Baclofen in the treatment of alcohol dependence with or without liver disease
Results from the BacALD study

Presented by
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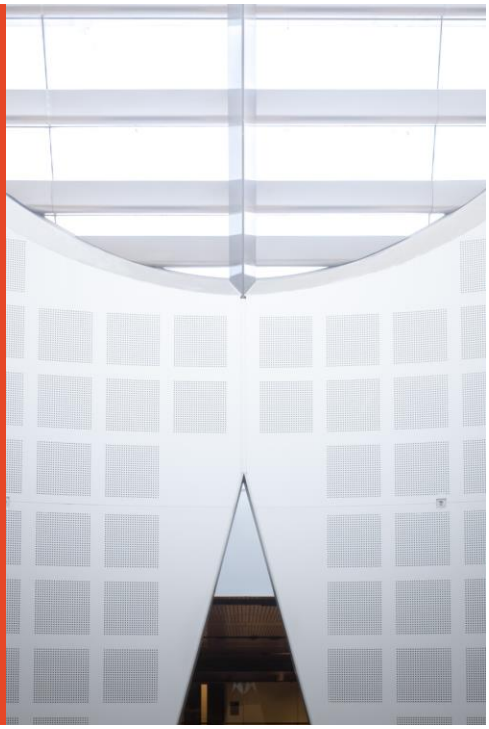
NHMRC CRE in Mental Health and Substance Use

THE UNIVERSITY OF SYDNEY



PROJECT TEAM……

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Collaborators:
- Prof Jim Lagopolous (MRS)
- Dr Richard Morris (fMRI)
- Dr Natahsa Luquin /Prof Ron Trent (genetics)

Introduction

- New medications for reducing alcohol consumption needed. None approved for patients with advanced liver problems.
- Baclofen, $GABA_B$ receptor agonist with minimal liver metabolism
- Baclofen increased abstinence in patients with ALD (eg Addolorato et al., 2007)
- Expanded use in community to treat alcohol dependence
- Mixed results in non ALD (Behera et al., 2016, Muller et al., 2015, Reynard et al., 2017).
- NHMRC grant: baclofen reduce alcohol consumption in ALD (including non ALD)

Methods: BacALD study

- Morley et al (2013): A multi-site, randomized, double-blind, placebo-controlled trial
- 3 arms:

Placebo	Baclofen 30 mg	Baclofen 75 mg
• 3 x day	• 10 mg 3 x day	• 25 mg 3 x day

- 12 week trial
- 2 separate randomised groups AD and ALD run in parallel
- 2013-2016: 3 outpatient treatment centres in Sydney

Methods

Inclusion criteria:

ICD-10 criteria alcohol dependence, abstinence between 3-28days, resolution of withdrawal (CIWA-AR), > 48 hours after ceasing diazepam

For ALD group: presence of symptoms of LD, fibroscan, alcohol use > 60g/day in women and >80g/day men > 10 years

Exclusion criteria:

Pregnancy, hepatic encephalopathy, peptic ulcer, unstable diabetes, psychosis or active major mental disorder associated with suicide risk, concurrent psychotropic medication other than antidepressants

Methods

Primary outcome measures (predefined 2013):

i. Time to lapse (any drink)

ii. Time to relapse ($\geq$4 drinks for women and $\geq$5 for men)

iii. Composite measure of drinking at follow-up:

Number of heavy drinking days ($\geq$4 drinks for women and $\geq$5 drinks for men), Drinks per drinking day, abstinence % days

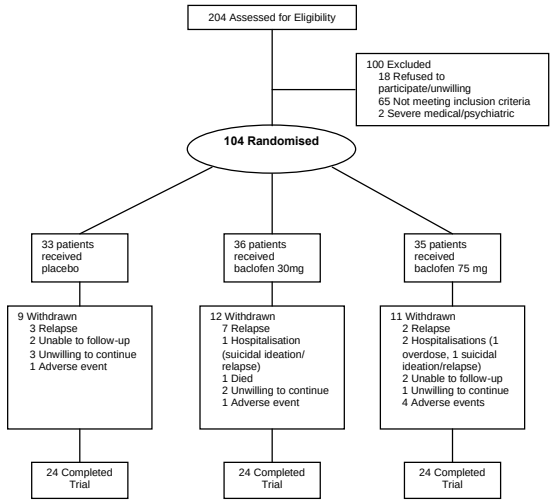
Secondary outcome measures:

Craving, depression, anxiety, sleep, LFT's, tolerability and safety

Data analyses (predefined 2013):

Intention-to-treat, active (both doses) versus placebo, dose response

CONSORT FLOW CHART



Results: Baseline characteristics

	Placebo (n = 33)	Baclofen 30 mg (n = 36)	Baclofen 75 mg (n = 35)
Age, y	48.18 +/- 9.91	46.25 ± 8.81	50.71 +/- 10.59
Gender, % F	30	29	29
Unemployed, %	39	47	54
Drinks per drinking day	14.10 +/- 7.04	17.03 ± 12.09	13.78 +/- 9.47
Abstinence days	3.52 +/- 5.08	5.47 +/- 6.81	4.94 +/- 6.66
Alcoholic Liver Disease, %	55	56	57
Antidepressant use, %	55	58	57
ADS	17.41 +/- 9.12	21.94 ± 9.12	17.65 +/- 10.47
PACS craving	17.97 +/- 6.53	17.11 ± 8.08	15.44 +/- 7.57
DASS Depression	19.88 +/- 12.56	15.44 +/- 9.72	15.53 +/- 12.56
DASS Anxiety	10.56 +/- 8.58	14.72+/-10.00	11.82 +/- 8.92
GGT	236.04 +/- 391.22	221.26 +/- 216.83	239.00 +/- 472.69
ALT	62.77 +/- 51.98	52.39 +/- 26.84	49.84 +/- 36.74
AST	65.58 +/- 57.03	61.83 +/- 37.81	55.72 +/- 48.03

Results

Subject retention

71% completed study protocol and interviews, 89% of drinking data obtained

73% PL vs 69% BAC 30 mg vs 71% BAC 75 mg (ns)

Treatment compliance (ITT)

79% PL (66 days) vs 74% BAC 30 mg (62 days) vs 79% BAC 75 mg (67 days) (ns)

Quality control

Compliance self-report: Urinary baclofen 98% consistency

Alcohol self-report: %CDT 96% consistency

Double-blind upheld

Results: Main efficacy results (ITT)

Primary outcomes (active versus inactive):

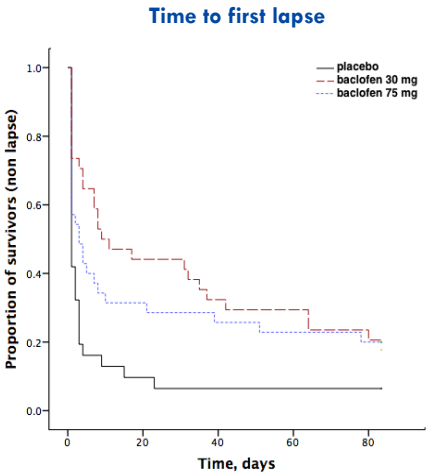
Significant effect on time to lapse, relapse,

Significant effect composite drinking measure (abstinence).

Outcome	Placebo (n = 33)	Baclofen 30 mg (n = 36)	Baclofen 75 mg (n = 35)
Time to first lapse (days) * +/- SEM	**11.10 +/- 4.52**	**31.16 +/- 6.18**	**24.97 +/- 6.37**
Time to first relapse (days) * +/- SEM	**16.67 +/- 5.11**	**34.97 +/- 6.40**	**32.26 +/- 6.80**
Percentage days abstinent+	**43**	**69**	**65**
Average drinks per drinking day+	7.50 +/- 6.46	8.82 +/- 10.38	4.67 +/- 4.86
Number of heavy drinking days+	2.46 +/- 2.77	2.28 +/- 2.89	1.65 +/- 2.48
Abstinence, %	10	21	23
Non Relapse, %	13	24	29

No significant dose response effect was observed.

Results: Main efficacy results



A **significant effect** of baclofen vs placebo on **time to lapse** (Log-rank test: $\chi^2 = 6.44$, $p < 0.05$).

Number needed to treat (NNT) based on the criterion of **continuous abstinence** at week 12 for BAC 30-75 mg/day: **8.3 (*d* = 0.56)**

Results: Secondary outcomes

- No significant effect of medication on DASS depression or anxiety scores, craving or sleep
- No significant effect of medication on LFT's (possible power)

Exploratory outcomes:

- **ALD versus non ALD:** stronger effect in survival curves for ALD group vs non ALD group

- ALD group = 18 SDDD vs non ALD group = 11 SDDD

- ALD group lower cortical GABA levels vs non ALD group ($p < 0.0001$)

Results: Tolerability

Side-effect profile(adverse events rated moderate, severe or very severe):

Clinical event	Placebo	Baclofen 30 mg	Baclofen 75 mg
Sedation or drowsiness*	**10 (30)**	**7 (20)**	**18 (51)**
Dizziness	3 (9)	2 (6)	7 (20)
Skin rash/itching	5 (15)	5 (14)	1 (3)
Constipation	2 (6)	3 (9)	3 (9)
Shortness of breath*	1 (3)	0 (0)	4 (11)
Dry mouth	1 (3)	3 (9)	1 (3)
Urination problems	0 (0)	1 (3)	2 (6)
Sleep disturbances	2 (6)	0 (0)	0 (0)

* significant differences between treatment groups ($p < 0.05$, chi square)

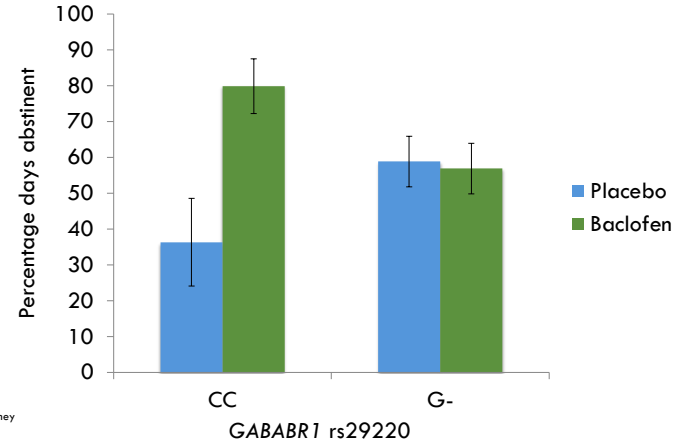
Results: Safety

Serious adverse events:

- 1 overdose (ED admission) BAC 75 mg
- 2 ED presentations with suicidal ideation + intoxication (30 mg, 75mg)
- 1 death (determined **unrelated** to medication by DSMB) BAC 30 mg
- 1 alcohol withdrawal seizure (determined **unrelated** to medication by DSMB) PL

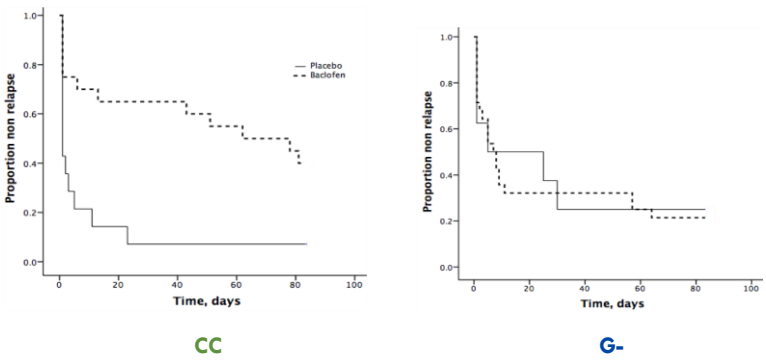
Pharmacogenetics

- *GABABR1* rs 29220 (association with AUD, Enoch et al., 2017)
- CC vs G-
- Genotype x baclofen effect (abstinence, relapse)
- CC beneficial response to baclofen



Pharmacogenetics

- Genotype x baclofen effect: time to relapse ($p < 0.05$)



GABABR1 rs 29220

Retrospective analysis:

Not balanced for baseline, eg trend for differences on craving (strength of effect weakened when placed in model)

However, consistency across multiple outcomes and paradigms:

- Genotype x baclofen effect on side effects (CC less dizziness, drowsiness)

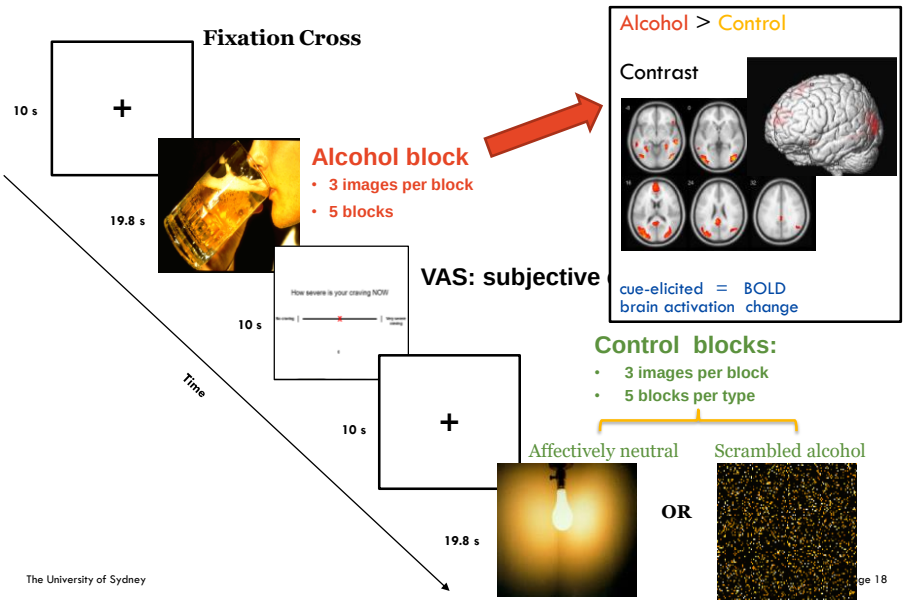
- Genotype x baclofen effect on cortical glutamate

CC carriers receive the benefit from baclofen treatment relative to G- carriers and also tolerate it better

CC: our AUD sample: 47%, Enoch et al., 2017 AUD association study: 30% so has clinical relevance.

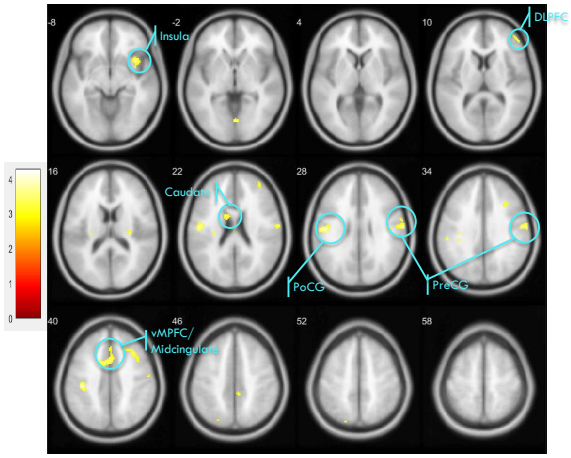
Highest population MAF 1000 genome G: 0.46

fMRI Cue Reactivity Task



fMRI Results

10 PLA > 17 BAC
Alcohol > Control contrast



- **Wide network of regions reactive to alcohol cues in PLA > BAC**
- Motivational pathways
  Mesocortical (caudate head)
- Insula
- Sensorimotor areas
- Prefrontal regions

→ PLA patients demonstrate greater brain activation in areas associated with alcohol cue reactivity compared to BAC patients

→ GABBR1 29220 genotype (CC vs G-) differences in activation

 P <.005; cluster threshold k >15

Conclusion

– There is some signal of efficacy for baclofen on treatment outcomes (NNT: 8.3)

– *Toxicity profile problematic:* requires supervision, limited to specialist services

– Beneficial baclofen response predicted by:

✓ higher drinking at baseline/ALD

? GABABR1 rs 29220

– Now: genotype x medication interaction on neural activation to alcohol cue

Future: prospective pharmacogenetic, cost-effectiveness RCT needed