TOPIRAMATE AND BACLOFEN

THE OFF LABEL ANTI-CRAVING DRUGS WORTH CONSIDERING

BACKGROUND

- 4.5% of the global burden of disease is due to alcohol
- Alcohol causes 60 disease types contributing to 2.5 million deaths per year
- The first medication approved for alcohol relapse prevention was Disulfiram (Antabuse) in 1951
- Since then Acamprosate (Campral) and Naltrexone (Revia) have also been approved

DISULFIRAM – SKINNER ET AL. META-ANALYSIS 2014

Study Mean (SD) or %	Disulfiram success Rate	Disulfiram N	Control success rate	Control N
Bardeleben et al 1999	93.3 (16.6)	20	89.6 (18.04)	40
Carroll et al 1993	2.4 (2.3)	9	10.4 (7.7)	9
Carroll et al 1998	53.00%	78	16.00%	44
Carroll et al 2004	87.50%	38	82.60%	25
Chick et al 1992	100 (70)	47	69 (67)	46
De Sousa & De Sousa 2004	82.00%	50	42.00%	50
De Sousa & De Sousa 2005	88.00%	50	46.00%	50
De Sousa et al 2008	90.00%	50	56.00%	50
De Sousa & De Sousa 2008	79.31%	29	51.72%	29
De Sousa & Jagtap 2009	81.25%	16	43.75%	16
Fuller & Roth 1979	21.00%	43	18.58%	85
Fuller et al 1986	18.80%	202	19.34%	403
Gerrein et al 1973	23.07%	26	8.70%	23
Grassi et al 2007	100.00%	4	12.50%	8
Laaksonen et al 2008	46.6 (27.5)	33	17,87 (21,03)	91
Ling et al 1983	9.80%	41	24.40%	41
Nava et al 2006	90.00%	31	80.11%	55
Niederhofer & Staffen 2003	53.80%	13	15.40%	13
Petrakis et al 2000	100.00%	8	57.00%	9
Petrakis et al 2005	77.30%	66	65.02	123
Pettinati et al 2008	17.00%	53	16.13%	106
Ulrichsen et al 2010	26.00%	19	20.00%	20

doi:10.1371/journal.pone.0087366.t003

- 22 RCTs from 1979-2010
- 2,262 participants
- 89% male subjects
- Assessing efficacy compared to other anticraving medication or no disulfiram

ACAMPROSATE

- 24 RCTs
- 6915 participants

- Significant reduction in risk of drinking NNT 9
- Increase in cumulative abstinence

- No significant changes to GGT levels or heavy drinking

- Contraindicated with severe renal impairment
- GI upset can limit doses

NALTREXONE

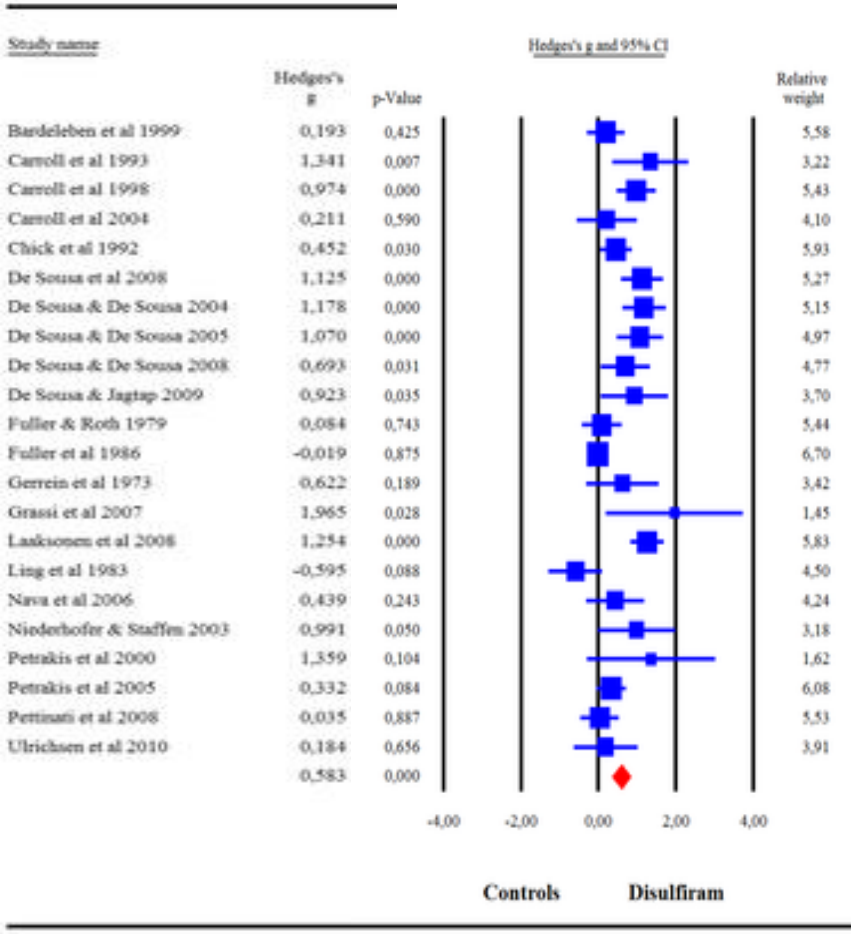
- 50 RCTs
- 7793 participants

- Reduction of risk of drinking NNT 9
- Decreased drinking days 4%

- improvements for no. of HDD, alcohol consumed, and GGT

- Contraindicated in acute hepatitis/ liver failure
- Cannot be used in patients with opioid analgesics
- GI upset, headaches, sedation

DISULFIRAM



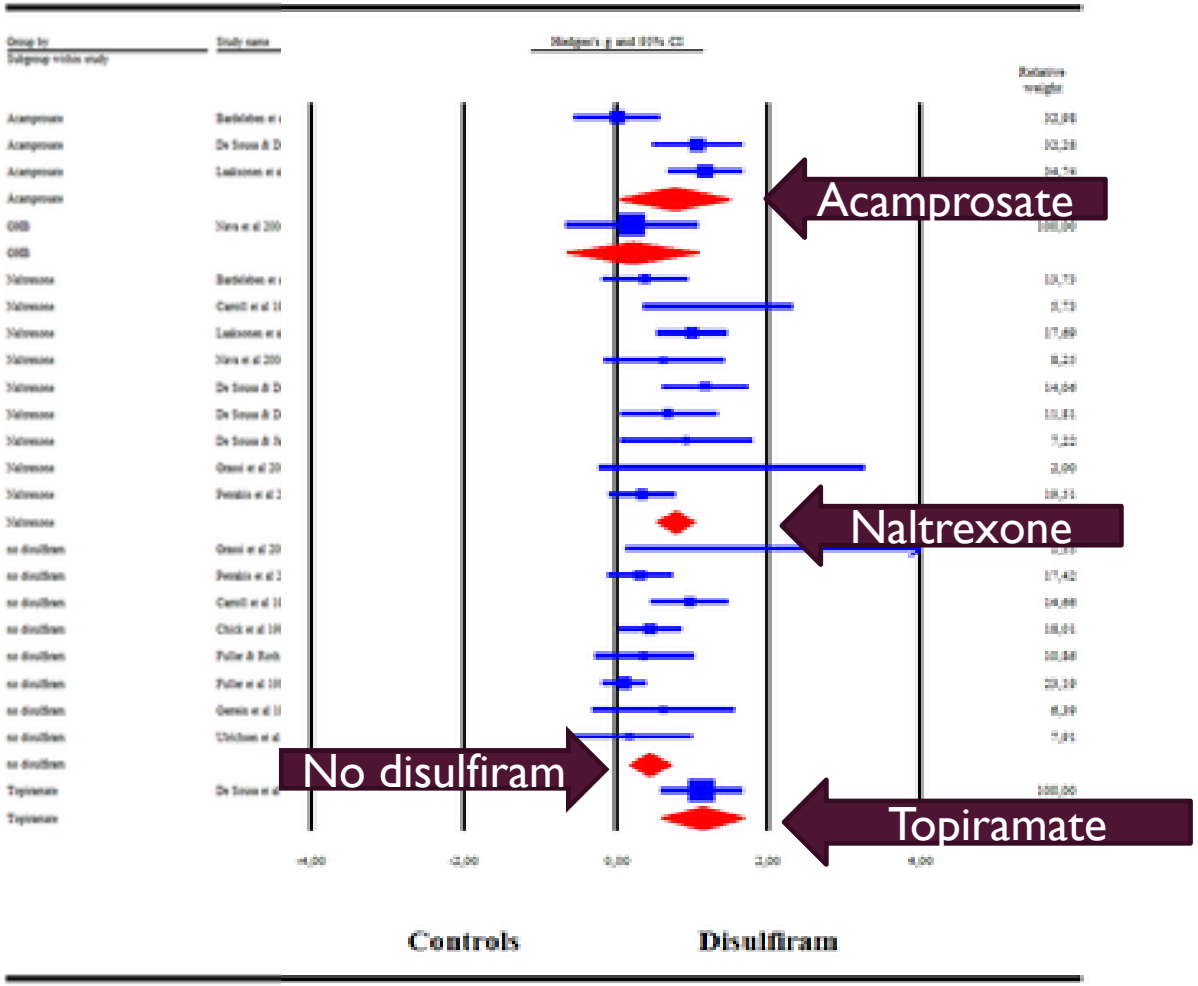
Meta-analysis of Hedges' g effect-size of all RCTs comparing the efficacy of disulfiram and controls.

- Antabuse efficacy for:
  - **Abstinence (total, 3-4wks of consecutive)**
  - **Time to first HDD**
  - **Mean days of alcohol use**

- Efficacy for Open label studies and supervised treatment
- Blind designs & unsupervised treatment not efficacious
- Asymmetry in funnel plot suggestive of publication bias

Skinner MD, Lahmek P, Pham H, Aubin HJ (2014) Disulfiram Efficacy in the Treatment of Alcohol Dependence: A Meta-Analysis. PLOS ONE 9(2): e87366. https://doi.org/10.1371/journal.pone.0087366 http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0087366

DISULFIRAM



More effective than:

- NALTREXONE
- ACAMPROSATE
- TOPIRAMATE

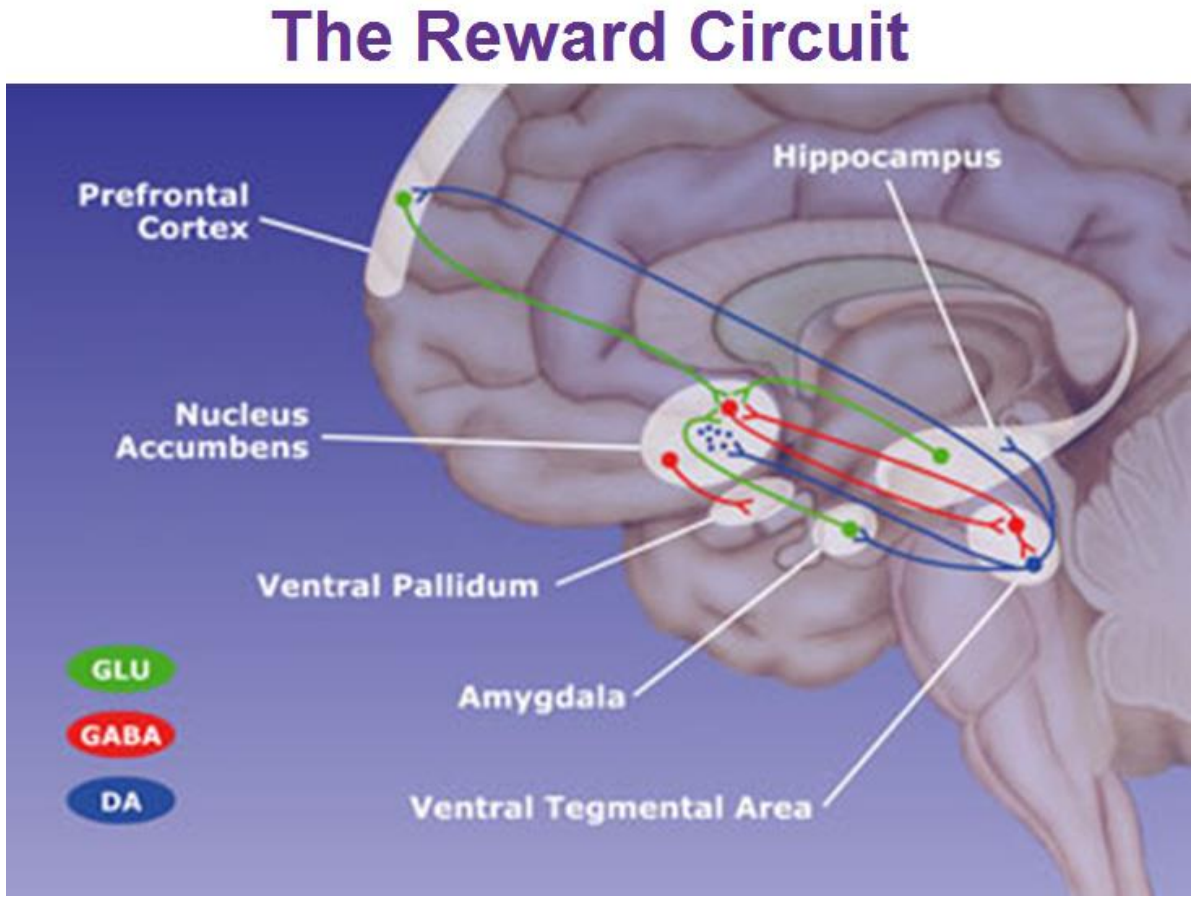
Figure 6. Subgroup analysis of Hedges' g effect-size comparing the efficacy of disulfiram and controls by control types.

DISULFIRAM

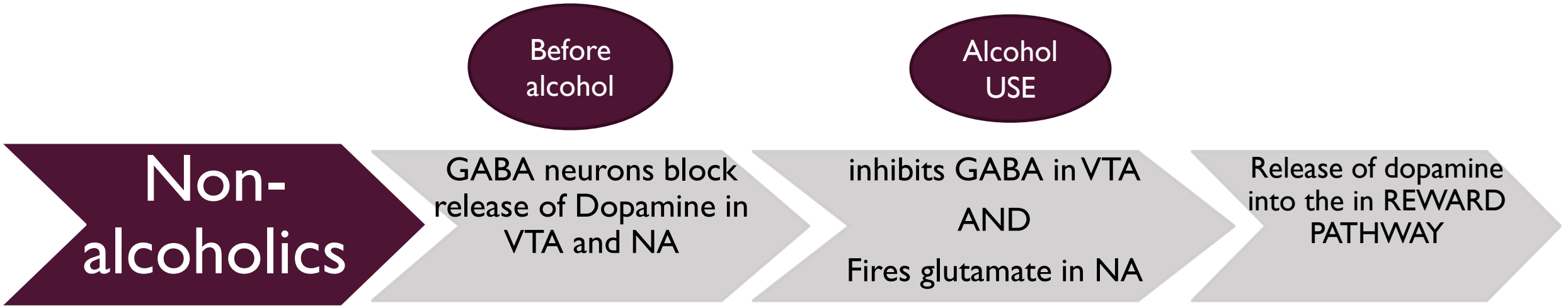
- Need caution when used with DM, hypothyroidism, epilepsy, HT, IHD
- Don't consume "hidden alcohol" (mouthwashes, perfumes, vinegar, deoderants, hair dyes
- Side effects of sedation, headaches, acne, visual dist, paraesthesia, agitation
- More serious effects: liver disease, persistant nausea/diarrhoea, abdo pain
- Adverse effects with alcohol
- Some patients too afraid to use it

ALCOHOLS EFFECT ON NEUROTRANSMITTERS & NEUROMODULATORS

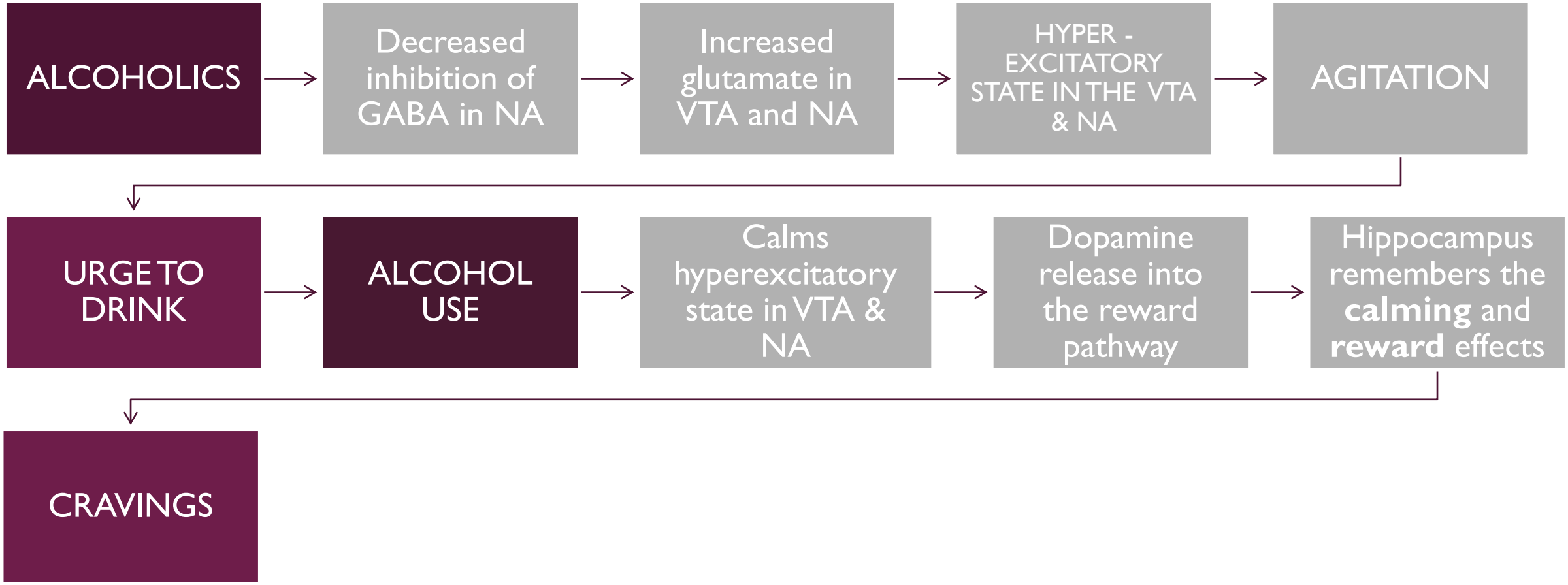
- Alcohol effects:
  - GABA
  - Glutamate
  - NMDA
  - Central dopamine
  - Central noradrenaline



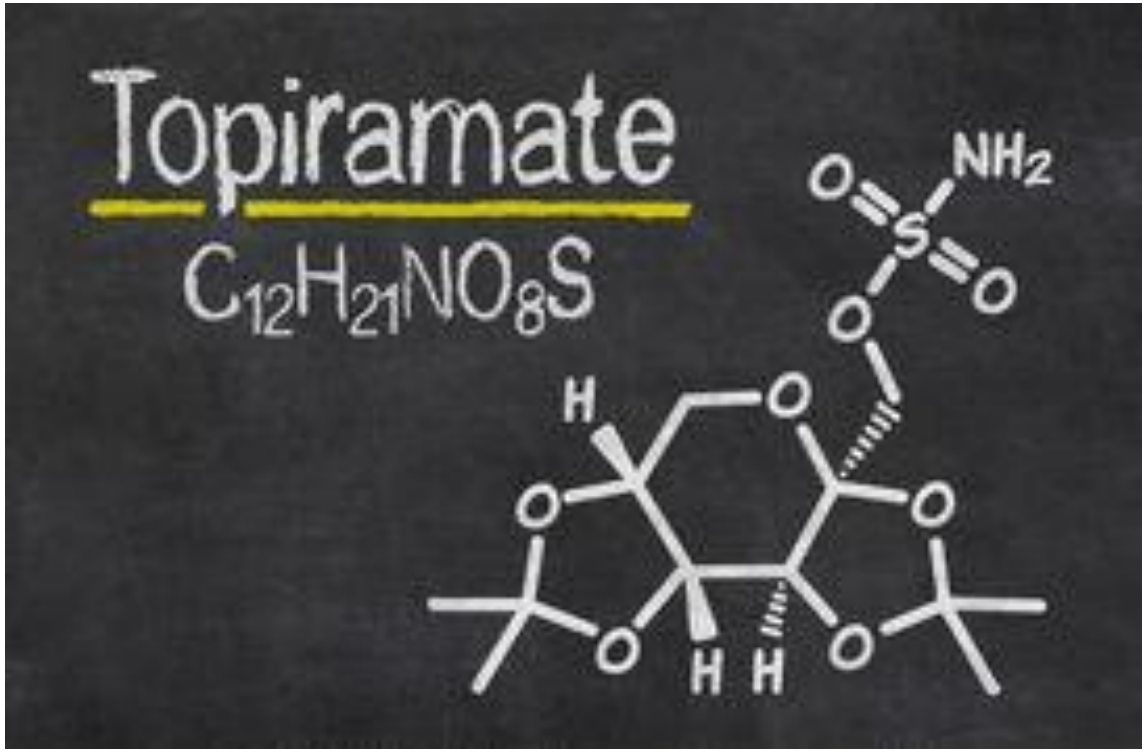
ALCOHOLS EFFECT ON NEUROTRANSMITTERS & NEUROMODULATORS



ALCOHOLS EFFECT ON NEUROTRANSMITTERS & NEUROMODULATORS



TOPIRAMATE



- Monosacharide D-fructose analogue
- PBS authorised for migraines and seizures
- Broad spectrum efficacy for addiction, epilepsy and migraines
- Structurally different and displaying a different mechanism of action to other anticonvulsants

TOPIRAMATE

- Mechanism of action:
  1. GABA-A agonist
  2. AMPA/kainite glutamate antagonist
  3. Blocks state dependent sodium channels
  4. Inhibits voltage-activated L-type calcium channels
  5. Weak inhibition of carbonic anhydrase isoenzymes

Main mechanisms for efficacy in AUD

TOPIRAMATE – POTENTIAL MECHANISM OF ACTION IN AUD

- **GABA-A agonist:**
  - increases GABA activity in the nucleus accumbens causing inhibition of VTA GABA excitability
  - Restores balance to the VTA dopamine hypofunction
  - Assists impulsive behaviours (aggression, ED, gambling, OCD, PTSD) and cravings, relapses.

TOPIRAMATE –POTENTIAL MECHANISM OF ACTION IN AUD

- **AMPA/kainite glutamate antagonist:**
  - suppresses alcohol-induced dopamine release from the nucleus accumbens
  - Reduces immediately the "reward potential" of alcohol

TOPIRAMATE – PHARMACOKINETICS & SIDE EFFECTS

- Rapid oral absorption (not affected by food)
- Bioavailablity of 80%
- Reaches maximum concentration between 1.3 -1.7 hrs
- Half-life of 19-23 hrs
- Reaches steady state in ~4 days
- Eliminated predominantly unchanged (70%) in the urine
- <20% metabolised in the liver

SIDE EFFECTS

- Paraesthesia
- Taste perversion
- Weight loss
- Cognitive slowing
- Poor conc/alertness/memory
- Sedation
- Nausea/diarrhoea
- Dizziness
- Abnormal skin sensations

TOPIRAMATE IN ALCOHOL USE DISORDERS: REVIEW
GUGLIELMO ET AL. CNS DRUGS (2015)

- 3 RCTs with 610 participants
- Efficacy at 3 dose regimes: <100, 200, 300mg/day
- Compared to placebo, topiramate:
  - Reduced drinking days
  - Reduced drinks per drinking day
  - Reduced % of heavy drinking days
  - Increased % of days abstinent

TOPIRAMATE IN ALCOHOL USE DISORDERS: REVIEW
GUGLIELMO ET AL. CNS DRUGS (2015)

- **Secondary measures:**
  - Reduces alcohol craving & obsessive drinking (OCDS)
  - Reduces GGT
  - Improves BP
  - Reduces cholesterol, BMI
  - Improves overall well-being and life satisfaction

TOPIRAMATE IN ALCOHOL USE DISORDERS: REVIEW
GUGLIELMO ET AL. CNS DRUGS (2015)

3 studies comparing Topiramate to Naltrexone

- 12wk RCT, 155 participants,
- NAL, TOP, placebo arms
- **TOP superior to placebo for:**
  - Abstinence
  - Weeks of heavy drinking
- **TOP superior to NAL:**
  - Time to first relapse
  - Abstinence duration
  - HD weeks

TOPIRAMATE IN ALCOHOL USE DISORDERS: REVIEW
GUGLIELMO ET AL. CNS DRUGS (2015)

3 studies comparing Topiramate to Naltrexone

- 2 x 6 month Naturalistic open label study
- 284 participants; TOP (200mg/day) and NAL (50mg/day)
- **TOP superior for:**
  - Craving
  - Reducing alcohol intake
  - % patients relapsing

TOPIRAMATE IN ALCOHOL USE DISORDERS: REVIEW GUGLIELMO ET AL. CNS DRUGS (2015)

- One study comparing Topiramate and Disulfiram
- Randomised, open label, 9 mths, 100 participants
- Family supervised administration of DIS
- **DIS superior to TOP:**
  - time to first relapse DIS (133 days) vs TOP (79 days)
  - % patients abstinent at 9mths (DIS 90% vs TOP 56%)

TOPIRAMATE IN ALCOHOL USE DISORDERS: REVIEW
GUGLIELMO ET AL. CNS DRUGS (2015)

Topiramate an evidence based treatment for alcohol relapse prevention

Brief weekly adherence counselling
rehabilitation or
Psychotherapy

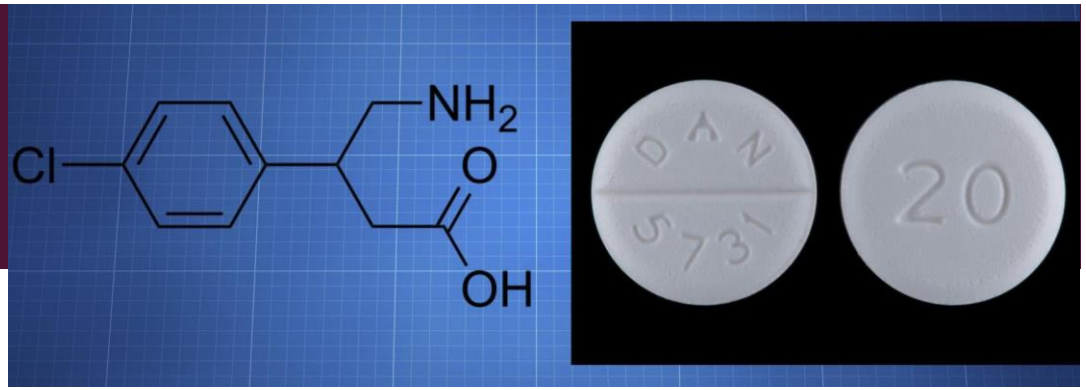
TOPIRAMATE - PRESCRIBING

- Begin at a dose of 25mg nocte
- Titrate gradually every 4 days
- Increase to ~ 150 - 200mg/day in divided doses
- Can titrate to 300mg/day

TOPIRAMATE – MONITORING

- Test **serum topiramate levels (therapeutic range 5-20mcg/mL)**
- Can be associated with elevation of **blood ammonia levels** (vomiting, sedation, cognitive effects)
- Can increase **body temperature** (decreased sweating)
- When taken with sodium valproate can decrease body temp & increases risk of elevated ammonia levels (tiredness, confusion)

BACLOFEN



- Agonist of the GABA-B receptors
  - GABA-B receptors highly expressed in the limbic region
  - Closely associated with surrounding dopamine neurons
- Baclofen originally approved by FDA in 1977 for use in spasticity for neurological conditions (e.g. MS, spinal cord lesions)

BACLOFEN – MECHANISM OF ACTION

- Increases GABA-B activity in the limbic region → improving control of anxiety
- Activation of GABA-B → Inhibits surrounding DOPAMINE neurons → Prevents alcohol release of dopamine into NA → Decreases positive reinforcement of alcohol in the reward pathway

BACLOFEN PHARMOKINETICS AND SIDE EFFECTS

- Peak concentration 2-3 hrs after ingestion
- Half-life 2-6 hrs (administer 3-4 times/day)
- 80% excreted primarily unchanged in the kidneys
- (available in 10mg and 25mg tablets)

SIDE EFFECTS

Headache
Nausea
Vertigo
Drowsiness
Change in sense of taste
Weight gain/loss of appetite
Sweating
Neurological: dizziness, vertigo, visual disturbances, paraesthesia, imbalance, speech disturbances

BACLOFEN – ADVERSE EFFECTS

SERIOUS ADVERSE EFFECTS

Seizures

Encephalopathy

Arrhythmia

Hallucinations

Depression

Manic episodes

Haematuria

BACLOFEN – EARLY RESEARCH

- Since 2000 there have been several Case Studies, Open label studies and Observational studies:
  - Small numbers
  - Varying doses (30mg/day -270mg/day)
  - Generally well tolerated
  - **MIXED RESULTS**

BACLOFEN – EARLY RCTS

Addolorato et al. 2002

39 participants

Daily drinks 14.2 +/- 7.9

Duration of use 12.6 +/- 4.8

Comorbities excluded

Baclofen 10mg QID 4 4ks

Abstinence: 70% v21.2%

Garbutt et al. 2010

80 participants

Daily drinks 7.3 +/- 3.7

Duration: 23.5 +/- 9.9 yrs

Comorbidities exluded

Baclofen 10mg TDS 12wks

HDD: 19.3% v24.7%

Addolorato et al.2007

84 participants

Daily drinks ?

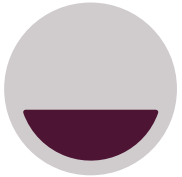
Duration: 22 +/- 5yrs

Cirrhosis

Baclofen 10mg tds 12 wks

Abstinence: 71% v 29%

BACLOFEN – EARLY RCTS



Addolorato et al. 2002

39 participants

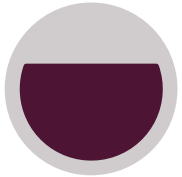
Daily drinks 14.2 +/- 7.9

Duration of use 12.6 +/- 4.8

Comorbities excluded

Baclofen 10mg QID 4 4ks

Abstinence: 70% v21.2%



Garbutt et al. 2010

80 participants

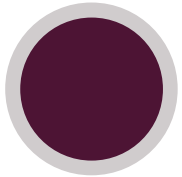
Daily drinks 7.3 +/- 3.7

Duration: 23.5 +/- 9.9 yrs

Comorbidities exluded

Baclofen 10mg TDS 12wks

HDD: 19.3% v24.7%



Addolorato et al.2007

84 participants

Daily drinks ?

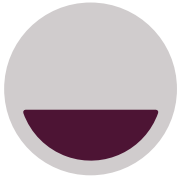
Duration: 22 +/- 5yrs

Cirrhosis

Baclofen 10mg tds 12 wks

Abstinence: 71% v 29%

BACLOFEN – EARLY RCTS



Addolorato et al. 2002

39 participants

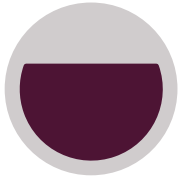
Daily drinks 14.2 +/- 7.9

Duration of use 12.6 +/- 4.8

Comorbities excluded

Baclofen 10mg QID 4 4ks

Abstinence: 70% v21.2%



Garbutt et al. 2010

80 participants

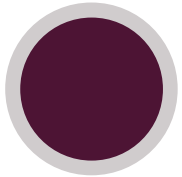
Daily drinks 7.3 +/- 3.7

Duration: 23.5 +/- 9.9 yrs

Comorbidities exluded

Baclofen 10mg TDS 12wks

HDD: 19.3% v24.7%



Addolorato et al.2007

84 participants

Daily drinks ?

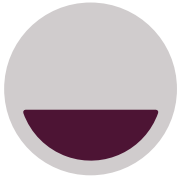
Duration: 22 +/- 5yrs

Cirrhosis

Baclofen 10mg tds 12 wks

Abstinence: 71% v 29%

BACLOFEN – EARLY RCTS



Addolorato et al. 2002

39 participants

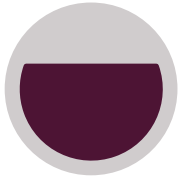
Daily drinks 14.2 +/- 7.9

Duration of use 12.6 +/- 4.8

Comorbities excluded

Baclofen 10mg QID 4 4ks

Abstinence: 70% v21.2%



Garbutt et al. 2010

80 participants

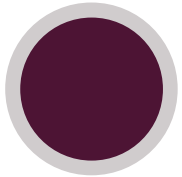
Daily drinks 7.3 +/- 3.7

Duration: 23.5 +/- 9.9 yrs

Comorbidities excluded

Baclofen 10mg TDS 12wks

HDD: 19.3% v24.7%



Addolorato et al.2007

84 participants

Daily drinks ?

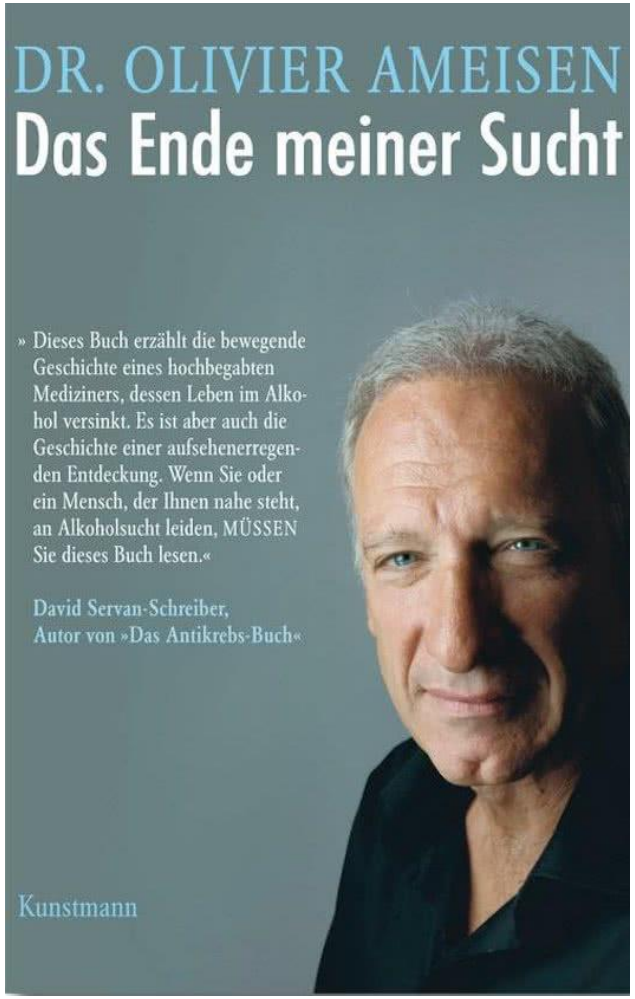
Duration: 22 +/- 5yrs

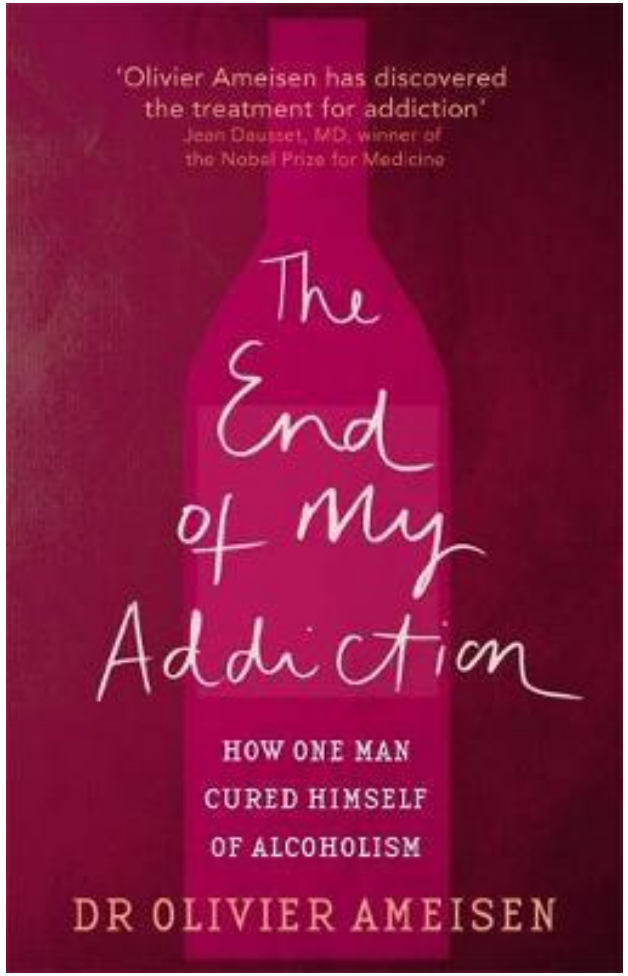
Cirrhosis

Baclofen 10mg tds 12 wks

Abstinence: 71% v 29%

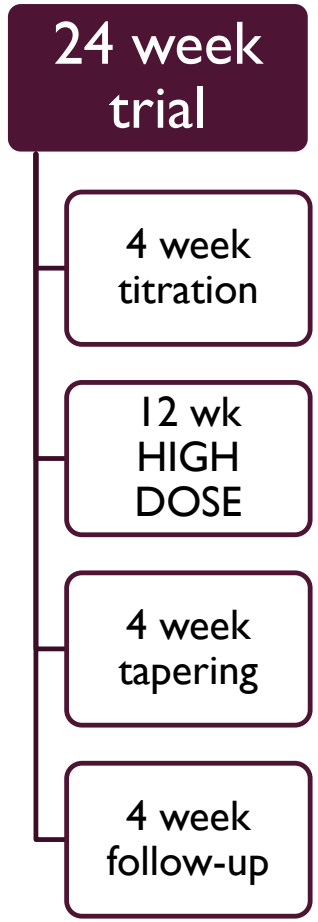
BACLOFEN – "PEOPLE POWER" FROM 2005





BACLOFEN - BACLAD

- Muller et al. 2015 (European Neuropsychopharmacology)
- RCT, double-blind
- 56 participants
- Exclusions: mental illness, epilepsy, significant medical condition
- Baclofen doses 30-270mg/day. Mean high dose **180mg**
- Primary outcome measures:
  - **Total abstinence**
  - **Cumulative abstinence duration**



BACLOFEN - BACLAD

Baclofen

28 participants, 22 reached HIGH DOSE

68.2% abstinent (15/22)

Cumulative abstinence 67.8 days

No adverse effects

Placebo

28 participants, 21 reached HIGH DOSE

23.8% abstinent (5/21)

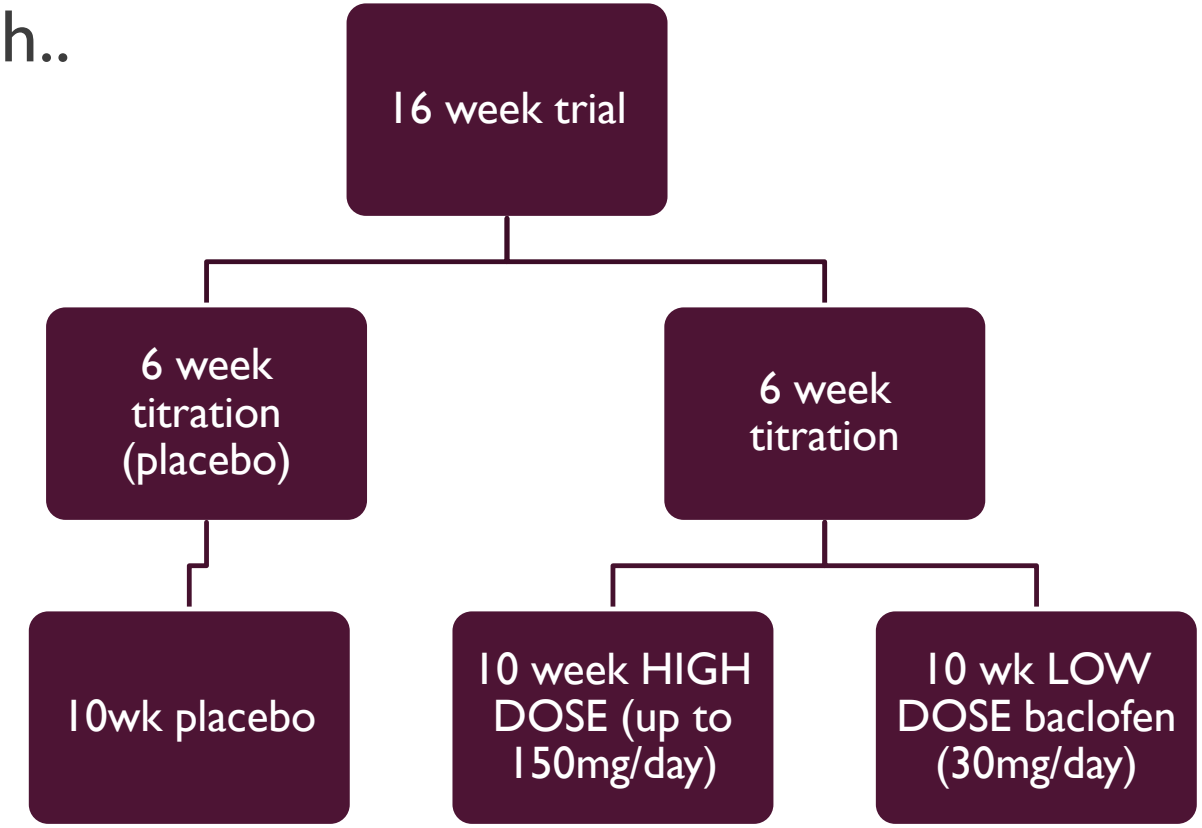
Cumulative abstinence 51.8 days

No serious adverse effects

No significance in secondary outcome measures such as **LFTs**, CDT, **HAM-A**, HAM-D, Obsessive Compulsive drinking scale (OCDS **craving scale)**

BACLOFEN – DUTCH STUDY 2016

- Beraha et al. (European Neuropsych.. 2016)
- Multicentre, double-blind, RCT
- Primary outcome measure
  - ➢ Time to first relapse
- 151 participants



BACLOFEN – DUTCH STUDY 2016

High dose baclofen	Low dose baclofen	Placebo
• 58 patients • **15.5% reached 150mg/day** • Mean dose 93.6mg/day • No significant difference in TFR • 27.5% patients relapsed • No difference in CDT • Decrease in craving, anxiety and depression (insignificant) • Frequent adverse effects related to dose	• 31 patients • **22.6% reached 30mg/day** • - • No significant difference in TFR • 20% patients relapsed • No difference in CDT • Decrease in craving, anxiety and depression (insignificant)	• 62 patients • **40.3% (12 pills/day)** • - • No significant difference in TFR • 25% patients relapsed • No difference in CDT • Decrease in craving, anxiety and depression (insignificant)

BACLOFEN – DUTCH STUDY 2016

High dose baclofen	Low dose baclofen	Placebo
• 58 patients • 15.5% reached 150mg/day • **Mean dose 93.6mg/day** • No significant difference in TFR • 27.5% patients relapsed • No difference in CDT • Decrease in craving, anxiety and depression (insignificant) • Frequent adverse effects related to dose	• 31 patients • 22.6% reached 30mg/day • - • No significant difference in TFR • 20% patients relapsed • No difference in CDT • Decrease in craving, anxiety and depression (insignificant)	• 62 patients • 40.3% (12 pills/day) • - • No significant difference in TFR • 25% patients relapsed • No difference in CDT • Decrease in craving, anxiety and depression (insignificant)

BACLOFEN – DUTCH STUDY 2016

High dose baclofen	Low dose baclofen	Placebo
• 58 patients • 15.5% reached 150mg/day • Mean dose 93.6mg/day • **No significant difference in TFR** • 27.5% patients relapsed • No difference in CDT • Decrease in craving, anxiety and depression (insignificant) • Frequent adverse effects related to dose	• 31 patients • 22.6% reached 30mg/day • - • **No significant difference in TFR** • 20% patients relapsed • No difference in CDT • Decrease in craving, anxiety and depression (insignificant)	• 62 patients • 40.3% (12 pills/day) • - • **No significant difference in TFR** • 25% patients relapsed • No difference in CDT • Decrease in craving, anxiety and depression (insignificant)

BACLOFEN – DUTCH STUDY 2016

High dose baclofen	Low dose baclofen	Placebo
• 58 patients • 15.5% reached 150mg/day • Mean dose 93.6mg/day • No significant difference in TFR • **27.5% patients relapsed** • **No difference in CDT** • **Decrease in craving, anxiety and depression (insignificant)** • Frequent adverse effects related to dose	• 31 patients • 22.6% reached 30mg/day • - • No significant difference in TFR • **20% patients relapsed** • **No difference in CDT** • **Decrease in craving, anxiety and depression (insignificant)**	• 62 patients • 40.3% (12 pills/day) • - • No significant difference in TFR • **25% patients relapsed** • **No difference in CDT** • **Decrease in craving, anxiety and depression (insignificant)**

BACLOFEN – DUTCH STUDY 2016

High dose baclofen	Low dose baclofen	Placebo
• 58 patients • 15.5% reached 150mg/day • Mean dose 93.6mg/day • No significant difference in TFR • 27.5% patients relapsed • No difference in CDT • Decrease in craving, anxiety and depression (insignificant) • **Frequent adverse effects related to dose**	• 31 patients • 22.6% reached 30mg/day • - • No significant difference in TFR • 20% patients relapsed • No difference in CDT • Decrease in craving, anxiety and depression (insignificant)	• 62 patients • 40.3% (12 pills/day) • - • No significant difference in TFR • 25% patients relapsed • No difference in CDT • Decrease in craving, anxiety and depression (insignificant)

BACLOFEN - BACLOVILLE

- Prof Philippe Jaury et al.
- Multicentre, pragmatic, randomized, double-blind **primary care** trial assessing the efficacy and safety of **high-dose baclofen v placebo** during **1 year**
- Sponsored by Descartes Universite, Publique-Hopitaux de Paris & private sponsors
- Study began May 2012 until June 2013
- Preliminary results presented at conferences in 2016/17, but awaiting secondary results.
- 320 participants, 68% male, mean alcohol intake 12.9 s.d./day
- Baclofen dose: 5mg tds titrated to 300mg/day depending on effective and tolerance (?average dose)

BACLOFEN - BACLOVILLE

Baclofen

- 162 allocated to baclofen
- 49 withdrew prematurely for the study
- 113 followed up for 12 months
- **56.8%** of pts with low-risk alcohol use or abstinence

Placebo

- 158 allocated to placebo
- 53 withdrew
- 105 followed up for 12 months
- **36.5%** of pts with low-risk alcohol us or abstinence

BACLOFEN

- Research results regarding baclofen treatment for alcohol dependence remain **mixed**
- Very popular in France – some small studies, case reports, novel, RCT (Bacloville)
- Possible benefits:
  - High dose baclofen ?150-300mg/day
  - Better for alcohol dependent patients who were heavier drinkers before treatment
  - Better for alcoholic patients who aren't also getting D&A counselling