A Double-Blind Placebo-Controlled, Randomized Trial of Divalproex Sodium for Posttraumatic Irritability Greater Than 1 Year After Mild to Moderate Traumatic Brain Injury

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mTBI Study Team

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"My Sweetest Child"/"DATC"/ "Rodeo"

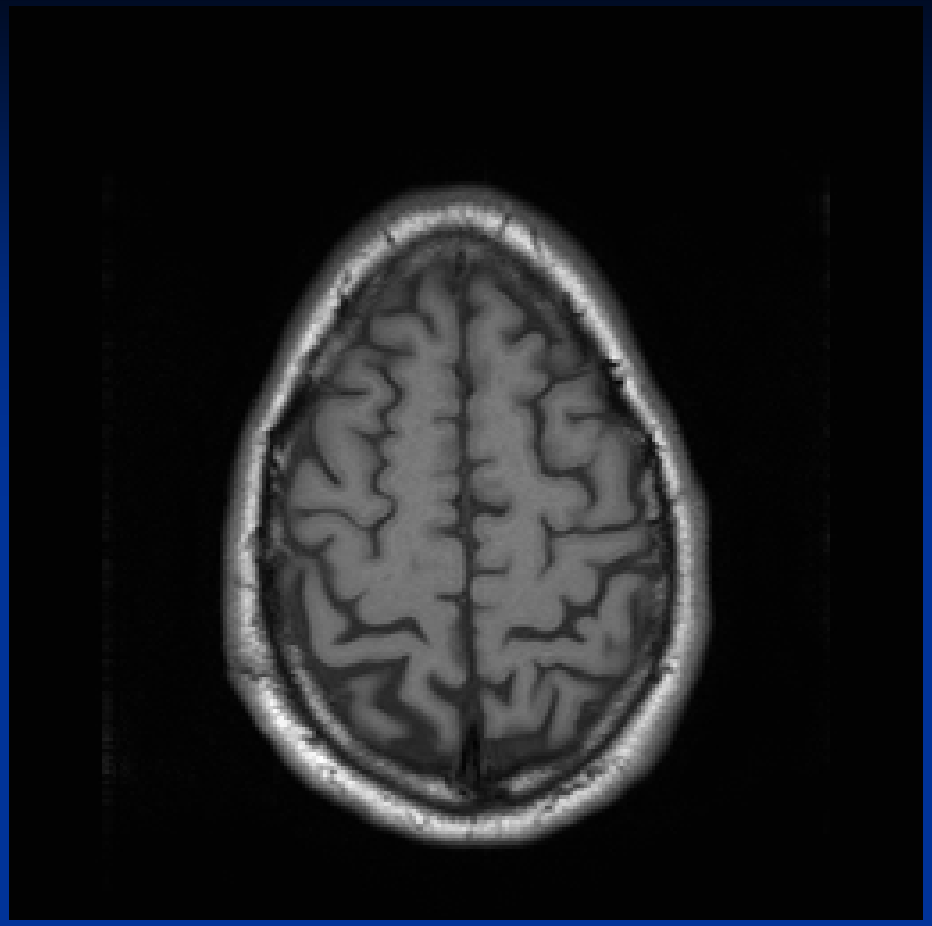
25 y/o AA male, OIF, E-3, HumVee turret gunner	37 y/o w male, OIF, E-9, tank commander	26 y/o w male, OIF, O-2, platoon leader
Roadside explosive	Rocket attack	Trap explosive

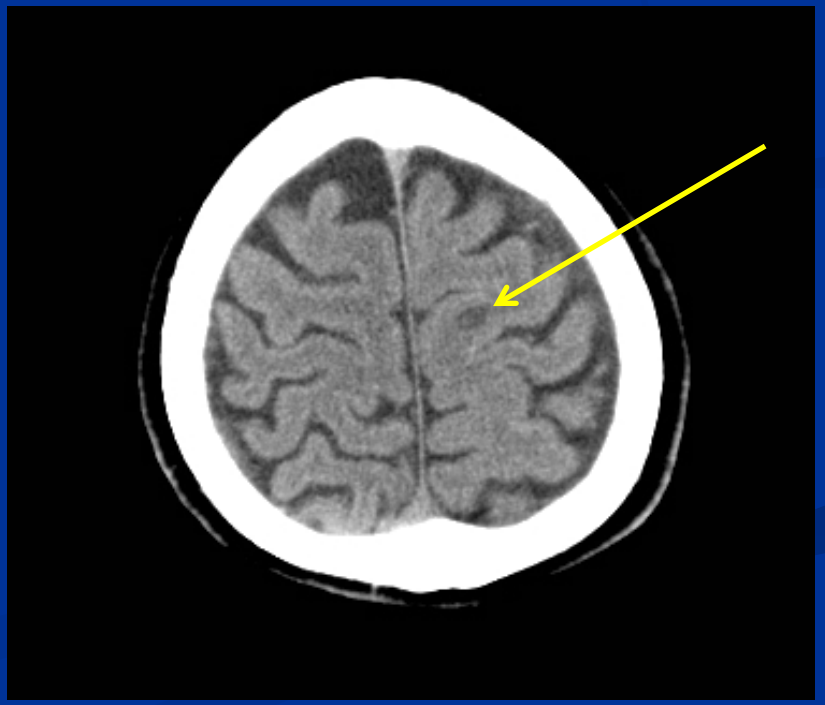
Immediate

- Loss of Consciousness ~ 1 hour
- No memory of the event
- Dazed concussive like symptoms for days
- No open cranium injury
- Brain MRI negative

At One Year

- Easily irritable with poor control
- Unable to participate in sustained relationships
- Unable to hold a job involving work with others





Study Background/Rationale

Clinical observation: 1) taking TBI histories in the SATP 2) drinking following head injury and in response to affective lability.

Rationale: treat "upstream"--valproate and carbamazepine clinically for affective control.

Clinical series: markedly reduced drinking in TBI cases

Beresford, TP, Arciniegas, DB, et al. Anticonvulsant Treatment Of Affective Lability and Alcohol Dependence Following Traumatic Brain Injury. *Brain Injury*, 19: 309-13, 2005

Proof: Can this be shown in double blind, randomized, placebo controlled trial?

Goal: A specific treatment for Irritability leading to improved function and recovery of work and family, and secondary effect of drinking reduction

Hypotheses

Hypothesized Path From TBI Through Irritability To Heavy Alcohol Use

Primary Hypothesis:

valproate > placebo in reducing Irritability

Secondary Hypothesis:

reduced alcohol use in the active drug group

Design and Methodology

Design: placebo controlled, randomized, double blind, 8 week trial, adults of both genders, vets and non-vets, N = 50 randomized cases, intent to treat analysis.

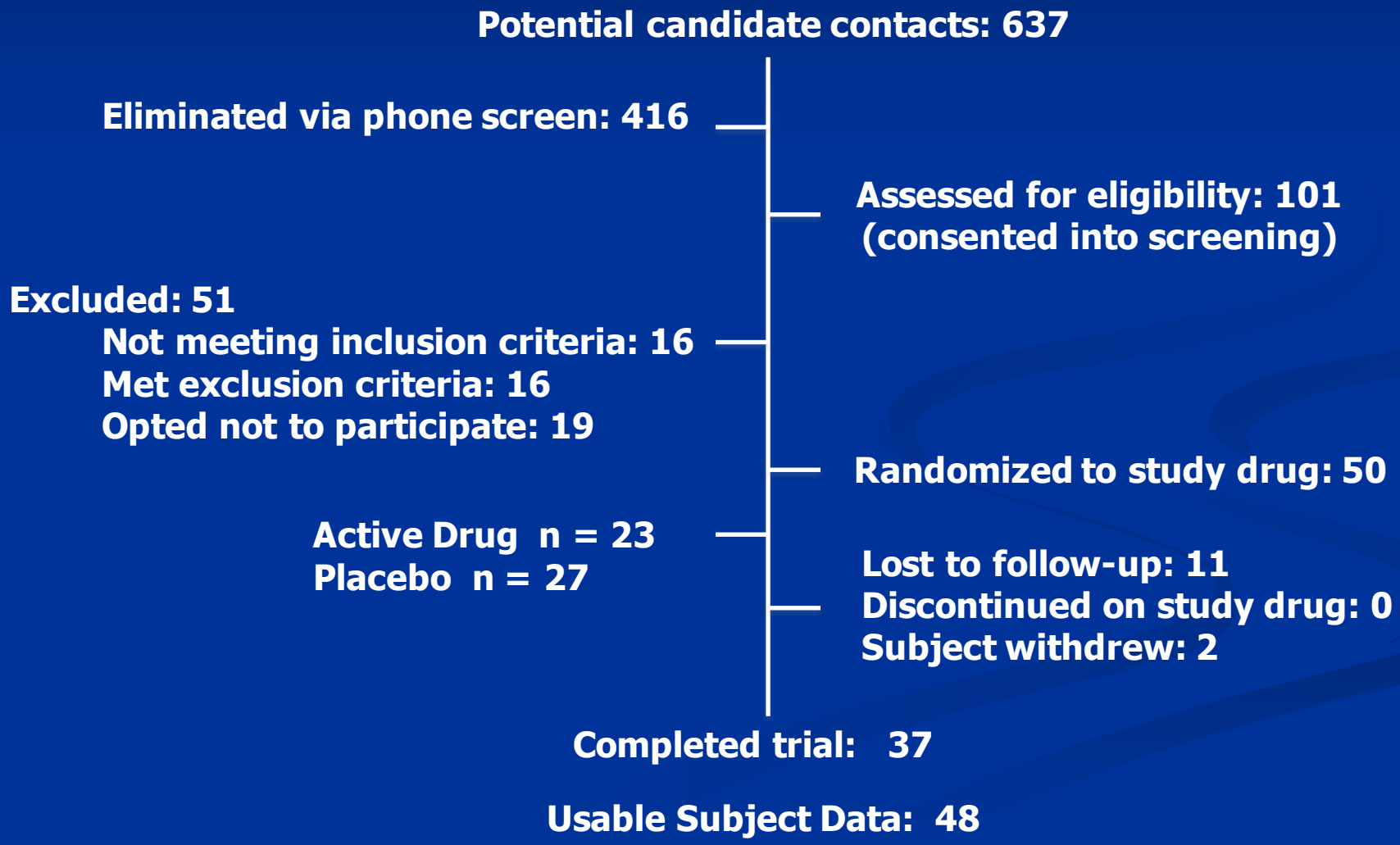
<u>Inclusion</u>: Irritability and alcohol abuse after mild to moderate TBI (non-penetrating), symptoms present 1 year after TBI; significant other (S/O) reports s's Irritability and problematic alcohol use.

<u>Exclusion</u>: penetrating injuries.

<u>Outcome measures</u>:

- **Subject and S/O: S's affective measures at interview**
- **Subject and S/O: Time Line Follow Back (TLFB) of S's Alcohol Use**

Enrollment Log



Results 1

Randomized: Drug 23 Placebo 27

Gender: 46 male, 4 female, equal distribution

Age: 47 yrs +/- 14 yrs; range 25 – 62 yrs

Subject Cognition (n = 45):

Frontal Assessment Battery (FAB):

below 2 stdev	5	11%
below 1 stdev	7	16%
below mean	10	22%
at/above mean	23	51%

Table 1: Demographics and Baseline Values Of Outcomes

	Divalproex sodium (n=23)	Placebo (n=27)	Overall (n=50)	p-value
Male - n (% in group)	20 (87.0%)	20 (74.1%)	40 (80.0%)	0.8572
Female – n (% in group)	3 (13.0%)	7 (25.9%)	10 (20.0%)	
TBI severity				0.5660
Mild	12 (57.1%)	13 (59.1%)	25 (58.1%)	
Moderate	5 (23.8%)	7 (31.8%)	12 (27.9%)	
Severe	4 (19.1%)	2 (9.1%)	6 (14.0%)	
Drinks/wk at baseline	19.5 (SD=33.2)	17.9 (SD=20.0)	18.7 (SD-26.7)	0.8370
Age at consent	46.2 (SD=10.99)	45.3 (SD=9.66)	45.7 (SD=10.23)	0.7498
FAB	16.0 (SD=16.04)	16.5 (SD=16.5)	16.3 (SD=1.57)	0.3329
Trails B	98.9 (SD=40.50)	87.6 (SD=34.22)	93.4 (SD=37.49)	0.3068
NRS	10.1 (SD=4.08)	12.3 (SD=4.38)	11.4 (SD=4.27)	0.0901
ABS - self	12.4 (SD=1.50)	12.7 (SD=2.16)	12.65 (SD=1.93)	0.5288
CGI - self	3.3 (SD=1.25)	3.5 (SD=1.60)	3.4 (SD=1.40)	0.6390
CGI - provider	3.3 (SD=1.14)	4.0 (SD=0.98)	3.7 (SD=1.09)	0.0311

Results 2

Primary Outcome (n=48):
mean S/O rated Agitated Behavior Scale

Drug, n=22: 12.7 +/- 1.1
Placebo, n=26: 16.3 +/- 1.3

p = 0.0399, Cohen's *d* = 0.44 medium

Secondary Outcome:
Mean standard drinks/week (TLFB)

VPA: 22.4 +/- 5.6
Placebo: 14.1 +/- 5.9

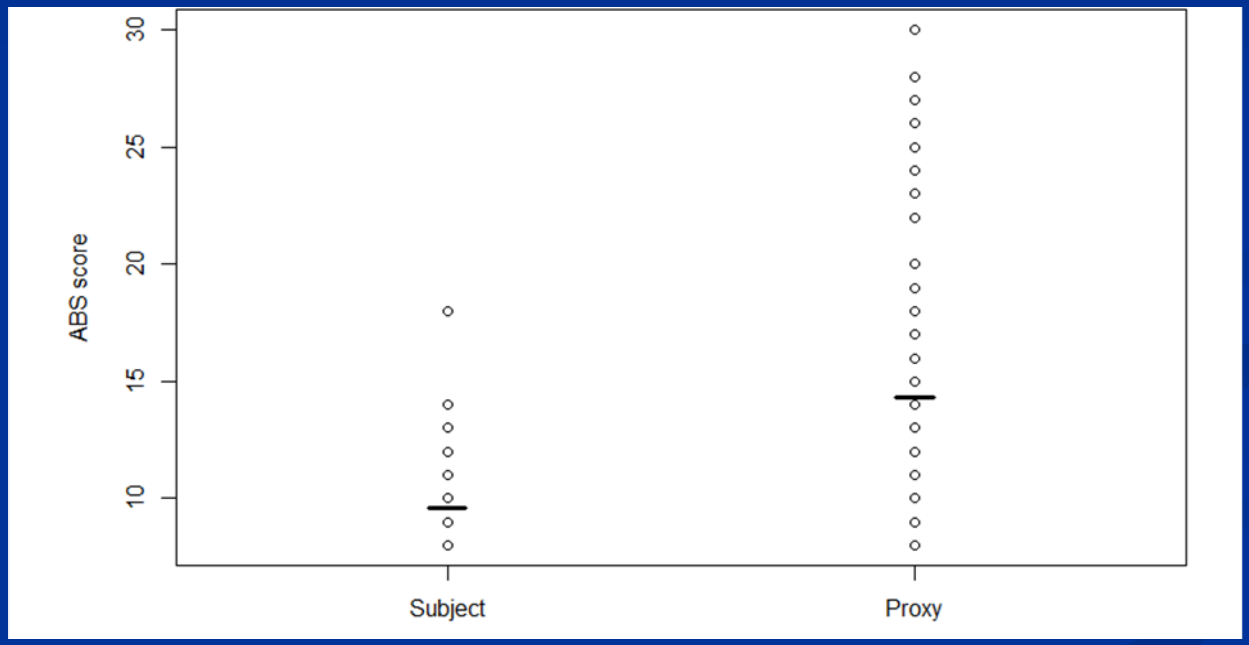
p = 0.31, n. s.

Table 3: Estimated Mean Outcomes Between Weeks 2 And 8, Adjusting For Repeated Measures, By Treatment Group

Outcome	Divalproex sodium Mean (SE)	Placebo Mean (SE)	p-value
TLFB	22.43 (5.63)	14.08 (5.92)	0.3081
Days drinking	2.31 (0.47)	1.59 (0.46)	0.2794
FAB	16.58 (0.38)	16.38 (0.33)	0.6953
Trails B	92.16 (10.00)	86.13 (9.59)	0.6725
NRS	5.16 (0.80)	6.63 (0.82)	0.2025
ABS - self	9.21 (0.24)	9.43 (0.25)	0.5141
ABS - proxy	12.72 (1.09)	16.25 (1.26)	0.0399
CGI - self	2.52 (0.27)	3.09 (0.28)	0.1523
CGI - provider	2.73 (0.25)	2.96 (0.26)	0.5362

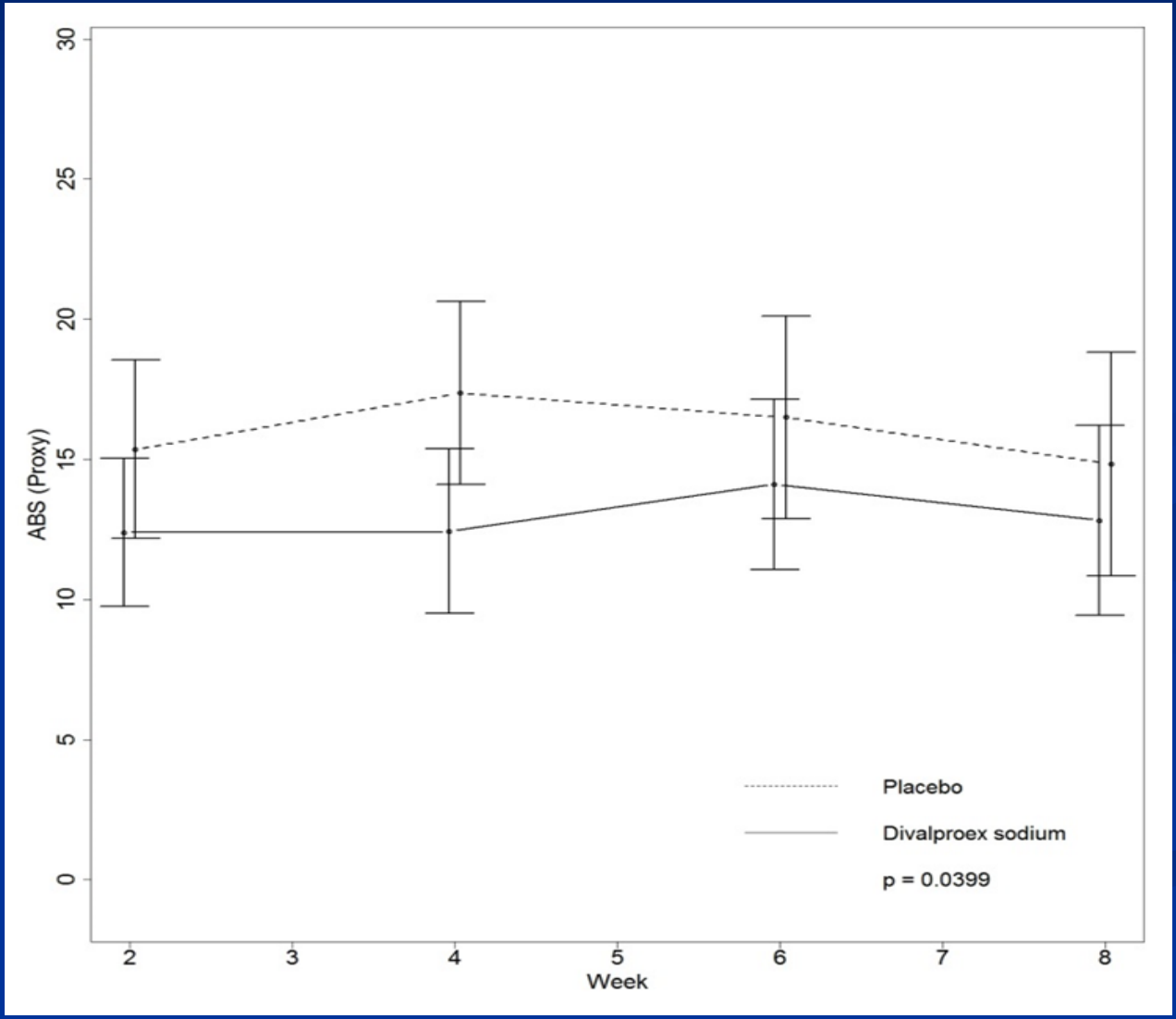
Figure 1: Self and Proxy ABS scores

Figure 2. Subject and Informant ABS Ratings At Baseline



Legend Figure 2. Means: Subject 9.5 ± 2.5, Informant 14.8 ± 3.2 ($p<0.05$)

Figure 2: Plot of ABS proxy scores (95% CIs) between 2 and 8 weeks by treatment group



Conclusions

Valproate appears effective against "permanent" Irritability after mild to moderate TBI.

Alcohol Dependence/Abuse (ICD-10) insufficient to test in this sample.

No statistical relation to Histories of PTSD, anxiety, or veteran status in this sample

Lessons

1) **TBI studies require data from SO's,** not just subjects and observers.
   --behaviors rather than words

   Anisognosia?

2) Does post-TBI Irritability impair family relations?

"Absence of evidence is not evidence of absence." -- Carl Sagan

LCTRP: improving practice by learning from practice

Deliverables:

-- Rational clinical assessment of alcoholic persons requesting liver transplant

-- Immunosuppressants reduce alcohol intake in mice; humans?

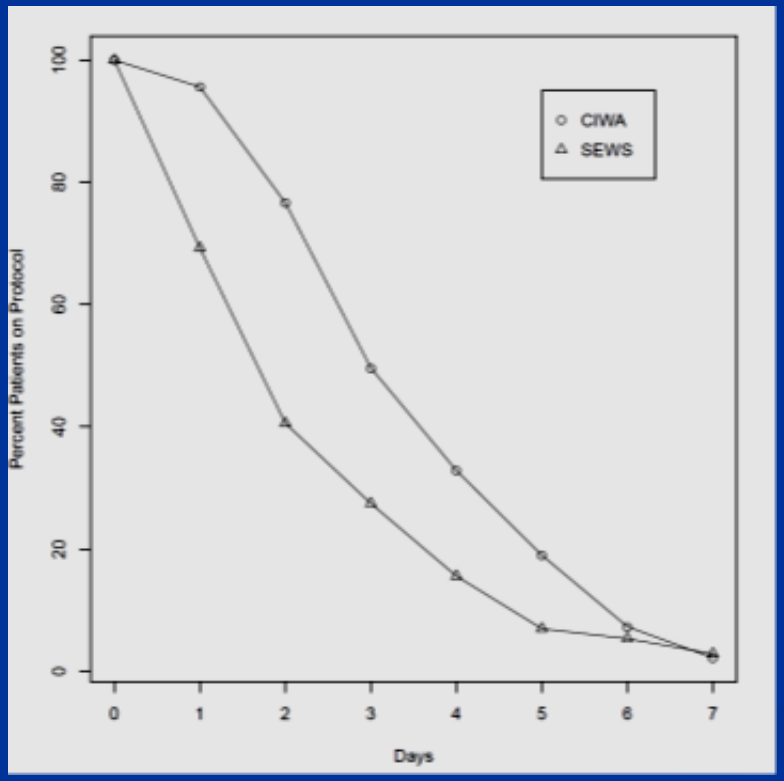
-- Methylphenidate treatment of central pontine myelinolysis brain effects

-- Practical approach to Psychological Adaptive Mechanism recognition

-- SEWS: Severity of Ethanol Withdrawal Scale – clinically effective

Improving Alcohol Withdrawal Treatment

- Figure: % on Protocol by Day SEWS (n = 244) and CIWA-Ar (n = 137)



SEVERITY OF ETHANOL WITHDRAWAL SCALE (SEWS)	YES	SCORE
ANXIETY: do you feel that something bad is about to happen to you right now?	3	
NAUSEA and DRY HEAVES or VOMITING?	3	
SWEATING (includes moist palms, sweating now)?	2	
TREMOR: with arms extended, eyes closed	2	
AGITATION: fidgety, restless, pacing	3	
ORIENTATION Name and place but not date Name but not place and date	 1 3	
HALLUCINATIONS Auditory only (check for major psychotic disorder) Visual, tactile, olfactory, gustatory (any)	 1 3	
VITAL SIGNS: ANY of the following Pulse >110 Diastolic BP >90 Temp >99.6	3	
TOTAL SCORE =		
Total Score < 6: low to mild withdrawal severity Total Score = or > 6: moderate severity Total Score = or > 12: high severity		