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TA-CD Vaccine: An Innovative Treatment for Cocaine Addiction

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ABSTRACT

Current therapies for cocaine addiction have demonstrated limited success in treating cocaine dependence. Development of the TA-CD vaccine provides an effective immunotherapeutic treatment for cocaine addicts. The vaccination provides an innovative approach to treating cocaine use disorder by effectively targeting cocaine's mechanism of action within the central nervous system (CNS). The vaccine consists of a cocaine derivative (succinyl-norcocaine) conjugated to the inactivated cholera toxin-B protein. Production of cocaine-specific antibodies with the capacity to bind cocaine molecules within the bloodstream results in the formation of immune complexes too large to cross the blood-brain barrier. By blocking entry of cocaine molecules into the central nervous system, the TA-CD vaccine effectively reduces the positive psychological effects associated with cocaine use. The success of the TA-CD vaccine in comparison to alternative therapies currently available for the treatment of cocaine use disorder demonstrates its potential clinical application.

INTRODUCTION

Research Question: Does the TA-CD vaccine have a more significant clinical impact towards reducing cocaine use than the cognitive behavioural therapy treatment in individuals meeting the DSM-V criteria for cocaine abuse disorder?

Cocaine (benzoyl-methyl-ecgonine) is the second most commonly abused illicit substance worldwide¹⁸. Cocaine use disorder is classified as a substance abuse disorder in the DSM-V¹. The number of symptoms detected during the diagnostic process allows individuals to be diagnosed with cocaine use disorder on a continuum of severity ranging from mild to severe¹.

North America ranks highest in rates of cocaine use worldwide:^{16, 17, 18.}

- Prevalence rate of cocaine use: 6.35 million
- Incidence rate of cocaine use disorder: 13 per 100 000

Risk factors associated with cocaine use disorder: 4, 16, 19.

- Low socioeconomic status
- Males (ages 22-35)
- Living in urban community
- Heavy tobacco/alcohol use
- Genetic basis for addiction

Cognitive Behavioural Therapy (CBT) is the current treatment standard for cocaine use disorder.

Limitations/adverse outcomes of current treatment programs:^{11, 13, 20, 21.}

- 50% average drop-out rate
- Adverse health outcomes of drop-out: relapse, homelessness, criminal offences, and co-morbidity with other mental illnesses
- Economic loss of 13 billion (US\$) attributed to health care costs and loss of productivity associated with institutionalization and incarceration for cocaine use
- Leading cause of emergency room visits in North America related to illicit drug use (30-40% illicit drug use related visits)
- Illicit drug related deaths attributed to cocaine use: 40%

The Canadian Controlled Drugs and Substances Act classifies cocaine as a Schedule I CNS stimulant². CNS stimulation following cocaine ingestion occurs through the mechanism of cocaine molecules blocking pre-synaptic reuptake pumps for monoamine neurotransmitters (primarily dopamine)³. The increased concentration of dopamine in the synapses creates the euphoric psychological response in cocaine users³. Chronic cocaine use alters the cortico-mesolimbic dopamine reward circuit within the brain through enhanced dopamine activity³. The neurophysiologic disruption is the central barrier for individuals attempting to break the cycle of addiction³. Individuals often experience severe withdrawal symptoms during prolonged periods of cocaine abstinence³. The Federal Drug Act (FDA) has yet to approve a pharmacotherapeutic treatment for cocaine use disorder¹². The addictive nature and life threatening consequences of cocaine addiction welcome the development of an innovative treatment such as the TA-CD vaccine¹⁷.

METHODS

The research was conducted using the A priori method. The initial search resulted in 245 articles, from which 7 articles were extracted based on the inclusion criteria. The researchers included only randomized experimental studies conducted among males and females between the ages of 18 and 55 meeting the DSM-V criteria for cocaine use disorder.

Search of Published Literature

- Search terms: "cocaine addiction treatment", "cocaine abuse", "cocaine use disorder", and "TA-CD vaccine"
- Databases: Medline, PubMed, and Scopus databases
- Inclusion Criteria: Articles published since 2000, in North America, in English, and conducted using experimental research method
- Exclusion Criteria: Articles published earlier than 2000 (104) and/or conducted on non-human subjects (89), and those focusing on treatments other than TA-CD vaccine (45)

Search of Grey Literature:

- Websites used: World Health Organization (WHO), Government of Canada, Canadian Mental Health Association (CMHA), and The United Nations Office on Drugs and Crime.

Standardized Literature and Data Extraction Method

- Articles and data were extracted using a standardized approach to enhance consistency in the comprehensive analysis of results.

RESULTS

The effectiveness of the TA-CD vaccine was evident by eliciting a cocaine-specific antibody response in cocaine users, predicting lower levels of future cocaine use. A significant dose-response relationship between the TA-CD vaccine administered and IgG cocaine-specific antibody levels was shown. Individuals reached peak levels of cocaine-specific antibodies at variable time points over the vaccination period, which may be genotype-specific. The pooled results of the three studies measuring the dose-response relationship between TA-CD vaccine and cocaine-specific antibody levels demonstrate a significant difference between the two therapies in eliciting cocaine-specific antibodies (Figure 1). Participants exposed to the TA-CD vaccine were significantly more likely to have higher levels of cocaine-specific antibodies than individuals that received the cognitive behavioural therapy treatment (OR=3.06, CI:1.44-6.48). IgG cocaine-specific antibody levels were negatively correlated with future cocaine use.

Study	Study Design and Participants	Results
Cocaine Vaccine for the Treatment of Cocaine Dependence in Methadone-Maintained Patients (Martelli et al, 2009)	Randomized, Double-blind Placebo controlled, 24 weeks N = 115	IgG Antibody levels: 38% attained levels >43 µg/mL, 62% attained levels <43 µg/mL, 2% did not achieve any level of detectable antibodies Cocaine positive urinalysis -Weeks 9-16: Frequency of cocaine free urine samples increased more quickly in vaccinated group: (placebo x time interaction: Z=5.4, P<0.001), (vaccine x time interaction: Z=8.7, P<0.001) -Weeks 16-24: stopped immunizing, no significant differences in frequency of cocaine-free urine samples -Subjects that attained 'high' IgG levels and the placebo group had significantly higher number of cocaine-free urine samples as the study progressed (placebo x time interaction: Z=5.4, P<0.001), (high IgG level x time interaction: Z=9.5, P<0.001), (low' IgG levels showed no significant change over time (Z=4.8, P<0.001)
Vaccine Pharmacotherapy for Treatment of Cocaine Dependence (Martelli, et al, 2005)	Open-label Dose-Escalation Clinical trial, 12 weeks N = 18	IgG Antibody levels Week 4 measures: Low dose group: mean 83.7 (SD: 171.7), -High dose group: mean 277.3 (SD= 277.3) Week 12 measures: Low dose group: 921.4 (SD: 351.3), High dose group: 1963.6 (SD= 16440) 6 months: Low dose group: 296 U/mL (SD= 297), High dose group: 474 (SD= 603) Cocaine positive urinalysis -High dose group less likely to have positive cocaine urine than Low dose group (Z= -3.17, p= 0.0015) -Of those who used cocaine (5 subjects in low dose group, 2 subjects in high dose group) 100% reported decrease in euphoric effects of cocaine (based on subjective reports) -6-month follow-up after last vaccination: Low dose: 89% subjects had positive cocaine urine levels, High dose: 43% subjects had positive cocaine levels
Human Therapeutic Cocaine Vaccine: Safety and Immunogenicity (Kostien et al, 2002)	Randomized Double-blind Placebo controlled trial, 1 year N= 34	IgG Antibody levels -Significant effects shown for time (F=5.6, d.f. = 6, 17; P<0.002), dose (F=3.8, d.f.=3, 22; p<0.03), and interaction of time by dose (F=6.0, d.f.=6, 14; P<0.01). -Contrast between high and low dose groups was significant (F=6.5, d.f. = 1, 19; P<0.02) Cocaine positive urinalysis: N/A
Cocaine-Specific Antibodies Blunt the Subjective Effects of Smoked Cocaine in Humans (Haney et al, 2010)	Randomized Control Clinical trial, 52 weeks N = 10	IgG Antibody levels -Significant effect of antibody levels on cluster ratings of Good Drug Effect (z=2.37, p=0.0177) and cocaine Quality (z=2.05, p=0.0399) -Higher antibody level correlated with lower rating of both measures Cocaine positive urinalysis -Influence of antibody levels on self-reported cocaine use approached significance (p=0.1166). -In week 3, the high antibody group reported spending \$89 ±50 on cocaine, and in week 13, \$40 ±12. Low antibody group averaged \$113 ±35 in week 3 and \$108 ±63 in week 13.
Spontaneous Development of IgM Anti-Cocaine Antibodies in Habitual Cocaine Users (Orson et al, 2013)	Double-blind Placebo-controlled vaccination trial, 24 weeks N = 55	IgG Antibody levels -Higher levels of IgM anti-cocaine antibodies pre-immunization were associated with lower response to the CTB carrier protein as supported by Spearman and Pearson correlations (P<0.01) -The vaccine stimulated IgG responses (especially those who did not have elevated IgM antibodies) as supported by Spearman and Pearson (p < 0.05) Cocaine positive urinalysis: N/A
DHB gene as Predictor of Response in a Cocaine Vaccine Clinical Trial (Kostien et al., 2013)	Randomized Double-blind Placebo-controlled Clinical trial, 16 weeks N = 114 subjects N = 71 (obtained DBH genotyping results)	IgG Antibody levels: N/A Cocaine positive urinalysis -Last 4 weeks: CT/TT genotype: decrease from 77% to 51%, CC genotype decrease from 83% to: 72% -Placebo: did not change significantly -CT/TT genotype: 66% to 50%, CC genotype: 67% to 59% -DBH-CT/TT (DBH -1021C/T) genotype associated with low DBH levels associated with decrease in cocaine positive urines in vaccine treated group
The K-opioid Receptor Gene as a Predictor of Response in a Cocaine Vaccine Trial (Nielsen et al 2013)	Randomized double-blind placebo-controlled trial, 16 weeks N= 66 (obtained genotype results)	IgG Antibody levels: N/A Cocaine-specific Antibody levels Last 4 weeks: Positive urine for AG/GG decreased from 82% to 77%, Positive urine for AA genotype decreased from 78% to 51% -Vaccine treatment remained effective only in AA group with point-wise (F=10.75; d.f.=1240;p<0.002) and experiment-wise significance (P<0.05) OPRK1 gene: For TT, positive urine decreased from 40%-16%, for CT/CC, positive urine decreased from 38%-21% -Overall, patients with OPRK1 rs6473797 AA genotype had reduced number of cocaine positive urine tests with vaccine. Urine rates dropped 8-fold more with the vaccine + gene group

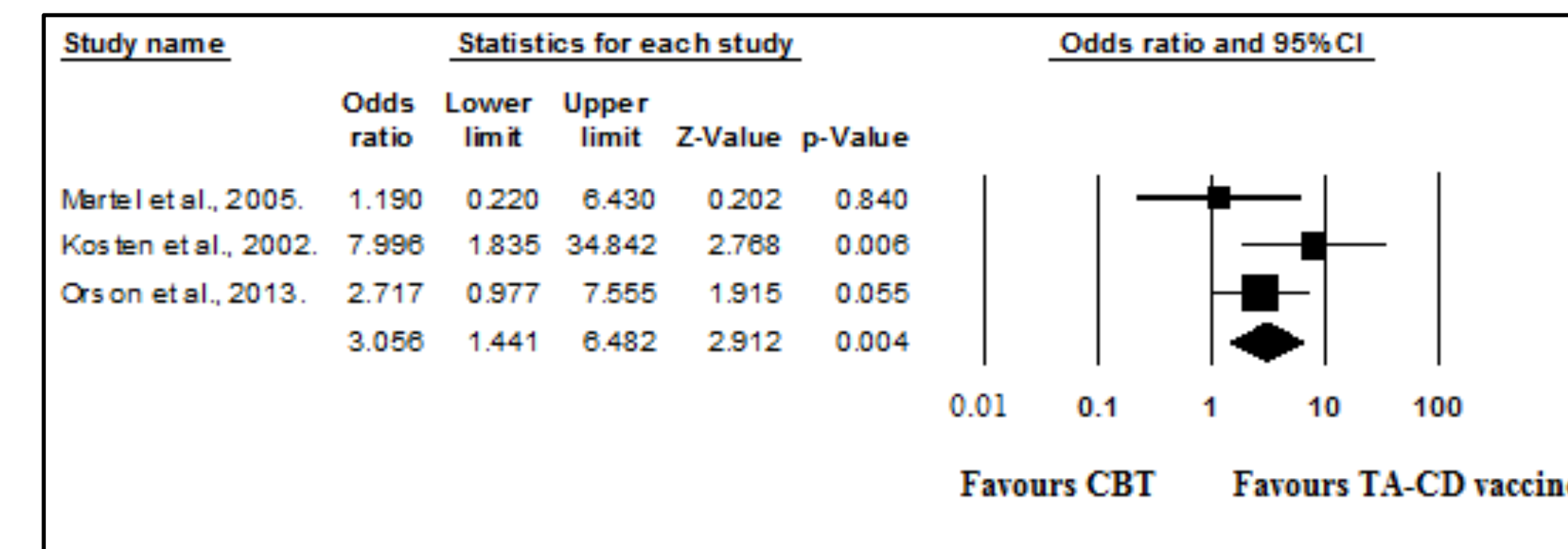


Figure 1. Comparison of CBT group (A) and TA-CD vaccine group (B) in eliciting cocaine-specific antibody response

DISCUSSION

Strengths of studies analyzed:

- Study designs and biological plausibility of the mechanism of the TA-CD vaccine.

Limitations of studies analyzed:

- Research was conducted in a controlled environment; therefore results may not be generalized to the public.

Limitations of analysis:

- Studies measured different variables
- A wider scope is required in order to fully understand the TA-CD vaccine

Research on the TA-CD vaccine has only reached phase II of clinical trials.

Further research is required:

- In which genotypes is the vaccine most effective? What is the mechanism?
- How can researchers improve efficacy of the vaccine in those who developed an IgM antibody response to cocaine?
- According to Haney⁶, there is a relationship between increased antibody levels and cocaine induced tachycardia. This relationship must be explored.

Ethical issues of TA-CD vaccine use:

- Free will and autonomy. Stigmatization of those who chose to use it.
- A replacement drug market and the consumption of greater doses of cocaine to attain the desired effect²²
- The TA-CD vaccine does reduce cocaine use in individuals addicted to cocaine, however, further research is required to increase the vaccine's efficacy and to address health and ethical concerns.

The findings present many implications for the practical use of the TA-CD vaccine as a treatment for individuals with cocaine use disorder:

Study Finding	Implication for Practical Use
Positive correlation between TA-CD and production of anti-cocaine antibodies ^{9, 11, 12, 13, 16}	Antibodies destroy cocaine and subjects do not experience the positive effect of the drug.
Inverse correlation between TA-CD vaccine and level of cocaine in urine test ^{6, 12, 13}	Those who receive TA-CD vaccine are less likely to take cocaine.
The TA-CD vaccine was found to have no effect on craving or desiring the consumption of cocaine ⁶	Cocaine addicts will continue to experience withdrawal even if they do not experience the positive effect of cocaine.
Vaccine not effective in those who have developed an IgM antibody response to cocaine from recreational exposure ¹⁶	The TA-CD vaccine may not be effective in those who regularly use cocaine for recreation.
Antibody levels were not sustained over a long period of time ¹⁶	Vaccines use over an extended period of time may lead to compliance issues in patients. A booster shot is required to increase efficacy.
Participants with OPRK1 rs 6473797 AA genotype responded better to the TA-CD vaccine ¹⁴	TA-CD vaccine may not be effective in some genotypes.
Participants with the DBH-1021 CT/TT genotype decreased levels of cocaine in urine tests ¹⁵	TA-CD vaccine may not be effective in some genotypes.

CONCLUSION

- TA-CD vaccine has a more significant clinical impact in reducing cocaine use than the cognitive behavioural therapy treatment in individuals meeting the DSM-V criteria for cocaine abuse disorder.
- TA-CD vaccine increased cocaine-specific IgG antibodies and resulted in decreased levels of cocaine metabolites in urinalysis of study participants.
- Due to the success of these findings, research is expected to continue to stage III clinical trials. Future research must be conducted in a large study population to explore efficacy, safety and ethics.
- The results suggest that a future treatment may be available for individuals with cocaine abuse disorder. Results indicate that in combination with cognitive behavioural therapy, the TA-CD vaccine is highly effective.

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