazepines, was found.

   Cluster 3

   In cluster 3, the most acute manifestation of affective and anxiety disorders was found.

   Cluster 4

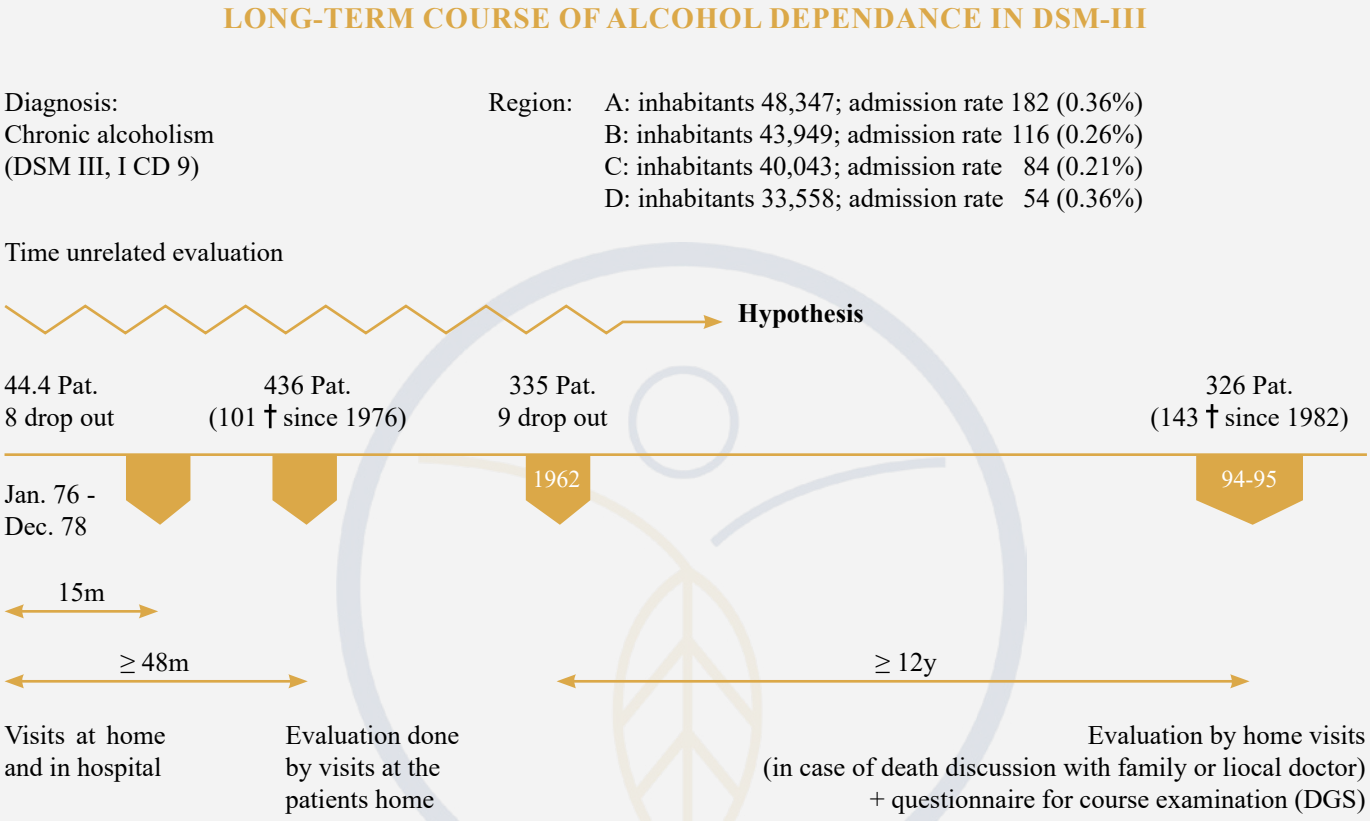
   In cluster 4, the highest level of alcohol abuse regarding both amount and duration was found. These clusters showed significant gender differences. In Cluster 4, significantly more men have been defined, whereas more women were defined in clusters 1-3. These clusters are in line with the clusters described by Zucker RA and Gomberg E, Schuckit MA, Del Boca FK and Hesselbrock MN, Hesselbrock VM and Lesch OM[35]

3. **Subgroups according to Lesch (Lesch's typology)**

   a) Framework for the definition of Lesch's typology

   Already in 1973, for scientific purposes, we defined a "catchment area" in Austria that encom-

passed around 160,000 inhabitants. The established care system enabled us to prospectively examine the long-term progression of diverse disorders such as paraphrenic psychoses, depressive disorders and alcohol addiction (Lesch OM et al, 1985)[37]. Alcohol dependents were of course also cared for in this setting and these were cross-sectionally assessed so that they could be included in prospective therapy studies and basis research (Lesch OM et al, 1988). The opportunities that were offered here for long-term support and long-term scientific observation led to Lesch's typology[37] (Figure 2).



72.2% of our sample could be assessed during the long-term course (drop-out rate 27.8%). During the 1st period of the design (1976-1982) 4 sub-groups of alcohol dependant patients could be defined.
These types reflect different biological, psychological and social platforms. During the 2nd period we confirmed the stability of the courses.

Figure 2. Longitudinal course of alcohol-dependent patients, according to DSM-III and ICD-9, study design (n = 444). Methodology of the longitudinal study on alcohol-dependent patients (according to DSM-III and ICD-9), used for the development of Lesch's typology. Modified from Lesch OM, et al. Forensic Science Int. 1988.

b) The four long-term illness courses used for Lesch's typology

These four types of disease courses were correlated with symptoms that were recorded before and during admission and were then later organized, and the findings were weighted to form "Lesch's typology" in a decision tree[38-41] (Table 1). A total of 136 items (social, biographical, somatic, consumption behaviour, withdrawal symptoms, etc.) were correlated with progression, and it was shown that only some items were clearly related to disease progression. When several items were related, the most important item was used for diagnostic purposes.

Table 1. Decision tree for Lesch's typology.

Sintomi prima dei 14 anni che hanno portato a un disturbo dello sviluppo

- Perinatal trauma
- Brain contusions
- Other acute brain diseases or
- Acute polyneuropathy with neurological dysfunctions or
- Epilepsy or
- Nail bitting and stuttering (for months):

→ **TYPE IV**

- Nocturnal enuresis after the age of 3: (for a longer period of time and socially impairing)

In case of nocturnal enuresis:

→ **TYPE IV OR TYPE III**

- No periodic drinking behaviour or
- No sleep-maintenance insomnia or
- No severe depressive episode (ICD-10) or
- No severe suicidal tendencies without alcohol

→ **TYPE IV**

In case of no nocturnal enuresis:

- Periodic drinking behaviour
- Sleep-maintenance insomnia
- Severe depressive episode (ICD-10) or
- Severe suicidal tendencies without the influence of alcohol

→ **TYPE III**

- Severe physical withdrawal syndrome with strong vegetative withdrawal symptoms and three-dimensional tremor or
- Withdrawal seizures (grand mal)

→ **TYPE I**

TYPE II

Alcohol as a coping strategy or dependent personality disorder according to ICD-10

A computer algorithm was established that produced classifications by group. Data are entered into the computer program, which is based on the decision tree. The program automatically classifies the Lesch types. In the decision tree, the diagnostic procedure starts with the symptoms of type IV and only if none of these items is present, the patient is assigned to type III, I or II, according to symptoms. If the patient has type III symptoms, he/she is grouped into type III, even if symptoms for type I or II are present. If no symptoms of type IV and III are present, severe withdrawal symptoms and/or withdrawal seizures then determine whether the patient is assigned to type I or type II. Type II is the remaining group with no symptoms of type I, III or IV, although the diagnosis "alcohol dependence" according to DSM-IV or ICD-10 does exist for this group of type II patients. Type II patients are dependent according to DSM-IV and ICD-11, representing a group with a mild long-term course. As international therapy centres tried to use this classification system from as early as 1990 onwards, this tool has been translated into several languages (Bulgarian, Czech, Danish, English, French, Greek, Ital-

ian, Norwegian, Portuguese, Russian). Today, this diagnostic computer program, developed together with Walter H, Munda P, and Ferenci P[37,39-41,42], is available, free of costs, in 17 languages (www.lat-online.at.) One page is the decision tree. If you fill in this tree, you automatically get a proposal for the therapy. Other pages deal with important case history information, independent of the typology, but important for course and treatment (e.g., age of onset, family history, traumatizations, criminal acts, interactions with smoking). Two pages define alcohol-related somatic disabilities. The typology represents a way to come from an overall diagnosis to an individualized therapy.

c) Studies with Lesch typology

Various research groups have validated these subgroups using the instrument www.lat-online.at, which were tested in regard to their prognostic significance and therapeutic procedure[43,44-55].

1) Studies on genetics

In the last 15 years, a lot of international research centres tried to find genetic differences between the types. They found in different genetic systems significant differences between the types, but these results still need reconfirmation by other research groups[56-68].

2) Studies on biology

A study with intoxicated alcohol dependents showed that elimination rates of ethanol and methanol significantly correlate with the typology[69]. Condensation products like the norharmanes significantly correlate with typology, although this might be linked to smoking behaviour because type I patients nearly almost always smoke (Fagerstroem-positive)[69].

Another study, in which alcohol dependents with or without polyneuropathy were examined, showed that patients with acute polyneuropathy (type IV-patients) eliminated ethanol and methanol at a significantly slower rate than patients with no polyneuropathy (type I, II or III patients). These results suggest that ethanol and methanol are linked to peripheral nerve damages, while central symptoms (withdrawal symptoms or withdrawal attacks) are mainly linked to aldehydes that are centrally active.

For many years, alcohol addiction has been associated with increased homocysteine levels[70,71]. In 2004, Bleich was able to show that the homocysteine level is only heightened in intoxicated type I patients with or without epileptic withdrawal convulsions. These high levels rapidly decrease during abstinence or can be reduced with folic acid therapy if drinking behaviour is continued[70]. An unpublished study found that especially type I dependents are admitted to cardiologic units. Kiefer F was able to support the notion that only type I patients benefit from Acamprosate. This suggests that homocysteine could be a biological indicator for a successful response to Acamprosate as a relapse prophylaxis in alcohol-related heart diseases[26].

Neuroendocrinological studies showed that the HPA-axis is linked to drinking behaviour, withdrawal, and craving during abstinence[26,44-46]. CRH-and ACTH-changes are associated with craving. Prolactin, which is closely related to dopaminergic functions, is also highly significant regarding craving. Hillemacher was able to show that, especially in the case of type II alcohol dependents, intensity of craving and changes in prolactin levels go hand in hand[45]. Another important aspect is the relationship between leptin and ghrelin and the regulation of the intensity of hunger and appetite. Inconsistent findings exist in the literature[26,72]. Hillemacher has pointed to a positive correlation between leptin and Lesch's type I and type II alcohol dependents, whereas ghrelin is only significantly correlated with Lesch's type I[46]. Condensation between acetaldehydes and indolamines results in beta carbolines like norharmanes und harmanes (condensation products). In animal studies, these products increase anxiety and depressive states[67,72]. Already in 1994, it could be shown that Lesch type 2 (alcohol is used to cope with anxiety) patients had exhibited norharman and harman levels[69]. Data[73] on microbiota and brain research show that inflammation markers are high and remain (over 3 weeks) high in type 1 (severe withdrawal), are high but less than 3 weeks in type 2 and stay normal in type 3.

3) Studies in Psychophysiology

In 1988, Gruenberger J et al showed that the four types of alcohol-dependent patients are significantly different in the assessment with dynamic pupillometry, indicating differences in acetylcholinergic activities[74]. The spontaneous fluctuation of the pupil's diameter, maximal pupil contraction and the absolute change were measured in 117 female and male typologically classified alcohol dependents by means of Josef Grünberger's dynamic pupillometry. They were compared to 107 control participants (no psychiatric diagnosis and no alcohol abuse). Lesch's type I patients differed from types II and III as well as from the control group. In type II and type III, significantly fewer spontaneous fluctuations could be observed in comparison to the control group. All types significantly differed from the control group with regards to an absolute change, whereas type I was characterized by the highest absolute change. During the last two years, these differences were examined in 300 alcoholics and the first results were largely confirmed (presentation ESBRA 2007, non-published data).

4) Studies in psychopathology

Hyperthymic temperaments are significantly more frequent in Type 1 (good prognosis). The cyclothymic and irritable temperaments are found to be significantly more frequent in Type 4 patients (poor illness course). Type 4 patients show further frontal lobe function deficits and are more often left-handed (might be related to a primary vulnerability)[51,55,65-67,75]. Nakamura-Palacios and her research team investigated type 4 patients and found that deep brain stimulation of the frontal lobe significantly reduces craving in type 4 patients[76].

In the long-term course of bipolar disorders, different types of bipolar disorders (bipolar 1 and 2) could be defined with different rates of suicidal behavior. Suicidal tendencies are also increased in type 3 and 4 alcohol-dependent patients[37,77].

5) Relapse prevention studies, anti-craving substances

In 2006, Hillemacher et al[44] examined alcohol-dependent patients, classified according to Lesch's typology, regarding different craving mechanisms (Table 2). By using Anton's OCDS[78], they were able to show that type IV had the highest craving scores. Furthermore, type II had higher craving scores than type I and III. Type IV had the highest number of acute withdrawal symptoms and correlated with the most severe craving symptoms. A significant relationship between craving and the number of earlier detoxifications could only be found in type I[40,44,45].

There are different craving mechanisms in the Lesch types. The subgroups use alcohol as a sedative, anti-depressant or as medication against withdrawal symptoms (Table 3). These different effects and their

Table 2. Craving with regards to Lesch's typology (Hillemacher T, et al, 2006).

Mean values					
	Lesch type I (no. 37)	**Lesch type II (no. 94)**	**Lesch type III (no. 38)**	**Lesch type IV (no. 23)**	**Population (no. 192)**
OCDS totala	17.4 ± 7.3	21.0 ± 7.2	19.0 ± 7.9	24.3 ± 6.9	20.3 ± 7.6
OCDS activity	6.8 ± 3.7	8.8 ± 4.8	7.7 ± 5.09	9.8 ± 5.3	8.3 ± 4.9
OCDS compulsive thoughts[a]	10.5 ± 3.7	12.1 ± 3.5	11.3 ± 3.6	14.5 ± 3.2	12.0 ± 3.7
Age (years)	43.3 ± 8.8	43.9 ± 9.0	44.8 ± 8.2	41.4 ± 9.3	43.7 ± 8.8
Onset of disease (years)	25.8 ± 10.6	26.2 ± 9.2	24.9 ± 9.5	22.4 ± 8.1	25.4 ± 9.4
No. of previous detoxification[a]	9.0 ± 10.4	8.2 ± 10.1	14.7 ± 29.1	18.8 ± 17.1	10.9 ± 16.8
Daily intake in g	217.9 ± 123.3	263.3 ± 219.0	233.9 ± 190.0	230.1 ± 108.6	244.8 ± 186.9

[a]significant differences between the types according to Lesch examined by the Kruskal-Walls-Test for independent samples (OCDS total score, Chi-square $p < 0.05$)

Table 3. Craving according to Lesch's typology and scientific hypotheses of craving (Walter, et al, 2006, modified).

Type I	The effect of alcohol on withdrawal symptoms (neuroadaptation)
Type II	Alcohol as an anxiolytic (social learning and cognitive models)
Type III	Alcohol as an antidepressant
Type IV	Alcohol as an impulse control disorder and/or a compulsion with previous cerebral damage, alcohol to cope with social situations (socio-cultural-organic model)

possible biological aetiologies have been summarized in 1997. From this, the following considerations for research about animal models and clinical therapy research can be suggested[37].

These considerations suggest that different etiological vulnerabilities need different pharmacological and psychotherapeutic therapies. Relapse prevention studies with disulfiram, acamprosate, naltrexone, nalmefene, sodium oxybate, flupentixol, baclofene and neramexane clearly showed that the relapse rate can be positively and negatively influenced by each individual medication. Acamprosate and naltrexone are internationally used as anti-craving substances[37,48,79-82].

In conclusion, there is data on medical withdrawal treatment and relapse prevention regarding Lesch typology for various medications and this is why our recommendations for relapse prophylaxis medication are always made in accordance with typologies. As the withdrawal symptoms differ with types, withdrawal symptoms should also be treated differently, always about typology.

Summarising our results and including our experience of 20 years of practical work with withdrawal and relapse prevention treatment, we recommend the following medication[27,37,83-92].

6) Lesch's typology from an international comparative perspective

All typologies in alcohol dependents overlap to a certain extent. Typologies that differentiate two subgroups (e.g., Cloninger CR and Babor TF) are often described more precisely by typologies that define four subgroups. The onset of an alcohol dependence, which Cloninger CR and Babor TF describe as a fundamental factor, does not play an important role in Schuckit's MA or Lesch's OM typology (the so-called "primary alcoholism" according to Schuckit is represented by Lesch's type I and IV, whereas the "secondary alcoholism" according to Schuckit is in line with Lesch's type II and III. Table 4 illustrates that those typologies, which are divided into four subgroups, show a clear concordance. Mild and episodic disease progressions, as well as the progression accompanied by social problems, are mirrored by the respective types according to Lesch, namely type II (mild progression), III (episodic progression) and IV (negative progression). Lesch's type I, which is only defined by regular and high amounts of drinking with acute withdrawal symptoms and/or withdrawal seizures, has no matching typologies (US and England). Typologies originating from the US and England always include a group of polytoxicomanics. In those countries, Lesch's type I patients might fall into the group of polytoxicomanics. In Portugal, Cardoso showed a significant correlation between the NETER-typology and types II, III and IV, according to Lesch, but he also defined a group of very young polytoxicomanics as a separate subgroup[49]. Alongside this typological classification, other factors play an important role. As depicted by many other studies, the onset of the alcohol addiction, genetic vulnerabilities and an antisocial personality disorder seem to be important factors, significant for therapy and progression.

Table 4. Overview medication for alcohol dependence according to Lesch typology.

	Withdrawal treatment	Relapse prevention
Type I	Benzodiazepines	Acamprosate, Disulfiram Cave: D1-antagonists
Type II	Sodium oxybate, Pregabalin	Acamprosate, Baclofen, Moclobemid, in relapse Sodium oxybate Cave: Benzodiazepines
Type II	Sodium oxybate	Naltrexone, Nalmefene, Sodium oxybate, Anti-depressives, Baclofen, Topiramate in early onset, Valproic acid or Lithium Cave: D1-antagonists
Type IV	Sodium oxybate, Carbamazepine, atypical neuroleptics	Naltrexone, Nalmefene, Sodium oxybate, Quetiapine, Valproic acid, Topiramate in early onset, Sodium oxybate as a substitution procedure

SUMMARY AND CONCLUSIONS

We hope that we can present data showing that the diagnosis of alcohol dependence according to ICD-11 or DSM 5 is not precise enough to start with a treatment process. You need subgroups to define a realistic and reachable goal to choose the effective withdrawal treatment and to choose a sufficient relapse prevention strategy. Four subgroups seem to be sufficient, and Lesch typology shows a lot of data using the instrument www.lat-online.at (Table 5).

Table 5. Comparison of different typologies.

Subgroups in alcohol dependence				
Lesch 1990	Zucker 1997	Del Bocka-Hasselbrock 1996	Windle-Scheidt 2004	Cardoso Neves et al 2006
Type II	More mild course subtype	Low risk, low severity	Mild course cope with stressors	Anxiopathic – typifies an anxious functioning
Type III	Negative effect	Negative effect	Major depressive generalized anxiety	Anxiopathic – typifies by affective symptomatology
Type IV	Antisocial alcoholic	Chronic/ASP	Chronic/ASP	Sociopathic – characterized by disruptive behaviours under alcohol influence
Type I			Polydrug use?	Heredopathic – congregates familiar and genetic influences on alcoholism
Babor and Cloninger 2 type solutions, personality traits of Cloninger fit very well to Lesch typology (e.g., harm avoidance type II)			Adictopathic – isolates younger individuals who consume alcohol and other types of psychoactive	

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Dilling H, Mombour W, Schmidt MH. Internationale Klassifikation psychischer Störungen. Verlag Hans Huber Bern Göttingen Toronto (WHO), 1991.
2. Lesch OM. Addiction in DSM V and ICD-11 state of the art in Fortschritte Neurologia Psychiatrie, 2009.
3. World Health Organization: ICD-11 for Mortality and Morbidity Statistics (ICD-11 MMS), 2018.
4. American Psychiatric Association. DSM IV. Diagnostic and statistical manual of mental disorders. Fourth Edition, 1994.
5. Widiger TA, Frances AJ, Picus HA, First MB, Ross R, Davis W. DSM-IV Sourcebook. Volume 1. American Psychiatric Association, 1994.
6. Humphreys K and Lingford-Hughes A. Edwards' Treatment of Drinking Problems: A Guide for the helping profession. 6th Ed., Cambridge Press, 2016.
7. UNODC and WHO: International Standards for the Treatment of Drug Use Disorders – Draft for Field Testing, March, 2016.
8. American Psychiatric Association. DSM 5. Diagnostic and statistical manual of mental disorders. Fifth Edition, 1994. Arlington VA. American Psychiatric Association, 2013.
9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition DSM-5TM. American Psychiatric Publishing, Washington, DC, 2013.
10. Johnson B. Handbook of Clinical Alcoholism Treatment, Create Space Independent Publishing Platform, 2017.
11. Saunders JB. Substance use and addictive disorders in DSM 5 and ICD 10 and the draft ICD 11. Curr Opin Psychiatry 2017;30(4):227-237.
12. Jellinek EM. The disease concept of alcoholism. Hillhouse. New Brunswick RI, 1960.
13. Foucault M. Power/Knowledge: Selected Interviews and Other Writings 1972-77, (1980). Pantheon, New York. Gilligan SB, Reich T, Cloninger CR. Etiologic heterogeneity in alcoholism. Gen Epidemiol 1987;4:395-414.
14. Malka R, Fouquet P, Vachorfrance G. Alcoologie. Masson, Paris, 1983.
15. Bleuler M. Lehrbuch der Psychiatrie. 15. Auflage, Springer Verlag, 1983.
16. Morey LC and Blashfield RK. Empirical classifications of alcoholics. J Stud Alcohol 1981;42:925-937.
17. Rounsaville BJ, Dolinsky ZS, Babor TF, Meyer RE. Psychopathology as a predictor of treatment outcome in alcoholics. Arch Gen Psychiatr 1987;44:505-513.
18. Tarter REH, McBride RN, Bounparte N, Schneider DU. Differentiation of alcoholics. Arch Gen Psychiatr 1997;34:761-768.
19. Gsellhofer B, Fahrner EM, Weiler D, Vogt M, Hron U. Deutsche Version: (IFT Institut für Therapieforschung) und J. Platt (Hahnemann University); nach dem amerikanischen Original von T. McLellan, 5th. Ed., 1992, und der europäischen Version EuropASI von A. Kokkevi, Ch. Hartgers, P. Blanken, E.-M. Fahrner, G. Pozzi, E. Tempesta & A. Uchtenhagen, 1993.
20. Van den Brink W, Montgomery SA, Van Ree JM, van Zwieten-Boot BJ. ECNP Consensus Meeting March 2003 Guidelines fort the investigation of efficacy in substance use disorders. Eur Neuropsychopharmacology 2006;16:224-230.

21. Schuckit MA. The clinical implications of primary diagnostic groups among alcoholics. Arch Gen Psychiatry 1985;42:1043-1049.
22. Schuckit MA, Tipp J, Smith TL, Shapiro E, Hesselbrock V, Bucholz K, Reich T, Nurnberger JI Jr. An evaluation of Type A and Type B alcoholics. Addiction 1995;90:1189-1204.
23. Borland R, Murray K, Gravely S, Fong GT, Thompson ME, McNeill A, O´Connor RJ, Goniewicz ML, Young HH, Levy DT, Heckmann BW, Cummings KM. A new classification system for describing concurrent use of nicotine vaping products alongside cigarettes (so-called "dual use"): findings from the ITC-4 country smoking and Vaping wave I survey. Addiction. 2019;114 (1):24-34.
24. Cloninger CR. Neurogenetic adaptive mechanisms in alcoholism. Science 1987;236:410-416.
25. Kiefer F, Jiménez-Arriero MA, Klein O, Diehl A, Rubio G. Cloninger's typology and treatment outcome in alcohol-dependent subjects during pharmacotherapy with naltrexone. Addict Biol 2007;13:124-129.
26. Kiefer F, Helwig H, Tarnaske T, Otte C, Jahn H, Wiedemann K. Pharmacological relapse prevention of alcoholism: clinical predictors of outcome. Eur Addict Res 2005;11:83-91.
27. Johnsons BA, Alho H, Addolorato G, Lessch OM, Reich J, Liu L, Schu7yler V. A prospective Pharmacogenentic Phase 3 Clinical Trial of Low Dose Ondansetron (5-HT3 Antagonist) to teat Heavy and very heavy Drinkers with alcohol use disorder. Trsearch Square. Posted Oct. 18th, 2022. DOI: https://doi.org/10.21203/rs.3.rs-2156237/v
28. Babor T, De Hoffman MI, Boca F, Hesselbrock V, Meyer R, Dolinsky Z, Rounsaville B. Types of alcoholics. I. Evidence for an empirically derived typology based on indicators of vulnerability and severity. Arch Gen Psychiatry 1992;49:599-608.
29. Brown J, Babor TF, Litt M, Kranzler H. The Type A/Type B distinction. Subtyping alcoholics according to indicators of vulnerability and severity. Babor T, Hesselbrock V, Meyer R, Shoemaker W. Types of Alcoholics. Ann NY Acad Sci 1994;708:23-33.
30. Del Boca FK. Sex, gender, and alcoholic typologies. Ann N Y Acad Sci 1994;708:34-48.
31. Del Boca FK, Hesselbrock MN. Gender and alcoholic subtypes. Alcohol Health Res World 1996;20:56-66.
32. Del Boca FK. Two subtypes or more, much work remains: a commentary on Windle and Scheidt. Addiction Dec 2004;99(12):1609-1610.
33. Kranzler HR, Burleson JA, Brown J, Babor TF. Fluoxetine treatment seems to reduce the beneficial effects of cognitive behavioral therapy in type B alcoholics. Alcohol Clin Exp Res 1996;20:1534-1541.
34. Hesselbrock MN, Hesselbrock V, Del Boca F. Typology of alcoholism, gender and 20-year mortality. Alcohol Clin Exp Res 2001;25:151A.
35. Hesselbrock VM, Hesselbrock MN. Are there empirically supported and clinically useful subtypes of alcohol dependence? Addiction 2006;101(1):97-103.
36. Windle M, Scheidt DM. Alcoholic subtypes: are two sufficient? Addiction, Dez 2004;99(1):1508-1519.
37. Lesch OM, Walter H, Wetschka CH, Hesselbrock MN, Hesselbrock V, and Pombo S. Alcohol and Tobacco, Medical and Sociological Aspects of Use, Abuse and Addiction. 2nd Ed. Springerverlag, 2020.
38. Lesch OM. Chronischer Alkoholismus – Typen und ihr Verlauf – eine Langzeitstudie. Thieme Copythek, Georg Thieme Verlag Stuttgart New York, 1985; 235 Seiten, 116 Tabellen.
39. Lesch OM, Grünberger J, Rajna P. Outpatient Treatment of Alcohol Addicts – the Burgenland Model. Medicine and Law, Springer Verlag 1985;4:71-76.
40. Lesch OM, Dietzel M, Musalek M, Walter H, Zeiler K. The course of alcoholism. Long-Term prognosis in different types. Forensic Sci Int 1988;36(1-2):121-138.
41. Lesch OM, Kefer J, Lentner S, Mader R, Marx B, Musalek M, Nimmerrichter A, Preinsberger H, Puchinger H, Rustembegovic A, Walter H, Zach E. Diagnosis of Chronic Alcoholism – Classificatory Problems. Psychopathology 1990;23(2):88-96.
42. Lesch OM, Walter H. Therapy of Withdrawal Syndroms, Addiction Disorders and Substitution Therapies. NeuroPsychopharmacotherapy Vol. 3, pp. 4525-4542, ed. Riederer P, Laux G, Nagatsu T, Le W, Riederer Ch, Springer Nature, 2022.
43. Bogenschutz MP, Scott Tonigan J, Pettinati HM. Effects of alcoholism typology on response to naltrexone in the COMBINE study. Alcohol Clin Exp Res 2009;33(1):10-18.
44. Hillemacher T, Bayerlein K, Wilhelm J, Bönsch D, Poleo D, Sperling W, Kornhuber J, Bleich S. Recurrent detoxifications are associated with craving in patients classified as type 1 according to Lesch's typology. Alcohol Alcohol 2006;41(1):66-69.
45. Hillemacher T, Bayerlein K, Wilhelm J, Frieling H, SperlingW, Kornhuber J, Bleich S. Prolactin serum levels and alcohol craving – an analysis using Lesch's typology. Neuropsychobiology 2006;53:133-136.
46. Hillemacher T, Bleich S. Neurobiology and treatment in alcoholism – recent findings regarding Lesch's typology of alcohol dependence. Alcohol and Alcoholism Alcohol Alcohol 2008;43(3):341-346.
47. Leggio L, Kenna GA, Fenton M, Bonenfant E, Swift RM. Typologies of alcohol dependence. From Jellinek to genetics and beyond. Neuropsychol Rev 2009;19(1):115-129.

48. Lesch OM, Riegler A, Gutierrez K, Hertling I, Ramskogler K, Semler B, Zoghlami A, Benda N, Walter H. The European Acamprosate trials: conclusions for research and therapy. J Biomed Sci 2001;8(1):89-95.
49. Pombo S, Reizinho R, Ismail F, Barbosa A, Figueira ML, Cardoso JM, Lesch OM. NETER 1 alcoholic 5 subtypes: Validity with Lesch four evolutionary subtypes. Int J Psychiatry Clin Pract 2008;12(1):55-64.
50. Pombo S, Lesch OM. The alcoholic phenotypes among different multidimensional typologies: similarities and their classification procedures. Alcohol Alcohol 2009;44(1):46-54.
51. Vyssoki B, Blüml V, Gleiss A, Friedrich F, Kogoj D, Walter H, Zeiler J, Höfer P, Lesch OM, Erfurth A. The impact of temperament in the course of alcohol dependence. J Affect Disord 2011;135(1-3):177-183.
52. Vyssoki B, Steindl-Munda P, Ferenci P, Walter H, Höfer P, Blüml V, Friedrich F, Kogoj D, Lesch OM. Comparison of alcohol-dependent patients at a gastroenterological and a psychiatric ward according to the Lesch alcoholism typology: implications for treatment. Alcohol Alcohol 2010;45(6):534-540.
53. Walter H, Ramskogler-Skala K, Dvorak A, Gutierrez-Lobos K, Hartl D, Hertling I, Munda P, Thau K, Lesch OM, De Witte P. Glutamic acid in withdrawal and weaning in patients classified according to Cloninger's and Lesch's typologies. Alcohol Alcohol 2006;41(5):505-511.
54. Weinland C, Braun B, Mühle C, Kornhuber J, Lenz B. Cloninger Type 2 Score and Lesch Typology Predict Hospital Readmission of Female and Male Alcohol-Dependent Inpatients During a 24-Month Follow-Up. Alcohol Clin Exp Res 2017;41(10):1760-1767.
55. Zago-Gomes Mda P, Nakamura-Palacios EM. Cognitive components of frontal lobe function in alcoholics classified according to Lesch's typology. Alcohol Alcohol 2009;44(5):449-457.
56. Benyamina A, Saffroy R, Blecha L, Pham P, Karila L, Debuire B, Lemoine A, Reynaud M. Association between MTHFR 677C-T polymorphism and alcohol dependence according to Lesch and Babor typology. Addict Biol 2009;14(4):503-505.
57. Biermann T, Reulbach U, Lenz B, Muschler M, Sperling W, Hillemacher T, Kornhuber J, Bleich S. Herp mRNA expression in patients classified according to Lesch's typology. Alcohol 2009;43(2):91-95.
58. Bönsch D, Bayerlein K, Reulbach U, Fiszer R, Hillemacher T, Sperling W, Kornhuber J, Bleich S. Different allele-distribution of MTHFR 677 C -> T and MTHFR -393 C -> A in patients classified according to subtypes of Lesch's typology. Alcohol Alcohol 2006;41(4):364-367.
59. Foroud T, Bucholz KK, Edenberg HJ, Goate A, Neuman RJ, Porjesz B, Koller DL, Rice J, Reich T, Bierut LJ, Cloninger CR, Nurnberger JI, Li TK Jr., Conneally PM, Tischfield JA, Crowe R, Hesselbrock V, Schuckit M, Begleiter H. Evidence for linkage of an alcohol-related phenotype to chromosome 16. Alcohol Clin Exp Res 1998;22:2035-2042.
60. Grzywacz A, Małecka I, Korostyński M, Przewłocki R, Bieńkowski P, Samochowiec J. GABA-A receptor genes do not play a role in genetics of Lesch's typology in Caucasian subjects. Arch Med Sci 20129;8(2):357-361.
61. Lee SH, Lee BH, Lee JS, Chai YG, Choi MR, Han DM, Ji H, Jang GH, Shin HE, Choi IG. The association of DRD2 -141C and ANKK1 TaqIA polymorphisms with alcohol dependence in Korean population classified by the Lesch typology. Alcohol Alcohol 2013;48(4):426-432.
62. Procopio DO, Saba LM, Walter H, Lesch O, Skala K, Schlaff G, Vanderlinden L, Clapp P, Hoffman PL, Tabakoff B. Genetic markers of comorbid depression and alcoholism in women. Alcohol Clin Exp Res 2013;37(6):896-904.
63. Saffroy R, Pham P, Chiappini F, Gross-Goupil M, Castera L, Azoulay D, Barrier A, Samuel D, Debuire B, Lemoine A. The MTHFR 677 C>T polymorphism is associated with an increased risk of hepatocellular carcinoma in patients with alcoholic cirrhosis. Carcinogenesis 2004;25(8):1443-1448.
64. Samochowiec J, Kucharska-Mazur J, Grzywacz A, Pelka-Wysiecka J, Mak M, Samochowiec A, Bienkowski P. Genetics of Lesch's typology of alcoholism. Prog Neuropsychopharmacol Biol Psychiatry 2008;32(2):423-427.
65. Samochowiec A. The influence of parents personality measured by temperamental and character inventory (TCI) on course of alcoholism characterized by Cloninger's and Lesch's typologies. Ann Acad Med Stetin 2010;(2):33-39.
66. Samochowiec A, Horodnicki JM, Samochowiec J. The influence of parents personality and DRD4 and 5HTT genes polymorphisms on predisposition to alcohol dependence in their sons. Psychiatr 2011;45(3):337-347.
67. Samochowiec A, Chęć M, Kopaczewska E, Samochowiec J, Lesch O, Grochans E, Jasiewicz A, Bienkowski P, Łukasz K, Grzywacz A. Monoamine oxidase a promoter variable number of tandem repeats (MAOA-uVNTR) in alcoholics according to Lesch typology. Int J Environ Res Public Health 2015;19;12(3):3317-3326.
68. Samochowiec A, Chęć M, Kopaczewska E, Samochowiec J, Lesch O, Jasiewicz A, Grochans E, Jabłoński M, Bieńkowski P, Kołodziej Ł, Grzywacz A. Case control study of ANKK1 Taq 1A polymorphism in

patients with alcohol dependence classified according to Lesch's typology. Postepy Hig Med Dosw (Online) 2016;4;70:420-424.
69. Leitner A, Gierth L, Lentner S, Platz WE, Rommelspacher H, Schmidt L, Lesch OM. Untergruppen Alkoholkranker. Gibt es biologische Marker? Harmann- und Norharman- Befunde. In: P. Baumann (Hrsg.): Biologische Psychiatrie der Gegenwart, 1994; pp. 636-640.
70. Bleich S, Bayerlein K, Reulbach U, Hillemacher T, Bonsch D, Mugele B, Kornhuber J, Sperling W. Homocysteine levels in patients classified according to Lesch's typology. Alcohol Alcohol 2004;39(6):493-498.
71. Hultberg B, Berglund M, Andersson A, Fran K. Elevated plasma homocysteine in alcoholics. Alcohol, Clin. Exp Res 1993;17:687-689.
72. Addolorato G, Capristo E, Leggio L, Ferrulli A, Abenavoli L, Malandrino N, Farnetti S, Domenicali M, D'Angelo C, Vonghia L, Mirijello A, Cardone S, Gasbarrini G. Relationship between ghrelin levels, alcoholcraving and nutritional status in current alcoholics. Alcohol Clin Exp Res 2006;30:1933-1937.
73. Hanak C, Benoit J, Fabry L, Hein M, Verbanck P, de Witte P, Walter H, Dexter DT, Ward RJ. Changes in Pro-Inflammatory Markers in Detoxifying Chronic Alcohol Abusers, Divided by Lesch Typology, Reflect Cognitive Dysfunction. Alcohol Alcohol 2017;52(5):529-534.
74. Grünberger J, Lesch OM, Linzmayer L. Bestimmung von vier Alkoholikertypen mit Hilfe der statischen und licht-evozierten dynamischen Pupillometrie. Wiener Zeitschrift für Suchtforschung 1988;11(4):29-34.
75. Sperling W, Frank H, Martus P, Mader R, Barocka A, Walter H, Lesch M. The concept of abnormal hemispheric organization in addiction research. Alcohol Alcohol 2000;35(4):394-399.
76. Nakamura-Palacios EM, de Almeida Benevides MC, da Penha Zago-Gomes M, de Oliveira RW, de Vasconcellos VF, de Castro LN, da Silva MC, Ramos PA, Fregni F. Auditory event-related potentials (P3) and cognitive changes induced by frontal direct current stimulation in alcoholics according to Lesch alcoholism typology. Int J Neuropsychopharmacol 2012;15(5):601-616.
77. Reulbach U, Biermann T, Bleich S, Hillemacher T, Kornhuber J, Sperling W. Alcoholism and homicide with respect to the classification systems of Lesch and Cloninger. Alcohol Alcohol 2007;42(2):103-107.
78. Anton RF, Moak DH, Latham P. The Obsessive Compulsive Drinking Scale: a self-rated instrument for the quantification of thoughts about alcohol and drinking behaviour. Alcohol Clin Exp Res 1995;1992-1999.
79. Attilia F, Perciballi R, Rotondo C, Capriglione I, Iannuzzi S, Attilia ML, Vitali M, Alessandrini G, Scamporrino MCM, Fiore M, Ceccanti M. Pharmacological treatment of alcohol use disorder. Scientific evidence. Riv Psichiatr 2018;53(3):123-127.
80. Caputo F, Addolorato G, Lorenzini F, Domenicali M, Greco G, del RE A, Gasbarrini G, Stefanini GF, Bernardi M. Gamma-hydroxybutyric acid versus naltrexone in maintaining alcohol abstinence: an open randomized comparative study. Drug Alcohol Depend 2003;70(1):85-91.
81. Caputo F, Addolorato G, Stoppo M, Francini S, Vignoli T, Lorenzini F, Del Re A, Comaschi C, Andreone P, Trevisani F, Bernardi M. Alcohol Treatment Study Group. Comparing and combining gamma-hydroxybutyric acid (GHB) and naltrexone in maintaining abstinence from alcohol: an open randomised comparative study. Eur Neuropsychopharmacol. 2007;17(12):781-789.
82. Soyka M, Koller G, Schmidt P, Lesch OM, Leweke M, Fehr C, Gann H, Mann K. The cannabinoid receptor 1 antagonist SR 141716 (Rimonabant) for treatment of alcohol dependence – results fro a placebo-controlled double-blind trial. J Clin Psychopharmacol 2008;28(3):317-324.
83. Addolorato G, Lesch OM, Maremmani I, Walter H, Nava F, Raffaillac Q, Caputo F. Post-marketing and clinical safety experience with sodium oxybate for the treatment of alcohol withdrawal syndrome and maintenance of abstinence in alcohol-dependent subjects. Expert Opin Drug Saf 2020 Feb;19(2):159-166.
84. Burnette EM, Nieto SJ, Grodin EN, Meredith LR, Hurley B, Miotto K, Gillis AJ, Ray LA. Novel Agents for the Pharmacological Treatment of Alcohol Use Disorder. Drugs. 2022 Feb;82(3):251-274.
85. Guiraud J, Addolorato G, Antonelli M, Aubin HJ, de Bejczy A, Benyamina A, Cacciaglia R, Caputo F, Dematteis M, Ferrulli A, Goudriaan AE, Gual A, Lesch OM, Maremmani I, Mirijello A, Nutt DJ, Paille F, Perney P, Poulnais R, Raffaillac Q, Rehm J, Rolland B, Rotondo C, Scherrer B, Simon N, Skala K, Söderpalm B, Somaini L, Sommer WH, Spanagel R, Vassallo GA, Walter H, van den Brink W. Sodium oxybate for the maintenance of abstinence in alcohol-dependent patients: an international, multicenter, randomized, double-blind, placebo-controlled trial. J Psychopharmacol 2022;36(10):1136-1145.
86. Guiraud J, Addolorato G, Aubin HJ, Bachelot S, Batel P, de Bejczy A, Benyamina A, Caputo F, Couderc M, Dematteis M, Goudriaan AE, Gual A, Lecoustey S, Lesch OM, Maremmani I, Nutt DJ, Paille F, Perney P, Rehm J, Rolland B, Scherrer B, Simon N, Söderpalm B, Somaini L, Sommer WH, Spanagel R, Walter H, van den Brink W. Sodium Oxybate for Alcohol Dependence: A Network Meta-Regression Analysis Consid-

ering Population Severity at Baseline and Treatment Duration. Alcohol Alcohol 2023;58(2):125-133.
87. Johnson BA, Ait-Daoud N, Akhtar FZ, Ma JZ. Oral topiramate reduces the consequences of drinking and improves the quality of life of alcohol-dependent individuals: a randomized controlled trial. Arch Gen Psychiatry 2004;61(9):905-912.
88. Johnson B, Addolorato G, Lesch O, Liu L, Rodd ZA. A critical scientific evaluation of a purportedly negative data report - response to Seneviratne et al. 2022. Front Psychiatry 2023;14:1271229.
89. Rolland B, Paille F, Gillet C, Rigaud A, Moirand R, Dano C, Dematteis M, Mann K, Aubin HJ. Pharmacotherapy for Alcohol Dependence: The 2015 Recommendations of the French Alcohol Society, Issued in Partnership with the European Federation of Addiction Societies. CNS Neurosci Ther 2016;22(1):25-37.
90. Scherrer B, Guiraud J, Addolorato G, Aubin HJ, de Bejczy A, Benyamina A, van den Brink W, Caputo F, Dematteis M, Goudriaan AE, Gual A, Kiefer F, Leggio L, Lesch OM, Maremmani I, Nutt DJ, Paille F, Perney P, Poulnais R, Raffaillac Q, Rehm J, Rolland B, Simon N, Söderpalm B, Sommer WH, Walter H, Spanagel R. Baseline severity and the prediction of placebo response in clinical trials for alcohol dependence: A meta regression analysisto develop an enrichment strategy. Alcohol Clin Exp Res 2021;45(9):1722-1734.
91. van den Brink W, Addolorato G, Aubin HJ, Benyamina A, Caputo F, Dematteis M, Gual A, Lesch OM, Mann K, Maremmani I, Nutt D, Paille F, Perney P, Rehm J, Reynaud M, Simon N, Söderpalm B, Sommer WH, Walter H, Spanagel R. Efficacy and safety of sodium oxybate in alcohol-dependent patients with a very high drinking risk level. Addict Biol 2018;23(4):969-986.
92. Van den Brink W, Addolorato G, Aubin HJ, Benjamina A, Caputo f, Dematteis M, Gual A, Lesch OM, Mann K, Maremanni I; Nutt D, Paille F, Perney P, Rehm J, Reynaud M, Simon N, Söderpalm B, Sommer WH, Walter H, Spanagel R. Efficacy and safety of sodium oxybate in alcohol dependent patients with a very high drinking risk level. Addict Biol 2018;23(4):969-986.