New Developments in Tx of alcohol dependence: Baclofen and sodium oxybate

Wim van den Brink, MD PhD
Amsterdam University Medical Centers, location AMC
Amsterdam, The Netherlands

Colloque International “Addictions, Toxicomanies, Hepatites, SIDA” (ATHS)
Biarritz, 2 October 2019

Disclosure

Interest	Name of organization
Grants	Alkermes
Honoraria	Lundbeck, Merck Serono, Eli Lilly, Indivior, Pfizer, Angelini
Advisory Board/Consultant	Lundbeck, Merck Serono, Indivior, Mundipharma, D&A Pharma, Bioproject, Novartis, Kinnov Therapeutics, Opiant Pharmaceuticals, Takeda

Content

- Addiction: a treatable brain disease
- Pharmacological Treatments of Alcohol Dependence
- Substitution Treatment
- Baclofen, Sodium Oxybate, and C_2H_5OH
- Conclusions and recommendations

Addiction a Treatable Brain Disease

History of the concept of alcoholism

1. Moral model

2. Pharmacological model

3. Symptomatic model

4. Disease model

5. Learning model

6. Social model

7. Brain disease model

Empirical

Ideological

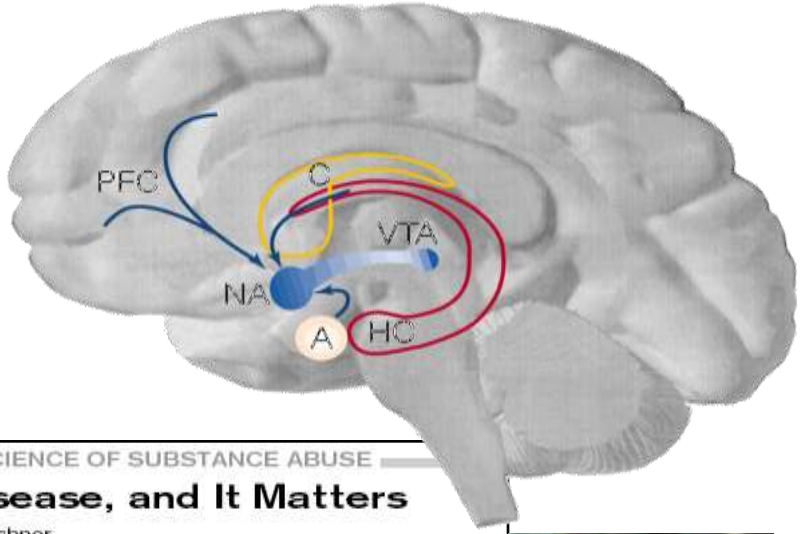
1976: Edwards & Gross

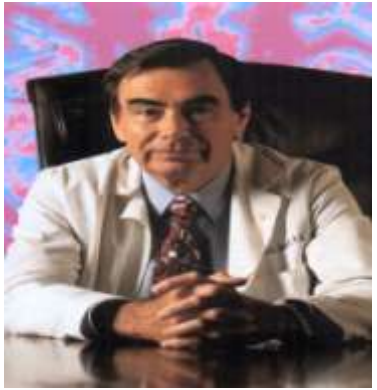
Biopsychosocial Model

Alcohol dependence syndrome

Addiction is (also) a treatable brain disease

Nora Volkow





Charles O'Brien

FRONTIERS IN NEUROSCIENCE: THE SCIENCE OF SUBSTANCE ABUSE

Addiction Is a Brain Disease, and It Matters

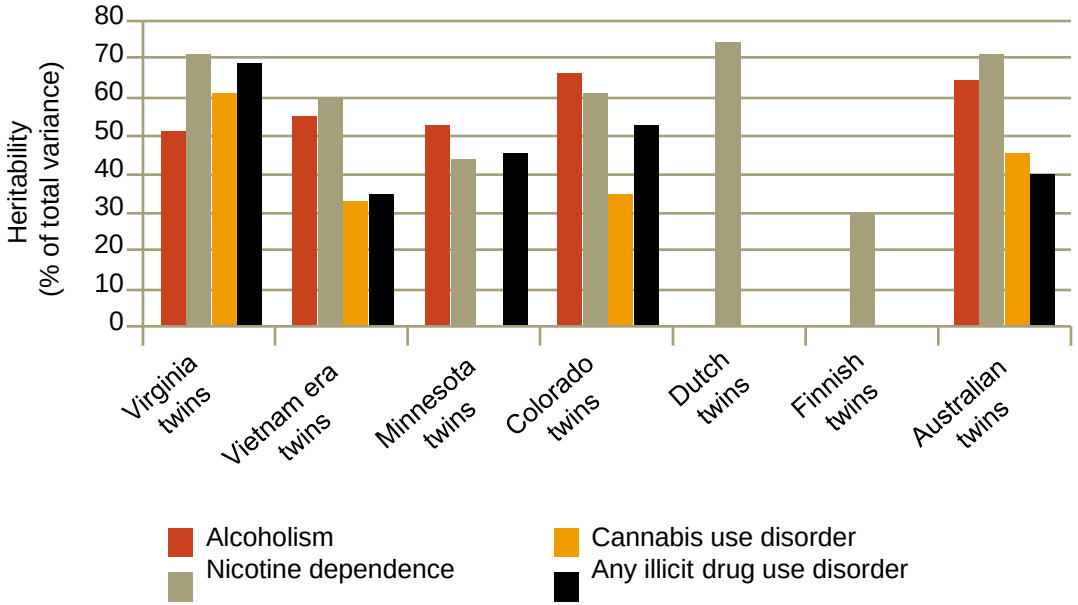
Alan I. Leshner

Scientific advances over the past 20 years have shown that drug addiction is a chronic, relapsing disease that results from the prolonged effects of drugs on the brain. As with many other brain diseases, addiction has embedded behavioral and social-context aspects that are important parts of the disorder itself. Therefore, the most effective treatment approaches will include biological, behavioral, and social-context components. Recognizing addiction as a chronic, relapsing brain disorder characterized by compulsive drug seeking and use can impact society's overall health and social policy strategies and help diminish the health and social costs associated with drug abuse and addiction.

affects both the health of the individual and the health of the public. The use of drugs has well-known and severe negative consequences for health, both mental and physical. But drug abuse and addiction also have tremendous implications for the health of the public, because drug use, directly or indirectly, is now a major vector for the transmission of many serious infectious diseases—particularly acquired immunodeficiency syndrome (AIDS), hepatitis, and tu-

Heritability estimates

Heritability estimates for alcohol dependence, nicotine dependence, cannabis and other illicit drug use disorders across samples of twins



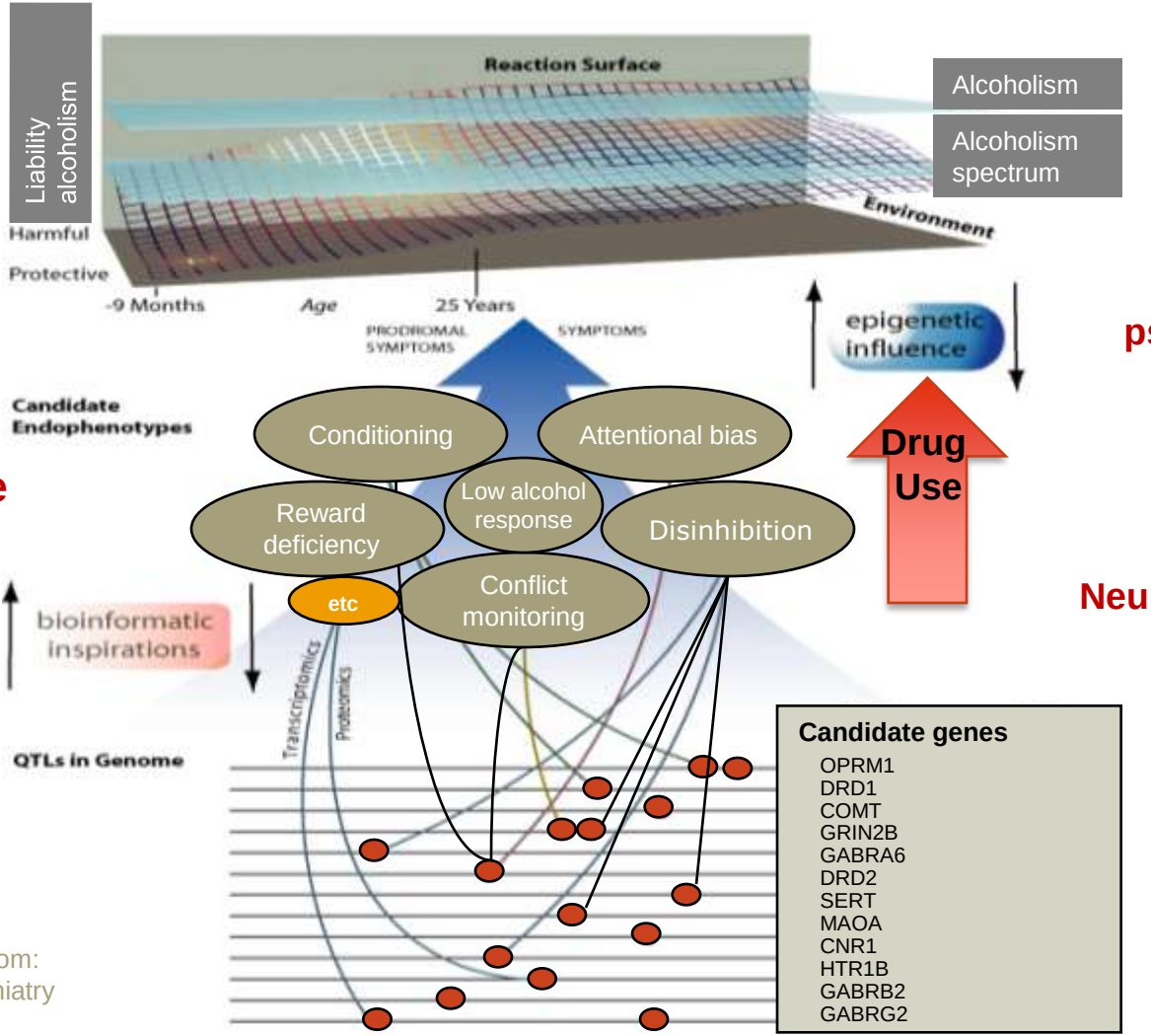
Type of dependence	Heritability
Alcohol	50–70%
Nicotine	50–75%
Cannabis	35–75%
Cocaine	35–80%
Heroin	40–60%

Agrawal & Lynskey. Addiction 2008;103(7):1069–1081

Phenotype

Endophenotype

Genotype



Social support

Insight-oriented psychotherapy

CBT

Medication Neuromodulation

Pharmaco-genetics

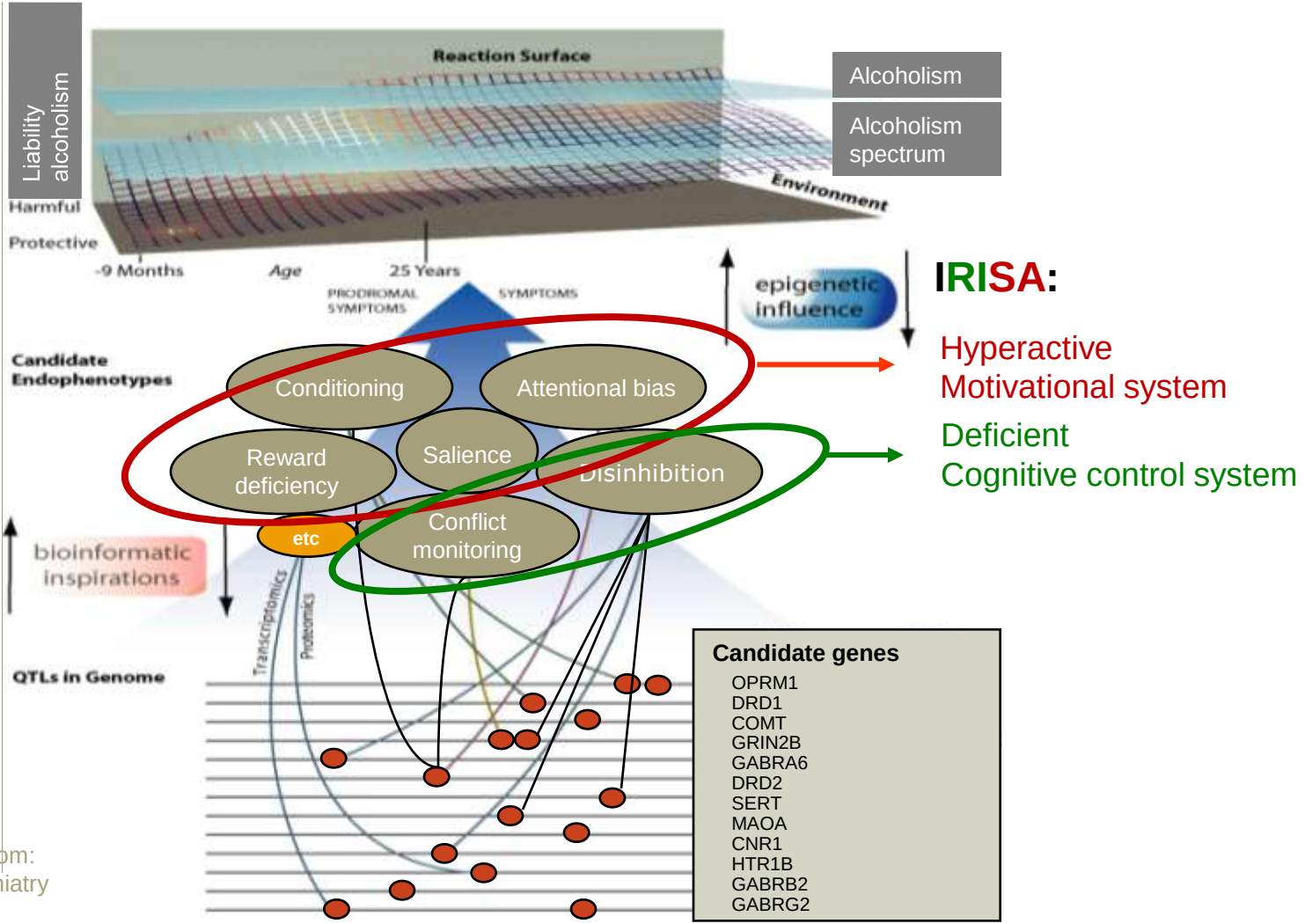
Gene therapy

Ooteman et al (2006) adapted from: Gottesman & Gould. Am J Psychiatry 2003;160:636–645

Fenotype

Endofenotype

Genotype



Ooteman et al (2006) adapted from:
Gottesman & Gould. Am J Psychiatry 2003;160:636–645

Reward → attentional bias → cue-reactivity → craving - deficient cognitive control - → relapse

Repeated reward

Attentional bias → Cue-reactivity → Craving → **Relapse**

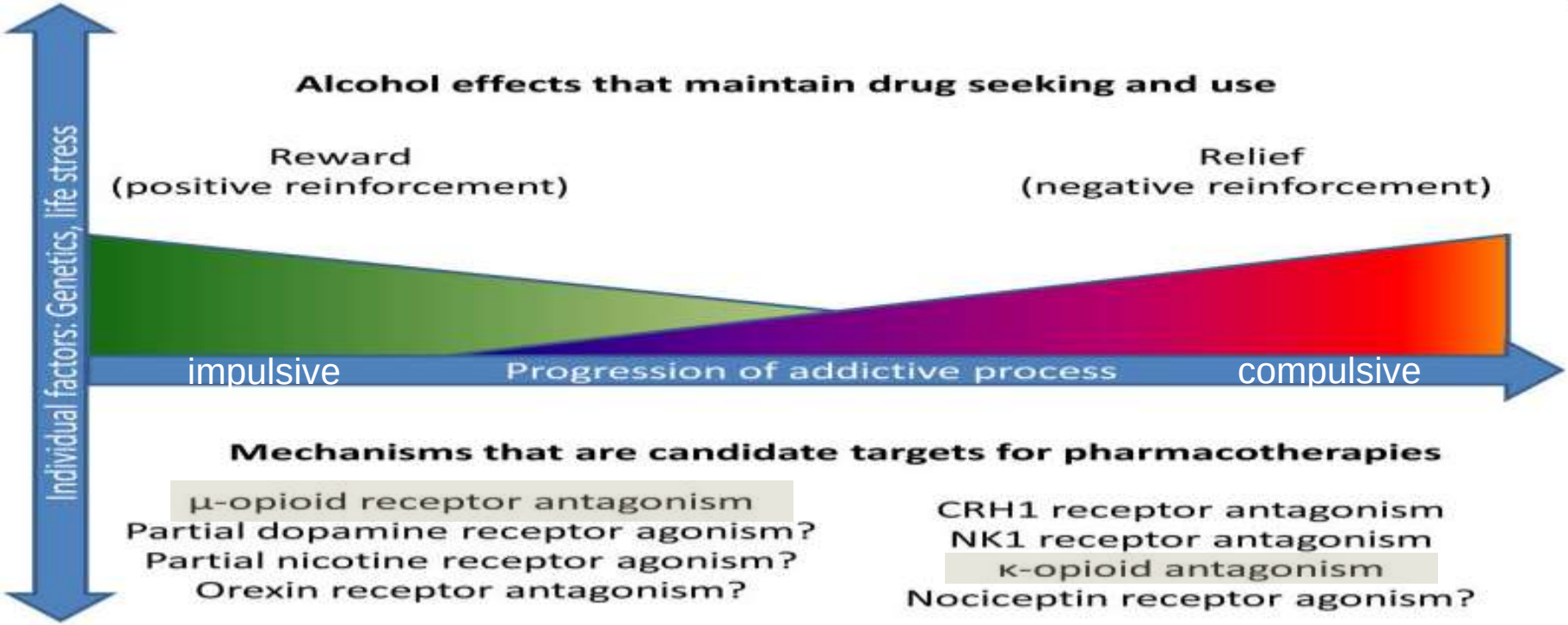
Detection threshold

Inhibition

Conflict registration

Drug-related stimulus

From reward to relief and from impulsive to compulsive



Adapted from Heilig et al., 2010

Reward → attentional bias → cue-reactivity → craving - deficient cognitive control - → relapse

Repeated reward

Attentional bias → Cue-reactivity → Craving → **Relapse**

Detection threshold

Inhibition

Conflict registration

Drug-related stimulus

STRESS

WITHDRAWAL

Conceptual Treatment Models
Pharmacological Tx

Model for Pharmacotherapy of Addiction

Repeated reward

Antagonist

Attentional bias → Cue-reactivity

Stress

Drug-related stimulus

Anti-stress medication

Detection threshold

Anti-craving medication

Craving

Inhibition

Cognitive enhancer

Agonist

Relapse

Conflict registration

Pharmacotherapy Alcohol Use Disorder

Repeated reward

Antagonist

- **Disulfiram**
- **Naltrexone**
- **Nalmefene**

Attentional bias → Cue-reactivity

Drug-related stimulus

Stress

Anti-stress drug

doxazosine

Detection threshold

Anti-craving drug

- **Acamprosate**
- Topiramate?
- Varenicline?

Craving

Inhibition

Agonist

- HD Baclofen?
- Sodium Oxybate?
- Gabapentin?
- C_2H_5OH (alcohol)

Cognitive enhancer

- Modafinil?
- LSD/Psilocybin??

Relapse

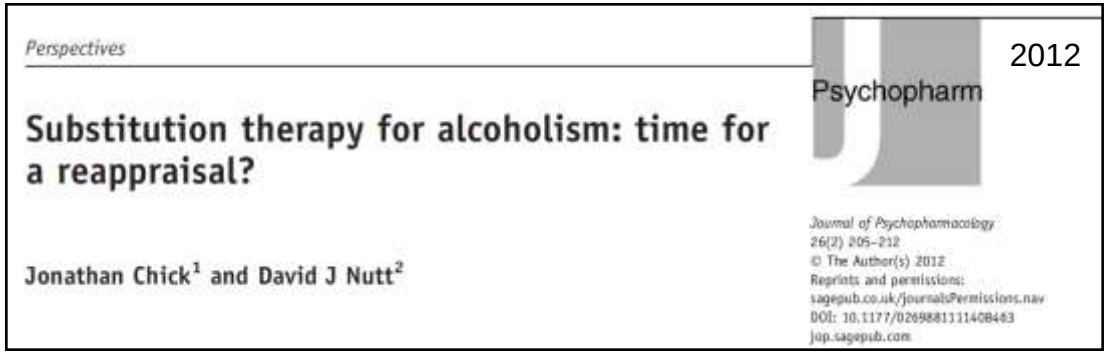
Effective Pharmacotherapy Alcohol Dependence

Treatment Goal	1st Choice	2nd Choice	3rd Choice
Abstinence ↕ Reduced Drinking	**Acamprosate** (NNT=11**)** **Naltrexon??** (NNT=20)	**Disulfiram** (NNT=25; NS)*	Baclofen? Sodium Oxybate?
	Naltrexon# (NNT=11)	Topiramaat?	Gabapentin? Modafinil?? Varenicline? Doxasozine??

* no supervision
# off-label

Substitution Treatment in Alcohol Dependence

Position papers



Perspectives

Substitution therapy for alcoholism: time for a reappraisal?

Jonathan Chick[1] and David J Nutt[2]

Psychopharm

2012

Journal of Psychopharmacology
26(2) 205–212
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sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/0269881111408463
jop.sagepub.com

ADDICTION

SSA SOCIETY FOR THE STUDY OF ADDICTION

FOR DEBATE

doi:10.1111/add.13158

Which medications are suitable for agonist drug maintenance?

Shane Darke & Michael Farrell

National Drug and Alcohol Research Centre, University of New South Wales, Sydney, NSW, Australia

2015

Requirements:

* Agonist (effect)
* Oral use with longer effect
* Low toxicity

Safety measures

* Tx setting: specialist+support
* Combine with psychosocial
* Define outcomes
* No effect on polydrug use

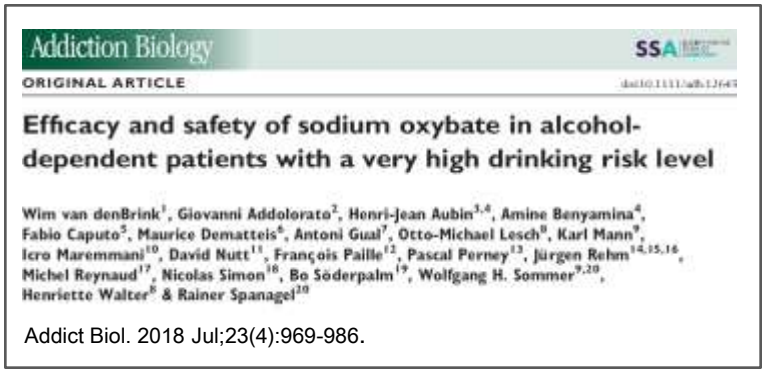
Effective Pharmacotherapy Alcohol Dependence

Treatment Goal	1st Choice	2nd Choice	3rd Choice
Abstinence ↕ Reduced Drinking	**Acamprosate** (NNT=11**)** **Naltrexone??** (NNT=20)	**Disulfiram** (NNT=25; NS)*	**Baclofen?** **Sodium Oxybate?**
	Naltrexone# (NNT=11) **Nalmefene?**	Topiramate?	*Gabapentin?* Modafinil?? Varenicline? Doxasozine??

* no supervision
# off-label

Third choice substitution medications

Recent Consensus Statements



Addiction Biology

SSA

ORIGINAL ARTICLE

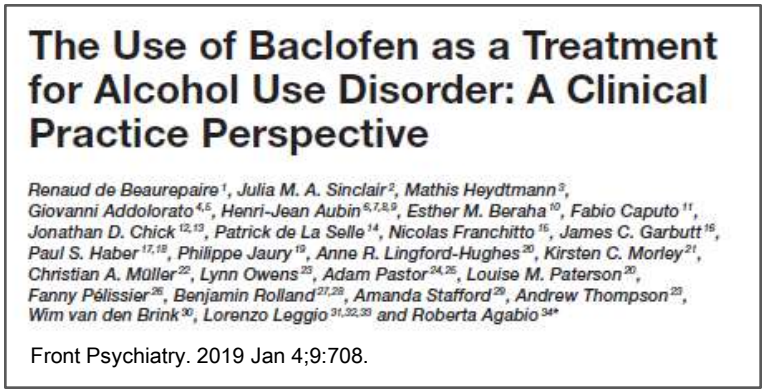
Efficacy and safety of sodium oxybate in alcohol-dependent patients with a very high drinking risk level

Wim van denBrink[1], Giovanni Addolorato[2], Henri-Jean Aubin[3,4], Amine Benyamina[4], Fabio Caputo[5], Maurice Dematteis[6], Antoni Gual[7], Otto-Michael Lesch[8], Karl Mann[9], Icro Maremmani[10], David Nutt[11], François Paille[12], Pascal Perney[13], Jürgen Rehm[14,15,16], Michel Reynaud[17], Nicolas Simon[18], Bo Söderpalm[19], Wolfgang H. Sommer[9,20], Henriette Walter[8] & Rainer Spanagel[20]

Addict Biol. 2018 Jul;23(4):969-986.

Sodium oxybate (GHB)

Baclofen (LD/HD)



The Use of Baclofen as a Treatment for Alcohol Use Disorder: A Clinical Practice Perspective

Renaud de Beaurepaire[1], Julia M. A. Sinclair[2], Mathis Heydtmann[3], Giovanni Addolorato[4,5], Henri-Jean Aubin[6,7,8,9], Esther M. Beraha[10], Fabio Caputo[11], Jonathan D. Chick[12,13], Patrick de La Selle[14], Nicolas Franchitto[15], James C. Garbutt[16], Paul S. Haber[17,18], Philippe Jaury[19], Anne R. Lingford-Hughes[20], Kirsten C. Morley[21], Christian A. Müller[22], Lynn Owens[23], Adam Pastor[24,25], Louise M. Paterson[20], Fanny Pélissier[26], Benjamin Rolland[27,28], Amanda Stafford[29], Andrew Thompson[23], Wim van den Brink[30], Lorenzo Leggio[31,32,33] and Roberta Agabio[34]

Front Psychiatry. 2019 Jan 4;9:708.

Baclofen for the treatment of alcohol use disorder: the Cagliari Statement

**Roberta Agabio, Julia MA Sinclair, Giovanni Addolorato, Henri-Jean Aubin, Esther M Beraha, Fabio Caputo, Jonathan D Chick, Patrick de La Selle, Nicolas Franchitto, James C Garbutt, Paul S Haber, Mathis Heydtman, Philippe Jaury, Anne R Lingford-Hughes, Kirsten C Morley, Christian A Müller, Lynn Owens, Adam Pastor, Louise M Paterson, Fanny Pélissier, Benjamin Rolland, Amanda Stafford, Andrew Thompson, Wim van den Brink, Renaud de Beaurepaire, Lorenzo Leggio*

Lancet Psychiatry. 2018 Dec;5(12):957-960.

A meta-analysis of the efficacy of gabapentin for treating alcohol use disorder

ADDICTION

2019

Henry R. Kranzler[1,2], Richard Feinn[3], Paige Morris[1] & Emily E. Hartwell[1,2]

Table 2 Meta-analysis results.

Outcome	*Number of studies*	*Number of subjects*	*Effect[a] size*	*95% CI*	*P-value*
Complete abstinence	6	673	1.33	0.84–2.10	0.23
Relapse to heavy drinking	6	673	0.80	0.57–1.13	0.21
Percentage of days abstinent	4	476	0.26	−0.16 – 0.69	0.23
Percentage of heavy drinking days	7	730	−0.64	−1.22 – −0.06	0.03
Drinks/day	5	652	−0.15	−0.64 – 0.35	0.56
GGT concentration	4	352	−0.12	−0.37 – 0.13	0.39

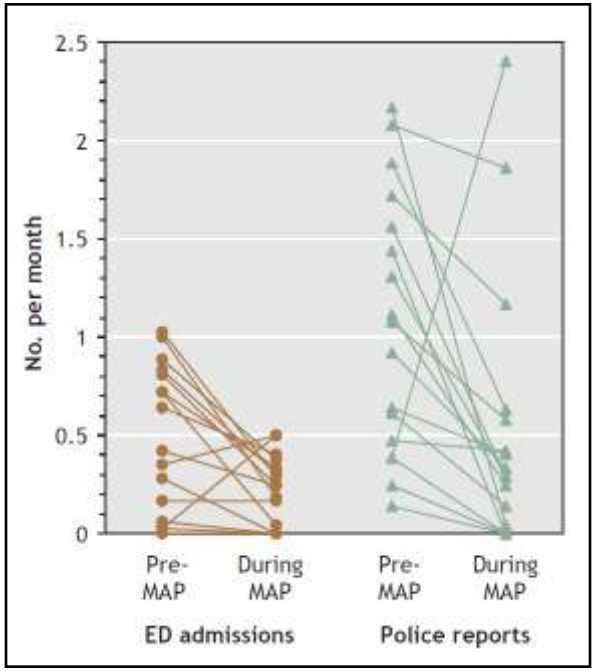
Gabapentin probably only effective in reducing the % of heavy drinking days
→ Can gabapentin really be regarded to be a substitution treatment?

Shelter-based managed alcohol administration to chronically homeless people addicted to alcohol

CMAJ

Tiina Podymow, Jeff Turnbull, Doug Coyle, Elizabeth Yetisir, George Wells

CMAJ · JANUARY 3, 2006 · 174(1)



Lower total alcohol intake

Fewer emergency room admissions

Fewer police reports

6 MAPs → Idem + improved functioning

Does managing the consumption of people with severe alcohol dependence reduce harm? A comparison of participants in six Canadian managed alcohol programs with locally recruited controls

TIM STOCKWELL[1,2], BERNIE PAULY[1,3], CLIFTON CHOW[1], REBEKAH A. ERICKSON[1,2], BONNIE KRYSOWATY[1], AUDRA ROEMER[1,2], KATE VALLANCE[1], ASHLEY WETTLAUFER[1] & JINHUI ZHAO[1]

Drug and Alcohol REVIEW

Drug and Alcohol Review (2017)

Baclofen

Baclofen Efficacy

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frontiers in Psychiatry

January 2019 | Volume 9 | Article 708

After promising preclinical evidence [for review see Colombo and Gessa (1)], clinical studies started to investigate whether baclofen may be useful in the treatment of alcohol use disorder (AUD). However, to date, clinical studies have yielded conflicting results. Despite the lack of consistent evidence, baclofen is often used off-label in clinical practice to treat AUD, especially in some European countries and Australia (2). In this manuscript, a large group of researchers and clinicians combine their expertise in this area to provide (a) a review of the current research evidence and clinical experience of using baclofen in the treatment of AUD, (b) a description of the two different approaches used to administer baclofen in clinical practice settings ("fixed doses" or "flexible doses") to treat AUD, and (c) a brief overview of the clinical use of baclofen to treat AUD.

* Clinical studies show conflicting results
* Baclofen is often used off-label for AD

→

Review by researchers and clinicians

(a) Evidence efficacy from all studies

(b) Description two treatment strategies

(c) Clinical use today

TABLE 1 | Randomized double-blind placebo-controlled trials.

15 baclofen RCTs

References	Daily dose of baclofen; Number of participants	Mean of drinks per drinking days	Weeks of duration	Significant difference between baclofen and placebo	Effects of baclofen compared to placebo
Addolorato et al. (33)	BAC (30 mg): 20 PLA: 19	BAC (30 mg): 18.0[a] PLA: 10.0	4	Yes	BAC (30 mg): ↓ 100.0% DD PLA: ↓ 60.0% DD
Garbutt et al. (34)	BAC (30 mg): 40 PLA: 40	BAC (30 mg): 7.3[b] PLA: 6.9	12	No	BAC (30 mg): 51.7% abstinent days PLA: 51.6% abstinent days
Addolorato et al. (35)	BAC (30 mg): 42 PLA: 42	BAC (30 mg): N.A. PLA: N.A.	12	Yes	BAC (30 mg): 71.4% abstinent patients PLA: 28.6% abstinent patients
Hauser et al. (36)	BAC (30 mg): 88 PLA: 92	BAC (30 mg): 7.1[b] PLA: 7.6	12	No	BAC (30 mg): 32.3% abstinent days PLA: 31.1% abstinent days
Ponizovsky et al. (37)	BAC (50 mg): 32 PLA: 32	BAC (50 mg): 7.4[a] PLA: 8.2	12	No	BAC (50 mg): 46.1% abstinent days PLA: 47.5% abstinent days
Krupitsky et al. (38)	BAC (50 mg): 16 PLA: 16	BAC (50 mg): 0.1[a] PLA: 0.3	12	No	BAC (50 mg): 100% abstinent days last week PLA: 100% abstinent days last week
Addolorato et al. (39)	BAC (30 mg): 14 BAC (60 mg): 14 PLA: 14	BAC (30 mg): 13.9[a] BAC (60 mg): 9.6 PLA: 12.0	12	Yes	BAC (30 mg): ↓ 53% DD BAC (60 mg): ↓ 88% DD PLA: N.A.
Morley et al. (40)	BAC (30 mg): 14 BAC (60 mg): 14 PLA: 14	BAC (30 mg): 15.5[c] BAC (60 mg): 15.1 PLA: 14.3	12	No	BAC (30 mg): 5.9 DDD BAC (60 mg): 5.6 DDD PLA: 2.8 DDD BAC (30 mg) induced positive effects among patients with comorbid anxiety
Morley et al. (41)	BAC (30 mg): 36 BAC (75 mg): 35 PLA: 33	BAC (30 mg): 17.0 [c] BAC (75 mg): 13.8 PLA: 14.1	12	Yes	BAC (30 mg): 68.5% abstinent days BAC (75 mg): 64.6% abstinent days PLA: 43.3% abstinent days
Leggio et al. (42)	BAC (80 mg): 15 PLA: 15	BAC (80 mg): N.A. PLA: N.A.	12	Yes	BAC (80 mg): 12.1% abstinent days from alcohol and tobacco PLA: 3.5% abstinent days from alcohol and tobacco
Garbutt et al. unpublished	BAC (30 mg) BAC (90 mg) PLA	-	-	-	-
Beraha et al. (43)	BAC (30 mg): 31 BAC (up to 150 mg): 58 PLA: 62	BAC (30 mg): 11.0 [a] BAC (up to 150 mg): 12.2 PLA: 11.8	16	No	BAC (30 mg): 41.9% abstinent patients BAC (up to 150 mg): 43.1% abstinent patients PLA: 46.8% abstinent patients
Reynaud et al. (44)	BAC (up to 180 mg): 155 PLA: 155	BAC (up to 180 mg): 8.0 [a] PLA: 7.8	26	No	BAC (up to 180 mg): 11.9% abstinent patients PLA: 10.5% abstinent patients
Müller et al. (45)	BAC (up to 270 mg): 28 PLA: 28	BAC (up to 270 mg): 17.2 [a] PLA: 16.0	12	Yes	BAC (up to 270 mg): 68.2% abstinent patients PLA: 23.8% abstinent patients
Jaury et al., unpublished	BAC (up to 300 mg) PLA	-	-	-	-

*1 drink = 12 g of alcohol; [b]1 drink = 14 g of alcohol [c]1 drink = 10 g of alcohol; BAC, baclofen; DD, drinking days; DDD, drinks per drinking days; N.A., not applicable; PLA, Placebo.

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4 meta-analyses

TABLE 2 | Meta-analyses.

	Lesouef et al. (66)	Bschor et al. (67)	Pierce et al. (69)	Rose and Jones (70)
RCTs	2014	2018	2018	2018
Addolorato et al. (33)	X	X	X	X
Addolorato et al. (35)	X	X	X	X
Beraha et al. (43)		X	X	X
Garbutt et al. (34)	X	X	X	X
Garbutt et al. (34)	X	X		
Hauser et al. (36)		X	X	X
Jaury (66)		X	X	
Krupitsky et al. (71)				X
Krupitsky et al. (38)		X	X	X
Leggio et al. (42)		X	X	X
Mishra et al. (72)	X			
Morley et al. (40)		X	X	X
Morley et al. (41)		X	X	
Müller et al. (45)		X	X	X
Ponizovsky et al. (37)		X	X	X
Reynaud et al. (44)		X	X	X
Total number of studies	5	14	13	12
NUMBER OF PARTICIPANTS				
Baclofen	137	799	789	582
Placebo	135	723	713	543
Total participants	272	1,522	1502	1,125

15 baclofen RCTs

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January 2019 | Volume 9 | Article 708

4 meta-analyses

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Krupitsky et al. (38)		X	X	X
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Mishra et al. (72)	X			
Morley et al. (40)		X	X	X
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Reynaud et al. (44)		X	X	X
Total number of studies	5	14	13	12
NUMBER OF PARTICIPANTS				
Baclofen	137	799	789	582
Placebo	135	723	713	543
Total participants	272	1,522	1502	1,125

First meta-analysis (2014)

Thérapie 2014 Septembre-Octobre; 69 (5): 427–435

Efficacy of Baclofen on Abstinence and Craving in Alcohol-dependent Patients: a Meta-analysis of Randomized Controlled Trials

Nicolas Lesouef[1], Florelle Bellet[1], Geneviève Mounier [1] and Marie-Noëlle Beyens[1,2]

Design: Fixed-effect meta-analysis of 5 early (2002-2010) **LD Baclofen RCT**s.

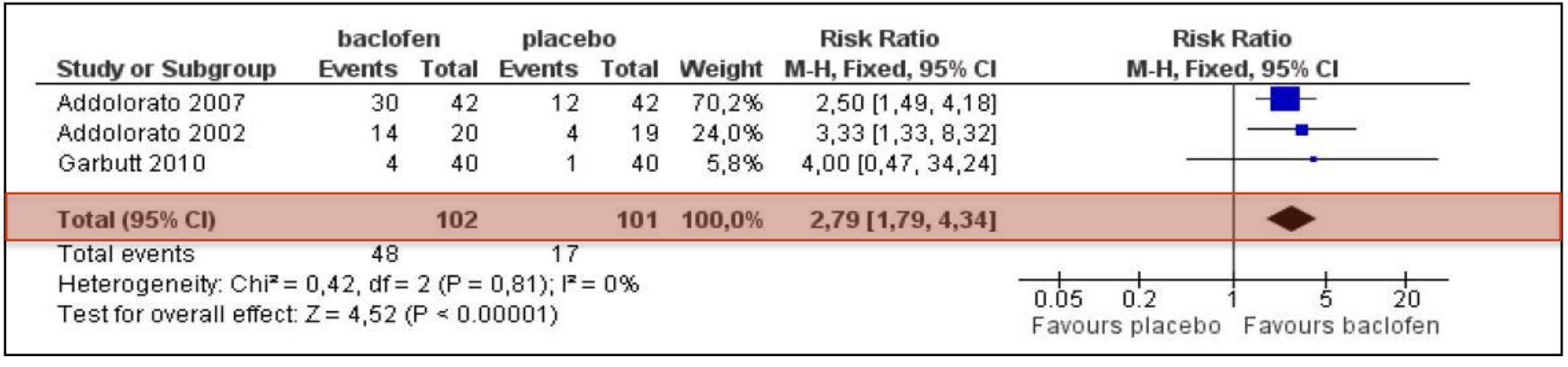
Results: Compared to placebo, baclofen was associated with a significant increase of 179% in percentage of abstinent patients at the end of the trial. For secondary outcome measures, no significant effect of baclofen was observed compared to placebo.

Conclusions. Our meta-analysis brings weak support towards an efficacy of **low dosages** of baclofen on the maintenance of abstinence in alcohol-dependent patients.

Studies and Findings Lasouef et al., 2014

Table I. Characteristics of randomized controlled trials included in the meta-analysis.

Trial	Year	Comparator (mg)	Baclofen dose (mg)	Treatment duration (w)	Follow-up (w)	N treatment	N comparator
Addolorato[18]	2002	Placebo	5 t.i.d D1-D3 10 t.i.d D4-D28	4	0, 1, 2, 3, 4	20	19
Addolorato[19]	2007	Placebo	5 t.i.d D1-D3 10 t.i.d D4-D84	12	0, 1, 2, 3, 4, 6, 8, 10, 12	42	42
Mishra[20]	2010	Acamprosate 666 t.i.d D1-D84	5 t.i.d D1-D3 10 t.i.d D4-D84	12	4, 8, 12	25	24
Garbutt[21] (Bac+Nal)	2010	Placebo	5 t.i.d D1-D3 10 t.i.d D4-D84	12	0, 1, 2, 3, 4, 6, 8, 10, 12	10*	10
Garbutt[22]	2010	Placebo	10 t.i.d	12	0, 1, 2, 3, 4, 6, 8, 10, 12	40	40



Fixed-effect meta-analysis of 3 small LD baclofen studies shows effect on abstinence

15 baclofen RCTs

TABLE 1 | Randomized double-blind placebo-controlled trials.

References	Daily dose of baclofen; Number of participants	Mean of drinks per drinking days	Weeks of duration	Significant difference between baclofen and placebo	Effects of baclofen compared to placebo
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Morley et al. (41)	BAC (30 mg): 36 BAC (75 mg): 35 PLA: 33	BAC (30 mg): 17.0 [c] BAC (75 mg): 13.8 PLA: 14.1	12	Yes	BAC (30 mg): 68.5% abstinent days BAC (75 mg): 64.6% abstinent days PLA: 43.3% abstinent days
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ADDICTION
REVIEW
SSA SOCIETY FOR THE STUDY OF ADDICTION
doi:10.1111/add.14191

Baclofen: its effectiveness in reducing harmful drinking, craving, and negative mood. A meta-analysis

Abigail K. Rose & Andrew Jones

February 2018

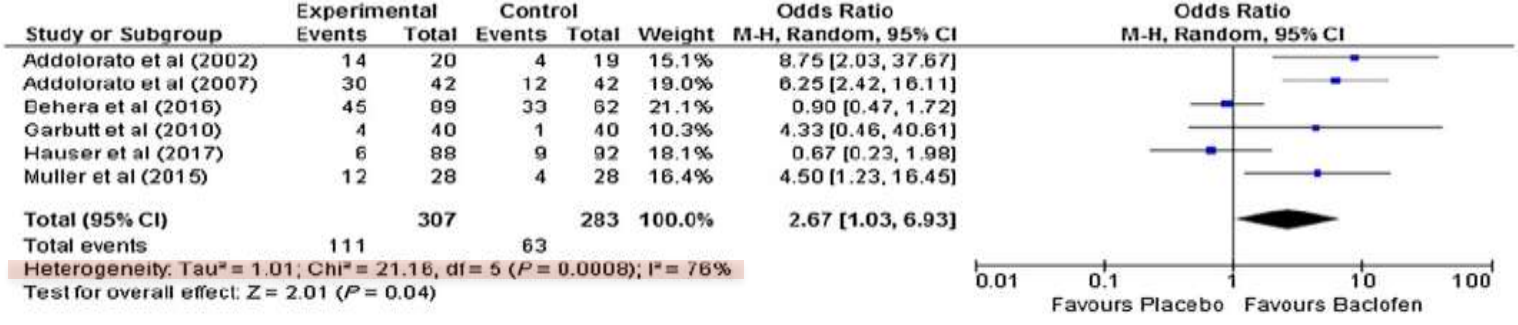

Figure 3 Forest plot of effect sizes comparing baclofen to placebo on abstinence rates following treatment completion [Colour figure can be viewed at wileyonlinelibrary.com]

Random-effects meta-analysis including 12 RCTs
Overall significant effect of baclofen on abstinence rate (n=6: OR=2.67; NNT=8);
No sign. effect on any of the other alcohol outcomes, craving, anxiety, depression
No stratified analysis for HD vs. LD!!

TABLE 1 | Randomized double-blind placebo-controlled trials.

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Efficacy, tolerability, and safety of low-dose and high-dose baclofen in the treatment of alcohol dependence: A systematic review and meta-analysis

Mimi Pierce[a], Arjen Sutterland[b], Esther M. Beraha[c], Kirsten Morley[d], Wim van den Brink[b,*]

2018

- Systematic search RCTs baclofen vs placebo → 13 RCTs
- **Dose** (# studies)
  * LD baclofen (n=7), HD baclofen (n=4); LD en HD baclofen (n=2)
- **Outcomes** (# studies; # patients)
  * TTL = Time To Lapse (n=8; N=852)
  * PDA = Percent abstinence Days (n=7; N=457)
  * PAE = Percent Abstinent at Endpoint (n=8; N=1244)
- **Statistics**
  * Random effect model with evaluation over complete study period
  * Stratification for dose (≤ 60 mg/day vs. > 60 mg/day)
  * Meta-regression for alcohol use at intake

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Mimi Pierce[a], Arjen Sutterland[b], Esther M. Beraha[c], Kirsten Morley[d], Wim van den Brink[b,*]

2018

Table 3 Summary of findings.

Outcome	Relative effect (95% CI)	Approximate OR	No. of participants (studies)
Time to lapse overall	SMD 0.42 (0.19-0.64)	2.14 (1.41-3.19)	852 (8)
Time to lapse LD	SMD 0.57 (0.30-0.84)	2·81 (1.72-4.59)	439 (6)
Time to lapse HD	SMD 0.12 (−0.07 to 0.28)	1.24 (1.14-1.66)	508 (3)
Percentage days abstinent	SMD 0.21 (−0.24 to 0.66)	1·46 (1.55-3.31)	457 (7)
Percentage abstinent at end point overall	OR 1·93(1.17-3·17)		1244 (8)
Percentage abstinent at end point LD	OR 2.29 (0.95-5.51)		424 (5)
Percentage abstinent at end point HD	OR 1.63 (0.89-2.99)		874 (5)

SMD: standardized mean difference, LD: low dose, HD: high dose, OR: odds ratio, 95% CI: 95% confidence interval.

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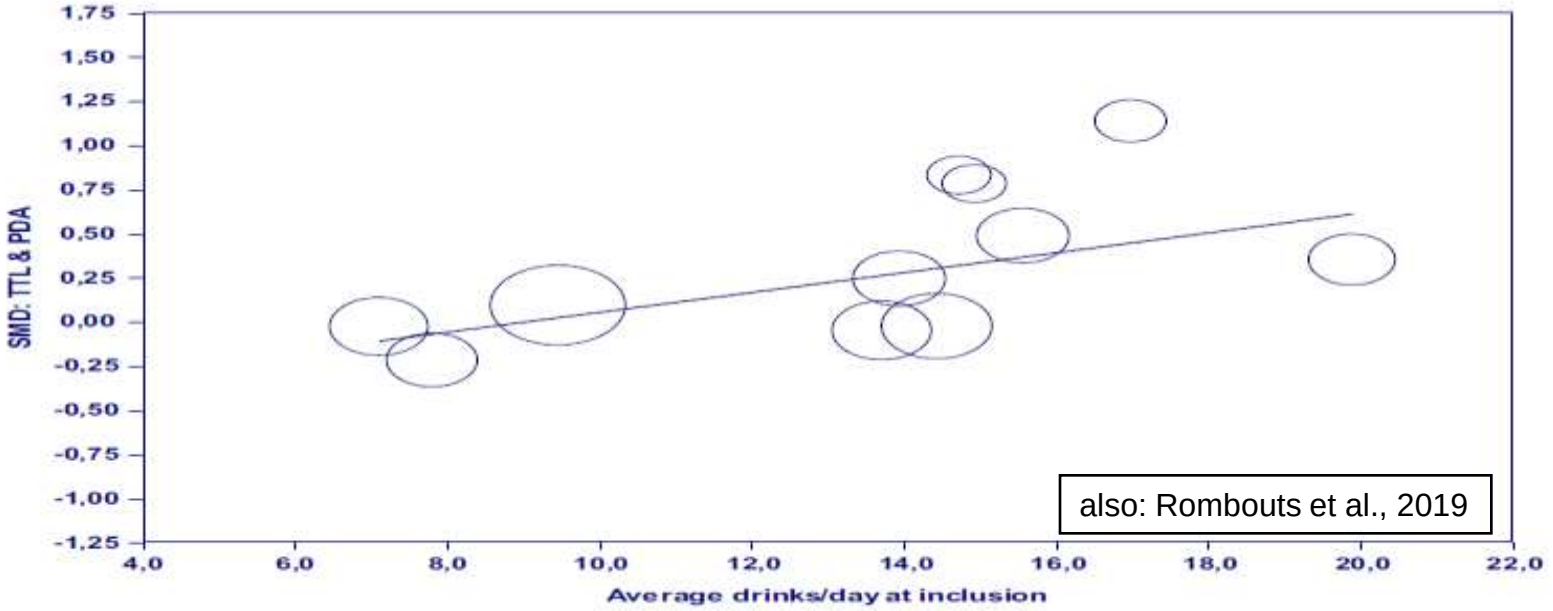


also: Rombouts et al., 2019

Figure 5 Meta-regression: average daily alcohol intake at inclusion (Random-effects).

Baclofen for the Treatment of Alcohol Dependence and Possible Role of Comorbid Anxiety

K.C. Morley[1,*], A. Baillie[2], S. Leung[3], G. Addolorato[4], L. Leggio[5,6,7] and P.S. Haber[1,8]

Alcohol and Alcoholism Vol. 49, No. 6, pp. 654–660, 2014

Table 3. Intention to treat outcomes

	Placebo ($n = 14$)	Baclofen 30 mg/day ($n = 14$)	Baclofen 60 mg/day ($n = 14$)
Primary outcomes			
Days to lapse[+]	3.14 (1.90–4.39)	13.14 (2.79–23.49)	17.64 (3.45–31.84)
Days to relapse[+]	7.07 (2.37–11.77)	23.79 (9.62–37.95)	19.17 (4.91–34.52)
Drinks per drinking day[x]	2.82 (0.01–5.65)	5.86 (2.80–8.92)	5.64 (3.20–8.08)
Heavy drinking days per week[x]	1.36 (0.32–3.04)	2.07 (0.26–3.88)	1.89 (0.43–3.34)
Secondary outcomes:			
STAI State Anxiety[x]	32.44 (22.59–42.29)	33.18 (24.13–42.22)	36.61 (28.24–44.98)
OCDS Obsessive[x,*]	4.66 (2.20–7.12)	4.08 (1.63–6.52)[c]	4.47 (2.53–6.42)
OCDS Compulsive[x]	6.98 (2.70–11.26)	6.93 (2.67–11.19)	8.22 (4.87–11.56)
Stratified for comorbid anxiety[xx]			
Days to lapse[+,**]			
Absence of comorbid anxiety	3.57 (1.31–5.83)	5.29 (0.00–13.36)	15.27 (0.00–30.78)
Presence of comorbid anxiety	2.71 (1.53–3.90)	21.00 (3.12–38.88)[a]	26.33 (0.00–65.70)
Days to relapse[+,**]			
Absence of comorbid anxiety	9.14 (0.00–18.36)	17.14 (0.00–37.63)	15.09 (0.56–29.62)
Presence of comorbid anxiety	5.00 (2.70–7.30)	30.43 (10.68–50.18)[a]	36.67 (0.00–33.10)[b]

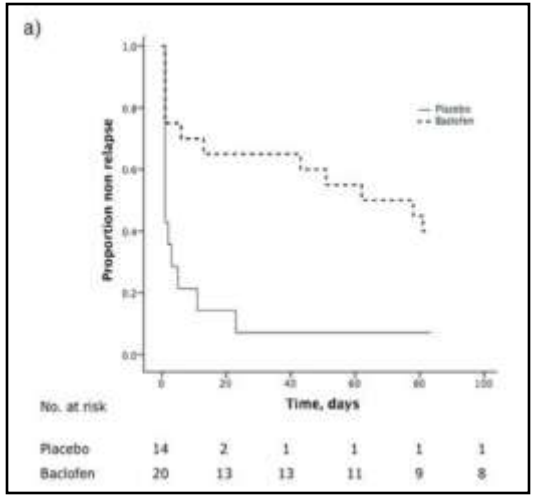
Small study (N=42) with significant effects of baclofen only in the subgroup of patients with a life-time anxiety disorder (also: CC genotype of GABAB1 receptor gene).

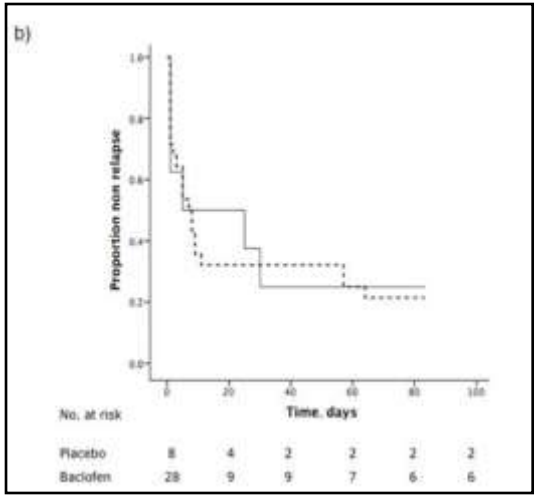
Baclofen and GABA-B receptor subunit 1 gene

Article Title: **Moderation of baclofen response by a GABAB receptor polymorphism: Results from the BacALD study**

Authors: Kirsten C Morley; Natasha Luquin; Andrew Baillie; Isabel Fraser; Ronald J Trent; Glenys Dore; Nghi Phung; Paul S Haber

Addiction. 2018 Dec;113(12):2205-2213





Tx * genotype interaction is significant: p=0.049

a) GABBR1 genotype CC → relapse
HR=0.32 → large effect

b) GABBR1 genotype G- → relapse
HR=1.07 → no effect

Relatively small study showing strong interaction effect with baclofen only being effective in patients with CC genotype of GABAB1 gene (or lifetime anxiety disorder?)

Baclofen Safety

Baclofen and Alcohol-Dependent Patients: A Real Risk of Severe Self-Poisoning

David Boels[1,2], Caroline Victorri-Vigneau[2,3], Marie Grall-Bronnec[2,4], Ali Touré[1], Anais Garnier[1], Alain Turcant[5] and Gaël Le Roux[1]

Basic & Clinical Pharmacology & Toxicology, 2017, **121**, 353–359

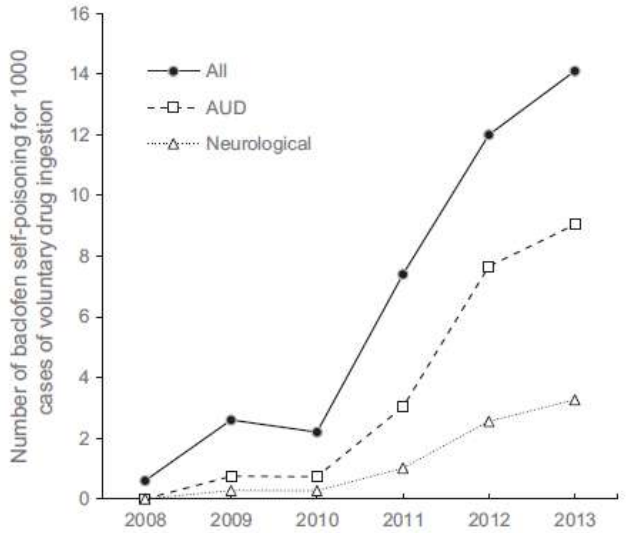


Fig. 1. Number of self-poisonings with baclofen, for 1000 cases of voluntary drug ingestion each year reported to the western France Poison Control Center from 2008 to 2013.

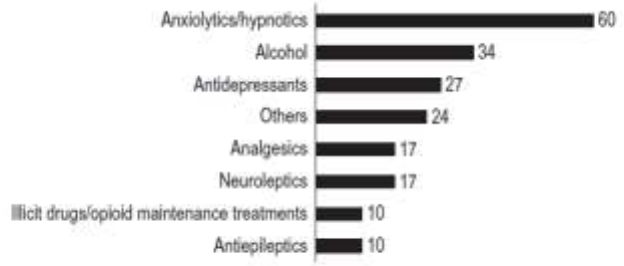


Fig. 2. Co-ingestion of other drugs for all cases of self-poisoning with baclofen (n = 111) reported to western France Poison Control Center from 2008 to March 2014.

Strong increase baclofen poisoning in Western France between 2010 & 2013; often combined with benzo's and **alcohol** and more often in patients with psychiatric comorbidity.
Dose: mean 325 mg (range 10-3100 mg)!!

A Review of Baclofen Overdoses in Australia: Calls to a Poisons Information Centre and a Case Series

Nazila Jamshidi[1,*], Kirsten C. Morley[2], Rose Cairns[3], Andrew Dawson[1,3,4], and Paul S. Haber[1,2,4]

Alcohol Alcohol. 2019 Jan 1;54(1):73-78

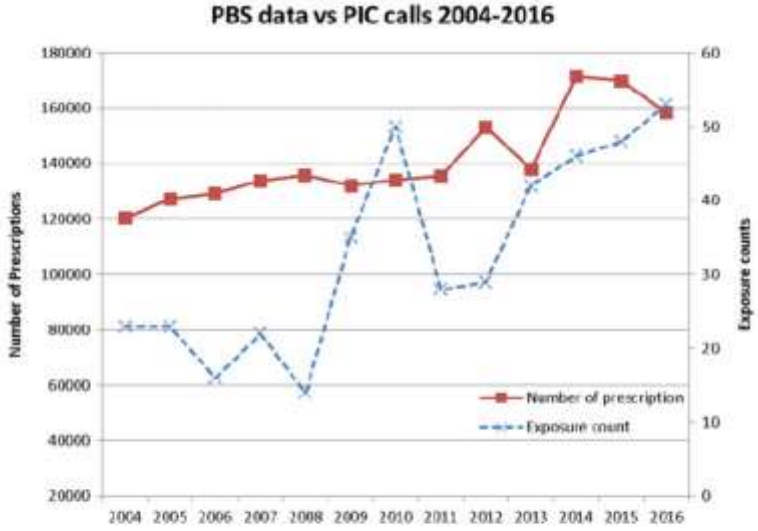


Fig. 1. Exposure to baclofen reported to the New South Wales Poisons Information Centre, 2004–2016 (dashed line, right *y*-axis) compared to pharmaceutical benefit scheme (PBS) baclofen dispensings (red squares, left *y*-axis).

Increasing prescription of baclofen is paralleled by increasing number of self-poisenings

77% needed medical care
35% with GCS<9
19% needed ventilation

53% with 0ne or more coingestants

Baclofen only prescribed by (GP) experts and not for impulsive patients (e.g. BPD)

Baclofen for alcohol dependence: Relationships between baclofen and alcohol dosing and the occurrence of major sedation

Benjamin Rolland[a,b,*], Julien Labreuche[c], Alain Duhamel[c,d], Sylvie Deheul[e], Sophie Gautier[b,f], Marine Auffret[f], Baptiste Pignon[a], Thomas Valin[g], Régis Bordet[b,e,f], Olivier Cottencin[a,h]

European Neuropsychopharmacology (2015) 25, 1631-1636

Table 2 Univariate association between the occurrence of major sedation and the amount of alcohol or the dose of baclofen consumed.

EMS in 20% of all patients

VAS ≥ 7/10

	Number Patient-months	EMS, n (%)	OR (95%CI)	P
AWAC, sd/week				
0	556	5 (0.9)	1.00 (reference)	-
1-35	625	34 (5.4)	5.52 (2.22-13.65)	<0.001
>35	330	31 (9.4)	9.90 (4.28-22.85)	<0.001
		OR per 20 sd/w=	*1.14 (1.04-1.26)*	*0.004*
DDB, mg/dl				
<100	911	24 (2.6)	1.00 (reference)	-
100-200	533	38 (7.1)	2.59 (1.22-5.47)	0.013
>200	69	8 (11.6)	4.14 (1.34-12.75)	0.013
		OR per 20 mg/d=	*1.19 (1.09-1.31)*	*<0.001*

Abbreviations: AWAC= average weekly alcohol consumption (standard-drinks per week= sd/w), CI=confidence interval, DDB= daily dose of baclofen (mg/d), EMS= episode of major sedation, OR= odds ratio.

AWAC en DDB both associated with EMS, but AWAC stronger than DDB

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Interaction of AWAC with DDB on risk of EMS

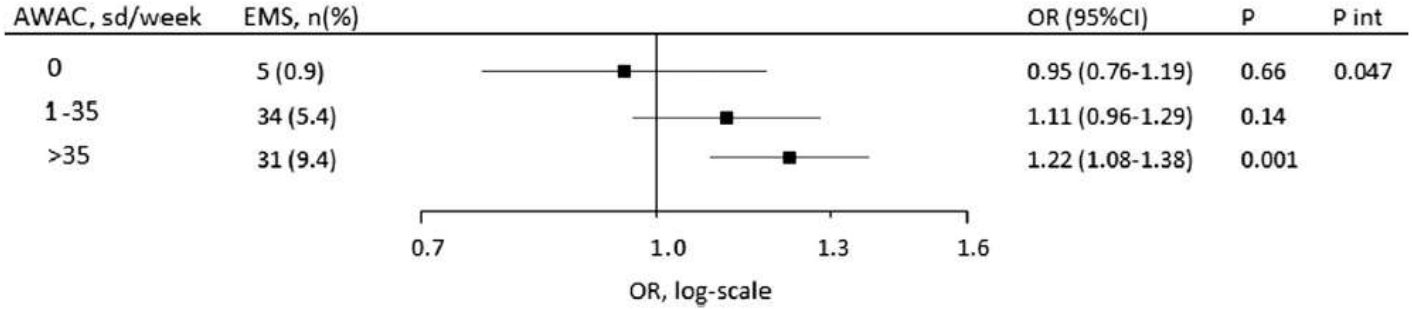

Figure 1 Odds ratio of EMS occurrences per 20 mg/d increases in DDB according to AWAC. Abbreviations: AWAC=average weekly alcohol consumption, CI=confidence interval, EMS=episode of major sedation, OR=odds ratio. *P* int indicates the *p*-value for interaction between alcohol consumption (treated as a continuous) and daily dose of baclofen.

Interaction (p=0.047): AWAC>35 →22% more risk of EMS with each 20mg extra baclofen

Tolerability of High-dose Baclofen in the Treatment of Patients with Alcohol Disorders: A Retrospective Study

Alcohol and Alcoholism, 2015, 50(5) 551–557

Laurent Rigal[1,*], Léa Legay Hoang[1], Constance Alexandre-Dubroeucq[1], Juliette Pinot[1], Claire Le Jeunne[2], and Philippe Jaury[1]

Table 2. Characteristics of adverse effects

	% (*n*)[a]	Baclofen dosage at initiation—mg/day					Persistent %	Consequence for continuation of treatment—% (*n*)			
		m ± sd[b]	≤90	[90–120]	[120–180]	>180		Stopped	Dose increase limited	Symptomatic treatment	None
Somnolence	45 (52)	93 ± 55	58	23	11	8	48	10 (5)	4 (2)	42 (22)[c]	44 (23)
Bouts of somnolence	26 (30)	124 ± 85	47	23	10	20	43	7 (2)	7 (2)	43 (13)[c]	43 (13)
Asthenia	23 (27)	97 ± 63	56	22	15	7	56	15 (4)	3 (1)	41 (11)	41 (11)
Insomnia	20 (23)	117 ± 68	52	17	17	13	52	4 (1)	0 (0)	43 (10)	52 (12)
Vertigo	20 (23)	87 ± 54	65	13	18	4	35	26 (6)	13 (3)	4 (1)	57 (13)
Headaches	13 (15)	102 ± 52	60	13	20	7	33	13 (2)	27 (4)	0 (0)	60 (9)
Memory lapses	12 (14)	116 ± 80	57	0	21	21	64	36 (5)	7 (1)	43 (6)	14 (2)
Concentration disorders	11 (13)	118 ± 82	46	15	15	23	46	23 (3)	8 (1)	54 (7)	15 (2)
Excitation	10 (12)	84 ± 72	58	25	8	8	50	0 (0)	0 (0)	8 (1)	92 (11)
Increased libido	9 (11)	68 ± 45	73	18	9	0	55	0 (0)	0 (0)	0 (0)	100 (11)
Sweating	9 (11)	132 ± 67	18	55	18	9	91	9 (1)	9 (1)	9 (1)	73 (8)
Nausea	9 (11)	73 ± 51	82	0	18	0	55	36 (4)	0 (0)	36 (4)	27 (3)
Dysgeusia	8 (9)	80 ± 58	67	11	22	0	56	0 (0)	0 (0)	0 (0)	100 (9)
Reduced libido	8 (9)	108 ± 33	33	44	22	0	33	0 (0)	0 (0)	11 (1)	89 (8)
Hypomania	7 (8)	80 ± 34	88	0	13	0	63	25 (2)	0 (0)	13 (1)	63 (5)

Frequent AEs in HD baclofen:
somnolence,insomnia, dizziness, headache, memory/concentration

50% persistent!

Tolerability of High-dose Baclofen in the Treatment of Patients with Alcohol Disorders: A Retrospective Study

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Laurent Rigal[1,*], Léa Legay Hoang[1], Constance Alexandre-Dubroeucq[1], Juliette Pinot[1], Claire Le Jeunne[2], and Philippe Jaury[1]

Table 3. Association of patient characteristics with the number of adverse effects and with their consequences for continuation of treatment (stopping baclofen or limiting dose increases)

	N	Number of adverse effects		Stopping baclofen or limiting dose increases	
		m ± sd[a]	*P*	%	*P*
Male (Yes/No)	69/47	2.3 ± 1.7/3.5 ± 2.7	0.02	9/26	0.01
Alcohol dependence (Yes/No)	87/29	2.8 ± 2.9/2.9 ± 2.1	0.9	17/10	0.6
Other addictions					
Smoking (Yes/No)	100/16	2.9 ± 2.7/2.4 ± 2.9	0.6	13/31	0.1
Cannabis (Yes/No)	50/66	2.5 ± 2.4/3.0 ± 2.9	0.3	12/18	0.4
Cocaine (Yes/No)	28/ 88	2.3 ± 1.9/3.0 ± 2.9	0.1	7/18	0.2
Heroin (Yes/No)	22/94	2.0 ± 1.8/3.0 ± 2.8	0.05	9/17	0.5
Psychiatric disorders					
Depression(Yes/No)	71/45	3.2 ± 3.0/2.2 ± 2.1	0.07	18/11	0.3
Psychosis (Yes/No)	8/108	0.9 ± 1.7/2.9 ± 2.7	0.04	12/16	1.0
Anxiety (Yes/No)	100/16	3.0 ± 2.8/1.6 ± 1.9	0.06	18/0	0.07
Bipolar disorders (Yes/No)	12/104	3.0 ± 2.9/2.8 ± 2.7	0.8	17/15	1.0
Borderline personality (Yes/No)	29/87	2.9 ± 2.5/2.8 ± 2.8	0.8	14/16	1.0
Treatment at baseline					
Anxiolytics (Yes/No)	74/42	2.5 ± 2.7/3.3 ± 2.8	0.1	15/17	0.8
Hypnotics (Yes/No)	49/67	2.6 ± 2.6/2.9 ± 2.8	0.6	12 /18	0.4
Antidepressants (Yes/No)	44/72	2.5 ± 2.5/3.3 ± 3.0	0.1	22/11	0.09
Neuroleptics (Yes/No)	14/102	1.5 ± 1.6/3.0 ± 2.8	0.008	14/16	1.0
Mood regulators (Yes/No)	4/112	0.8 ± 1.5/2.9 ± 2.7	0.12	0/16	1.0
Opiate substitutes (Yes/No)	21/95	2.0 ± 1.8/3.0 ± 2.9	0.06	10/17	0.5
Non-psychotropic drugs (Yes/No)	45/71	3.2 ± 2.8/2.5 ± 2.6	0.2	18/14	0.6

More AEs of HD baclofen among women

Fewer AEs of HD baclofen in patients with psychosis/antipsychotic medication

Baclofen Conclusions

Panel: Consensus statement of the Cagliari Expert Consensus Group on the use of baclofen to treat patients with moderate-to-severe alcohol use disorder

General statements on the treatment of patients with alcohol use disorder

1 Each country differs regarding medication regulations, laws, models of care, and reimbursement systems that need to be considered in the prescribing of medications and the provision of treatment.
2 Pharmacotherapy is only one component of the treatment of moderate-to-severe alcohol use disorder. Patient-centred individualised treatment plans should be used. These plans should also include psychotherapy, in-person or web-based treatments, and community and peer support groups.
3 The goal of a pharmacological treatment for patients with alcohol use disorder can be both abstinence and reducing alcohol consumption, ideally below harmful amounts. However, in certain subgroups of patients, the goal should be complete abstinence.[45]

Effectiveness of baclofen in the treatment of patients with alcohol use disorder

4 Baclofen is not licensed as an approved treatment of alcohol use disorder, and its use is therefore off-label.
5 Clinical research evidence is not clear about the most effective setting for baclofen treatment, but patients with alcohol use disorder may be treated in a range of treatment settings by clinicians with appropriate experience and training.
6 The majority of clinical trials started baclofen after detoxification and obtaining abstinence. In clinical practice, some physicians prescribe off-label baclofen while the patient is still drinking. These patients should be warned of the risks of side-effects (eg, excessive sedation) due to the pharmacological interaction of baclofen and alcohol.
7 Baclofen should be considered a second-line pharmacotherapy in patients who have not responded to approved pharmacological treatments for alcohol use disorder. However, the off-label use of baclofen may be considered among first-line pharmacological treatments in patients with contraindication to approved medications (eg, patients with advanced liver disease for whom the use of disulfiram or naltrexone may be contraindicated).
8 The daily baclofen dose should be based on safety, tolerability, and patient's response.
9 The daily dose of baclofen required to achieve abstinence, a substantial reduction in alcohol consumption, or a substantial decrease in craving for alcohol can vary widely between patients, over a ten-fold range.
10 Baclofen should be started at a low dose (5 mg three times per day) and slowly titrated upwards (eg, 5–10 mg per day, every three days) to minimise possible side-effects, including sedation and overdose.
11 There is no evidence on the use of baclofen in combination with other medications for alcohol use disorder (eg, disulfiram, naltrexone, acamprosate, or nalmefene).
12 Baclofen should not be used instead of benzodiazepines in the treatment of alcohol withdrawal syndrome, as there is no evidence of its efficacy in preventing the development of potentially life-threatening complications of alcohol withdrawal syndrome, such as seizures and delirium tremens.

Safety of baclofen in the treatment of patients with alcohol use disorder

13 History of renal impairment needs to be considered before starting baclofen, because the drug is mainly excreted by the kidneys. If prescribed, the management of baclofen in patients with renal impairment requires close supervision because of the higher risk of baclofen toxicity.
14 The most frequent side-effects observed among patients with alcohol use disorder include: sedation, fatigue, drowsiness, tiredness, somnolence, sleep disorders or insomnia, dizziness, headache, dry mouth, paresthesia, fasciculations, nausea, myalgia, and arthralgia. Most side-effects occur at the beginning of baclofen treatment, or if the dose is increased too rapidly.
15 Many side-effects tend to be dose-related, although the contribution of other factors to the onset or severity of side-effects cannot be ruled out.
16 Particular caution is needed for the combination of baclofen with other sedative medications (including alcohol) since there are additive side-effects (eg, sedation, drowsiness, and somnolence).
17 Particular caution is needed among patients with alcohol use disorder and other comorbidities, such as patients with a history of epilepsy, because baclofen can lower the seizure threshold, patients with mood disorders, because baclofen can increase the risk of hypomanic and manic episodes, and patients with suicidal ideation or a history of suicide attempts, because of the risk of intentional overdose.
18 Treatment with baclofen should not be abruptly interrupted to avoid the risk of withdrawal symptoms. The daily dose should be slowly reduced (eg, 5–10 mg per week).

Baclofen for the treatment of alcohol use disorder: the Cagliari Statement

www.thelancet.com/psychiatry **Published online November 6, 2018**

*Roberta Agabio, Julia MA Sinclair, Giovanni Addolorato, Henri-Jean Aubin, Esther M Beraha, Fabio Caputo, Jonathan D Chick, Patrick de La Selle, Nicolas Franchitto, James C Garbutt, Paul S Haber, Mathis Heydtman, Philippe Jaury, Anne R Lingford-Hughes, Kirsten C Morley, Christian A Müller, Lynn Owens, Adam Pastor, Louise M Paterson, Fanny Pélissier, Benjamin Rolland, Amanda Stafford, Andrew Thompson, Wim van den Brink, Renaud de Beaurepaire, Lorenzo Leggio

THE LANCET Psychiatry

* Baclofen not (yet) licensed for Tx alc. dep.
* Most experience with baclofen after detox
* Baclofen is (in principle) 2nd/3rd line treatment
* Dose dependent on effect, tolerability, safety
* Start low (15mg), go slow (5-10mg/3 days)
* No evidence for baclofen during withdrawal
* Most side effects are dose dependent
* Baclofen Tx should not be abruptly stopped

Sodium Oxybate

Sodium Oxybate Efficacy

Efficacy and safety of sodium oxybate in alcohol-dependent patients with a very high drinking risk level

Wim van denBrink[1], Giovanni Addolorato[2], Henri-Jean Aubin[3,4], Amine Benyamina[4], Fabio Caputo[5], Maurice Dematteis[6], Antoni Gual[7], Otto-Michael Lesch[8], Karl Mann[9], Icro Maremmani[10], David Nutt[11], François Paille[12], Pascal Perney[13], Jürgen Rehm[14,15,16], Michel Reynaud[17], Nicolas Simon[18], Bo Söderpalm[19], Wolfgang H. Sommer[9,20], Henriette Walter[8] & Rainer Spanagel[20]

Addict Biol. 2018 Jul;23(4):969-986.

In this article, a European expert group of alcohol researchers and clinicians summarizes data (a) from published trials, (b) from two new—as yet unpublished—large clinical trials (GATE 2 (n = 314) and SMO032 (n = 496), (c) from post hoc subgroup analyses of patients with different WHO-defined DRLs and (d) from multiple meta-analyses. These data provide convergent evidence that sodium oxybate is effective especially in a subgroup of alcohol-dependent patients with VH DRLs. Depending on the study, abstinence rates are increased up to 34 percent compared with placebo with risk ratios up to 6.8 in favor of sodium oxybate treatment. These convergent data are supported by the clinical use of sodium oxybate in Austria and Italy for more than 25 years. Sodium oxybate is the sodium salt of γ-hydroxybutyric acid that is also used as a recreational (street) drug suggestive of abuse potential. However, a pharmacovigilance database of more than 260 000 alcohol-dependent patients treated with sodium oxybate reported very few adverse side effects and only few cases of abuse. We therefore conclude that sodium oxybate is an effective, well-tolerated and safe treatment for withdrawal and relapse prevention treatment, especially in alcohol-dependent patients with VH DRL.

Efficacy and safety of sodium oxybate in alcohol-dependent patients with a very high drinking risk level

Wim van denBrink[1], Giovanni Addolorato[2], Henri-Jean Aubin[3,4], Amine Benyamina[4], Fabio Caputo[5], Maurice Dematteis[6], Antoni Gual[7], Otto-Michael Lesch[8], Karl Mann[9], Icro Maremmani[10], David Nutt[11], François Paille[12], Pascal Perney[13], Jürgen Rehm[14,15,16], Michel Reynaud[17], Nicolas Simon[18], Bo Söderpalm[19], Wolfgang H. Sommer[9,20], Henriette Walter[8] & Rainer Spanagel[20]

2018

Sodium Oxybate Efficacy Pilotstudies (1992-2007)

Table 3 Summary of randomized placebo/naltrexone-controlled trials with a standard dose of 50 mg/kg/day of sodium oxybate in alcohol-dependent patients.

RCTs	*N*	*Comparator*	*Results in primary endpoints Treatment difference*
Gallimberti *et al.* (1992)	82	Placebo	PDA: +17.5% ($P < 0.001$) TAC: −4.6 drinks/day ($P < 0.01$)
Caputo *et al.* (2003)	35	Naltrexone	Abstinence rate: +31.4% ($P = 0.02$)
Caputo *et al.* (2007)	55	Naltrexone	Abstinence rate: +34.1% ($P = 0.04$)
Nava *et al.* (2006)	55	Naltrexone	Abstinence rate: +16.0% ($P = 0.08$)
Di Bello *et al.* (1995)	17	Placebo	Abstinence rate: +16.7% ($P = 0.50$)

Primary endpoints were either percentage of days abstinent (PDA), total alcohol consumption (TAC) or percentage abstinence rates. Treatment duration was 3 months in all studies except Nava *et al.* (12 months) and Di Bello *et al.* (6 months).

Sodium oxybate (Alcover®) more effective than placebo and NTX in reaching abstinence

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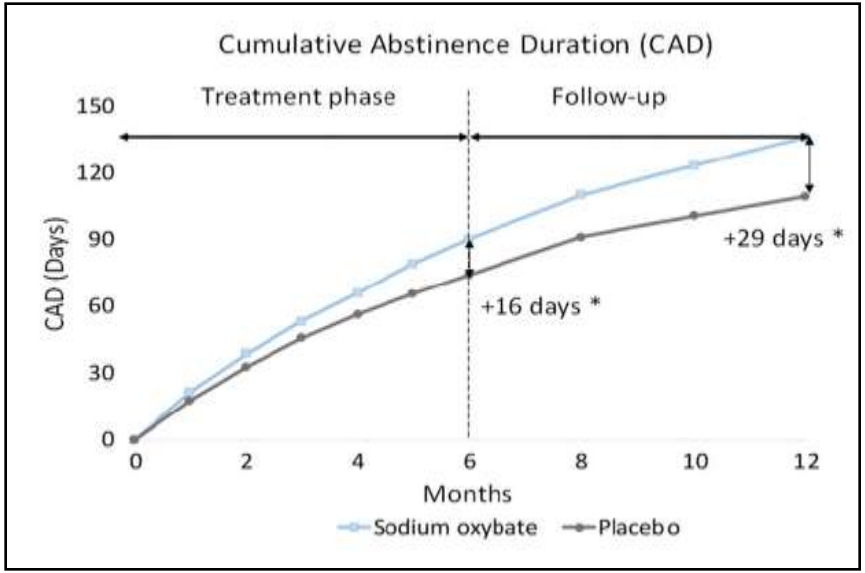
2018

Sodium Oxybate
Efficacy
Phase III trials

GATE 2 Study

RCT, double-blind, placebo-controlled
N=314
Significant longer CAD at month 6 and 12



SMO032

RCT, double-blind, placebo-controlled
N=496
12 weeks treatment + 1 week FU
4 different doses (0.75-2.25 g t.i.d.)
No sign. effect (high placebo response)

Post-hoc analyses (DRL)

Efficacy and safety of sodium oxybate in alcohol-dependent patients with a very high drinking risk level

Wim van denBrink[1], Giovanni Addolorato[2], Henri-Jean Aubin[3,4], Amine Benyamina[4], Fabio Caputo[5], Maurice Dematteis[6], Antoni Gual[7], Otto-Michael Lesch[8], Karl Mann[9], Icro Maremmani[10], David Nutt[11], François Paille[12], Pascal Perney[13], Jürgen Rehm[14,15,16], Michel Reynaud[17], Nicolas Simon[18], Bo Söderpalm[19], Wolfgang H. Sommer[9,20], Henriette Walter[8] & Rainer Spanagel[20]

2018

Sodium Oxybate
Efficacy
Phase III trials: SMO023

Table 4 Treatment difference in SMO032 of four pooled doses of sodium oxybate and of 1.75 g t.i.d. versus placebo in abstinence rate, responder rate (patients with alcohol consumption <40 g/day at month 3), percentage of days abstinent (PDA), adjusted change from baseline (CfB) in heavy drinking days (HDD) and total alcohol consumption (TAC) at month 3 in a subgroup with low/medium DRL and a subgroup with H/VH DRL at baseline.

Treatment difference (results expressed in excess rate/mean difference)	*Low or medium DRL pooled doses, N = 339*	*High or very high DRL pooled doses, N = 154*	*High or very high DRL 1.75 g t.i.d., N = 70*
Abstinence rate (%)	−5.2 ($P = 0.455$)	+18.1 ($P = 0.04$)	+19.9 ($P = 0.060$)
Responder rate (%)	N/A	+22.9 ($P = 0.027$)	+26.5 ($P = 0.029$)
PDA treatment period (%)	−9.93 ($P = 0.026$)	+14.98 ($P = 0.022$)	+16.76 ($P = 0.053$)
PDA at month 3 (%)	−16.14 ($P = 0.007$)	+24.26 ($P = 0.003$)	+25.52 ($P = 0.019$)
CfB in TAC (g/day)	+9.39 ($P = 0.011$)	−21.00 ($P = 0.027$)	−28.75 ($P = 0.018$)
CfB in HDD (HDD/month)	+2.82 ($P = 0.005$)	−5.03 ($P = 0.015$)	−6.89 ($P = 0.017$)

Significant effect (abstinence, HDD, TAC) of Sodium Oxybate in subgroup with H/VH DRL

Sodium Oxybate Safety

Efficacy and safety of sodium oxybate in alcohol-dependent patients with a very high drinking risk level

Wim van denBrink[1], Giovanni Addolorato[2], Henri-Jean Aubin[3,4], Amine Benyamina[4], Fabio Caputo[5], Maurice Dematteis[6], Antoni Gual[7], Otto-Michael Lesch[8], Karl Mann[9], Icro Maremmani[10], David Nutt[11], François Paille[12], Pascal Perney[13], Jürgen Rehm[14,15,16], Michel Reynaud[17], Nicolas Simon[18], Bo Söderpalm[19], Wolfgang H. Sommer[9,20], Henriette Walter[8] & Rainer Spanagel[20]

2018

Sodium Oxybate

Safety

Table 10 Incidence of abuse/misuse, central nervous system depression and dependence to sodium oxybate in alcohol-dependent patients (EMA 2017).

Number of events (incidence)	*Clinical trials, N = 3436*	*Pharmacovigilance database, N = 260 000*
Abuse/misuse	100 (2.91%)	6 (0.002%)
CNS depression	19 (0.55%)	14 (0.005%)
Dependence/withdrawal	4 (0.12%)	2 (0.001%)

CNS depression refers to 'depressed level of consciousness' and 'sedation' cases.

*** Overall the incidence of SAEs and AEs was low.**

* Of the 100 abuse/misuse cases in the clinical trials, 64 were in patients with severe psychiatric comorbidity and or comorbid cocaine/heroin dependence.

* In this specific subgroup, abuse/misuse was 12%! → be careful!

Sodium Oxybate Conclusions

Conclusions

- Indications for efficacy especially in H/VH DRLs
- Extensively used and registered in Austria and Italy
- No indication of serious abuse/misuse or SAEs

Conclusions and Recommendations

Conclusions and recommendations

- Alcohol use disorder (AUD) is (also) a treatable brain disease
- Many pharmacological treatments with limited effect size available
- New alcohol substitution treatments available, including off-label use of baclofen and sodium oxybate as 2nd/3rd line treatments
- Careful dosing (titration/tapering): side-effects/overdose, withdrawal
- Prescription only by (GP) addiction experts in non-comorbid cases?

Thank You

Wim van den Brink: w.vandenbrink@amc.uva.nl