Efficacy, tolerability and safety of LD and HD baclofen in the Tx of alcohol dependence: A systematic review and meta-analysis

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theguardian

The little pill that could cure alcoholism

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2016

Pills prescribed for alcoholism might not work, study finds

Review of five drugs – including one linked to deaths – says there is no body of reliable evidence behind any of them

2017

Baclofen in France

- March 2014: Temporary recommendation: baclofen in dosages up to 300mg/day

- July 2017: max. dose reduced to 80mg/day
  - Motivation: epidemiological study conducted by CNAMTS, French ANSM & the French Inserm

Relevance and motivation..

- Popular and sensitive topic of debate
- Is HD worth the risk?
- No meta-analysis on both HD and LD baclofen published

Search

- **PubMed**: “alcoholism"[MeSH Terms] AND "baclofen"[Mesh Terms] Filters: Randomized Controlled Trial
- **Clinical Trial register** (ClinicalTrials.gov): "alcohol" AND "baclofen”
- **Netherlands Trial Register** (trialregister.nl): “baclofen”

- *39 records screened -> 13 eligible for inclusion in this review*

Eligibility Criteria

- *Participants*: adult patients, alcohol dependence DSM-IV or ICD10
- *Interventions*: baclofen vs. placebo, min 4 weeks
- *Outcomes*: data on days of abstinence or days to consumption of alcohol
- *Studies*: RCT, double-blind, placebo-controlled, no language requirements, unpublished studies also included

Study characteristics

LD studies

HD studies

LD&HD studies

Trial	Year of Publication	Country	Intervention duration (weeks)	Baclofen dose (mg/day)	N patients
Addolorato et al.	2002	Italy	4	30	**B:** 20
					P: 19
Addolorato et al.	2007	Italy	12	30	**B:** 42
					P: 42
Behara et al.	2016	The Netherlands	16	150 (mean: 93.6), 30	**B(150):** 58
					B(30): 31
					P: 62
Garbutt et al.	2010	USA	12	30	**B:** 40
					P: 40
Hauser et al.	2017	USA	12	30	**B:** 88
					P: 92
Jaury et al.	Unpublished	France	52	300 (mean: 160)	**B:** 162
					P:158
Krupitsky et al.	2015	Russia	12	50	**B:** 16
					P: 16
Leggio et al.	2014	USA	12	80	**B:** 15
					P: 15
Morley et al.	2014	Australia	12	60, 30	**B(30):** 14
					B(60): 14
					P: 14
Morley et al.	Unpublished	Australia	12	75 (mean: 44.8), 30	**B(30):** 36
					B(75): 35
					P: 33
Müller et al.	2015	Germany	24	270 (mean: 191.8)	**B:** 28
					P: 28
Ponizovsky et al.	2015	Israel	12	50	**B:** 32
					P: 32
Reynaud et al.	2017	France	26	180 (mean: 153.5)	**B:** 155
					P: 155

Methods

Outcomes:

1. **Time to lapse** = no. of days within the study until first alcohol consumption:

   ** 7 RCTs, 738 patients*

2. **Percentage days abstinent** = (total no. of days of abstinence / no. of days in study) * 100

   ** 5 RCTs, 323 patients*

3. **Percentage of patients abstinent at end point** = (no. of patients achieving and maintaining abstinence until end of study / total no. of patients) * 100

   ** 6 RCTS, 960 patients*

Subgroup analysis

- HD vs. LD (TTL & PAE)

Meta-regression:

- Average daily alcohol intake before inclusion (combined SMD data TTL & PDA)

Heterogenity and publication bias

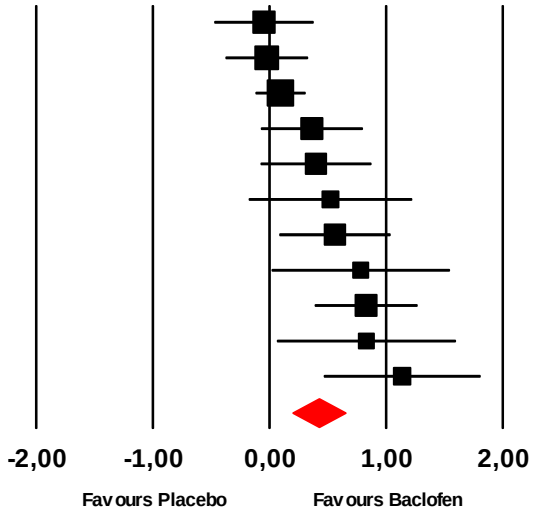
Results

Time to Lapse

Study name (year, dose mg)	Std diff in means	Standard error	Lower limit	Upper limit	p-Value
Beraha et al. (2016, 30)	-0,048	0,220	-0,479	0,384	0,829
Beraha et al. (2016, 150)	-0,024	0,183	-0,382	0,335	0,898
Reynaud et al. (2017, 180)	0,095	0,112	-0,124	0,314	0,396
Garbutt et al. (2010, 30)	0,364	0,225	-0,078	0,806	0,107
Morley et al. (unpublished, 75)	0,399	0,245	-0,081	0,879	0,103
Krupitsky et al. (2015, 50)	0,523	0,360	-0,181	1,228	0,146
Morley et al. (unpublished, 30)	0,561	0,246	0,079	1,043	0,022
Morley et al. (2014, 30)	0,783	0,392	0,015	1,552	0,046
Addolorato et al. (2007, 30)	0,828	0,227	0,383	1,274	0,000
Morley et al. (2014, 60)	0,831	0,394	0,059	1,603	0,035
Addolorato et al. (2002, 30)	1,138	0,345	0,461	1,814	0,001
	0,418	0,115	0,192	0,644	0,000

Statistics for each study

Std diff in means and 95% CI



Meta Analysis with random effects model

SMD = 0.42 (0.19-0.64)

Heterogenity:
I2 = 60%
P = 0.005
Q = 235.4

Publication bias:
- Egger's test P value = 0.006
- Duval and Tweedie's Adj SMD = 0.22 (-0.02-0.46)

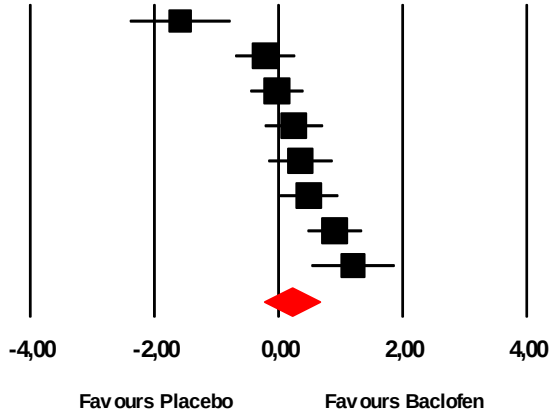
Conclusion: Small but significant advantage of baclofen over placebo.

Results

Percentage Days Abstinent

Studyname (date, dose mg)	Std diff in means	Standard error	Variance	Lower limit	Upper limit	p-Value
Leggio et al. (2014, 80)	-1,584	0,419	0,175	-2,404	-0,764	0,000
Ponizovsky et al. (2014, 50)	-0,216	0,251	0,063	-0,707	0,276	0,390
Garbutt et al. (2010, 30)	-0,026	0,224	0,050	-0,464	0,412	0,907
Morley et al. (unpublished, 75)	0,246	0,244	0,059	-0,231	0,723	0,312
Muller et al. (2015, 270)	0,353	0,269	0,073	-0,175	0,881	0,190
Morley et al. (unpublished, 30)	0,488	0,245	0,060	0,009	0,967	0,046
Addolorato et al. (2007, 30)	0,906	0,229	0,053	0,457	1,355	0,000
Addolorato et al. (2002, 30)	1,201	0,348	0,121	0,519	1,883	0,001
	0,205	0,228	0,052	-0,242	0,653	0,368

Statistics for each study



Meta Analysis with random effects model

SMD = 0.21 (-0.24-0.66)

Heterogenity:
$I^{2 =}$ 83%
P = 0.000
Q = 40.8

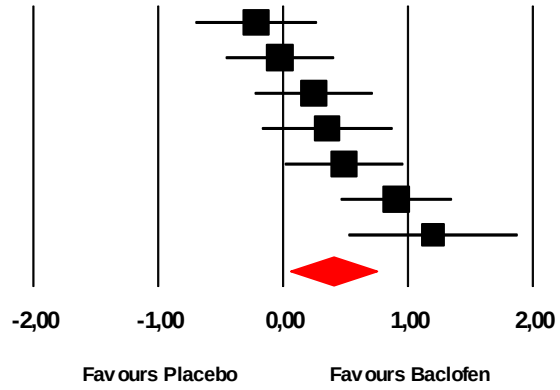
Publication bias:
- Egger's test P-value = 0.202
- Duval and Tweedie's adj SMD, remained the same

Conclusion: Insignificant advantage of baclofen over placebo.

Results

Percentage Days Abstinent Outlier removed

Studyname (date, dose mg)	Std diff in means	Standard error	Variance	Lower limit	Upper limit	p-Value
Ponizovsky et al. (2014, 50)	-0,216	0,251	0,063	-0,707	0,276	0,390
Garbutt et al. (2010, 30)	-0,026	0,224	0,050	-0,464	0,412	0,907
Morley et al. (unpublished, 75)	0,246	0,244	0,059	-0,231	0,723	0,312
Muller et al. (2015, 270)	0,353	0,269	0,073	-0,175	0,881	0,190
Morley et al. (unpublished, 30)	0,488	0,245	0,060	0,009	0,967	0,046
Addolorato et al. (2007, 30)	0,906	0,229	0,053	0,457	1,355	0,000
Addolorato et al. (2002, 30)	1,201	0,348	0,121	0,519	1,883	0,001
	0,397	0,176	0,031	0,051	0,743	0,024



Meta Analysis with random effects model

SMD = 0.40 (0.05-0.74)

Heterogenity:

I^2 = 70%

P = 0.002

Q = 20.26

Publication bias:

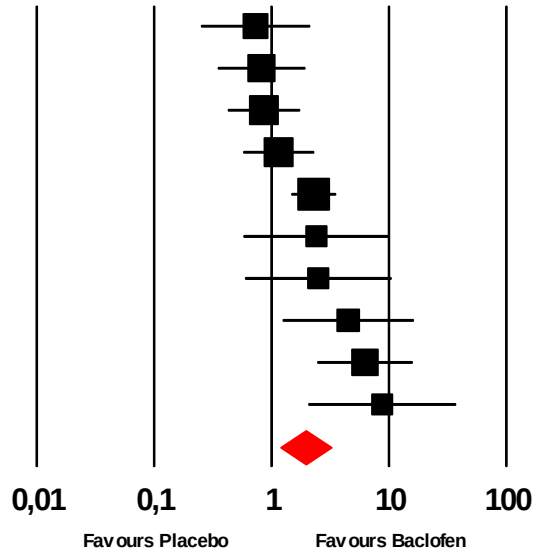
- Egger's test P-value = 0.158
- Duval and Tweedie's adj SMD, remained the same

Conclusion: Small but significant advantage of baclofen over placebo.

Results

Percentage of Patients Abstinent at Endpoint

Study name (year, dose mg)	Odds ratio	Lower limit	Upper limit	p-Value
Hauser et al. (2017, 30)	0,731	0,248	2,153	0,569
Beraha et al. (2016, 30)	0,822	0,344	1,963	0,659
Beraha et al. (2016, 150)	0,862	0,419	1,772	0,686
Reynaud et al. (2017, 180)	1,151	0,568	2,335	0,696
Jaury et al. (unpublished, 300)	2,285	1,458	3,579	0,000
Morley et al. (unpublished, 30)	2,414	0,569	10,245	0,232
Morley et al. (unpublished, 75)	2,500	0,588	10,628	0,215
Muller et al. (2015, 270)	4,500	1,231	16,452	0,023
Addolorato et al. (2007, 30)	6,250	2,425	16,108	0,000
Addolorato et al. (2002, 30)	8,750	2,032	37,671	0,004
	1,930	1,174	3,173	0,010



Meta Analysis with random effects model

OR = 1.93 (1.17-3.17)

Heterogenity:
I^2 = 65%
P = 0.002
Q = 25.8

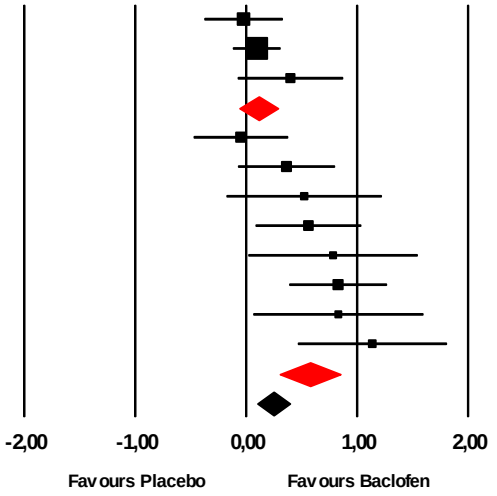
Publication bias:
- Egger's test P-value = 0.248
- Duval and Tweedie's adj OR = 1.73 (1.04-2.87)

Conclusion: Significant advantage of baclofen over placebo.

Results: HD vs. LD

Subgroup Analysis (TTL): Baclofen Dose

Group by Dose	Studyname (year, dose mg)	Statistics for each study: Std diff in means	Standard error	Lower limit	Upper limit	p-Value
High	Beraha et al. (2016, 150)	-0,024	0,183	-0,382	0,335	0,898
High	Reynaud et al. (2017, 180)	0,095	0,112	-0,124	0,314	0,396
High	Morley et al. (unpublished, 75)	0,399	0,245	-0,081	0,879	0,103
High		0,107	0,089	-0,067	0,281	0,229
Low	Beraha et al. (2016, 30)	-0,048	0,220	-0,479	0,384	0,829
Low	Garbutt et al. (2010, 30)	0,364	0,225	-0,078	0,806	0,107
Low	Krupitsky et al. (2015, 50)	0,523	0,360	-0,181	1,228	0,146
Low	Morley et al. (unpublished, 30)	0,561	0,246	0,079	1,043	0,022
Low	Morley et al. (2014, 30)	0,783	0,392	0,015	1,552	0,046
Low	Addolorato et al. (2007, 30)	0,828	0,227	0,383	1,274	0,000
Low	Morley et al. (2014, 60)	0,831	0,394	0,059	1,603	0,035
Low	Addolorato et al. (2002, 30)	1,138	0,345	0,461	1,814	0,001
Low		0,570	0,139	0,298	0,843	0,000
Overall		0,241	0,075	0,095	0,388	0,001



Meta Analysis with random effects model

High dose group:

SMD = 0.12 (-0.07-0.28)

Low dose group

SMD = 0.57 (0.23-0.84)

Conclusion: Significant advantage of baclofen over placebo for LD, but not for HD.

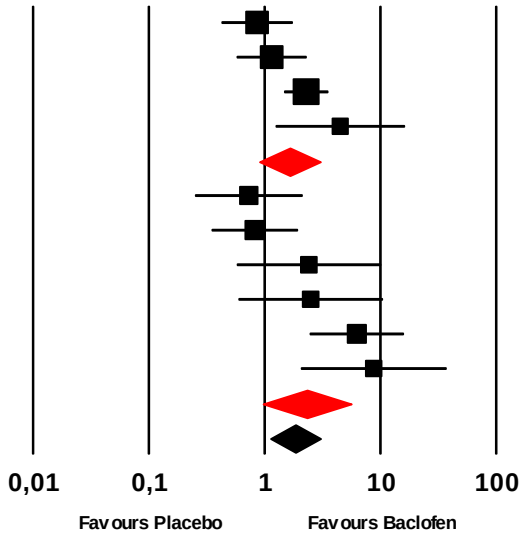
Results: HD vs. LD

Subgroup Analysis (PAE): Baclofen Dose

Group by Dose		Odds ratio	Lower limit	Upper limit	p-Value
High	Beraha et al. (2016, 150)	0,862	0,419	1,772	0,686
High	Reynaud et al. (2017, 180)	1,151	0,568	2,335	0,696
High	Jaury et al. (unpublished, 300)	2,285	1,458	3,579	0,000
High	Muller et al. (2015, 270)	4,500	1,231	16,452	0,023
High		1,632	0,890	2,991	0,113
Low	Hauser et al. (2017, 30)	0,731	0,248	2,153	0,569
Low	Beraha et al. (2016, 30)	0,822	0,344	1,963	0,659
Low	Morley et al. (unpublished, 30)	2,414	0,569	10,245	0,232
Low	Morley et al. (unpublished, 75)	2,500	0,588	10,628	0,215
Low	Addolorato et al. (2007, 30)	6,250	2,425	16,108	0,000
Low	Addolorato et al. (2002, 30)	8,750	2,032	37,671	0,004
Low		2,294	0,955	5,512	0,063
Overall		1,822	1,106	2,999	0,018

Statistics for each study

Odds ratio and 95% CI



Meta Analysis with random effects model

High dose group

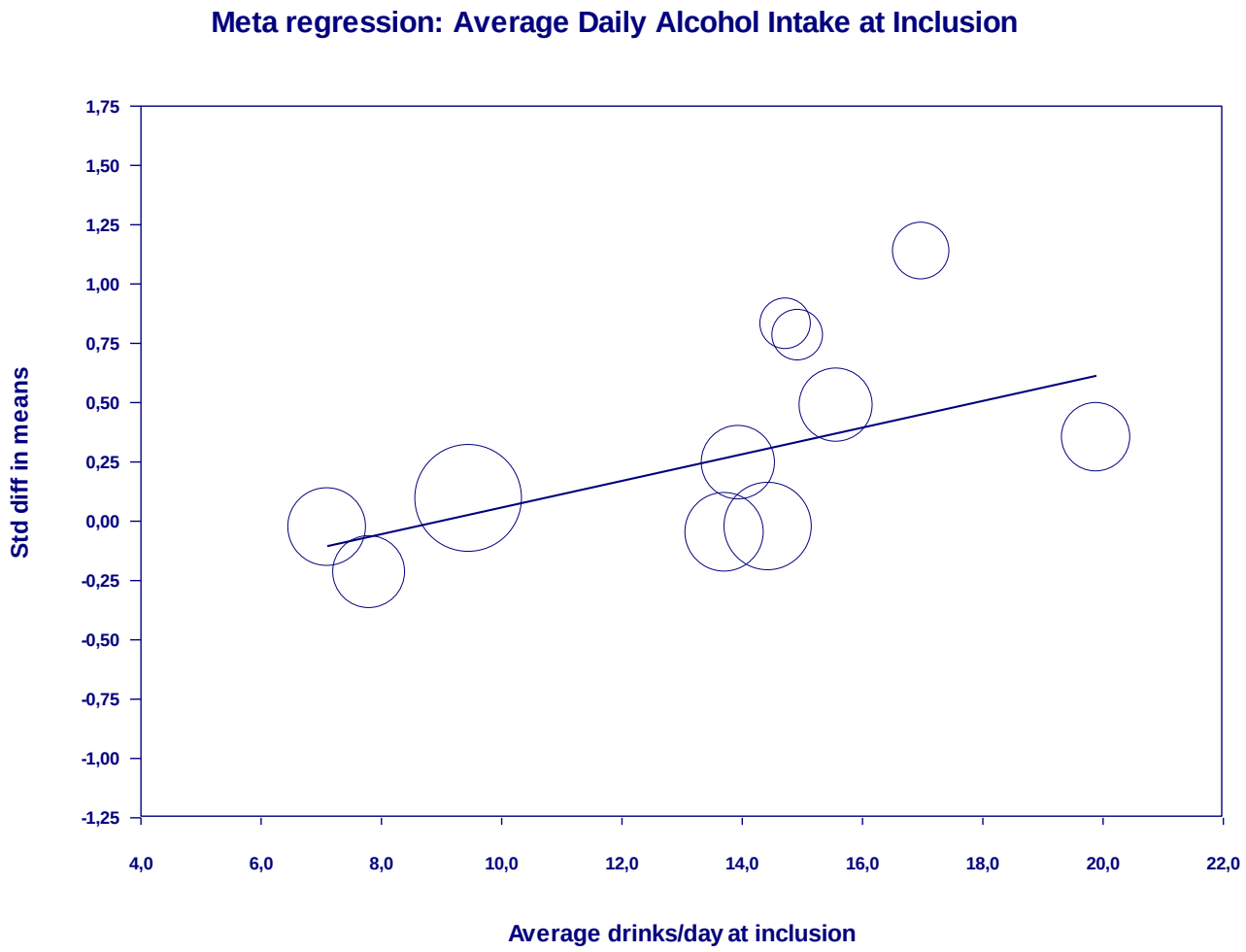
OR = 1.63 (0.89-2.99)

Low dose group

OR = 2.29 (0.95-5.51)

Conclusion: No significant advantage of baclofen over placebo in either dose group.

Results:



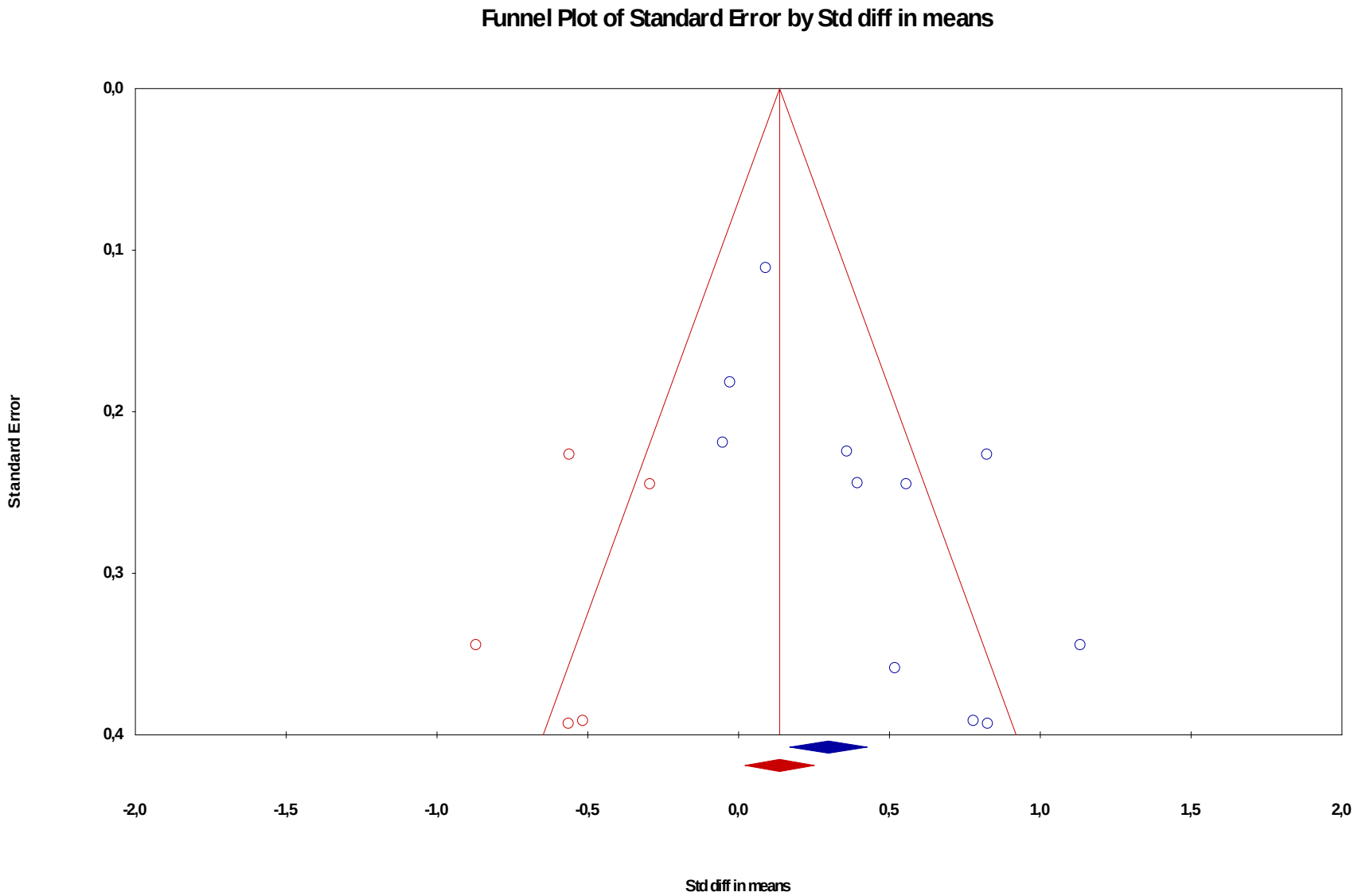
Z = 2.34

2-sided P value = 0.02

R^2 = 0.46

Conclusion: higher daily aclohol intake associated with a greater baclofen effect

Publication bias: TTL



Duval and Tweedie's Adjusted SMD
0.22 (-0.02-0.46)

Safety & Tolerability of baclofen

- 9/13 studies no SAE's reported
- Patients with **liver cirrhosis** (Addolorato et al. 2007): no hepatic or renal side effects, good tolerability
- Veterans with **chronic hep C** (Hauser et al. 2014): well tolerated, no SAE's or deaths

Tolerability of HD baclofen

Study	% patients reaching max dose	Intended max dose (mg/day)	Actual mean max dose (mg/day)
Beraha et al.	15.5%	150	93.6
Jaury et al.*	-	300	150
Morley et al.*	96%	75	44.8
Muller et al.	35.7%	270	180
Reynaud et al.	65.6%	180	153.5

* Unpublished studies

Summary of evidence

- 13 studies, 7 LD, 4 HD, 2 HD & LD
- Overall small positive significant effect of baclofen on 2/3 outcomes
- Heterogenity: dose, alcohol use before inclusion
- No evidence for the advantage of HD over LD baclofen
- Acceptability of HD baclofen problematic and tolerability limited
  - Feasability?

Conclusion

- Baclofen may have a beneficial effect on abstinence related outcomes in alcohol dependent patients
  - But not HD (low tolerability and feasibility)
  - For specific patient groups -> personalized medicine
    - Patients with severe alcohol dependence

Thank you for listening

and thank you to several first authors of the papers included in this review for providing extra data, specifically: Addolorato Giovanni, Alexander Pozinovksy, Christian Muller, Evgeny Krupitsky and James Garbutt

Results: spread of studies

Trial	Dose (mg/day)	Average Daily Alcohol Intake Before Inclusion (drinks/day)
Garbutt et al. 2010	30	7,1
Ponizovsky et al. 2015	50	7,8
Reynaud et al. 2017	180	9,46
Hauser et al. 2017	30	10,4
Behara et al. 2016	30	13,71
Morley et al.2017	75	13,94
Behara et al. 2016	150	14,44
Morley et al. 2014	60	14,73
Morley et al. 2014	30	14,93
Morley et al.2017	30	15,57
Addolorato et al. 2002	30	16,98
Müller et al. 2015	270	19,89

LD

HD

Risk of Bias

	Addolorato et al.	Addolorato et al.	Beraha et al.	Garbutt et al.	Hauser et al.	Jaury et al.	Krupitsky et al.	Leggio et al.	Morley et al.	Morley et al.	Müller et al.	Ponizovsky et al.	Reynaud et al.
Random sequence generation (selection bias)	L	L	L	L	L	?	L	L	L	L	L	L	L
Allocation concealment (selection bias)	?	L	L	?	L	?	L	?	?	L	L	?	L
Blinding of participants and personnel (performance bias)	L	L	L	L	L	L	L	L	L	L	L	L	L
Blinding of outcome assessment (detection bias)	L	L	L	L	L	L	L	L	L	L	L	L	L
Incomplete outcome data (attrition bias)	M	M	M	L	?	L	L	L	M	M	M	M	L
Selective reporting (reporting bias)	L	L	L	L	L	?	?	?	L	?	L	L	L
Other sources of bias	L	L	L	L	L	L	L	L	L	?	L	L	L