FARMACI OFF-LABEL NEL COCAINISMO

VERONA, 31-3-2022

ERNESTO DE BERNARDIS

SERT DI LENTINI (SR)

LISTA DEI FARMACI CON INDICAZIONE NEL COCAINISMO

INFORMATIVA CONSENSO INFORMATO
TERAPIA DIPENDENZA COCAINA
(ai sensi del D.Ass. 13-9-2006 n.47 e della legge 94-1998)

Sono al corrente che ad oggi non sono disponibili farmaci con indicazione, in scheda tecnica approvata dal Ministero della Salute, per la dipendenza da cocaina, e che non esistono nella Letteratura scientifica corrente indicazioni assolute per alcun farmaco in tale patologia.
Sono al corrente che le terapie farmacologiche oggi comunque utilizzate vengono applicate al di fuori delle indicazioni della scheda tecnica registrata al Ministero della Salute, e pertanto richiedono l' espressione di un consenso informato da parte del paziente (legge 94/98 art. 3 comma 2), ed inoltre che i relativi farmaci non possono essere rimborsati dal Sistema Sanitario Nazionale (legge 94/98 art. 3 comma 4).
Si tratta in ogni caso di terapie che utilizzano farmaci regolarmente registrati in Italia per altre indicazioni, con impiego noto e conforme a lavori apparsi su pubblicazioni scientifiche accreditate in campo internazionale.
Sono al corrente che le terapie farmacologiche proposte hanno specifici effetti collaterali e controindicazioni che mi sono state illustrate dal medico del SerT di Lentini che insieme a me firma il presente consenso; inoltre, che esse possono determinare **sonnolenza e capogiri** e quindi **possono rendere pericolosa la guida di veicoli o l'utilizzazione di macchinari, attività che pertanto vengono sconsigliate**.
In alternativa al trattamento farmacologico proposto, è possibile effettuare un trattamento di tipo psicologico e/o sociale, con controllo delle condizioni di salute psicofisica ed interventi di prevenzione, senza inclusione di interventi farmacologici.
Accetto dunque la terapia farmacologica con i seguenti farmaci alla luce dei vantaggi e svantaggi che mi sono stati illustrati:

☐ desipramina	☐ gabapentin	☐ amisulpride	☐ fluoxetina
☐ paroxetina	☐ fluvoxamina	☐ venlafaxina	☐ amantadina
☐ baclofene	☐ sodio oxibato	☐ carbamazepina	☐ oxcarbazepina
☐ citalopram	☐ valproato	☐ reboxetina	☐ citicolina
☐ cabergolina	☐ pramipexolo	☐ escitalopram	☐ disulfiram
☐ acetilcisteina	☐ duloxetina	☐ naltrexone	☐ topiramato

☐ altri (specificare): _____

ESPRESSIONE DEL CONSENSO

☐ **esprimo il** consenso
all'esecuzione del trattamento Data e firma del pz._____ del medico_____

☐ **revoco** il consenso
all'esecuzione del trattamento Data e firma del pz._____ del medico_____

☐ **non esprimo** il consenso
all'esecuzione del trattamento Data e firma del pz._____ del medico_____

JAMA Network | Open

Original Investigation | Substance Use and Addiction

Comparison of Treatments for Cocaine Use Disorder Among Adults
A Systematic Review and Meta-analysis

Brandon S. Bentzley, MD, PhD; Summer S. Han, PhD; Sophie Neuner, BS; Keith Humphreys, PhD; Kyle M. Kampman, MD; Casey H. Halpern, MD

Bentzley, B. S., Han, S. S., Neuner, S., Humphreys, K., Kampman, K. M., & Halpern, C. H. (2021 05 03). Comparison of Treatments for Cocaine Use Disorder Among Adults: A Systematic Review and Meta-analysis. *JAMA Netw Open*, *4*(5), e218049. https://doi.org/10.1001/jamanetworkopen.2021.8049

Conclusions

In this systematic review and meta-analysis, we specifically designed our approach to search for a signal of treatment benefit present among the broad treatment categories defined by previous systematic reviews. Given the largely negative results of published meta-analyses of treatments for cocaine use disorders, we expanded our search beyond the typical restrictions that lead to data exclusion. This approach allowed us to look broadly across the extant literature; however, this broad reach came at the expense of granularity and strength of conclusion. Our comprehensive analyses suggested that contingency management approaches were associated with reductions in cocaine use. Thus, there may not be a case for therapeutic pessimism regarding cocaine use disorder. Prioritizing implementation research that informs health care systems regarding beneficial and viable adoption approaches (eg, examining current limits on patient incentive programs)[201] may produce greater public health benefits than additional efforts to assess whether contingency management programs are generally beneficial for the treatment of cocaine use disorders.

Table 2. Outcomes for Primary Analyses

Treatment category	Without imputed data				With imputed data			
	No.				No.			
	Studies	Treatment groups	Participants	OR (95% CI)	Studies	Treatment groups	Participants	OR (95% CI)
Anticonvulsants	14	17	570	2.32 (1.15-4.67)[a]	16	20	683	1.39 (0.59-3.29)
Antidepressants	8	15	482	1.96 (0.91-4.25)	11	18	574	1.36 (0.63-2.91)
Antipsychotics	8	11	241	1.59 (0.68-3.71)	9	12	281	1.02 (0.41-2.53)
Contingency management	38	69	2744	2.09 (1.59-2.75)[b]	50	88	3301	2.13 (1.62-2.80)[b]
Dopamine agonists	10	18	645	1.55 (0.80-3.00)	12	20	710	1.04 (0.51-2.14)
Miscellaneous medications	26	38	1455	1.64 (0.88-3.06)	37	54	1751	1.14 (0.60-2.17)
Opioids	49	142	4686	2.32 (1.54-3.49)[b]	55	159	5139	1.70 (0.98-2.94)
Other therapies	12	21	1577	2.19 (1.07-4.49)[c]	15	26	1805	1.35 (0.72-2.53)
Placebo	65	78	2889	1.48 (0.86-2.53)	80	96	3381	1.03 (0.59-1.80)
Psychostimulants	13	19	645	2.48 (1.27-4.85)[d]	17	24	702	1.74 (0.81-3.74)
Psychotherapy	98	258	10 773	1.08 (0.74-1.58)	131	330	13 213	1.18 (0.81-1.73)

Abbreviation: OR, odds ratio.

[a] $P = .02$.

[b] $P < .001$.

[c] $P = .03$.

[d] $P = .008$.

Drug and Alcohol Dependence 226 (2021) 108904

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Patterns of reduced use and abstinence in multi-site randomized controlled trials of pharmacotherapies for cocaine and methamphetamine use disorders

Masoumeh Amin-Esmaeili [a,b,*], Ryoko Susukida [a], Renee M. Johnson [a,c], Mehdi Farokhnia [a,d], Rosa M. Crum [a,c,e], Johannes Thrul [a], Ramin Mojtabai [a,e]

Amin-Esmaeili, M., Susukida, R., Johnson, R. M., Farokhnia, M., Crum, R. M., Thrul, J., & Mojtabai, R. (2021 09 01). Patterns of reduced use and abstinence in multi-site randomized controlled trials of pharmacotherapies for cocaine and methamphetamine use disorders. *Drug Alcohol Depend*, *226*, 108904. https://doi.org/10.1016/j.drugalcdep.2021.108904

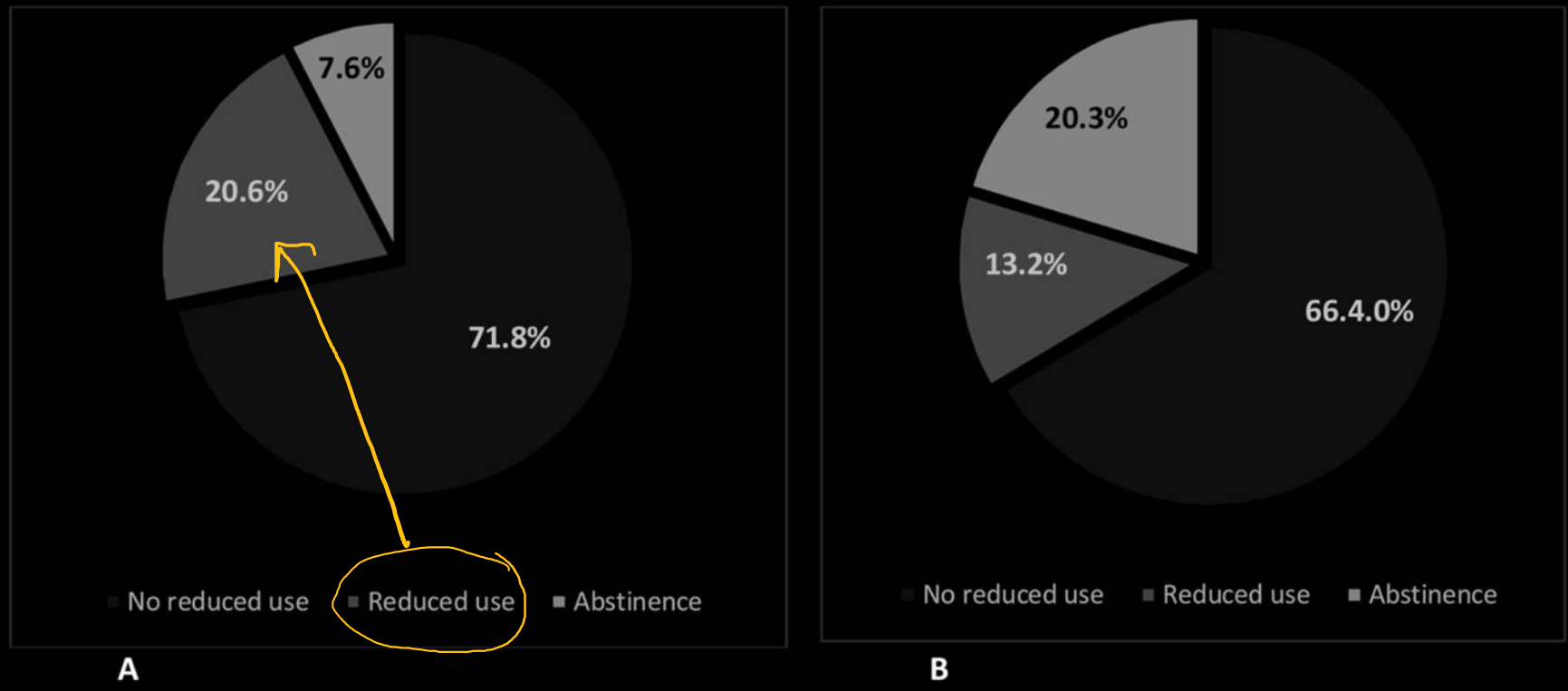

Fig. 1. **A)** Pattern of cocaine use at the end of the trial in the cocaine RCTs. **B)** Pattern of methamphetamine use at the end of the trial in methamphetamine RCTs.

ADDICTION OPINION AND DEBATE doi:10.1111/add.15242

Pharmacotherapeutic strategies for treating cocaine use disorder—what do we have to offer?

Laura Brandt[1], Thomas Chao[1,2], Sandra D. Comer[1] & Frances R. Levin[1]

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A critical issue for interpreting a medication's effectiveness is the expectation we hold about medication effects themselves. This begs the question: are we having difficulty finding an efficacious medication because of an insistence on abstinence as the only acceptable end-point?

As highlighted by most of the studies referenced here, complete abstinence is difficult to achieve for most individuals with CUD. It is intuitive that other end-points, similar to 'percent subjects with no heavy drinking days' as an efficacy end-point for medications used to treat AUD [146,147], may also indicate meaningful change [145,148]. Given the many physical and psychosocial issues that accompany CUD [148], treatment benefits are perhaps better measured through subjective indicators, such as quality of life and daily functioning, or perhaps those on a more macro scale, such as the individual burdens imposed on our health-care resources [145]. Regardless, the constraints of time and resources often preclude the direct observation of such changes. Therefore, reductions in stimulant use that are predictive of clinically relevant improvements in one's relative functioning and wellbeing may be conceived as useful alternative indicators of treatment success. Nevertheless, the jury is still out on the constituents of meaningful change, and there remains to be established a 'safe' level of stimulant use or a standard stimulant drug dose [145].

Table 2 Procedural and

Subject-related factors
Cocaine use severity
Comorbid substance use disorders
Co-occurring attention deficit hyperactivity disorder (ADHD)
Sex
Genetic subgroups
Procedural factors
Medication dose
Titration schedule
Medication adherence
Incentive structure
Release formulation

CUD = cocaine use disorder; amphetamine salts.

Brandt, L., Chao, T., Comer, S. D., & Levin, F. R. (2021 04). Pharmacotherapeutic strategies for treating cocaine use disorder-what do we have to offer? *Addiction*, *116*(4), 694–710. https://doi.org/10.1111/add.15242

Pharmacotherapy for Cocaine Use Disorder—a Systematic Review and Meta-analysis

Brian Chan, MD MPH[1,2], Karli Kondo, PhD MA[3,4], Michele Freeman, MPH[3], Chelsea Ayers, BA[3], Jessica Montgomery, MPH[3], and Devan Kansagara, MD MCR[1,3,5]

[1]Division of General Internal Medicine and Geriatrics, Oregon Health & Science University, Portland, OR, USA; [2]Central City Concern, Portland, OR, USA; [3]Evidence Synthesis Program Center, VA Portland Health Care System, Portland, OR, USA; [4]Research Integrity Office, Oregon Health & Science University, Portland, OR, USA; [5]Department of Medicine, VA Portland Health Care System, Portland, OR, USA.

Chan, B., Kondo, K., Freeman, M., Ayers, C., Montgomery, J., & Kansagara, D. (2019 12). Pharmacotherapy for Cocaine Use Disorder-a Systematic Review and Meta-analysis. *J Gen Intern Med*, *34*(12), 2858–2873. https://doi.org/10.1007/s11606-019-05074-8

Table 1 Brief Summary of Findings

	Abstinence	Use	Lapse	Relapse	Retention	Harms
All Antidepressants: Bupropion, Desipramine, Fluoxetine, Mirtazapine, Nefazodone, Paroxetine, Sertraline, Venlafaxine	★★	★★	★	★	★★★	★★
Aminoketone: Bupropion	★	★	NA	NA	★★	Ø
SSRIs: Fluoxetine, Paroxetine, and Sertraline	NA	NA	Ø	Ø	★★	★
SSRI in patients abstinent at Baseline: Sertraline	NA	NA	★	★	★	Ø
All Antipsychotics: Aripiprazole, Haloperidol, Lamotrigine, Olanzapine, Quetiapine, Risperidone, Reserpine	★	★	Ø	Ø	★★	Ø
Psychostimulants: Dexamphetamine, Lisdexamfetamine, Mazindol, Methamphetamine, Methylphenidate, Mixed Amphetamine Salts, Modafinil, Selegiline	★	★	NA	NA	★★	★★
Cognitive Enhancing Drugs: Memantine, Atomoxetine	Ø	Ø	NA	Ø	Ø	Ø
Anxiolytic: Buspirone	Ø	NA	Ø	Ø	Ø	Ø
Anticonvulsants/Muscle Relaxants: Baclofen, Carbamazepine, Gabapentin, Lamotrigine, Phenytoin, Tiagabine, Topiramate, Vigabatrin	**NA**	★★	NA	NA	★★	**Ø**
Anticonvulsant: Topiramate	★	**Ø**	NA	NA	★★	**Ø**
Drugs for other substance use disorders: Acamprosate, Buprenorphine, Buprenorphine + Naloxone, Disulfiram, Naltrexone, Methadone, Varenicline	★	Ø	Ø	Ø	Ø	Ø
Disulfiram	★	★	NA	NA	★★	★
Dopamine agonists: Amantadine, bromocriptine, L dopa/Carbidopa, pergolide, cabergoline hydergine, and pramipexole	★	**NA**	NA	NA	★★	**NA**

Shading represents the direction of effect:

(No color)	Unclear
Grey	No difference
Green	Evidence of benefit
Red	Favors placebo

Symbols represent the strength of the evidence:

NA	No evidence or not applicable
Ø	Insufficient
★	Low
★★	Moderate
★★★	High

ANTIDEPRESSIVI

Addiction

RESEARCH REPORT

doi:10.1111/j.1360-0443.2011.03552.x

Sertraline delays relapse in recently abstinent cocaine-dependent patients with depressive symptoms

Alison Oliveto[1], James Poling[2], Michael J. Mancino[1], D. Keith Williams[1], Jeff Thostenson[1], Rhonda Pruzinsky[2], Kishorchandra Gonsai[2], Mehmet Sofuoglu[2], Gerardo Gonzalez[3], Shanti Tripathi[1] & Thomas R. Kosten[4]

Oliveto, A., Poling, J., Mancino, M. J., Williams, D. K., Thostenson, J., Pruzinsky, R., … Kosten, T. R. (2012). Sertraline delays relapse in recently abstinent cocaine-dependent patients with depressive symptoms. *Addiction, 107*(1), 131–41. https://doi.org/10.1111/j.1360-0443.2011.03552.x

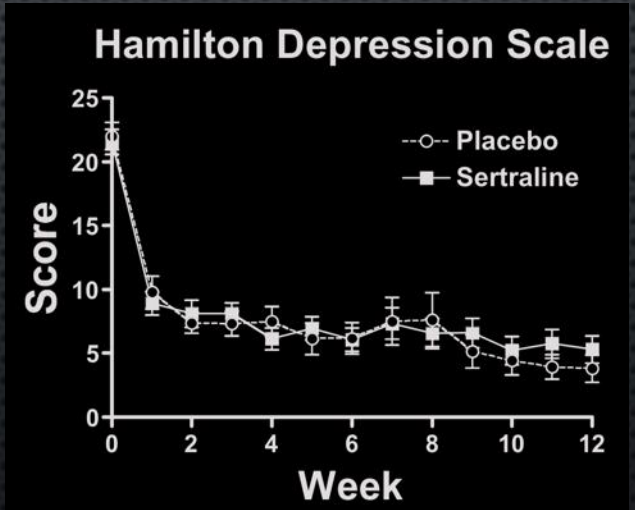

Figure 4 Weekly scores on the Hamilton Depression Scale during the 12-week trial: placebo (open circles), sertraline (closed circles). Each point represents the mean score across all participants for a given week. Bars represent standard deviation of the mean

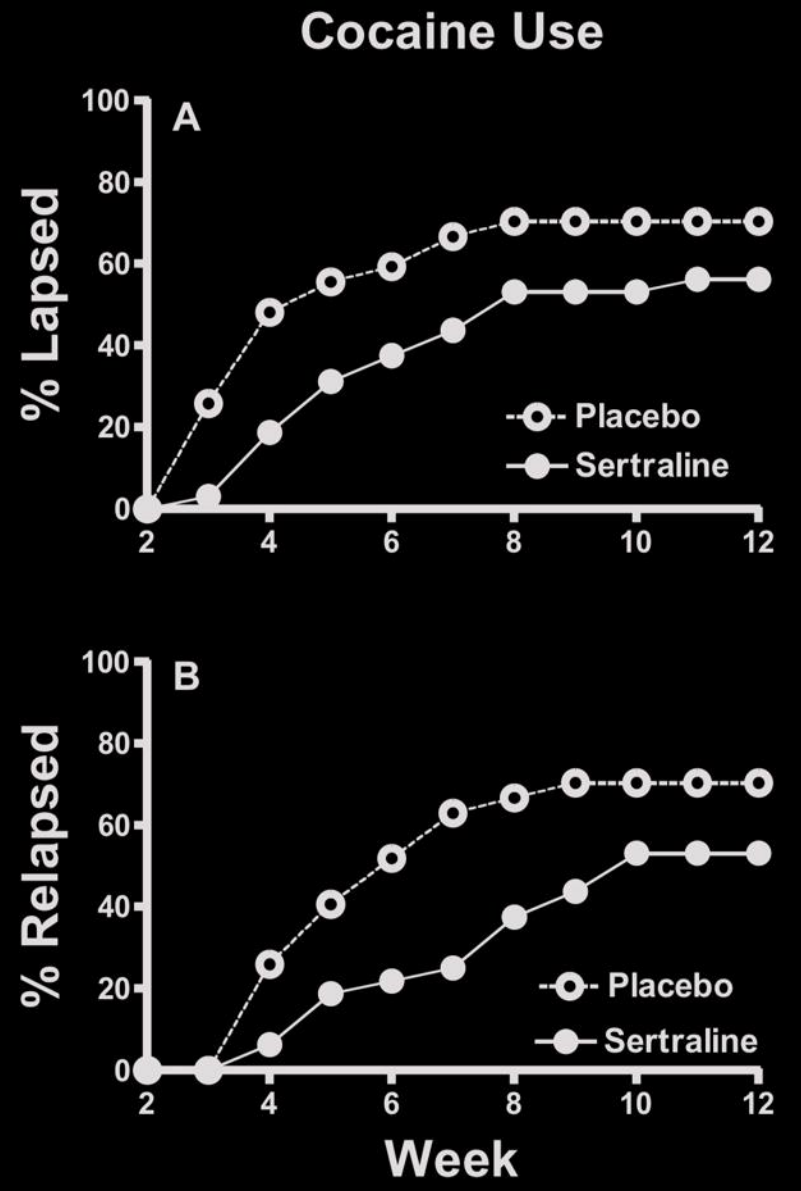

Figure 3 The percentage of participants who lapsed (i.e. first urine sample positive for cocaine; top panel) or relapsed (i.e. first two consecutive urine samples positive for cocaine; bottom panel) each week across the out-patient portion of the 12-week trial: placebo (open circles), sertraline (closed circles)

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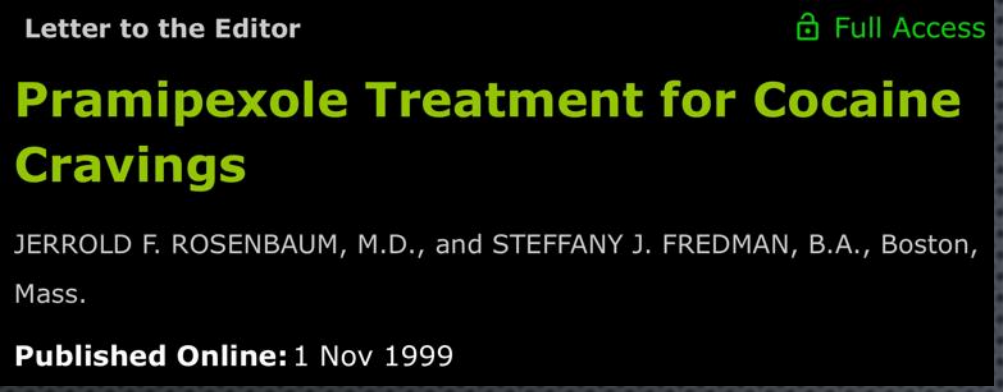

Letter to the Editor

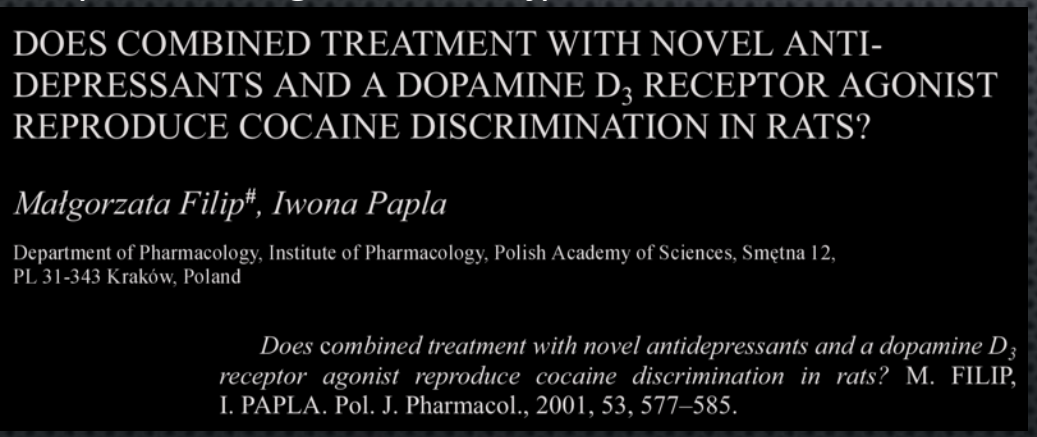
Full Access

Pramipexole Treatment for Cocaine Cravings

JERROLD F. ROSENBAUM, M.D., and STEFFANY J. FREDMAN, B.A., Boston, Mass.

Published Online: 1 Nov 1999

Rosenbaum, J. F., & Fredman, S. J. (1999). Pramipexole treatment for cocaine cravings. *Am J Psychiatry*, *156*(11), 1834. https://doi.org/10.1176/ajp.156.11.1834


DOES COMBINED TREATMENT WITH NOVEL ANTI-DEPRESSANTS AND A DOPAMINE D_3 RECEPTOR AGONIST REPRODUCE COCAINE DISCRIMINATION IN RATS?

Małgorzata Filip[#], *Iwona Papla*

Department of Pharmacology, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

Does combined treatment with novel antidepressants and a dopamine D_3 receptor agonist reproduce cocaine discrimination in rats? M. FILIP, I. PAPLA. Pol. J. Pharmacol., 2001, 53, 577–585.

Filip, M., & Papla, I. (2001). Does combined treatment with novel antidepressants and a dopamine D3 receptor agonist reproduce cocaine discrimination in rats? *Pol J Pharmacol*, *53*(6), 577–85.


Psychiatry Res. 2015 November 30; 230(1): 44–49. doi:10.1016/j.psychres.2015.07.073.

Dopamine D3 receptor-preferring agonist enhances the subjective effects of cocaine in humans

Thomas F. Newton[*], **Colin N. Haile**, **James J. Mahoney III**, **Ravi Shah**, **Christopher D. Verrico**, **Richard De La Garza II**, and **Thomas R. Kosten**

Highlights

- Studies associate pramipexole with pathological gambling and impulse control disorders suggesting a role for D3 receptors in reinforcement processes.
- We examined the impact of pramipexole treatment on the subjective effects produced by cocaine in volunteers with cocaine use disorder.
- Pramipexole produced upwards of two-fold increases in positive subjective effects ratings following cocaine.
- These results indicate that chronic D3 receptor activation increases the subjective effects of cocaine in humans.
- Caution should be used when prescribing pramipexole to patients that may also use cocaine.

Newton, T. F., Haile, C. N., Mahoney, J. J., Shah, R., Verrico, C. D., De La Garza, R., & Kosten, T. R. (2015). Dopamine D3 receptor-preferring agonist enhances the subjective effects of cocaine in humans. *Psychiatry Res*, *230*(1), 44–9. https://doi.org/10.1016/j.psychres.2015.07.073

TOPIRAMATO

REVIEW

CME/MOC

Topiramate Pharmacotherapy for Alcohol Use Disorder and Other Addictions: A Narrative Review

Ajay Manhapra, MD, Anirban Chakraborty, MBBS, and Albert J. Arias, MD, MS

cally drug or alcohol using persons. Topiramate putatively exerts it effects on midbrain dopaminergic (DA) pathways projecting from ventral tegmental area (VTA) to the nucleus accumbens (NAcc) by enhancing GABAergic neurotransmission and antagonizing glutamatergic neurotransmission, leading to suppression of dopaminergic surges at the NAcc. These

et al., 2011). Topiramate has been suggested to inhibit the expression of addiction-related automatic behavior through glutamatergic receptor inhibition. A dual effect of GABAergic potentiation and AMPA/Kainate mediated glutamatergic suppression has been hypothesized as the potential pathway of topiramate efficacy in AUD as well as other SUDs (Shank and Maryanoff, 2008). Recent small imaging studies have impli-

Together these data suggest that topiramate may have some beneficial effect in cocaine use disorder, but the clinical utility is still marginal. However, it has been suggested that topiramate offers better therapeutic benefit than the other meager pharmacotherapeutic choices in the treatment of cocaine use disorder (Johnson et al., 2013). The utility of

Manhapra, A., Chakraborty, A., & Arias, A. J. (2019). Topiramate Pharmacotherapy for Alcohol Use Disorder and Other Addictions: A Narrative Review. *J Addict Med*, *13*(1), 7–22. https://doi.org/10.1097/ADM.0000000000000443

TABLE 4. Studies of Topiramate for Cocaine Use Disorder

Year, Author and Design	Sample	Duration and Dose	Primary and Secondary outcomes	Results	Limitations/comments
Kampman et al. (2004); DBRPCT; Both groups received CBT	n = 40; TOP: 20; PLC: 20	13 weeks; TOP: 200 mg/d, titrated over 8 weeks and maintained	Abstinence to cocaine verified by twice weekly urine benzoylecgonine test	Both groups did well.; TOP group did significantly better than PLC group to be abstinent	Small sample size, only participants with moderate dependence and low withdrawal were enrolled, only 1 female participant
Reis et al. (2008); Open-label trial	n = 28 (all males)	12 weeks; TOP: 25–300 mg/d (mean: 127 mg/d)	To assess action of TOP on craving, cocaine use, and tolerability	Significant changes in craving measures, but not overall reduction in cocaine use	Open-label design, lack of a control group, small study
Mariani et al. (2012); DBRPCT; Comparing MAS-ER + TOP with PLC	n = 81; MAS-ER + TOP: 39; PLC: 42	12 weeks; MAS-ER: 60 mg/d (titrated over 2 weeks); TOP: 300 mg/d (initiated at 25 mg/d titrated over 6 weeks)	1° proportion of individuals who achieved 3 consecutive weeks of abstinence	MAS-ER + TOP group had a larger proportion of 3 consecutive weeks of abstinence.	Does not address whether both medications are necessary for efficacy
Johnson et al. (2013); DBRPCT	n = 142; TOP: 71; PLC: 71	12 weeks; TOP: 300 mg/d (started with 50 mg/d titrated over 6 weeks)	1° difference in proportion of cocaine non-use days from baseline; 2° cocaine-free weeks, craving, global functioning	Intention to treat analysis.; TOP more efficacious in increasing cocaine non use days.; More likelihood of urinary cocaine free weeks, decrease in craving and increase global functioning	
Nuijten et al. (2014); Open-label trial; Both groups received CBT	n = 74	12 weeks; TOP: 200 mg/d	Acceptance and effectiveness of TOP as an adjunctive to CBT in crack cocaine dependence	Intention to treat analysis. TOP neither improved treatment retention nor reduced cocaine use	
Kampman et al. (2013); DBRPCT in comorbid cocaine and alcohol dependence	n = 170; TOP:83; PLC:87	13 weeks; TOP: 300mg/d	Primary outcome measures: self-reported alcohol and cocaine use, and thrice weekly urine drug screens. Secondary outcome measures: cocaine and alcohol craving, Addiction Severity Index results, cocaine withdrawal symptoms, and clinical global improvement ratings	Increased retention with TOP, TOP group had greater abstinence in last 3 weeks of trial, worse withdrawal symptoms associated with better cocaine outcomes for TOP group	

MAS-ER, mixed amphetamine salts extended release; DBRPCT, double blind randomized placebo controlled trial; TOP, topiramate; PLC, placebo.

Original Investigation

Topiramate for the Treatment of Cocaine Addiction

Bankole A. Johnson, DSc, MD; Nassima Ait-Daoud, MD; Xin-Qun Wang, MS; J. Kim Penberthy, PhD; Martin A. Javors, PhD; Chamindi Seneviratne, MD; Lei Liu, PhD

Johnson, B. A., Ait-Daoud, N., Wang, X.-Q., Penberthy, J. K., Javors, M. A., Seneviratne, C., & Liu, L. (2013). Topiramate for the treatment of cocaine addiction: a randomized clinical trial. *JAMA Psychiatry*, *70*(12), 1338–46. https://doi.org/10.1001/jamapsychiatry.2013.2295

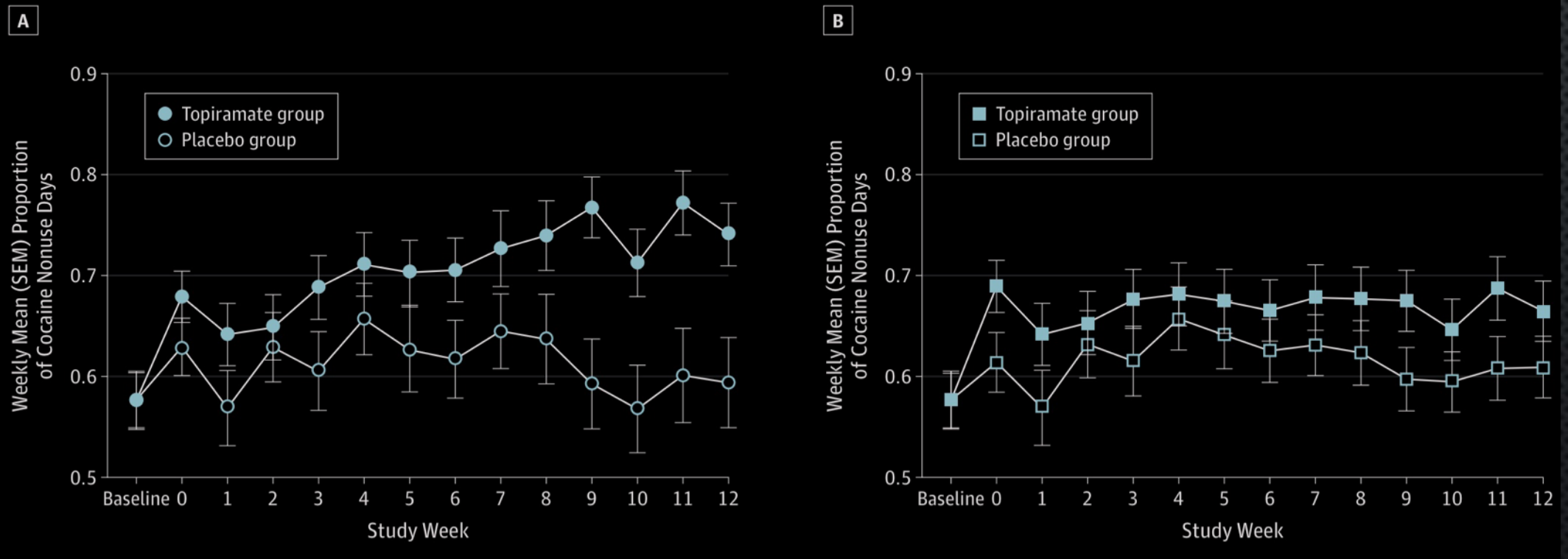
Table 1. Topiramate Dosing Schedule[a]

Week[b]	Morning Dose	Nighttime Dose	Total Daily Dose, mg
0-1	1 × 25-mg capsule	1 × 25-mg capsule	50
1-2	2 × 25-mg capsules	2 × 25-mg capsules	100
2-3	1 × 25-mg capsule + 1 × 50-mg capsule	1 × 25-mg capsule + 1 × 50-mg capsule	150
3-4	1 × 100-mg capsule	1 × 100-mg capsule	200
4-5	1 × 100-mg capsule + 1 × 25-mg capsule	1 × 100-mg capsule + 1 × 25-mg capsule	250
5-6	1 × 100-mg capsule + 2 × 25-mg capsules	1 × 100-mg capsule + 2 × 25-mg capsules	300
6-12	1 × 100-mg capsule + 2 × 25-mg capsules	1 × 100-mg capsule + 2 × 25-mg capsules	300

5 gg

4 gg

Figure 2. Weekly Mean Proportion of Cocaine Nonuse Days From Baseline Through Study Week 12



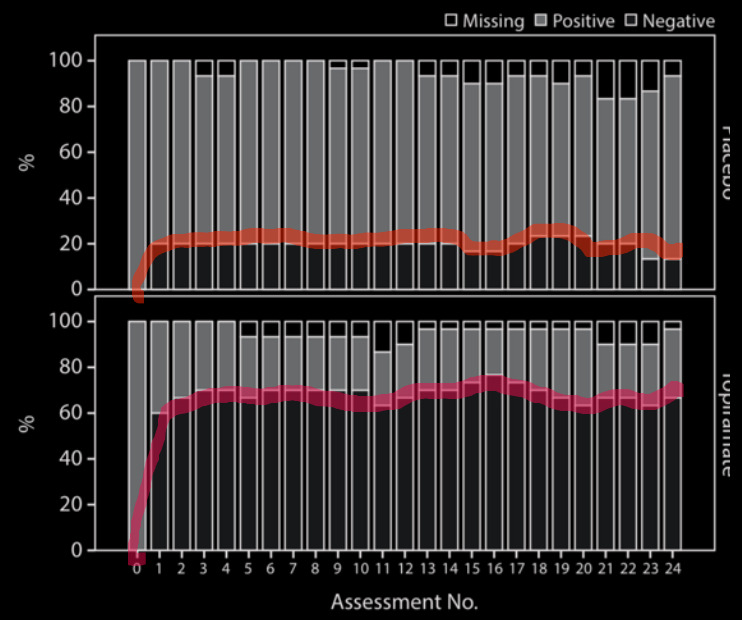
Efficacy of Topiramate in the Treatment of Crack Cocaine Dependence: A Double-Blind, Randomized, Placebo-Controlled Trial

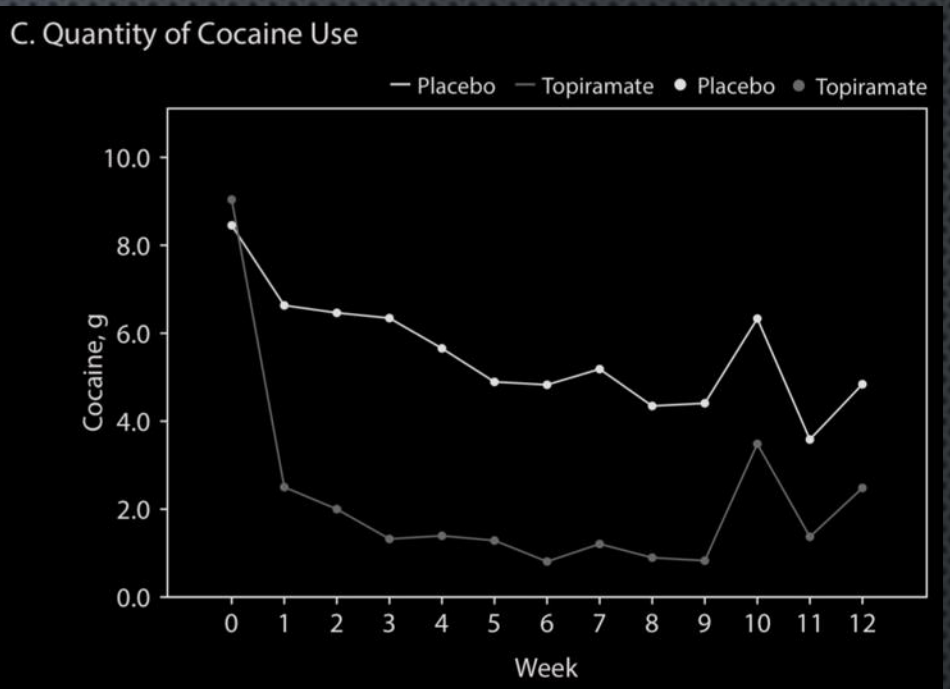
Leonardo Baldaçara, MD, PhD[a,*]; Hugo Cogo-Moreira, PhD[b]; Bruna Leal Parreira, MD[a]; Thaynne Almeida Diniz, MD[a]; Jaqueline Jerônimo Milhomem, MD[a]; Camila Campitelli Fernandes, MD[a,c]; and Acioly Luiz Tavares Lacerda, MD, PhD[d]

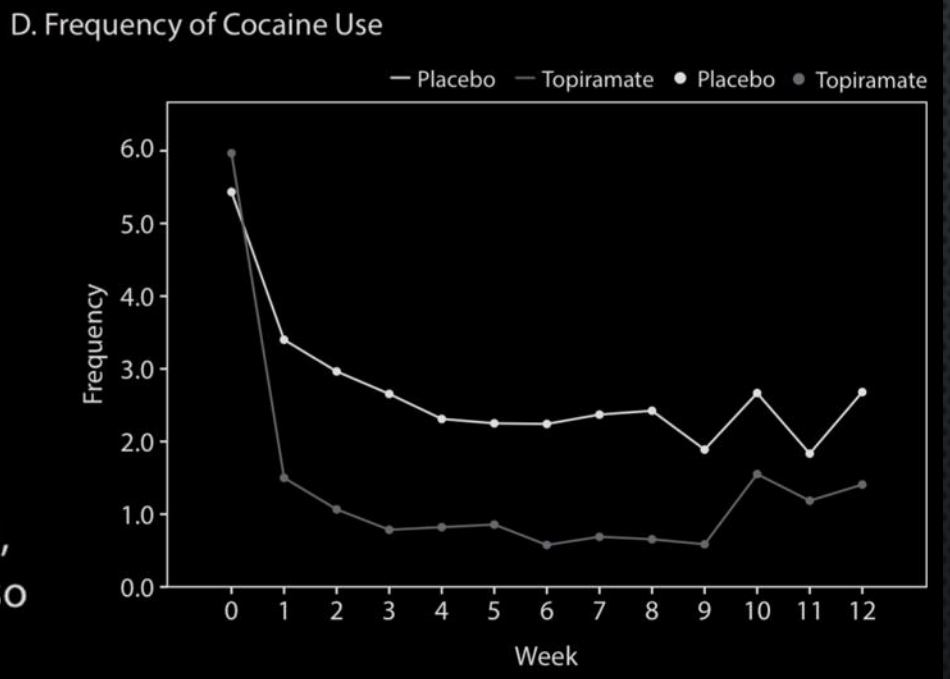
Article *in* The Journal of Clinical Psychiatry · March 2016

DOI: 10.4088/JCP.14m09377

Baldaçara, L., Cogo-Moreira, H., Parreira, B. L., Diniz, T. A., Milhomem, J. J., Fernandes, C. C., & Lacerda, A. L. T. (2016). Efficacy of topiramate in the treatment of crack cocaine dependence: a double-blind, randomized, placebo-controlled trial. *J Clin Psychiatry*, *77*(3), 398–406. https://doi.org/10.4088/JCP.14m09377







Method: Sixty men who were dependent on cocaine (*DSM-IV*) (exclusive use of crack cocaine) were selected. The subjects were randomly assigned to either a topiramate group (subjects received 50–200 mg of topiramate per day for 12 weeks) or a control group (subjects received placebo). The initial daily treatment dose was 50 mg, and this dose was increased weekly at increments of 25 to 50 mg, based on the subject's tolerability, to a maximum of 200 mg. All of the subjects also participated in motivational interviews and group therapy. The primary outcome

FARMACI PER ADHD

International Journal of
Environmental Research and Public Health

MDPI

Article

Remarkable Reduction of Cocaine Use in Dual Disorder (Adult Attention Deficit Hyperactive Disorder/Cocaine Use Disorder) Patients Treated with Medications for ADHD

Corrado Manni [1], Giada Cipollone [1], Alessandro Pallucchini [1], Angelo G. I. Maremmani [2,3,4], Giulio Perugi [5] and Icro Maremmani [3,4,6,*]

Manni, C., Cipollone, G., Pallucchini, A., Maremmani, A. G. I., Perugi, G., & Maremmani, I. (2019 10 15). Remarkable Reduction of Cocaine Use in Dual Disorder (Adult Attention Deficit Hyperactive Disorder/Cocaine Use Disorder) Patients Treated with Medications for ADHD. *Int J Environ Res Public Health*, *16*(20), E3911. https://doi.org/10.3390/ijerph16203911

disorder (A-ADHD). *Methods*: In the present retrospective study, a sample of 20 consecutive patients (aged from 18 to 65 years) with dual disorder (A-ADHD/CUD), under treatment with methylphenidate (MPH) or atomoxetine (ATM) medications, was followed to study the effects of A-ADHD treatment on cocaine use. Patients were followed for a mean period of 7 months (minimum 1, maximum 30 months). All individuals were assessed with standardized questionnaires to evaluate diagnosis, treatment

3.2. *End-Point/Baseline Changes Regarding CPSI and CGI Related to ADHD and CUD*

Table 2 reports changes in the CPSI-Questionnaire. All patients obtained an improvement (negative rankings) on the CPSI total score. On the question of the frequency of cocaine use at baseline, only one patient (5.0%) used cocaine once a week or less. Ten (50.0%) used cocaine 4–6 times per week and nine (45.0%) every day. At end point, all our patients reported use of "once a week or less".

	Negative Rankings T1 < T0	Positive Rankings T1 > T0	Ties T1 = T0	*z*	Two-Tailed *p*
CPSI-Questionnaire					
1-Length of use					
2-Frequency of use	19 (95.0%)	0 (0.0%)	1 (5.0%)	−3.904	0.000
3-Type of cocaine use	9 (45.0%)	0 (0.0%)	11(55.0%)	−2.80	0.005
4-Quantity of use	17 (85.0%)	0 (0.0%)	3 (15.0%)	−3.72	0.000
5-Longest consecutive period in the last year	13 (65.0%)	0 (0.0%)	7 (35.0%)	−3.241	0.001
6-Depressive symptoms/craving when having stopped cocaine use	12 (60.0%)	0 (0.0%)	8 (40.0%)	−3.093	0.002
7-Other somatic symptoms after having stopped cocaine use	10 (50.0%)	0 (0.0%)	10 (50.0%)	−2.844	0.004
8-Other drugs: frequency of use	9 (45.0%)	0 (0.0%)	11 (55.0%)	−2.682	0.007
9-Alcohol: frequency of use	8 (40.0%)	2 (10.0%)	10 (50.0%)	−2.339	0.019
10-Working difficulties due to cocaine use	8 (40.0%)	2 (10.0%)	10 (50.0%)	−2.339	0.019
11-Relationship difficulties due to cocaine use	13 (65.0%)	0 (0.0%)	7 (35.0%)	−3.220	0.001
12-Household difficulties due to cocaine use	14 (70.0%)	0 (0.0%)	6 (30.0%)	−3.376	0.001
13-Financial difficulties due to cocaine use	14 (70.0%)	0 (0.0%)	6 30.0%)	−3.345	0.001
14-Importance of cocaine in sexual activities	12 (60.0%)	0 (0.0%)	8 (40.0%)	−3.108	0.002
15-Friends using cocaine	12 (60.0%)	1 (5.0%)	7 (35.0%)	−2.977	0.003
16-Friends using alcohol	12 (60.0%)	0 (0.0%)	8 (40.0%)	−3.097	0.002
17-Cocaine: supply of	16 (80.0%)	0 (0.0%)	4 (20.0%)	−3.704	0.000
18-Severity	17 (85.0%)	0 (0.0%)	3 (15.0%)	−1.604	0.109
Total CPSI	20 (100.0%)	0 (0.0%)	0 (0.0%)	−3.921	0.000

T0 = baseline; T1 = endpoint; z = z test of Wilcoxon signed-rank test.

Drug and Alcohol Dependence
Volume 188, 1 July 2018, Pages 135-140

Full length article

How treatment improvement in ADHD and cocaine dependence are related to one another: A secondary analysis

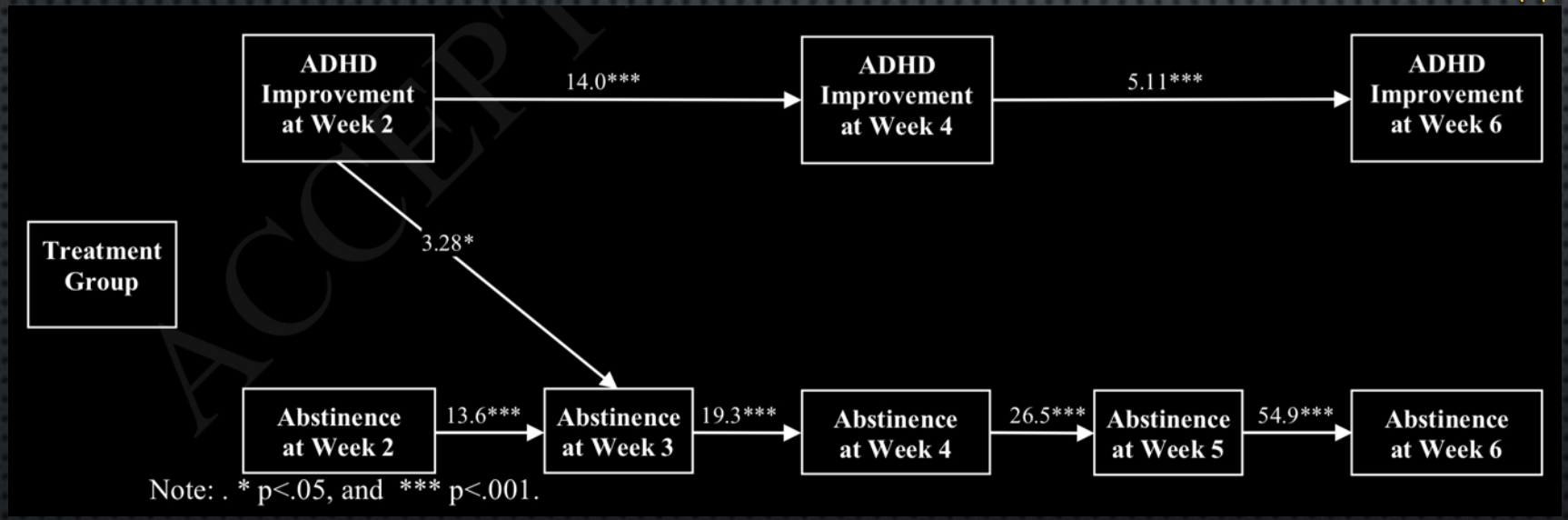
Frances R. Levin [a, b], C. Jean Choi [e], Martina Pavlicova [c], John J. Mariani [a, b], Amy Mahony [a], Daniel J. Brooks [a], Edward V. Nunes [a, b], John Grabowski [d]

Highlights

ABSTINENCE 48%

- Participants were Cocaine Dependent (CD) and in a stimulant medication trial.
- Participants were diagnosed with Attention Deficit Hyperactivity Disorder (ADHD).
- The relationship between ADHD and cocaine use outcomes were examined.
- When ADHD improvement and cocaine abstinence occurred, ADHD usually improved first.
- Few individuals became cocaine abstinent without an ADHD symptom reduction.

MIXED AMPH SAUS



Levin, F. R., Choi, C. J., Pavlicova, M., Mariani, J. J., Mahony, A., Brooks, D. J., … Grabowski, J. (2018 07 01). How treatment improvement in ADHD and cocaine dependence are related to one another: A secondary analysis. *Drug Alcohol Depend, 188*, 135–140. https://doi.org/10.1016/j.drugalcdep.2018.03.043

ACETILCISTEINA

Review Article

N-Acetylcysteine for the Treatment of Psychiatric Disorders: A Review of Current Evidence

Soo Liang Ooi,[1] Ruth Green,[2] and Sok Cheon Pak[2]

Ooi, S., Green, R., & Pak, S. (2018). N-Acetylcysteine for the Treatment of Psychiatric Disorders: A Review of Current Evidence. *Biomed Res Int*, *2018*, 2469486. https://doi.org/10.1155/2018/2469486

Table 1: Summary of included reviews: N-acetylcysteine for addiction and substance abuse disorders.

Authors (Year)	Type	Inclusion	No. Studies (Study Size)	Conclusion
Asevedo et al. (2014) [14]	SR	Clinical trials that assessed NAC with outcomes related to an addiction.	Total = 9 (n = 295): Cocaine = 3 (n = 60); Cannabis = 2 (n = 140); Nicotine = 2 (n = 51); Methamphetamine = 1 (n = 31); Gambling = 1 (n = 13)	Included studies suggest a potential role for NAC in the treatment of addiction, especially cocaine and cannabis dependence.
Deepmala et al. (2015) [15]	SR	Clinical trials of psychiatric and neurological disorders which reported a direct clinical effect of NAC as an outcome.	Total = 19 (n = 781): Cocaine = 5 (n = 168); Cannabis = 3 (n = 229); Nicotine = 6 (n = 253); Methamphetamine = 2 (n = 63); Gambling = 3 (n = 68)	Limited evidence for NAC as a treatment for addiction. Positive results for cocaine, but only for those who were abstinent. Some evidence for cannabis, even though results are inconsistent. Premature to make recommendations for or against the use of NAC in other types of addiction.
Minarini et al. (2017) [16]	SR	Clinical trials that assessed NAC use as the independent variable and clinical outcomes related to a psychiatric disorder.	Total = 18 (n = 711): Cocaine = 5 (n = 168); Cannabis = 4 (n = 252); Nicotine = 6 (n = 188); Methamphetamine = 2 (n = 63); Gambling = 1 (n = 40)	The clinical usefulness of NAC for SUDs, apart from cannabis use disorder in young people, is not currently supported by good enough evidence.
Nocito Echevarria et al. (2017) [17]	SR	Human or animal studies using NAC as an intervention for cocaine dependence.	Total (Cocaine) = 6 (n = 188) (Human trials only)	Promising data from preliminary studies, but results from a double-blind placebo trial was mainly negative. Current data suggest NAC may be better suited for avoiding relapse in already abstinent subjects.
Duailibi et al. (2017) [18]	SR+MA	RCTs of NAC for treatment of SUD with standardized assessment of craving.	Total = 7 (n = 245): Cocaine = 2 (n = 43); Cannabis = 1 (n = 89); Nicotine = 3 (n = 67); Methamphetamine = 1 (n = 46)	NAC was significantly superior for reducing craving symptoms compared to placebo (Hedges' g = 0.94; 95% CI: 0.55–1.33). NAC has a potential clinical use for craving in SUDs.

Abbreviation. Confidence interval (CI); meta-analysis (MA); N-acetylcysteine (NAC); randomised control trial (RCT); substance use disorder (SUD); systematic review (SR).

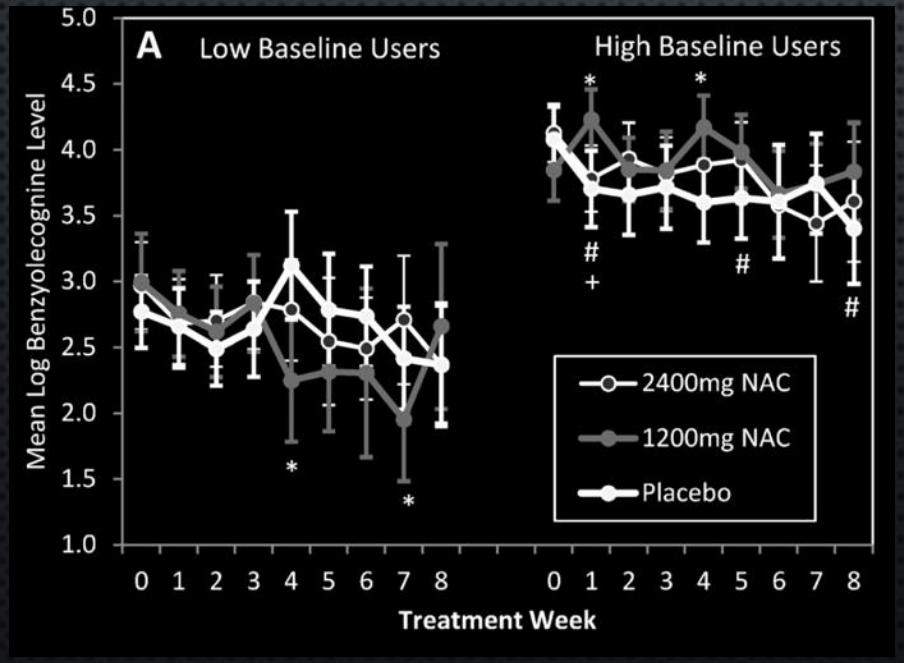
The American Journal on Addictions, 22: 443–452, 2013

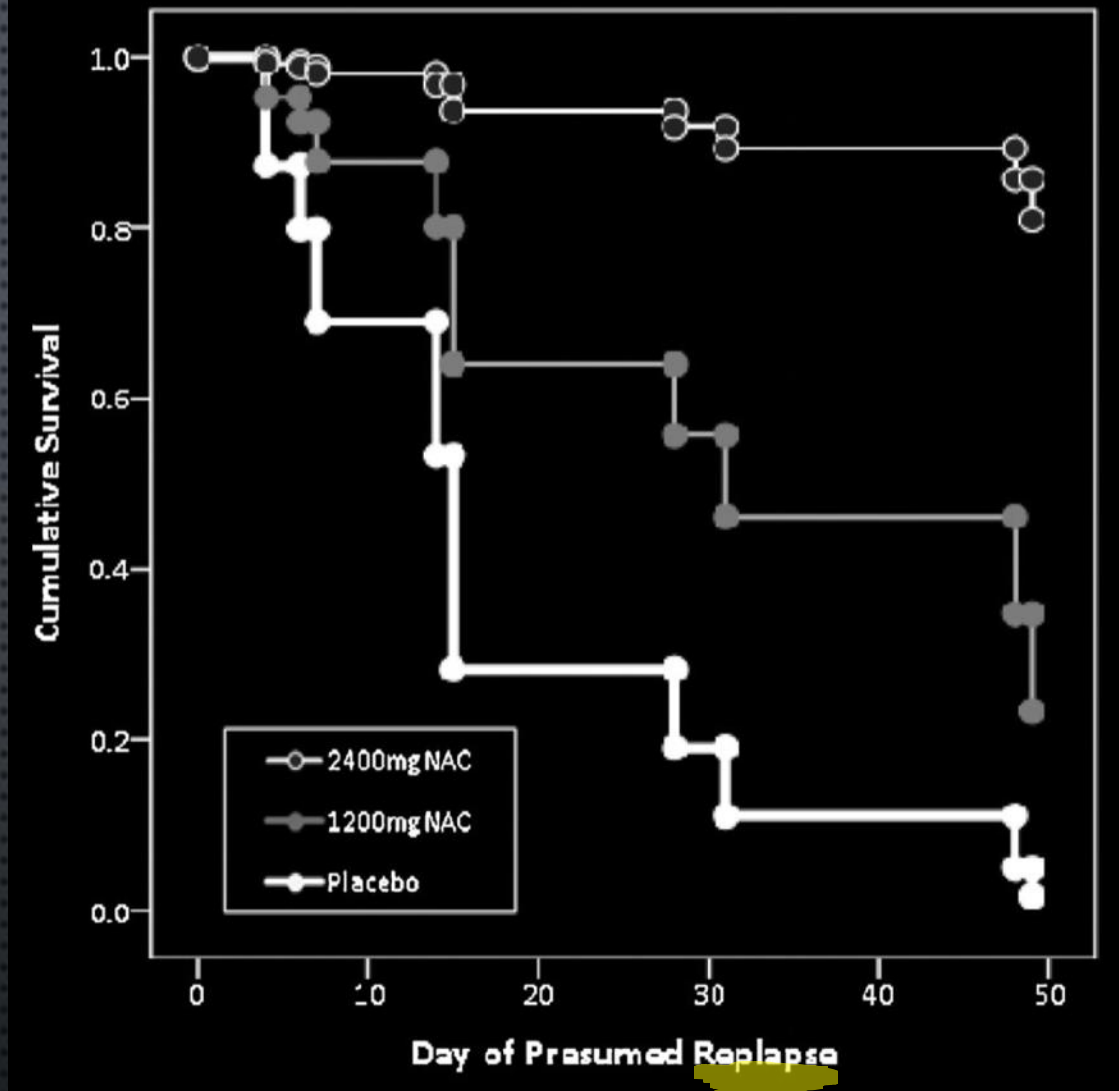
ISSN: 1055-0496 print / 1521-0391 online
DOI: 10.1111/j.1521-0391.2012.12034.x

A Double-Blind Placebo-Controlled Trial of *N*-Acetylcysteine in the Treatment of Cocaine Dependence

Steven D. LaRowe, PhD,[1,2] Peter W. Kalivas, PhD,[3] Joyce S. Nicholas, PhD,[3,4] Patrick K. Randall, PhD,[2] Pascale N. Mardikian, MD,[2] Robert. J. Malcolm, MD[2]

LaRowe, S. D., Kalivas, P. W., Nicholas, J. S., Randall, P. K., Mardikian, P. N., & Malcolm, R. J. (2013). A double-blind placebo-controlled trial of N-acetylcysteine in the treatment of cocaine dependence. *Am J Addict*, *22*(5), 443–52. https://doi.org/10.1111/j.1521-0391.2013.12034.x





Note: Placebo *n*=8, 1200mg NAC *n*=4, 2400mg NAC *n*= 5

FIGURE 2. Results of exploratory analysis of time to relapse for subjects who were abstinent for at least 1 week prior to entering the medication trial. Placebo $n = 8$, 1,200 mg NAC $n = 4$, 2,400 mg NAC $n = 5$.

BUPRENORFINA

ADDICTION

SSA SOCIETY FOR THE STUDY OF ADDICTION

RESEARCH REPORT

doi:10.1111/add.13375

Buprenorphine + naloxone plus naltrexone for the treatment of cocaine dependence: the Cocaine Use Reduction with Buprenorphine (CURB) study

Walter Ling[1], Maureen P. Hillhouse[1], Andrew J. Saxon[2], Larissa J. Mooney[1], Christie M. Thomas[1], Alfonso Ang[1], Abigail G. Matthews[4], Albert Hasson[1], Jeffrey Annon[1], Steve Sparenborg[3], David S. Liu[3], Jennifer McCormack[4], Sarah Church[5], William Swafford[6], Karen Drexler[7], Carolyn Schuman[8], Stephen Ross[9], Katharina Wiest[10], P. Todd Korthuis[11], William Lawson[12], Gregory S. Brigham[13], Patricia C. Knox[14], Michael Dawes[15] & John Rotrosen[16]

Ling, W., Hillhouse, M. P., Saxon, A. J., Mooney, L. J., Thomas, C. M., Ang, A., … Rotrosen, J. (2016 08). Buprenorphine + naloxone plus naltrexone for the treatment of cocaine dependence: the Cocaine Use Reduction with Buprenorphine (CURB) study. *Addiction*, *111*(8), 1416–27. https://doi.org/10.1111/add.13375

Table 2 Cocaine use during evaluation period (days 25–54) and follow-up.

30 giorni

	PLB	BUP4	BUP4 versus PLB	BUP16	BUP16 versus PLB
Primary outcome					
Number of days of cocaine use during the evaluation period					
n	102	100		100	
Mean (SD)	8.2 (6.84)	7.8 (7.23)		7.9 (7.72)	
P-value (one-sided)	–	0.262		0.185	
Rank-biserial correlation		−0.09		−0.08	

Naltrexone XR

European Journal of Clinical Pharmacology
https://doi.org/10.1007/s00228-022-03302-5

PHARMACOGENETICS

Moderation of buprenorphine therapy for cocaine dependence efficacy by variation of the *Prodynorphin* gene

David A. Nielsen[1,2,3] · Robrina Walker[4] · David P. Graham[1,3] · Ellen M. Nielsen[1] · Sara C. Hamon[5] · Maureen Hillhouse[6] · Dikla Shmueli-Blumberg[7] · William B. Lawson[8] · Kathy Shores-Wilson[4] · Beverlyn D. Settles-Reaves[8] · John Rotrosen[9] · Madhukar H. Trivedi[4] · Andrew J. Saxon[10] · Walter Ling[6] · Thomas R. Kosten[1]

Received: 18 February 2021 / Accepted: 20 February 2022

Abstract

Purpose The aim of this secondary analysis was to identify *prodynorphin* (*PDYN*) genetic markers moderating the therapeutic response to treatment of cocaine dependence with buprenorphine/naloxone (Suboxone®; BUP).

Methods Cocaine-dependent participants ($N=302$) were randomly assigned to a platform of injectable, extended-release naltrexone (XR-NTX) and one of three daily medication arms: 4 mg BUP (BUP4), 16 mg BUP (BUP16), or placebo (PLB) for 8 weeks (Parent Trial Registration: Protocol ID: NIDA-CTN-0048, Clinical Trials.gov ID: NCT01402492). DNA was obtained from 277 participants. Treatment response was determined from weeks 3 to 7 over each 1-week period by the number of cocaine-positive urines per total possible urines.

Results In the cross-ancestry group, the PLB group had more cocaine-positive urines than the BUP16 group ($P=0.0021$). The interactions of genetic variant × treatment were observed in the rs1022563 A-allele carrier group where the BUP16 group ($N=35$) had fewer cocaine-positive urines ($P=0.0006$) than did the PLB group ($N=26$) and in the rs1997794 A-allele carrier group where the BUP16 group ($N=49$) had fewer cocaine-positive urines ($P=0.0003$) than did the PLB group ($N=58$). No difference was observed in the rs1022563 GG or rs1997794 GG genotype groups between the BUP16 and PLB groups. In the African American-ancestry subgroup, only the rs1022563 A-allele carrier group was associated with treatment response.

Conclusion These results suggest that *PDYN* variants may identify patients who are best suited to treatment with XR-NTX plus buprenorphine for cocaine use disorder pharmacotherapy.

Keywords Buprenorphine · Cocaine · Polymorphism · Prodynorphin · Gene

Nielsen, D. A., Walker, R., Graham, D. P., Nielsen, E. M., Hamon, S. C., Hillhouse, M., … Kosten, T. R. (2022). Moderation of buprenorphine therapy for cocaine dependence efficacy by variation of the Prodynorphin gene. *Eur J Clin Pharmacol*. https://doi.org/10.1007/s00228-022-03302-5

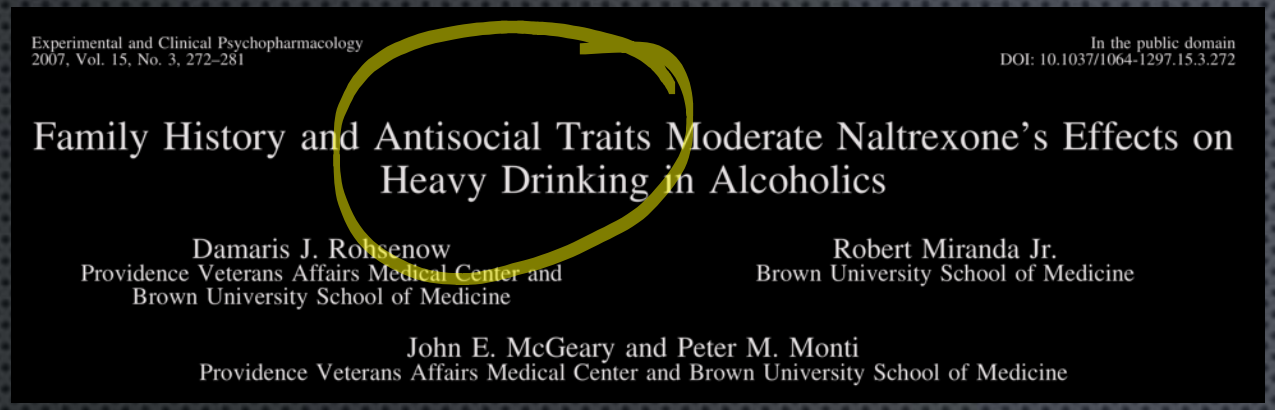
NALTREXONE

CNS Drugs
DOI 10.1007/s40263-016-0373-0

REVIEW ARTICLE

Naltrexone: A Pan-Addiction Treatment?

Elias Aboujaoude[1] · Wael O. Salame[2]



Experimental and Clinical Psychopharmacology
2007, Vol. 15, No. 3, 272–281

In the public domain
DOI: 10.1037/1064-1297.15.3.272

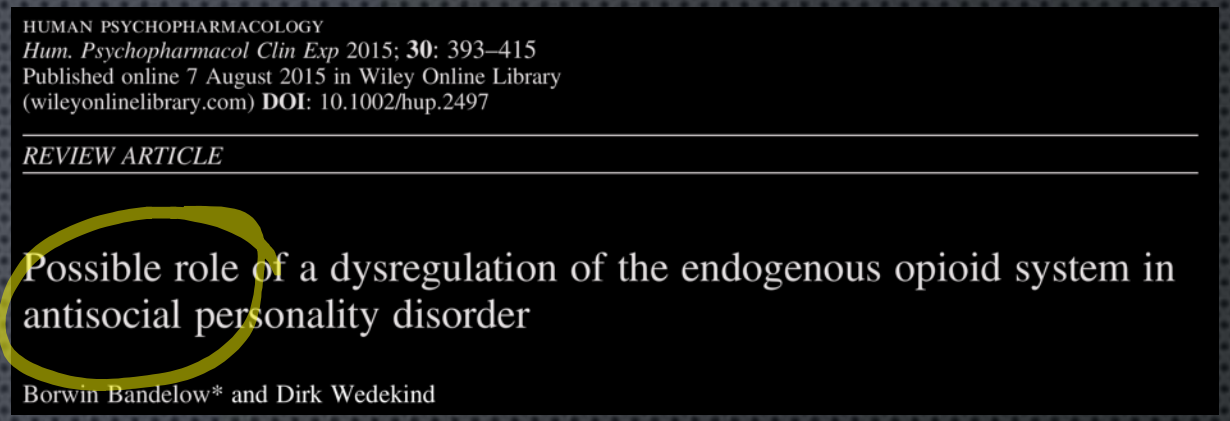
Family History and Antisocial Traits Moderate Naltrexone's Effects on Heavy Drinking in Alcoholics

Damaris J. Rohsenow
Providence Veterans Affairs Medical Center and Brown University School of Medicine

Robert Miranda Jr.
Brown University School of Medicine

John E. McGeary and Peter M. Monti
Providence Veterans Affairs Medical Center and Brown University School of Medicine

Rohsenow, D. J., Miranda, R., McGeary, J. E., & Monti, P. M. (2007). Family history and antisocial traits moderate naltrexone's effects on heavy drinking in alcoholics. *Exp Clin Psychopharmacol*, *15*(3), 272–81. https://doi.org/10.1037/1064-1297.15.3.272



HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2015; **30**: 393–415
Published online 7 August 2015 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hup.2497

REVIEW ARTICLE

Possible role of a dysregulation of the endogenous opioid system in antisocial personality disorder

Borwin Bandelow* and Dirk Wedekind

Bandelow, B., & Wedekind, D. (2015). Possible role of a dysregulation of the endogenous opioid system in antisocial personality disorder. *Hum. Psychopharmacol Clin Exp*, *30*(6), 393–415. https://doi.org/10.1002/hup.2497

Received: 14 October 2020 | Revised: 5 May 2021 | Accepted: 6 May 2021

DOI: 10.1002/hup.2800

RESEARCH ARTICLE

WILEY

Efficacy of naltrexone in borderline personality disorder, a retrospective analysis in inpatients

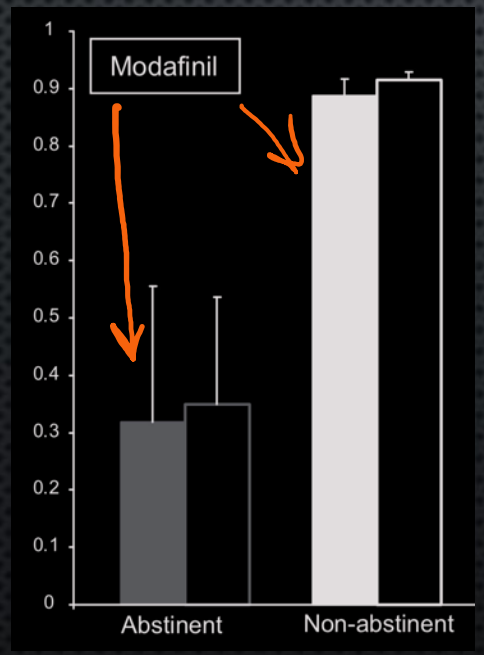
Charles Timäus[1] | Miriam Meiser[1] | Jens Wiltfang[1,2,3] | Borwin Bandelow[1] | Dirk Wedekind[1]

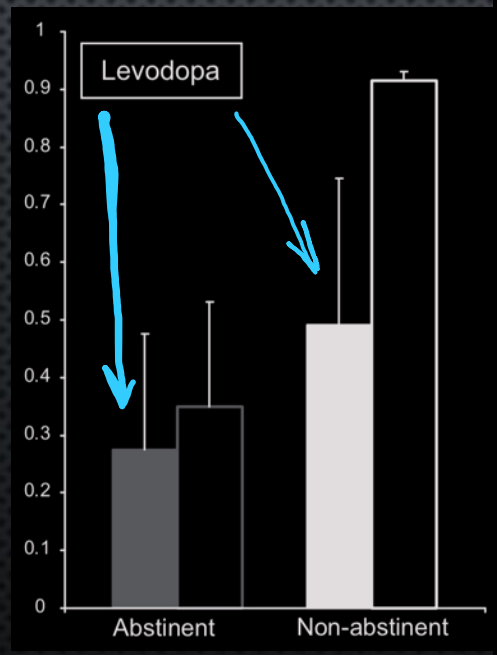
TABLE 5 Frequency of treatment responders/non-responders among BPD patients with/without naltrexone treatment

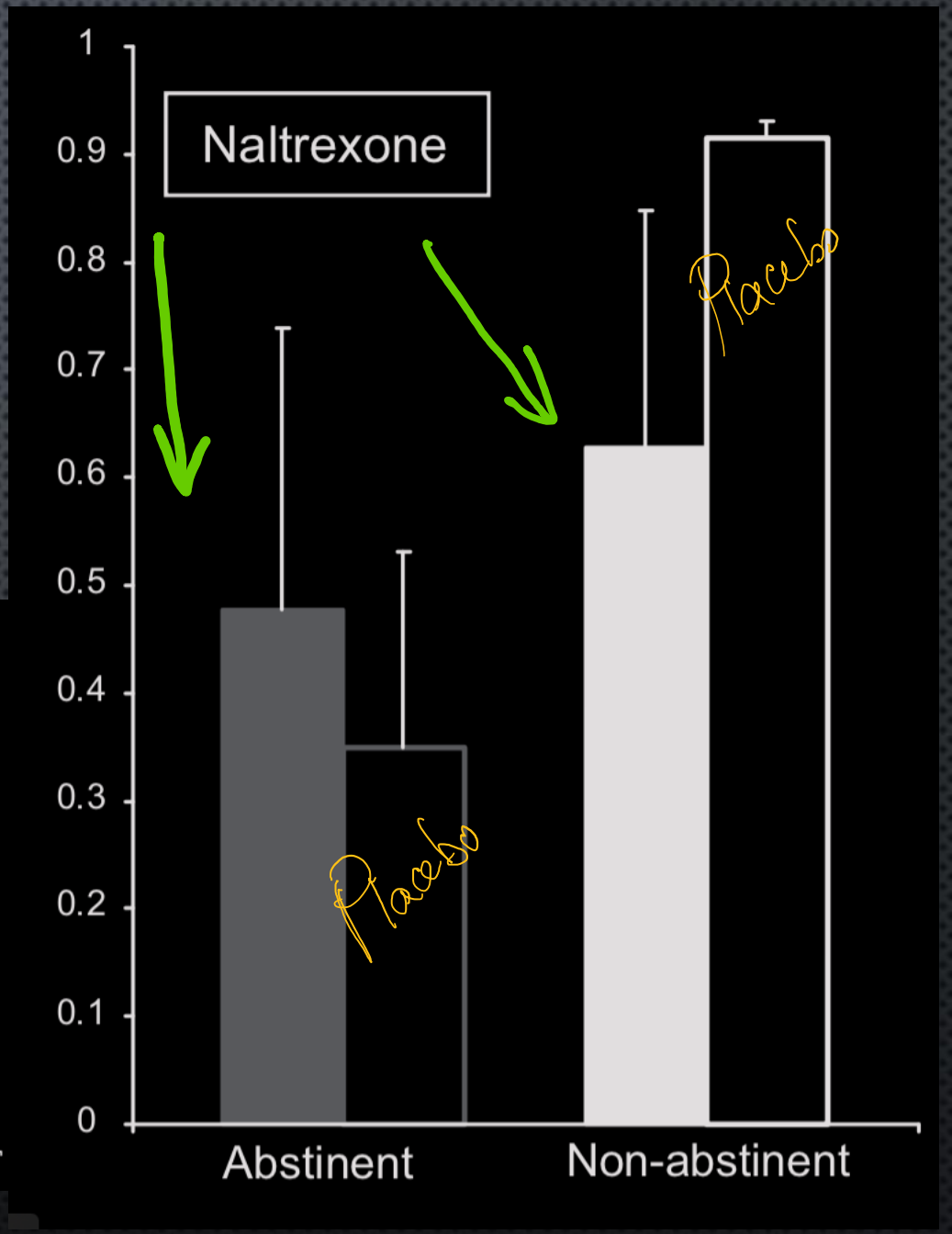
	Non-responders		Responders	
	(*N*)	(%)	(*N*)	(%)
Without naltrexone	76	71.7	30	28.3
Naltrexone (total)	10	18.2	45	81.8
Naltrexone (low dose)[a]	9	22.0	32	78.1
Naltrexone (high dose)[b]	1	7.1	13	92.9

Timäus, C., Meiser, M., Wiltfang, J., Bandelow, B., & Wedekind, D. (2021). Efficacy of naltrexone in borderline personality disorder, a retrospective analysis in inpatients. *Hum Psychopharmacol*, *36*(6), e2800. https://doi.org/10.1002/hup.2800

Schmitz, J. M., Green, C. E., Stotts, A. L., Lindsay, J. A., Rathnayaka, N. S., Grabowski, J., & Moeller, F. G. (2014). A two-phased screening paradigm for evaluating candidate medications for cocaine cessation or relapse prevention: modafinil, levodopa-carbidopa, naltrexone. *Drug Alcohol Depend, 136*, 100–7. https://doi.org/10.1016/j.drugalcdep.2013.12.015







Pergamon

ADDICTIVE BEHAVIORS

Addictive Behaviors 26 (2001) 167–180

Naltrexone and relapse prevention treatment for cocaine-dependent patients

Joy M. Schmitz*, Angela L. Stotts, Howard M. Rhoades, John Grabowski

Ritenzione 49%
Compliance 75%
Astenzione 14%

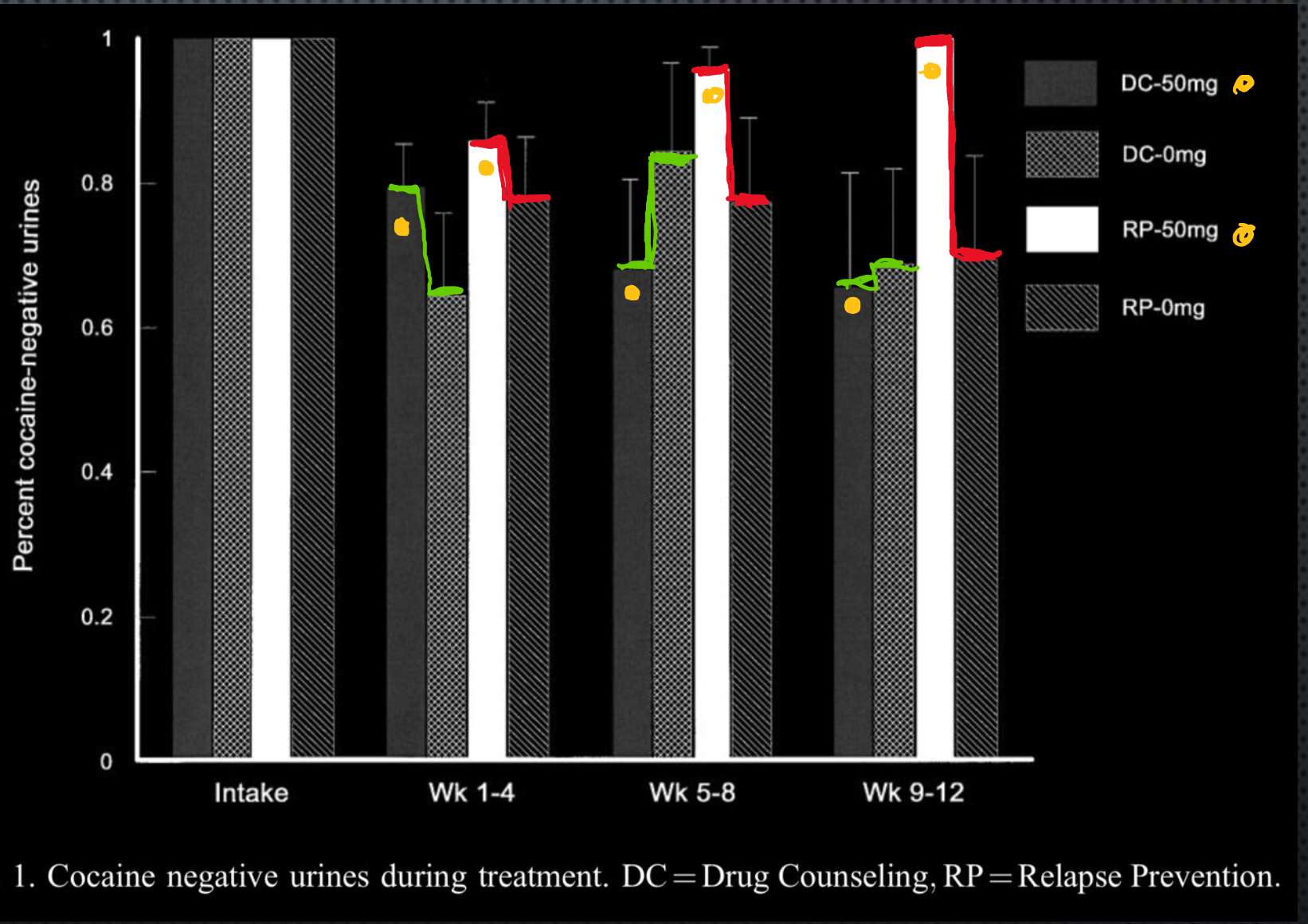


Fig. 1. Cocaine negative urines during treatment. DC = Drug Counseling, RP = Relapse Prevention.

Schmitz, J. M., Stotts, A. L., Rhoades, H. M., & Grabowski, J. (2001). Naltrexone and relapse prevention treatment for cocaine-dependent patients. *Addict Behav*, *26*(2), 167–80. https://doi.org/10.1016/s0306-4603(00)00098-8

Treatment of cocaine craving with as-needed nalmefene, a partial κ opioid receptor agonist: first clinical experience

Martin Grosshans[a], Jochen Mutschler[b] and Falk Kiefer[a]

Case report

A 43-year-old patient had been addicted to cocaine for 7 years. Six months ago, she requested our Department to take over the management of her CD. Although the patient has been continually abstinent from cocaine for over a year, she still regularly had heavy cravings for cocaine (about 4–6 times a week). At first, we suggested a sustained daily treatment with disulfiram, topiramate, or pregabalin, but she resolutely refused to take any of these substances. She was concerned that they would

use. In the following 5 months, the patient took nalmefene at a dose of 18 mg whenever she developed a craving for cocaine. For most of these interventions, the patient reported an abatement of her craving, with subsidence of the corresponding symptoms (feelings of unrest, sweating, and imaginations of cocaine intake). At any rate, she could avoid relapse into cocaine consumption after entrusting us with the management of her CD. The patient had no complaints in terms of nalmefene affecting her wakefulness or cognition, and she also did not develop other side effects such as nausea or vomiting. Thus, she wished to continue the treatment with nalmefene in the manner described.

Grosshans, M., Mutschler, J., & Kiefer, F. (2015). Treatment of cocaine craving with as-needed nalmefene, a partial κ opioid receptor agonist: first clinical experience. *Int Clin Psychopharmacol*, *30*(4), 237–8. https://doi.org/10.1097/YIC.0000000000000069

Available online at www.sciencedirect.com
ScienceDirect
ELSEVIER
ADDICTIVE BEHAVIORS
Addictive Behaviors 33 (2008) 651–667

A double blind, placebo-controlled trial that combines disulfiram and naltrexone for treating co-occurring cocaine and alcohol dependence ☆

Helen M. Pettinati [a,*], Kyle M. Kampman [a], Kevin G. Lynch [a], Hu Xie [a], Charles Dackis [a], Amanda R. Rabinowitz [a], Charles P. O'Brien [a,b]

Pettinati, H. M., Kampman, K. M., Lynch, K. G., Xie, H., Dackis, C., Rabinowitz, A. R., & O'Brien, C. P. (2008). A double blind, placebo-controlled trial that combines disulfiram and naltrexone for treating co-occurring cocaine and alcohol dependence. *Addict Behav*, *33*(5), 651–67. https://doi.org/10.1016/j.addbeh.2007.11.011

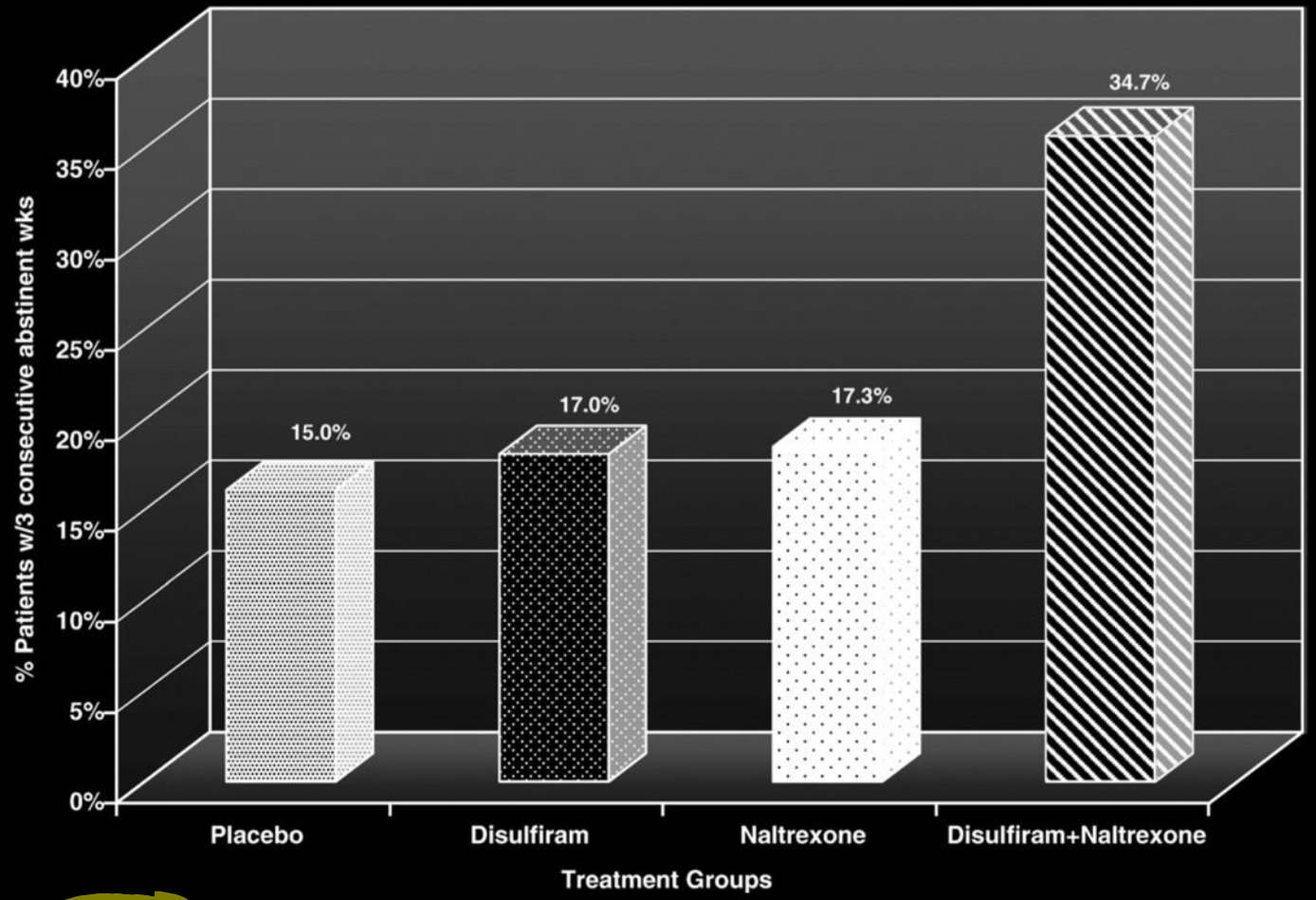


Fig. 1. The percent of cocaine-alcohol dependent patients (via DSM-IV criteria) that achieved at least 3 consecutive weeks of abstinence from both cocaine and alcohol in an 11-week controlled clinical trial of four randomized groups, assigned to placebo, or 250 mg/day of disulfiram, or 100 mg/day of naltrexone, or the combination of these two medications at the dosages specified.

DISULFIRAM

Rev Bras Psiquiatr. 2013;35:097-098

Revista Brasileira de Psiquiatria
RBPPsychiatry
Official Journal of the Brazilian Psychiatric Association
Volume 35 • Number 1 • February/2013

Letter to the Editors

Could disulfiram be a new treatment for crack cocaine dependence? A pilot study

Baldaçara, L., Diniz, T. A., Parreira, B. L., Milhomem, J. J., Almeida, L. J. C. de, & Fernandes, C. C. (2013). Could disulfiram be a new treatment for crack cocaine dependence?: a pilot study. *Braz J Psychiatry*, *35*(1), 97–8. https://doi.org/10.1016/j.rbp.2012.10.006

The subjects were randomly divided by permuted blocks into two groups; 15 subjects (28.6 ± 4.4 years of age) received 250 mg of disulfiram daily for 60 days, and 15 controls (matched by gender, age and diagnosis) received placebo.

Table 1 Outcome measures

	Baseline		Endpoint		Effect-size		
Parameter	Disulfiram	Placebo	Disulfiram	Placebo	Disulfiram	Placebo	p-value
Treatment adherence*	-	-	14 (93%)	10 (67%)	-	-	.068
Drug frequency use**	4.9 ± 1.5	4.5 ± 1.4	0.6 ± 0.2	1.4 ± 0.9	-4.7 ± 2.6	-2.9 ± 2.0	.015
Drug dosage**	3.9 ± 1.5	3.8 ± 2.1	0.6 ± 0.2	1.9 ± 1.7	-3.7 ± 1.6	-2.1 ± 1.4	.009
Drug free*	-	-	13 (87%)	7 (47%)	2.5***	-	.020
Side-effects*	-	-	3 (20%)	1 (6.6%)	7.46****	-	.283

*n (%); ** mean ± SD; *** number needed to treat (NNT); **** number needed to harm (NNH).

Drug and Alcohol Dependence 136 (2014) 36–42

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

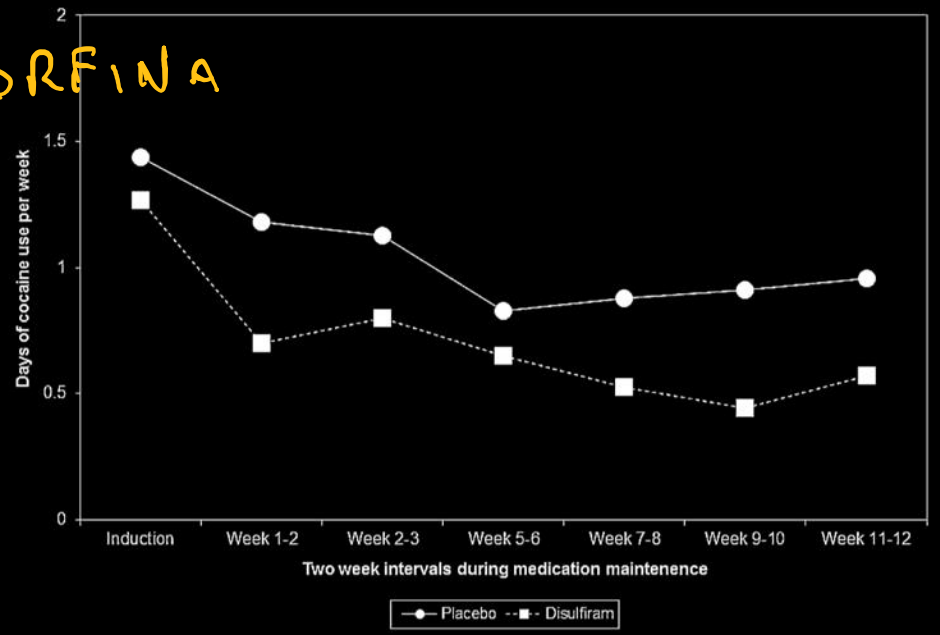
Full length article

Randomized clinical trial of disulfiram for cocaine dependence or abuse during buprenorphine treatment

Richard S. Schottenfeld[a,*], Marek C. Chawarski[a], Joseph F. Cubells[b], Tony P. George[c], Jaakko Lappalainen[a], Thomas R. Kosten[d]

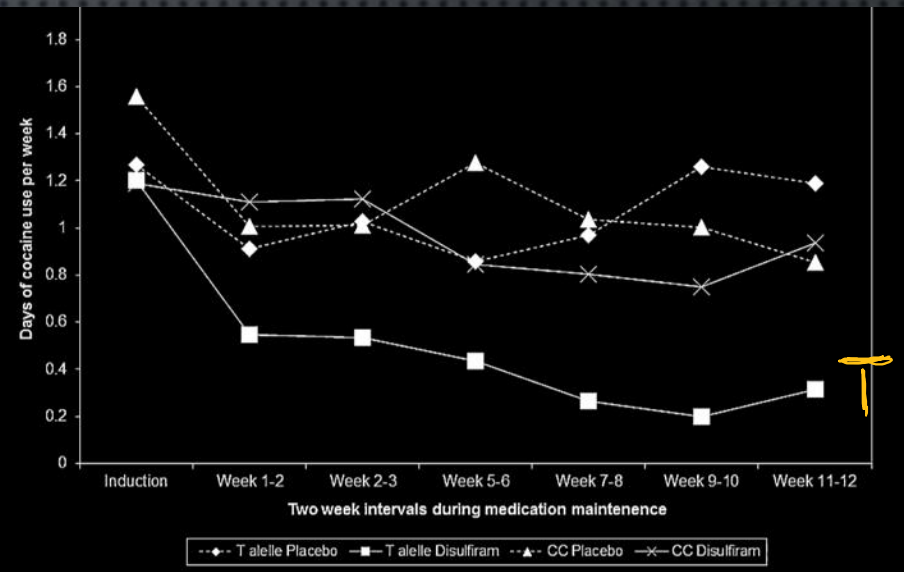
Schottenfeld, R. S., Chawarski, M. C., Cubells, J. F., George, T. P., Lappalainen, J., & Kosten, T. R. (2014). Randomized clinical trial of disulfiram for cocaine dependence or abuse during buprenorphine treatment. *Drug Alcohol Depend*, *136*, 36–42. https://doi.org/10.1016/j.drugalcdep.2013.12.007

CON BUPRENORFINA



Placebo	86	85	75	69	57	49	50
Disulfiram	91	87	81	64	60	47	45

Fig. 2. Disulfiram effects on frequency of cocaine use—Intention-to-treat sample ($N = 177$). Figure shows the mean days per week of cocaine use in each treatment group in the intention-to-treat sample ($N = 177$) during successive two-week time intervals from the two-week pre-randomization induction period until the end of week 12 of treatment with disulfiram 250 mg daily or placebo. The numbers of participants in each treatment group evaluated during the successive time periods are shown below the *X*-axis in the figure.



T alelle Placebo	29	29	28	27	23	20	20
T alelle Disulfiram	40	40	38	29	29	23	24
CC Placebo	44	43	39	36	29	26	27
CC Disulfiram	40	39	37	30	27	23	20

Fig. 3. Disulfiram effects for T allele carriers and CC homozygous subjects ($N = 155$). Figure shows the mean days per week of cocaine use during successive two-week time intervals from the two-week pre-randomization induction period until the end of week 12 of treatment for CC-homozygous participants treated with disulfiram 250 mg daily ($n = 40$) or placebo ($n = 44$) and for T-allele carriers treated with disulfiram 250 mg daily ($n = 40$) or placebo ($n = 29$). The numbers of participants in each treatment group evaluated during the successive time periods are shown below the *X*-axis in the figure.

ARCHIVAL REPORT

Pharmacogenetic Randomized Trial for Cocaine Abuse: Disulfiram and Dopamine β-Hydroxylase

Thomas R. Kosten, Guiying Wu, Wen Huang, Mark J. Harding, Sara C. Hamon, Jaakko Lappalainen, and David A. Nielsen

CON METADONE

Kosten, T. R., Wu, G., Huang, W., Harding, M. J., Hamon, S. C., Lappalainen, J., & Nielsen, D. A. (2013). Pharmacogenetic randomized trial for cocaine abuse: disulfiram and dopamine β-hydroxylase. *Biol Psychiatry*, *73*(3), 219–24. https://doi.org/10.1016/j.biopsych.2012.07.011

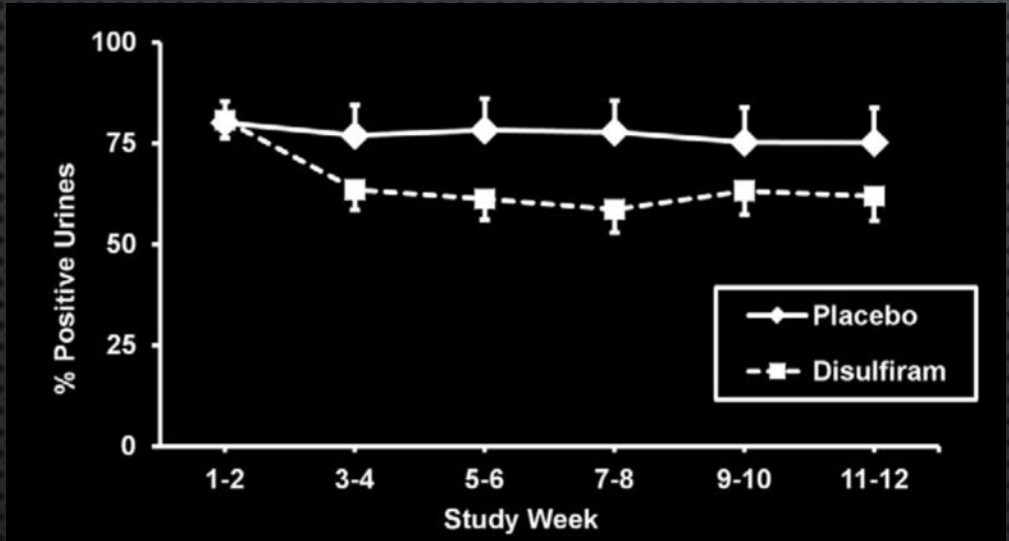


Figure 1. Percentage of cocaine-positive urine toxicology screens for 2-week time blocks across the 12-week trial for the placebo (solid line, n = 40) vs. disulfiram (250 mg/day) (dashed line, n = 34) treatment groups. Standard error bars are shown at each time point.

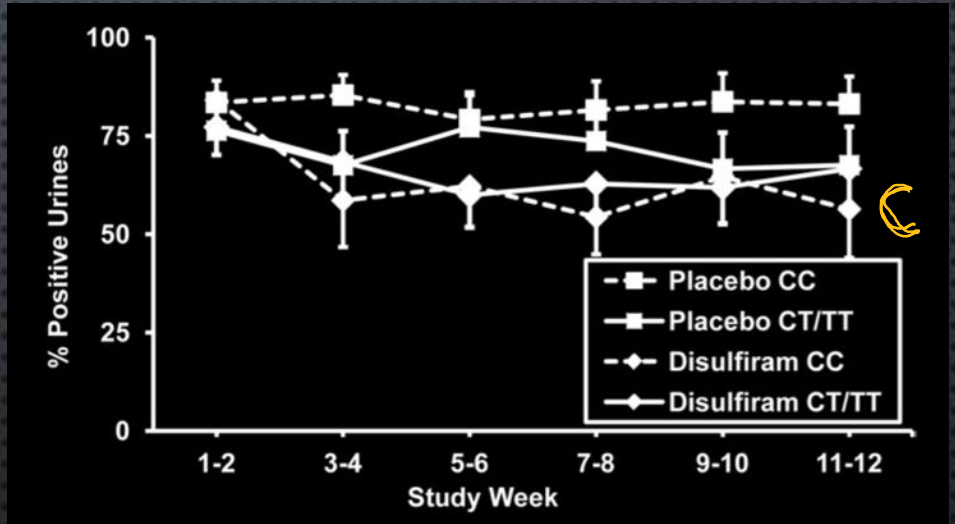


Figure 2. Percentage of cocaine-positive urine toxicology screens for 2-week time blocks across the 12-week trial for the placebo vs. disulfiram (250 mg/day) treatment groups. Subjects with the CC genotype (solid squares, dashed line, n = 21) and those with CT/TT genotypes (solid squares, solid lines, n = 19) in the placebo group and subjects with the CC genotype (solid diamonds, dashed line, n = 17) and the CT/TT genotypes (solid diamonds, dashed line, n = 17) in the disulfiram group are shown. Standard error bars are shown at each time point.

BACLOFENE

Baclofène et addiction à la cocaïne
Quelques cas cliniques

Dr Karima Koubaa, Toulouse (31)

De nombreuses études dans l'alcool et dans l'addiction à la cocaïne…

En 2008 paraissait le livre « Le dernier verre » d'Olivier Ameisen, qui revenait sur son parcours avec l'alcool, ses difficultés et son auto-expérimentation du baclofène à hautes doses, lui ayant permis de devenir indifférent vis-à-vis de l'alcool.

Dès cette période, il relate dans son ouvrage l'existence de nombreux articles qui suggèrent que le baclofène pourrait être un traitement efficace de l'alcoolodépendance. En effet, dès les années 90, de premières études avaient été publiées. Leurs auteurs ont retrouvé un impact du baclofène sur la consommation d'alcool que ce soit chez l'animal (EM Krupitsky et al.1993)[1] ou chez l'homme (R. Agabio et al. 2014).[2]

Les résultats des études contrôlées Alpadir et Bacloville ont été présentés en septembre 2016. Ils semblent confirmer l'intérêt du baclofène sur la réduction de la consommation d'alcool et du craving que de nombreux cliniciens observent maintenant depuis plusieurs années auprès de leurs patients.

Si l'usage du baclofène dans les troubles liés à l'usage de l'alcool est désormais courant (50 000 patients auraient bénéficié de ce traitement en 2015), il existe également des études sur son utilisation dans l'addiction à la cocaïne.

- Chez le rat, le baclofène a permis de réduire l'auto-administration de cocaïne (Roberts et al. 1997 ; Shoaib et al.).[3 4]
- Et plus récemment, des publications ont fait état de résultats contrastés chez l'homme, (Shoptaw et al. 2003 ; Kahn et al. 2009).[5 6]

Le baclofène pourrait donc être un traitement potentiel de l'addiction à la cocaïne. Dans notre CSAPA, nous avons été amenés à l'utiliser chez quelques patients. Avec cet article, nous avons voulu fait part de notre pratique au travers de quelques cas cliniques.

Cas n°1 - Fabien 33 ans : une stabilisation de sa consommation de cocaïne après introduction d'un traitement par baclofène

Entre 16 et 20 ans, Fabien multipliait les consommations (LSD, ecstasy, héroïne, cocaïne…) avec un usage qui s'est ensuite arrêté pendant une période de 7 ans, sans aucun traitement.

A 27 ans, après une rupture sentimentale, Fabien reprend ses consommations d'héroïne. Il la consomme par voie intraveineuse en même temps que de la Ritaline® et de la cocaïne. Deux ans plus tard, un traitement de substitution par méthadone est instauré, permettant un arrêt des opiacés illicites et une stabilisation de sa situation psycho-sociale. Cependant, sa consommation de cocaïne se poursuit avec un craving de plus en plus important.

A 31 ans, il effectue un séjour en CTR (Centre Thérapeutique Résidentiel) puis en ATR (Appartement Thérapeutique Relais). Il reprend progressivement sa consommation de cocaïne 1 fois par semaine et associe des hypnotiques (injections de zolpidem) pour gérer la descente.

Début 2016, un traitement par baclofène est initié. La posologie est augmentée progressivement à 3 comprimés / jours (matin – midi – soir) associée à de la venlafaxine LP 37,5 mg/jour. La méthadone est quant à elle stabilisée à 100 mg/jour.

https://blog.sitd.it/2017/02/14/baclofene-dipendenza-cocaina-serie-casi-clinici/

- CASO N.1 – Fabien, 33 anni: stabilizzazione del consumo di cocaina dopo l'inizio del trattamento con baclofene
- CASO N.2 – Marine, 39 anni: disgustata dalla cocaina dopo trattamento con baclofene
- CASO N.3 – Eric, 51 anni: riduzione del craving per cocaina ed alcol
- CASO N.4 – Laura, 31 anni: interruzione dell'uso di cocaina
- CASO N.5 – Etienne, 40 anni: riduzione evidente del consumo
- CASO N.6 – Hervé, 37 anni: trattamento con baclofene a basse dosi
- CASO N.7 . Robert, 35 anni: riduzione del consumo di alcol e cocaina

Revue de Flyer

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Baclofen as Adjunctive Treatment for a Patient With Cocaine Dependence and Schizoaffective Disorder

To the Editors:

Drugs that act as receptor agonists at γ-aminobutyric acid type B receptors may be used as adjunctive treatments for substance abuse disorders. Many studies using animal models have demonstrated that γ-aminobutyric acid type B agonist baclofen reduces the rewarding effects of drugs of abuse, such as opiates, cocaine, nicotine, and ethanol.[1,2] Recent clinical reports show that baclofen treatment blocks drug craving and improves abstinence in drug-abusing patients.[3,4] Patients with schizophrenia are more likely to have a substance abuse disorder than persons without mental illness, and comorbidly ill patients are more vulnerable to psychotic relapses and poorer medication responses.[5] Given these problems for patients with both substance dependence and schizophrenia, novel treatment approaches to address both conditions are sought. This is the first case report on the safe and beneficial use of baclofen as an adjunctive treatment for a patient with cocaine dependence and schizoaffective disorder.

CASE REPORT

The patient is a 58-year-old African American male who started abusing both cocaine and alcohol at 24 years of age. The patient reported experiencing auditory hallucinations at the age of 25. He also reported autonomous episodes of mania and depression starting in his 20s and 30s. There have been significant periods of abstinence in this patient's history in which psychotic and affective symptoms were present. The patient was diagnosed with schizoaffective disorder–bipolar type (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria), and his prominent symptoms included command auditory hallucinations, paranoid delusions, depression, mania, and suicidal ideation that resulted in major dysfunction. He was also diagnosed with cocaine and alcohol dependence and cannabis abuse, but he and his clinicians identified cocaine use as his primary drug problem. Consequences of his cocaine use included physical, family, and legal problems. For periods, he used high doses of alcohol on a daily basis and demonstrated compulsive use, tolerance, and withdrawal symptoms. He also used cannabis on a daily basis for periods of time. Between 1970 and 1998, the patient was hospitalized 15 to 20 times for his comorbid addictive and schizoaffective disorders and was treated with neuroleptics and serotonin reuptake inhibitors. During that period, his longest period of abstinence was only 6 months.

Since 2000, he was treated with fluoxetine 40 mg orally once daily and risperidone 2 to 3 mg orally twice daily. Despite this treatment, he experienced command auditory hallucinations, heavy and frequent cocaine use, depression, persistent suicidal ideation, and suicide attempts and was admitted to an acute inpatient unit on 3 occasions. After each inpatient discharge, he relapsed to cocaine use and stopped his medications soon thereafter. Because of his chronic and persistent craving for cocaine, he was tried on baclofen at the end of 2001. He was started at a dose of 5 mg, and it was increased to 10 mg orally 3 times daily. There was no other psychotherapeutic changes or changes in his psychosocial status.

Within 2 months of the initiation of baclofen treatment, the patient reported that his cravings had decreased considerably and he was better able to maintain drug abstinence. Because some cravings persisted, the baclofen dose was increased to 20 mg orally 3 times daily and he remained on risperidone and fluoxetine. Several months later, the patient stopped his baclofen, and within 2 weeks, he relapsed to cocaine use. Abrupt cessation of baclofen can produce a withdrawal syndrome within 12 to 72 hours after discontinuation that consists of agitation, psychosis, confusion, insomnia, hypertonia, fever, and/or seizures.[6] No such syndrome developed in this patient. He was admitted to an inpatient substance abuse treatment facility and restarted on baclofen 20 mg orally 3 times daily, risperidone 1 mg orally daily, and fluoxetine 40 mg orally daily. After discharge, urine toxicology screens and blood alcohol levels were performed randomly on a regular basis and were always negative.

For a 1-year period from 2002 to 2003, the patient had been stable on baclofen, risperidone, and fluoxetine and did not demonstrate previous symptoms of auditory hallucinations, depression, or suicidality. He regularly reported that his cocaine cravings were substantially reduced, and he maintained abstinence from all drugs of abuse. This has been the longest period of stability in the course of his comorbid psychiatric illnesses, and he required no hospitalizations. Adjunctive treatment with baclofen was well tolerated, and there were no side effects even while taking antipsychotic medication. It appears unlikely that the anticraving effects cannot be attributed to the antipsychotic treatment (risperidone 1 mg every day), because the dose of this medication was reduced in dosage throughout the baclofen trial.

Some exciting preliminary work demonstrates the efficacy of baclofen as an adjunct in the treatment of both addictive and psychotic disorders. In one study, alcoholic patients were treated with baclofen (10 mg orally 3 times daily) or placebo for 30 consecutive days.[7] Baclofen-treated alcoholics showed a significant improvement in abstinence, decreased obsessive and compulsive symptoms of craving, and reduced drug intake compared to the placebo-treated group. In a pilot study, open-label baclofen treatment (60 mg/d) reduced cocaine craving and use and produced periods of abstinence in 10 cocaine abusers in drug counseling.[8] In another open-label trial in cocaine abusers short-term baclofen treatment was given (10 to

Kaplan, G. B., McRoberts, R. L., & Smokler, H. J. (2004). Baclofen as adjunctive treatment for a patient with cocaine dependence and schizoaffective disorder. *J Clin Psychopharmacol*, *24*(5), 574–5. https://doi.org/10.1097/01.jcp.0000138778.78633.45

LETTER TO THE EDITORS

Baclofen as a Cocaine Anti-Craving Medication: A Preliminary Clinical Study

Ling, W., Shoptaw, S., & Majewska, D. (1998). Baclofen as a cocaine anti-craving medication: a preliminary clinical study. *Neuropsychopharmacology*, *18*(5), 403–4. https://doi.org/10.1016/S0893-133X(97)00128-0

20 mg × 3 modifiable

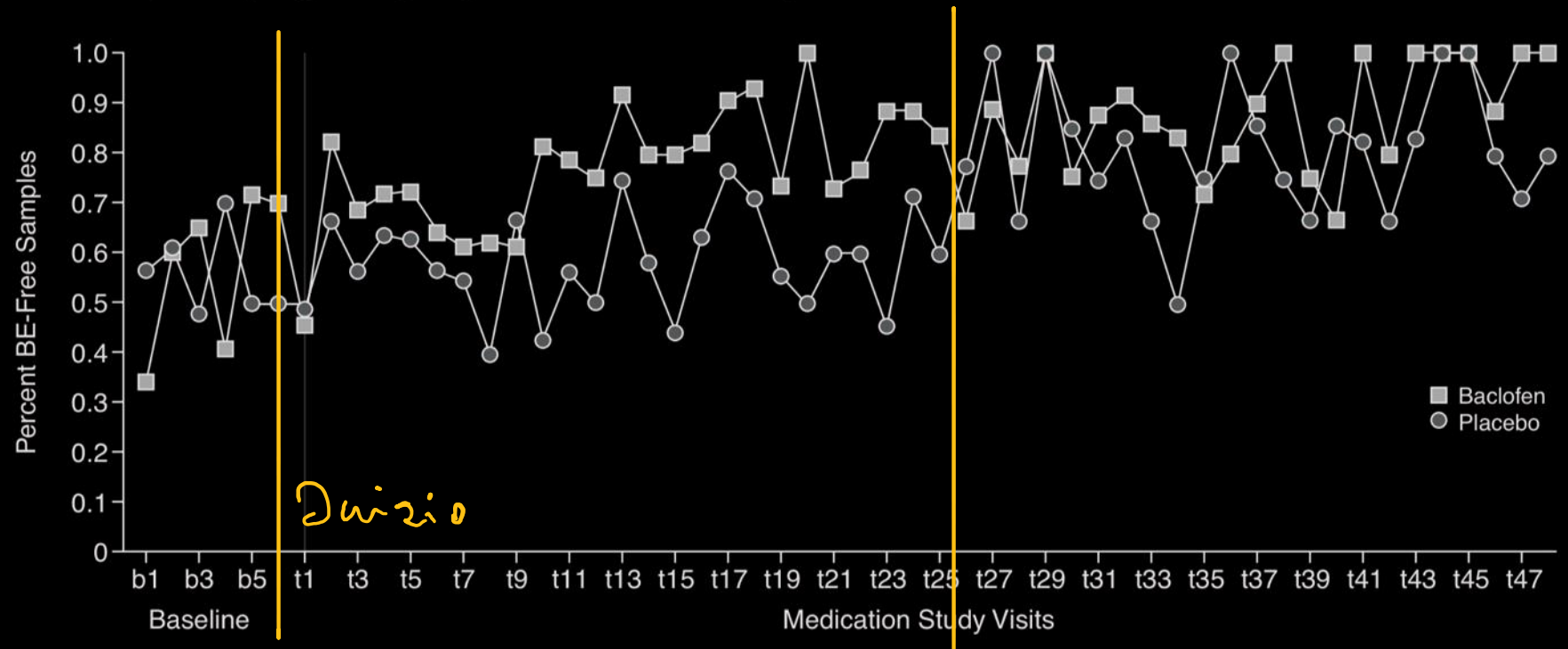
Patients generally reported decreased cocaine craving and reduction in cocaine use, which was verified by urinalysis. Urine samples negative for cocaine for the ten patients ranged from 0% to 98%, with an average of 60.8%. Continuous cocaine abstinence averaged 4.8 weeks (range = 0–14 wks) and treatment length for the group averaged 10.3 weeks (range = 1–17 wks). Nine

Randomized Placebo-Controlled Trial of Baclofen for Cocaine Dependence: Preliminary Effects for Individuals With Chronic Patterns of Cocaine Use

Steven Shoptaw, Ph.D.; Xiaowei Yang, Ph.D.; Erin J. Rotheram-Fuller, M.A.; Ya-Ching M. Hsieh, M.S.; Prudencia C. Kintaudi, M.D.; V. C. Charuvastra, M.D.; and Walter Ling, M.D.

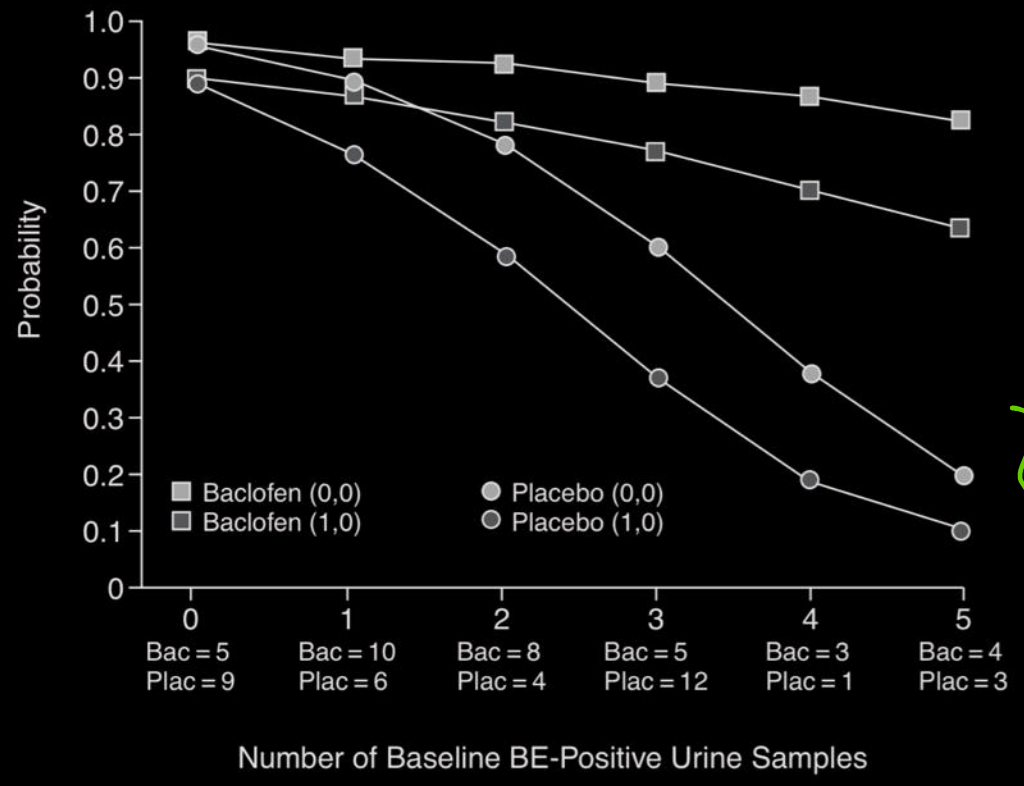
Shoptaw, S., Yang, X., Rotheram-Fuller, E. J., Hsieh, Y.-C. M., Kintaudi, P. C., Charuvastra, V. C., & Ling, W. (2003). Randomized placebo-controlled trial of baclofen for cocaine dependence: preliminary effects for individuals with chronic patterns of cocaine use. *J Clin Psychiatry*, *64*(12), 1440–8. https://doi.org/10.4088/jcp.v64n1207

Figure 3. Percentage of Urine Samples Provided by Participants in Each of the 2 Treatment Conditions That Tested Free of Cocaine Metabolite (Benzoylecgonine[BE]) at Each Point During the Trial[a]

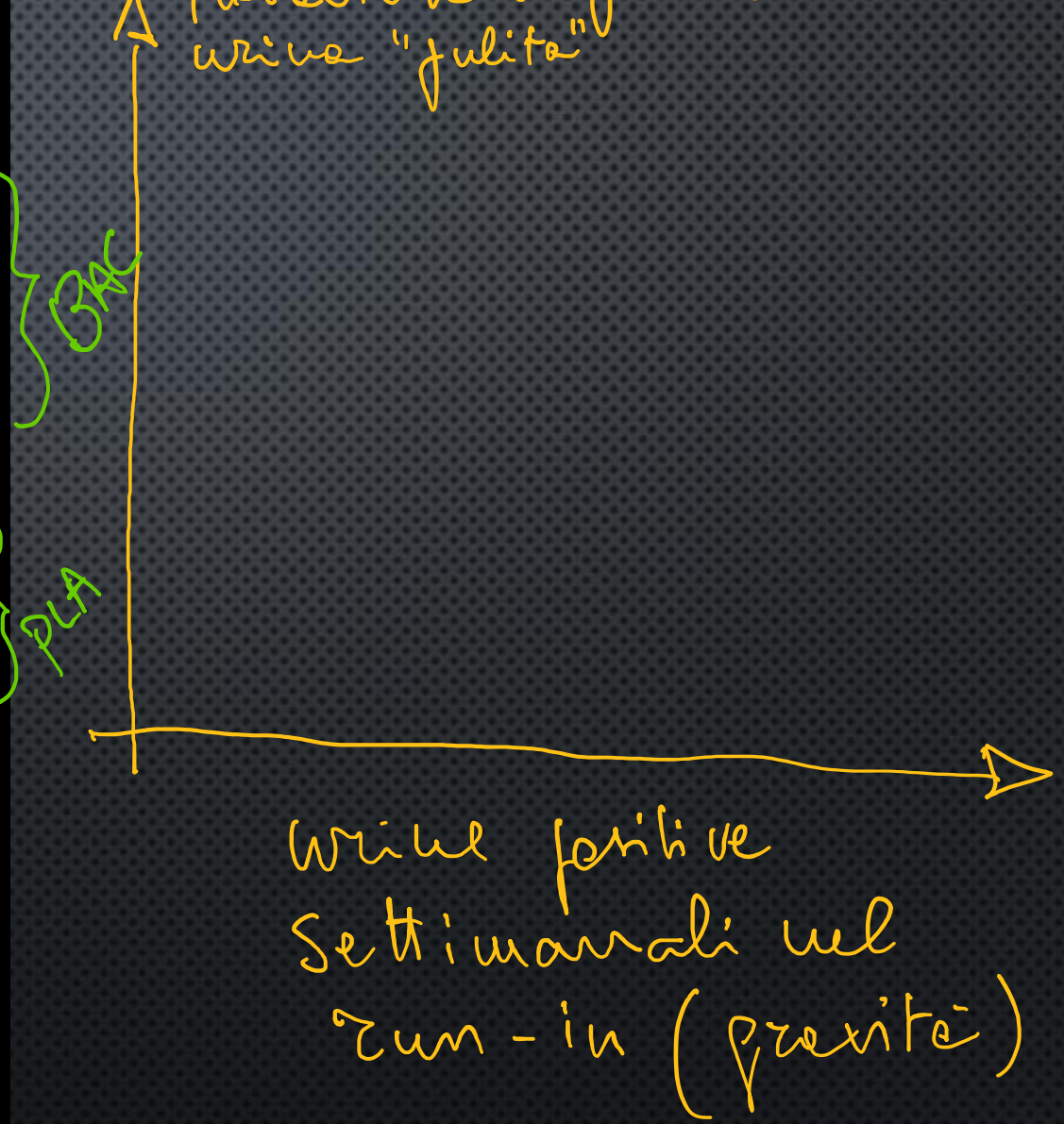


[a]The first 6 points (b1 to b6) represent the percentage of BE-free urine samples by condition during the baseline period. The line through t1 denotes randomization into treatment condition and the initiation of study medication. Points t1 to t48 represent the percentage of BE-free urine samples by condition during the treatment period. The upward drift for both lines over the treatment period represents the effect of attrition on these proportions.

Figure 4. Transitional Probability That a Participant Will Provide a Benzoylecgonine (BE)-Negative Urine Sample Given the Result of the Immediately Previous Urine Sample as a Function of the Number of Urine Tests Provided at Baseline That Were BE-Positive[a]



[a]The numbers of participants by condition that provided each level of BE-positive urine samples during baseline are represented across the top of the figure. No participants provided 6 BE-positive urine samples during baseline; hence, the range was 0–5 BE-positive urine samples. These transitional probabilities depict the effect of successful treatment at any point during the medication period and are represented by the probability of providing 2 consecutive BE-free urine samples ("0,0"—maintaining cocaine abstinence) and of providing a BE-free urine sample following a BE-positive urine sample ("1,0"—initiating cocaine abstinence).



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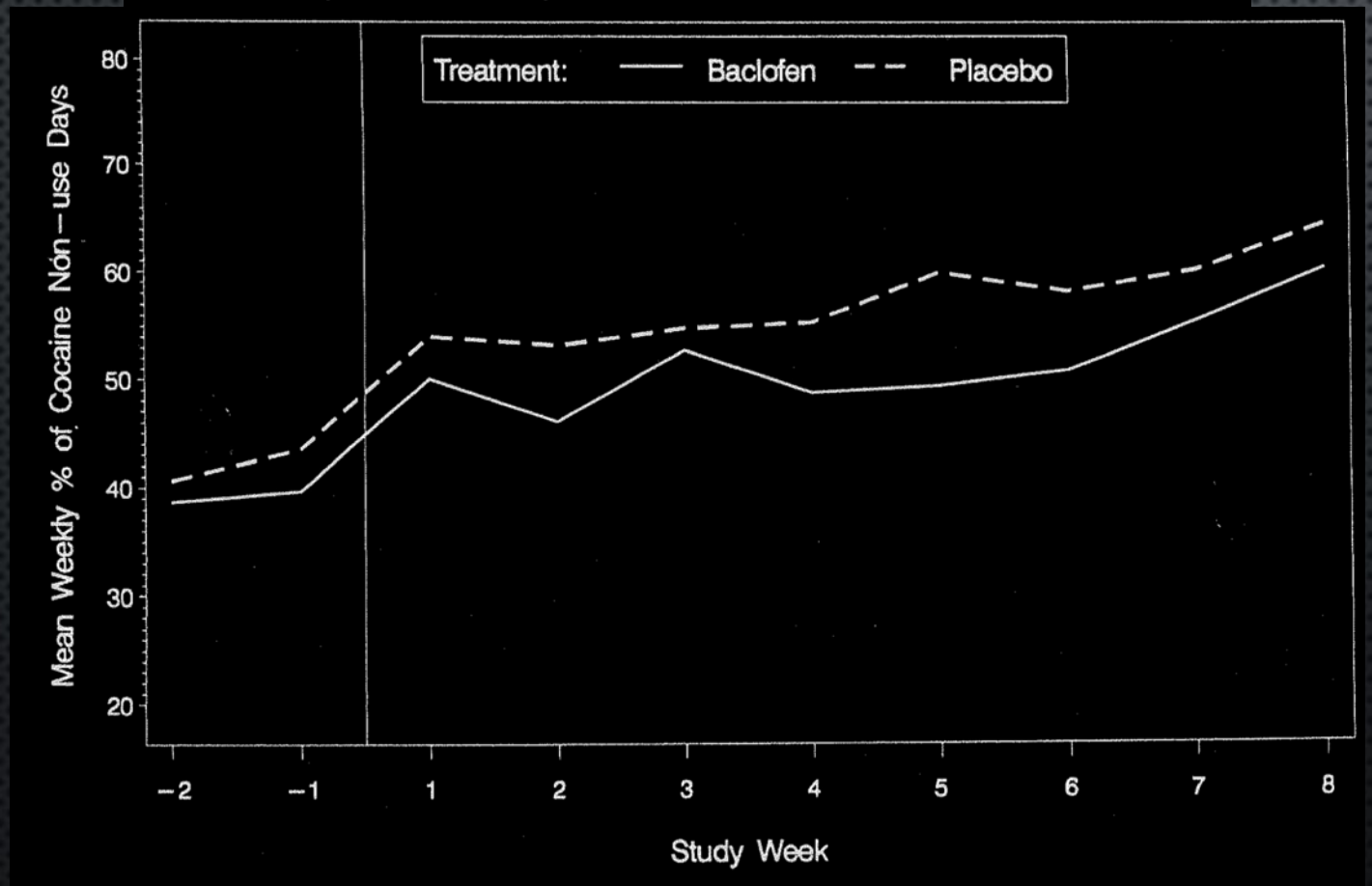
Drug Alcohol Depend. 2009 July 1; 103(1-2): 59–64. doi:10.1016/j.drugalcdep.2009.03.011.

Multi-Center Trial of Baclofen for Abstinence Initiation in Severe Cocaine Dependent Individuals

Roberta Kahn[a,*], Kousick Biswas[b], Anna-Rose Childress[e], Steve Shoptaw[d], Paul J. Fudala[c], Liza Gorgon[a], Ivan Montoya[a], Joseph Collins[b], Frances McSherry[b], Shou-Hua Li[a], Nora Chiang[a], Husam Alathari[f], Donnie Watson[d,g], Joseph Liberto[h], Thomas Beresford[i], Christopher Stock[j], Christopher Wallace[k], Valerie Gruber[l], and Ahmed Elkashef[a]



Kahn, R., Biswas, K., Childress, A.-R., Shoptaw, S., Fudala, P. J., Gorgon, L., … Elkashef, A. (2009). Multi-center trial of baclofen for abstinence initiation in severe cocaine-dependent individuals. *Drug Alcohol Depend*, *103*(1–2), 59–64. https://doi.org/10.1016/j.drugalcdep.2009.03.011

I farmaci che non abbiamo ancora

- Metadonizzare la cocaina
- Il Narcan per la cocaina

Ann. Med. Interne, 2000
151, suppl. B, pp. B44-B48

Perspectives et expériences

Coca leaf chewing as therapy for cocaine maintenance

Jorge HURTADO-GUMUCIO

SUMMARY: **Coca leaf chewing as therapy for cocaine maintenance.**

Major ethnic groups in Bolivia (Aymaras and Quechuas) have chewed the coca leaf for generations upon generations without health problems. The effects of coca leaf chewing produce a level of social and economic adaptation that is beyond what is normally possible. This was a major factor during the Spanish colonization of Bolivia, when forced native labor was used extensively.

The cocaine base, or "pasta", may be seen as a type of South American crack. Its obligatory method of administration is smoking. A primary condition of the "pasta" smoker is compulsive drug-search behavior and addiction to cocaine base destroys emotional and mental balance. Socio-economic maladjustment is the norm amongst "pasta" addicts.

Since 1984 I have recommended the chewing of the coca leaf, between 100 to 200 grams of coca leaf per week for the treatment of cocaine dependence. Since this treatment was dispensed on an ad hoc basis, it was not possible to measure the relapses. However, an assessment was conducted on the basis of mental condition and level of social and economic adaptation before and after treatment.

The patent's level of social acceptance, before treatment, only reached 60% at most, and after treatment, 26% improved their level of adaptation. Four patients among 50 reached an adaptation level of 100%. Upon final assessment, the level of social adaptation prior to treatment was only 28%, after treatment as many as 48.8% of the patients were socially adapted.

RÉSUMÉ : **La feuille de coca comme traitement de substitution chez les patients cocaïnomanes.**

Les plus importants groupes ethniques de Bolivie (Aymara et Quechua) ont mâché la feuille de coca pendant des générations sans retentissement médical. La mastication des feuilles de coca, par son effet, avait pour but de faciliter une meilleure insertion sociale et économique. Cet effet était également très recherché lors de la colonisation espagnole de la Bolivie, période pendant laquelle la force de travail des autochtones était intensivement exploitée.

La cocaïne base, ou « pasta », peut être assimilée au crack d'Amérique du Sud. Elle est obligatoirement fumée. Le fumeur de « pasta » a un comportement compulsif à la recherche de produit, et l'addiction à la cocaïne base finit par détruire son équilibre émotionnel et mental. La désinsertion socio-économique est la règle chez les personnes dépendantes de la « pasta ». Depuis 1984, j'ai recommandé la mastication de la feuille de coca (entre 100 et 200 g par semaine) dans le traitement et la prise en charge des patients dépendant à la cocaïne. Depuis que ce traitement a été dispensé, de façon informelle, il n'a pas été possible de mesurer le taux de rechute. Cependant, une évaluation avant et après traitement, basée sur des critères psychiatriques et d'intégration socio-économique, a été réalisée sur 50 patients. À l'évaluation finale, 48,8 % des patients étaient bien adaptés socialement, alors que ce taux n'était que de 28 % avant traitement.

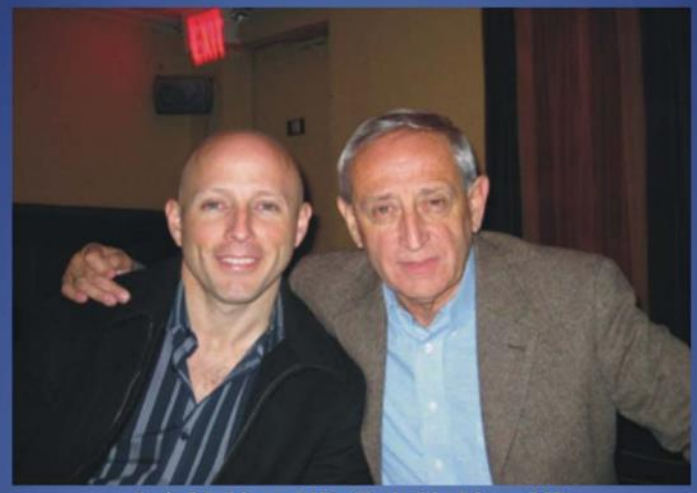
Hurtado-Gumucio, J. (2000). Coca leaf chewing as therapy for cocaine maintenance. *Ann Med Interne (Paris)*, *151 Suppl B*, B44-8.

Jorge Hurtado Gumucio, médico psiquiatra, director fundador del Museo de la Coca, activista y militante por los derechos de la hoja de coca, visionario, autor del clásico "Cocaína: en busca del paraíso perdido" (1984), fundador de COCAWASI la casa-museo en los Yungas

Luis M. Llosa, MD

Brief Review of Oral Cocaine for the Treatment of Cocaine Dependence

History, Botany, Chemistry, Sources, Pharmacology, Toxicology, Toxicity, Substitution, Classification, Clinical Researches, Legal Status, References.



Luis M. Llosa, MD, Teobaldo Llosa, MD

In recent years agonist therapy have aroused much interest among clinicians and researchers for treating cocaine dependence. The use of cocaine by oral route as agonist therapy has been investigated since the 1980s and has demonstrated effectiveness in reducing the number of relapses and prolong and maintain abstinence in patients addicted to various forms of cocaine (cocaine hydrochloride , crack, coca paste).

In Peru the sale of products made from coca leaves for oral and dermal use is legal and no age restrictions. Currently infusions of coca (coca tea) and coca powder are used for treatment of cocaine dependent patients. In the 1980s, the psychiatrist Teobaldo Llosa began the use of oral cocaine for agonist treatment called Cocalization (Cocalización) and Cocainization (Cocainización) according to the form of oral cocaine use.

In this brief review Luis M. Llosa, psychiatrist, lists the main characteristics of agonist therapy with oral cocaine and presents the appropriate criteria for use in the treatment of dependence to cocaine.

Juan Gutemberg
Editores Impresores EIRL

JOURNAL OF THE NEUROLOGICAL SCIENCES

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REVIEW ARTICLE | VOLUME 434, 120098, MARCH 15, 2022

Current status of vaccines for substance use disorders: A brief review of human studies

Thanh Thuy Truong • Thomas R. Kosten

Published: December 16, 2021 • DOI: https://doi.org/10.1016/j.jns.2021.120098 •

- Vaccines for substance use disorders have faced significant challenges in transition for use in humans.
- More helpful for some lethal substances as part of overdose prevention
- The cocaine and nicotine vaccines have not been successful at promoting abstinence or reducing use in humans.

Truong, T. T., & Kosten, T. R. (2021). Current status of vaccines for substance use disorders: A brief review of human studies. *J Neurol Sci*, *434*, 120098. https://doi.org/10.1016/j.jns.2021.120098

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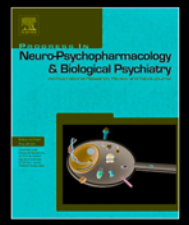

A plant-derived cocaine hydrolase prevents cocaine overdose lethality and attenuates cocaine-induced drug seeking behavior

Katherine E. Larrimore[a,1], Latha Kannan[a,b,2], R. Player Kendle[a,3], Tameem Jamal[a,4], Matthew Barcus[a,5], Kathryn Stefanko[a,6], Jacquelyn Kilbourne[b], Stephen Brimijoin[c], Chang-Guo Zhan[d], Janet Neisewander[a], Tsafrir S. Mor[a,b,*]

Larrimore, K. E., Kannan, L., Kendle, R. P., Jamal, T., Barcus, M., Stefanko, K., … Mor, T. S. (2020 08 30). A plant-derived cocaine hydrolase prevents cocaine overdose lethality and attenuates cocaine-induced drug seeking behavior. *Prog Neuropsychopharmacol Biol Psychiatry*, *102*, 109961. https://doi.org/10.1016/j.pnpbp.2020.109961

GRAZIE