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 generalised anxiety disorder, how effective is pregabalin, compared to treatment as usual, in managing symptoms of anxiety and improving patient outcomes?"

Clarification of question using PICO structure

Patients: Adults with generalised anxiety disorder
Intervention: Pregabalin
Comparator: Treatment as usual
Outcome: Managing symptoms of anxiety and improving patient outcomes

Clinical and research implications

No definite clinical implications can be made from the available evidence. The current research has not been well-reported, or has methodological limitations. Although there is some evidence to suggest that pregabalin is superior compared to placebo, data on the efficacy of pregabalin compared to other treatments is limited. There is a general consensus among the study authors that more randomised controlled trials with long-term follow-up are needed to evaluate pregabalin, and that these studies need to consider other patient outcomes such as quality of life.

What does the evidence say?

Number of included studies/reviews (number of participants)
Three systematic reviews (SRs) (Samuel *et al*. 2011; Boschen *et al*. 2011; Baldwin *et al*. 2011) and one randomised controlled trial (Feltener *et al.* 2008) met the inclusion criteria for this BEST summary.

Main Findings
The first SR by Samuel *et al*. (2011) aimed to evaluate the efficacy and safety of various treatments in adult generalised anxiety disorder (GAD) patients who were non-responders to previous treatment. Of eight studies included in this review, only one RCT evaluated the effectiveness of pregabalin (Miceli *et al*. 2009). This was, apparently, one of the most robust trials included in their review, with a study duration of 8 weeks and a sample size of 356 patients. In comparison with placebo, treatment with pregabalin resulted in a significant reduction in the Hamilton Anxiety Scale (HAM-A) score.

The second SR specifically focused on pregabalin for GAD and identified seven relevant studies that evaluated anxiety symptoms as measured using the HARS (Boschen *et al*. 2011). In their meta-analysis of 869 patients, the authors reported a significant effect in favour of pregabalin compared to placebo for HARS total score: Hedges' g = 0.364 (95% CI 0.256 to 0.471), n=869. We note that Miceli *et al.* (2009) was not included in this SR, presumably because this study did not use the HARS.

The third SR primarily focused on presenting the results of a mixed treatment meta-analysis (rather than presenting the results of the SR *per se* (Baldwin *et al*. 2011). This paper reported on 27 studies (5 of which also appear to have been included in the Boschen *et al.* 2011 SR), and analysed nine different treatments, and placebo, in patients with GAD. When analyses were restricted to only those drugs currently licenced in the UK (duloxetine, escitalopram, paroxetine, venlaflaxine, and pregabalin), duloxetine was ranked first for response (third across all treatments evaluated), escitalopram was ranked first for remission (second across all treatments) and pregabalin was ranked first for tolerability (second across all treatments), with a 7.7% probability of being the best tolerated of all the treatments considered. All treatments were favoured over placebo for response and remission, but not for tolerability.

The RCT aimed to evaluate the efficacy of pregabalin in preventing relapse in patients with GAD (Feltener *et al*. 2008). This trial consisted on four phases including a screening phase, an 8-week open-label phase, a 24-week double-blind phase (that only included patients who responded to

treatment in the 8-week phase), and a 2-week discontinuation phase. The authors reported that a fixed daily dose of pregabalin 450 mg was significantly more effective than placebo in preventing relapse in patients (who responded to 8 weeks of acute treatment), and also resulted in significant and sustained improvements compared to placebo in all secondary efficacy measures including anxiety symptoms (HAM-A total score), depression symptoms (HAM-D score), work impairment, social impairment, and impairment of family life/home responsibilities (SDS subscale scores).

Authors Conclusions
Samuel et al. (2011) did not make any definite conclusions on efficacy of pregabalin but reported that further high-quality trials of augmentation treatment on refractory GAD are required.

Boschen et al. (2011) concluded that pregabalin was an effacious therapy for GAD, although the effect sizes were small to moderate.

Baldwin et al. (2011) concluded that SSRIs were the most effective drug treatment option for patients with GAD and that among the five UK licensed treatments, duloxetine, escitalopram, and pregabalin may offer some advantages over venlafaxine and paroxetine.

Feltener et al. (2008) concluded that pregabalin 450 mg/day demonstrated significant efficacy compared with placebo in preventing relapse of GAD during double-blind treatment among patients who responded initially to 8 weeks of acute pregabalin treatment.

Reliability of conclusions/Strength of evidence
All of the included studies had methodological shortcomings (e.g. no formal quality assessment of the included studies were reported), or they did not report enough information to facilitate a critical assessment. Thus, the studies included in this BEST summary were considered to have a high or unclear risk of bias, so that the results of the studies are either not likely to be reliable, or the reliability of the results are uncertain. As one of the SRs included only one scale to measure anxiety, the results from this review will be limited and will not present a full picture of evidence for this outcome.

What do guidelines say?

NICE guidelines for anxiety (2011, CG113) make the following recommendations regarding pharmacological interventions for generalised anxiety disorder;

"Offer either

- an individual high-intensity psychological intervention

or

- drug treatment

● Provide verbal and written information on the likely benefits and disadvantages of each mode of treatment, including the tendency of drug treatments to be associated with side effects and withdrawal syndromes.
● Base the choice of treatment on the person's preference as there is no evidence that either mode of treatment (individual high-intensity psychological intervention or drug treatment) is better." (pp.268)

"If a person with GAD chooses drug treatment, offer a selective serotonin reuptake inhibitor (SSRI). Consider offering sertraline first because it is the most cost-effective drug, but note that at the time of publication (January 2011)17 sertraline did not have UK marketing authorisation for this indication." (pp.269)

"If sertraline is ineffective, offer an alternative SSRI or a serotonin–noradrenaline reuptake inhibitor (SNRI)." (pp.269)

"If the person cannot tolerate SSRIs or SNRIs, consider offering pregabalin." (pp.269)

"Before prescribing any medication, discuss the treatment options and any concerns the person with GAD has about taking medication. Explain fully the reasons for prescribing and provide written and verbal information on:
● the likely benefits of different treatments
● the different propensities of each drug for side effects, withdrawal syndromes and drug interactions
● the risk of activation with SSRIs and SNRIs, with symptoms such as increased anxiety, agitation and problems sleeping.
● the gradual development, over 1 week or more, of the full anxiolytic effect
● the importance of taking medication as prescribed and the need to continue treatment after remission to avoid relapse." (pp.269)

Date question received: 13/02/2014
Date searches conducted: 17/02/2014
Date answer completed:

References

SRs

Baldwin, D., Woods, R., Lawson, R. and Taylor, D. (2011) Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. *British Medical Journal 342*:d1199

Boschen, M.L. (2011) A Meta-Analysis of the Efficacy of Pregabalin in the Treatment of Generalized Anxiety Disorder. *The Canadian Journal of Psychiatry 56* **(9)** pp. 558-566

Samuel, M., Zimovetz, E.A., Gabriel, Z. and Beard, S.M. (2011) Efficacy and safety of treatments for refractory generalized anxiety disorder: a systematic review. *International Clinical Psychopharmacology 26* pp.63-68.

RCTs

Feltner, D., Wittchen, H-U., Kavoussi, R., Brock, J., Baldinetti, F. and Pande, A.C. (2008) Long-term efficacy of pregabalin in generalized anxiety disorder. *International Clinical Psychopharmacology 23* **(18)** pp.18-28.

Guidelines

National Institute for Health and Care Excellence (2011) Anxiety disorder in adults: Management in primary, secondary and community care. CG113. London: National Institute for Health and Care Excellence.

Results
Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Baldwin et al. (2011)	30/01/ 2009	P: Adults aged ≥18 years receiving any active drug treatment for generalised anxiety disorder. I: Any active drug treatment C: Placebo and any other active drug. O: Response (the proportion of patients who experienced a reduction of at least 50% from their baseline score on the HAM-A)and remission the proportion of patients with a final score of ≤7 (HAM-A). S: Randomised controlled trials of any duration; systematic reviews and meta-analyses of RCTs	27 RCTs	This systematic review reported the results of a mixed treatment meta-analysis. When analysis was restricted to the five drugs currently licenced in the UK, duloxetine was ranked first for response (third across all treatments), escitalopram was ranked first for remission (second across all treatments) and pregabalin was ranked first for tolerability (second across all treatments), with a 7.7% probability of being the best tolerated of all the treatments considered. All treatments were favoured over placebo for response and remission, but not for tolerability.	High
Boschen (2011)	12/2010	P: Adults with GAD (n=1352) I: Pregabalin C: Placebo O: Change in somatic and psychic anxiety levels (HARS) S: Randomised controlled trials	7 RCTs	After 4 to 8 weeks of treatment, there was a significant effect in favour of pregabalin compared to placebo for HARS total score: Hedges' g = 0.364 (95% CI 0.256 to 0.471), n=869. Similar results were observed for psychic anxiety subscale: Hedges' g = 0.349 (95% CI 0.256 to 0.471), and somatic anxiety symptoms: Hedges' g = 0.239 (95% CI 0.107 to 0.370).	High
Samuel et al. (2011)	Search dates not reporte d	P: Adults ≥18 years old with refractory GAD, defined as patients who have failed to respond adequately to at least one earlier treatment for GAD. I: Benzodiazepines, anticonvulsants, azapirones,	8 (4 RCTs and 4 single-arm open-label studies)	Only one of the included studies evaluated pregabalin (Miceli *et al*. 2009). In this RCT (n=356), a significant reduction in the HAM-A score was found at 8 weeks: -1.2 (95% CI -2.16 to -0.26, p=0.012) compared with placebo. HAM-A score (responder rates) were 50% in	High

		SSRIs, SNRIs, tricylics, antipsychotics or antihistamines. C: Placebo or other active comparators. O: Change in anxiety scores (HAM-A).		the pregabalin group and 37% in the placebo group (OR 1.86 [95% CI 1.08 to 3.22]). HAM-A score (remission rates) were 32% in the pregabalin group and 24% in the placebo group (OR 1.55 [95% CI 0.85 to 2.83]). The OR for CGI-I score (responder rates) was 1.70 [95% CI 1.13 to 2.54]). Rates of severe adverse events (≥ 1 event) were not significantly different between the treatment groups (7.8% vs. 7.4%).	

RCTs

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Feltener et al. (2008)	P: Males and female adults (≥18 years) who met the diagnostic criteria for GAD according to DSM-IV for a minimum of 1 year and a score of ≥20 on HAM-A, ≥9 on Covi-Anxiety Scale and ≤7 on Raskin Depression Scale. All took part in a open-label phase of treatment which involved perceiving pregabalin 300mg/day for 3 days then 450mg/day for 8 weeks. Eligible for the next stage (randomisation) if after this the HAM-A total score ≤11 and ≥50% reduction from baseline HAM-A. I: Pregabalin 450 mg/day (150mg thrice daily) C: Placebo O: Time to relapse and change in anxiety symptoms (HAM-A), and adverse events.	N=624	Among patients with GAD ***who responded initially to open-label pregabalin*** and were randomised into the double-blind phase (54%), the efficacy of pregbalin in preventing or slowing the relapse of anxiety was found to be superior to placebo (p<0.0001). Treatment was also significantly more effective than placebo in maintaining reduction in the severity of GAD symptoms (as measured using the CGI-S scale) p<0.0001. Pregabalin was more effective than placebo in maintaining a reduced level of depressive symptoms as assessed by the difference in the HAM-D score (p=0.0002). In addition, work productivity (p=0.003), social and family responsibilities (p=0.017 and p=0.0027) were sustained over the course of the 24-week double-blind phase (SDS subscale scores). Pregabalin was well tolerated.	Unclear

Risk of Bias: SRs

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Baldwin et al. (2011)	☺	?	☹	☹	☺
Boschen (2011)	☺	☹	?	?	☹
Samuel (2011)	☺	☹	☺	☹	☺

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Feltner et al. (2008)	?	?	☺	?	☺	☺

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Generalised Anxiety	170	1
DARE	1 (pregabalin OR lyrica) 2 (anxiet*) 3 (anxious*) 4 MeSH DESCRIPTOR Anxiety EXPLODE ALL TREES 5 MeSH DESCRIPTOR Anxiety Disorders EXPLODE ALL TREES 6 #2 OR #3 OR #4 OR #5 7 #1 AND #6	15	2
Primary studies			
CENTRAL	#1 "generalized anxiety disorder" 826 #2 "generalised anxiety disorder" 198 #3 pregablin or pregabalin 536 #4 #1 or #2 988 #5 #4 and #3 49 Central only 33	33	
PsycINFO	1. PsycINFO; GENERALIZED ANXIETY DISORDER/; 1641 results. 2. PsycINFO; "generalised anxiety disorder".ti,ab; 229 results. 3. PsycINFO; 1 OR 2; 1796 results. 4. PsycINFO; PREGABALIN/; 297 results. 5. PsycINFO; pregabalin.ti,ab; 449 results. 6. PsycINFO; 4 OR 5; 492 results. 7. PsycINFO; 3 AND 6; 58 results. 8. PsycINFO; CLINICAL TRIALS/; 7311 results. 9. PsycINFO; random*.ti,ab; 126306 results.	39	

	10. PsycINFO; groups.ti,ab; 359721 results. 11. PsycINFO; (double adj3 blind).ti,ab; 17598 results. 12. PsycINFO; (single adj3 blind).ti,ab; 1369 results. 13. PsycINFO; EXPERIMENTAL DESIGN/; 8935 results. 14. PsycINFO; controlled.ti,ab; 78687 results. 15. PsycINFO; (clinical adj3 study).ti,ab; 7735 results. 16. PsycINFO; trial.ti,ab; 66561 results. 17. PsycINFO; "treatment outcome clinical trial".md; 26003 results. 18. PsycINFO; 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17; 556105 results. 19. PsycINFO; 7 AND 18; 39 results.		
Embase	9. EMBASE; "generalised anxiety disorder".ti,ab; 543 results. 10. EMBASE; 8 OR 9; 5543 results. 11. EMBASE; PREGABALIN/; 7164 results. 12. EMBASE; pregabalin.ti,ab; 2856 results. 13. EMBASE; 11 OR 12; 7378 results. 14. EMBASE; 10 AND 13; 363 results. 15. EMBASE; random*.ti,ab; 885470 results. 16. EMBASE; factorial*.ti,ab; 23012 results. 17. EMBASE; (crossover* OR cross-over*).ti,ab; 70018 results. 18. EMBASE; placebo*.ti,ab; 201942 results. 19. EMBASE; (doubl* ADJ blind*).ti,ab; 144517 results. 20. EMBASE; (singl* ADJ blind*).ti,ab; 14459 results. 21. EMBASE; assign*.ti,ab; 240569 results. 22. EMBASE; allocat*.ti,ab; 83314 results. 23. EMBASE; volunteer*.ti,ab; 178421 results. 24. EMBASE; CROSSOVER PROCEDURE/; 39960 results. 25. EMBASE; DOUBLE BLIND PROCEDURE/; 120573 results. 26. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 367720 results. 27. EMBASE; SINGLE BLIND PROCEDURE/; 19046 results.	121	

	28. EMBASE; 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27; 1424989 results. 29. EMBASE; 14 AND 28; 121 results.		
Medline	8. MEDLINE; GENERALIZED ANXIETY DISORDER/; 0 results. 8. MEDLINE; GENERALIZED ANXIETY DISORDER/; 0 results. 9. MEDLINE; "generalised anxiety disorder".ti,ab; 344 results. 9. MEDLINE; "generalised anxiety disorder".ti,ab; 344 results. 10. MEDLINE; 8 OR 9; 344 results. 10. MEDLINE; 8 OR 9; 344 results. 11. MEDLINE; PREGABALIN/; 0 results. 11. MEDLINE; PREGABALIN/; 0 results. 12. MEDLINE; pregabalin.ti,ab; 1561 results. 12. MEDLINE; pregabalin.ti,ab; 1561 results. 13. MEDLINE; 11 OR 12; 1561 results. 13. MEDLINE; 11 OR 12; 1561 results. 14. MEDLINE; "generalized anxiety disorder".ti,ab; 3443 results. 15. MEDLINE; 9 OR 14; 3775 results. 16. MEDLINE; 12 AND 15; 98 results. 17. MEDLINE; "randomized controlled trial".pt; 362670 results. 18. MEDLINE; "controlled clinical trial".pt; 87530 results. 19. MEDLINE; randomized.ab; 283145 results. 20. MEDLINE; placebo.ab; 149793 results. 21. MEDLINE; "drug therapy".fs; 1661607 results. 22. MEDLINE; randomly.ab; 205850 results. 23. MEDLINE; trial.ab; 291983 results. 24. MEDLINE; groups.ab; 1316613 results. 25. MEDLINE; 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24; 3251800 results. 26. MEDLINE; 16 AND 25; 77 results.	77	
Summary	**NA**	**NA**	

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