

Lesch Alcoholism Typology Medical Treatment and Research

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Summary

Aim. Alcohol abuse and alcohol dependence produce very high health costs. Nowadays, early detection and intervention are very well accepted. Due to the well proven theory regarding the heterogeneity of alcohol dependence and for the purpose of research and therapy, four subgroups of alcohol dependence have been established.

Methods. The Lesch Typology was developed as a result of a prospective long - term study and led to a decision tree identifying alcohol dependent patients' subgroups. The results show that each subgroup requires different and specific treatments. Within the framework of a computer programme (www.LAT-online.at) the decision tree can be used very easily. Meanwhile, this method has been field – tested in numerous basic and clinical trials. After the diagnostic procedure, a protocol of the questionnaire displays reachable and realistic treatment goals. Furthermore, it provides information about the guidance and treatment of each patient subgroup.

Conclusion. Nowadays, the heterogeneity of the disease alcohol dependence is without any doubt an accepted certainty. By utilizing the Lesch Typology, specific treatment approaches of the diverse subgroups may be applied accordingly.

Discussion. Using the subgroups defined in the Lesch Typology for basic and clinical research subgroup customized treatments can be prescribed, and consequently even better treatment outcomes in alcohol dependent patients can be awaited.

alcohol dependence/ Lesch typology/ subtypes/ withdrawal and relapse prevention treatment

INTRODUCTION

Alcohol dependence represents a chronic brain disease with a relapsing course and a high burden of alcohol related disabilities. Smoking combined with alcohol dependence is a common phenomenon, leading to significantly increased mortality rates (NIAAA-website [1]). Medical

treatment is mainly used for alcohol withdrawal and for relapse prevention. For withdrawal most authors recommend treatment with benzodiazepines (Johnson B. [2, 3], Lesch OM et al.). In clinical routine however, many centres also use Tiapride, Carbamazepine, Clomethiazole, Trazodone and Sodium Oxybate.

Relapse prevention includes pharmaceutical and psychotherapeutic approaches. Currently almost every psychotherapeutic method is used. For pharmaceutical relapse prevention medications with significantly different biological actions are recommended.

In a literature review Hester and Miller [4] showed that all these drugs are only effective in

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Figure 1. Pharmacological substances presently used for relapse prevention in chronic alcoholism

Pharmacotherapeutic relapse prevention	
Serotonergic System	Zimelidine (Balldin et al. [5]) Buspirone (Kranzler et al. [6]) Ondansetron (Kranzler HR et al. [7]) Mirtazapine (Lesch et al. unpublished) Sertraline plus Naltrexone (Pettinati et al. [8])
Noradrenergic System	Imipramine (McGrath PJ et al. [9])
Dopaminergic System	Tiapride (Shaw GK et al. [10,11]) Lisuride (Schmidt LG et al. [12])
GABA-ergic System	Gamma-Hydroxybutyric -acid (Gallimberti et al. [13])
Endorphinergic System	Naltrexone (O 'Malley et al. [14]) Nalmefene (ongoing European Study)
Glutamatergic System	Homotaurin -Calcium (Lhuintre JP. [15] Paille FM et al. [16]; Lesch OM. [17])
Aversive Medication	Disulfiram (Fuller RK and Gordis E, [18])
Mood Stabiliser:	Lithium (Merry et al. [19]; Fawcett et al.[20])

a small subgroup of alcohol dependent patients. Every drug trial in alcohol dependence has positive but also negative data. Some drugs could also increase relapse rates [21, 22]. Acamprosate and Naltrexone are two examples with positive as well as negative data [3, 4].

All these data clearly show that Alcohol Dependence is a heterogeneous disease and that we need the definition of treatment-relevant subgroups (with specific treatment for each type). Internationally, a consensus in favour of the "4-type solution" exists, meaning that a distinction into 4 subtypes is best concerned the fulfilling of the following criteria: Homogeneity in the type, Heterogeneity between the types, multidimensionality and easy to be used. [23].

Fig. 2 (*next page*) shows an empirically supported and clinically feasible classification into four subgroups [23].

Following this approach of four subgroups the pharmaceutical effect of alcohol in this subgroups can be defined as follows: Fig. 3 (*next page*).

These heterogeneous mechanisms reflect a different underlying biological vulnerability, so, as a consequence, that fact should result in an individual anticraving medication. However any

typology is only a subset of the mechanisms that lead to a relapse. In a pathway analysis on 83 alcohol dependent patients diagnosed according to ICD-10 and DSM-IV we were able to show the multifarious interactions which should be considered in clinical relapse prevention trials. Fig. 4 (*page 40*).

Comment: Pathway analysis showing how many factors contribute to relapse

Drinking pattern, craving and subgroups of alcohol dependence have the main impact on relapse rates but there are also other psychosocial dimensions directly or indirectly influencing relapse rates.

Following these international developments we would like to present the four subtypes according to the Lesch Typology, because these types fit very well with the above mentioned developments, they are neurophysiologically and biologically validated, are being used in treatment trials and also used in daily work in our country and in some others (Lesch OM et. al. [3]).

Figure 2. Types of V. and M. Hesselbrock

Are there empirically supported and clinically useful subtypes of alcohol dependence?

- Chronic/severe drinking and withdrawal type
- Mildly affected type
- Depressed/anxious type
- Antisocial type

Hesselbrock VM and Hesselbrock MN, 2006

Figure 3. Craving is different according to types

Heterogeneous Craving

**Type I - to cope withdrawal
(Neuroadaptation)**

**Type II - to cope anxiety
(Social learning and Cognitive model)**

**Type III - to cope depression
(Self-treatment model)**

**Type IV - pre-alcoholic damage,
to cope with surroundings
(Socio-cultural, organic model)**

Lesch et al. 2010

LESCH TYPOLOGY:

The Lesch Typology is based on data derived from a longitudinal prospective study on alcohol dependent patients (according to ICD-9) in a catchment area of 210,000 inhabitants. All alcohol dependent patients admitted to any psychiatric department were assessed during their hospital stay, while at the same time assessment procedures in the patients' families were undertaken.

In the next step we explored the patients six times a year over a period of 4 to 7 years. After 12 years, patients were yet again examined by two independent psychiatrists in their family environment, with particular emphasis on the

stability of the previously approved sub-groups. Fig 5 (*next page*).

Following the long term course of alcohol dependent patients we could show that alcohol dependence is a severe medical condition. During the first period 101 out of 436 patients died. In the following 12 years, an additional 143 patients died. While describing the long term course of the patients, we could define four different long term courses. Fig. 6 (*page 41*).

After the long term observation period we attempted to correlate psychosocial and medical items with these four different courses. One hundred thirty-six items we assessed with this questionnaire, but out of these 136 items only a few showed statistical power. Finally, 11 items

Figure 4. Pathway analyses of relapse in alcohol dependence (n=83) (Unpublished data)

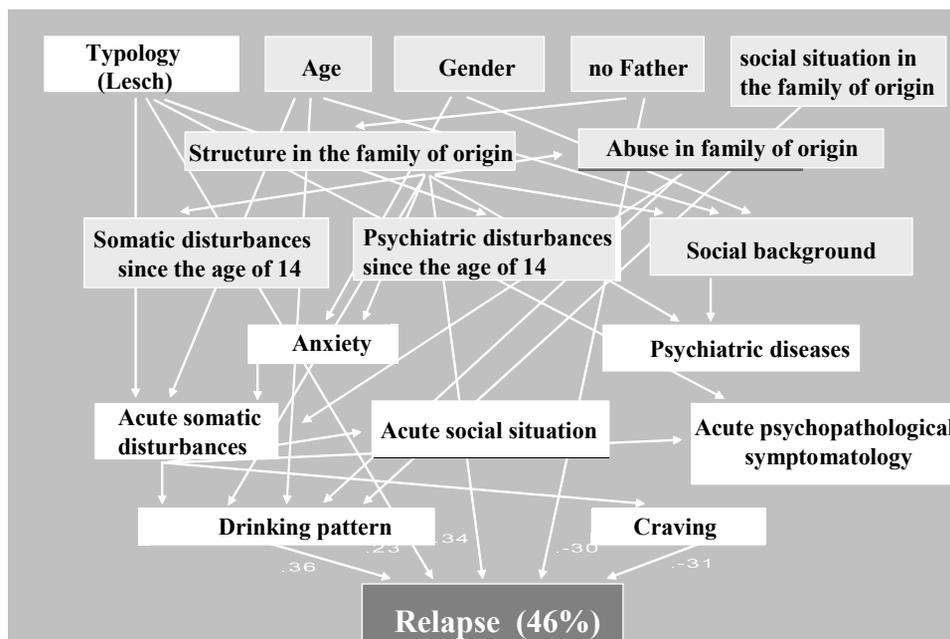
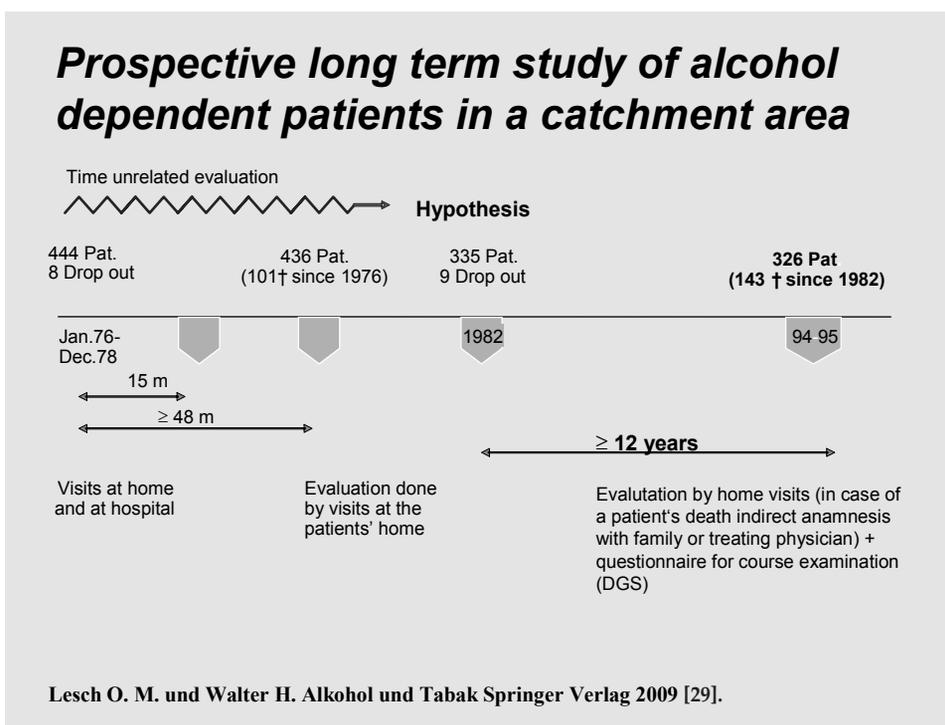


Figure 5. Study design as developed by OM Lesch to develop the 4 types



were used as predictors for these different courses to establish a decision tree, published 1990 in Psychopathology (Lesch et al. [24]). Fig. 7 (next page).

If a single item belonging to Type IV was present, the patients did not change their drinking habits. If items of Type III were present, an episodic illness course could be observed. With-

out any items of the Types III and IV, and with a severe withdrawal or withdrawal seizures present, Type I was assigned, showing a good illness course with good long-term abstinence. Patients without items of the Types I, III and IV showed a mild disease course without loss of control and were assigned to Type II.

Figure 6. Naturalistic patterns of drinking

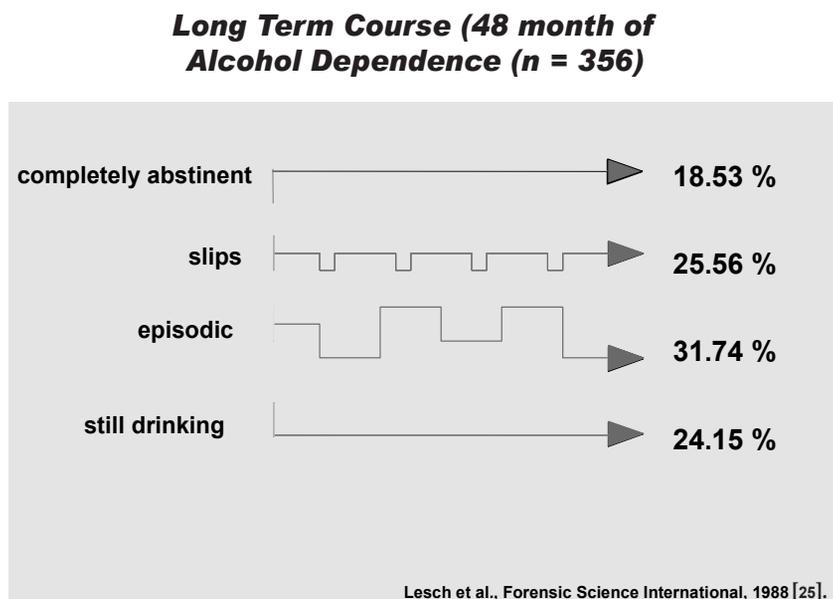
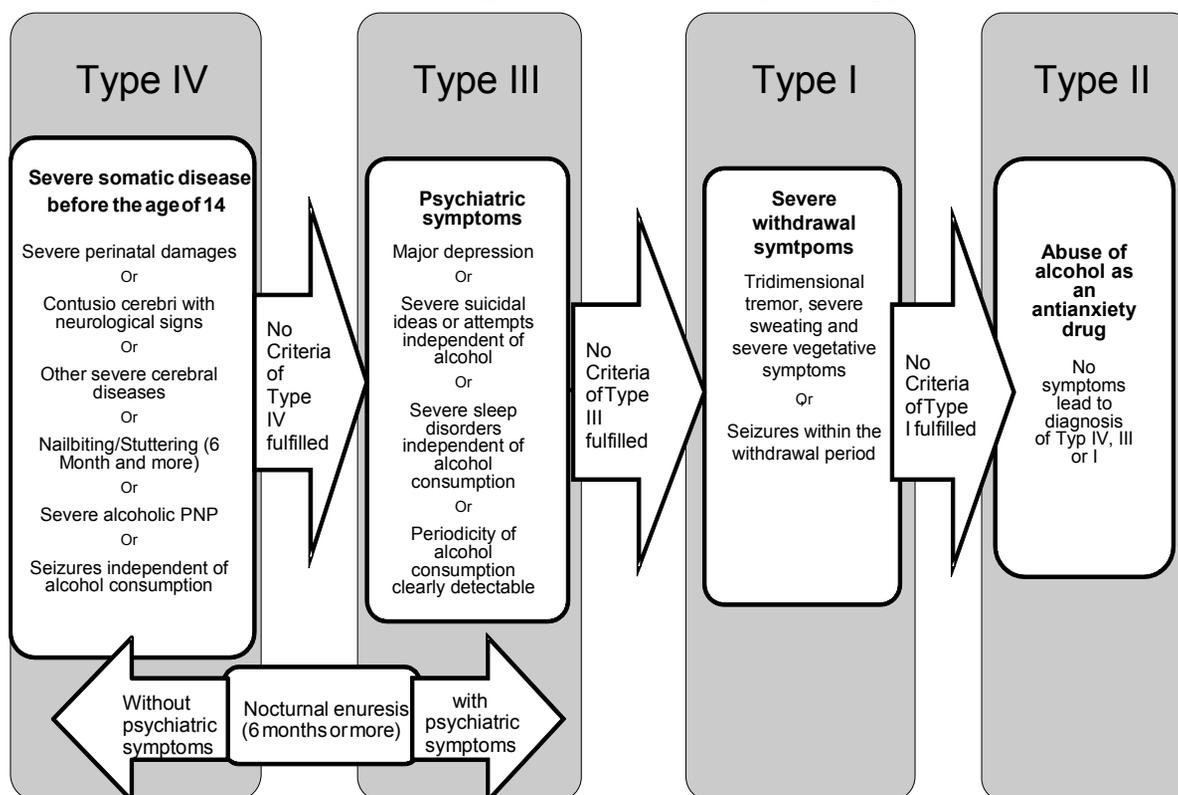


Figure 7.

Basis for diagnostic-process of Alkcohol Dependence according do Lesch's Typology



The survey instrument has now been translated into most European languages (English, Greek, Spanish, French, Polish, etc.), and has

been validated by basic research, neurophysiologic research and treatment trials (www.LAT-online.at, Lesch et al. [3]).

Further studies have confirmed a sex dependent distribution among the different Lesch Types (Sperling et al. [26]). Depending on the clinical setting (e.g. gastroenterologic ward versus psychiatric ward), the distribution of the types varied (Vyssoki et al. [27], in print). As for relapse prevention, e.g. with Acamprosate (Lesch et al. [17]), similarly different types proved to be effi-

cient. Genetic studies also confirmed differences in the various subgroups. (Samochowicz J. et al. [30], Benyamina A et al. [31], Bönsch et al. [32], etc.).

The differences could be found in other typologies as well. Thus, in 2009 Leggio et al. published an article presenting evidence based treatments applied to relapse prevention.

Figure 8. Medications for relapse prevention;

Typologies and medication		
	Evidence-based medication in relapse-prevention according to typologies	Hypothesis: medication for relapse prevention
Naltrexone	Type A CloningerII Lesch Typ III & IV	LO-A
Acamprosate	CloningerII Lesch I & II	Babor B EO-A
Ondansetron	EO-A Babor B	CloningerII
Setraline	Babor A	CloningerI LO-A

Leggio L. et al, Neuropsychol Rev. 2009

Comment to Fig. 8: EO=early onset; LO=late onset.

According to our research and based on our clinical experience, we recommend the following treatment procedure for alcohol-dependent patients.

TREATMENT ACCORDING TO THE LESCH TYPOLOGY (Lesch et al., Soyka M, Lesch Om et al. [3, 28])

Type I – “Allergy Model”

Symptoms:

Alcohol is used to reduce withdrawal symptoms. The symptomatology is caused by biological vulnerability (high levels of acetaldehyde also in the time of abstinence). Withdrawal can be understood as a kind of rebound phenomenon (GABA-hypersensitivity, glutamate-GABA imbalance).

If Type I patients change their drinking habits or stop their alcohol intake they often develop severe withdrawal symptoms, and/or withdraw-

al seizures (Grand Mal on the first or second day after quantity changes in drinking or after sudden abstinence). The withdrawal symptoms develop rapidly (often within hours) and disappear within a few days. A rough, three-dimensional tremor, profuse sweating (“wet withdrawal”), restlessness, and in many cases epileptic seizures can be observed. Without proper treatment withdrawal symptoms increase and can lead to a life-threatening delirium tremens. The patients can very clearly describe the amount of alcohol they need in the morning in order to end withdrawal symptoms. This amount of alcohol helps to define the needed dosage of benzodiazepines (e.g. 20g pure alcohol versus 140g pure alcohol). The aim of the medication is to avoid withdrawal symptoms and therefore it should be started as early as possible and the dosage should not be too low.

Withdrawal treatment:

1. Benzodiazepines: e.g. Lorazepam (mainly benzodiazepines, which are not degraded in long-acting metabolites)
 - Dosage 150-600 mg/day (depending on the quantity of alcohol, indicating the patient to be effective against the withdrawal symptoms)
 - the degree of alcohol blood level
 - severity of current withdrawal syndrome
 - the severity of previous withdrawal syndromes
2. Caroverine: 3x20mg/day; in case of severe craving: 3x40mg/day
3. Acamprosate: 3-0-0-3 capsules daily for patients over 60kg and 2-0-0-2 for patients weighing less than 60kg. The full satiety of Acamprosate is reached after 2 to 3 weeks. Thus concomitant therapy with Caroverine is recommended for the first 3 weeks.
4. Antipsychotics such as Flupentixol, Lisuride and similar substances. Tiapride is contraindicated (positive chronotrope, danger of seizures and increase relapse rates)
5. Adequate hydration should be ensured.
6. During withdrawal, basic vital functions (blood pressure, heart rate) are often found to be unstable, however, in most cases, these disturbances need no special drug treatment.

Relapse prevention treatment:**Psychosocial Therapy:**

Type I alcoholism can be considered as a physical disease. Type-I patients typically exhibit no personality disorders. A brief behaviorally oriented intervention might be advisable for some patients. Self-help groups such as AA are very helpful and should be suggested. Regular appointments and regular check ups (alcohol breathing analyzer, blood alcohol level) increase sobriety rates significantly.

Medical Relapse Prevention:

Disulfiram (Antabus®): Should only be given to highly motivated type-I patients who are exposed to high pressure of consuming alcohol,

for example at the workplace (e.g. jobs related to alcohol).

Dosage: initially 800mg/day over 2 to 3 days, then 100-200mg/day. It is recommended to combine Disulfiram with Acamprosate.

Acamprosate (Campral®): Is recommended to be prescribed for a period of 18 months or longer, beginning at the onset of withdrawal.

Dosage: 4 pills per day (< 60kg), 6 pills per day (>60kg)

Acamprosate may take up to 3 months to develop its full potential

Medical treatment of relapse:

Sodium Oxibate (Gammahydroxy-butyric acid), (Alcover®): This drug is given to patients to end a brief "lapse" of only a few days, in order to prevent a full blown drift into high intake.

Dosage: 3 times 10ml Alcover® per day for a period of 3 days. (10ml of Alcover ~ 1,750 mg GHB)

Naltrexone (Revia®) may diminish the magnitude and length of a relapse. In case of a relapse, after a prolonged period of abstinence, it is recommended to take Naltrexone immediately. It should only be taken until abstinence is restored. Patients should always have Naltrexone available.

In case of a severe relapse, GHB and Naltrexone can be combined to achieve an optimal effect.

In this subgroup total abstinence is a realistic goal and absolute necessity. Using this approach in prospective trials, we could show that 85% of these patients are completely sober after two years.

TYPE II – "Problem Solving and Anxiety Model"**Symptoms:**

Type II patients use alcohol because of its anxiolytic effect as a self-medication and conflict so-

lution strategy. In abstinent phases, patients of this group often show features of an “ego weakness”, a very low self esteem and, a passive-avoidant personality (Cloninger). These patients are also often in (or were in) relationships with dominant partners. The conversion of a drug to another is common in this group.

Type II patients show a withdrawal with two-dimensional tremor, sweating, and often a slight, but stable, increase in blood pressure and heart rate. There is no history of epileptic seizures occurring. The withdrawal symptoms can be observed up to two to three weeks (a mixture of withdrawal and anxiety-based disorder).

Withdrawal treatment:

For withdrawal treatment Tiapride with its anxiolytic properties is recommended. The dose depends on the severity of anxiety symptoms and difficulties of falling asleep. Usually a dose of 150-300mg/day is sufficient. Treatment with antiepileptic compounds is not necessary.

Cave: Both GHB and benzodiazepines are contraindicated in this group, because many of these patients learn that Benzodiazepines are very effective, and later on they abuse not only alcohol but also Benzodiazepines. If the symptoms are mild, also sedating antidepressants e.g. Trazodone can be used.

Relapse prevention treatment

Psychosocial therapy:

A major aim of the therapy is to make patients conscious of their harmful interactive processes. Patients need the caring attention of others in a dependent way. Therefore a therapeutic approach for dependent personality disorders is necessary.

Strategies, which can be used to reduce anxieties and have their origin in the personality structure, rather than environmental stimuli, need to be learned (e.g. ego-strengthening, or ego-structuring and learning to avoid dependent relationships by identifying early warning signs).

Stress and crisis related coping mechanisms should be developed, replacing alcohol as a strategy. The social environment has to be considered, too. Often the patient’s partner may also

suffer from a psychiatric or psychosomatic disease, in which case, systemic therapy is recommended. On occasions it may also be necessary to involve the patient’s children into the systemic therapeutic process.

Self-help groups, thematically focusing on anxiety, and/or ego-strengthening are recommended. Alcohol centered groups such as AA are not recommended (Witkiewitz K et al. [33]).

Medical relapse prevention:

Acamprosate	always combined with psychotherapy. Acamprosate should be taken for at least 15 months, in a daily dosage of 4 tablets (<60kg) or 6 tablets (>60kg).
Moclobemide	A dosage from 300 to 600mg/day diminishes levels of anxiety, and is therefore beneficial for the psychotherapeutic process.
Trazodone	(Trittico®): According to our experiences a dosage of 100 to 250 mg/day has positive effects, especially if administered in the evening.

The realistic goal of this subgroup is long term sobriety with short slips without loss of control. After effective psychotherapeutic work with significantly increased self esteem these patients do not rely on alcohol any longer in order to cope with stress and life events.

TYPE III – “Alcohol as an Antidepressant Model”

Symptoms:

In this group alcohol is abused for mood enhancing properties. Although alcohol seems to be soporific, it destroys the sleep architecture subsequently. Similar to Type II patients, patients of Type III show a two-dimensional, fine tremor (often visible only by checking the pronator drift), light sweating (mostly on the hands, increased less on the trunk) and a stable, tight circulation (blood pressure and heart rate). Epileptic seizures in the history are rare, but should be considered. During withdrawal, Type III patients show anxious-depressive states with guilt, fear and often suicidal thoughts. Familial clustering of mood disorders is also present. After some months of

abstinence, the depressive disorder (mostly bipolar II) improves in many cases.

Suicidal thoughts and suicidal tendencies in this period are very common (interruption of the therapy chain can be considered as medical malpractice, hospital - inpatient - outpatient treatments should be networked together, so that continuity is guaranteed in the therapy! - Crisis intervention concept according to G. Sonneck [34]).

Withdrawal treatment:

Type III patients are preferably withdrawn with GHB 4 x 7.5 ml to 10 ml/day. Already after the first dose it can be assessed whether this treatment is sufficient or not. If the desired effect is not achieved, then an additional benzodiazepine-abuse has to be assumed. In this case, treatment with GHB would be inadequate and drug therapy with benzodiazepines should be continued accordingly. The dose should be chosen to avoid withdrawal symptoms and then reduced slowly over many weeks. Overlapping with the reduction of benzodiazepines antidepressants with increasing dosages should be used.

In this group antipsychotic medication is strictly contraindicated, because they tend to increase the relapse rate! Naltrexone should already be established during withdrawal treatment (reduce craving and decreases early relapses).

In this group, short term admissions are often necessary, depending on the severity of psychopathological disturbances, e.g. severe suicidal tendencies or severe depressive episodes.

Relapse prevention treatment:

After the symptoms of withdrawal have subsided (commonly with transient depressive/anxious symptoms) therapy-relevant personality traits become apparent. Patients often have inflexible values and set high demands for themselves. Their body awareness predominantly constitutes of pain and other displeasing perceptions.

Only under the influence of alcohol, however, they permit themselves to experience emotions.

Psychosocial therapy:

In the beginning information and education about the above mentioned processes are necessary. At first it is essential to do this from a more

cognitive perspective; emotional factors should be focused on only later.

The therapist should encourage the patient to regain some body-awareness; to allow themselves to experience emotions; and relax their controlling behavior.

Early signs of the onset of depressive episodes have to be identified, and coping strategies internalized. If patients experiences disturbances in their sleeping pattern along with weight loss, they should immediately seek psychiatric advice.

Medical relapse prevention:

Patients who go through a major depressive episode are treated accordingly with the appropriate antidepressants and mood stabilizers, such as Lithium, Valproic acid or Carbamazepine, serving as relapse prevention. Many of these patients display bipolar II patterns, where appropriate medications based on recommendations for such patients should be followed and prescribed.

Medications to treat a depressive episode will depend on the chronobiological disturbance and any co-morbid physical symptoms. For example tricyclic and dual acting antidepressants may be beneficial. In case of a mild depression, "bright light" therapy and/or Trazodone or Sertraline may be sufficient.

Dopamine antagonists, such as antipsychotics, are not recommended because they increase relapse rates.

Naltrexone 50mg should be given once a day as an 'anti-craving-substance'. In some cases the dosage should be increased to 100mg daily (e.g. eating disorders in case history). Sometimes Naltrexone only reduces the time and severity of a relapse, but doesn't prevent it. If a severe relapse occurs, GHB should be prescribed for about 3 days (7.5ml - 3 times daily).

TYPE IV – "Conditioning Model"

Symptoms:

Significant abnormalities can already be found in the patient's childhood (before 14th year of age), during the phase of brain development, long before the person's drinking career even begun. Cerebral damages and difficult family backgrounds lead to child behavioural conspicuousness (such as: long-term stuttering, nail bit-

ing and/or nocturnal enuresis after the age of 3). Because of an obsessive-compulsive behaviour and a lack of criticism of drinking alcohol patients are not able to resist against the society's drinking pressure or the "current craving".

This chronic alcohol abuse combined with the already existing pre-damages leads to severe physical symptoms (e.g.: polyneuropathy, epilepsy, etc.). Severe cognitive impairment with corresponding psychopathological syndromes are often seen in the long term course.

Mild withdrawal states occur with a cerebellar tremor, a stable blood-circulation, almost no sweating (so-called "dry deprivation"). Often epileptic seizures occur, regardless of alcohol intake or alcohol withdrawal. Severe gait disorders are often observed (polyneuropathy).

Marked impairment of intellectual capacity and memory, (confabulations and/or perseverations) can be assessed. In some cases, Type-IV-patients interpret cases normal perceptions as delusions, sometimes there are also illusionary misidentifications or even hallucinations (paranoid hallucinatory syndrome). These symptoms increase during treatment with benzodiazepines.

The cause of the symptoms is not primarily due to the toxicity of alcohol, but is instead caused by the existing organic brain disturbances. In this case alcohol is a trigger and should be seen as a complicating factor. The precise differential diagnosis of other causes of organic psychoses is particularly important (stroke, brain tumours, hypoglycaemia, inflammation, etc.).

Withdrawal treatment:

The focus of withdrawal therapy should be seen in an optimal nursing care, a secure atmosphere in an abstinent environment (family or hospital) with supportive measures and adequate activation (e.g. bright light).

The underlying somatic conditions - including pain (!) - must be treated accordingly.

Carbamazepine has been proven (300-900mg/day) to prevent seizures. GHB 3x7,5ml/day is recommended for withdrawal symptoms.

Nootropics, e.g. Memantine, improve the cognitive performance and also work as anticraving substances. Infusions with 300mg Thiamine over 3 days are recommended.

If there are delusional symptoms, atypical antipsychotics are indicated (e.g. Quetiapine). Tranquillisers intensify the symptoms and should be administered in this group only in emergency situations (e.g. heaped epileptic seizures).

Relapse prevention therapy

Psychosocial therapy:

Educational work relies on repetition. At the beginning patients should see their therapist daily, then once a week, later on once a month. Ideally, these appointments should take place with the same therapist at fixed intervals, times and places.

Some patients should be given social support, such as a place in a social housing scheme. Management of finances in some cases incapacitation and state custodianship may be inevitable. Self-help groups, that tolerate relapses and even offer support during a relapse, are advisable. A daily routine is supportive. The patient should be encouraged to engage in meaningful activities in 'safe' places away from the usual 'drinking-environment';

Many Type-IV patients can only remain abstinent in hospital or hospital-like settings. Ideally patients should be able to continue out-patient treatment for a period of at least 1 year, in the same hospital in which they had been admitted as inpatients.

Medical relapse prevention:

To improve cognitive performance, nootropics may be given in the long run. Antiepileptic medication (e.g. Carbamazepine) should only be given long-term if tonico-clonic fits are not associated with alcohol consumption. Parenterally administered high dosages of thiamine are necessary to treat polyneuropathy.

Naltrexone 50mg/day is used as an anti-craving medication in order to reduce the severity and length of a relapse.

GHB is used as a maintenance drug. It is necessary to monitor the drinking habits and the GHB prescription in a medical setting.

CONCLUSION

The heterogeneity of the disease Alcohol Dependence is without any doubt a well established theory. Using the Lesch Typology it is possible to apply more specific treatment approaches. An overview of the medication is given in the Fig. 9 (*next page*). By combining these

Figure 9.

Summary of the pharmacological therapy according to the typology of Lesch		
	Withdrawal treatment	Relapse prevention
Type I	Benzodiazepines Clomethiazol	Acamprosat, Disulfiram Cave: D1-Antagonists
Type II	Tiapride Cave: Benzodiazepines, GHB-Acid	Acamprosat Cave: Benzodiazepines, GHB-Acid, Clomethiazole, Meprobamate
Type III	GHB-Acid Benzodiazepines only for Benzodiazepine-abusing patients	Naltrexon, Antidepressants (e.g. Sertralin, Milnacipran), Mood Stabilizer (e.g. Carbamazepin) Cave: D1-Antagonists Topiramate??
Type IV	GHB-Acid, Carbamazepine, atypical antipsychotics	Naltrexon, nootropics, atypical antipsychotics Ondansetron?? Topiramate??

Lesch and Soyka, 2005, 2009

medications with sufficient psychotherapeutic approaches and defining a realistic and reachable treatment goal it is possible to significantly increase sobriety rates. A continuation of basic research, using these subgroups will render new insights concerning the aetiology and long term course of the disease Alcohol Dependence.

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