Mises jour en médecine interne: Alcoologie en 2012

ANP3SM- 19/06/2012

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Xavier Preud'homme, MD Financial/Affiliations Disclosure

1) Recipient of 2010 Pfizer OAB-LUTS grant investigating *Makers of voiding urgency during daytime using heart rate variability in OAB and healthy controls* - **PI**
2) Small 2011 CFAR grant investigating the feasibility of CBT treatment of insomnia in PLWHA - **PI**
3) NIDDK – sponsored *Investigation of nocturia in OAB, nocturnal polyuria, insomnia & healthy controls* - **Sub-investigator**
4) Investigator-initiated research - sponsored by Astellas *Investigation of nocturia & bladder function in women with OAB* -**Sub-investigator**
5) ***ATTENTION: Discussion de 2 médicaments dans des indications non approuvées par le FDA ni l'EMA***

Merci Dr Ameisen

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CASE REPORT

COMPLETE AND PROLONGED SUPPRESSION OF SYMPTOMS AND CONSEQUENCES OF ALCOHOL-DEPENDENCE USING HIGH-DOSE BACLOFEN: A SELF-CASE REPORT OF A PHYSICIAN

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(*Received* 2 *October* 2004; *first review notified* 19 *October* 2004; *in revised form* 10 *November* 2004; *accepted* 11 *November* 2004)

Abstract — Aims: To test whether the dose-dependent motivation-suppressing effect of baclofen in animals could be transposed to humans, and suppress craving and sustain abstinence. **Methods:** Neurologists safely use up to 300 mg/day (10 times the dosage currently used for alcohol dependence) of high-dose oral baclofen, to control spasticity, in order to avoid invasive therapy. I am a physician with alcohol dependence and comorbid anxiety. I self-prescribed high-dose baclofen, starting at 30 mg/day, with 20 mg increments every third day and an (optional) additional 20–40 mg/day for cravings. **Results:** Cravings became easier to combat. After reaching the craving-suppression dose of 270 mg/day (3.6 mg/kg) after 5 weeks, I became and have remained free of alcohol dependence symptoms effortlessly for the ninth consecutive month. Anxiety is well controlled. Somnolence disappeared with a dosage reduction to 120 mg/day, now used for the eighth consecutive month. **Conclusions:** High-dose baclofen induced complete and prolonged suppression of symptoms and consequences of alcohol dependence, and relieved anxiety. This model, integrating cure and well-being, should be tested in randomized trials, under medical surveillance. It offers a new concept: medication-induced, dose-dependent, complete and prolonged suppression of substance-dependence symptoms with alleviation of comorbid anxiety.

2004: baclofène contre l'appétence

- Chez l'homme alcoolique: 0.5 mg/kg aide l'abstinence[2000]
- Chez le rat: 3 mg/kg supprime la consommation d'alcool[1997]
- Spasticité: 300 mg/jour

Utilisation hors du cadre de l'AMM *versus* Mediator-1

REVIEW ARTICLE

CNS Drugs 2012; 26 (1): 69-78
1172-7047/12/0001-0069/$49.95/0

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Defining the Role of Baclofen for the Treatment of Alcohol Dependence

A Systematic Review of the Evidence

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This material is

2012: Où en est l’évidence?

- 3 études prospectives, randomisées en double-aveugle contre placébo
- 2 démontrent une efficacité statistique dans le traitement de l’alcoolo-dépendance avec plus d’abstinence et moins d’anxiété
- 1 ne montre pas d’avantage mais les patients étaient moins sévèrement atteints
- 0 problème même chez les cirrhotiques

Baclofène 30 mg/jour *versus* 129 +/- 71 mg/jour

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ORIGINAL ARTICLE

Abstinence and 'Low-Risk' Consumption 1 Year after the Initiation of High-Dose Baclofen: A Retrospective Study among 'High-Risk' Drinkers

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Abstract — **Aims**: The aim of the study was to assess the proportions of 'high-risk' drinkers' abstinent or with 'low-risk' consumption levels 1 year after the initiation of high-dose baclofen. **Methods**: This is a retrospective 'open' study; the outcome of this study was to assess the level of alcohol consumption in the 12th month of treatment. **Results**: Of the 181 patients included, a follow-up evaluation was possible in 132 patients. The initial alcohol consumption of the 132 patients analysed averaged 182 ± 92 g/day. After 1 year, 80% of the 132 (i.e. 58% of 181) were either abstinent ($n = 78$) or drinking at low-risk levels ($n = 28$) in their 12th month of treatment. The mean baclofen dose at 1 year was 129 ± 71 mg/day. **Conclusion**: High-dose baclofen should be tested in randomized placebo-controlled trials among high-risk drinkers.

Etude rétrospective, sans groupe contrôle mais…

- Durée d'un an parmi 181consommateurs à risque (*OMS >40 g/jour & 60 g/jour respectivement pour les femmes et les hommes*)
- 132 patients buvant 182 +/- 92 g/jour
- 106 soit 80% (58% des 181) sont abstinents (n=78) ou consommateurs à moindre risque (n=28) (*OMS <=20 g/jour & <=40 g/jour respectivement pour les femmes et les hommes*)

L'hépatite alcoolique

NEJM 2011;365:1781-9

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Glucocorticoids plus *N*-Acetylcysteine in Severe Alcoholic Hepatitis

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Mortalité à 6 mois de 35% malgré les glucocorticoïdes

Cause

- Augmentation de la perméabilité intestinale
- Stimulation des cellules de Kupffer
- TNF-alpha active la mort cellulaire

Effet

- Plus grand risque d'endotoxémie
- Production de cytokines pro-inflammatoires
- Les mitochondries hépatiques libèrent plus d'anions superoxide, perdent leurs réserves en gluthatione, deviennent encore plus sensibles aux effets toxiques du TNF-alpha

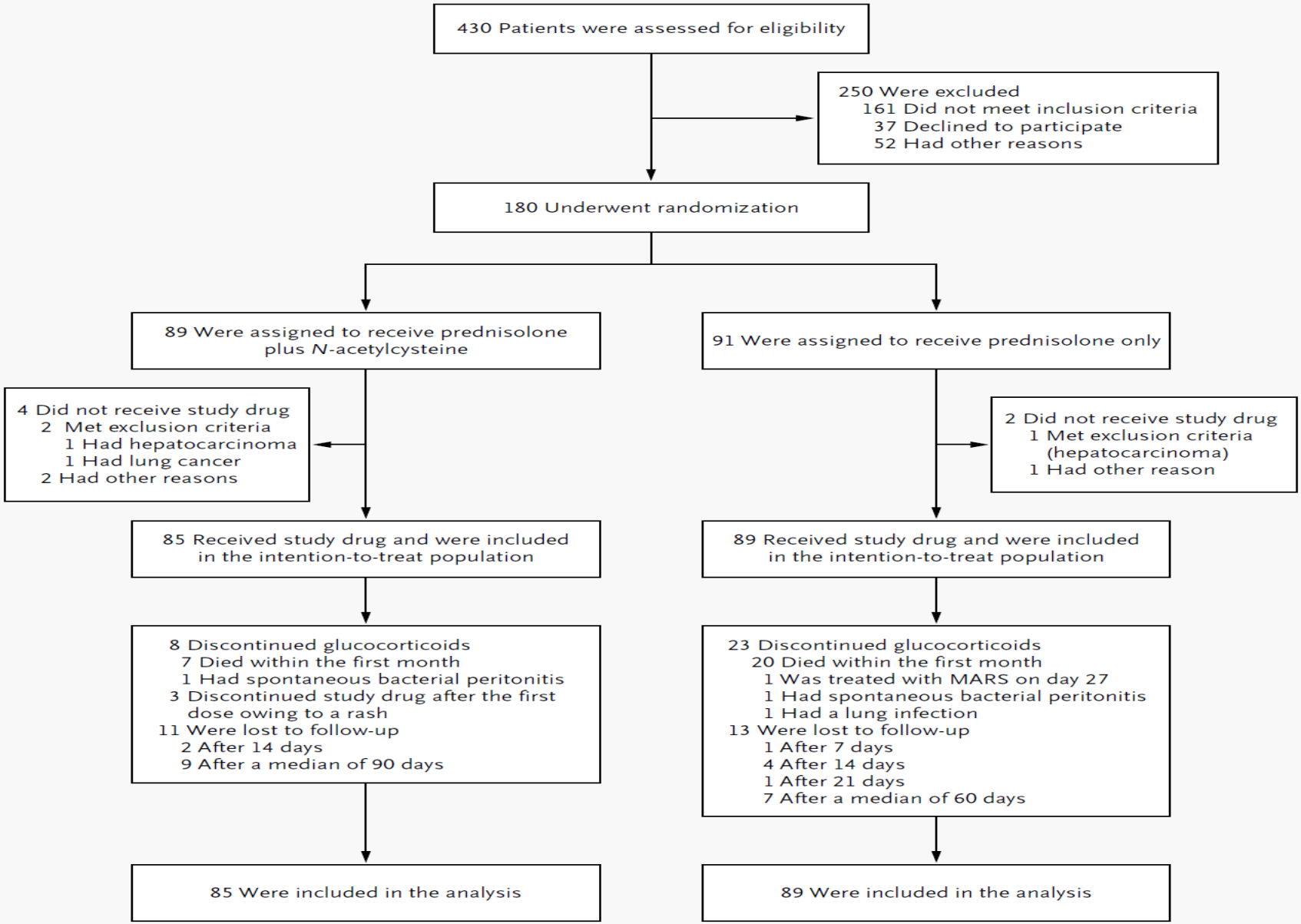
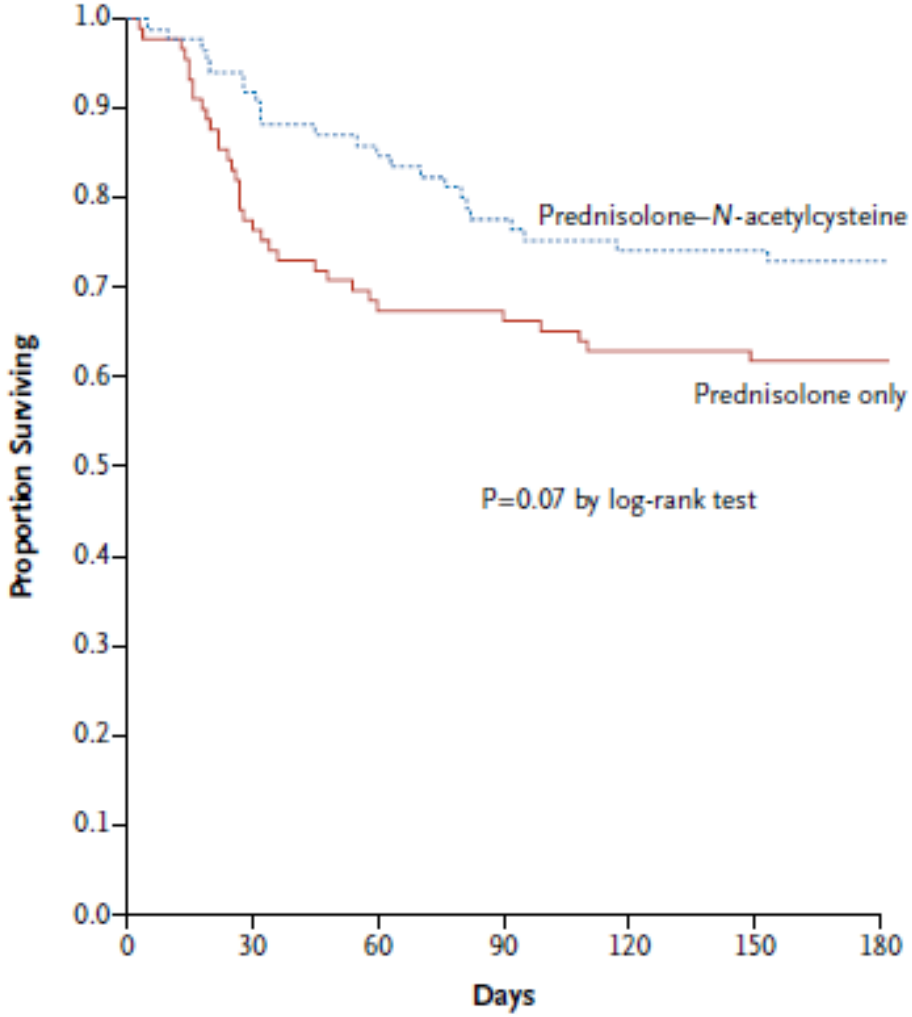


Figure 1. Enrollment and Outcomes.

Data on mortality were available for all patients in the intention-to-treat population, including those lost to follow-up. MARS denotes molecular adsorbent recirculating system.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Reference Range	Prednisolone Only (N=89)	Prednisolone–*N*-Acetylcysteine (N=85)	P Value
Age — yr		52.2±8.5	52.8±8.7	0.66
Male sex — no. (%)		50 (56)	55 (65)	0.25
Time between hospital admission and start of treatment in trial — days		7.9±6.7	7.2±6.6	0.45
Alcohol intake — g/day		108.8±55.3	107.2±58.0	0.86
AUDIT score†		22.6±7.4	22.5±7.4	0.91
CAGE score‡		3.2±0.9	3.3±0.9	0.28
Child–Pugh score§		11.3±1.3	11.0±1.5	0.35
Maddrey's discriminant function¶		58.2±20.0	54.0±18.2	0.11
Hepatic encephalopathy — no. (%)		39 (44)	38 (45)	0.46
Ascites — no. (%)		62 (70)	59 (69)	1.00
Prothrombin time — % of normal	70–100	37.5±9.9	39.9±10.9	0.12
Bilirubin — μmol/liter	0–19	260.1±171.0	238.1±136.0	0.35
Albumin — g/liter	37–45	24.9±5.4	24.3±5.9	0.42
Aspartate aminotransferase — U/liter	<35–45	109.9±49.1	127.5±83.9	0.10
γ-Glutamyltransferase — U/liter	0–85	223.0±240.0	308.9±289.0	0.05
Alkaline phosphatase — U/liter	0–240	176.8±161.5	174.8±83.8	0.90
Creatinine — μmol/liter	45–120	73.1±21.0	73.3±29.9	0.96
White-cell count — per mm^3	4000–10,000	10,901±5640	10,528±6534	0.69
Polymorphonuclear-neutrophil count — per mm^3	1400–7500	8179±5205	7530±6254	0.48



No. at Risk

Prednisolone only	89	69	61	60	56	55	46
Prednisolone–*N*-acetylcysteine	85	78	73	66	63	63	48

Figure 2. Kaplan–Meier Curves for 6-Month Survival in the Intention-to-Treat Population.

Table 2. Adverse Events.

Event	Prednisolone Only (N = 89)	Prednisolone–*N*-Acetylcysteine (N = 85)
	no. (%)	
Hepatorenal syndrome*	22 (25)	10 (12)
All infections†	37 (42)	16 (19)
Spontaneous bacterial peritonitis	9 (10)	5 (6)
Lung infection	8 (9)	3 (4)
Urinary system infection	7 (8)	4 (5)
Erysipelas	3 (3)	0
Staphylococcal septicemia	2 (2)	2 (2)
Gram-negative septicemia	2 (2)	2 (2)
Esophageal candidiasis	2 (2)	0
Otitis externa	1 (1)	0
Infection of unknown cause	3 (3)	0
Esophageal variceal hemorrhage	8 (9)	10 (12)
Esophageal ulcer hemorrhage	1 (1)	0
Gastroduodenal ulcer hemorrhage	0	3 (4)
Umbilical variceal hemorrhage	0	1 (1)
Thigh hematoma	0	1 (1)
Hepatic encephalopathy	4 (4)	3 (4)
Hepatic hydrothorax‡	0	1 (1)
Functional kidney failure	0	1 (1)
Inguinal hernia occlusion	1 (1)	0
Lumbar vertebral collapse	1 (1)	1 (1)
Cerebral hemorrhage	2 (2)	1 (1)
Cancer of the pharynx	1 (1)	0
Uterine fibroid hemorrhage	1 (1)	0
Calf hematoma	1 (1)	0
Torsade de pointes	1 (1)	0
Rash after first injection of *N*-acetylcysteine	0	3 (4)
MARS use§	1 (1)	0
Liver transplantation§	0	1 (1)
Relapse of alcohol use after 1 month	15 (17)	15 (18)

Adding *N*-acetylcysteine to prednisolone reduced early mortality in severe alcoholic hepatitis

Clinical impact ratings: HO ★★★★★★☆ GI ★★★★★★☆

Prednisolone (pred) plus *N*-acetylcysteine (NAC) vs pred only in patients with severe acute alcoholic hepatitis†

Outcomes	Pred + NAC	Pred only	RRR (95% CI)	NNT (CI)
Mortality at 6 mo	27%	38%	32% (–5 to 57)	NS
Mortality at 1 mo	8%	24%	39% (22 to 84)	11 (6 to 20)
Hepatorenal syndrome at 6 mo	12%	25%	52% (2 to 79)	8 (6 to 268)
Infection at 6 mo	19%	42%	54% (22 to 77)	5 (4 to 12)

†NS = not significant; other abbreviations defined in Glossary. RRR, NNT, and CI calculated from control event rates, hazard ratios (mortality), and odds ratios (hepatorenal syndrome, infection) in article.

Both groups received 40 mg of oral prednisolone per day for 28 days. For the first 5 days, patients in the prednisolone–*N*-acetylcysteine group received intravenous infusions of *N*-acetylcysteine (Fluimucil, Zambon Group). On day 1, they received 150 mg per kilogram of body weight in 250 ml of 5% glucose solution over a period of 30 minutes, 50 mg per kilogram in 500 ml of glucose solution over a period of 4 hours, and 100 mg per kilogram in 1000 ml of glucose solution over a period of 16 hours. On days 2 through 5, they received 100 mg per kilogram per day in 1000 ml of glucose solution. The patients in the

Technique: Traitement par acétylcystéine

Vu la dilution dans une solution de glucose 5% => recommande une prophylaxis par de la thiamine au moins 200 mg iv par jour

Questions?