

Prophylactic Treatment of Migraine Headaches

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Goals

Discuss

- Epidemiology
- Diagnostic Criteria
- Comparative Efficacy and Side Effects of Prophylactic Treatment



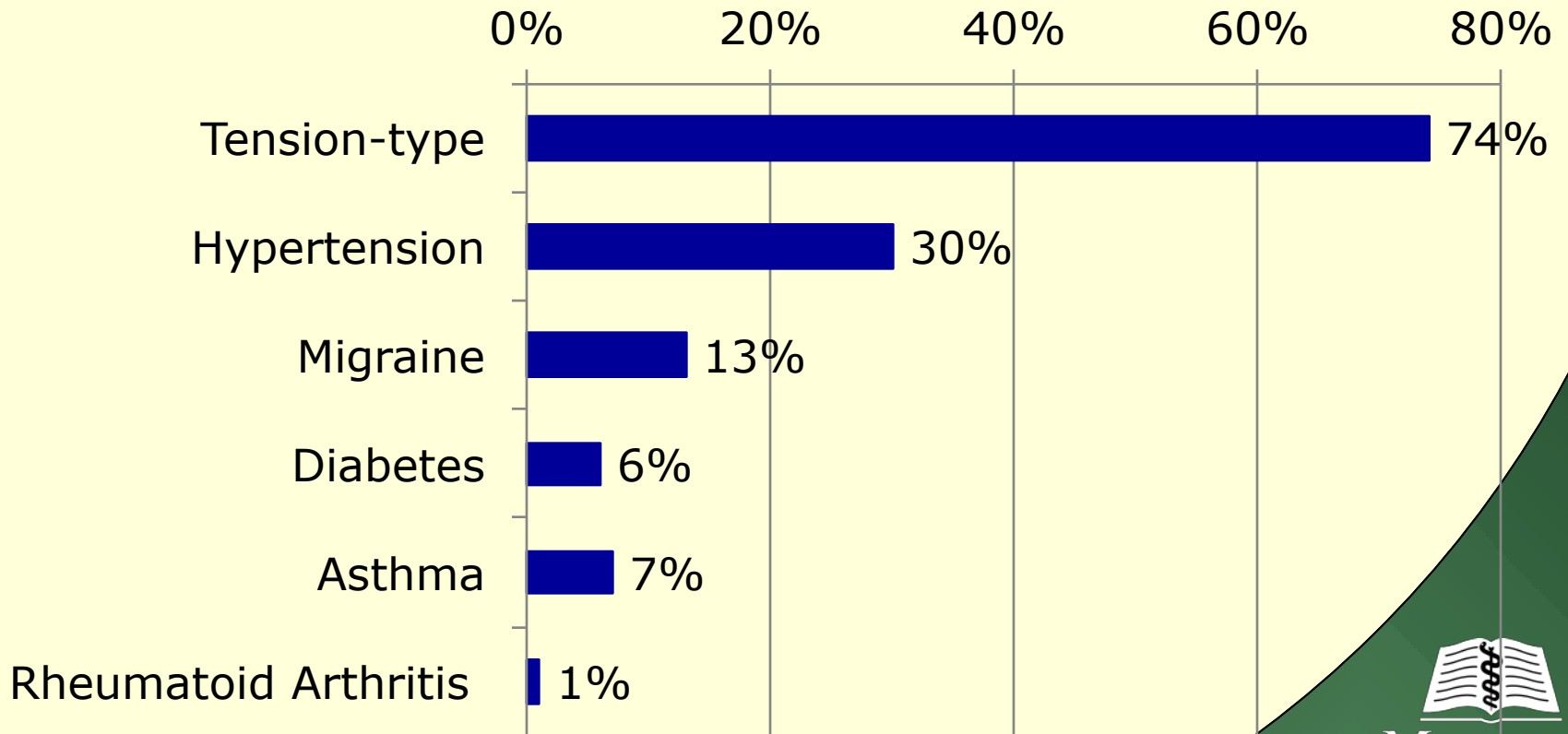
Epidemiology

- Common
 - Prevalence 8.4-18%
- Peaks 25-55 years
- Female predilection (73%)
- Costly
 - \$1 billion US medical costs
 - \$16 billion productivity losses
- High morbidity



COMMON

Frequency in US Adults



Headache Classification

- Primary
 - Tension-type
 - Migraine
 - Cluster
- Secondary
 - Medication Overuse
 - Trauma
 - Vascular/ intracranial disorder
 - Substance abuse
 - Infection
 - Cranial/facial/oral
 - Sleep Apnea



Primary Headaches

- Migraine
 - With Aura
 - Without aura
- Probable migraine
 - With/without aura
- Tension-type Headache



Migraine Headache

- At least 5 attacks (Lifetime)
- Lasting 4-72 hours
- Characterized by (at least 2):
 - Unilateral
 - Pulsating
 - Moderate-severe
 - Aggravated by routine activity
- At least one of:
 - Nausea/vomiting
 - Photophobia/phonophobia



Tension-type Headache

- At least 10 attacks
- Lasting 30 minutes to 7 days
- Characterized by (at least 2):
 - Bilateral
 - Pressing/tight (nonpulsating)
 - Mild-moderate
 - Not aggravated by routine activity
- Both of:
 - No nausea/vomiting
 - No photophobia/phonophobia



Headaches

- Migraine
 - Episodic <15 headaches/month
 - Chronic Migraine 15 or more HA/month
- Tension Type
 - Infrequent episodic
<1 ha/month, < 12 ha/year
 - Frequent episodic vs. Chronic
15 headaches/month



Headache types you'll see

- Migraines
- Chronic tension-type
- Medication Overuse
 - Triptans, opiates,
 - >10 days/month, > 3 months
 - Analgesics
 - >15 days/month, >3 months



When to consider prophylaxis

- Individualized decision based on
 - Frequency, severity, burden
 - Response to abortive Rx
- Strongly consider when
 - Triptan/opiate use approaches 10 days/mo
 - Analgesic use approaches 15 days/mo



Potential Drugs

Alpha antagonists
Ace-inhibitors
ARBs
Anti-convulsants
Beta-blockers
Botulinum Injections

Calcium channel blockers
Serotonin agonists
SNRIs
SSRIs
TCAs



How to Choose?

- “Drug selection should be tailored based on patient comorbidities, provider comfort with drug, costs and side effects”
- Choice is hampered by the paucity of head to head trials



Systematic Review

- What is the comparative effectiveness and relative side effects of:

Alpha antagonists

Ace-inhibitors

Angiotensin receptor blockers

Anti-convulsants

Beta-blockers

Botulinum Injections

Calcium channel blockers

Pizotifen

Serotonin agonists

SNRIs

SSRIs

Tricyclic antidepressants

Jackson JL et al. Botox...*JAMA* 2012;307(16):1736-45

Jackson JL et al TCAs...*BMJ* 2010; 341:c5222

Tomkins GE et al Antidepressants... *AM J Med* 2001;111(1):54-63

El-Chamin et al. *JAMA Pediatr.* 2013;167(3):250-258.



Systematic Review

- What is the comparative effectiveness and relative side effects of:

Alpha antagonists

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Beta-blockers

Botulinum Injections

Calcium channel blockers

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Serotonin agonists

SNRIs

SSRIs

Tricyclic antidepressants

Jackson JL et al. Plos One. 2015 Jul 14;10(7):e0130733.



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RESULTS



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Records identified through database searching
n=5435

Additional records identified through other sources n=53

Records screened
n=5488

Records excluded
n=4115

Full-text articles assessed for eligibility
n=1373

Records excluded after full review								
	ACE (n=9)	ARB (n=20)	AC (n=689)	BB (n=91)	CCB (n=134)	Pizotifen (n=65)	SSRI (n=74)	TCA (n=154)
Endothelial study	1							
Acute Migraine			23		4			5
Case Series	2	3	148	66	28	8	26	20
Data not extractable			78	3		3		3
Duplicate Data			2	2	1		2	8
IV treatment			1			1		
Not RCT			32	2			5	24
Pediatric			78	17	11	18	2	
Review	6	17	300	1	87	34	39	7
Safety Trial			27		3	3		87

Studies included in quantitative synthesis (meta-analysis)

Ace Inhibitors (n=1)	Calcium Channel Blockers (n=19)
Angiotensin Receptor Blockers (n=2)	Pizotifen (n=25)
Anticonvulsants (n= 30)	Selective Serotonin Reuptake Inhibitors (n=6)
Beta Blockers (n= 37)	Tricyclic Antidepressants (n=11)

Placebo Controlled Trials

Headache Type	Drug Class	Number of Trials
Episodic Migraines (n=113)	ACE	1
	ARB	2
	Alpha Blocker	9
	Anticonvulsants	23
	Beta-Blockers	37
	Calcium/Channel Blockers	17
	Pizotifen	9
	SSRI	6
	SNRI	1
	Serotonin Agonist	9
TCA	8	
Chronic Migraines (n=6)	Alpha Blocker	1
	Anticonvulsant	4
	Beta-Blocker	1
Chronic Daily Headaches (n=5)	Anticonvulsant	3
	SSRI	1
	TCA	1

EPISODIC MIGRAINES



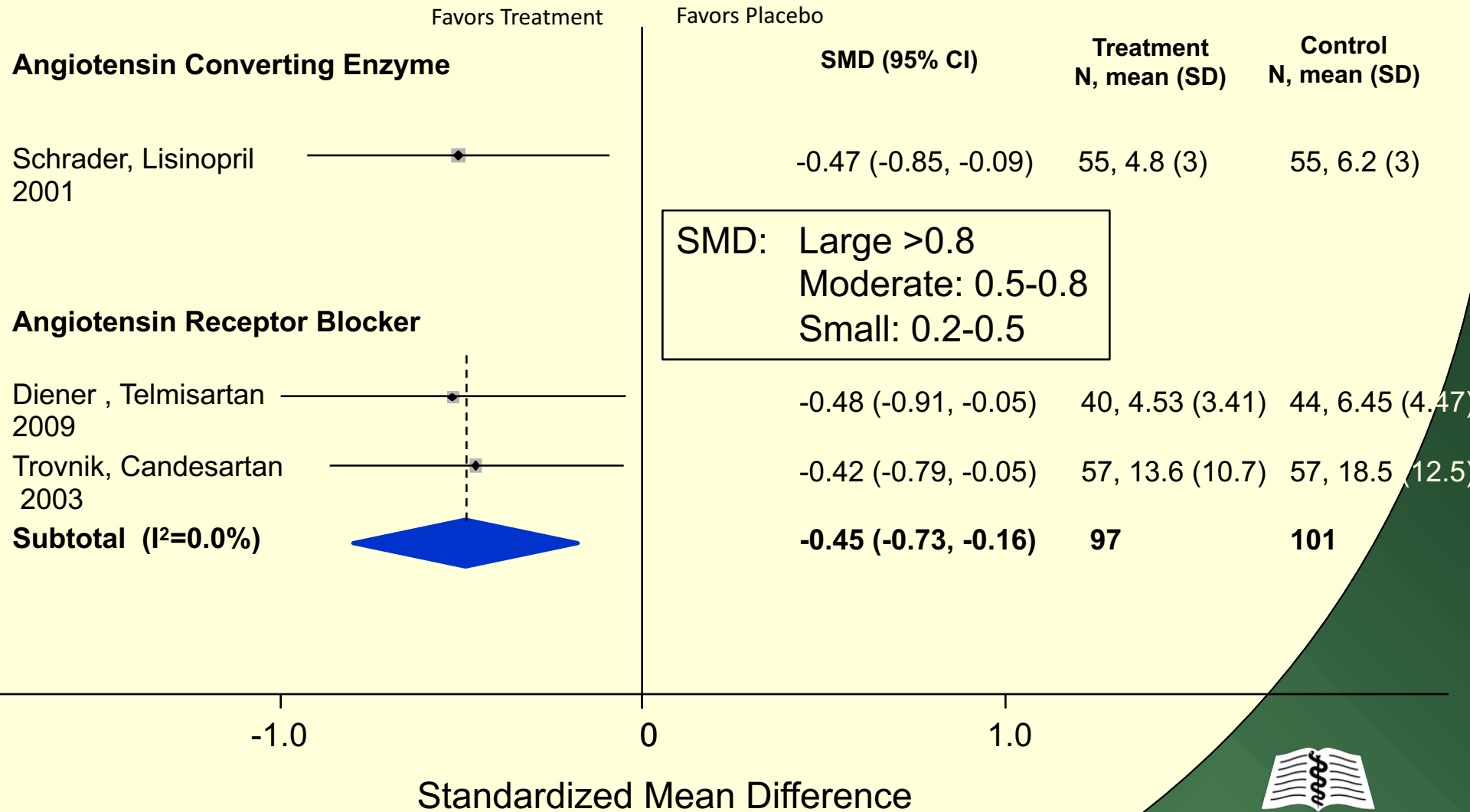
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ACE/ARBS



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Episodic Migraines

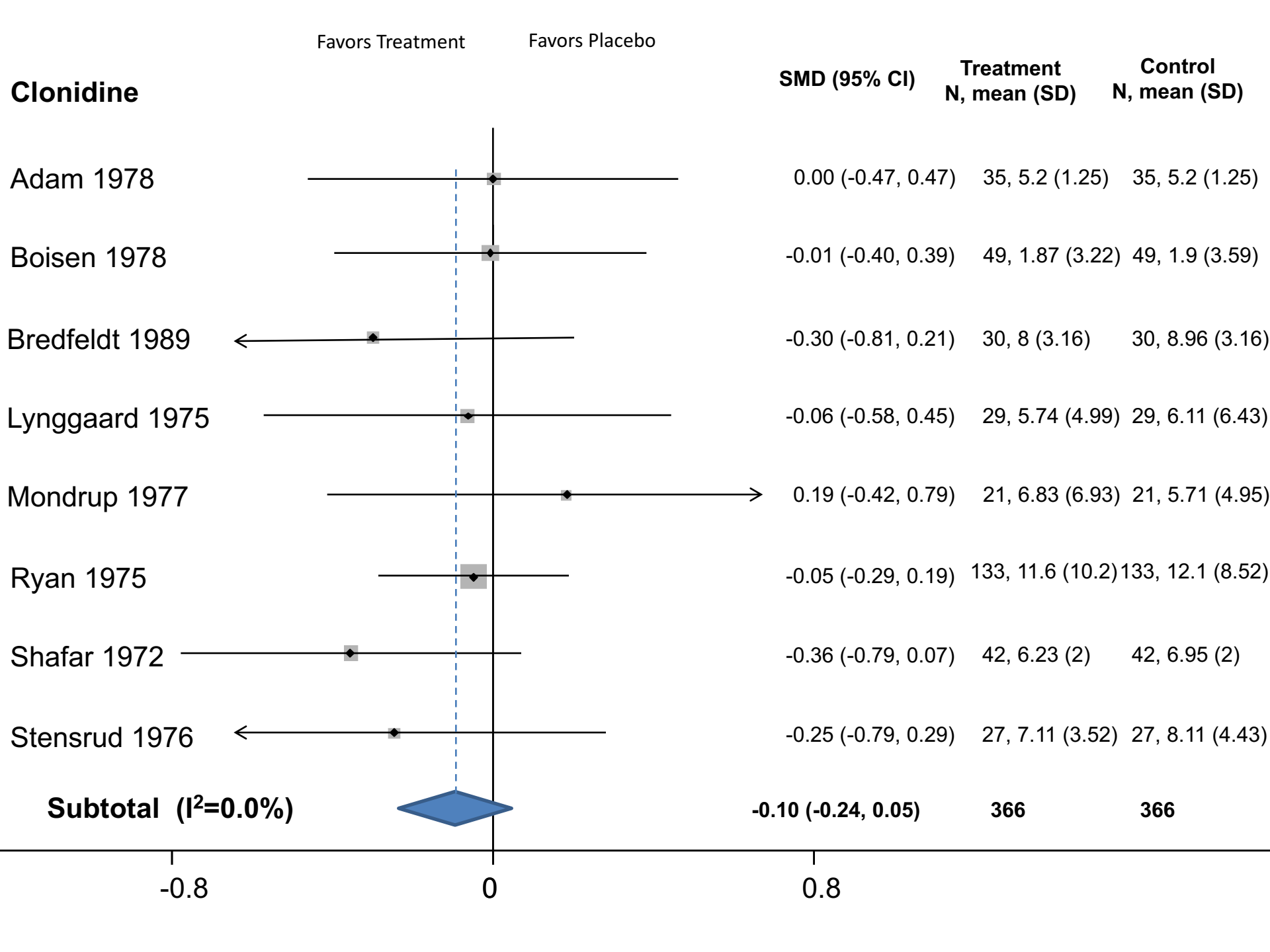


ALPHA BLOCKERS

(CLONIDINE)



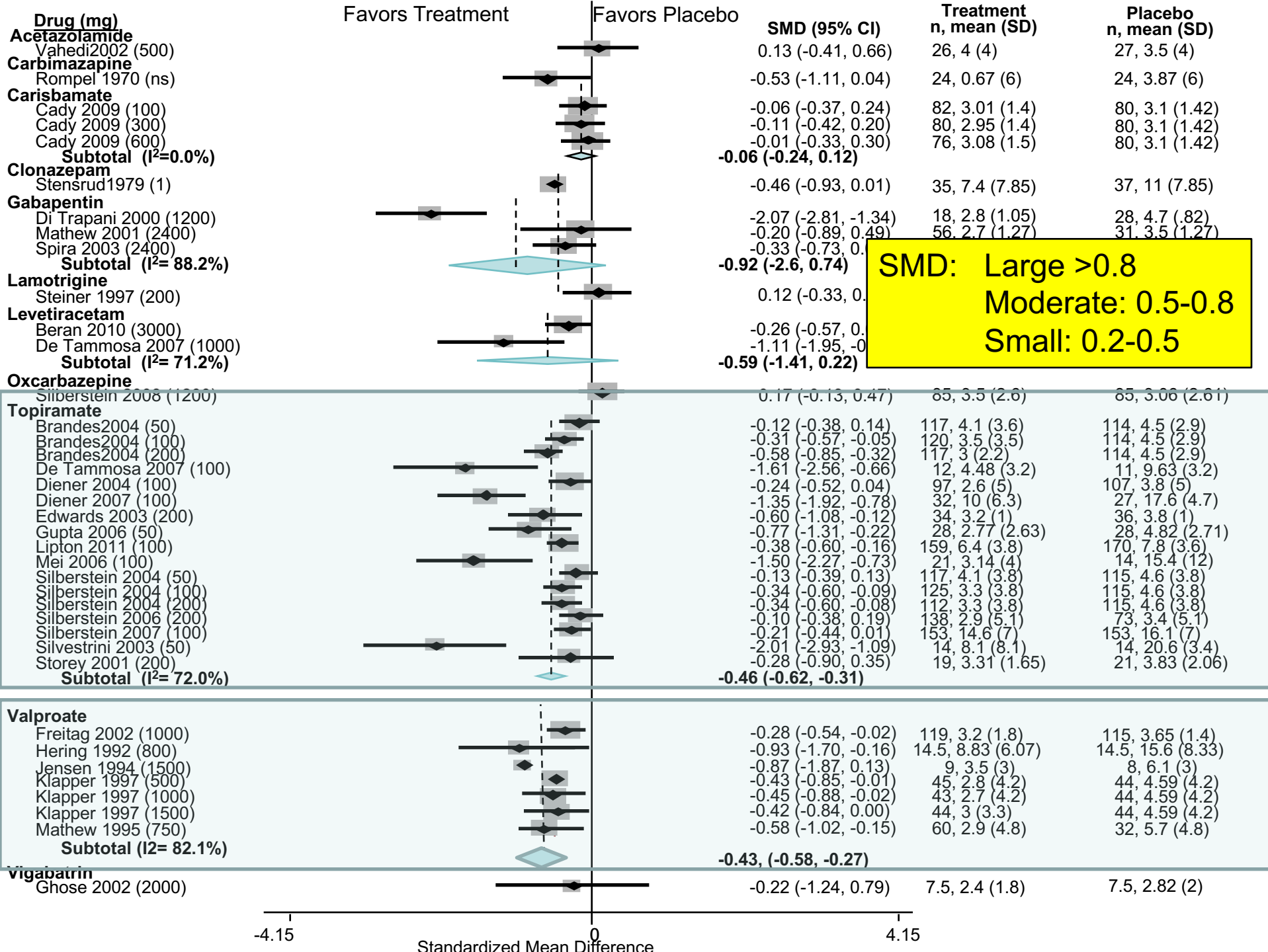
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ANTICONVULSANTS



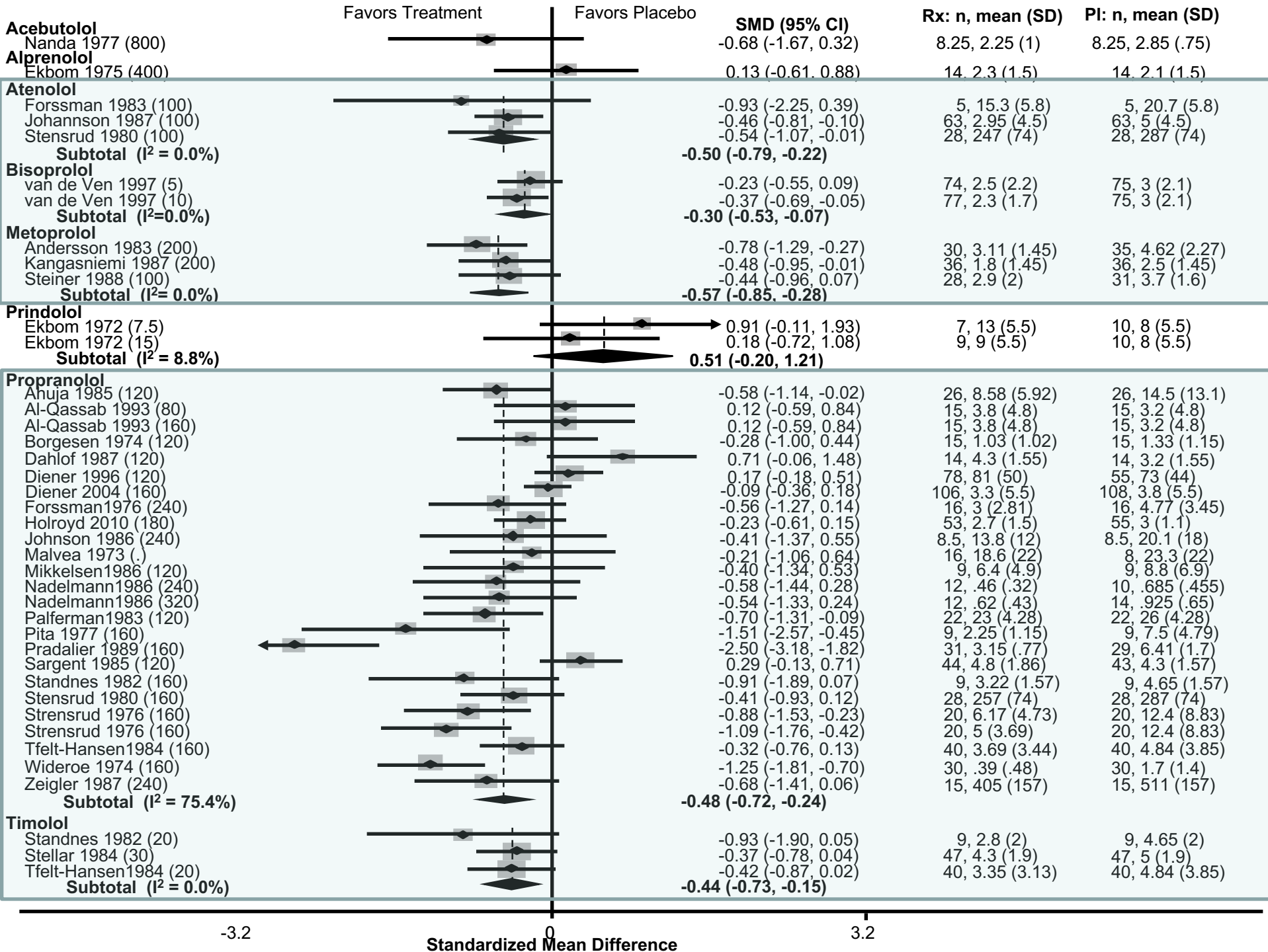
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BETA-BLOCKERS



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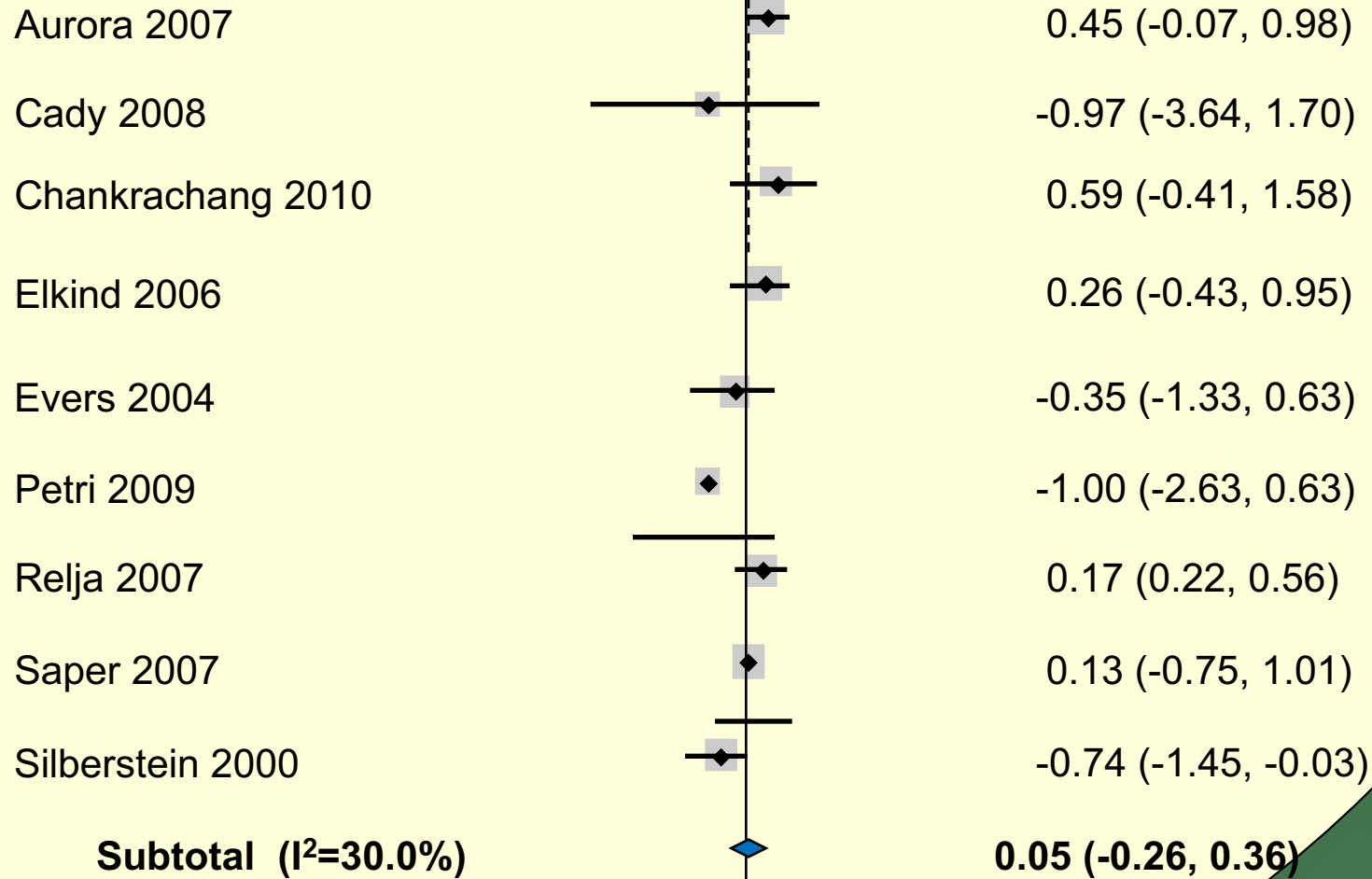


BOTOX



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Episodic Migraine



Note: box size is proportional to study weight

-9.0 -6.0 -3.0 0 3.0 6.0 9.0

Difference in Headaches/Month

Favors Botulinum

Favors Placebo

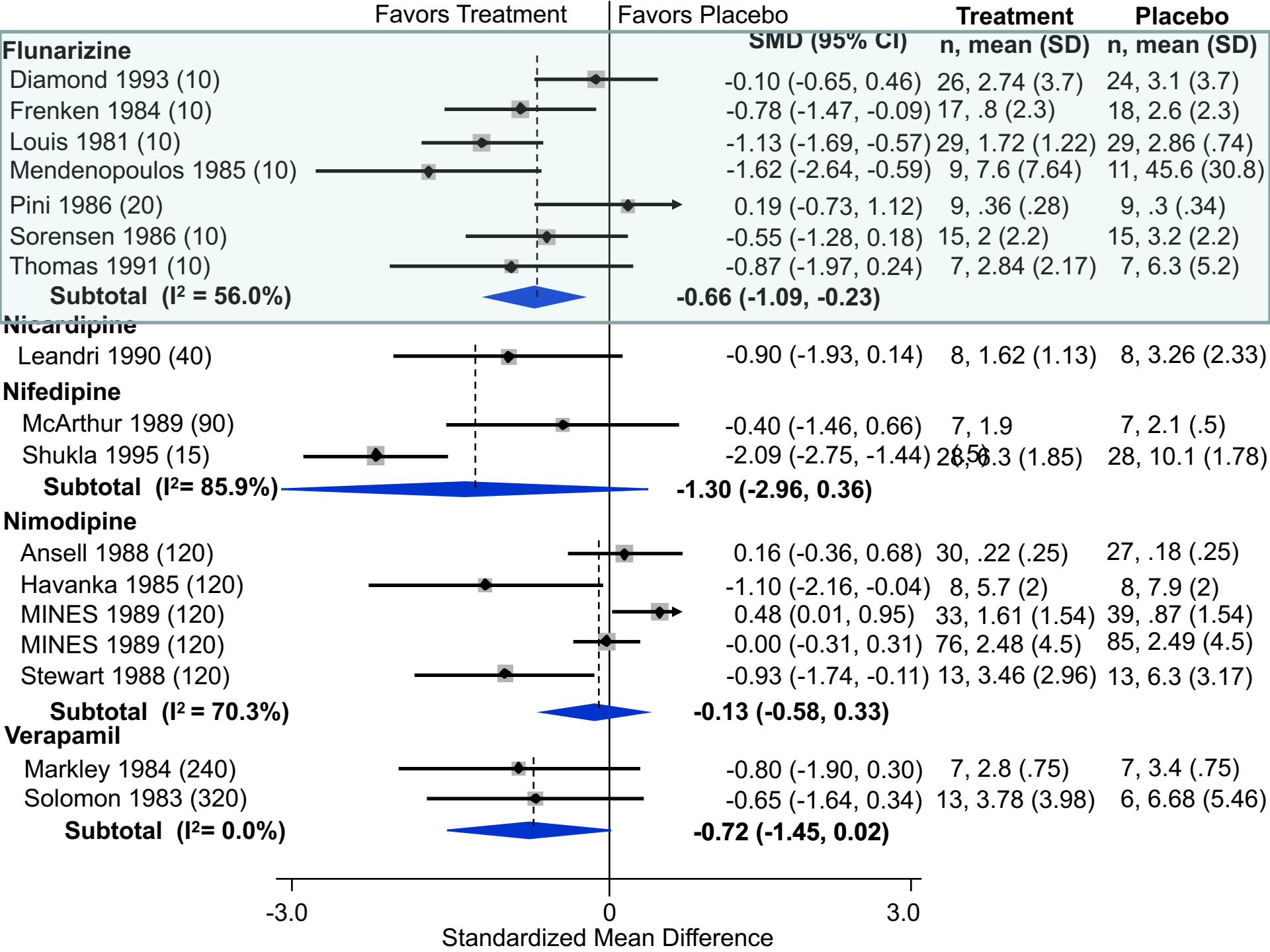
Headaches/Month
(95% CI)



CALCIUM CHANNEL BLOCKERS



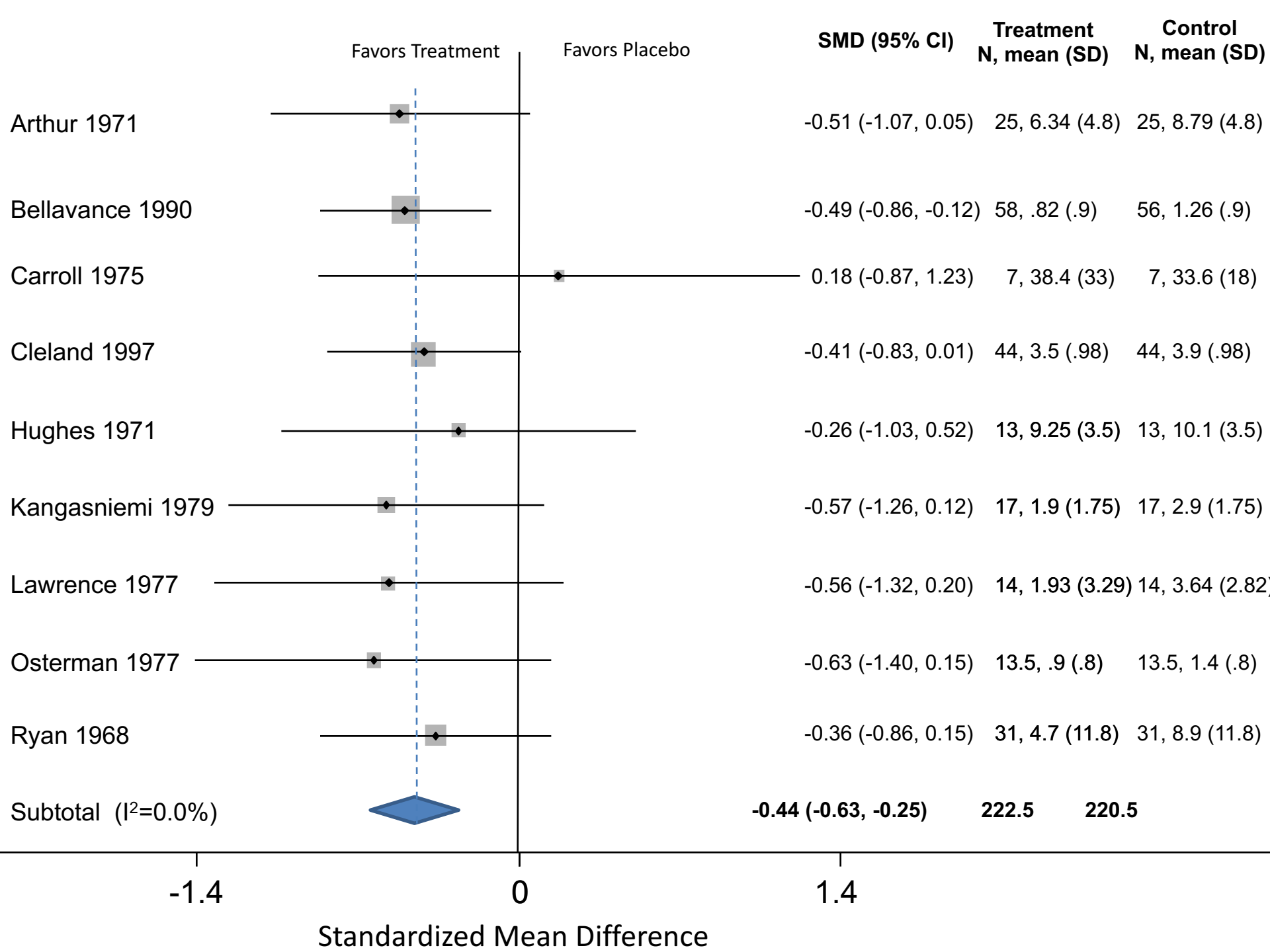
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PIZOTIFEN



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SSRI/SNRI'S

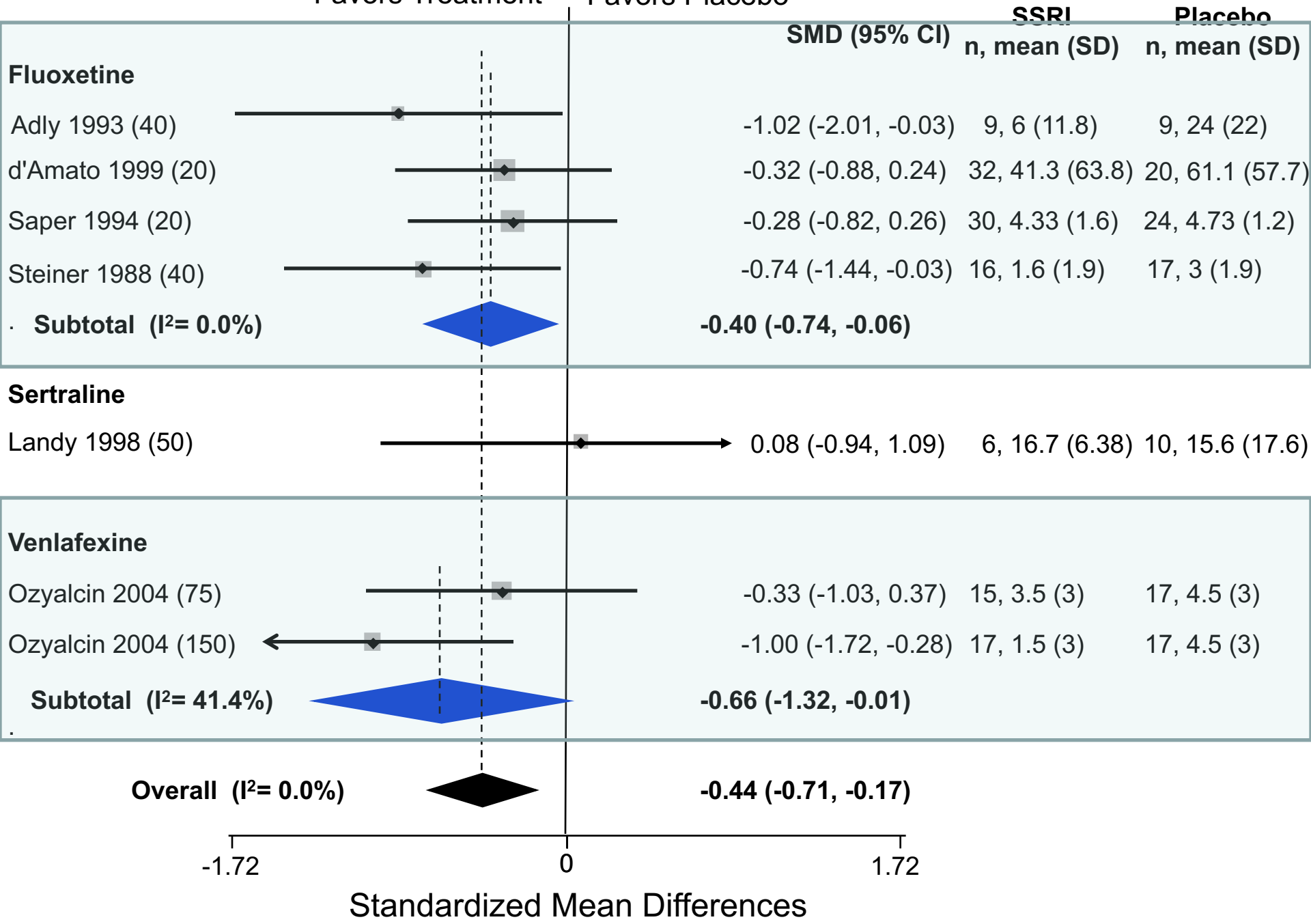


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Episodic Migraines

Favors Treatment

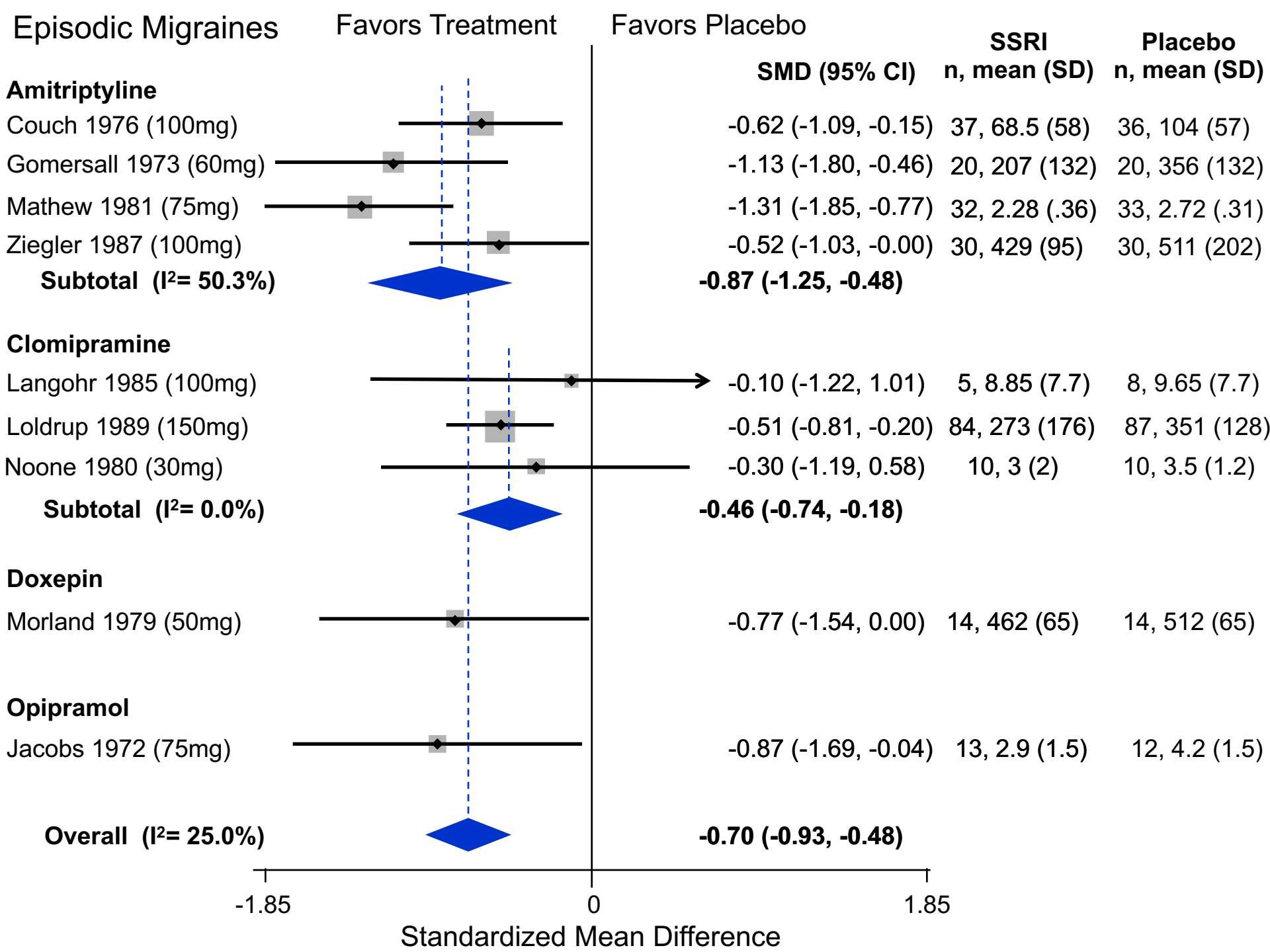
Favors Placebo

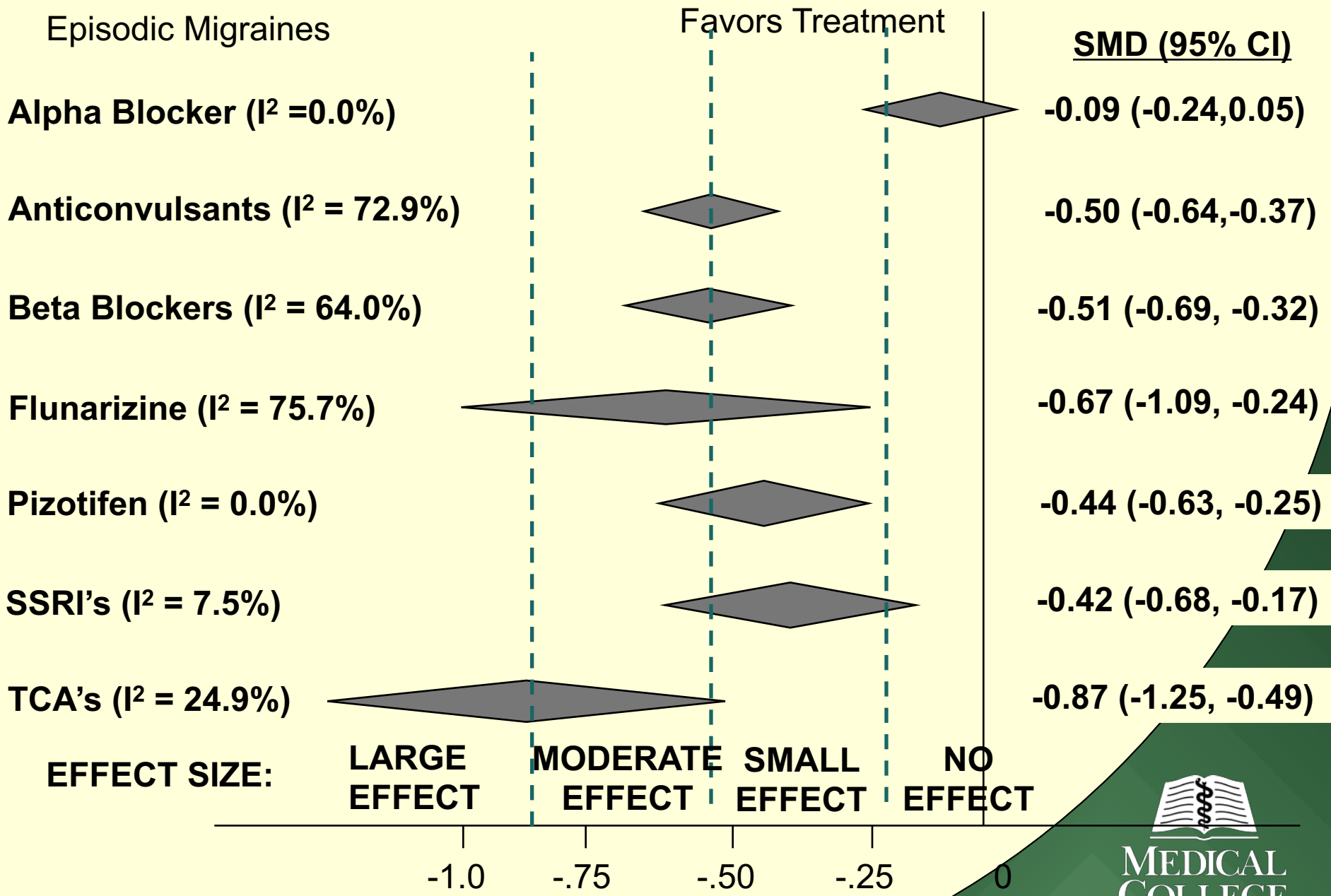


TCA'S



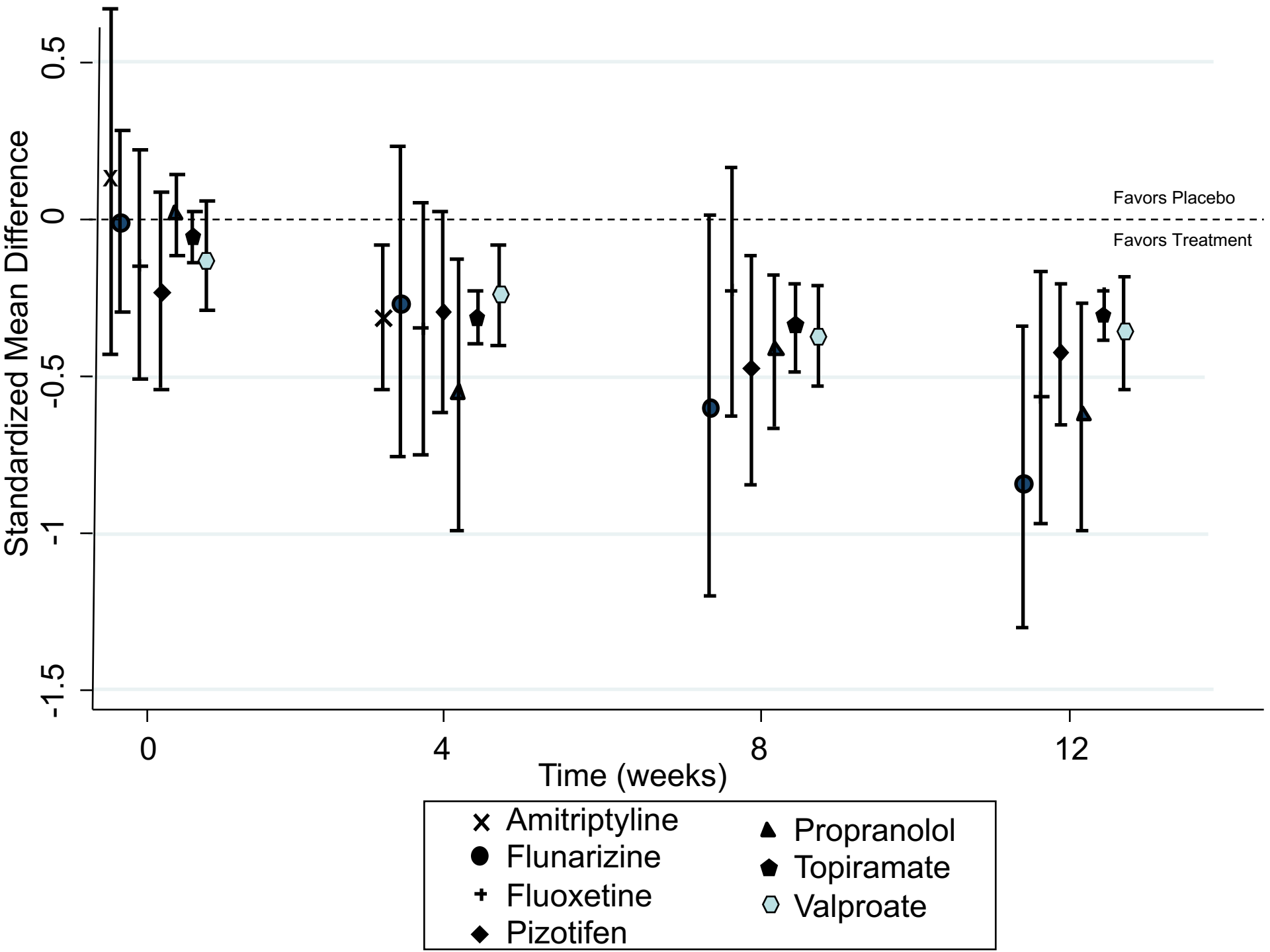
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Specific Drugs

Effect	Drug	Trials (n)
Large	Amitriptyline	4
Moderate	Atenolol	3
	Metoprolol	3
	Propranolol	22
	Topiramate	12
	Valproate	5
	Flunarizine	7
Small	Venlafaxine	1
	Bisoprolol	1
	Timolol	3
	Pizotifen	10
	Fluoxetine	4

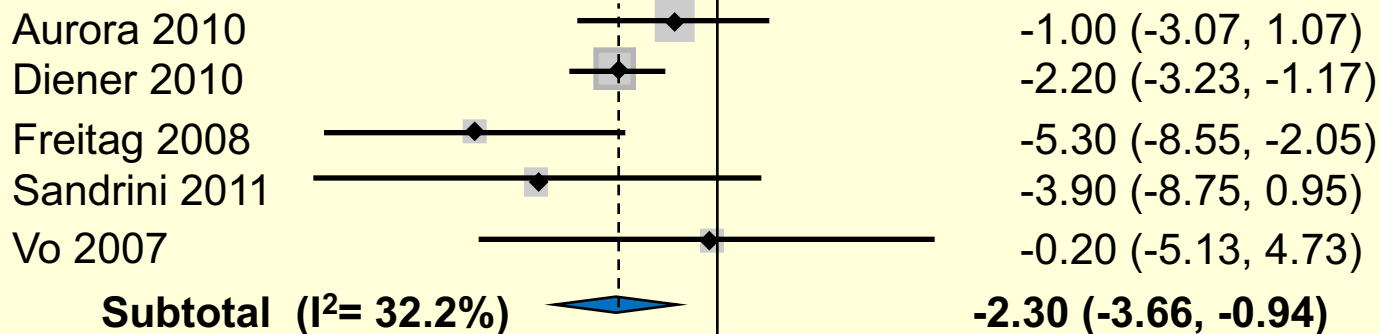


CHRONIC MIGRAINES

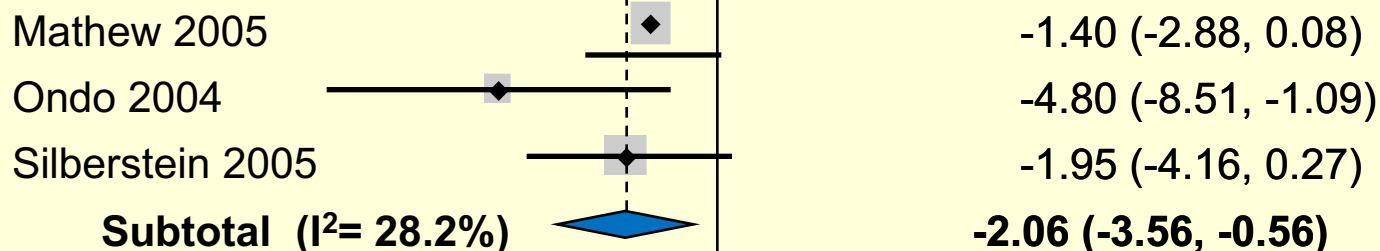


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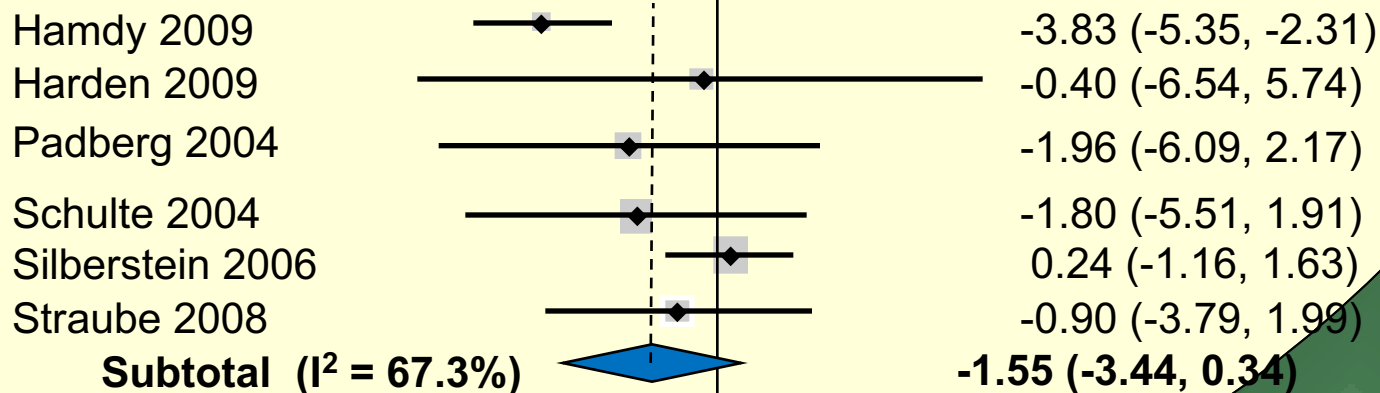
Chronic Migraine



Chronic Daily Headache



Chronic Tension Type



Note: box size is proportional to study weight

-9.0 -6.0 -3.0 0 3.0 6.0 9.0

Difference in Headaches/Month



Chronic Daily Headache

Anticonvulsant

Gabapentin (Spira 2003) -0.33 (-0.73, 0.08) 48, 22.3 (9.5) 48, 25.1 (7.6)

Levetiracetam (Beran 2010) -0.26 (-0.57, 0.04) 82, 80.9 (13.6) 83, 84.5 (13.6)

SSRI

Fluoxetine (Saper 1994) -0.28 (-0.82, 0.26) 30, 4.33 (1.6) 24, 4.73 (1.2)

TCA

Amitriptyline (Couch 2011) -0.09 (-0.30, 0.13) 155, 10.5 (8.3) 165, 11.2 (8.1)

-0.90 0 0.90

Chronic Migraines

Anticonvulsant

Diener 2007 (Topiramate) -1.35 (-1.92, -0.78) 32, 10 (6.3) 27, 17.6 (4.7)

Mei 2006 (Topiramate) -1.50 (-2.27, -0.73) 21, 3.14 (4) 14, 15.4 (12)

Silberstein 2007 (Topiramate) -0.21 (-0.44, 0.01) 153, 14.6 (7) 153, 16.1 (7)

Silvestrini 2003 (Topiramate) -2.01 (-2.93, -1.09) 14, 8.1 (8.1) 14, 20.6 (3.4)

Yurekli 2008 (Valproate) -3.05 (-4.15, -1.95) 17, 5.2 (5) 12, 22.3 (6.4)

Subtotal (I²=92.2%) **-1.55 (-2.52, -0.57)** **237** **220**

Beta Blocker

Stensrud 1980 (Atenolol) 1.20 (0.05, 2.35) 7, 13 (2.5) 7, 10 (2.5)

Stensrud 1980 (Propranolol) 1.21 (0.06, 2.36) 7, 12.3 (1.9) 7, 10 (1.9)

Palferman 1983 (Propranolol) -0.70 (-1.31, -0.09) 22, 23 (4.28) 22, 26 (4.28)

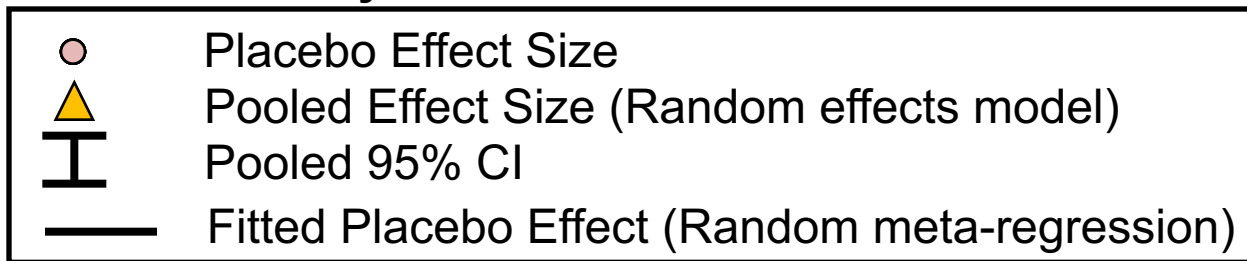
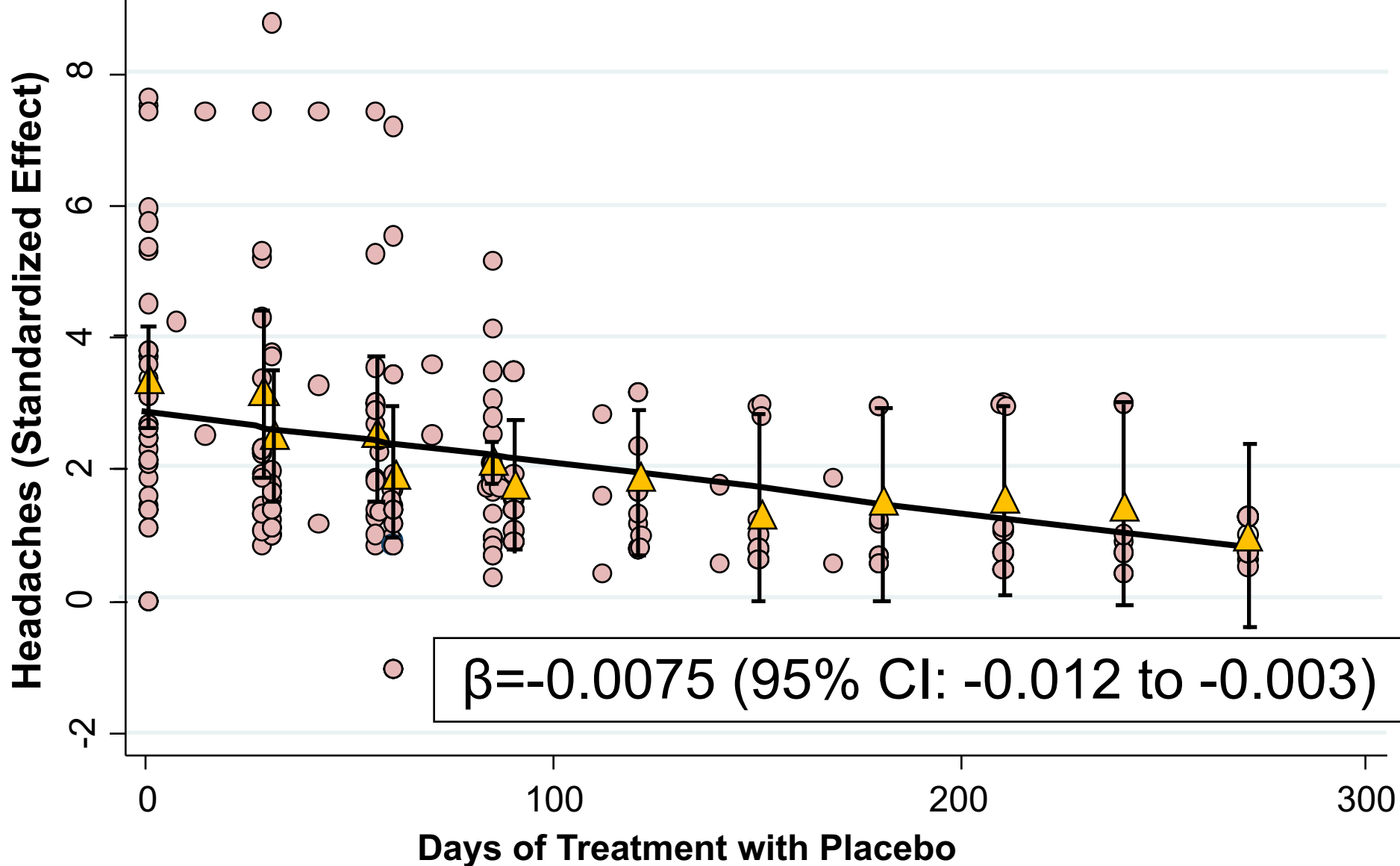
Subtotal (I²=85.1%) **0.50 (-0.94, 1.94)** **36** **36**

-4.15 0 4.15

PLACEBO EFFECT



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SIDE EFFECTS



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"Any" Side Effect

Drug Class	OR (95% CI)
Anticonvulsant	1.88 (1.09-2.29)
Beta-blockers	1.25 (1.07-1.46)
Calcium Channel Blockers	1.12 (0.97-1.29)
SSRI	1.00 (0.51-1.96)
TCA	1.49 (1.20-1.85)



Withdrew from Study

Drug Class	OR (95% CI)
Anticonvulsant	1.25 (1.08-1.45)
Beta-blockers	1.20 (0.97-1.48)
Calcium Channel Blockers	1.14 (0.98-1.33)
SSRI	1.02 (0.74-1.39)
TCA	1.16 (0.98-1.37)



Side Effects

- Side effects—expected patterns:
 - Alpha blockers: dizziness, hypotension
 - Anticonvulsants: fatigue, paresthesias, “clouded” thinking
 - Flunarizine: Weight gain
 - SSRI’s: diarrhea, sexual dysfunction
 - TCA’s: fatigue, dry mouth, orthostatic hypotension, urinary retention



Conclusions

- Several Drugs have good evidence of efficacy for episodic migraine prophylaxis:
 - Gabapentin, Topiramate, Valproate
 - Flunarizine
 - Atenolol, Bisoprolol, Metoprolol, Propranolol, Timolol
 - Pizotifen
 - Fluoxetine
 - Amitriptyline



Conclusions

- More effective drugs (TCA's) tend to have greater side effects than lesser effective drugs (beta-blockers, SSRIs)
- Some commonly used drugs have no proven benefit for prophylaxis of migraine headaches (clonidine, calcium channel blockers).



Conclusions

- There are few trials of chronic migraines, topiramate and valproate have good evidence of efficacy.
- Botox has minimal benefit for chronic migraine headaches.

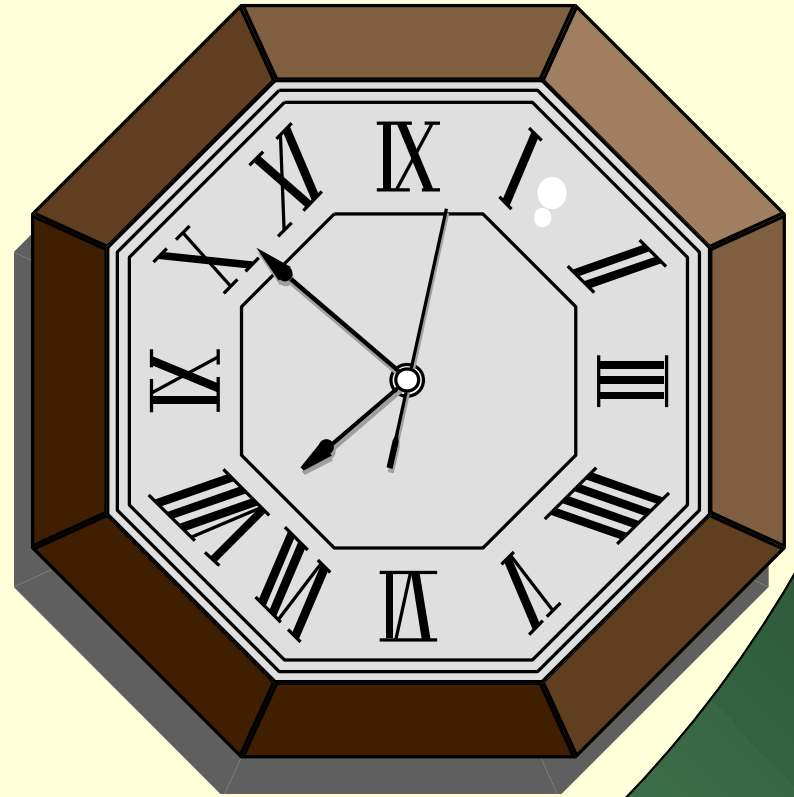


Conclusions

- The guideline recommendations that “Drug selection should be tailored based on patient comorbidities, provider comfort with drug, costs and side effects” is justified by the data, though providers can give more evidence-based recommendations on the relative efficacy of the various available drugs.



Questions?



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Lifetime Prevalence

Primary Headache

Prevalence

Tension-type headache	78%
Migraine	16%

Secondary Headache

Fasting	19%
Nose/sinus	15%
Head trauma	4%
Intracranial disease	0.5%

Rasmussen J Clin Epidem 1991;44:1147-1157.



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