Efficacy of Disulfiram (Antabuse®) in the Treatment of Cocaine Dependence

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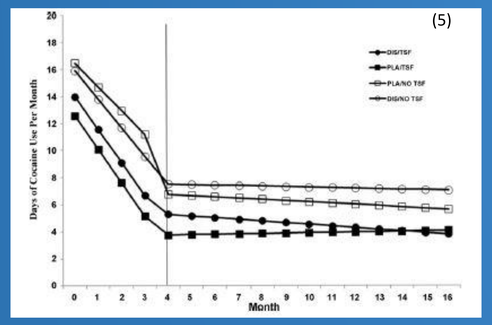
Concurrent alcohol and cocaine usage:

The initial idea behind disulfiram's usage in cocaine dependence was due to its effect in alcoholism treatment.

- Consumption of alcohol while on disulfiram causes severe stomach pain.
- Alcohol abuse is common with cocaine dependent individuals, therefore it was hypothesized that the negative effects of disulfiram – alcohol reaction would associate negative feelings with cocaine usage.(4)
- It was also hypothesized that disulfiram may act independently from it's effect on alcohol consumption.

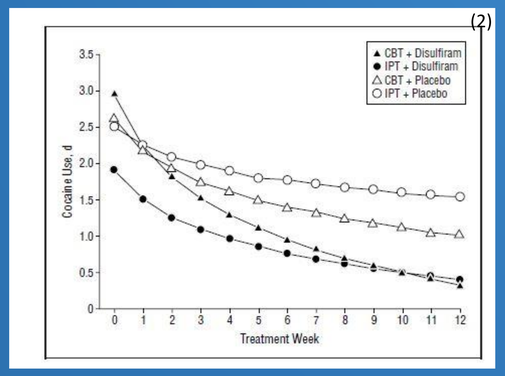
The results of early disulfiram trials were mixed.

- A trial that Implemented disulfiram with different behavioral therapies was able to show that there was a significant abstinence out to one year after completion.(3)(4)
- Another trial focused on stabilizing patients off of alcohol with the use of Naltrexone in order to see if disulfiram would still be effective, which was successful in showing a significant reduction in cocaine usage.(7)(10)



Left: A trial by Carroll et al. testing the helpfulness of Twelve Step Facilitation when in combination with disulfiram, in which significance was not proven.

Right: Carroll et al. testing the utility of Cognitive Behavioral Therapy in combination with disulfiram, in which significance was proven for a decrease in cocaine usage.

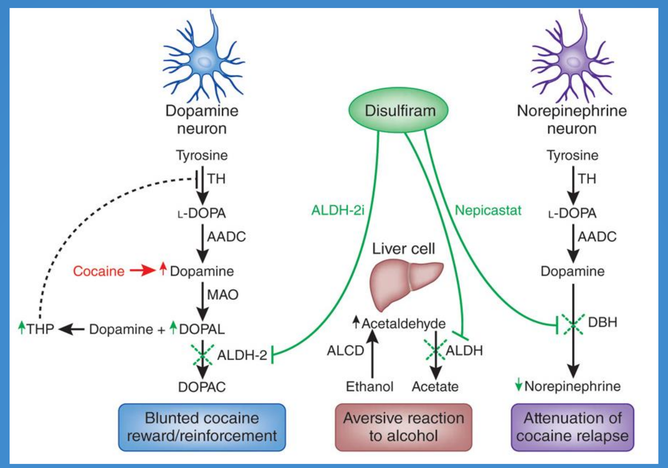


General Drug Information:

Approved Indication: Management of chronic alcoholism

Mechanism of Action:

- Disulfiram inhibits Dopamine β – hydroxylase and aldehyde dehydrogenase.(15)



Cocaine Dependence:

How does it occur?

- Cocaine inhibits of Dopamine, Serotonin, and Norepinephrine transporters.
- Dopamine is main chemical involved in the brain's reward pathway.
- Cocaine results in increased stimulation in the nucleus accumbens, causing a reinforcement of cocaine use.

How do we treat it?

- No approved pharmacological treatments
- New therapies are currently begin tested that include dopamine receptor antagonists, and GABA / Glutamate modifiers.(14)(15)
- Disulfiram has been an experimental way to treat cocaine dependence, but will it be approved?
- Behavioral therapy has shown to effective and is the only current treatment.(2)

Pharmacogenomic applications:

Genotype	Enzyme plasma level	Proposed Response
CC	Normal	No / minimal inhibition
CT	Between CC and TT	Average Inhibition
TT	6-10 fold less	High inhibition

There are three genotypes that are observed in humans for the dopamine b-hydroxylase enzyme.

- T-allele carriers should have the best response because the level of enzyme would be sufficiently lower than others(8)(13)

There have only been two pharmacogenomics based trials to this date both with different results.

- The first trial went against the original hypothesis, with CC allele groups having the greatest response.(8)
- The second trial's results agreed with the original hypothesis, having TT allele patients show the greatest response.(13) Further work is required with more selective DBH inhibitors or testing for allele differences in aldehyde dehydrogenase.(14)

Results(1-13):

The results of trials with disulfiram have been a positive and negative mix.

- There have been trials that have shown significant decreases in cocaine usage.
- Behavioral therapy has shown to be the greatest complement to disulfiram.(2)
- Pharmacogenomics have opened the door to a new sector of clinical trials.