Best Evidence Summaries of Topics in Mental Healthcare

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

Question

In people with PTSD (including single and multiple event trauma) how effective is prazosin compared with either no treatment, psychological therapy alone, or a combination of prazosin and psychotherapy, in reducing trauma related nightmares. What information is there around the duration of treatment required, and the return of nightmares upon cessation?

Clarification of question using PICO structure

Patients: People with PTSD
Intervention: prazosin
Comparator: Any other treatment
Outcome: reduction in nightmares

Clinical and research implications

Four small US based studies conducted mainly in male military veterans suggest that prazosin is an effective and well-tolerated treatment in reducing trauma related nightmares. One RCT suggested that a behavioural sleep intervention had similar effectiveness to prazosin. Very limited evidence from single studies suggests that the treatment effect is seen after 3 weeks of treatment (the earliest time point after treatment initiation for which data were available) and is greater after 8 weeks of treatment. Nightmares appear to return immediately upon treatment cessation although this was based on data from one very small (n=10) cross-over trial and so should be interpreted with caution. There is a need for larger studies conducted in a broader range of participants; the only study not conducted in military personnel included only 13 participants.

What does the evidence say?

Number of included studies/reviews (number of participants)
Four RCTs (n=113) were included. All were conducted in the US and three were conducted in ex-military personnel, mainly in men (93%). The remaining study was conducted in outpatients with post-traumatic stress disorder (PTSD) who had frequent nightmares and sleep disturbance and consisted of mainly women (11/13). Mean age ranged from 41 to 56 years. Two of the four studies used a randomised cross-over design (n=23), the other two used a parallel group design and were larger in size (n=90). All studies compared prazosin (mean final dose 3.1mg to 13.3 mg) to placebo; one of the parallel group studies also included a third treatment arm consisting of a behavioural

sleep intervention (BSI), which involved a manualised treatment combining educational and behavioural techniques.

Main Findings
All four RCTs reported significant beneficial effects in favour of prazosin on nightmare/distressing dreams frequency and on sleep quality, with one of the studies stating that "prazosin shifted dream characteristics from those typical of trauma-related nightmares toward those typical of normal dreams". Specifically, compared to placebo, prazosin was associated with significantly greater improvements in wake time after sleep onset (1 RCT), total sleep time (2 RCTs), REM sleep time (1 RCT), mean REM duration (1 RCT), non-nightmare distressed awakening (1 RCT), global improvement (3 RCTs), PTSD dream rating scale (2 RCTs), sleep specific treatment response (1 RCT), and difficulty falling/staying asleep (2 RCTs) Not all outcomes assessed in the trial showed significantly greater improvements in the prazosin compared to placebo arms. Single RCTs did not report significant improvements for each of the following outcomes: overall treatment response, daytime PTSD severity, difficulty falling or staying asleep, sleep onset latency, and one RCT only showed a trend for improvement in Hamilton depression rating scale (1 RCT; p=0.08).

The trial that included an additional BSI treatment arm reported that effects were similar between BSI and prazosin groups. Improvements were seen after 3, 4, 6 and 8 weeks of follow-up depending on the trial protocol.

All RCTs reported that adverse events were generally minor and similar between groups. Two patients in one RCT experienced mild blood pressure decreases and dizziness while taking prazosin which resolved as the dose was increased.(4) However, there were no significant changes in blood pressure in the prazosin or placebo groups in two other RCTs.(1, 3) In one of the cross-over RCTs,(4) the five patients who were randomised to receive placebo as the second treatment all experienced a rapid return of their nightmares during the post prazosin washout. Four of these patients discontinued the study during the placebo phase so that they could be given open label prazosin.

Authors Conclusions
All RCTs concluded that prazosin is an effective and well-tolerated treatment for nightmares and sleep disturbance in patients, in particular military veterans, with PTSD.

Reliability of conclusions/Strength of evidence
All four RCTs were well conducted. Three of the four RCTs did not report details on method of randomisation or allocation concealment and so were rated as "unclear" risk of bias for these domains; the other RCT was rated as low risk of bias for these domain.(3) All RCTs were rated as low risk of bias on all other domains. The results of these studies are therefore likely to be reliable. However, the small sample size of the included studies and relatively small number of studies most of which were conducted in one very focused patient population (US ex-military) mean that the generalizability of the results of these studies may be limited.

What do guidelines say?

No information was found in relation to the treatment of PTSD with prazosin in UK clinical guidelines.

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Date searches conducted: 27/11/2012
Date answer completed: 4/12/2012

References

RCTS

1. GERMAIN, A., RICHARDSON, R., MOUL, E., MAMMEN, O., HAAS, G., FORMAN, D., RODE, N., BEGLEY, A. & NOFZINGER, A. 2012. Placebo-controlled comparison of prazosin and cognitive-behavioral treatments for sleep disturbances in US Military Veterans. Journal of Psychosomatic Research, 72, 89-96.

2. RASKIND, A., PESKIND, R., HOFF, J., HART, L., HOLMES, A., WARREN, D., SHOFER, J., O'CONNELL, J., TAYLOR, F., GROSS, C., ROHDE, K. & MCFALL, E. 2007. A Parallel Group Placebo Controlled Study of Prazosin for Trauma Nightmares and Sleep Disturbance in Combat Veterans with Post-Traumatic Stress Disorder. Biological Psychiatry, 61, 928-934.

3. RASKIND, A., PESKIND, R., KANTER, D., PETRIE, C., RADANT, A., THOMPSON, E., DOBIE, J., HOFF, D., REIN, J., STRAITS-TROSTER, K., THOMAS, G. & MCFALL, M. 2003. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: A placebo-controlled study. The American Journal of Psychiatry, 160, 371-373.

4. TAYLOR, B., MARTIN, P., THOMPSON, C., WILLIAMS, J., MELLMAN, A., GROSS, C., PESKIND, R. & RASKIND, A. 2008. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: A placebo-controlled study. Biological Psychiatry, 63, 629-632.

Results

RCTs

Author (year)	Study details	Number of participants	Summary of results	Risk of bias
Germain (2012)(1)	*Study design – parallel group* *Population* – US military veterans with clinically meaningful sleep disturbances (Pittsburgh Sleep Quality Index and the nightmare item of Pittsburgh Sleep Quality Index accompanied by at least one daytime functional impairment of sleep disruption, persistent for more than 1 month) *Intervention* – prazosin titrated from 1mg to 15mg. Mean final dose 10.4 mg (sd = 5.7mg) *Comparison* – Behavioural sleep intervention (BSI; a manualised treatment combining educational and behavioural techniques) and placebo. *Outcomes* – The Insomnia Severity Index, the Pittsburgh Sleep Quality Index (PSQI), the PSQI Addendum for PTSD, Pittsburgh Sleep Diary (PghSD), and global measures of clinical improvement and self report of sleep and psychiatric symptoms *Study duration* - 8 weeks treatment, follow-up 4 months post-treatment	N=50 (prazosin n=18, BSI n=17, placebo n=15), mean age 41 (sd =13), 45 men	**Sleep improvements** were found in 62% of those who completed the active treatments and 25% of those randomised to placebo. Both the BSI and prazosin groups showed significantly greater improvements in the following outcome measures but did not differ from one another: **insomnia severity** ($p<0.01$), **wake time after sleep onset (**$p<0.01$), **total sleep time** ($p<0.01$), **sleep efficiency** ($p<0.01$), **mean weekly nightmare** ($p=0.045$). There was no difference between the two active treatment groups and placebo for the **CGI-defined criterion** of **treatment response** ($p=0.07$), but there was a significant improvement for the criterion of **sleep-specific treatment response** ($p<0.02$). There was no treatment x time interaction for **sleep latency**, **wake time after sleep onset**, or **sleep efficiency** or for **daytime PTSD** symptom severity. **Adverse events** were minor and similar across treatment groups. Two patients withdrew from the placebo group and one withdrew from the prazosin group due to side effects. There were no significant changes in blood pressure in the prazosin or placebo groups.	Unclear

Author (year)	Study details	Number of participants	Summary of results	Risk of bias
Taylor (2008)(2)	*Study design* – Randomised crossover design *Population* – Outpatients with frequent nightmares and sleep disturbance; met the DSM-IV criteria for PTSD, scored at least 40 on the PTSD Checklist-Civilian Version (PCL-C), at least 4 (of a maximum of 8) on the Clinician Administered PTSD Scale (CAPS) "recurrent distressing dreams" item, and at least 4 on the CAPS "difficulty falling asleep/staying asleep" item. *Intervention* – Prazosin initiated at 1mg at bedtime, titrated up by 1mg per 2-3 days (mean final dose 3.1mg, sd=1.3mg) *Comparison* – Placebo *Outcomes* – measured through objective measures; sleep time, REM sleep time, REM latency, REM period duration. The CAPS "recurrent distressing dreams" and "sleep disturbance" items, non-nightmare distressed awakening scale, the subject rated PCL-C, the Clinical Global Impression-Improvement (CGI-I), and the civilian version of the PTSD Dream Rating SCALE (PDRS). *Study duration:* Two 3 week treatment periods separated by 1 week washout period	N=13 (11 women, 2 men, mean age 48 years (SD=10 years)	Significantly greater improvement from baseline were seen in the prazosin group compared to placebo group for **CAPS recurrent distressing dreams** (item 2), **non-nightmare distressed awakening, total PCL-C score**, **CGI-I scores**, **PTSD Dream Rating Scale (p<0.05).** The only outcome that did not differ between groups was CAPS **"difficulty falling asleep/staying asleep**" (item 13) (p=0.35). Compared to placebo, prazosin significantly: Increased **total sleep time**: 374 (sd = 86) minutes vs 280 (sd =105) minutes, p<0.01 Increased **REM sleep time**: 138 (sd=63) minutes vs 97 (sd =70) minutes, p<001 Mean **REM period duration**: 27 (sd=9) minutes vs 18 (sd=9) minutes, p<0.05 Did not alter **sleep onset latency** (no difference between groups, data not reported). **Adverse events** were similar between groups.	Unclear
Raskind (2007)(3)	*Study design* – Randomised, parallel group *Population* – US military veterans with	N=40 (34 evaluated), mean age 56 (sd=9)	Compared to placebo, prazosin significantly: Improved **recurrent distressing dreams**: change in	Low

Author (year)	Study details	Number of participants	Summary of results	Risk of bias
	chronic trauma nightmares and sleep disturbance who met DSM-IV criteria for PTSD related to combat exposure *Intervention* – prazosin initiated at 1mg titrated upward based upon clinical response with a therapeutic goal of complete absence of trauma nightmares (mean final dose 13.3mg, sd=3mg). *Comparison* – Placebo *Outcomes* – Primary outcomes included the CAPS "recurrent distressing dreams" item, the Pittsburgh Sleep Quality Index (PSQI), and the Clinical Global Impression of Change (CGIC). Secondary measures included the total 17-item CAPS score, the Nightmare Frequency Questionnaire Revised (NFQ), and the Hamilton Depression Rating Scale. *Study duration* – 8 weeks, outcomes also assessed at 4 weeks	years, 38 men	prazosin 2.9 (sd 2.6) vs change in placebo 1.1 (sd 1.8), p=0.02. Improved **global clinical status** (sense of well being and ability to function): 2.4 (sd=1.1 (minimally to moderately improved in prazosin) vs 3.7 (sd=1.2) (unchanged to minimally improved in placebo), p=0.002. Improved **sleep quality**: 9.7 (sd=3.9) in prazosin vs 12.6 (sd 4.1) in placebo), p=0.008. Similar results were observed with an ITT analysis and for follow-up after 4 weeks of treatment, although greater treatment effects were observed after 8 weeks of treatment. Secondary outcomes including **nightmare frequency** and **PTSD dream rating scale** showed significant improvements from baseline in prazosin compared to placebo groups (p<0.05). The **Hamilton Depression Rating Scale** also showed a trend towards a significant improvement from baseline compared to placebo (p=0.08). **Total CAPS score** was similar between groups (p=0.3) 6 patients withdrew; 2 from placebo lost to follow-up, 4 withdrew due to adverse events 3 from prazosin and 1 from placebo. Adverse events included dizziness (9 prazosin, 6 placebo), nasal/sinus congestion (6 prazosin, 1 placebo), headache (3 prazosin 1 placebo)	

Author (year)	Study details	Number of participants	Summary of results	Risk of bias
			initial insomnia (1 prazosin, 1 placebo), dry mouth (2 prazosin). Blood pressure was similar between groups	
Raskind (2003)	*Study Design* – Randomised crossover design *Population* – US Vietnam veterans with chronic PTSD (DSM-IV criteria) and severe trauma related nightmares (score of 6 or higher on the Clinician-Administered PTSD Scale recurrent distressing dreams item). *Intervention* - prazosin initiated at 1mg titrated upward based upon clinical response with a therapeutic goal of complete absence of trauma nightmares. Mean dose 9.5 (sd=0.5) mg/day at bedtime *Comparison* – Placebo *Outcomes* - nightmares, sleep disturbance, and global change in PTSD severity and functional status *Study duration* – 20 weeks: 3 week dose titration, 6-week maintenance, 2 week wash-out, 3-week dose-titration, 6 week maintenance	N=10, mean age 53 (sd=3), all men	Patients treated with prazosin experienced significantly greater improvements from baseline in all outcome compared to those treated with placebo ($p<0.01$): **Recurrent distressing dreams** at endpoint: 3.6 (sd=2.8) in prazosin, 6.7 (sd=1.6) in placebo, $p<0.001$ **Difficulty falling/staying asleep** item of the Clinician Administered PTSD Scale: 4.0 (sd=2.3) in prazosin, 7.1 (sd=1.9) in placebo, $p<0.01$ **Clinical Global Impression of Change** at endpoint: 2.0 (sd=0.5) in prazosin, 4.5 (sd=1.8) in placebo, $p<0.01$ Two patients experienced mild **blood pressure** decreases and dizziness while taking prazosin which resolved as the dose was increased. The five patients who were randomised to receive placebo as the second treatment all experienced a rapid return of their nightmares during the post prazosin washout. Four of these patients discontinued the study during the placebo phase so that they could be given open label prazosin.	Unclear

Risk of Bias:RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Germain (2012)(1)	?	?	☺	☺	☺	☺
Taylor (2008)(2)	?	?	☺	☺	☺	☺
Raskind (2007)(3)	☺	☺	☺	☺	☺	☺
Raskind (2003)(4)	?	?	☺	☺	☺	☺

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Prazosin	7	0
DARE	(PTSD) IN DARE (post ADJ2 traumatic ADJ2 stress ADJ2 disorder) IN DARE (posttraumatic ADJ2 stress ADJ2 disorder) IN DARE #1 OR #2 OR #3 (prazosin) IN DARE (alpha ADJ2 blocker) IN DARE (Minipress) IN DARE #5 OR #6 OR #7		0
Primary studies			
CENTRAL	#1 MeSH descriptor: [Prazosin] explode all trees 688	6	4

	#2 prazosin:ti,ab,kw (Word variations have been searched) 761 #3Enter terms for searc#1 or #2963 #4 MeSH descriptor: [Stress Disorders, Post-Traumatic] explode all trees 735 #5Enter terms for searcPTSD921 #6Enter terms for searc"post-traumatic stress"469 #7Enter terms for searc"posttraumatic stress"696 #8Enter terms for searc#5 or #6 or #71370 #9Enter terms for searcnightmare*193 #10Enter terms for searcdream*540 #11Enter terms for searcsleep12863 #12Enter terms for searc#9 or #10 or #1113296 #13Enter terms for searc#3 and #8 and #126		
PsycINFO	1. PsycINFO; CLINICAL TRIALS/; 6426 results. 2. PsycINFO; random*.ti,ab; 113915 results. 3. PsycINFO; groups*.ti,ab; 334451 results. 4. PsycINFO; (doubl* adj3 blind*).ti,ab; 16803 results. 5. PsycINFO; (singl* adj3 blind*).ti,ab; 1411 results. 6. PsycINFO; EXPERIMENTAL DESIGN/; 8412 results. 7. PsycINFO; controlled.ti,ab; 71111 results. 8. PsycINFO; (clinical adj3 study).ti,ab; 7043 results. 9. PsycINFO; trial.ti,ab; 59981 results. 10. PsycINFO; "treatment outcome clinical trial".md; 23027 results. 11. PsycINFO; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10; 514328 results. 12. PsycINFO; prazosin.ti,ab; 475 results. 13. PsycINFO; hypovase.ti,ab; 0 results. 14. PsycINFO; POSTTRAUMATIC STRESS DISORDER/; 18964 results. 15. PsycINFO; "posttraumatic stress".ti,ab; 16496 results.	23	

	16. PsycINFO; "post-traumatic stress".ti,ab; 5830 results. 21. PsycINFO; ptsd.ti,ab; 17147 results. 17. PsycINFO; NIGHTMARES/; 744 results. 18. PsycINFO; (nightmare* OR dream*).ti,ab; 18807 results. 19. PsycINFO; sleep.ti,ab; 40114 results. 20. PsycINFO; 17 OR 18 OR 19; 55840 results. 22. PsycINFO; 14 OR 15 OR 16 OR 21; 25104 results. 23. PsycINFO; 11 AND 12 AND 20 AND 22; 23 results.		
EMBASE	24. EMBASE; PRAZOSIN/; 21042 results. 25. EMBASE; prazosin.ti,ab; 10985 results. 26. EMBASE; hypovase.ti,ab; 1 results. 27. EMBASE; 24 OR 25 OR 26; 22587 results. 28. EMBASE; PTSD.ti,ab; 13206 results. 29. EMBASE; "posttraumatic stress".ti,ab; 11610 results. 30. EMBASE; "post-traumatic stress".ti,ab; 7055 results. 31. EMBASE; STRESS DISORDERS, POST-TRAUMATIC/; 29914 results. 32. EMBASE; 28 OR 29 OR 30 OR 31; 31779 results. 33. EMBASE; nightmare*.ti,ab; 2405 results. 34. EMBASE; dream*.ti,ab; 9806 results. 35. EMBASE; sleep.ti,ab; 119034 results. 36. EMBASE; 33 OR 34 OR 35; 128349 results. 37. EMBASE; 27 AND 32 AND 36; 82 results. 38. EMBASE; random*.tw; 767196 results. 40. EMBASE; placebo*.tw; 181853 results. 39. EMBASE; factorial*.tw; 19768 results. 41. EMBASE; (crossover* OR cross-over*).tw; 63482 results. 42. EMBASE; (doubl* adj3 blind*).tw; 132426 results. 43. EMBASE; (singl* adj3 blind*).tw; 14790 results. 44. EMBASE; assign*.tw; 212522 results.	39	

	45. EMBASE; allocat*.tw; 71825 results. 46. EMBASE; volunteer*.tw; 161787 results. 47. EMBASE; CROSSOVER PROCEDURE/; 35555 results. 48. EMBASE; DOUBLE-BLIND PROCEDURE/; 111920 results. 49. EMBASE; SINGLE-BLIND PROCEDURE/; 16668 results. 50. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 332920 results. 51. EMBASE; 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50; 1257260 results. 52. EMBASE; NIGHTMARE/; 3166 results. 53. EMBASE; 33 OR 34 OR 35 OR 52; 129968 results. 54. EMBASE; 27 AND 32 AND 51 AND 53; 39 results.		
MedLine	1 MEDLINE "randomized controlled trial".pt 2 MEDLINE "controlled clinical trial".pt 84256 3 MEDLINE randomi?ed.ab 286706 4 MEDLINE placebo.ab 135476 5 MEDLINE "drug therapy".fs 1521839 6 MEDLINE randomly.ab 175750 7 MEDLINE trial.ab 249075 8 MEDLINE groups.ab 1153146 9 MEDLINE 1 OR 2 OR 3 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 2918219 10. MEDLINE; PRAZOSIN/; 7350 results. 11. MEDLINE; prazosin.ti,ab; 9922 results. 12. MEDLINE; hypovase.ti,ab; 1 results. 13. MEDLINE; 10 OR 11 OR 12; 11981 results. 14. MEDLINE; PTSD.ti,ab; 10448 results. 15. MEDLINE; "posttraumatic stress".ti,ab; 9740 results.	22	

	16. MEDLINE; "post-traumatic stress".ti,ab; 5464 results. 17. MEDLINE; STRESS DISORDERS, POST-TRAUMATIC/; 18876 results. 18. MEDLINE; 14 OR 15 OR 16 OR 17; 23165 results. 19. MEDLINE; nightmare*.ti,ab; 1892 results. 20. MEDLINE; dream*.ti,ab; 7988 results. 21. MEDLINE; sleep.ti,ab; 92552 results. 22. MEDLINE; 19 OR 20 OR 21; 100312 results. 23. MEDLINE; 9 AND 13 AND 18 AND 22; 22 results.		
Summary	**NA**	**NA**	

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