

Lesch Alcoholism Typology

Spindleruv Mlyn, April 27th, 2010

Otto M. Lesch
Medical University of Vienna
Department of Psychiatry and
Psychotherapy



What do we treat?

- **Addiction can be seen as a brain disease with a high probability of a chronic relapsing course defined by ICD 10 and DSM IV**
- **The heterogeneity is undoubted and we need the definition of subgroups for basic and clinical research**

What happens today ?

- **At least 88 different therapies are applied**
- **world- wide (Hester & Miller, 2003)**
- **Most of them are not evidence based**

Some examples for heterogeneous results:

Cognitive Therapy in Relapse Prevention

AUTHOR	YEAR	SEVERITY	MQS	OLS	PRODUCT
Brandsma	1980	4	14	2	28
Oei	1982	4	12	2	24
Oei	1984	3	11	2	22
O'Connell	1987	4	9	2	18
Koski-Jännes	1992	4	6	- 1	- 6
Rosenberg	1986	2	8	- 1	- 8
Ito	1988	4	11	- 1	- 11
Christianson	1983	4	12	- 1	- 12
Jackson	1978	4	6	- 2	- 12
Monti	1990	4	11	- 2	- 22

CES = + 21

Disulfiram in Relapse Prevention

AUTHOR	YEAR	SEVERITY MQS		OLS	PRODUCT
Fuller	1986	4	17	2	34
Carroll	2000	4	15	2	30
Azrin	1982	4	14	2	28
Chick	1992	4	14	2	28
Wilson	1978	4	13	2	26
Wilson	1980	4	12	2	24
Wallerstein	1957	4	9	2	18
Malla	1988	4	8	2	16
Whyte	1974	4	8	2	16
Hoff	1953	4	5	2	10
Reinert	1958	4	8	1	8
Hussain	1972	3	6	1	6
Gerrein	1973	4	6	-1	-6
Aharan	1967	3	8	-1	-8
Levy	1967	4	8	-1	-8
Glotzbach	1984	4	9	-1	-9
Ludwig	1969	4	13	-1	-13
Miller	2001 (1)	4	15	-1	-15
Smith	1998	4	15	-1	-15
Fuller	1979	3	16	-1	-16
Gallant	1968a	4	9	-2	-18
Aliyev	1993	4	11	-2	-22
Ling	1983	4	11	-2	-22
Powell	1985	3	11	-2	-22
Johnsen	1987	4	12	-2	-24
Dahlgren	1989	3	13	-2	-26
Johnsen	1991	4	13	-2	-26

CES = - 6

Characteristics of a useful classification system

- Homogeneity within categories
- Heterogeneity between categories
- Stability
- Comprehensiveness and Specificity
- Multidimensionality
- Utility

Babor & Meyer, 1986

Withdrawal Treatments

- Benzodiazepines
- Tiapride
- Carbamazepine
- Clomethiazol
- Trazodon
- Gammahydroxybuturic Acid

Pharmacotherapeutic relapse prevention

- Serotonergic system: Zimelidine (Balldin 1994)
Buspirone (Kranzler 1994)
Odansetron (Rmach 1991), Mirtazapin (5HT3-Antagonist)
- Noradrenergic substances: TCA (Imipramin; Mc Grath, P.J. 1996)
- Dopaminergic substances: Tiapride (Shaw, G.K. 1987, 1994)
Lisuride (Schmidt, L.G. 1994)
- Gabaergic substances: Gammahydroxybutyric acid (Gallimberti 1990, 1992)
- Substances with effects on endorphinergic substances:
Naltrexone (Volpicelli 1990, 1994, O'Malley 1992)
- Glutamatergic substances: Homotaurin-Calcium
(Lhuintre J.P. 1985, Pelc 1990, Paille, F.M. 1995,
Ades J. 1992, Aubin, H.J. 1995, Withworth, A.B.
1996, Lesch O.M. 1994)
- Aversive medication: Disulfiram (Fuller 1986, 1992)
- Mood stabilizer: Lithium (Fawcett 1984, 1987, Merry 1976)

Which alcoholic patient
benefits most
from what treatment ?

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

2 Cluster:

Cloninger and Babor

4 Cluster:

Del Boca and Hesselbrock

Windle and Scheidt

Lesch

Foroud et al.

Zucker and Gomberg

5 Cluster:

Neter Typology

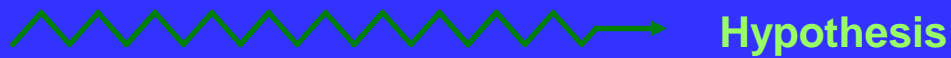
Conclusion: 4 Cluster

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

Catchment area study, 4th step

Time unrelated evaluation



444 Pat.
8 Drop out

436 Pat.
(101 † since 1976)

335 Pat.
9 Drop out

326 Pat.
(143 † since 1982)

Jan.76-
Dec.78

15 m

≥ 48 m

1982

94-95

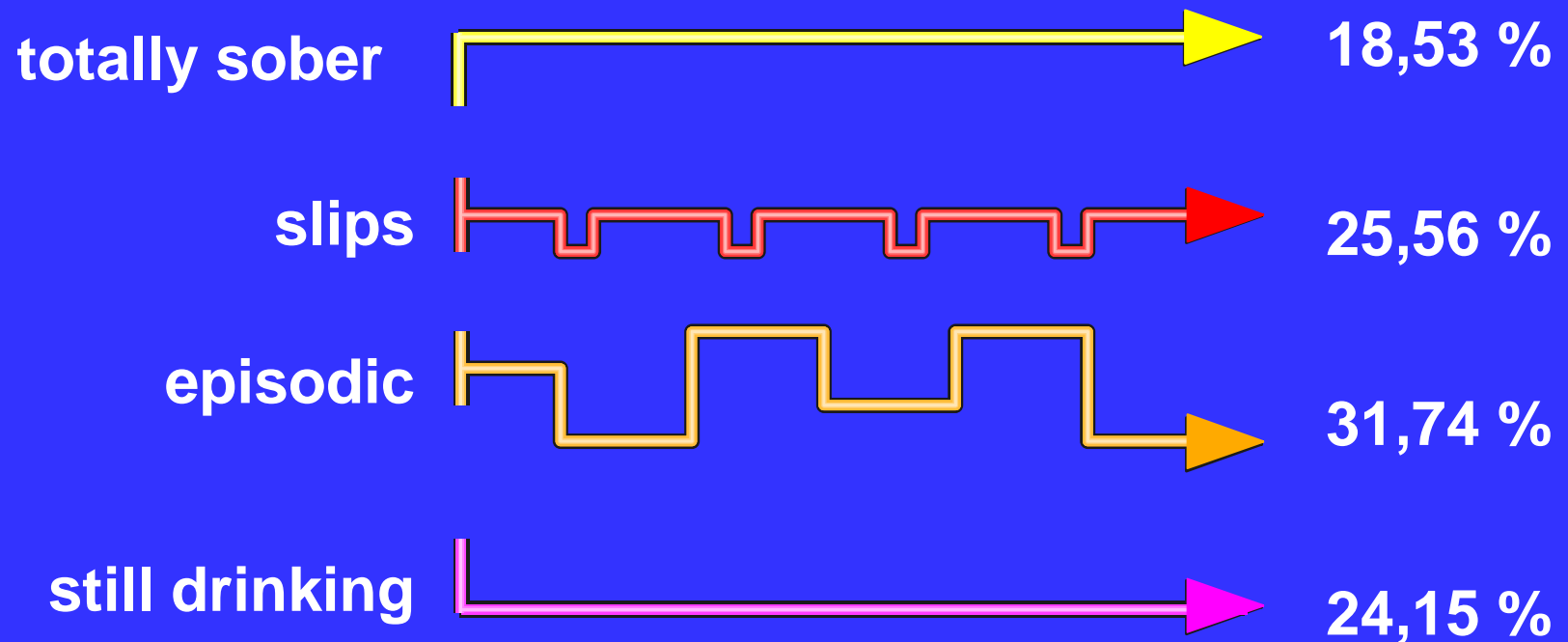
≥ 12 years

Visits at home
and in hospital

Evaluation done
by visits at the
patients home

Evaluation by home visits
(in case of death discussion
with family or local doctor)
+ questionnaire for course
examination (DGS)

Long Term Course (48 month) of Alcohol Dependence (n = 356)



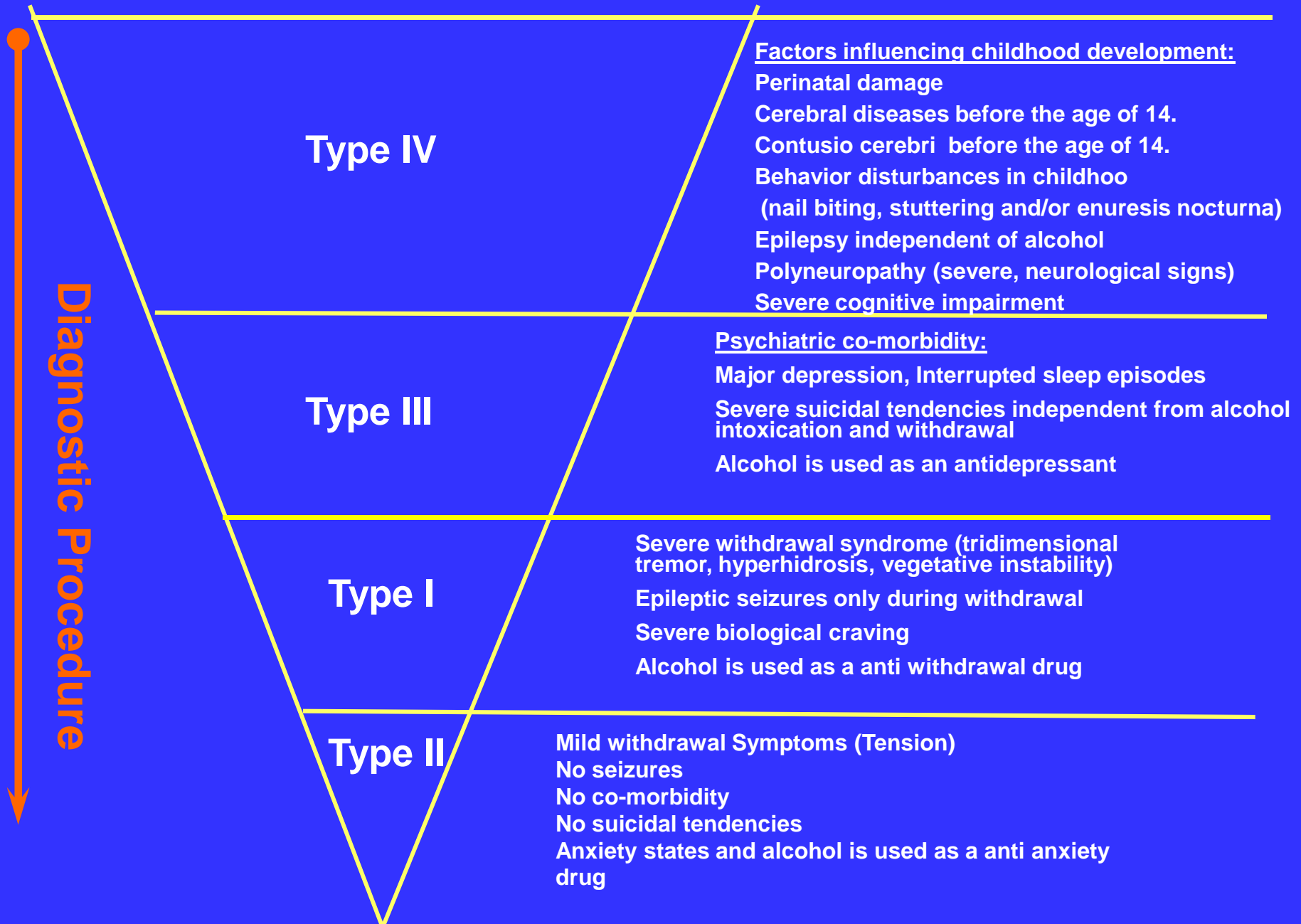
Place and Mode of Admission and Long-term Course > 4 years

- **Psychiatric Hospital Mauer** **338 alcohol dependent patients**
307 voluntary patients
31 compulsory patients
- **Anton-Proksch-Institute (API)** **87 patients – all voluntary**
(specialised for alcoholism treatment)
- **11 Patients compulsory in the Psychiatric Hospital Mauer and voluntarily in the API.**

Place and mode of admission for treatment did not correlate with outcome.

Frequency and quality of the follow up treatment significantly influenced illness course and outcome.

Typology according to Lesch in alcohol



Diagnosis of Chronic Alcoholism – Classificatory Problems

O.M. Lesch^{a,b}, J. Kefer^b, S. Lentner^b, R. Mader^b, B. Marx^b, M. Musalek^a,
A. Nimmerrichter^b, H. Preinsberger^b, H. Püschinger^b, A. Rustembegovic^b, H. Walter^a,
E. Zach^b

^aPsychiatric University Clinic, Vienna, and ^bAnton Proksch Institute, Kalksburg, Austria

Abstract. Since Magnus Huss introduced the diagnosis of 'chronic alcoholism' into medical literature in 1849, two unsolved problems concerning classification have remained: (1) Differentiation between problem drinkers and chronic alcoholics fluctuates, whereby the cut point of differentiation between abuse and addiction remains differently defined by different authors. Some authors view alcohol-induced damage as a building-stone of diagnosis of chronic alcoholism whereas other authors define these damages as illnesses developed as a consequence of chronic alcohol intake. This fact is also mirrored in the different definitions of chronic alcoholism by different classification systems, like ICD-9, DMS-III or DMS-III-R. Valid and reliable questionnaires, like the Munich Alcoholism Test or the Problem Drinking Scale did not succeed in solving this problem of definition, either. (2) The fact that chronic alcoholics are sick – in the sense of a biological-medical approach – is undoubted. Our research group was able to prove that chronic alcoholic patients metabolize methanol in a different way from that of healthy persons. The biological, sociological and psychopathological heterogeneity of this illness has been stressed for more than a century. A prospective long-term study carried out over 4–7 years has led to the development of a new typology in chronic alcoholism that is able to differentiate subgroups of chronic alcoholic patients cross-sectionally in a clinical, biochemical and neurophysiological way. Diagnosis according to this typology qualitatively differentiates patients in many spheres other than drinking behavior. These subgroups also require correspondingly modified therapeutic strategies.

Heterogeneous Craving

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

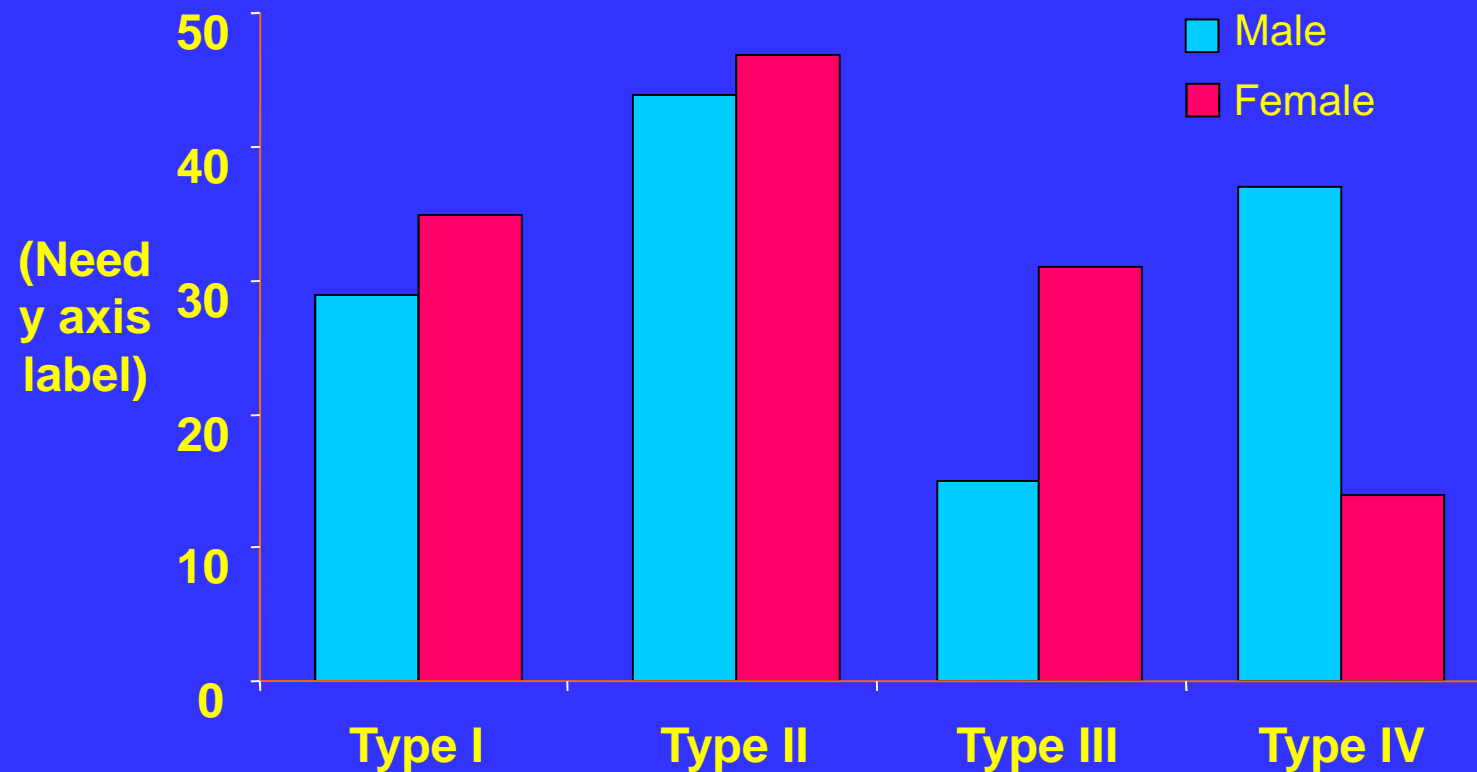
**Type II - to cope anxiety
(Social learning and Cognitive model)**

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

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

Walter et al. 2006

Gender Distribution Lesch Typology (n=250)



Sperling et al. Alcohol & Alcoholism, 2000.

Temperament and the Lesch typology of alcoholism

- Cyclothymic temperament (16%-84%: 11-20)

• Typology	Mean +/-	SD	% of patients above 84%
• I	16	6,2	25
• II	13,9	5,9	23
• III	17,7	4,9	27
• IV	21,6	8,3	68 !!!

- Hyperthymic temperament (16%-84%: 16-22)

• I	22,7	6,8	67 !!!
• II	21,5	6,7	46
• III	21,5	6,7	38
• IV	20,5	5,4	37

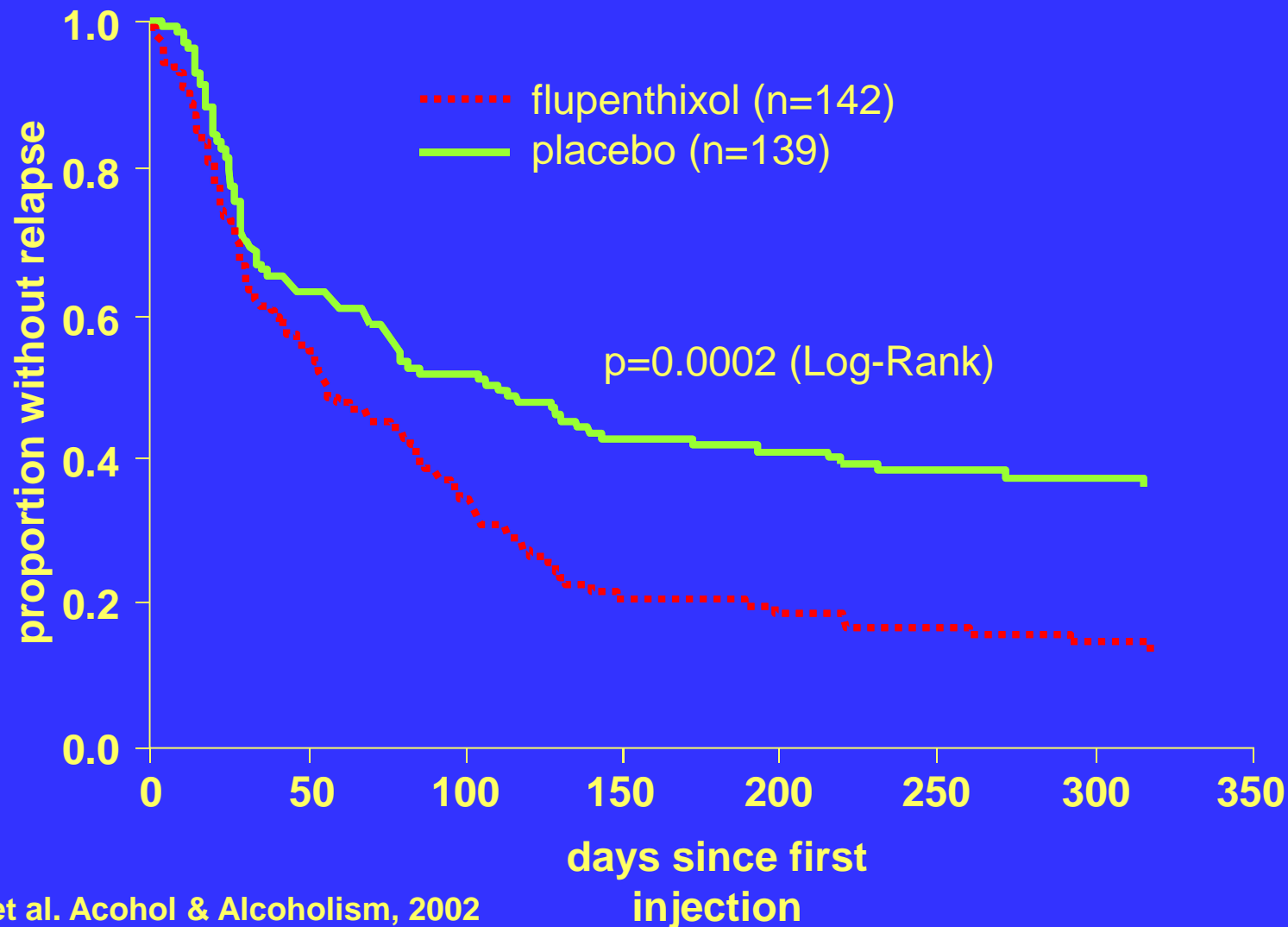
- Temperament auto-questionnaire TEMPS-A (Erfurth et.al 2003)

Lesch, Erfurth in prep.

Flupenthixol 10 mg vs. placebo

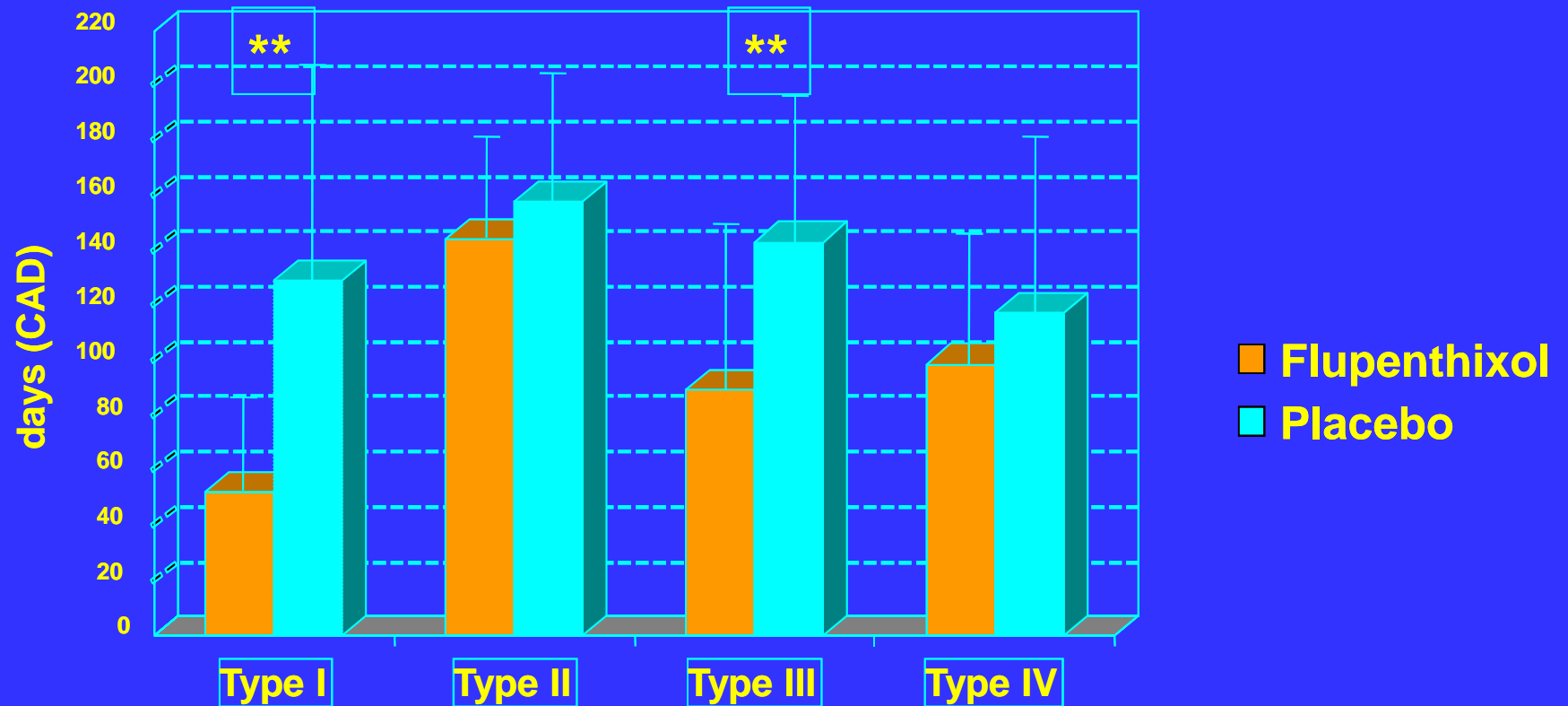
6 months study in alcohol dependent patients (n=281)

Survival curve (ITT-analysis)

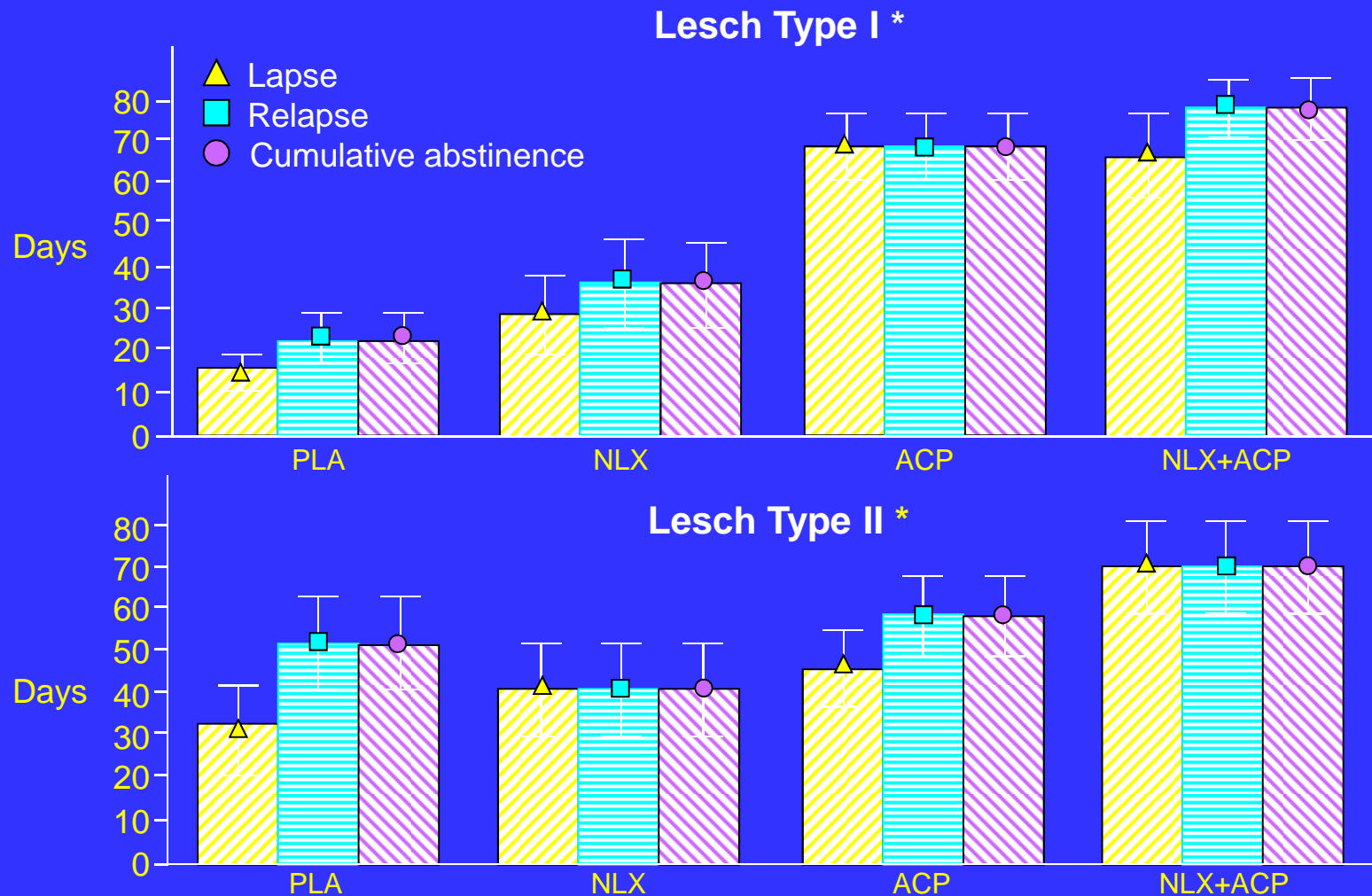


Flupenthixol 10 mg vs. Placebo

*6 months trial on alcohol dependent persons (n=122)
cumulative abstinence period*



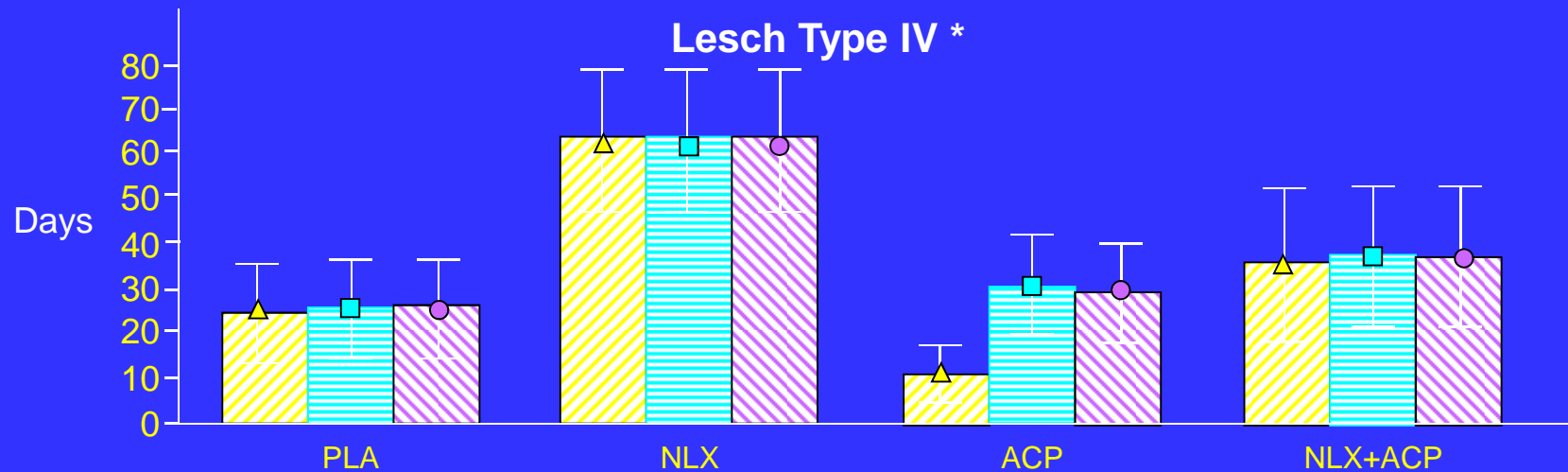
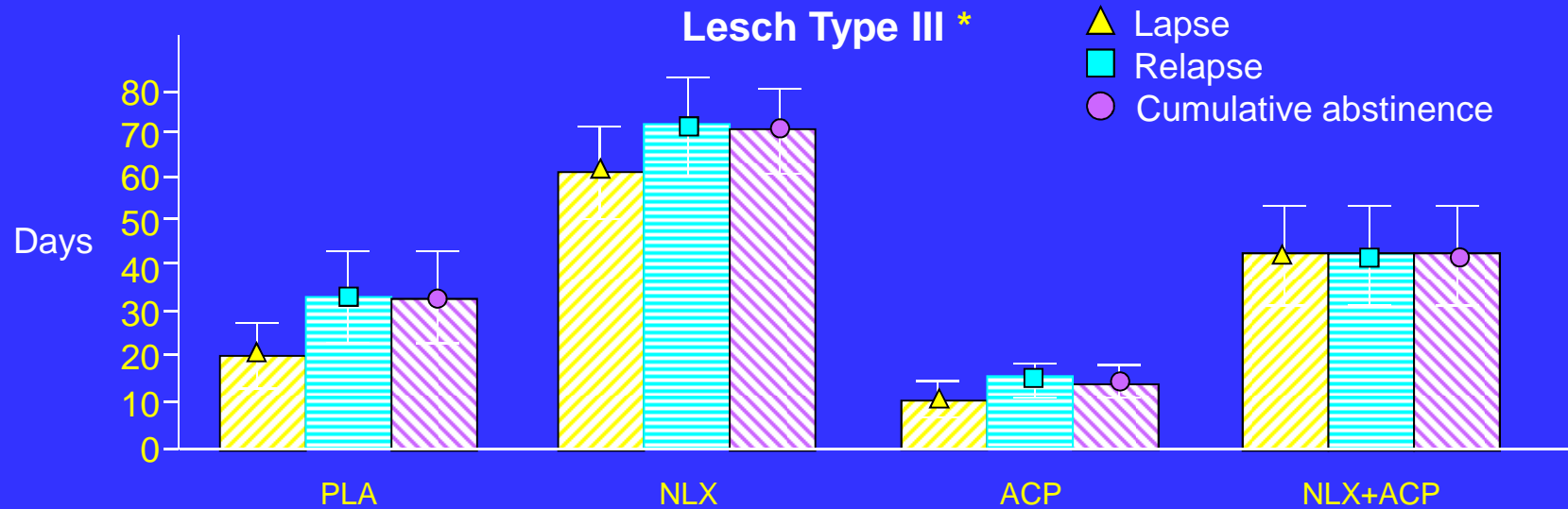
NALCAM Study: Lesch's Subgroups (I, II) **(Total Sample: N=160; PLA vs. NLX vs. ACP vs. Combined Medication)**



*Preliminary data, NALCAM Study.
 PLA=placebo; NLX=naltrexone; ACP=acamprosate.

NALCAM Study: Lesch's Subgroups (III, IV)

(Total Sample: N=160; PLA vs. NLX vs. ACP vs. Combined Medication)



*Preliminary data, NALCAM study.

Typologies and medications

- Medication for relapse prevention according to typologies (evidence based)
- Hypothesis: Medication for relapse prevention

Naltrexone	Type A Cloninger II Lesch III & IV	LO-A
Acamprosate	Cloninger II Lesch I & II	Babor B EO-A
Ondansetron	EO-A Babor B	Cloninger II
Setraline	Babor A	Cloninger I LO-A

Summary of the medicamentation therapy according to the typology of Lesch

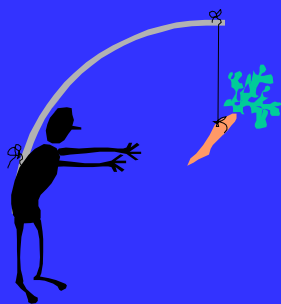
	Withdrawal treatment	Relapse prevention
Type I	Benzodiazepines, Clomethiazole	Acamprosate, Disulfiram, Cyanamid, Cave: D1-Antagonists
Type II	Tiapride, Cave: Benzodiazepines, Gamma-Hydroxy- Butyric Acid	Acamprosate, Cave: Benzodiazepines, Gamma- Hydroxy-Butyric-Acid, Clomethiazole, Meprobamate
Type III	Benzodiazepines	Naltrexone, Antidepressants e.g. Milnacipran, Carbamazepine, Cave: D1-Antagonists, Topiramate ???
Type IV	Carbamazepine, atypical neuroleptics	Naltrexone, Nootropics, Atypical Neuroleptics, Ondansetron ???

Psychotherapy or Self-help group in Relapse Prevention

- **Type I** →
 - Supportive PT, Self-help-group, concerned with alcohol related topics
- **Type II** →
 - Ego strengthening PT, learn to tolerate own emotions. Not focussed on drinking.
- **Type III** →
 - PT for finding access to emotions. Main focus not on drinking. PT not too early.
- **Type IV** →
 - Supportive PT, no psycho-analytically oriented PT. Training of strategies helping to avoid relapses. Self-help-groups are effective.

Therapy aims

- **Type I:** Absolute abstinence (necessary because of the biologic factor and because of the psychical conditions also realistic)
- **Type II:** Long intervals with absolute abstinence, seldom short relapses (“slips”) without loss of control can be accepted.
- **Type III:** Reduction of the frequencies of severe relapses. Changes of personality traits.
- **Type IV:** There can be severe relapses despite therapy; minimizing of the severity code of the relapse, social dependence stands in front, that means with a good socio-therapeutic leading abstinence is possible!!



Alcohol and Tobacco Medical and Sociological Aspects of Use, Abuse and Addiction

Otto-Michael Lesch

Henriette Walter

Christian Wetschka

Michi Hesselbrock

Victor Hesselbrock

Springer International Wien New York 2010 (in press)

Assessment and Treatment of Alcohol Problems

- Henriette Walter
 - Otto Lesch

Otto.lesch@meduniwien.ac.at

www.ausam.at

www.lat-online.at



Assessment Procedure

- How to use the programm
- Videotape of one patient
- Discussion how to use it

Type IV

- Factors influencing childhood development:
- Perinatal damage
- Cerebral diseases before the age of 14.
- Contusio cerebri before the age of 14.
- Behavior disturbances in childhood (nail biting, stuttering and/or enuresis nocturna)

- Epilepsy independent of alcohol
- Polyneuropathy (severe, neurological signs)

Type II

- **Mild withdrawal Symptoms (Tension)**
- **No seizures**
- **No co-morbidity**
- **No suicidal tendencies**

Type III

- Psychiatric co-morbidity:
- Major depression
- Interrupted sleep episodes
- Severe suicidal tendencies independent from alcohol intoxication and withdrawal

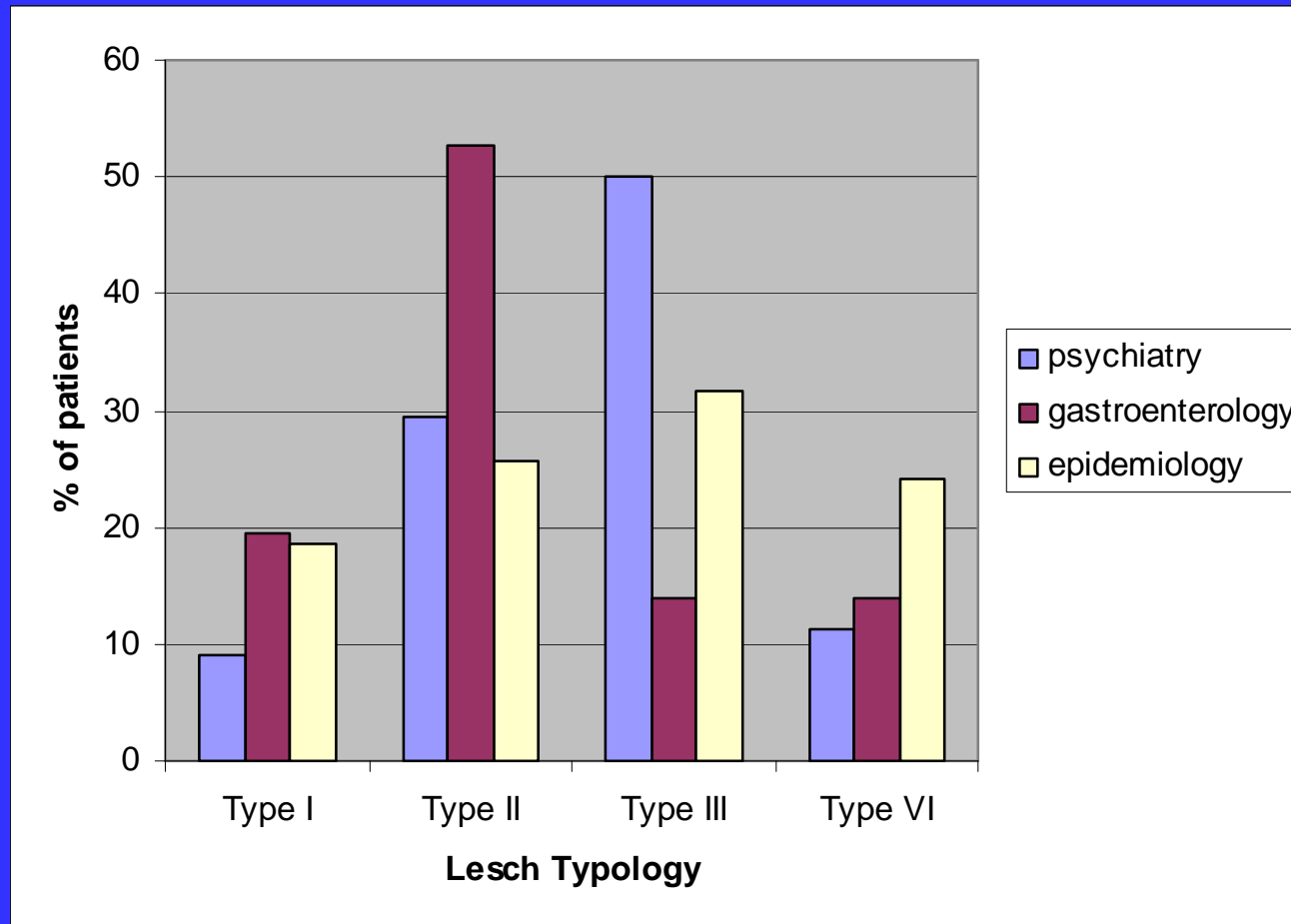
Type I

- **Severe withdrawal syndrome (tridimensional tremor, severe hyperhidrosis, vegetative instability, blood pressure, heart rate)**
- **Epileptic seizures only during withdrawal**

Subgroups in Alcohol dependence

Lesch 1990	Zucker 1997	Del Bocka & Hesselbrock 1996	Windle & Scheidt 2004	Cardoso Neves et al, in A&A 2006
Type II	More mild course subtype	Low risk, low severity	Mild course cope with stressors	Anxiopathic - typifies an anxious functioning
Type III	Negative affect	Negative affect	Major depressive generalized anxiety	Thimopathic - typified by affective symptomatology
Type IV	Antisocial alcoholics	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 substances

Alcohol dependence and liver disease



44 psychiatric admissions and 36 gastroenterological admissions and admission in hospitals from a catchment area (n=356),

publication in preperation, Vyssoki B et al.

Symptomatology caused by alcohol withdrawal or by decompensated liver disease

Alcohol

cognitive impairment

Organic caused by psychopathology
(Durchgangssyndrome)

Severe sweating

RR \downarrow \uparrow Frequency \uparrow \downarrow

duration: days

Type I 3dimensional Tremor

Withdrawal seizures

Liver

cognitive impairment

Organic caused by
psychopathology
(Durchgangssyndrom)

No sweating, dry skin

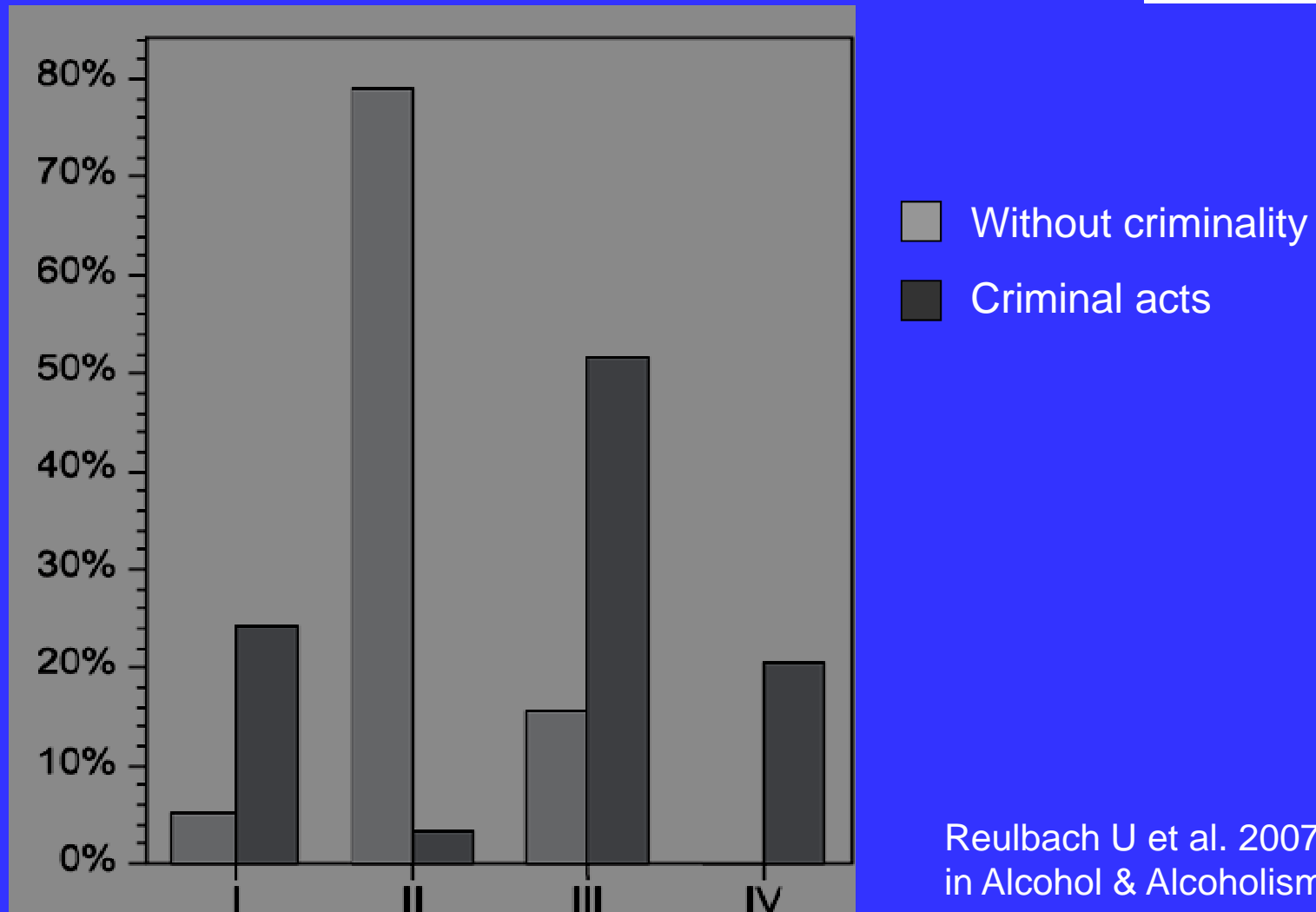
RR and frequency stable

duration: weeks to months

(Type IV) cerebellum Tremor

Flapping tremor

Lesch Typology and Homocide (n=48, Mann-Whitney-U Test: P<0,001)

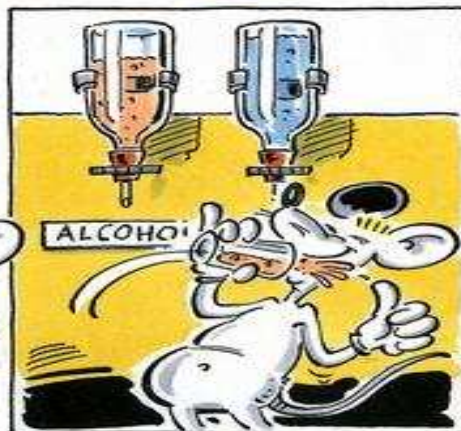
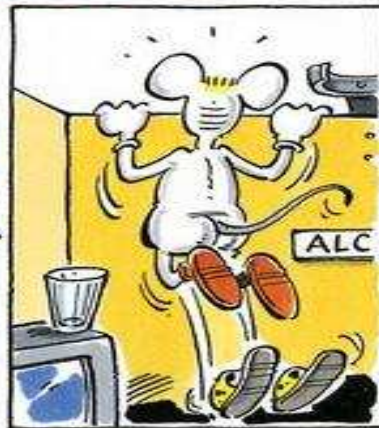
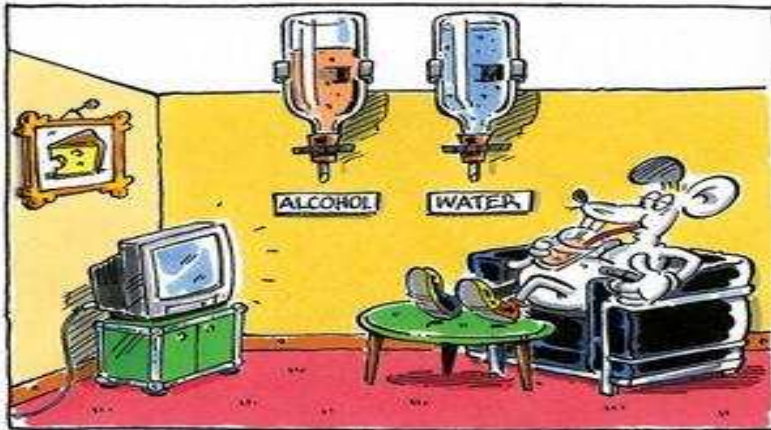


Reulbach U et al. 2007
in Alcohol & Alcoholism

Nicotine Dependence according to Alcohol Typology (Lesch)

N=100	Type I	Type II	Type III	Type IV	Total
Smoking without dependence	6	18	10	2	36
Nicotine dependence	14	13	20	17	64
Total	20	31	30	19	100

ALCOHOL DEPRIVATION EFFECT



Genetic and Lesch Typologie

Bönsch et al (2006) Alc& Alc

Saffroy et al (2006) in press

Samochowiec et al (2006)

Neuroscience in press

Folic acid forming reductase MTHFR (Bönsch et al, 2006)

- MTHFR -393 Polymorphisms CC-CA-AA

	CC	CA/AA
Lesch I	68%	32%
Lesch II	86%	13% (seldom)
Lesch III	92%	7% (seldom)
Lesch IV	60%	40% (often)

Samochowiec J. et al, 2006

- N = 122 (99 males, 23 fem); 409 controls
- Lesch nur Typen I und II ausgewertet
- Lesch type II vs controls:
- DRD-2 ins/del-C141 promotor region polymorphism: higher frequency of del –C141 alleles and increase of del/del in Lesch Type II.
- DAT 1 40bp VNTR (=Dopamin transporter) higher frequency of A9/A9

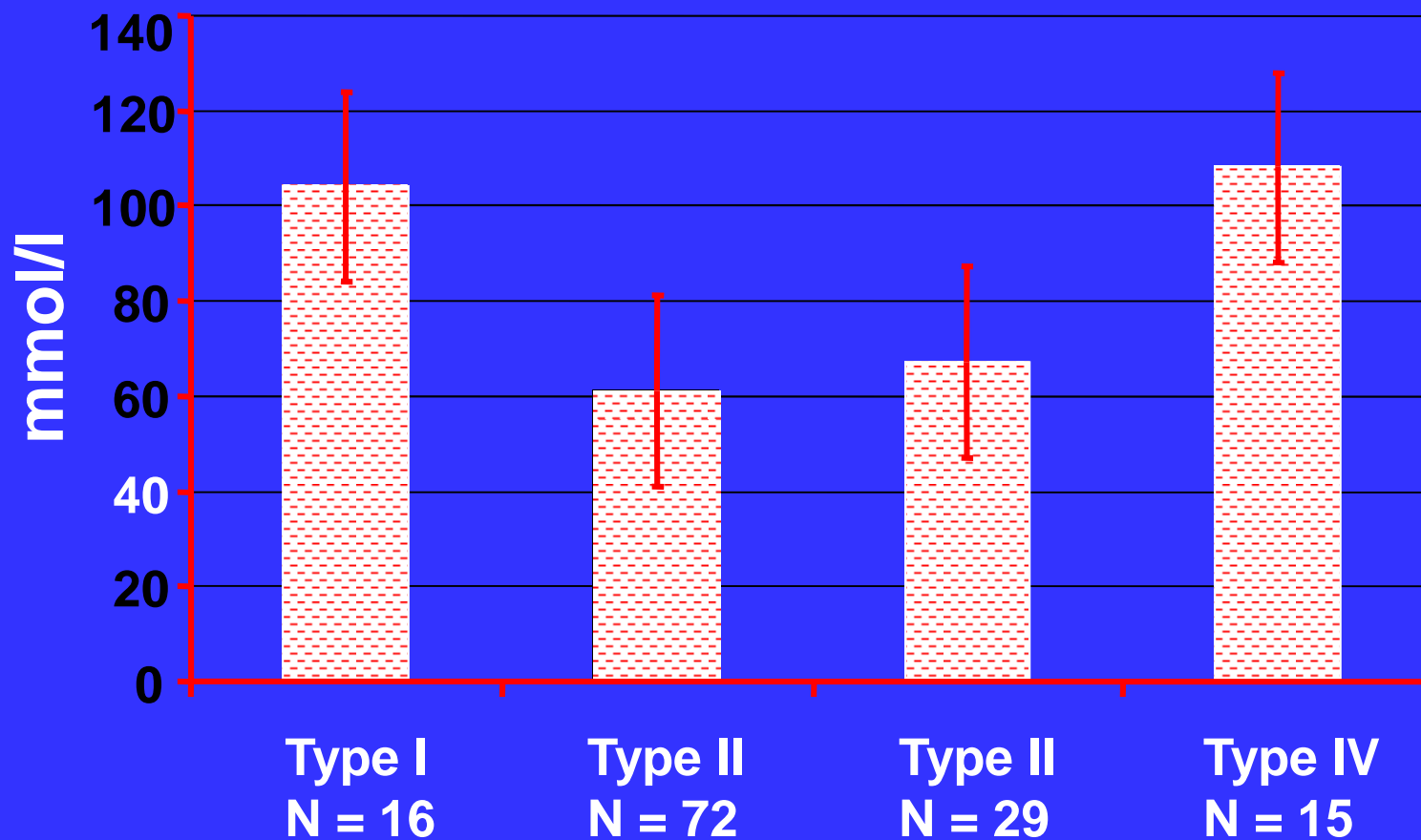
Glutamat and Lesch Typology

Significant higher Glutamat level
in Lesch type I and IV.

(Walter et al., Alc&Alc, 2006).

- Lesch I – “kindling” effects (Lechtenberg and Worner, 1991; Becker and Hale, 1993; Booth and Blow, 1993; Moak and Anton 1996; Worner, 1996)
- Lesch IV – repeated withdrawals (Hillemacher et al., 2006).

Typology and Glutamic acid age 47, 3a, days of abstinence 39,3



Normal value: 10-131 mmol/l

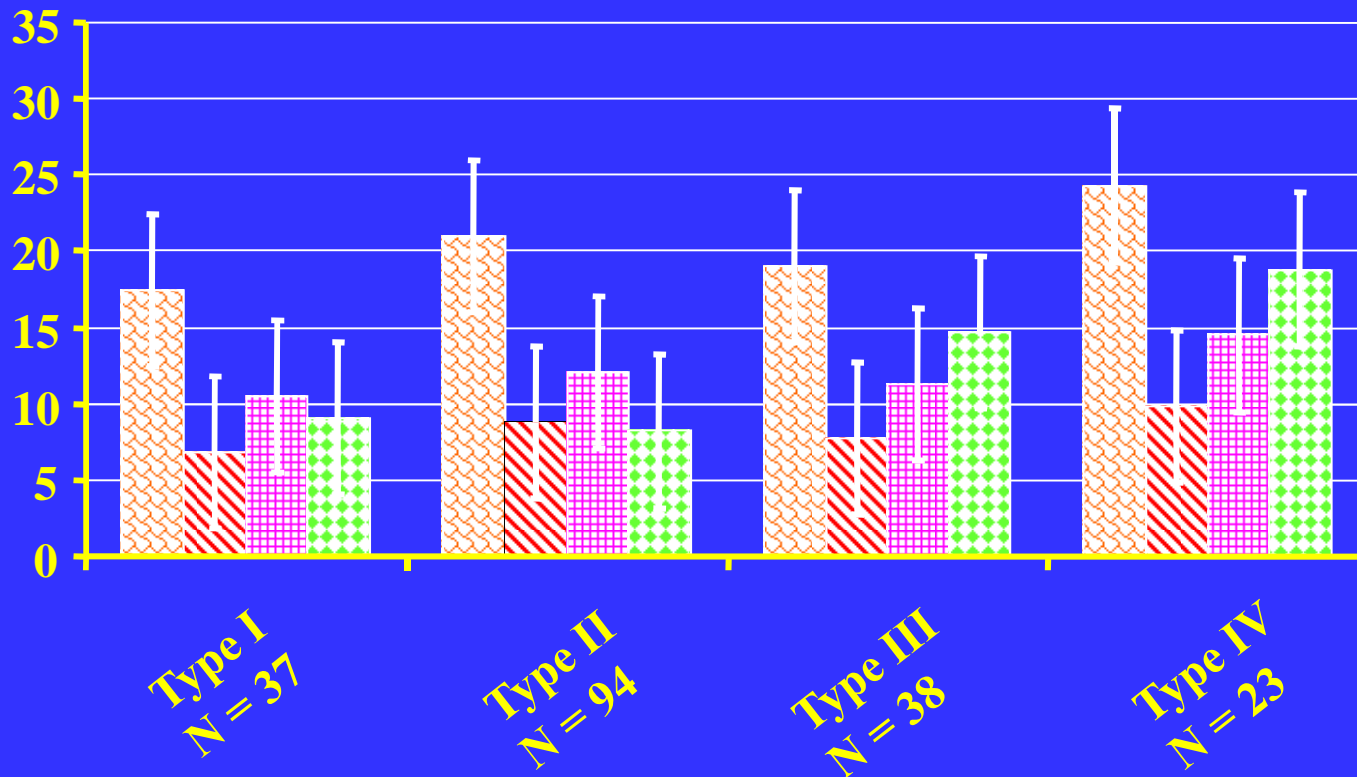
Typology vs Homocystein

Type 1 patients have significantly increased plasma homocysteine levels, (Kruskal-Wallis test: d.f.3, $\chi^2 = 10.14$; $P < 0.05$).

All patients with a history of alcohol withdrawal seizures had significantly elevated plasma homocysteine concentrations at admission (Mann-Whitney U, $P < 0.001$)

Typology and Craving

OCDS total OCDS obsessive
OCDS compulsive Number of preceding withdrawal



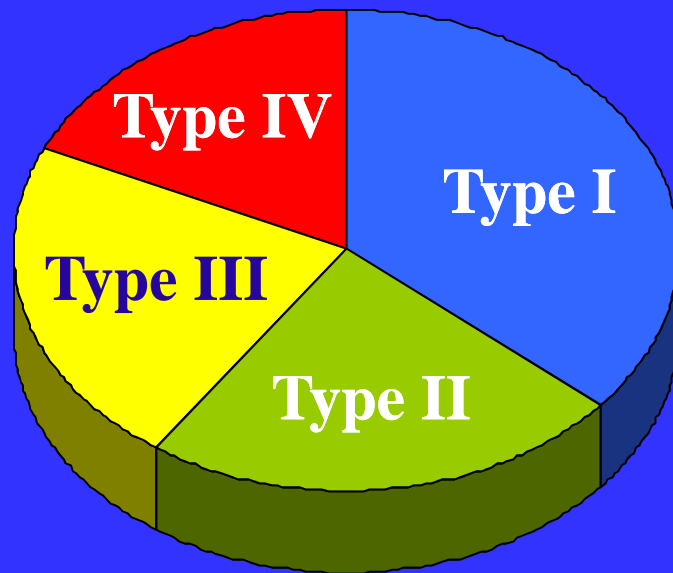
OCDS total, compulsive
and withdraw $p < 0,05$

No difference between the groups in age, age of onset, daily intake

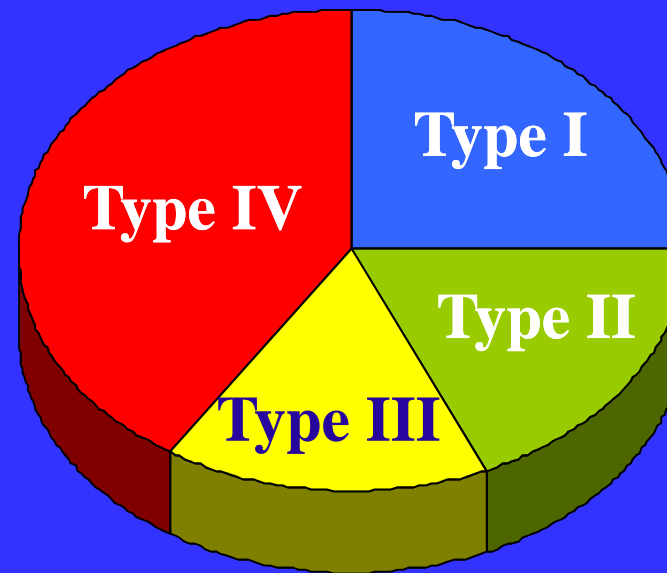
Hillemann et al, 2006

***Acamprosate study according to the Lesch Typology
Comparison between Vienna and the 2 main centers in the UK study***

API (n = 260)



Socialpsychiatry (n = 149)



out of 149:
32 deceased
76 could be reached

Alcohol and Tobacco Medical and Sociological Aspects of Use, Abuse and Addiction

Otto-Michael Lesch

Henriette Walter

Christian Wetschka

Michi Hesselbrock

Victor Hesselbrock

Springer International Wien New York 2010 (in press)

Many, many thanks

- My Research Team
- Henriette Walter, Benny Schlaff, Benny Vissocky, Peter Höfer,
- Research Networks with Portugal, Italy, Germany, France, Belgium, Chech. Republic, Poland, and USA.
- Many scientists had a great impact on our work, naming only a few of them: DeWitte, Zima, Hesselbrock, Tabakoff, Johnson, Chick, Crews, Pombo, Hillemacher, Bleich, Platz, Wiesbeck, Gessa, Addolorato, Samochowiec and many, many others...