

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Arana A, Wentworth CE, Ayuso-Mateos JL, Arellano FM. Suicide-related events in patients treated with antiepileptic drugs. *N Engl J Med* 2010;363:542-51.

SUICIDALITY QUESTIONNAIRE

Practice ID	Patient ID	Sex	Year of Birth	Date of Death

Please answer all the questions according to the information held in the patient's written records by ticking the appropriate box or writing in the space provided.

This form was completed: using written records from memory (please tick)

1. Did the patient have an episode of suicidality (defined as suicidal thoughts, actions or attempts)?

- Yes
- No
- Unknown

2. Has the patient died, and if so, what was the cause of death?

- Patient is still alive
- Patient died – verdict suicide
- Patient died – verdict not known
- OTHER cause – please state cause if known

For patients who have died, please complete the Patient Detail Form so we may obtain a copy of Death Certificate.

Researcher's Ref -

Online Table 1: Demographics and risk factors for patients with epilepsy, depression and BD stratified by AED use*

Risk factors	Depression only		Depression and AED use		BD only		BD and AED use	
	N Pts	%	N Pts	%	N Pts	%	N Pts	%
Total	435,790	100	30,772	100	3,814	100	1,809	100
Males	139,921	32.1	9,888	32.1	1,598	41.9	679	37.5
Age in years								
<20	16,794	3.9	186	0.6	37	1.0	10	0.6
20-34	128,855	29.6	3,683	12.0	705	18.5	323	17.9
35-64	213,698	49.0	17,435	56.7	2,041	53.5	1,080	59.7
65+	70,489	16.2	9,376	30.5	1,014	26.6	394	21.8
Missing	5,954	1.4	92	0.3	17	0.4	2	0.1
Mean (SD)	44.6	(18.1)	54.7	(17.2)	51.7	(17.9)	50.2	(16.2)
Mean length of study in years (SD)	5.9	(4.8)	4.3	(4.0)	5.9	(5.0)	5.2	(4.2)
Antipsychotic use in prior year	27,907	6.4	5,839	19.0	1,379	36.2	1,046	57.8
Antidepressant use in prior year	148,814	34.1	19,704	64.0	1,343	35.2	943	52.1
Lithium use in prior year	1,558	0.4	737	2.4	1,266	33.2	712	39.4
Drug abuse ever in past	727	0.2	102	0.3	17	0.4	10	0.6

Online Table 1: Demographics and risk factors for patients with epilepsy, depression and BD stratified by AED use*

Risk factors	Depression only		Depression and AED use		BD only		BD and AED use	
	N Pts	%	N Pts	%	N Pts	%	N Pts	%
Diagnosed mental disorder ever prior	250,800	57.6	25,983	84.4	2,793	73.2	1,595	88.2
Alcohol abuse ever	15,876	3.6	2,055	6.7	222	5.8	144	8.0
Chronic disease score								
Mean (SD)	1.18	(1.48)	3.43	(2.05)	1.07	(1.36)	2.58	(1.66)
Score = 0	202,776	46.5	1,109	3.6	1,804	47.3	62	3.4
1	87,515	20.1	4,941	16.1	873	22.9	480	26.5
2	70,943	16.3	5,009	16.3	599	15.7	502	27.8
3	38,644	8.9	5,923	19.2	303	7.9	306	16.9
4	20,157	4.6	5,299	17.2	137	3.6	212	11.7
≥5	15,755	3.6	8,491	27.6	98	2.6	247	13.7

* AED = antiepileptic drug; BD = bipolar affective disorder; SD = standard deviation

Online Table 1: Demographics and risk factors for patients with epilepsy, depression and BD stratified by AED use*

Risk factors	Epilepsy and Depression		Epilepsy, Depression and AED use		Epilepsy and BD		Epilepsy, BD and AED use	
	N Pts	%	N Pts	%	N Pts	%	N Pts	%
Total	3,391	100	7,870	100	47	100	171	100
Males	1,223	36.1	3,056	38.8	22	46.8	77	45.0
Age in years								
<20	119	3.5	192	2.4	0	0.0	2	1.2
20-34	1,031	30.4	1,720	21.9	7	14.9	37	21.6
35-64	1,757	51.8	4,109	52.2	25	53.2	88	51.5
65+	438	12.9	1,768	22.5	15	31.9	44	25.7
Missing	46	1.4	81	1.0	0	0.0	0	0.0
Mean (SD)	43.4	(17.0)	48.9	(18.4)	54.4	(17.6)	50.3	(17.3)
Mean length of study in years (SD)	4.9	(4.5)	5.0	(4.3)	4.5	(4.2)	4.8	(3.9)
Antipsychotic use in prior year	325	9.6	1,200	15.2	20	42.6	109	63.7
Antidepressant use in prior year	1,318	38.9	3,551	45.1	24	51.1	79	46.2
Lithium use in prior year	12	0.4	58	0.7	9	19.1	57	33.3
Drug abuse ever in past	4	0.1	23	0.3	1	2.1	0	0.0

Online Table 1: Demographics and risk factors for patients with epilepsy, depression and BD stratified by AED use*

Risk factors	Epilepsy and Depression		Epilepsy, Depression and AED use		Epilepsy and BD		Epilepsy, BD and AED use	
	N Pts	%	N Pts	%	N Pts	%	N Pts	%
Diagnosed mental disorder ever prior	968	28.5	5,852	74.4	41	87.2	131	76.6
Alcohol abuse ever	400	11.8	823	10.5	7	14.9	25	14.6
Chronic disease score								
Mean (SD)	1.32	(1.59)	2.84	(1.84)	2.06	(1.94)	2.88	(1.74)
Score = 0	1,457	43.0	263	3.3	13	27.7	6	3.5
1	704	20.8	2,043	26.0	11	23.4	34	19.9
2	559	16.5	1,565	19.9	5	10.6	47	27.5
3	326	9.6	1,467	18.6	5	10.6	24	14.0
4	176	5.2	1,118	14.2	7	14.9	30	17.5
≥ 5	169	5.0	1,414	18.0	6	12.8	30	17.5

* AED = antiepileptic drug; SD = standard deviation

Online Table 2: Incidence of completed suicide (events per 100,000 person years) according to disease groups and AED use

Cohorts	N	(n) suicide events	Person- years	Crude IR x 100,000	95% CI	
No epilepsy, depression or BD						
No AED (referent group)	4,514,366	262	28,189,879	0.93	0.82	1.05
Any use of AED	77,319	7	305,228	2.29	0.92	4.73
Epilepsy only (no depression or BD)						
No AED	16,120	4	86,504	4.62	1.26	11.84
Any use of AED	39,325	3	214,045	1.40	0.29	4.10
Depression only (no epilepsy or BD)						
No AED	435,790	156	2,554,713	6.11	5.19	7.14
Any use of AED	30,772	9	132,298	6.80	3.11	12.91
Bipolar affective disorder (no epilepsy)						
No AED	3,814	10	22,675	44.10	21.15	81.10
Any use of AED	1,809	4	9,320	42.92	11.69	109.89
Epilepsy and depression (no BD)						
No AED	3,392	3	16,561	18.12	3.74	52.94
Any use of AED	7,870	5	39,144	12.77	4.15	29.81
Epilepsy and bipolar affective disorder						
No AED	47	0	210	0.00	--	--
Any use of AED	171	1	826	121.11	3.07	674.76
Total	5,130,795	464	31,571,402	1.47	1.34	1.61

AED = Anti-epileptic drugs; BD = Bipolar affective disorder; IR = Incidence Rate; CI = Confidence Intervals.

Online Table 3: Incidence of completed suicides during current exposure to AED and prior exposure to AED

Suicides											
Cohorts	N Pts	Suicides	Current AED Person- years	Crude IR x 100,000	95% CI		Suicides	Prior AED Person- years	Crude IR x 100,000	95% CI	
AED (no epilepsy, depression or BD)	77,319	2	84,753	2.36	0.29	8.52	5	220,475	2.27	0.74	5.29
Epilepsy and AED (no depression or BD)	39,325	2	163,085	1.23	0.15	4.43	1	50,960	1.96	0.05	10.93
AED and depression (no epilepsy or BD)	30,772	2	33,300	6.01	0.73	21.70	7	98,997	7.07	2.84	14.57
AED and BD (no epilepsy)	1,809	1	4,785	20.90	0.53	116.43	3	4,535	66.15	13.64	193.33
Epilepsy, AED and depression (no BD)	7,870	4	28,734	13.92	3.79	35.64	1	10,410	9.61	0.24	53.52
Epilepsy, AED and BD	171	0	605	0.00	0.00	609.65	1	221	453.23	11.47	2525.21

AED = Anti-epileptic drugs; BD = Bipolar affective disorder; IR = Incidence Rate; CI = Confidence Intervals.

Online Table 4: Incidence of suicidality during current exposure to AED and prior exposure to AED

Suicidality											
Cohorts	N Pts	Suicide attempts*	Current AED Person-years	Crude IR x 100,000	95% CI		Suicide attempts*	Prior -AED Person-years	Crude IR x 100,000	95% CI	
AED (no epilepsy, depression or BD)	77,319	49	84,656	57.88	42.82	76.52	71	220,151	32.25	25.19	40.68
Epilepsy and AED (no depression or BD)	39,325	79	162,795	48.53	38.42	60.48	24	50,712	47.33	30.32	70.42
AED and depression (no epilepsy or BD)	30,772	95	33,103	286.98	232.19	350.82	137	97,751	140.15	117.67	165.68
AED and BD (no epilepsy)	1,809	17	4,711	360.86	210.21	577.77	23	4,354	528.26	334.87	792.65
Epilepsy, AED and depression (no BD)	7,870	60	28,466	210.78	160.84	271.31	36	9,985	360.52	252.51	499.12
Epilepsy, AED and BD	171	1	602	165.99	4.20	924.85	1	216	462.04	11.70	2574.34

AED = Anti-epileptic drugs; BD = Bipolar affective disorder; IR = Incidence Rate; CI = Confidence Intervals.

* First event of suicidality

Online Table 5. Effect of use of AED and other risk factors on suicidality

Risk Factors	OR	95% CI	
Prior epilepsy	1.52	1.23	1.88
Prior depression	1.48	1.35	1.63
Prior BD	2.11	1.36	3.27
Current Use AED	1.60	1.29	1.99
Prior Use AED	1.12	0.93	1.37
Age (per year)	0.97	0.96	0.98
Years of diagnosis (per year from dx)	0.98	0.97	0.99
Prior lithium use	2.48	1.76	3.49
Prior antipsychotic drug use	1.64	1.51	1.77
Prior antidepressant drug use	3.69	3.42	3.99
Prior alcohol abuse	6.45	5.68	7.32
Prior history of mental disorder	2.75	2.54	2.98
Chronic Disease Score	1.19	1.17	1.22

AED = antiepileptic drug; BD = bipolar affective disorder; OR = odds ratio; CI = Confidence Interval

OR derived from one conditional logistic regression model adjusted for the variables listed in the table; matched by age (+/- 5years), sex and practice.

Online Table 6. Effect of use of individual AEDs on suicidality

Risk Factors	OR	95% CI	
Current Use Carbamazepine	1.35	1.02	1.79
Current Use Gabapentin	0.89	0.45	1.77
Current Use Lamotrigine	1.07	0.58	1.98
Current Use Levetiracetam	0.70	0.12	4.00
Current Use Pregabalin	0.24	0.03	2.17
Current Use Topiramate	0.52	0.15	1.78
Current Use Valproate	1.44	0.99	2.08

AED = antiepileptic drug; OR = odds ratio; CI = Confidence Interval

OR derived from one conditional logistic regression model matched by age (+/- 5years), gender and practice; adjusted for age, duration of disease, current use of oxcarbazepine, tiagabine and zonisamir, prior AED use, prior lithium use, prior antipsychotic use, prior antidepressant use, alcohol abuse, prior history of mental disorder, and chronic disease score.