Trattamento farmacologico dell'alcol-dipendenza: nuove prospettive farmacologiche

dott. FABIO CAPUTO

Dirigente Medico di I Livello, U.O. Medicina Interna,
Ospedale SS. Annunziata, Cento (Ferrara)

Consulente presso il Centro per lo Studio ed il Trattamento Multidisciplinare dell'Uso Inadeguato dell'Alcol "G. Fontana", U.O. Semeiotica Medica, Università degli Studi di Bologna

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OBIETTIVI DEL TRATTAMENTO

- ASTINENZA

(Friedmann, N Engl J Med, 2013)

- RIDUZIONE DEL CONSUMO

(Aubin & Daeppen, Drug Alcohol Dep, 2013
van Amsterdam & van Den Brink, J Psychopharmacol, 2013)

Original Article

Reduced-risk drinking as a viable treatment goal in problematic alcohol use and alcohol dependence

Jan van Amsterdam* **and Wim van den Brink[1]**

Psychopharm

Journal of Psychopharmacology
0(0) 1–11

DOI: 10.1177/0269881113495320
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Abstract
This review describes and discusses studies related to reduced-risk drinking as an additional treatment option for patients with problematic alcohol use and alcohol dependence. The review provides some empirical support for the following statements: (a) reduced-risk drinking is a viable option for at least some problem and dependent drinkers; (b) abstinence and non-abstinence-based treatments appear to be equally effective; (c) allowing patients to choose their treatment goal increases the success rate. The relatively short follow-up period (1–2 years) of the studies hampers a proper evaluation of the added value of the reduced-risk drinking approach.

Keywords
Alcohol dependence, reduced-risk drinking, controlled drinking, abstinence, alcohol disorder

Drug and Alcohol Dependence xxx (2013) xxx–xxx

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Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

ELSEVIER

Review

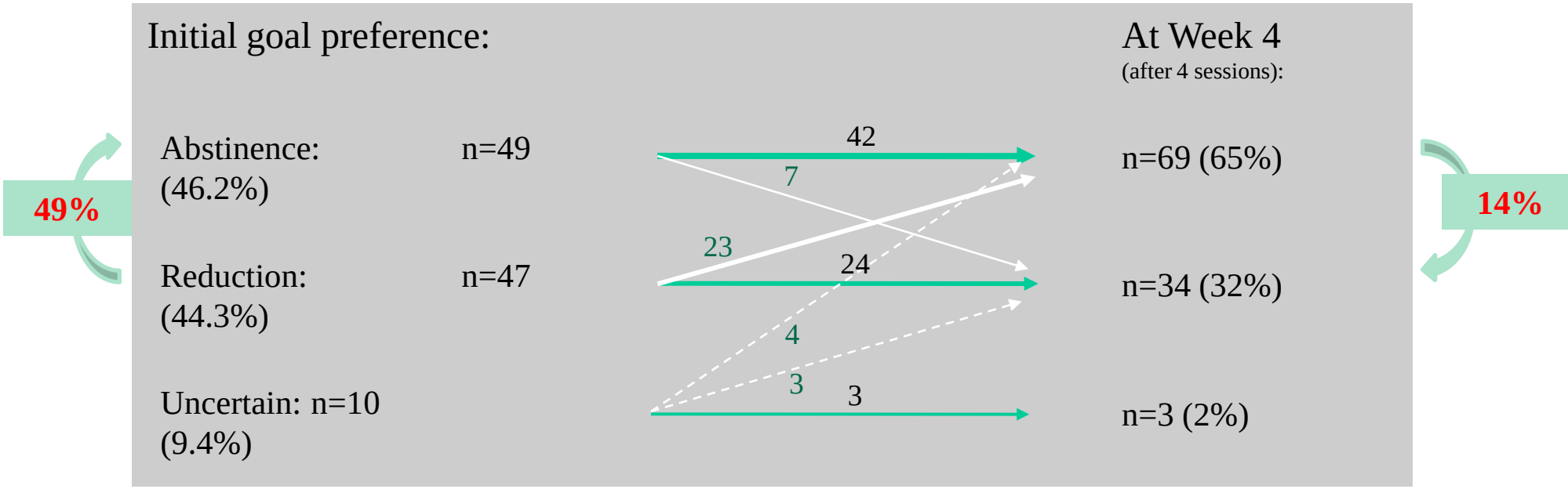
Emerging pharmacotherapies for alcohol dependence: A systematic review focusing on reduction in consumption☆

Henri-Jean Aubin[a,*], Jean-Bernard Daeppen[b,1]

[a] *Hôpital Paul Brousse, INSERM 669, Université Paris-Sud, Villejuif, France*
[b] *Alcohol Treatment Center, Lausanne University Hospital, Lausanne, Switzerland*

Movement from reduction goal to abstinence goal

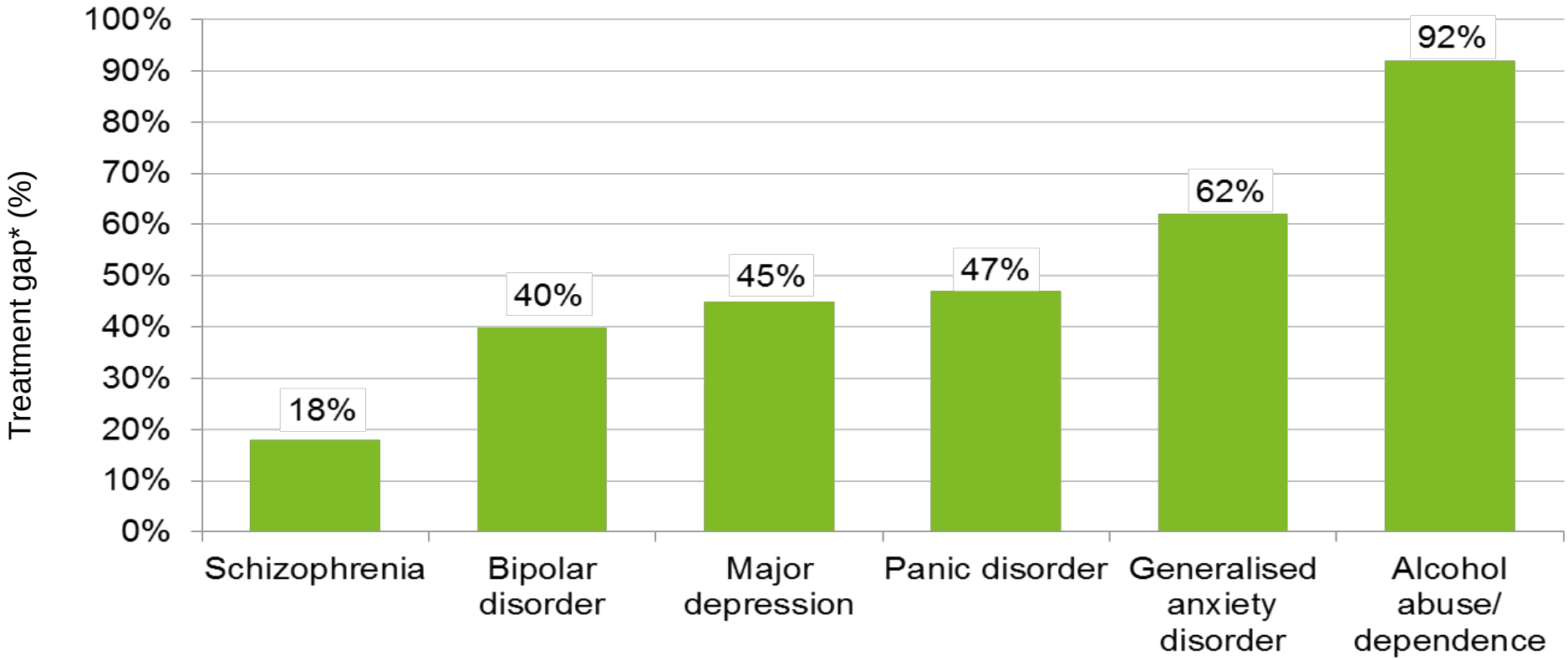
Initial goal preferences and changes at 4 weeks



49% of patients with an initial preference for a reduction goal changed to an abstinence goal within 4 weeks

(Hodgins et al., Addict Behav, 1997)

Treatment gap in alcohol dependence



(Kohn et al., Bull World Health Organ 2004)

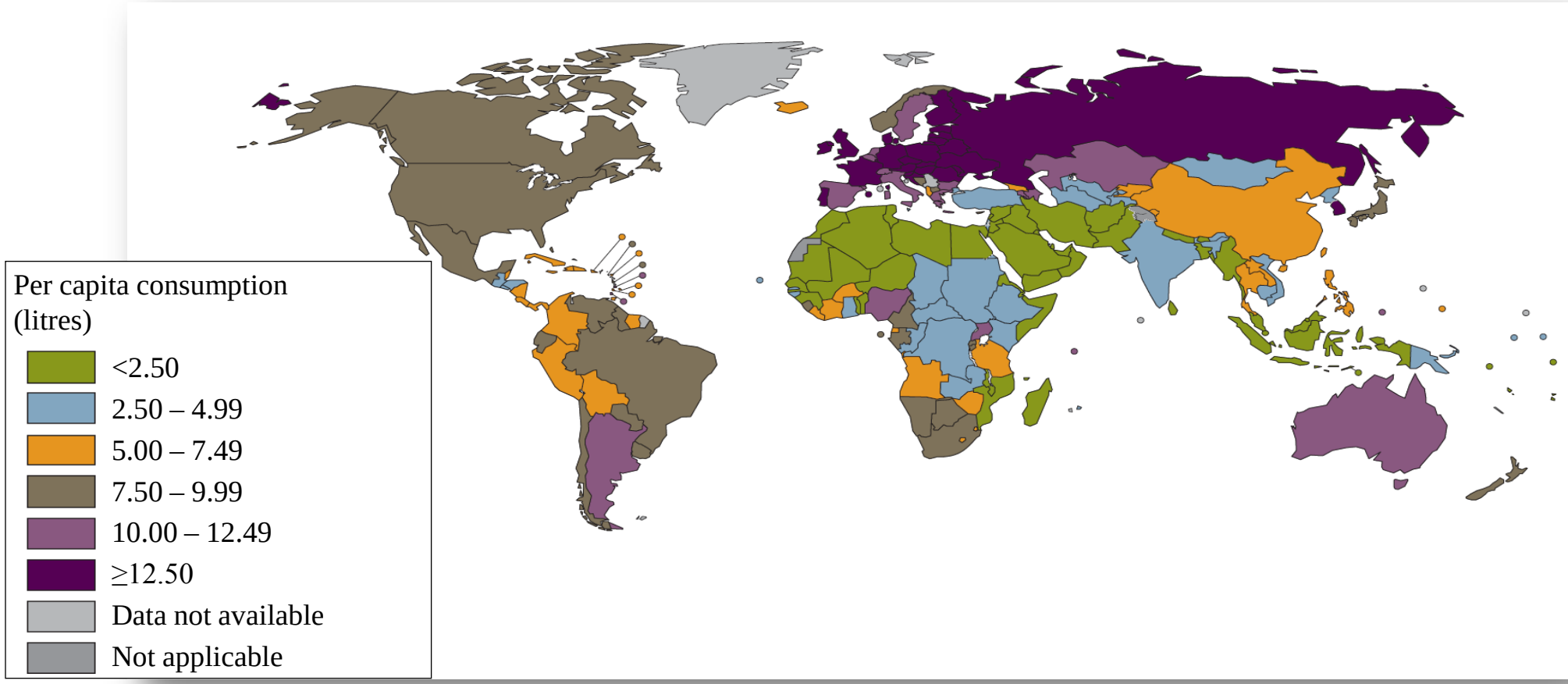
Epidemiologia

- 3.8% del totale dei decessi
  - Paesi Est Europa (Russia)
    - >50% dei decessi dai 15 ai 54 anni
    - ~20% dei decessi dai 55 ai 74 anni e nelle donne
- 5.5% del totale delle malattie
- disturbi da uso di alcol (~10% popolazione generale)
- disturbi da uso di alcol
  - fino al 30% ospedalizzati in U.O. di Medicina Interna
  - fino al 50% ospedalizzati in U.O. di Psichiatria

(Rehm et al., Lancet, 2009; Lim et al., Lancet, 2012)

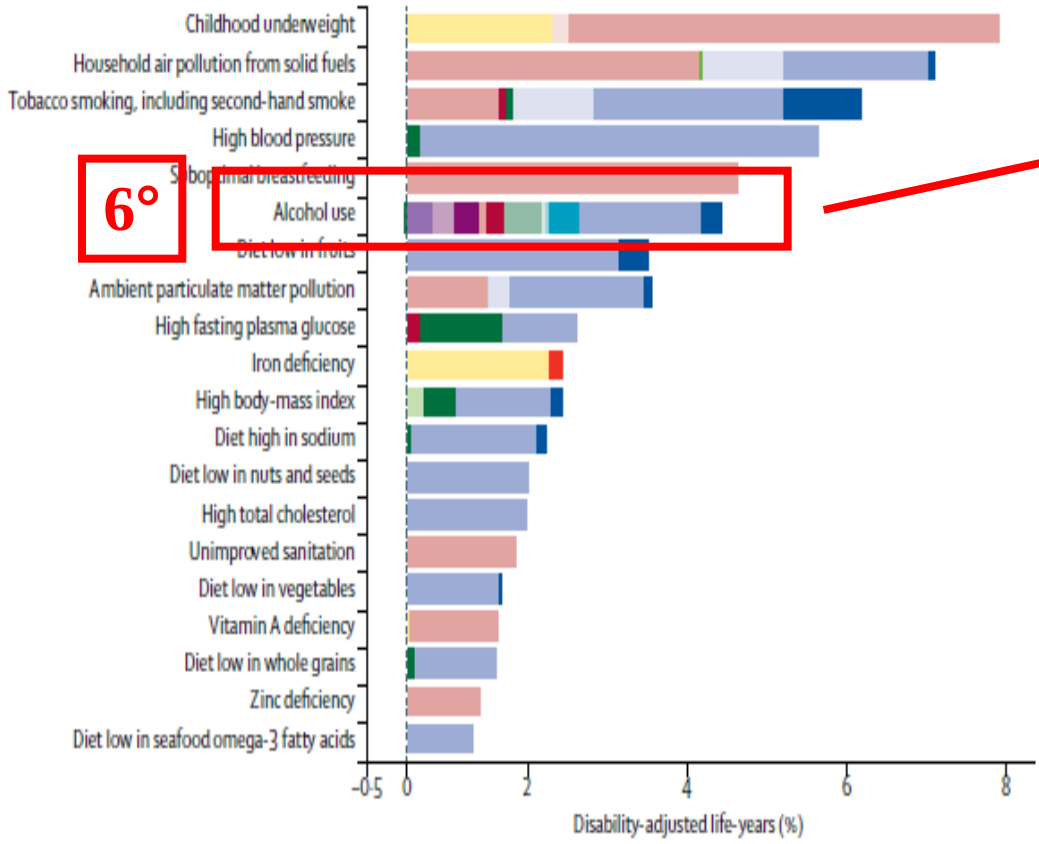
Alcohol consumption: a worldwide issue

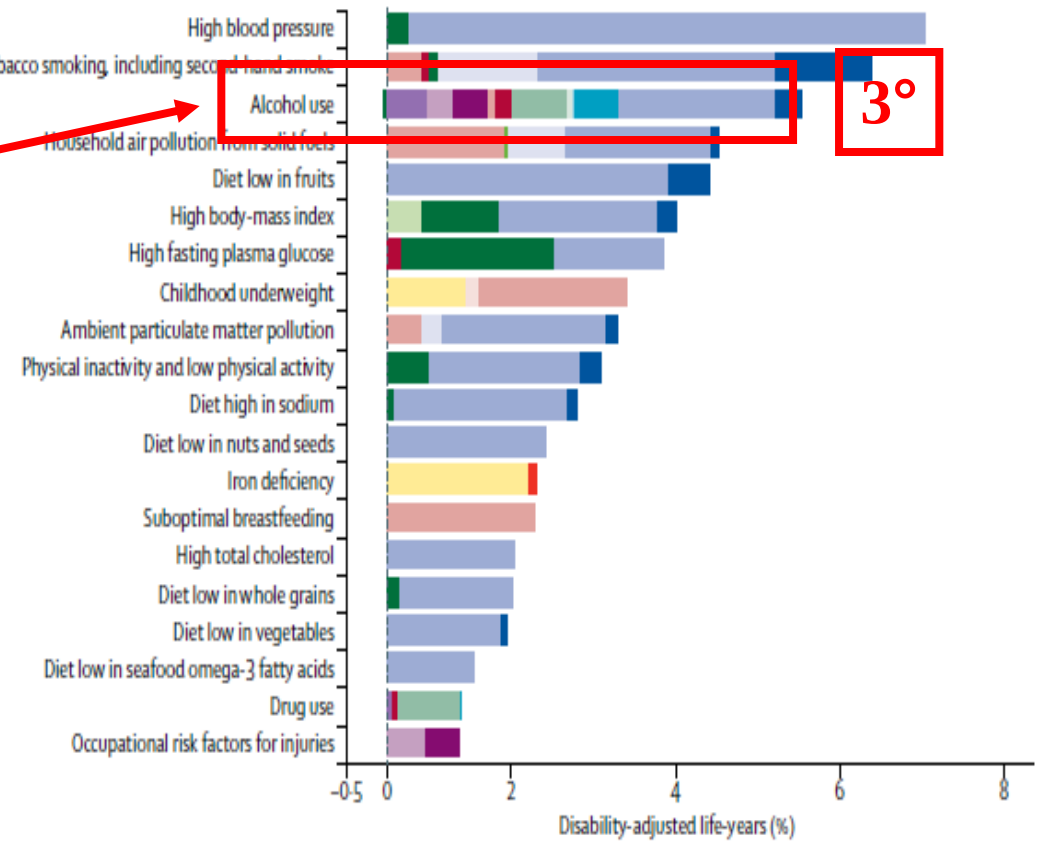
- Europe has the highest per capita pure alcohol consumption of all world regions



(WHO. Global status report on alcohol and health, 2011)

Variazione fattori di rischio (dal 1990 al 2010) attraverso il calcolo del DALYs: [anni vissuti con disabilità + anni di vita persi]





(Lim et al., Lancet 2012)

Reducing alcohol consumption has immediate health benefits

Improvements in:
Sleep disorders
Depression
Weight / nutrition
Blood pressure

(Anderson & Baumberg, Alcohol in Europe, 2006; Xin et al., Hypertension, 2001; Brown & Schuckit, J Stud Alcohol, 1988)

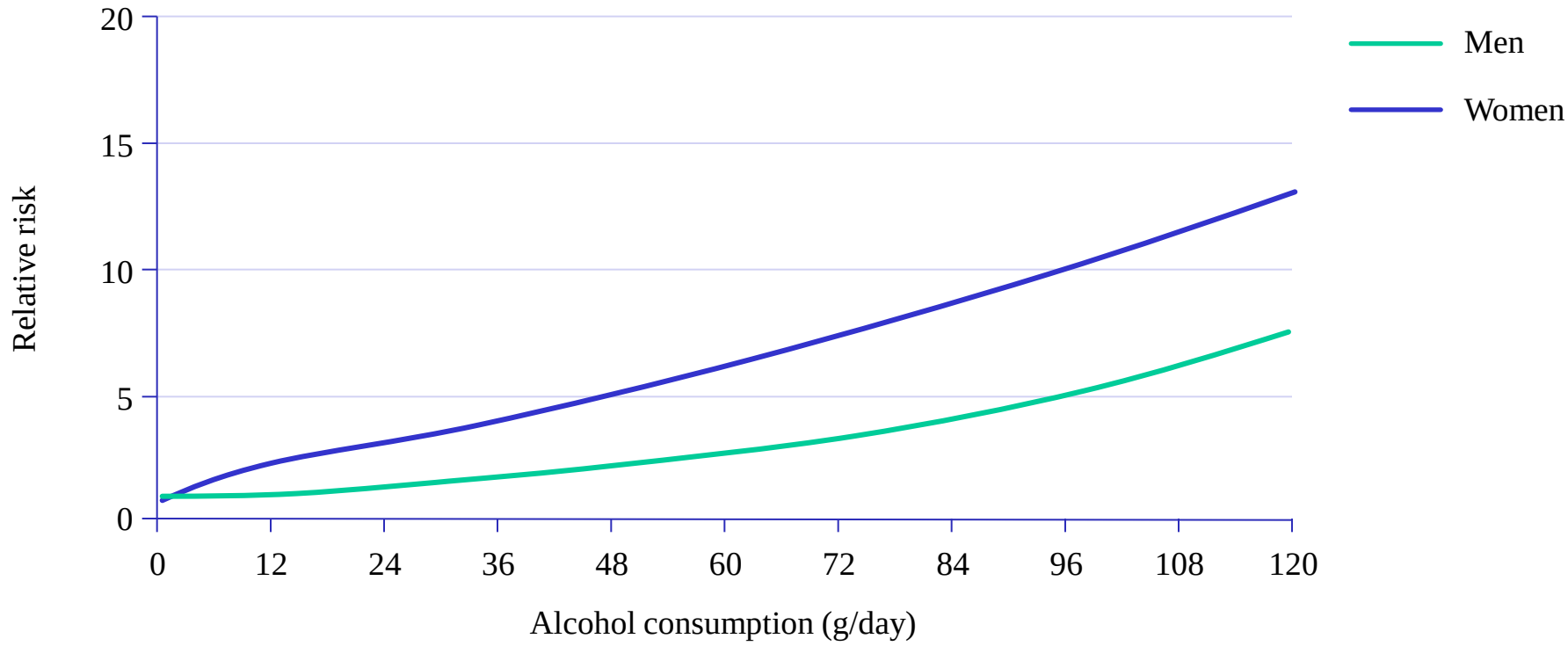
Reduction of alcohol consumption decreases the risk of morbidity

Lowers risks of:
Prenatal conditions
Liver cirrhosis
Lifetime development of: •Cancer •Cardiovascular disease •Osteoporosis •Pancreatitis

(Anderson & Baumberg, Alcohol in Europe, 2006)

Reduction in alcohol consumption decreases the risk of developing liver cirrhosis

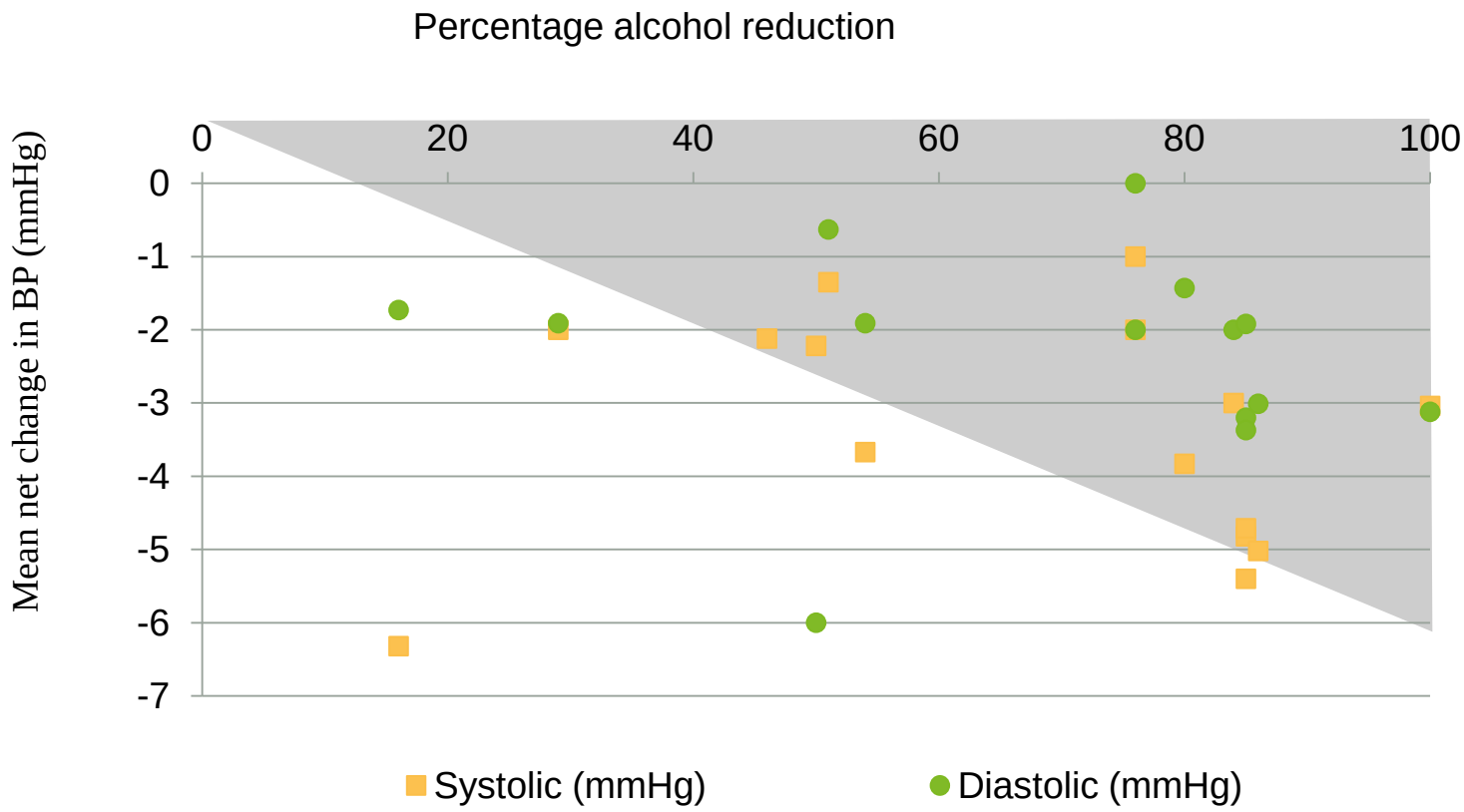
Relative risk of morbidity due to liver cirrhosis



(Rehm et al., Drug Alcohol Rev, 2010)

Correlation between reduction of alcohol consumption and reduced blood pressure

Percentage of alcohol reduction by mean net change in blood pressure



(Xin et al., Hypertension, 2001)

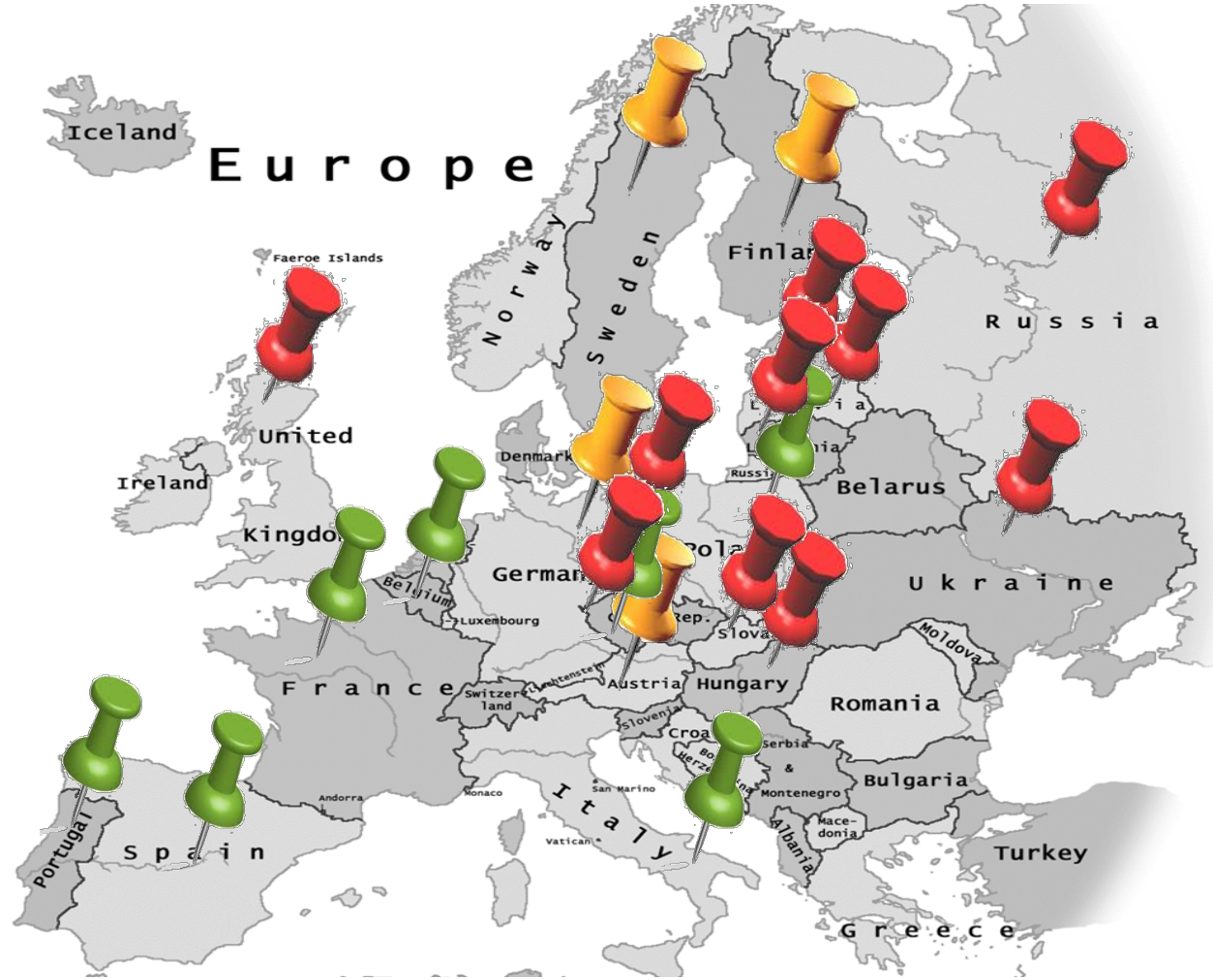
Risk levels of alcohol consumption (WHO)

Risk level	Total alcohol consumption (TAC) (g/day)	
	Men	Women
Low risk	1 to 40	1 to 20
Medium risk	>40 to 60	>20 to 40
High risk	>60 to 100	>40 to 60
Very high risk	>100	>60

(Adapted from World Health Organization, International guide for monitoring alcohol consumption and related harm, 2000)

Geographical overview

- **ESENSE 1**
  - **604 patients**
  - **6 mesi, rischio medio/alto**
- **ESENSE 2**
  - **718 patients**
  - **6 mesi, rischio medio/alto**
- **SENSE**
  - **675 patients**
  - **12 mesi, tollerabilità e rischio medio/basso**



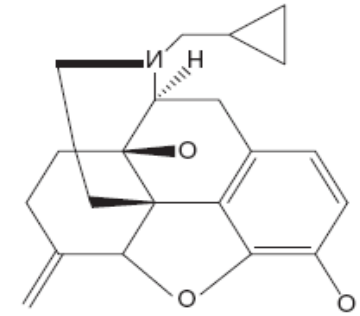
(Mann et al., Biol Psychiatry, 2013; Gual et al., Eur Neuropsychopharmacol, 2013; van den Brink et al., Alcohol Alcohol, 2013)

Nalmefene is an opioid system modulator with a distinct μ, δ, and κ profile

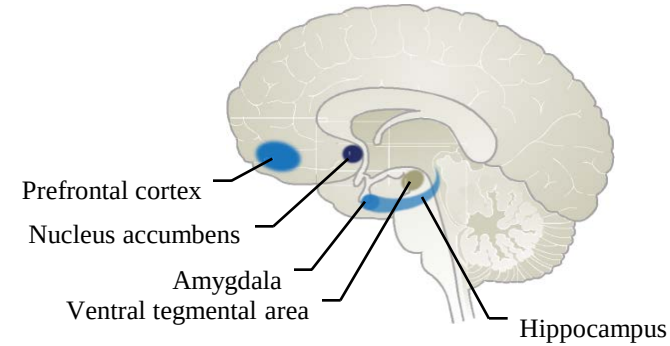
- Nalmefene is an opioid system modulator and acts as:
  - Antagonist at μ-opioid receptors
  - Antagonist at δ-opioid receptors
  - Partial agonist at κ-opioid receptors

- Nalmefene diminishes the reinforcing effects of alcohol, helping the patient to reduce drinking possibly by modulating cortico-mesolimbic functions

Nalmefene



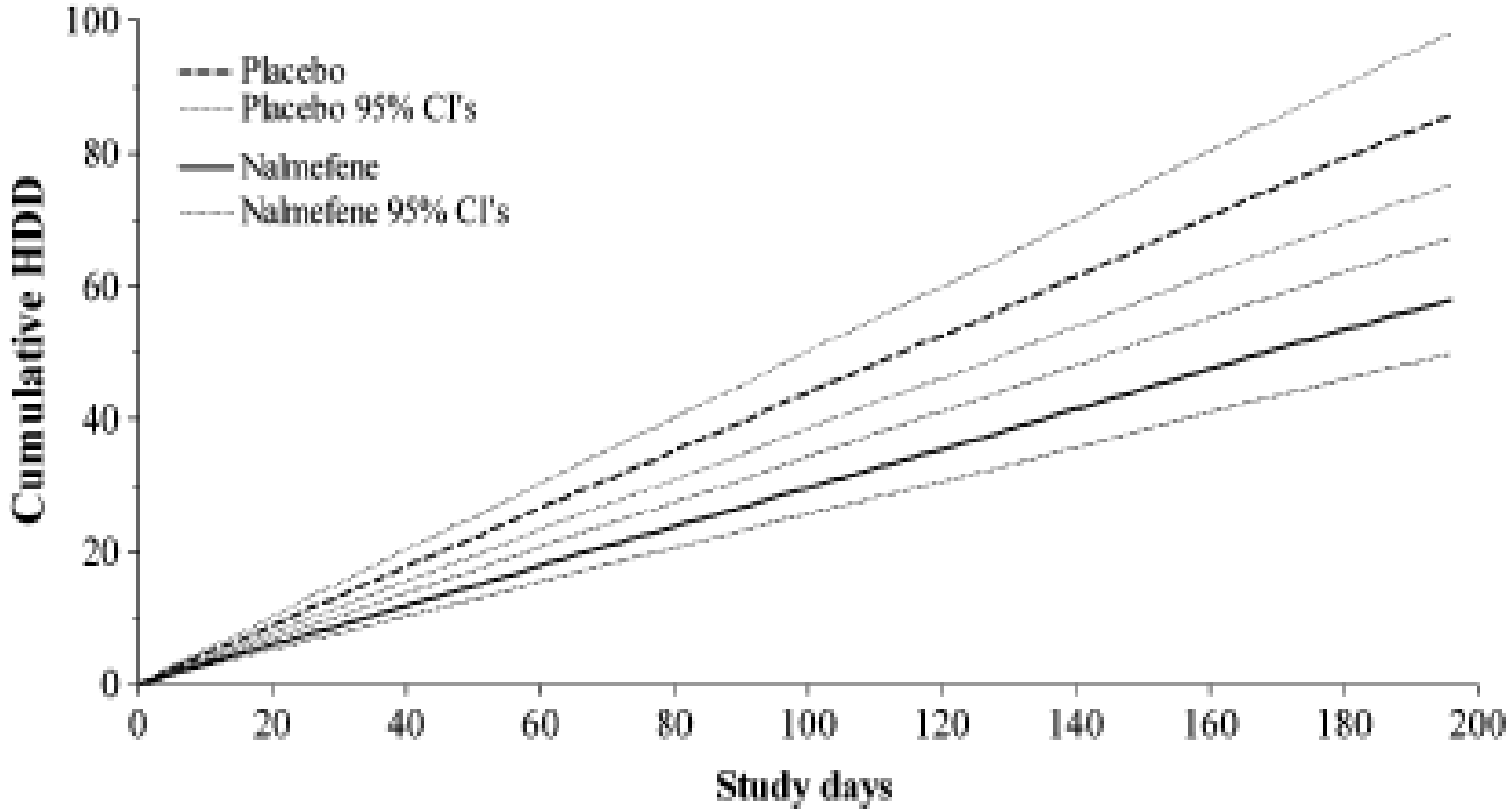
Areas in the brain affected by alcohol, including the mesolimbic dopamine system



(Nalmefene Summary of Product Characteristics, Nalmefene European Public Assessment Report, 2012; Clapp et al., Alcohol Res Health 2008)

Vol. 31, No. 7
July 2007

Targeted Nalmefene With Simple Medical Management in the Treatment of Heavy Drinkers: A Randomized Double-Blind Placebo-Controlled Multicenter Study



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Jon E. Grar
Marc N. Po
Eric Hollan
Renee Cun
Ph.D., M.P.
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Gerard Sm
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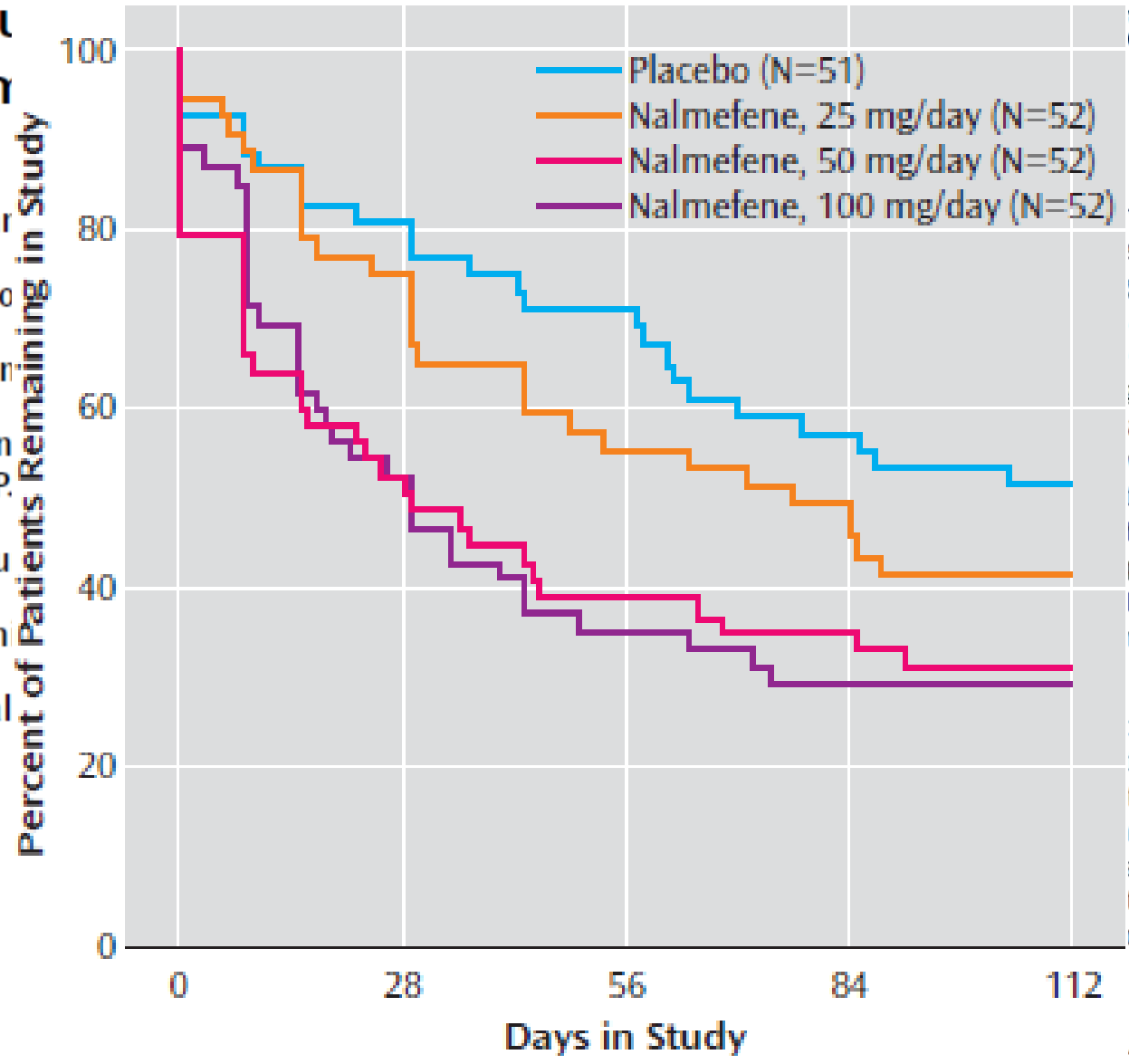

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lacebo. Adverse ex-
nausea, dizziness,

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efene (25 mg/day)
and was associated
ts. Higher doses (50
day) resulted in in-

2006; 163:303–312)

Studi clinici di fase III

- **Tre studi clinici multicentrici**, **randomizzati**, in **doppio cieco**, **placebo-controllati**, in pazienti con **dipendenza da alcol**
- Principio attivo: **Nalmefene 18 mg** (base)
- Posologia: **secondo necessità**

Nome dello studio	Durata dello studio	Pazienti
ESENSE 1 (12014A)	24 settimane più 4 settimane di run-out	604 306: Nalmefene + BRENDA 298: placebo + BRENDA
ESENSE 2 (12023A)	24 settimane più 4 settimane di run-out	718 358: Nalmefene + BRENDA 360: placebo + BRENDA
SENSE (12013A)	52 settimane	675 509: Nalmefene + BRENDA 166: placebo + BRENDA

1997 pazienti

Posologia “secondo necessità” (“as needed”)

- **Nalmefene**: Nalmefene 18 mg base, compresse, orale
- **Placebo**: compresse, orale

- Il paziente è stato istruito ad assumere **una compressa** di **Nalmefene al bisogno**, ovvero **ogni giorno** in cui **percepiva il rischio di assumere alcol**, preferibilmente **1-2 ore prima dell’ora prevista** per il consumo di alcol
- Se il paziente aveva **già iniziato a consumare alcol** senza aver preso Nalmefene, **doveva assumere una compressa il più presto possibile**
- La **dose massima** è di **una compressa al giorno**

PRIORITY COMMUNICATION

European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮–▮▮▮

Alcohol and Alcoholism pp. 1–9, 2013

doi: 10.1093/alcalc/agt061

ORIGINAL ARTICLE

Efficacy of As-Needed Nalmefene in Alcohol-Dependent Patients with at Least a High Drinking Risk Level: Results from a Subgroup Analysis of Two Randomized Controlled 6-Month Studies

Wim van den Brink[1,*], Henri-Jean Aubin[2], Anna Bladström[3], Lars Torup[3], Antoni Gual[4,†] and Karl Mann[5,†]

[1]Department of Psychiatry, Amsterdam Institute for Addiction Research, University of Amsterdam, Amsterdam, The Netherlands, [2]Hôpital Paul Brousse, INSERM 669, Université Paris-Sud, Villejuif, France, [3]H. Lundbeck A/S, Valby, Denmark, [4]Department of Psychiatry, Alcohol Unit, Institute of Neurosciences, Hospital Clinic, Barcelona, Spain and [5]Department of Addictive Behaviour and Addiction Medicine, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany

*Corresponding author: Academic Medical Center, University of Amsterdam, Department of Psychiatry, room PA1.188, PO BOX 22660, 1100 DD Amsterdam, The Netherlands. Tel.: +31-20-891-36-28; E-mail: w.vandenbrink@amc.uva.nl

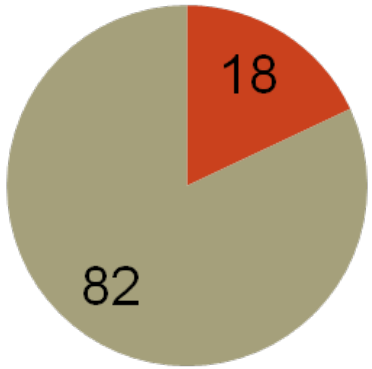
†Denotes equal contribution.

(*Received* 3 *May* 2013; *first review notified* 2 *June* 2013; *in revised form* 5 *June* 2013; *accepted* 6 *June* 2013)

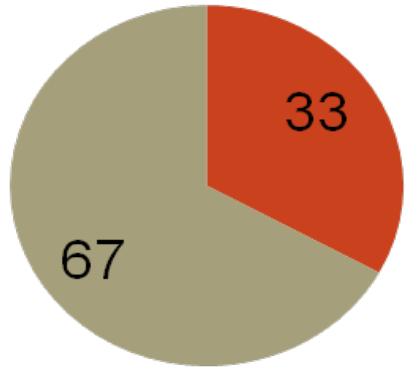
Abstract — **Aims:** The aim of the study was to investigate the efficacy and safety of as-needed use of nalmefene 18 mg versus placebo in reducing alcohol consumption in patients who did not reduce their alcohol consumption after an initial assessment, i.e. the pooled subgroup of patients with at least a high drinking risk level (men: >60 g/day; women: >40 g/day) at both screening and randomization from the two randomized controlled 6-month studies ESENSE 1 (NCT00811720) and ESENSE 2 (NCT00812461). **Methods:** Nalmefene 18 mg and placebo were taken on an as-needed basis. All the patients also received a motivational and adherence-enhancing intervention (BRENDA). The co-primary outcomes were number of heavy drinking days (HDDs) and mean total alcohol consumption (g/day) in Month 6 measured using the Timeline Follow-back method. Additionally, data on clinical improvement, liver function and safety were collected throughout the study. **Results:** The pooled population consisted of 667 patients: placebo $n = 332$; nalmefene $n = 335$. There was a superior effect of nalmefene compared with placebo in reducing the number of HDDs [treatment difference: −3.2 days (95% CI: −4.8; −1.6); $P < 0.0001$] and total alcohol consumption [treatment difference: −14.3 g/day (−20.8; −7.8); $P < 0.0001$] at Month 6. Improvements in clinical status and liver parameters were greater in the nalmefene group compared with the placebo group. Adverse events and adverse events leading to dropout were more common with nalmefene than placebo. **Conclusion:** As-needed nalmefene was efficacious in reducing alcohol consumption in patients with at least a high drinking risk level at both screening and randomization, and the effect in this subgroup was larger than in the total population.

Quanti pazienti riducono prima della randomizzazione (RIDUTTORI PRECOCI)?

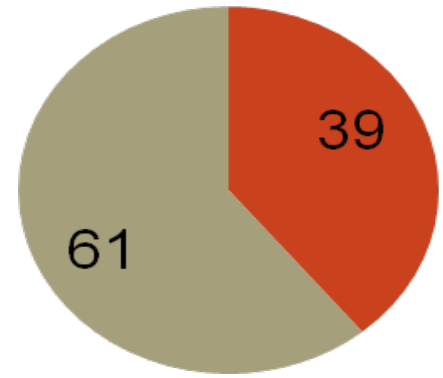
ESENSE 1
n=579



ESENSE 2
n=665



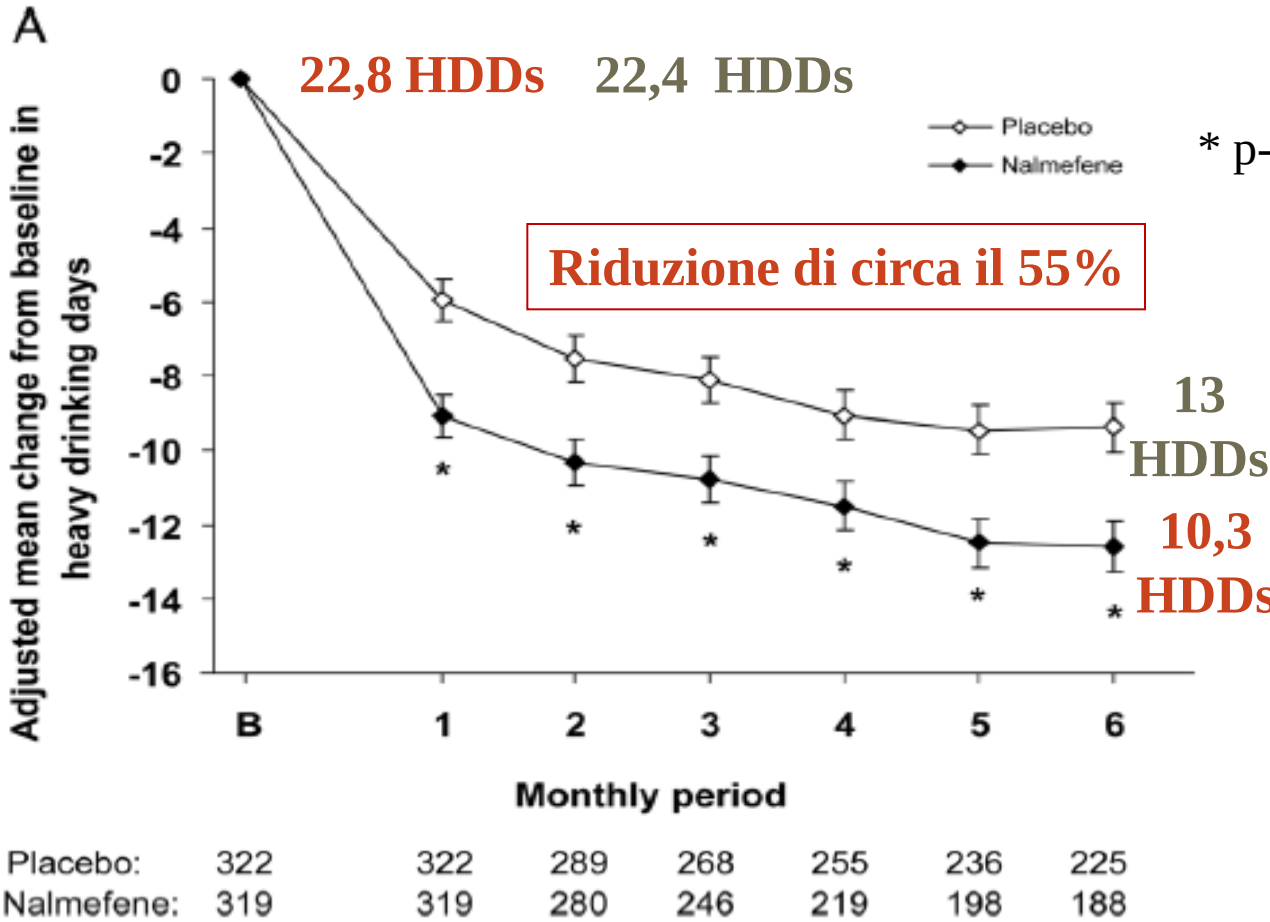
SENSE
n=552



Riduttori prima della randomizzazione

Non riduttori prima della randomizzazione

Heavy Drinking Days (HDD): ESENSE 1 & 2, dati aggregati, popolazione target



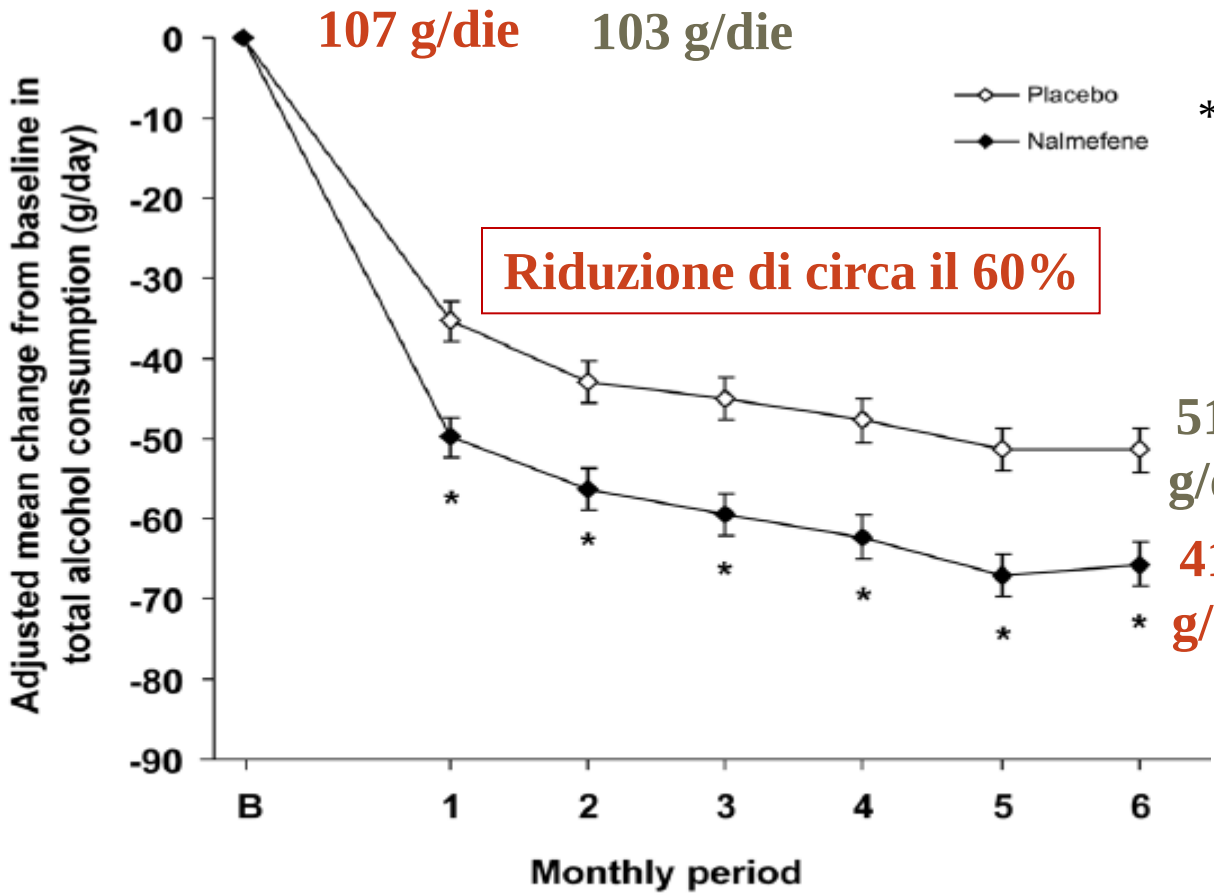
Variazione rispetto al basale: -9,4 HDD al mese

Variazione rispetto al basale: -12,6 HDD al mese

Differenza media Nalmefene verso placebo: -3,2 HDD/mese P<0,0001

(van den Brink et al., Alcohol Alcohol, 2013)

Total Alcohol Consumption (TAC): ESENSE 1 & 2, dati aggregati, popolazione target



* p-value<0.05

Riduzione di circa il 60%

51,8 g/die

41,5 g/die

Variazione rispetto al basale: -51,4 g7die

Variazione rispetto al basale: -65,7 g/die

Differenza media Nalmefene verso placebo: -14,3 g/die P<0,0001

(van den Brink et al., Alcohol Alcohol, 2013)

GGT e ALAT
ESENSE 1 & 2, popolazione target

Table 3. Liver enzymes γ-glutamyltransferase and alanine aminotransferase at Week 24 in patients with at least a high drinking risk level at both screening and randomization in ESENSE 1 and ESENSE 2

	Placebo		Nalmefene		Ratio to placebo		
Efficacy variable	*n*	Mean	*n*	Mean	Ratio	95% CI	*P*-value
ESENSE 1							
γ-Glutamyl transferase (IU/l)							
Baseline (geometric mean)	167	60.1	171	55.7			
Adjusted geometric mean at Week 24	112	53.9	87	39.5	0.73	(0.64; 0.84)	<0.001
Alanine aminotransferase (IU/l)							
Baseline (geometric mean)	166	29.3	171	29.4			
Adjusted geometric mean at Week 24	110	29.6	87	24.7	0.83	(0.75; 0.93)	0.001
ESENSE 2							
γ-Glutamyl transferase (IU/l)							
Baseline (geometric mean)	153	54.9	148	55.9			
Adjusted geometric mean at Week 24	108	52.4	100	47.3	0.90	(0.76; 1.07)	0. 244
Alanine aminotransferase (IU/l)							
Baseline (geometric mean)	153	29.0	148	29.3			
Adjusted geometric mean at Week 24	108	31.5	100	26.8	0.85	(0.75; 0.96)	0.010

SD, standard deviation; CI, confidence interval.

(van den Brink et al., Alcohol Alcohol, 2013)

Tollerabilità ESENSE 1 & 2, dati aggregati, popolazione target

Table 4. Adverse events in the *target safety population* ($n = 658$)

Preferred term	Placebo, $n = 327$	Nalmefene, $n = 331$
Patients with treatment-emergent adverse events	220 (67.3%)	256 (77.3%)
Treatment-emergent adverse events (≥5%):		
Dizziness	21 (6.4%)	78 (23.6%)
Nausea	23 (7.0%)	78 (23.6%)
Insomnia	15 (4.6%)	49 (14.8%)
Headache	33 (10.1%)	46 (13.9%)
Fatigue	20 (6.1%)	34 (10.3%)
Sleep disorder	2 (0.6%)	28 (8.5%)
Nasopharyngitis	36 (11.0%)	26 (7.9%)
Vomiting	12 (3.7%)	25 (7.6%)
Decreased appetite	4 (1.2%)	19 (5.7%)
Hyperhidrosis	3 (0.9%)	18 (5.4%)
Diarrhoea	21 (6.4%)	12 (3.6%)
Accidental overdose[a]	18 (5.5%)	8 (2.4%)
Patients with treatment-emergent adverse events leading to dropout	26 (8.0%)	58 (17.5%)
Treatment-emergent adverse events leading to dropout of ≥5 patients in either treatment group:		
Dizziness	0 (0.0%)	18 (5.4%)
Nausea	0 (0.0%)	16 (4.8%)
Headache	0 (0.0%)	8 (2.4%)
Fatigue	0 (0.0%)	5 (1.5%)
Sleep disorder	0 (0.0%)	5 (1.5%)

Data are numbers of patients (%).
[a]Defined as >1 tablet of study medication.

(van den Brink et al., Alcohol Alcohol, 2013)

Nalmefene: indicazioni

- Nalmefene è indicato per la riduzione del consumo di alcol in pazienti adulti con dipendenza da alcol che hanno livelli di consumo ad elevato rischio **(>60 g/die per gli uomini e >40 g/die per le donne)** senza sintomi fisici da sospensione e che non richiedono interventi immediati di disintossicazione

- Nalmefene deve essere prescritto solo congiuntamente ad un **supporto psicosociale** continuativo, mirato all'aderenza al trattamento ed alla riduzione del consumo di alcol

- Il trattamento con Nalmefene deve essere iniziato **solo in pazienti che continuano ad avere un livello di consumo ad elevato rischio** due settimane dopo la valutazione iniziale

(Nalmefene Summary of Product Characteristics)

Posologia

- Nalmefene deve essere assunto **secondo necessità**: il paziente deve assumere una compressa, preferibilmente 1-2 ore prima dell'orario previsto per il consumo di alcol, ogni giorno in cui percepisce il rischio di consumare alcol
- Se il paziente ha iniziato a consumare alcol senza avere assunto il Nalmefene, il paziente deve assumere una compressa il più presto possibile
- La dose massima di Nalmefene è di una compressa al giorno
- Nalmefene può essere assunto con o senza cibo

(Nalmefene Summary of Product Characteristics)

“… ricordate: dove passa l’acqua dei secoli
lascia delle tracce, l’alcol le cancella,
non cancellate con l’alcol
le vostre tracce”

Grazie per l’attenzione!!