# 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

#### • 22 RCTs from 1979-2010

- 2,262 participants
- 89% male subjects
- Assessing efficacy compared to other anticraving medication or no disulfiram

doi:10.1371/journal.pone.0087366.t003

#### ACAMPROSATE

#### NALTREXONE



- 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 impairmentGl upset can limit doses

#### - 50 RCTs

- 7793 participants

Reduction of risk of drinking NNT 9Decreased 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 <u>Open label studies</u> and <u>supervised treatment</u>
  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.008736

#### DISULFIRAM



More effective than:NALTREXONEACAMPROSATETOPIRAMATE

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

#### **The Reward Circuit**



#### 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:
  - I. 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
   I.3 I.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</p>

#### SIDE EFFECTS

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

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

### Secondary measures:

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

## 3 studies comparing Topiramate to Naltrexone

- I2wk RCT, I55 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

# 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

- 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 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)



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



#### 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



#### 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%



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# Addolorato et al.2007

#### BACLOFEN – "PEOPLE POWER" FROM 2005

#### DR. OLIVIER AMEISEN Das Ende meiner Sucht

 Dieses Buch erzählt die bewegende Geschichte eines hochbegabten Mediziners, dessen Leben im Alkohol versinkt. Es ist aber auch die Geschichte einer aufsehenerregenden Entdeckung. Wenn Sie oder ein Mensch, der Ihnen nahe steht, an Alkoholsucht leiden, MÜSSEN Sie dieses Buch lesen.«

David Servan-Schreiber, Autor von »Das Antikrebs-Buch«



the treatment for addiction' he HOW ONE MAN CURED HIMSELF OF ALCOHOLISM DR OLIVIER AMEISEN

'Olivier Ameisen has discovered

#### 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)

- Beraha et al. (European Neuropsych..
   2016)
- Multicentre, double-blind, RCT
- Primary outcome measure
  - Time to first relapse
- I5I participants



#### High dose baclofen

- 58 patients
- I5.5% reached I50mg/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

#### Low dose baclofen

- 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)

#### High dose baclofen

- 58 patients
- 15.5% reached 150mg/day
- Mean dose 93.6mg/day
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#### 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 I 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 <u>mixed</u>
- 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