EFFICACY AND SAFETY OF HIGH-DOSE BACLOFEN FOR THE TREATMENT OF ALCOHOL DEPENDENCE

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Study objectives

- Testing the efficacy and safety of high-dose baclofen
- Examining the presence of a dose-response relation

Study design

- Multicentre trial in two inpatient treatment centres (SolutionS Center & U-Center) and three outpatient treatment centres (The Home Clinic, Ready for Change, and Terwille) in the Netherlands
- N = 151 patients with AD
- 3 groups: high-dose baclofen (N= 58; up to 150 mg), low-dose baclofen (N= 31; 30 mg), and placebo (N=62)
- Duration: 16 weeks
- 6 weeks titration, 10 weeks high-dose phase

Inclusion criteria

- Detoxified patients with AD (18-70 years)
- ≥ 14 units (woman) and ≥ 21 units (man)/ week
- ≥ 96 hours and ≤ 21 days abstinent prior to the start of the study medication
- Contact person

Exclusion criteria

- Current severe axis I disorder (besides anxiety, depression, or bipolar disorder)
- Any primary diagnosis of substance dependence other than alcohol
- Severe physical illness or pregnancy
- Anti-hypertensive medication
- Current or recent pharmacological treatment for AD (acamprosate, naltrexone, disulfiram,……)
- Use of baclofen in the past 30 days

Medication & Titration

- Identical 10 mg tablets
- Three times a day
- Dose was increased with 30 mg/week (with physician consult)
- High-dose group: up to 150 mg/day within 6 weeks
- Low-dose group: 30 mg/day
- Double blind

Psychosocial treatment

- In-patients: 4 or 6 weeks inpatient treatment programme (Minnesota Model, CBT) followed by weekly outpatient groupsessions
- Out-patients: at least one weekly group- or individual therapy session

Procedure

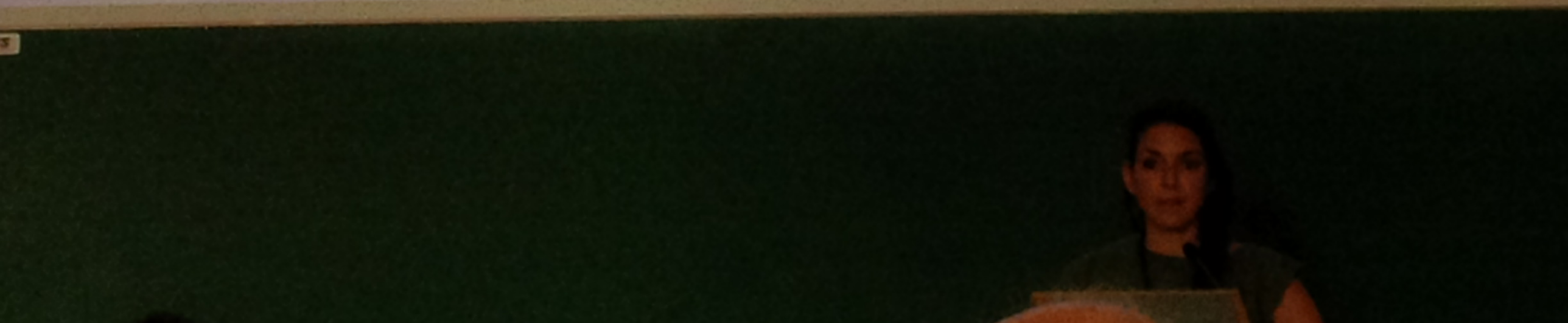
- screening
- 3 testsession: 0, 4, and 16 weeks
- 6 weekly visits with a physician during titration phase (6 weeks)
- 5 bi-weekly visits with a psychologist during the high-dose phase (10 weeks)
- After 16 weeks patients were deblinded from the independent physician

Assessments

- Testmoment 0: AUDIT, EuropAsi, MoCA, TLFB
- Testmoment 0, 4, and 16: OCDS; STAi-trait, BDI
- All visits: breath alcohol concentration, pill count, adverse events (GASE), craving (PACS), alcohol use (TLFB)

Outcome measures

- **Primary outcome measure:**
  - Time to first relapse
- **Secundary outcome measures:**
  - Proportion of patients relapsed
  - Proportion of patients continously abstinent
  - Safety and tolerability
  - Changes in craving, anxiety, and depression
  - Dose-response effect



Results

- Patient's characteristics

	Total (N=151)	High-dose baclofen (N=58)	Low-dose baclofen (N=31)	Placebo (N=62)
Demographics				
Age (years)	44.8 (9.6)	45.8 (9.2)	44.7 (11.3)	44.0 (9.2)
Men	104 (68.9%)	41 (70.7%)	20 (64.5%)	43 (69.4%)
Married	82 (54.3%)	36 (62.1%)	17 (54.9%)	29 (46.8%)
Employed	88 (58.3%)	37 (63.8%)	18 (58.1%)	33 (53.2%)
Alcohol use				
Alcohol (gr/day)	141.8 (84.8)	147.0 (84.9)	132.5 (85.2)	141.7 (85.5)
Days abstinent	11.8 (4.4)	11.9 (4.7)	11.9 (4.3)	11.8 (4.3)
Duration of alcohol abuse (years)	19.5 (11.5)	18.8 (10.7)	21.5 (13.1)	19.0 (11.5)
Number of previous detoxifications	1.6 (2.8)	1.1 (1.6)	1.8 (2.9)	2.0 (3.6)

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Results

- Good treatment adherence (> 85%)
- Mean dose of 94 mg baclofen/day in high-dose baclofen group
- Analysis of high-dose phase (10 weeks) and complete medication phase (16 weeks)

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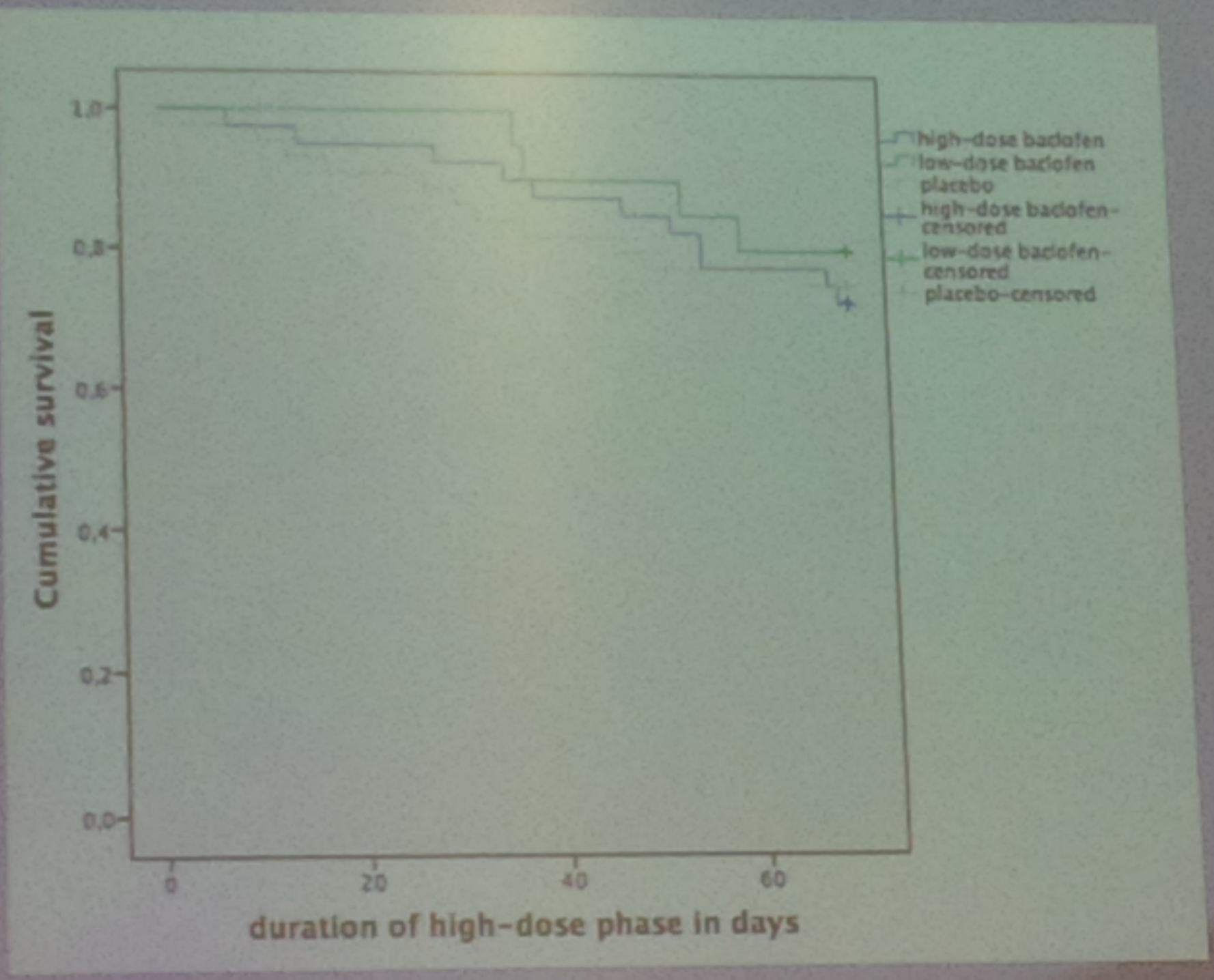

High-dose phase: χ^2=0.41, df=2, p=0.813

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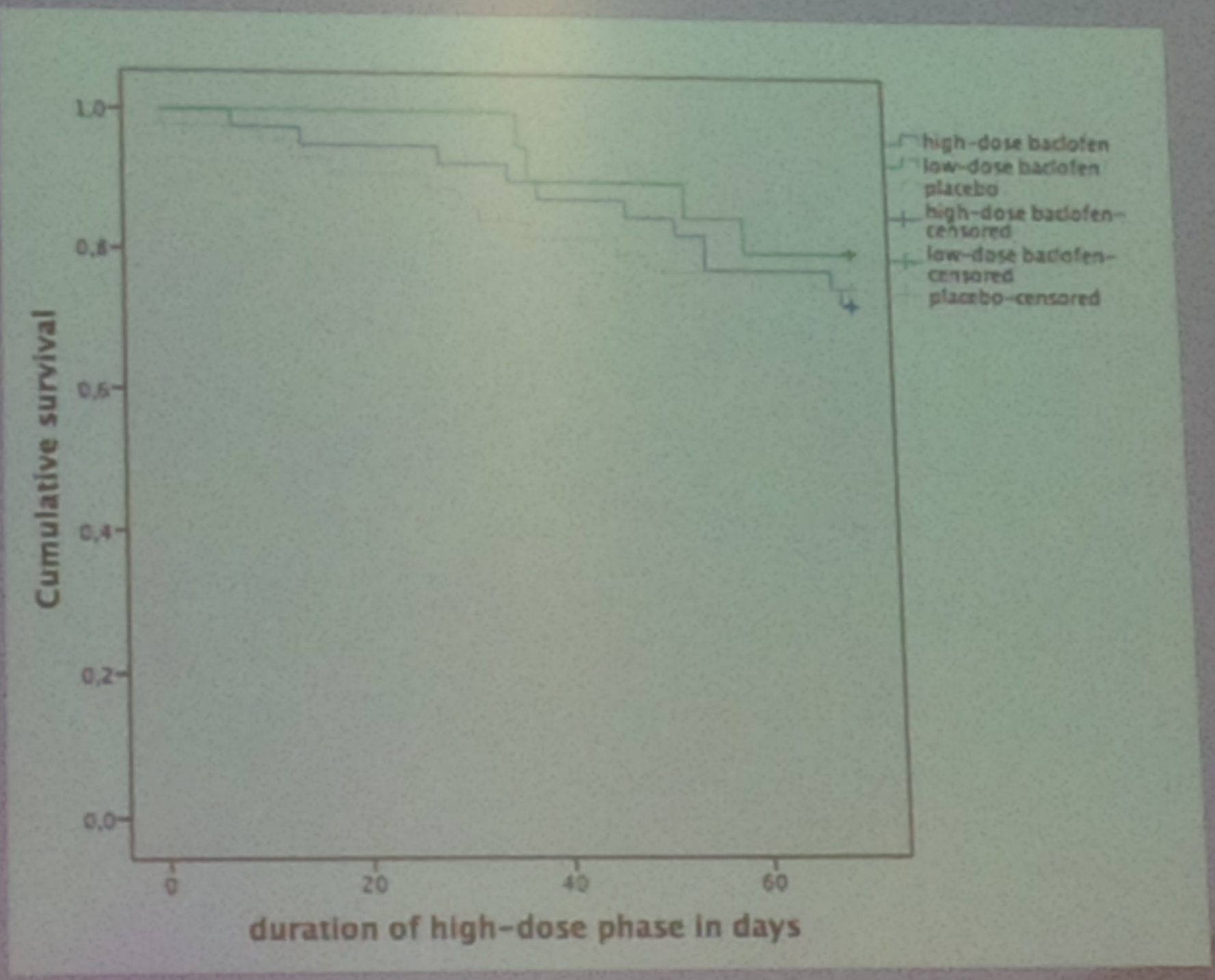

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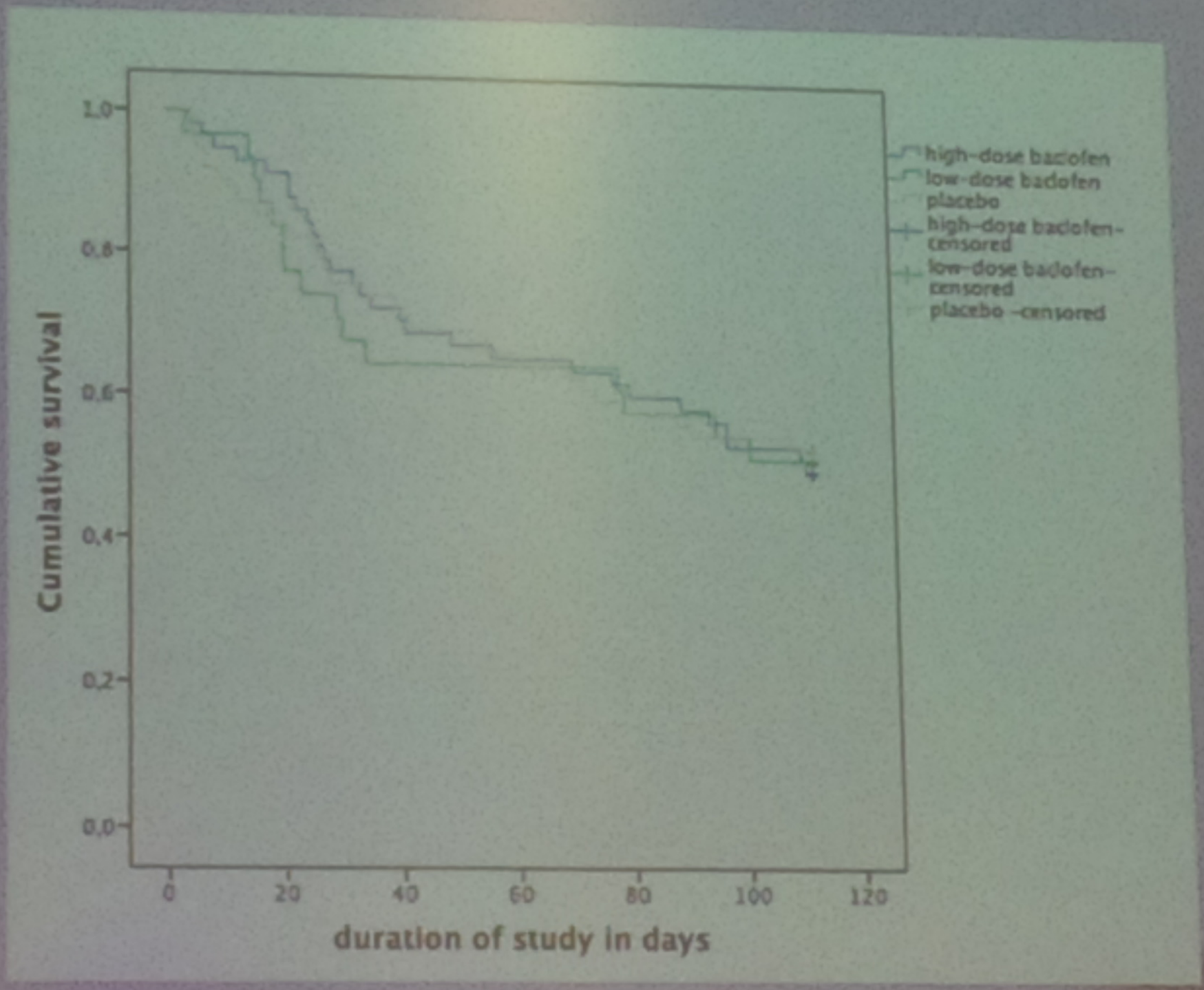


Complete medication phase: $\chi^2=0.04$, df=2, p=0.98

Patients who relapsed

High-dose phase:

High-dose baclofen: 11/40 (27,5%)

Low-dose baclofen: 4/20 (20%)

Placebo: 11/44 (25%)

χ^2=0.40, df=2, p=0.819

Complete medication phase:

High-dose baclofen: 29/58 (50%)

Low-dose baclofen: 15/31 (48,4%)

Placebo: 29/62 (46,8%)

χ^2=0.13, df=2, p=0.939

Patients remaining abstinent

- High-dose phase:

High-dose baclofen: 25/40 (62,5%)

Low-dose baclofen: 13/20 (65%)

Placebo: 29/44 (65,9%)

$\chi^2 = 0.11$, df=2, p=0.947

- Complete medication phase:

High-dose baclofen: 25/58 (43,1%)

Low-dose baclofen: 13/31 (41,9%)

Placebo: 29/62 (46,8%)

$\chi^2 = 0.26$, df=2, p=0.879

Patients remaining abstinent

- High-dose phase:

High-dose baclofen: 25/40 (62,5%)

Low-dose baclofen: 13/20 (65%)

Placebo: 29/44 (65,9%)

$\chi^2 = 0.11$, df=2, p=0.947

- Complete medication phase:

High-dose baclofen: 25/58 (43,1%)

Low-dose baclofen: 13/31 (41,9%)

Placebo: 29/62 (46,8%)

$\chi^2 = 0.26$, df=2, p=0.879

Most frequent adverse events (>10 %):

	Total (N = 151)	High-dose baclofen (N = 58)	Low-dose baclofen (N = 31)	Placebo (N=62)
Adverse event				
Fatigue	40 (26.5%)	22 (38.0%)	7 (22.6%)	11 (17.7%)
Sleepiness	40 (26.5%)	21 (36.2%)	8 (25.8%)	11 (17.7%)
Doziness	35 (23.2%)	17 (29.3%)	8 (25.8%)	10 (16.1%)
Dizziness	19 (12.6%)	11 (19.0%)	6 (19.4%)	2 (3.2%)
Dry mouth	15 (9.9%)	12 (20.7%)	2 (6.5%)	1 (1.6%)

Craving, anxiety, depression

- A significant decrease in craving, anxiety, and depression (all p's < 0.001), but no main effect of treatment or treatment x time interaction

Dose-response effect

- Cox's regression analysis:
  - Higher doses with longer time to first relapse (HR 0.99; 95% CI 0.98 – 1.0, p=0.022)
- Mann-Withney Test:
  - Doses were lower in relapsers (84,8 mg) compared to abstainers (102,4 mg); (U=282; p=0.029)
  - Only in complete medication phase, no effect in high-dose phase!!

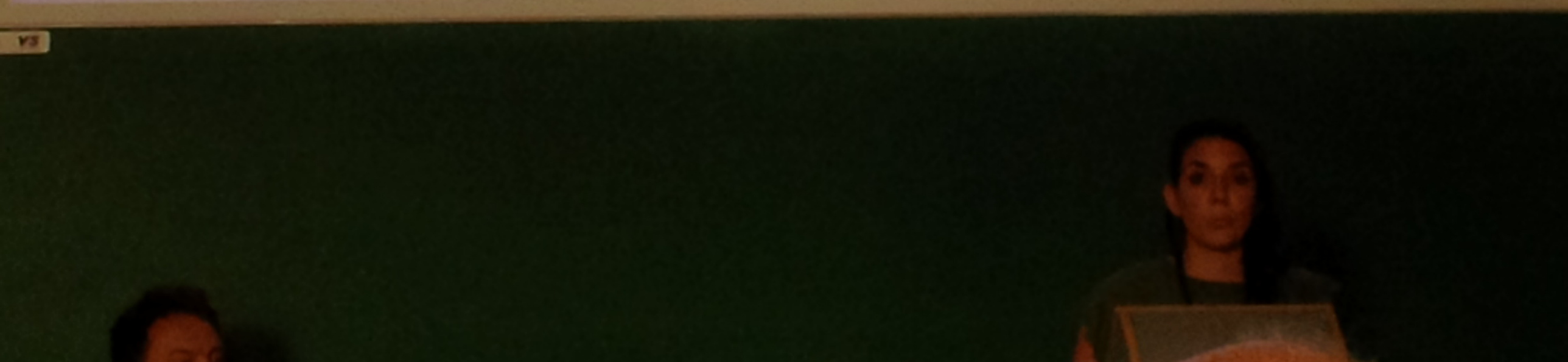
Discussion

- Contrary results to first RCT (Müller et al., 2015)
- Differences:

1) Doses
2) Treatment setting and psychosocial support
3) Patient population

1) Doses

- Max. dose of 150 mg and mean dose of 94 mg/day vs. max. 270 mg and mean dose of 180 mg (Müller et al., 2015)
- Dose-response effect
- BUT:
  - No dose-response effect in Müller et al., 2015
  - Positive outcomes with low doses (30-60 mg; Addolorato et al., 2001;2007; Carter et al., 2009)



2) Psychosocial support

- Majority (119 out of 151 patients) were inpatients for at least 28 days
- Extensive psychosocial treatment
- Low doses
- Large placebo effect

⟶ no additional effect to intensive inpatient treatment?

3) Patient population

- Difference in alcohol consumption:

140 gr/day vs. 200 gr/day (Müller et al.,2015)

- Only effective in patients with higher drinking levels?

Conclusion

- No positive effect of high-dose or low–dose baclofen
- Indications for a dose response effect
- Only effective for heavy drinking AD patients with limited psychotherapy?

Future directions

- Identifying the baclofen-responsive patient
- Studying the effect of baclofen on the brain – fMRI studies

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