

彰化基督教醫院
CHANGHUA CHRISTIAN HOSPITAL

精神科 實證期刊閱讀報告 EBM-style Journal Reading

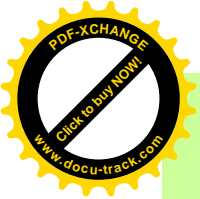
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指導臨床教師：許文郁醫師/廖以誠醫師

日期：8/6/2009

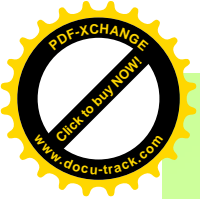
地點：鹿東分院二樓討論室



Clinical Scenario (臨床情境)

n 個案為31歲未婚女性，有憂鬱症和邊緣型人格的病史。自訴常衝動控制差，有破壞行為，想要傷害自己的衝動。門診藥物曾給予Valproic acid。欲討論Valproate在邊緣型人格違常的患者身上是否真的有治療衝動控制的療效？



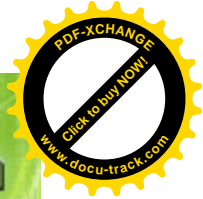
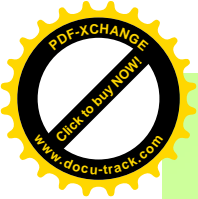


Clinical Uncertainty → PICO 問題

n Valproate 在邊緣型人格違常的患者身上
是否真的有治療衝動控制的療效？



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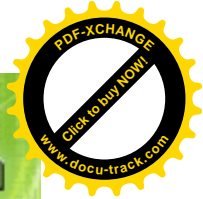
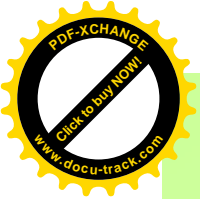


臨床個案的PICO



Patient / Problem	Patient who has borderline personality disorder with poor impulse control
Intervention	Valproate use
Comparison	Placebo
Outcome	Improvement of impulse control

Type of Question: Therapy



Search Terms & Strategy: (搜尋關鍵字與策略)

n 資料庫： Pubmed

n 搜尋日期： 4/23/2009

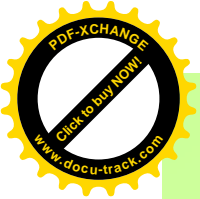
n 搜尋關鍵字與策略：

#1 Search (valproate or valproic acid or depakine) AND personality AND (impulse control) 06:18:49 [3](#)

#2 Search (valproate or valproic acid or depakine) AND personality AND (impuls*)06:19:49 [22](#)

#3 Select 6 document(s)06:21:22 [6](#)





Best available evidence: (挑選可獲得之最佳研究證據)

n Citation/s:

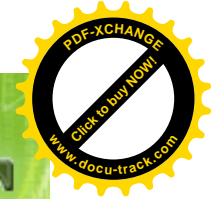
Divalproex in the Treatment of Impulsive Aggression

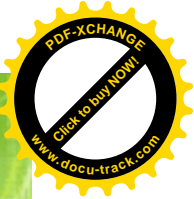
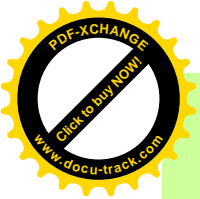
n Lead author's name :

Eric Hollander, Katherine A Tracy, Alan C Swann, Emil F Coccaro, Susan L McElroy, Patricia



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The Study: (研究效度) - 1

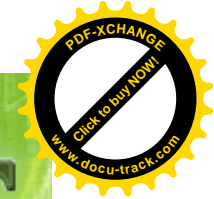
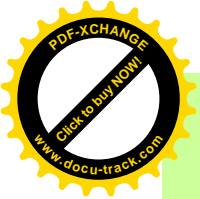
n Subjects and Method :

Ø Randomized, double-blind, placebo-controlled, parallel-group, multicenter (19 sites) trial, a 12-week double-blind treatment period, and a 1-week tapering period.

Ø Patients were randomized in equal numbers, within each of the three diagnostic groups, to receive either divalproex sodium delayed-release tablets or matching placebo. Divalproex was initiated at 500 mg/day (administered twice daily) and was increased by 250 mg every 3– 7 days during the first 3 weeks of treatment.



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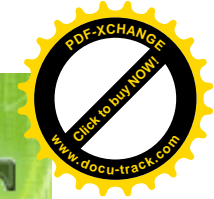
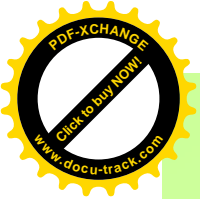
The Study: (研究效度) - 2

n Inclusion

- Ø Patients between 18 and 65 years of age with a diagnosis of Cluster B personality disorder, intermittent explosive disorder, or post-traumatic stress disorder(DSM-IV)
- Ø Patients were required to have, on average, two episodes of physical or verbal aggressive outbursts per week for at least the month prior to screening, causing marked distress or impairment in occupational or interpersonal function.
- Ø Overt Aggression Scale-Modified (OASM) > 15

n Exclusion

- Ø Lifetime bipolar I disorder, bipolar II disorder with hypomania in the past year or a baseline YMRS >12, major depressive disorder of significant severity (HAM-D > 15), history of schizophrenia or other psychotic disorder, or symptoms of dementia.
- Ø Patients with serious homicidal or suicidal ideation were also excluded from the study, patients with impulsive aggression that resulted from previous head trauma or other medical condition, pregnant or lactating females, and patients with clinically significant abnormal laboratory data, unstable medical conditions.

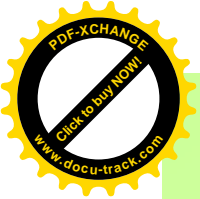


The Study: (研究效度) - 3

n Exception

- ∅ The exceptions included SSRIs , TCA, and stimulants (methylphenidate), only when patients had taken a stable dose of the allowable psychotropic medication for at least 2 months prior to screening and continued its use at the same dose throughout the study.
- ∅ Zolpidem tartrate (up to 10 mg/day) for up to 4 days per week, but not within 8 h prior to efficacy ratings.





The Study: (研究效度) - 4

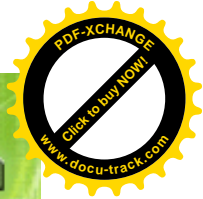
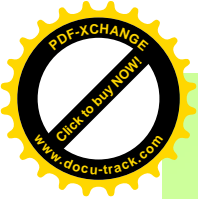
n Level of Evidence: 1b

(multicenter, randomized, double-blind, placebo-controlled study)



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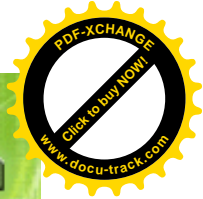
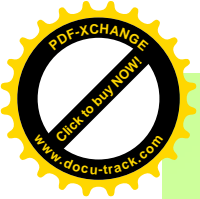


The Study: (研究效度) - 3

本篇文獻的PICO (T)

Patient / Problem	Patients with a diagnosis of Cluster B personality disorder, intermittent explosive disorder, or post-traumatic Stress Disorder
Intervention	Divalproex sodium delayed-release Tablets
Comparison	Matching placebo
Outcome	OAS-M Aggression score
Time	12-week double-blind treatment period, and a 1-Week tapering period.





The Evidence: (研究重要結果) - 1

n Clinical Evaluations

- ∅ The OAS-M evaluation was conducted at baseline and weekly thereafter, with telephone visits at weeks 5 and 7. The CGI evaluation (focused on global psychopathology, not solely aggression) was conducted at baseline and once a week, excluding weeks 5 and 7.
- ∅ The OAS-M is comprised of an Aggression score, which is the sum of individual items of verbal assault, assault against objects, assault against others, and assault against self. The OAS-M also assesses irritability (sum of 4 items) and suicidal tendencies (one item).
- ∅ The primary efficacy end point :
- ∅ Secondary efficacy end point :

n Results

- ∅ 246 patients were randomized 96 patients (47 divalproex and 49 placebo) Cluster B personality disorder, 116 patients (59 divalproex and 57 placebo) intermittent explosive disorder, and 34 patients (18 divalproex and 16 placebo) post-traumatic stress disorder. 233 (116 and 117 patients in the divalproex and placebo groups, respectively) were included in the intent-to-treat analyses



Table 1 Baseline Demographic and Clinical Characteristics of Intent-to-Treat Patients

Characteristic	Placebo (n = 117)	Divalproex (n = 116)
<i>Gender, n (%)</i>		
Female	37 (32%)	27 (23%)
Male	80 (68%)	89 (77%)
<i>Race</i>		
Caucasian	100 (85%)	95 (82%)
Black	10 (9%)	16 (14%)
Other	7 (6%)	5 (4%)
<i>Age (years)</i>		
Mean (± SD)	39.7 (11.55)	41.0 (11.80)
Range	20–67	19–64
<i>Weight (lb)</i>		
Mean (± SD)	186.5 (52.91)	188.0 (38.48)
Range	110–400	100–283
<i>Total no. of prior major depressive episodes</i>		
0	77 (66%)	78 (67%)
1–5	32 (27%)	31 (27%)
>5	8 (7%)	7 (6%)
<i>Age at first major depressive episode (years)</i>		
Mean (± SD)	26.6 (11.7)	27.7 (11.8)
Range	8–52	10–52
<i>Lifetime number of psychiatric hospitalizations</i>		
Never	99 (85%)	98 (84%)
1–5	16 (14%)	18 (16%)
>6	2 (2%)	0 (0%)
<i>Family history of psychiatric illness</i>	19 (16%)	24 (21%)
<i>Trauma history</i>		
Any trauma history	62 (54%)	70 (61%)
Physical abuse trauma history	35 (30%)	38 (33%)
Sexual abuse trauma history	16 (14%)	16 (14%)
<i>History of addictive behavior</i>		
History of alcohol abuse/dependence	38 (32%)	37 (32%)
History of drug abuse/dependence	17 (15%)	21 (18%)
<i>History of prosecution</i>		
History of arrest	53 (45%)	55 (47%)
History of incarceration	21 (18%)	31 (27%)
Median OAS-M Aggression score	33.7	43.7
Median irritability score	6.3	6.3

Note: $p > 0.05$ for all comparisons.



Table 2 Baseline and Average of Last 4 Weeks for OAS-M Aggression Scores in Intent-to-Treat Patients with a History of Impulsive Aggressive Behavior

	Placebo	Divalproex	$\chi^2_{(1)}$	p-Value ^a
<i>All patients</i>				
N	117	116		
Baseline ^b				
Median	33.7	43.7	1.552	0.213
Mean ± SD	62.3 ± 88.8	63.3 ± 61.8		
Average of last 4 weeks				
Median	12.3	10.6	0.000	0.989
Mean ± SD	32.1 ± 57.2	34.5 ± 71.3		
<i>Intermittent explosive disorder</i>				
N	54	55		
Baseline ^b				
Median	30.0	44.0	2.474	0.116
Mean ± SD	65.5 ± 114.3	62.0 ± 65.8		
Average of last 4 weeks				
Median	9.0	13.0	2.580	0.108
Mean ± SD	28.9 ± 59.9	28.9 ± 39.1		
<i>Cluster B personality disorder</i>				
N	48	43		
Baseline ^b				
Median	35.2	35.7	0.003	0.956
Mean ± SD	54.8 ± 56.3	54.9 ± 48.8		
Average of last 4 weeks				
Median	16.3	8.3	3.952	0.047
Mean ± SD	38.6 ± 61.1	29.2 ± 66.1		
<i>Post-traumatic stress disorder</i>				
N	15	18		
Baseline ^b				
Median	45.7	50.2	0.294	0.588
Mean ± SD	74.5 ± 69.9	86.9 ± 73.9		
Average of last 4 weeks				
Median	14.3	14.9	0.173	0.678
Mean ± SD	22.9 ± 27.1	64.2 ± 132.6		

^aOAS-M item scores had a minimum value of zero, but no upper limit on the maximum value, which resulted in highly skewed actual scores and change in scores. Therefore, van Elteren analyses were conducted for all patients and Wilcoxon rank-sum test was performed for diagnostic subgroups comparing median average of OAS-M scores over the last 4 weeks of treatment.

^bAverage of evaluations conducted prior to dosing.





Table 3 Median Baseline and Median Average of Last 4 Weeks for OAS-M Scores in Patients with Cluster B Personality Disorders and History of Impulsive Aggressive Behavior

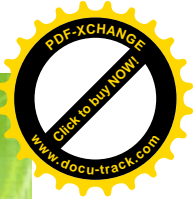
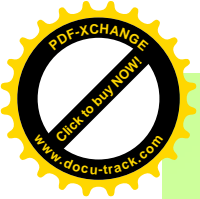
OAS-M subscale	Baseline ^a		For last 4 weeks		$\chi^2_{(1)}$	p-Value ^b
	Placebo	Divalproex	Placebo	Divalproex		
<i>Intent-to-treat data set^c</i>						
Aggression score	35.2	35.7	16.3	8.3	3.952	0.047
Verbal assault	25.7	22.3	10.8	6.0	3.536	0.060
Assault against objects	2.3	2.0	0.5	0.3	2.250	0.134
Assault against others	1.3	1.3	0.3	0.0	3.331	0.068
Assault against self	0.0	0.0	0.0	0.0	1.492	0.222
<i>Evaluable data set^d</i>						
Aggression score	33.6	34.3	16.3	6.8	5.779	0.016
Verbal assault	25.0	22.3	10.8	6.0	4.520	0.034
Assault against objects	2.3	2.0	0.5	0.3	3.982	0.046
Assault against others	1.3	1.3	0.3	0.0	4.333	0.037
Assault against self	0.0	0.0	0.0	0.0	1.254	0.263

^aAverage of evaluations conducted prior to dosing.

^bBased on Wilcoxon rank-sum test comparing average of OAS-M scores over the last 4 weeks of treatment.

^c $n = 43$ for divalproex and $n = 48$ for placebo.

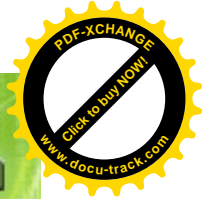
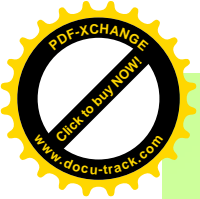
^d $n = 39$ for divalproex and $n = 46$ for placebo.



Comment & Discussion: -1

- n These data represent the first large, multicenter, double-blind, placebo-controlled trial conducted to evaluate treatment of impulsive aggression.
- n The divalproex response (77%) was comparable in the Cluster B group, but the placebo response was only 54%. These data raise the possibility that impulsive aggression may capture a biologically heterogeneous phenomenon and that there may be subgroups within the broad category of impulsive aggression that are homogeneous in their sensitivity to divalproex
- n Affective aggression is characterized by a high level of arousal and defensive behaviors and is performed in response to a perceived negative outcome. In contrast, predatory aggression involves little physiological arousal and offensive behaviors, and is directed toward a positive reward.

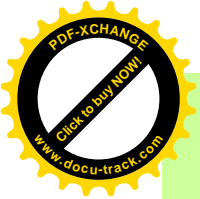




Comment & Discussion: -2

- n Divalproex is known to exert effects on GABA, 5-HT, nor-epinephrine, as well as on limbic kindling (Hollander et al, 2002), although it is unknown whether any of these mechanisms contribute to the anti-aggressive effect found in Cluster B personality disorder.
- n Several factors may have contributed to the negative findings of the overall data, and possibly those in the intermittent explosive disorder and post-traumatic stress disorder subgroups specifically, the most important of which is a considerable placebo response. (positive impact of interaction between patients and clinicians at the weekly visits)



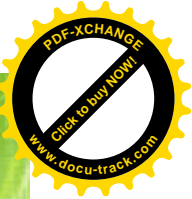


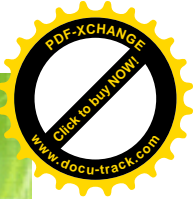
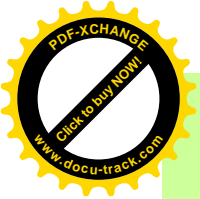
回到臨床個案情境

Clinical bottom line 臨床決策底線

n In the secondary analysis of this study ,
Divalproex was superior to placebo in the
treatment of impulsive aggression,
irritability, and global severity in patients
with cluster B disorders.

è 證據等級1b, 建議等級A

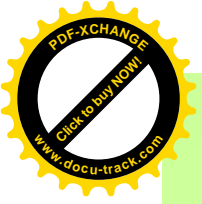




References:

1. Hollander E, et al. [Impact of trait impulsivity and state aggression on divalproex versus placebo response in borderline personality disorder.](#) Am J Psychiatry. 2005 Mar;162(3):621-4.
2. Simeon D, et al. An open-label trial of divalproex extended-release in the treatment of borderline personality disorder. CNS Spectr. 2007 Jun;12(6):439-43.





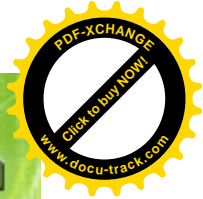
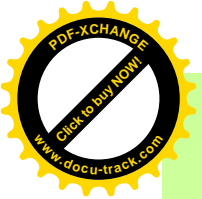
結論 (標題 Title)

Divalproex may be an effective agent in treating symptoms of aggressive behaviors in the cluster B personality disorder subgroup.

Kill or Update By (下次更新日期) :
Jun. 07, 2010



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