Anticonvulsive drugs in cocaine dependence: a systematic review and meta-analysis

M. Farré [1,3], Y. Alvarez [1,3], F. Fonseca [2,4], J. Camí 4, M. Torrens [2,3]

1 Pharmacology, IMIM-Hospital del Mar. 2 Drug Abuse Unit, IAPS-Hospital del Mar. 3 Universitat Autònoma Barcelona, UAB. 4 Universitat Pompeu Fabra, UPF

Introduction

Cocaine dependence is a chronic disease with a high rate of relapse and without a specific treatment. Much effort is being focused on the pharmacologic management of cocaine dependence and devoted to novel approaches. Among the drugs used more recently are some anticonvulsives. These drugs limit the repetitive firing of neurons (anti-kindling), an effect mediated by promoting the inactivated state of voltage-activated Na+ channels or enhancing the synaptic inhibition mediated by gamma-amino butyric acid (GABA).

Aim

To evaluate the efficacy of anticonvulsive treatment in improving retention in treatment and reducing illicit cocaine use in cocaine dependence subjects.

Design

A systematic review and meta-analysis according to the methodology developed by the Cochrane Collaboration and the QUOROM statement based on randomized controlled trials (RCTs) comparing anticonvulsive drugs with placebo.

Methods

A systematic search was carried out in Medline (1966-May 2007), Embase and Cochrane library. The following searching terms were used: cocaine, crack, anticonvulsivant, phenobarbital, primidone, carbamazepine, oxcarbazepine, valproic acid, sodium valproate, phenytoin, fosphenytoin, mephenytoin, ethotoin, felbamate, gabapentin, lamotrigine, felbamate, ethosuximide, levetiracetam, etiracetam, tiagabine, topiramate, vigabatrin, pregabalin, zonisamide. The abstracts were revised to select the eligible publications. The references in selected published articles, reviews and meta-analyses were checked for potential new sources. Unpublished studies were sought by using Clinicaltrials.gov, the UK National Research Register and by contacting experts. Conference acts were also looked for where necessary. The only restriction applied was publication language (English and Spanish).

Measurement

Two outcome measures: retention in treatment and cocaine use, measured by positive urine controls, were analysed.

Findings

Fifteen randomized, double blind, placebo controlled, clinical trials involving 1236 patients were found. On average, trials lost of follow up was around the 50% of enrolled participants (Table 1). Heterogeneity was found in the efficacy of seven anticonvulsive drugs analysed. Anticonvulsive treatments were not better than placebo in cocaine consumption, represented by retention in treatment RR 0.99 (95%IC: 0.90-1.11), neither by cocaine-positive urine RR 0.95 (95%IC: 0.85-1.06) (Figures 1 and 2).

TABLE 1: Systematic review on anticonvulsive treatment in cocaine dependence: characteristics of included studies

Study	Design	Participants	Interventions	Outcomes	JADAD
CARBAMAZEPINE					
Campbell *et al.* 2003 Missouri (USA)	RCT, placebo-controlled, double-blind, n=146, follow-up, 8 weeks	Average age 33.4 years, 70% male, and 82% black. Co-morbidity: 30% depression, 39% antisocial personality and 6% generalized anxiety	1. CBZ (n=47; 800 mg/d) 2. Placebo (n=50) Psychosocial methods	No retention Positive urine samples	4
Brady *et al.* 2002 South Carolina (USA)	RCT, placebo-controlled, double-blind, n=177, follow-up, 12 weeks, 4 groups (stratified by affective disorder)	Average age 31.8 years, 61.6% male, and 61% black. Consumption ≥ 3 use/week or 1.000$ in previous month	1. CBZ (n=72; 800 mg/d) 2. Placebo (n=67)	Positive urine samples	3
Halikas *et al.* 1997 Minnesota (USA)	RCT, placebo-controlled, double-blind, n=183, follow-up, 12 weeks, 3 groups	Average age 34.2 years, 75.4% male, and 78.9% white. 75% psychiatric disorder. Consumption ≥ 25 occasions in the 100 previous days	1. CBZ (n=49; 400 mg/d) 2. CBZ (n=50; 800 mg/d) 3. Placebo (n=51) Psychosocial methods	No retention Positive urine samples	4
Cornish *et al.* 1995 Philadelphia (USA)	RCT, placebo-controlled, double-blind, n=95, follow-up, 10 weeks	Average age 36.2 years, 98% male, and 89% black	1. CBZ (n=37; 200 mg/d) 2. Placebo (n=45) Psychosocial methods	No retention Positive urine samples	4
Montoya *et al.* 1995 Philadelphia (USA)	RCT, placebo-controlled, double-blind, n=72, follow-up, 8 weeks	Average age 33.2 years, 79% male, and 67.7% black. 25% antisocial personality, phobias. Consumption ≥ 14 g within last 3 months	1. CBZ (n=28/62; 600-800 mg/d) 2. Placebo (n=34/62) Psychosocial methods	No retention Positive urine samples	3
Kranzler *et al.* 1995 USA	RCT, placebo-controlled, double-blind, n=40, follow-up, 12 weeks	Average age 33.2 years, 100% male, and 67.7% black. 10% antisocial personality, 10% depression, 20% anxiety. Consumption ≥ 4 g cocaine last month	1. CBZ (n=20; 600 mg) 2. Placebo (n=20) Psychosocial methods	No retention Positive urine samples	4
Campbell et al. 1994 Missouri (USA)	RCT, placebo-controlled, double-blind, n=65, follow-up, 8, 12 weeks and 6 months	Average age 32 years, 63% male, and 90% black. 25% alcohol dependence, anxiety, antisocial personality, 17% depression	1. CBZ (n=19; 600 mg) 2. Placebo (n=25) Psychosocial methods	Positive urine samples	4
PHENYTOIN					
Crosby *et al.* 1996 Minnesota (USA)	RCT, placebo-controlled, double-blind, n=60, follow-up, 12 weeks	Average age 34.5 years, 80% male, and 57% black. >90% crack. Consumption 3.6-19.6 use/month	1. PHT (n=29 ; 300 mg) 2. Placebo (n=31) Psychosocial methods	No retention Positive urine samples	4
VALPROIC ACID					
Reid *et al.* 2005 New York (USA)	RCT, placebo-controlled, double-blind, n=32, follow-up, 10 weeks, CREST study	Average age 39 years, 78% male, and 87% black. Criterion of inclusion: ≥ 2 positive urine within pre-inclusion	1. VP (n=17; 1500 mg/d) 2. Placebo (n=15) Psychosocial methods	No retention Positive urine samples	3
TIAGABINE					
Winhusen *et al.* 2007 Massachusets, Ohio and Texas (USA)	RCT, placebo-controlled, double-blind, n=141, follow-up, 12 weeks	Average age 42 years, 67% male, and 66% black. 95% crack. Consumption 17 use/month	1. TG (n=70; 20 mg/d) 2. Placebo (n=71) Psychosocial methods	No retention Positive urine samples	3
Winhusen *et al.* 2005 Ohio (USA)	RCT, placebo-controlled, double-blind, n=34, follow-up, 10 weeks, CREST study	Average age 40 years, 82% male, and 100% black. Consumption 20 use/month	1. TG (n=17; 20 mg/d) 2. Placebo (n=17) Psychosocial methods	No retention	3
González *et al.* 2003 Connecticut (USA)	RCT, placebo-controlled, double-blind, n=30, follow-up, 10 weeks (2 for metadone induction), 3 groups, CREST study	Average age 38 years, 77.8% male, and 75.6% white. Opiod dependence. 28% antisocial personality, 24% depression. Use weekly	1. TG (n=15; 12 mg/d) 3. Placebo (n=15) Psychosocial methods	No retention Positive urine samples	4
TIAGABINE AND GABAPENTINE					
González *et al.* 2007 Connecticut (USA)	RCT, placebo-controlled, double-blind, n=76, follow-up, 10 weeks (2 for metadone induction), 3 groups	Average age 37 years, 76.5% male, and 70% white. Opioid dependence. Use weekly	1. TG (n=25; 24 mg/d) 2. GB (n=26; 2400 mg/d) 3. Placebo (n=25) Psychosocial methods	No retention Positive urine samples	4
GABAPENTINE AND LAMOTRIGINE					
Berger *et al.* 2005 Ohio (USA)	RCT, placebo-controlled, double-blind, n=45, follow-up, 10 weeks, 3 groups	Average age 40 years, 77% male, and 97% black	1. GB (n=15; 1800 mg) 2. LT (n=15; 150 mg) 3. Placebo (n=15) Psychosocial methods	No retention	3
TOPIRAMATE					
Kampman *et al.* 2004 Pennsylvania (USA)	RCT, placebo-controlled, double-blind, n=40, follow-up, 13 weeks	Average age 40 years, 97.5% male, and 90% black. Criterion of inclusion: ≥ 100$ and ≥ 3 d of abstinence before beginning	1. TPM (n=20; 200 mg/d) 2. Placebo (n=20) Psychosocial methods	No retention Positive urine samples	4

ASI: Addiction Severity Index; DIRS: Drug Impairment Rating Scale; CGI: Clinical Global Impression; RAB: Risk Assessment Battery; CREST: Cocaine Rapid Efficacy and Safety Trial; BE: Benzoilecgonine (cocaine metabolite); ITT: Intention-to-treat

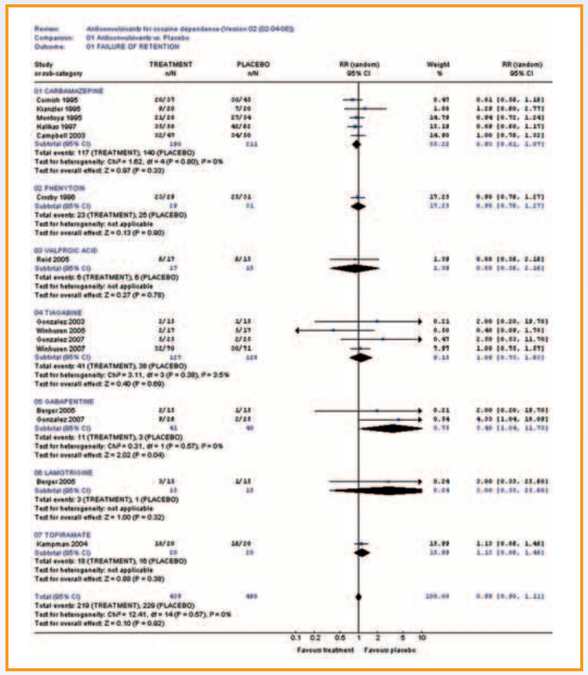

Figure 1. Efficacy of anticonvulsant drugs versus placebo in retention in treatment

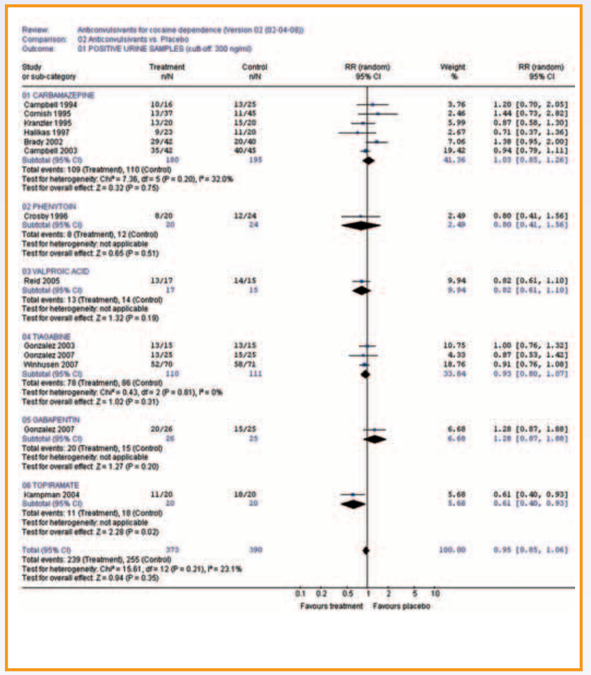

Figure 2. Efficacy of anticonvulsant drugs versus placebo on cocaine use assessed by means of urine analysis

Conclusions

Available clinical trials indicate that there is insufficient evidence to justify the use of anticonvulsive drugs in treating cocaine dependence. However, they are promising treatments to decrease cocaine-positive urines.

Concflict of interest

All authors declare that they have no conflicts of interest.

IMIM hospitaldelmar

iaps Institut d'Atenció Psiquiàtrica

Universitat Autònoma de Barcelona

C S B Consorci Sanitari de Barcelona

IMAS Institut Municipal d'Assistència Sanitària