Alcoholism treatment: moving towards the promised land?

EAP Award Lecture
Socidrogalcohol/EUFAS
Alicante
March 10th 2016

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Central Institute of Mental Health
Medical Faculty Mannheim
University of Heidelberg
The treatment gap in Europe

- **Schizophrenia:** 18%
- **Bipolar disorder:** 40%
- **Major depression:** 45%
- **Panic disorder:** 47%
- **Phobias:** 62%
- **Alcohol abuse/dependence:** 92%

*Kohn et al., 2004*
Academic Centers for Addiction Research (year 2000)
BMBF: German Addiction Research Network
Speaker: K Mann

Total grant: 25 Mio €
2002 – 2010

South-West:
K. Mann, S. Wellek

South-East:
U. Wittchen, J. Böning

North-East:
U. John, H-J. Rumpf

West:
M. Gastpar, N. Scherbaum
Evidence based treatments I:

- Motivational enhancement therapy
- Cognitive-behavioral treatment
- Alcoholics anonymous
- Communication skills training
- Marital and family therapy

Mean effect size: $d = 0.37$
Evidence based treatments II:

Approved by FDA and/or EMA:

- Disulfiram
- Acamprosate
- Naltrexone
- Nalmefene

Effect sizes between $d = 0.22$ and $0.46$

NICE Guidelines, UK 2011, German Guidelines, Mann et al. 2015
Why should we „personalize“ Medicine?

There is no single superior approach to treatment for all individuals.

Different types of individuals may respond best to different treatment approaches („matching“)

Institute of Medicine 1990
Motivation Enhancement Therapy (MET)
3 sessions

Social Behaviour Network Therapy (SBNT)
8 sessions

Pragmatic trial under conditions in which they would be applied in practice

Heather et al. 2010, Adamson et al. 2010
### UKATT: hypotheses and sample

<table>
<thead>
<tr>
<th>Hypotheses</th>
<th>Sample</th>
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<tr>
<td>- Clients with low levels of readiness to change do better with MET</td>
<td>Alcohol dependence or abuse N = 742</td>
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<td>- Clients with more symptom severity do better with SBNT</td>
<td>3 months follow-up: 93.0%</td>
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<tr>
<td>- Clients high in anger do better with MET</td>
<td>12 months follow-up: 83.2%</td>
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Heather et al. 2010, Adamson et al. 2010
UKATT Results

- Both groups improved in alcohol consumption, dependence and problems, mental health status
- No significant differences between the two treatments
- NO MATCHING EFFECT

Heather et al. 2010, Adamson et al. 2010
• Drinking days per month fell from 25 to 6
• Drinks per day decreased from 15 to 3
• Patients in all treatment modalities improved
• Depression, alcohol related problems and use of other drugs decreased

• NO MATCHING EFFECT
1. RCT with acamprosate, naltrexone or placebo (Three studies world-wide so far)

2. Define subtypes of alcoholics and test their response to targeted pharmacotherapy

3. Assess the value of additional psychotherapy (CBI) over counselling (MM) in a stepped care approach
PREDICT: Cluster of studies

- Genetics
- F-MRI N=72
- PET N=40
- CBI in relapsers RCT N=120
- Health Economy
- Predict Pre-clinical

Core RCT N=426

Mann et al 2009; BMBF Grant #01 EB 0410
PREDICT : the RCT

Placebo controlled randomized double-blind trial in 4 centers:

Acamprosate: N=173
Naltrexone: N=173
Placebo: N=  86
N=432

Duration : 12 weeks MM plus Medication
12 weeks MM  no  Medication

Follow up: 12 months
PREDICT vs. COMBINE
Time to 1st heavy drink (adherence rate > 80 %)

Survival functions

Mann et al. 2012

Survival (90 days)

cum. survival

Naltrexon Predict
Acamprosat Predict
Placebo Predict
Naltrexon Combine
Acamprosat Combine
Placebo Combine

Mann et al. 2012
Points to be covered:

1. Evidence for behavioural treatments

2. Personalized Medicine
   - Background and early studies
   - PREDICT: the core study, spin offs

3. Predicting Responders (PREDICT study)
   - Clinical
   - (Genetics)
   - fMRI
   - (Receptor-PET)
Mu opiate receptor gene and efficacy of naltrexone

A/G and GG:
- reduced relapse rates (p=0.044)
- time to first heavy drink (p=0.040)

Δ = 30%
Δ = 15%
PREDICT: Results in carriers of the AG Genotype

Product-Limit Survival Estimates

Survival Probability

time 90

0 20 40 60 80

Naltrexone N=30
Acamprosate N=33
Placebo N=21

OPRM1: AG/GG

Abstinence rate day 90
55.2%
50.0%
42.1%
p<0.1
PREDICT - Objectives

1. RCT with acamprosate, naltrexone or placebo (Three studies world-wide so far)

2. Define subtypes of alcoholics and test their response to targeted pharmacotherapy

3. Assess the value of additional psychotherapy (CBI) over counselling (MM) in a stepped care approach
Assessment of Subgroups

• Inventory of drinking situations
  Annis et al. 1982; Victorio-Estrada & Mucha 1997

• Acoustic Startle Paradigm
  Geier et al. 2000; Heinz et al. 2003

• Functional Imaging (f-MRI / PET)
  Braus et al. 2001; George et al. 2001; Tapert et al. 2003,
Alcoholic drinks
fMRI paradigm I

3 Alcohol stimuli (6.6 s)
5 blocks of 19.8 s

Fixation cross 19.8 s

3 abstract stimuli (je 6.6 s)
5 blocks of 19.8 s

Fixation cross 19.8 s

3 neutral stimuli (6.6 s)
5 blocks à 19.8 s
Grüsser et al. 2004
PREDICT Study / fMRI sub project

- N= 73 alcohol dependent patients
- 58 men, 15 women
- Age 43 ± 8 years
- 36 Naltrexone, 28 Acamprosate, 9 Placebo
**T1: Association medication – fMRI - relapse**

- **Outcome:**
  - time until 1st severe relapse

- **Cox regression:**
  - interaction medication x cue reactivity ("alcohol-neutral", ventral striatum), $p = .023$

- **Log rank:**
  - median split high/low reactivity $p = .014$

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*Naltrexone treatment*

*VS cue-reactivity

- low
- high

* $p = .014$*
Central µ-opiate receptor availability (V3’’)

Interpretation

Up-regulation of µ-opiate receptors, or reduced endogenous opioids

Heinz et al. 2005 Archives Gen Psychiatry
• Higher Carf binding potential (V3) associated
  – with higher risk for relapse
  – better efficacy of naltrexone

• Inclusion of N=40 patients

  Genotype A118G:
  – N = 31 genotype AA
  – N = 7 genotype AG
  – N = 2 dropout
Results: receptor PET and outcome

- Sign. correlation of BP with time to relapse
- No association of BP and naltrexone in AA allele carriers
- „Trend“ between BP and naltrexone in G allele carriers.
- **NB:** lower receptor density in post-mortem brains
  *(Hermann et al submitted with W. Sommer, R. Spanagel, Anita Hansson)*
Inventory of Drinking Situations

- **Annis 1982** (based on Marlatt and Gordon 1980)
  
  100 items, self rating, 8 subscales

- **Cannon et al. 1990**

- **Victorio-Estrada et al. 1996; Victorio-Estrada and Mucha, 1997** (German Version)

- **Stewart et al. 2000**

- **Glöckner-Rist, Leménager & Mann 2013**
Drinking Situations (IDS): Latent Class Analyses

Positive reinforced relapse (26 %)

Glöckner-Rist et al. 2013
Drinking Situations (IDS): Latent Class Analyses

Glöckner-Rist et al. 2013
Drinking Situations (IDS): Latent Class Analyses

49. to go out with friends
88. Friends invite to drink
73. To celebrate with others
48. Sitting in a restaurant
99. Eating with friends
81. Being depressed about life
87. Feeling being treated unfair
74. Feelings of guilt
94. Wasted opportunities in life

high craving (28%)
neg reinf craving (24%)
pos rein craving (26%)
low craving (22%)

BIC = 10 002.912
Support for Personalized Medicine in alcoholism:

- **IDS**  
  Reward Drinkers respond better to medication  
  *Mann et al (submitted)*

- **f-MRI**  
  cue induced activation of the VS  
  *Mann et al ACER 2014*

- **Genetics**  
  OPRM1 and GATA4

- **PET**  
  B-pot. may predict nalt. Response  
  *Hermann et al (submitted)*

- **Startle**  
  *(Lemenager et al. 2015  Int. J. of Psychophysiology)*

All points warrant further replication
Treating alcoholism reduces financial burden on care-givers and increases quality-adjusted life years

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ABSTRACT

Aims The study assessed the alcoholism-related financial burden borne by informal care-givers and relatives of German alcoholic patients. Design By using an exploratory approach, care-giver burden was assessed both prior to and 12 months after detoxification and withdrawal. Quality-of-life data for care-givers collected during follow-up were used to calculate the number of quality-adjusted life years (QALYs) gained by alcoholics’ family members while their relatives are undergoing treatment. Participants Forty-eight informal care-givers and relatives of alcoholic patients. Setting In-patient and out-patient departments of three psychiatric university hospitals in Germany. Measurements Expenditures of families related directly to the addiction disorder of alcoholic patients, quality of life of care-givers, relapses of patients. Findings Families’ expenditures related directly to their addicted member’s
Treating alcoholism reduces family burden and increases quality adjusted life years of family members

<table>
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<th>N=69/</th>
<th>Before tmt</th>
<th>1 year follow-up</th>
<th>p-Value</th>
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<tbody>
<tr>
<td>Familial non-medical expenditure related to alc patient</td>
<td>676 € (20% of fam. Income)</td>
<td>145 €</td>
<td>0.003</td>
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<tr>
<td>Cost and time spent for informal care to patient</td>
<td>275 € 32 hours/month</td>
<td>70 € 8 h/m</td>
<td>0.001</td>
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<td>QOL-Total Score</td>
<td>60</td>
<td>68</td>
<td>0.001</td>
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Salize et al. 2012