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 depression how effective is paroxetine compared to other anti-depressive agents for improving patient outcomes?"

Clarification of question using PICO structure

Patients:	Adults with depression
Intervention:	Paroxetine
Comparator:	Other anti-depressive agents
Outcome:	Any patient outcomes

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Clinical and research implications

No definite clinical implications can be made based on the available evidence. The authors of a well-conducted systematic review suggested that there were some possible differences between paroxetine and other antidepressants, but that the clinical meaning of these differences is uncertain, and that no definitive implications for clinical practice can be drawn. They also stated that more high quality studies are needed that consider rating scales as well as pragmatic outcome measures (for example hospitalisations, return to work, social functioning, etc.).

What does the evidence say?

Number of included studies/reviews (number of participants)
One Cochrane systematic review (Purgato et al. 2014) and one pilot randomised controlled trial (RCT)(Grunebaum et al. 2012) met the inclusion criteria for this BEST summary.

Main Findings
The Cochrane review (with a search date up to Sept 2012) aimed to assess the efficacy of paroxetine in comparison with other anti-depressive agents in alleviating the acute symptoms of Major Depressive Disorder (Purgato et al. 2014). A large number of RCTs (115 with 26,134 participants) were included in this systematic review, and the number of comparisons and outcomes were extensive. The primary outcome of this review was response rate – at treatment end point (6 to 12 weeks), at 1 to 4 weeks (early response), and at follow-up (16 to 24 weeks), and the results were presented for older antidepressants (ADs) (i.e. tricyclics, heterocyclics, MAOIs), SSRIs, and newer or non-conventional anti-depressive agents (e.g. SNRIs, hypericum), separately. For the primary outcome, the authors reported that paroxetine was more effective than reboxetine for early response (OR: 0.66, 95% CI 0.50 to 0.87, 3 RCTs, 1375 participants), and at treatment endpoint (OR: 0.82, 95% CI 0.66 to 1.02, 3 RCTs, 1369 participants). Paroxetine, however, was less effective than mirtazapine for early response (OR: 2.39, 95% CI 1.42 to 4.02, 3 RCTs, 726 participants). Paroxetine was also found to be less effective than citalopram in improving response to treatment at six to 12 weeks (OR: 1.54, 95% CI 1.04 to 2.28, 1 RCT, 406 participants). Regarding the secondary outcome - remission rate - the authors found a difference in favour of clomipramine, hypericum, mirtazapine and venlafaxine over paroxetine. In terms of acceptability, paroxetine was better than reboxetine and amitriptyline (dropouts due to side effects) and better than clomipramine, imipramine and also better than older ADs as a class (dropouts due to side effects and dropouts due to any cause). In contrast, paroxetine was associated with a higher rate of dropouts due to side effects than fluoxetine and tianeptine. Regarding the number of patients experiencing at least some side effects, paroxetine was better than amitriptyline, imipramine and older ADs as a class, but less well tolerated than agomelatine and hypericum.

The pilot RCT compared paroxetine with bupropion in participants with DSM IV major depression with a suicide attempt history or current suicidal ideation (Grunebaum et al. 2012). The authors found no treatment main effect or treatment time interaction on suicidal ideation or mHDRS-17. In exploratory models, however, the authors found that patients with more severe global depressive symptoms at baseline improved more in terms of depression when taking paroxetine (controlling for suicidal ideation at baseline). They also found that patients with more severe suicide ideation at

baseline, improved more in terms of suicide ideation, when taking paroxetine compared bupropion (controlling for baseline depression).

Authors Conclusions

Purgato et al. (2014) concluded that some possibly clinically meaningful differences between paroxetine and other ADs exist, but no definitive conclusions can be drawn.

Grunebaum et al. (2012) suggested that an adequately powered trial is warranted to determine whether SSRIs have clinically meaningful advantages vs non-serotonergic antidepressants on suicidal behaviour and ideation in depressed patients presenting with more severe suicidal ideation.

Reliability of conclusions/Strength of evidence

The systematic review by Purgato et al. (2014) was well conducted. The authors reported, however, that the included studies were generally at unclear or high risk of bias - and appropriately made cautious conclusions. The Grunebaum et al (2012) trial was well conducted, but because it is a pilot study with a small sample size, the results should be treated with caution.

What do guidelines say?

Neither National Institute for Health and Care Excellence (NICE) nor Scottish Intercollegiate Guidelines Network (SIGN) guidelines comment upon the effectiveness of paroxetine compared to other antidepressants for improving patient outcomes.

Date question received: 01/12/2014
Date searches conducted: 20/01/2015
Date answer completed: 20/02/2015

References

SRs

Purgato, M., Papola, D., Gastaldon, C., Trespidi, C., Magni, L. R., Rizzo, C., ... & Barbui, C. (2014). Paroxetine versus other anti-depressive agents for depression. *Cochrane Database of Systematic Reviews, Issue 4.* Art. No.: CD0006532. DOI: 10.1002/14651858.CD006531.pub2..

RCTs

Grunebaum, M. F., Ellis, S. P., Duan, N., Burke, A. K., Oquendo, M. A., & Mann, J. J. (2012). Pilot randomized clinical trial of an SSRI vs bupropion: Effects on suicidal behavior, ideation, and mood in major depression. *Neuropsychopharmacology*, *37*(3), 697-706.

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Purgato et al. (2014)	09/2012	*Participants*: Aged 18 and older, with a primary diagnosis of unipolar major depression according to standardised criteria (e.g., DSM; ICD-10). Exclusions: concurrent primary diagnosis of an Axis I or II disorder; concomitant medical illness. *Intervention*: Paroxetine. Any dose and pattern of administration. *Comparator*: Conventional antidepressants (e.g., tricyclics, heterocyclics, monoamine oxidase inhibitors (MAOI), selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitors (SNRI), hypericum). *Outcome*: Primary outcomes: Response rate (e.g., no. participants showing a reduction of at least 50% on the Hamilton Rating Scale for Depression (HRSD), Montgomery and Asberg Depression Rating Scale (MADRS), or any other depression rating scale, or 'much or very improved' on the Clinical Global Impression Scale (CGI)). Secondary outcomes: remission rate; depressive symptoms (e.g. change scores on the HRSD, MADRS, or any other depression scale); social adjustment; quality	115 RCTs (26,134 participants)	In 54 studies paroxetine was compared with older ADs (Tricyclics; Heterocyclics; MAOIs), in 21 studies with another SSRI, and in 40 studies with a newer or non-conventional antidepressant other than SSRIs. **Paroxetine versus older ADs:** There was no statistically significant difference in response rate, or remission rates, between paroxetine and older ADs as a class. In head-to-head comparisons, a difference was found in favour of clomipramine over paroxetine for remission at endpoint (six to 12 weeks) (OR: 3.39, 95% CI 1.50 to 7.65, number needed to treat to provide benefit (NNTb) = 4, 95% CI 2 to 11, 1 RCT, 120 participants). **Paroxetine versus SSRIs:** In terms of responders at endpoint (6 to 12 weeks), there was a difference in favour of citalopram over paroxetine (OR: 1.54, 95% CI 1.04 to 2.28, NNTb = 9, 95% CI 5 to 102, 1 RCT, 406 participants). There were no differences between paroxetine and	Low

		of life. *Study design*: Randomised controlled trial (RCTs).		individual SSRIs for early response rate (one to four weeks) and follow-up response rate (16 to 24 weeks). No differences between paroxetine and individual SSRIs were observed for early remission rates, and remission at endpoint. There was no difference between paroxetine and individual SSRIs for patients who dropped out during the trial for any reason and dropouts due to inefficacy. In terms of dropouts due to side effects, paroxetine was less well tolerated than fluoxetine (OR: 1.34, 95% CI 1.06 to 1.70, NNTh = 29, 95% CI 16 to 137, 11 RCTs, 2491 participants). **Paroxetine versus newer or nonconventional ADs:** In terms of number of patients who responded to treatment at endpoint, and also at one to four weeks, there was a trend in favour of paroxetine over reboxetine (OR: 0.82, 95% CI 0.66 to 1.02, 3 RCTs, 1369 participants, and OR: 0.66, 95% CI 0.50 to 0.87, NNTb = 16, 95% CI 10 to 50, 3 RCTs, 1375 participants, respectively). In contrast, here was a difference in favour of mirtazapine over paroxetine for response at one to four weeks (i.e. early response) (OR: 2.39, 95% CI 1.42 to 4.02, NNTb = 8, 95% CI 5 to 14, 3 RCTs, 726 participants). In terms of efficacy	

				as number of patients who responded to treatment at 16-24 weeks, there was no difference between paroxetine and newer or non-conventional ADs. In terms of efficacy as number of patients who remitted (at 6 to 12 weeks), there was a difference in favour of hypericum (OR: 1.84, 95% CI 1.11 to 3.06, NNTb = 7, 95% CI 4 to 38, 1 RCT, 251 participants), mirtazapine (OR: 1.52, 95% CI 1.13 to 2.06, NNTb = 11, 95% CI 6 to 37, 4 RCTs, 766 participants) and venlafaxine (OR: 1.57, 95% CI 1.08 to 2.29, NNTb = 11, 95% CI 6 to 54, 4 RCTs, 807 participants) over paroxetine. In terms of efficacy as number of patients who remitted at one to four weeks, there was a difference between paroxetine and mirtazapine, in favour of mirtazapine (OR: 2.31, 95% CI 1.04 to 5.11, NNTb = 18, 95% CI 11 to 54, 3 RCTs, 726 participants). A difference in favour of mirtazapine was also observed for remission rate at 16 to 24 weeks (OR: 1.89, 95% CI 1.01 to 3.54, NNTb = 8, 95% CI 4 to 265, 1 RCT, 197 participants) Paroxetine was associated with a lower rate of adverse events than amitriptyline, imipramine and older ADs as a class, but was less well tolerated than agomelatine and hypericum. Included studies were generally	

				at unclear or high risk of bias due to poor reporting of allocation concealment and blinding of outcome assessment, and incomplete reporting of outcomes.	

RCTs

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Grunebaum et al. (2012)	*Participants*: Patients aged 18-75 meeting DSM-IV criteria for depression, with a suicide attempt history or current suicidal ideation. Exclusions: Bipolar disorder, psychosis, anorexia or bulimia nervosa, current SSRI or bupropion use for other indications, drug/alcohol dependence within past 6 months, unstable medical illness. *Intervention*: Paroxetine. 25mg/d for weeks 1 and 2, 37.5mg/d for weeks 3 and 4. After week 4, paroxetine was increased to a maximum of 50mg/d if required. There was a 16 week continuation phase. *Comparator*: Bupropion. 150mg/d for weeks 1 and 2, 300mg/d for weeks 3 and 4. After week 4, bupropion was increased to a maximum of 450mg/d if required. There was a 16 week continuation phase.	74 (36 to paroxetine and 38 to buproprion)	Treatment was not associated with time to the first suicidal event during the week 1-8 acute phase (p=0.31) or the complete 24-week follow-up (p=0.68). There was no treatment main effect or treatment time interaction on suicidal ideation or mHDRS-17. Exploratory model selection showed modest advantages for paroxetine on: (1) mHDRS- 17 (p = 0.02); and (2) in a separate model adjusted for baseline depression, for suicidal ideation measured with the Beck Scale for Suicidal Ideation (p = 0.03), with benefit increasing with baseline severity. Depressed patients with greater baseline suicidal ideation treated with paroxetine compared with bupropion appeared to experience greater acute improvement in suicidal ideation, after adjusting for global depression.	Low

	Outcome: Primary outcome: Suicidal behaviour and ideation (Scale for Suicidal Ideation, SSI). Secondary outcomes: depressive symptoms (Hamilton Rating Scale for Depression).			

Risk of Bias:

SRs

Author (year)	RISK OF BIAS				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Purgato et al. (2014)	☺	☺	☺	☺	☺

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Grunebaum et al. (2012)	☺	☺	☺	☺	☺	?

☺ Low Risk ☹ High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	paroxetine depression	17	0
Primary studies			
CENTRAL	#1 MeSH descriptor: [Paroxetine] explode all trees 775 #2 MeSH descriptor: [Depression] explode all trees 5487 #3 MeSH descriptor: [Depressive Disorder] explode all trees 7578 #4 #2 or #3 12729 #5 #1 and #4 412 Central only 386	0	1
PsycINFO	1. PsycINFO; MAJOR DEPRESSION/; 90653 results. 2. PsycINFO; depression.ti,ab; 176516 results. 3. PsycINFO; 1 OR 2; 190757 results. 4. PsycINFO; PAROXETINE/; 1551 results. 5. PsycINFO; Paxil.ti,ab; 51 results. 6. PsycINFO; 4 OR 5; 1586 results. 7. PsycINFO; 3 AND 6; 881 results. 8. PsycINFO; CLINICAL TRIALS/; 8275 results. 9. PsycINFO; random*.ti,ab; 137223 results. 10. PsycINFO; groups.ti,ab; 381596 results. 11. PsycINFO; (double adj3 blind).ti,ab; 18448 results. 12. PsycINFO; (single adj3 blind).ti,ab; 1488 results. 13. PsycINFO; EXPERIMENTAL DESIGN/; 9447 results. 14. PsycINFO; controlled.ti,ab; 85018 results. 15. PsycINFO; (clinical adj3 study).ti,ab; 8295 results. 16. PsycINFO; trial.ti,ab; 72201 results.	450	0

	17. PsycINFO; "treatment outcome clinical trial".md; 28737 results. 18. PsycINFO; 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17; 592438 results. 19. PsycINFO; 7 AND 18; 450 results.		
Embase	30. EMBASE; MAJOR DEPRESSION/; 38664 results. 31. EMBASE; depression.ti,ab; 284068 results. 32. EMBASE; 30 OR 31; 297319 results. 33. EMBASE; PAROXETINE/; 23258 results. 34. EMBASE; Paxil.ti,ab; 121 results. 35. EMBASE; 33 OR 34; 23272 results. 36. EMBASE; 32 AND 35; 8519 results. 37. EMBASE; random*.ti,ab; 923123 results. 38. EMBASE; factorial*.ti,ab; 23806 results. 39. EMBASE; (crossover* OR cross-over*).ti,ab; 71050 results. 40. EMBASE; placebo*.ti,ab; 206020 results. 41. EMBASE; (doubl* ADJ blind*).ti,ab; 145911 results. 42. EMBASE; (singl* ADJ blind*).ti,ab; 15029 results. 43. EMBASE; assign*.ti,ab; 247439 results. 44. EMBASE; allocat*.ti,ab; 87507 results. 45. EMBASE; volunteer*.ti,ab; 180896 results. 46. EMBASE; CROSSOVER PROCEDURE/; 41027 results. 47. EMBASE; DOUBLE BLIND PROCEDURE/; 116908 results. 48. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 356075 results. 49. EMBASE; SINGLE BLIND PROCEDURE/; 19250 results. 50. EMBASE; 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49; 1464495 results. 51. EMBASE; 36 AND 50; 2233 results. 52. EMBASE; 51 [Limit to: Publication Year 2011-2015]; 507 results. 53. EMBASE; (rats OR mice).ti,ab [Limit to: Publication Year 2011-2015]; 364847 results. 54. EMBASE; 52 not 53 [Limit to: Publication Year 2011-2015]; 503 results	503	0

Medline	8. MEDLINE; MAJOR DEPRESSION/; 0 results. 9. MEDLINE; depression.ti,ab; 222935 results. 10. MEDLINE; 8 OR 9; 222935 results. 11. MEDLINE; PAROXETINE/; 3500 results. 12. MEDLINE; Paxil.ti,ab; 71 results. 13. MEDLINE; 11 OR 12; 3523 results. 14. MEDLINE; 10 AND 13; 1113 results. 15. MEDLINE; DEPRESSION/; 78013 results. 16. MEDLINE; exp DEPRESSIVE DISORDER/; 81747 results. 17. MEDLINE; 9 OR 15 OR 16; 278873 results. 18. MEDLINE; 13 AND 17; 1579 results. 19. MEDLINE; "randomized controlled trial".pt; 381448 results. 20. MEDLINE; "controlled clinical trial".pt; 88431 results. 21. MEDLINE; randomized.ab; 305328 results. 22. MEDLINE; placebo.ab; 156803 results. 23. MEDLINE; "drug therapy".fs; 1725254 results. 24. MEDLINE; randomly.ab; 221628 results. 25. MEDLINE; trial.ab; 315020 results. 26. MEDLINE; groups.ab; 1401805 results. 27. MEDLINE; 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26; 3421269 results. 28. MEDLINE; 18 AND 27; 1402 results. 29. MEDLINE; 28 [Limit to: Publication Year 2011-2015]; 144 results.	144	0
Summary	**NA**	**NA**	

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