

Data supplement

Table DS1 Excluded randomised controlled trials of adults (without an intellectual disability or organic disorder) treated with a mood stabiliser in which anger or aggression was measured

Study	Study population	Reasons for exclusion
Carbamazepine Gardner & Cowdry (1986) ²⁷	Female out-patients with borderline personality disorder and behavioural dyscontrol	Not recruited specifically for treatment of aggression Insufficient measure of aggression (Rating of benefit)
Cowdry & Gardner (1988) ²⁸	Female out-patients with borderline personality disorder and behavioural dyscontrol	Not recruited specifically for treatment of aggression Insufficient measure of aggression (Rating of benefit)
Mattes (1990) ²⁹	In-patients with intermittent explosive disorder	No placebo control (propranolol) Insufficient measure of aggression (Rating of benefit)
De la Fuente & Lotstra (1994) ³⁰	In-patients with borderline personality disorder	Not recruited for treatment of aggression Insufficient measure of aggression behaviour (SCL-90-R)
Topiramate Nickel <i>et al</i> (2004) ³¹	Female out-patients with borderline personality disorder	Not recruited specifically for treatment of aggression Insufficient measure of aggressive behaviour (STAXI)
Nickel <i>et al</i> (2005) ³²	Female out-patients with depression	Not recruited specifically for treatment of aggression Insufficient measure of aggression behaviour (STAXI)
Nickel <i>et al</i> (2005) ³³ Loew (2006) ³⁴	Male out-patients with borderline personality disorder Female out-patients with borderline personality disorder (although elevated measure at baseline)	Insufficient measure of aggressive behaviour (STAXI)
Lamotrigine Tritt <i>et al</i> (2005) ³⁵	Female out-patients with borderline personality disorder	Insufficient measure of aggressive behaviour (STAXI)
Divalproex Hollander <i>et al</i> (2001) ³⁶ Frankenburg & Zanarini (2002) ³⁷	Out-patients with borderline personality disorder Female out-patients with borderline personality disorder	Not recruited specifically for treatment of aggression Not recruited specifically for treatment of aggression
Lithium Marini & Sheard (1976) ³⁸	Male prisoners	No measure of aggression Same study as Sheard (1976) ²²
Links <i>et al</i> (1990) ³⁹	Out-patients with borderline personality disorder	Not recruited specifically for treatment of aggression (rating of benefit) Insufficient measure of aggression (SCL-90-R, Symptom Checklist-90-Revised; STAXI, State-Trait Anger Inventory.)

Table D2 Summary of included randomised placebo-controlled trials of mood stabilisers for the treatment of aggressive behaviour

Study	Study population	Number in analysis: treatment, placebo (study design)	Outcome measure	Length of treatment	Proportion of those randomised included in analysis	Intention-to-treat analysis	Selective reporting of measure	Jadad score	Finding
Phenytin Maltzky (1974) ¹⁶	Male out-patients referred with problems with violence Met criteria for episodic dyscontrol	12, 12 (parallel)	Frequency of aggressive outbursts Severity of aggressive outbursts (4-point scale)	Up to 12 weeks	Unclear. No individuals dropping out were reported	Unclear	No	2	Significant reduction in severity and frequency of aggression in treatment group
Barraatt (1991) ¹⁷	Male prisoners with impulsive aggression	19, 19 (cross-over)	Frequency of aggressive acts	4 weeks	68%	No	No	2	Significant reduction in those taking 300 mg per day
Barraatt (1997) ¹⁸	Prisoners with impulsive aggressive behaviour	30, 30 (cross-over)	OAS-M frequency AND intensity	6 weeks	84%	No	150 randomised of whom 126 completed. Results presented for 30 completers who had primarily impulsive aggression	3	Significant reduction in frequency and intensity of aggressive acts
Stanford (2001) ¹⁹ / Houston (2006) ²⁰	Out-patient volunteers with intermittent explosive disorder ^a	30, 30 (cross-over)	OAS -frequency of aggressive behaviour	6 weeks	73%	Yes	OAS severity data not reported other than no significant difference	3	No significant reduction in frequency or severity of aggressive behaviour
Stanford (2005) ²¹	Out-patient volunteers with intermittent explosive disorder ^a	7, 8 (parallel)	OAS – global severity of aggression	6 weeks	75%	No	No	4	Significant reduction in aggression in treatment group
Lithium Sheard (1976) ²²	Male prisoners with history of chronic impulsive aggressive behaviour	28, 31 (parallel)	Frequency of infractions of institutional rules	Up to 12 weeks	83%	No	No	4	Significant reduction in frequency of aggression in treatment group
Valproate/divalproex Hollander (2003) ²³	Cluster B personality/intermittent explosive disorder/PTSD with ≥ 2 episodes of impulsive aggression per week and elevated baseline aggression scores	116, 117 (parallel)	OAS-M – total aggression	12 weeks	95%	Yes	No	4	No significant difference overall. Significant reduction in aggressive participants with borderline personality disorder
Stanford (2005) ²¹	Out-patient volunteers with intermittent explosive disorder ^a	7, 8 (parallel)	OAS – Aggression Scale (weighted sum of most severe behaviour in each category)	6 weeks	75%	No	No	4	Significant reduction in aggression in treatment group
Carbamazepine/ oxcarbazepine Mattes (2005) ²⁴	Out-patient volunteers with impulsive aggression	21, 24 (parallel)	Revised OAS-M	10 weeks	50%	Yes	No	3	Significant reduction in aggression in treatment group
Stanford (2005) ²¹	Out-patient volunteers with intermittent explosive disorder ^a	7, 8 (parallel)	OAS – global severity of aggression	6 weeks	75%	No	No	4	Significant reduction in aggression in treatment group
Levetiracetam Mattes (2008) ²⁵	Out-patient volunteers with intermittent explosive disorder ^a	19, 20 (parallel)	Revised OAS-M total aggression	10 weeks	48%	Yes	No	3	No difference between groups

OAS-M: Overt Aggression Scale – Modified; OAS: Overt Aggression Scale; PTSD: post-traumatic stress disorder.

a. Intermittent explosive disorder criteria 1 and 2: that is not excluding those with personality disorder or history of substance misuse.

Additional references

- 27 Gardner DL, Cowdry RW. Positive effects of carbamazepine on behavioural dyscontrol in borderline personality disorder. *Am J Psychiatry* 1986; **143**: 519–22.
- 28 Cowdry RW, Gardner DL. Pharmacotherapy of borderline personality disorder: alprazolam, carbamazepine, trifluoperazine, tranylcypromine. *Arch Gen Psychiatry* 1988; **45**: 111–9.
- 29 Mattes JA. Comparative effectiveness of carbamazepine and propranolol for rage outbursts. *J Neuropsychiatry Clin Neurosci* 1990; **2**: 159–64.
- 30 De la Fuente JM, Lotstra F. A trial of carbamazepine in borderline personality disorder. *Eur Neuropsychopharmacol* 1994; **4**: 479–86.
- 31 Nickel MK, Nickel C, Mitterlehner FO, Tritt K, Lahmann C, Leiberich PK, et al. Topiramate treatment of aggression in female borderline personality disorder patients: a double-blind, placebo-controlled study. *J Clin Psychiatry* 2004; **65**: 1515–9.
- 32 Nickel C, Lahmann C, Tritt K, Muehlbacher M, Kaplan P, Kettler C, et al. Topiramate in treatment of depressive and anger symptoms in female depressive patients: a randomized, double-blind, placebo-controlled study. *J Affect Disord* 2005; **87**: 243–52.
- 33 Nickel MK, Nickel C, Kaplan P, Lahmann C, Muhlbacher M, Tritt K, et al. Treatment of aggression with topiramate in male borderline patients: a double-blind, placebo-controlled study. *Biol Psychiatry* 2005; **57**: 495–9.
- 34 Loew TH, Nickel MK, Muehlbacher M, Kaplan P, Nickel C, Kettler C, et al. Topiramate treatment for women with borderline personality disorder: a double-blind, placebo-controlled study. *J Clin Psychopharmacol* 2006; **26**: 61–6.
- 35 Tritt K, Nickel C, Lahmann C, Leiberich PK, Rother WK, Loew TH, et al. Lamotrigine treatment of aggression in female borderline-patients: a randomized, double-blind, placebo-controlled study. *J Psychopharmacol* 2005; **19**: 287–91.
- 36 Hollander E, Allen A, Lopez RP, Bienstock CA, Grossman R, Siever LJ, et al. A preliminary double-blind, placebo-controlled trial of divalproex sodium in borderline personality disorder. *J Clin Psychiatry* 2001; **62**: 199–203.
- 37 Frankenburg FR, Zanarini MC. Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double-blind placebo-controlled pilot study. *J Clin Psychiatry* 2002; **63**: 442–6.
- 38 Marini JL, Sheard MH. Sustained-release lithium carbonate in a double-blind study: serum lithium levels, side effects and placebo response. *J Clin Pharmacol* 1976; **16**: 276–83.
- 39 Links PS, Steiner M, Boiago I, Irwin D. Lithium therapy for borderline patients: preliminary findings. *J Personal Disord* 1990; **4**: 173–81.

Online supplement

Search terms

anger OR “problem anger” OR “intermittent explosive disorder” OR “anger problem\$” OR “impulsive aggress\$” OR “rage attacks” OR “anger attacks” OR “episodic dyscontrol” OR angry OR temper OR rage OR frustrat\$ OR fury OR furious OR argument\$

AND

pharmacological\$ OR Pharmaceutical\$ OR pharmacotherap\$ OR drug OR “drug treatment” OR “drug therapy” OR medicat\$ OR treatment\$ OR therap\$ OR “anger management” OR “anger control” OR “mood stabiliser\$” OR “mood stabilizer\$” OR anti-convulsant\$ OR anti-convulsant\$ OR lithium OR Lamotrigine OR Levetiracetam OR Topiramate OR Topiramate OR Phenytoin OR Carbamazepine OR Oxcarbazepine OR Tiagabine OR Valproate\$ OR Divalproex OR Gabapentin

AND

(aggress\$ NOT cardiac NOT cancer NOT surgery) OR “aggressive behaviour” OR “aggressive behavior” OR “aggression control” OR violen\$ OR “antisocial behaviour” OR “antisocial behavior” OR “anti-social behaviour” OR “anti-social behavior” OR offend\$ OR “offending behaviour” OR “offending behavior” OR “criminal offence” OR convict\$ OR prison OR recidivism OR hostil\$ OR abus\$ OR (attack\$ NOT heart attack) OR assault\$ OR “self control” OR “emotional control” OR “emotional liability”