

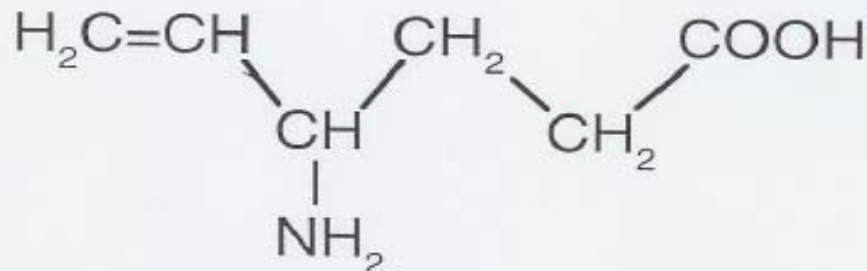


Vigabatrin for the Treatment of Stimulant Dependence

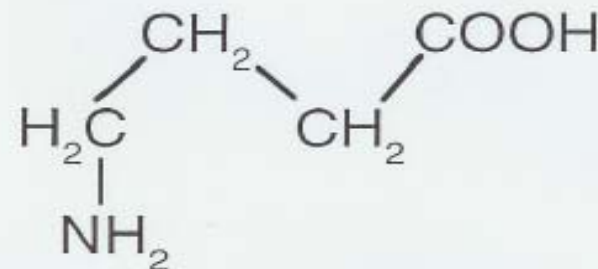
College on Problems of Drug Dependence
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Scottsdale, AZ
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Structures of Vigabatrin and GABA



Vigabatrin
(4-amino-5-hexenoic acid)



GABA
(γ -aminobutyric acid)

- Vigabatrin is an analogue of the inhibitory neurotransmitter GABA
- Vigabatrin was rationally designed to irreversibly inhibit the enzyme GABA transaminase

- Trade Names: Sabril[®], Sabrilex[®]
- Other Names: Gamma-Vinyl GABA; GVG; VGB
- Approved in ~65 countries since 1989
- Investigational drug: Vigabatrin (CPP-109)
tablets 500mg
- Indications:
 - Adjunctive therapy for treatment-resistant partial epilepsy, with or without secondary generalization
 - Monotherapy for infantile spasms

Key Pharmacokinetic Characteristics



Tmax	1 - 4 Hours (unaffected by food)
T _{1/2}	5 – 7 Hours
Protein binding	95% Free
Elimination	Renal
Active metabolites	None
Drug interactions	Minimal
Blood levels	Not related to efficacy
Liver enzyme induction	None
Accumulation	None

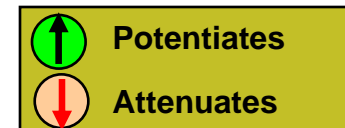
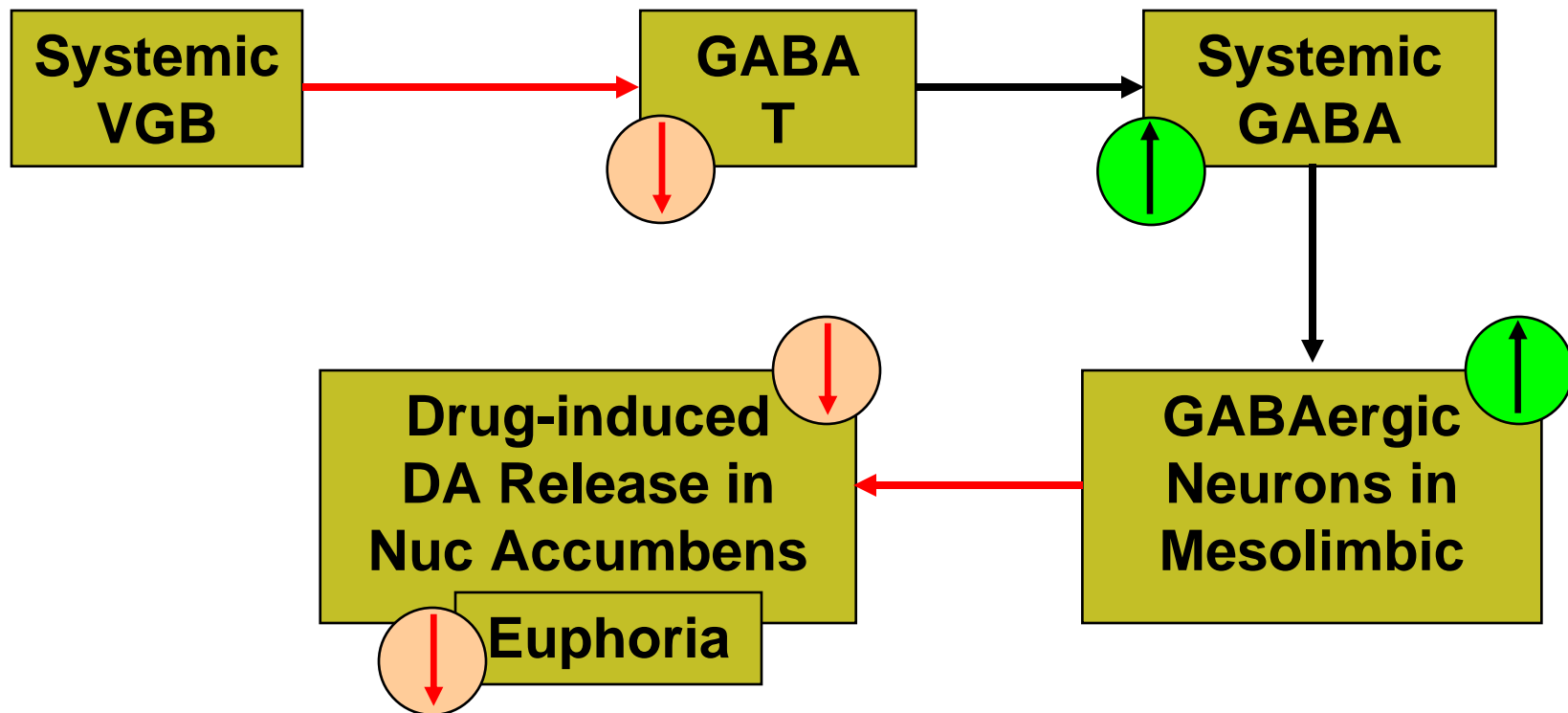
MOST COMMON AE's (%); U.S .CONTROLLED STUDIES (adults with epilepsy; add-on Rx)



Event	Pbo (N=135)	Vgb (N=222)	Event	Pbo (N=135)	Vgb (N=222)
Drowsiness	17.8	27.5	Depression	3.0	9.5
Fatigue	15.6	27.5	Asthenia	2.2	5.0
Dizziness	13.3	20.7	Impaired concentration	1.5	5.0
Weight gain	3.7	7.2	Paresthesia	2.2	8.6
Agitation	7.4	11.3	Confusion	1.5	5.4
Abn. Vision	5.9	11.3	Abnormal thinking	0.7	5.0
Amnesia	3.0	9.5			
Nystagmus	8.1	14.9			

- Visual field defects (VFD's) observed in some epilepsy patients taking vigabatrin long-term
 - Up to one-third of chronic users; concentric, binasal, temporal sparing; central acuity generally not impaired.
 - Do not progress when use of vigabatrin is discontinued, but may be irreversible.
 - Low incidence of VFD's when cumulative dosage < 1,500 grams.
 - Unknown if related to use by epilepsy patients, combined with other AED's, duration of use, or cumulative dose; may be related to GABA accumulation in the retina; also associated with light exposure and possibly taurine deficiency.
- Royal College of Ophthalmology (U.K.) recommends visual field exams every 6 mos. for epilepsy patients undergoing chronic treatment; FDA recommends every 3 mos.
- Expected VGB treatment dosage for stimulant abuse < 250 grams (12 weeks)

Pharmacologically Potentiating GABAergic neurons in the NAcc Attenuates Cocaine-Induced Increases In Synaptic Dopamine (DA)



- Pretreatment of rats and non-human primates with VGB attenuates cocaine-induced surges of dopamine in the nucleus accumbens and striatum.
- VGB decreases cocaine self-administration in rats.
- VGB dose-dependently raises brain stimulation reward thresholds in rats.
- VGB dose-dependently attenuates the cocaine induced lowering of brain stimulation reward thresholds in rats.
- VGB blocks the acquisition and expression of the cocaine induced conditioned place preference in rats.
- VGB abolishes the increases in nucleus accumbens dopamine levels caused by exposure to conditioned place preference.

- Outpatient; open label; fixed dose
- N=20; DSM-IV criteria for cocaine addiction; minimum 3 years of continuous use; mean daily dose app. 1.7 gm
- VGB dosing:
 - Week 1: escalating to 2 gm bid
 - Weeks 2 – 5: maintenance at 2 gm bid
 - Weeks 6 - 9: taper
- 8 Subjects completed the trial; reports of eliminated craving in 2 – 3 weeks; were drug free for 46 to 58 days

- 12 subjects terminated early: 8 determined they did not want to discontinue cocaine use within 10 days; 4 stayed for 25 – 43 days, 3/4 reduced cocaine use 50% to 80%
- Side effects: transient somnolence in first 10 days; intermittent low-grade headaches; weight gain
- No subjects reported visual disturbances
- Brodie JD, et al., Synapse 50:261-265 (2003)

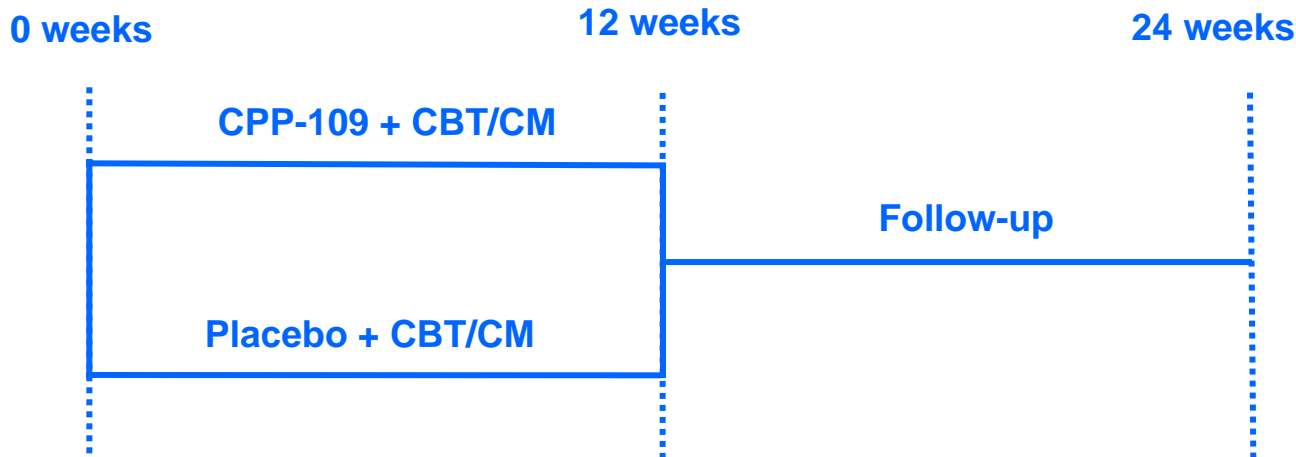
- Outpatient; open label; fixed dose
- N=30; DSM-IV criteria for dependence on methamphetamine (10/30), cocaine (3/30), or both (17/30); mean duration of dependence 12.8 years; mean daily dose app. 0.9 gm
- VGB dosing:
 - Weeks 1 – 2: escalating to 1.5 gm bid
 - Weeks 3 – 6: maintenance on 1.5 gm bid
 - Weeks 7 – 9: taper
- 18 subjects completed the trial; 16/18 tested negative for methamphetamine & cocaine for last 6 weeks of the trial

- 15/30 achieved abstinence followed by 21 drug-free days; median days drug free was 42/63 for this group
- Perimetry (Humphreys 60-4 protocol) performed at baseline, middle and end of study; at one to two months follow-up. No VFD detected
- Brodie JD, et al., Synapse 55:122-125 (2005)
- Fechtner RD, et al., Archives of Ophthalmology 124:1257-62 (2006)

- NYU – investigator-sponsored study
 - JD Brodie, Ph.D., M.D. and E. Figueroa, M.D.
 - Clintrials.Gov reg. #: NCT00527683
- Outpatient; double-blind; placebo-controlled; randomized
- N=103 (50 vigabatrin; 53 placebo); DSM-IV criteria for dependence on cocaine; mean duration of dependence 8.9 yrs; mean daily dose ~1.8 gm
- VGB dosing:
 - Weeks 1 – 2: escalating to 3.0 gm qd
 - Weeks 3 – 6: maintenance on 3.0 gm qd
 - Weeks 7 – 9: taper

- 18 patients met primary efficacy endpoint of abstinence from cocaine use for the last 3 weeks of treatment
 - 14 received vigabatrin (28% of 50)
 - 4 received placebo (7.5% of 53)
 - **HIGHLY STATISTICALLY SIGNIFICANT (p=0.009)**
- Durability of abstinence response
 - 12/50 (24%) on vigabatrin maintained abstinence throughout 4 week follow-up
 - 2/53 (3.8%) on placebo maintained abstinence
- Self report data indicate increased rates of abstinence from alcohol use
 - End of study abstinence (self report) 43.5% vigabatrin vs. 6.3% placebo; (p≤0.03)
- Brodie JD, et al., Am J Psychiatry 166:1269-77 (2009)

CPP-01004 Phase II Cocaine Trial



- Primary endpoint: Proportion of each treatment group achieving drug abstinence during the final two weeks of the active phase (trial weeks 11 and 12)
- Secondary endpoints: Reduction in craving, drug use & drug use days
- 11 centers, mostly academic
- Trial design similar to other NIDA-sponsored studies (CTO & MDS)
- Urine specimens collected 3x/week sent to central lab to maintain site blinding
- Computerized cognitive behavioral therapy & counseling (1/week) + contingency management

- Study did not meet protocol specified primary and secondary endpoint analyses, but:
 - BE levels were consistently lower in the vigabatrin group vs. placebo ($p = 0.006$)
- Vigabatrin safe
 - No visual field defects observed
 - Changes in blood pressure observed did not appear to differ between vigabatrin and placebo groups
 - No unexpected SAE's or AE's, so no safety concerns going forward

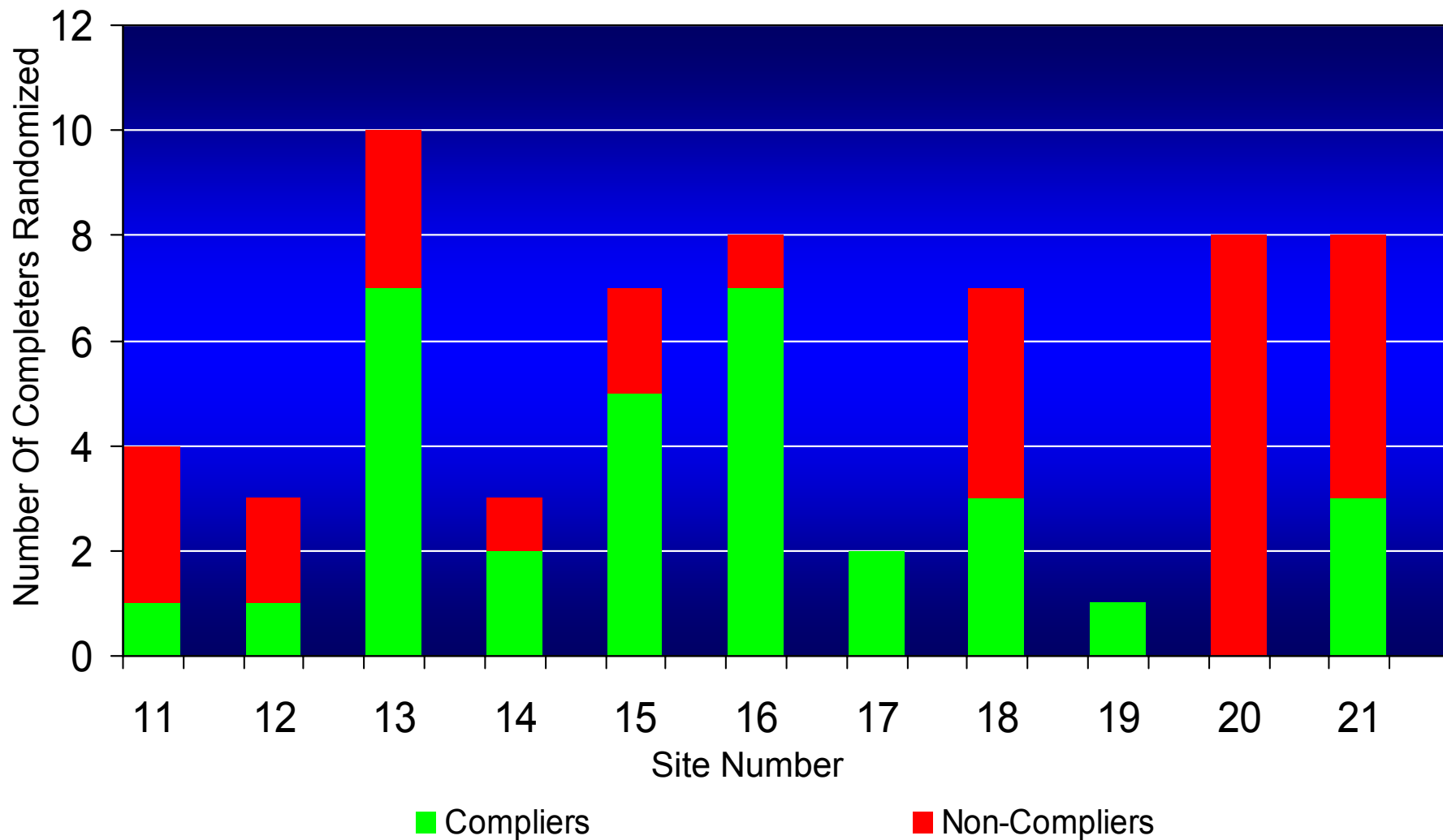
U.S Phase II Cocaine Trial Results

Post Hoc Medication Compliance Analysis



- Because of the discrepancy between the results of Mexico III and CPP-01004, compliance with taking medication was more closely examined.
- Urine was quantitatively analyzed for VGB from subjects considered 'completers' (125/186).
- Based on known PK and urinary excretion of VGB and the protocol definition of compliance, a urine VGB concentration was established to define a "complier."
- Placebo compliers were estimated using a statistical methodology (CACE, Complier-Average Causal Effect).
- This analysis was completed while still blinded to trial outcome (i.e. identities of responders).
- Compliance was found to be substantially lower than by self-report/pill count (e.g. 39% compliance by urine VGB versus 92% compliance by self-report/pill count in study completers).
- Low compliance makes the interpretation of the results of CPP-01004 particularly uncertain.

Number Of Vigabatrin Completers/Drug Compliers By Site



- **Why do we believe trial failed and not the drug:**
 - BE levels consistently lower in Per-Protocol vigabatrin group vs. placebo ($p = 0.064$)
 - Cocaine use days also consistently lower in Complier vigabatrin group vs. Non-complier group ($p=0.084$)
 - Compliers ($p = 0.001$) had consistently fewer cocaine use days than non-compliers.
 - Vigabatrin group ($p = 0.006$) consistently used less cocaine than placebo group (ITT).
 - **Mexico III trial results showed a significant effect of VGB versus PBO!!**
- **Safety analyses**
 - No visual field defects or abnormalities
 - No drug related SAEs
 - Generally the drug was very safe
- **Medication compliance significant problem**
 - <40% of subjects took medication as prescribed vs. >85% by pill count
- **Difficulty to attract treatment motivated subjects**
 - At 5/11 sites, <50% of subjects took medication as prescribed

- **Lessons From the CPP-01004 Trial**
 - Address issue of medication adherence of subjects
 - More observed doses and/or
 - Add marker substance to vigabatrin and placebo formulations (e.g. riboflavin)
 - Address issue of attracting subjects motivated to seek treatment (subjects with a real desire to change their lives)
 - Better screening out of non-treatment seeking candidates
 - Advertising directed at demographic more likely to be seeking treatment
 - Try to find a clinical setting which more replicates Mexico III; i.e. treatment centers
 - Address perceived issues related to Contingency Management

- **A new trial is currently being initiated in collaboration with NIDA and the VA Cooperative Studies Program.**



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THANK YOU