BEST in Mental Health
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Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

In adults with impulsive aggressive behaviour (intermittent explosive disorder or episodic dyscontrol syndrome) how effective are pharmacological interventions, compared to any other intervention, in improving patient outcomes?

Clarification of question using *PICO* structure

Population: Adults with intermittent explosive disorder/ episodic dyscontrol syndrome
Intervention: Any pharmacological Intervention
Comparator: Any other or no intervention
Outcomes: All patient outcomes

Plain language summary

No firm conclusions can be made from the available evidence, only two articles were found which found fluoxetine to be effective compared to placebo and no significant findings for the use of mood stabilisers. The need for further research into the use of pharmacological interventions impulsive aggressive behaviour was identified.

Clinical and research implications

No definite clinical implications may be made based on the evidence presented in this BEST summary. In one of the included papers, there was evidence of the effectiveness of fluoxetine compared with placebo, but the authors stated that "fluoxetine should not be considered a 'magic bullet' for the treatment of impulsive aggression in intermittent explosive disorder (IED)" and that "other agents and modalities will be needed for the successful treatment of most individuals with IED or with problematic histories of impulsive aggression." It was also suggested that further studies are needed to replicate the fluoxetine study. A SR that evaluated mood stabilisers did not recommend any particular evidence, and highlighted the need for further well-conducted RCTs to investigate different mood stabilisers for the treatment of aggression.

What does the evidence say?

Number of included studies/reviews (number of participants)

One systematic review (SR) (Jones et al. 2011) and one randomised controlled trial (RCT) (Coccaro et al. 2009) met the inclusion criteria for this BEST summary.

Main findings

The SR by Jones et al. (2011) assessed the effectiveness of mood stabilisers (anticonvulsants/lithium) for adults with impulsive or repetitive aggression. The authors searched for relevant literature up to November 2009, and included 10 RCTs (n=489) in their review. The authors found that when all studies were included in their meta-analysis, those taking mood stabilisers showed a significant reduction in the frequency/severity of aggressive behaviour compared to people who were given placebo – but this finding became non-significant when only four studies with a low risk of bias were included in the analysis. When specific drugs were evaluated, significant differences between the groups were observed for phenytoin (SMD -1.34 [95% CI -2.16 to -0.52], 3 studies, n=159, I^2=78%), lithium (SMD -181 [95% CI -1.35 to -0.28], 1 study, n=59), and carbamazepine/oxcarbazepine (SMD -1.20 [95% CI -1.83 to -0.56], 2 studies, n=60, I^2=92%), but not for valproate/divalproex (2 studies, n=248), or levetiracetam (1 study, n=39).

The RCT by Coccaro et al. (2009) evaluated the effectiveness of fluoxetine compared with placebo in 100 adults with intermittent explosive disorders. After 12 weeks, significantly lower mean scores were observed in the treatment group for three outcomes assessed: the number and severity of impulsive aggressive events (as measured by OAS-M aggression [p=0.006]), global severity of impulsive aggressive behaviour (as measured by OAS-M irritability [p=0.001]), and global response to treatment (measured using the Clinical Global Impression-Improvement scale (CGI-I) [p<0.001]).

Authors conclusions

Jones et al. (2011) concluded that "mood stabilisers as a group are significantly better than placebo in reducing aggressive behaviour, but not all mood stabilisers appear to share this effect." They also stated, however, that many studies "were at risk of bias and so further randomised controlled trials are recommended."

Coccaro et al. (2009) concluded that "fluoxetine treatment has a clear antiaggressive effect in impulsive aggressive individuals with IED. However, while fluoxetine's antiaggressive effects appear

robust, they lead to full or partial remission of IED in less than 50% of subjects treated with fluoxetine."

Reliability of conclusions/Strength of evidence

The SR by Jones et al. (2011) had a low risk of bias, so that the results, and their cautious conclusions are likely to be reliable. The RCT by Coccaro et al. (2009) had unclear risk of bias, so that it is uncertain whether or not the results of this study are likely to be reliable.

What do guidelines say?

Neither National Institute for Health and Care Excellence (NICE) nor Scottish Intercollegiate Guidelines Network (SIGN) guidelines comment on effective medications for treating impulsive aggressive behaviour.

Date question received: 30/11/15
Date searches conducted: 01/12/15
Date answer completed: 11/12/15

References

Systematic reviews

1. Jones, R. M., Arlidge, J., Gillham, R., Reagu, S., van den Bree, M., & Taylor, P. J. (2011). Efficacy of mood stabilisers in the treatment of impulsive or repetitive aggression: systematic review and meta-analysis. *The British Journal of Psychiatry*, *198*(2), 93-98.

Randomized Control Trials

1. Coccaro, E. F., Lee, R. J., & Kavoussi, R. J. (2009). A double-blind, randomized, placebo-controlled trial of fluoxetine in patients with intermittent explosive disorder. *The Journal of clinical psychiatry*, 70(5), 653-662

Results

Systematic reviews

Author (year)	Search date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Jones et. al. 2011	Nov 2009	***Participants*:** Adults that have a history of frequent impulsive aggressive including Intermittent Explosive Disorder and Episodic dyscontrol syndrome. Most participants were outpatient volunteers, others were adult male prisoners. ***Intervention*:** Pharmacological interventions (mood stabilisers) including; - Phenytoin (300mg per day) - Lithium (serum levels 0.6–1 mEq/l) - Divalproex (serum levels maintained between 80–120 mg/ml) - Valproate (750mg per day) - Carbamazepine (450mg per day) - Oxcarbazepine (dose 1200–2400 mg per day) Levetiracetam (dose 1000–3000 mg per day) ***Comparator*:**	10 RCTs (N=489)	All trials were between 6 and 12 weeks duration. Pooling the data in a meta-analysis showed a significant reduction in the severity of aggressive behaviour with mood stabilisers compared to placebo (SMD -1.02 [95% CI -1.54 to -0.50], 10 studies, n=565) but considerable heterogeneity was observed (I^2=85%). The authors also presented data by type of drug: phenytoin (SMD -1.34 [95% CI -2.16 to -0.52], 3 studies, n=159, I^2=78%); lithium (SMD -181 [95% CI -1.35 to -0.28], 1 study, n=59); valproate/divalproex (SMD -1.31 [95% CI -4.01 to 1.39], 2 studies, n=248, I^2=92%); carbamazepine/oxcarbazepine (SMD -1.20 [95% CI -1.83 to -0.56], 2 studies, n=60, I^2=92%); levetiracetam (SMD 0.23	Low

		Placebo ***Outcome*:** Frequency/severity of aggressive behaviour measured by Overt Aggression scale (OAS) and Overt Aggression Scale-Modified (OAS-M). ***Study design*:** All studies included in this systematic review and meta-analysis were randomised placebo-controlled trials.		[95% CI -0.40 to 0.86], 1 study, n=39). When each study was removed from the analysis, there was little change in the amount of heterogeneity. When only those studies considered to have a low risk of bias were included in the analysis, no significant results were observed (SMD -0.28 [95% CI -0.73 to 0.17], 4 studies, n=347, I^2=71%).	

Randomised controlled trials

Author (year)	**Inclusion criteria**	**Number of participants**	**Summary of results**	**Risk of bias**
Coccaro et.al. (2009)	***Participants*:** Male and female adults meeting the DSM-IV diagnostic criteria for personality disorder and defined histories of impulsive aggressive behaviour. ***Intervention*:** Fluoxetine: 2 weeks of placebo medication at the start of the study for baseline assessment, followed by 12 further weeks of 20mg – 60mg of Fluoxetine once per	N=100 (65 in the fluoxetine group and 35 in the placebo group)	After 12 weeks, significantly lower mean scores were observed in individuals who received fluoxetine compared those who received placebo for OAS-M aggression (F = 8.05, df = 1,97; p=0.006), OAS-M irritability (F =12.44, df = 1,97; p=0.001), and the Clinical Global Impression-Improvement scale (CGI-I) (6.2% vs. 28.6%, p<0.001). *Scores were presented for successive 2-week windows, but only endpoint data have been extracted here.* Post hoc analyses showed significant effects for	Unclear

	day. ***Comparator*:** Placebo: 2 weeks of placebo baseline assessments, followed by 12 weeks of 1-3 capsules of placebo medication taken once per day. ***Outcome*:** - Overt aggression and irritability; Overt Aggression Scale-Modified (OAS-M) - Lifetime history of impulsive aggressive behaviours; Lifetime History of Aggression Interview Scale. - Clinical response to treatment; Clinical Global Impressions-Improvement scale (CGI-I) - Depressive and anxiety symptoms; Hamilton Rating scale for Depression (HAM-D-21), Hamilton Rating Scale for Anxiety (HAM-A-14)		OAS-M "verbal aggression" (ANCOVA F for endpoint: F = 8.18, df = 1,97; p =0.005) and "aggression against objects" (ANCOVA F for endpoint: F = 4.91, df = 1,97; p = 0.029) but not for "aggression against persons" (ANCOVA F for endpoint: F = 0.266, df = 1,97; p = 0.607). There was no significant differences between the groups for the percentage of adverse events (fluoxetine 59% vs placebo 49%, p=0.402), although those taking fluoxetine has significantly greater frequencies of sexual dysfunction, sleep disturbance, nausea/vomiting, and jitterness/restlessness. Of those participants who were treated with fluoxetine (n=65), 29% achieved full remission, and 46% achieved full plus partial remission. In the subgroup of fluoxetine responders (n=43), 44% reported no significant aggressive outbursts at the time of study completion or exit, 26% reported one significant aggressive outburst, and 33% reported 2 or more significant aggressive outbursts.	

Risk of bias

Systematic reviews

Author (year)	RISK OF BIAS				
	Inclusion criteria	Searches	Review process	Quality assessment	Synthesis
Jones et al. (2011)	☺	☺	☺	☺	☺

Randomised controlled trials

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Coccaro et.al. (2009)	?	?	☺	☺	☺	?

☺ Low risk ☹ High risk ? Unclear risk

Search details

Source	Search Strategy	Number of hits	Relevant evidence identified
Guidelines			
NICE & SIGN	Intermittent explosive disorder Episodic dyscontrol syndrome Impulsive aggression	2 0 4	0 0 0
Systematic Reviews & Primary studies			
MEDLINE	1 intermittent explosive disorder.ab,ti. 211 2 episodic dyscontrol syndrome.ab,ti. 16 3 1 or 2 225 4 exp Drug Therapy/ 1134649 5 (pharmacological adj (treatment or intervention or therapy)).ab,ti. 17533 6 (pharmaceutical adj (treatment or intervention or therapy)).ab,ti. 1165 7 medication.ab,ti. 152426 8 (drug adj (treatment or intervention or therapy)).ab,ti. 55422 9 4 or 5 or 6 or 7 or 8 1310755 10 3 and 9 19	19	1
EMBASE	1 intermittent explosive disorder.ab,ti. 264 2 episodic dyscontrol syndrome.ab,ti. 18 3 1 or 2 279	39	1

	4 exp Drug Therapy/ 2031744 5 (pharmacological adj (treatment or intervention or therapy)).ab,ti. 25972 6 (pharmaceutical adj (treatment or intervention or therapy)).ab,ti. 1820 7 medication.ab,ti. 230095 8 (drug adj (treatment or intervention or therapy)).ab,ti. 74425 9 4 or 5 or 6 or 7 or 8 2217266 10 3 and 9 39		
PsycINFO	1 intermittent explosive disorder.ab,ti. 293 2 episodic dyscontrol syndrome.ab,ti. 11 3 1 or 2 303 4 exp Drug Therapy/ 107561 5 (pharmacological adj (treatment or intervention or therapy)).ab,ti. 5060 6 (pharmaceutical adj (treatment or intervention or therapy)).ab,ti. 197 7 medication.ab,ti. 46556 8 (drug adj (treatment or intervention or therapy)).ab,ti. 8872 9 4 or 5 or 6 or 7 or 8 139181 10 3 and 9 47	47	
CENTRAL	#1 MeSH descriptor: [Impulse Control Disorders] explode all trees 286 #2 intermittent explosive disorder 25 #3 episodic dyscontrol syndrome 5 #4 #1 or #2 or #3 309	41	

	#5	MeSH descriptor: [Drug Therapy] explode all trees 119533		
	#6	pharmacological adj (treatment or intervention or therapy) 621		
	#7	pharmaceutical adj (treatment or intervention or therapy) 679		
	#8	medication 37824		
	#9	drug adj (treatment or intervention or therapy) 1954		
	#10	#5 or #6 or #7 or #8 or #9 150014		
	#11	#4 and #10 in Trials 41		

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