BEST in Mental Health
BEST.awp.nhs.uk

Best Evidence Summaries of Topics in Mental Healthcare

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

Question

"In adults with frontotemporal dementia presenting with agitation, how effective are pharmacological interventions, compared to treatment as usual, in managing agitation?"

Clarification of question using PICO structure

Patients:	Adults with frontotemporal dementia presenting with agitation
Intervention:	Pharmacological interventions
Comparator:	Treatment as usual
Outcome:	Agitation

Email: awp.BESTinMH@nhs.net Phone: 0117 378 4232/4233/4335 @BESTinMH

Clinical and research implications

There is some weak evidence, from four very small randomised controlled trials (RCTs), that pharmacological interventions may have some effect on behavioural symptoms in people with frontotemporal dementia. Each of the four studies assessed a different intervention (paroxetine, trazodone, memantine, and single dose oxytocin) all of which showed some potential for the treatment of behavioural symptoms in frontotemporal dementia. Only trazodone showed a significant treatment effect specific to agitation, however, it should be noted that these data were derived from one very small, shot-term crossover trial.

Larger scale, high quality parallel group RCTs are needed to confirm the initial observations reported in this evidence summary. Future trials should include long-term follow-up and direct comparisons of these and other pharmacological interventions.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified four small randomised controlled trials (RCTs), which provided data relevant to this evidence summary.[1,2,3,4] Two of the studies were short term, crossover trials;[2,3] one compared trazodone (150-300 mg/day) to placebo over two six week treatment periods,[2] and the other compared a single, 24 IU intra-nasal does of oxytocin to placebo.[3] The remaining two studies were parallel group trails conducted over approximately one year; one compared paroxetine (20 mg/day) to piracetam (1,200 mg/day),[1] and the other compared memantine (10 mg bid) to placebo.[4] Two studies were conducted in patients with frontotemporal dementia according to Lund and Manchester criteria,[1,2] and two were conducted in patients who met Neary's criteria for behavioural variant frontotemporal dementia.[3,4] All studies reported a variety of outcome measures including measures of cognitive function and depression, as well as behavioural measures which include items for aggitation (Neuropsychiatric Inventory (NPI),[1,2,3,4] Behavioural Pathology in Alzheimer's Disease rating Scale (BEHAVE-AD),[1] and Frontal Behaviour Inventory (FBI)[3,4]). Two studies reported data for individual items on the behaviour scores.[2,3]

Main Findings

All studies found some limited evidence of a possible treatment effect. The trial comparing paroxetine to piracetam found that paroxetine was associated with significant improvement, in terms of change from baseline to 14 month, in both NPI (-8.25) and BEHAVE-AD (-2.50), however, no data were reported specifically for agitation.[1] The trial comparing memantine with placebo found no significant differences over one year, with the exception that FBI score increased more rapidly in the placebo group.[4] The crossover trial comparing trazodone to placebo found that trazodone was associated with a statistically significant decrease in NPI score, over six weeks, compared to placebo; this study also reported a significant treatment effect for the agitation item of the NPI score.[2] Finally, the crossover trail which assessed the effects of single dose of oxytocin found a significant acute (8 hours after administration) treatment effect (difference in total NPI score between oxytocin and placebo, -2.70 (95% CI: -5.29 to -0.11)), however, this effect was not significant for FBI score, or for individual items on the NPI or FBI, and did not persist at one week post-administration.[3]

Authors Conclusions

The authors of the studies of paroxetine, oxytocin and memantine concluded that these drugs showed some potential promise for the treatment of frontotemporal dementia, but that further research is needed. The authors of the trazodone trial concluded that their results suggest that trazodone is an effective treatment for the behavioural symptoms of frontotemporal dementia.

Reliability of conclusions/Strength of evidence

All four of the trials included in this evidence summary were very small and reporting of study methods, particularly with respect to methods of randomisation and allocation concealment, was generally weak. The limited evidence available suggests that paroxetine,[1] trazodone,[2], oxytocin,[3] and memantine[4] may all have some potential for the treatment of behavioural symptoms in frontotemporal dementia. Only trazodone showed a significant treatment effect specific to agitation, however, it should be noted that these data were derived from one very small, shot-term crossover trial.[2]

What do guidelines say?

NICE guidelines for dementia (CG 42, 2006) makes the following recommendations for dealing with agitation, although does not refer specifically to a diagnosis of frontotemporal dementia;

'Behaviour that challenges' encompasses a wide range of difficulties that are often experienced by people with dementia and that may have an effect on those who provide care. It may include aggression, agitation, wandering, hoarding, sexual disinhibition, apathy and disruptive vocal activity such as shouting.' (pp.29)

'People with dementia who develop non-cognitive symptoms or behaviour that challenges should be offered a pharmacological intervention in the first instance only if they are severely distressed or there is an immediate risk of harm to the person or others. The assessment and care-planning approach, which includes behavioural management, should be followed as soon as possible (see recommendation 1.7.1.1). If distress and/or agitation are less severe, the interventions described in recommendations 1.7.1.2, 1.8.1.2 and 1.8.1.3 should be followed before a pharmacological intervention is considered.' (pp.30)

"Healthcare professionals who use medication in the management of violence, aggression and extreme agitation in people with dementia should:
be trained in the correct use of drugs for behavioural control, specifically benzodiazepines and antipsychotics

- be able to assess the risks associated with pharmacological control of violence, aggression and extreme agitation, particularly in people who may be dehydrated or physically ill
- understand the cardiorespiratory effects of the acute administration of benzodiazepines and antipsychotics and the need to titrate dosage to effect
- recognise the importance of nursing people who have received these drugs in the recovery position and of monitoring pulse, blood pressure and respiration
- be familiar with and trained in the use of resuscitation equipment
- undertake annual retraining in resuscitation techniques
- understand the importance of maintaining an unobstructed airway." (pp.33)

“For people with dementia who are at significant risk to themselves or others because of violence, aggression and extreme agitation, immediate management should take place in a safe, low-stimulation environment, separate from other service users.”

“Drug treatments for the control of violence, aggression and extreme agitation should be used to calm the person with dementia and reduce the risk of violence and harm, rather than treat any underlying psychiatric condition. Healthcare professionals should aim for an optimal response in which agitation or aggression is reduced without sedation.”

“Violent behaviour should be managed without the prescription of high doses or combinations of drugs, especially if the person with dementia is elderly or frail. The lowest effective dose should be used.”

“Drugs for behavioural control should be used with caution, particularly if the person with dementia has been restrained, because of the following risks:

- loss of consciousness instead of sedation
- over-sedation with loss of alertness
- damage to the relationship between the person with dementia, their carers and the health and social care team
- specific issues related to age and physical and mental health.”

“People with dementia who have received involuntary sedation and their carers should be offered the opportunity to discuss their experiences and be provided with a clear explanation of the decision to use urgent sedation. This should be documented in their notes.” (pp.34)

“If drugs are necessary for the control of violence, aggression and extreme agitation, oral medication should be offered before parenteral medication.”

“If parenteral treatment is necessary for the control of violence, aggression and extreme agitation, the intramuscular (IM) route should be preferred because it is safer than intravenous administration. Intravenous administration should be used only in exceptional circumstances.”

“Vital signs should be monitored after parenteral treatment for the control of violence, aggression and extreme agitation. Blood pressure, pulse, temperature and respiratory rate should be recorded at regular intervals agreed by the multidisciplinary team until the person with dementia becomes active again. If the person appears to be or is asleep, more intensive monitoring is required.” (pp.35)

The evidence included in this summary is consistent with current guidelines.

Date question received: 31/03/2014
Date searches conducted: 07/04/2014
Date answer completed: 05/05/2014

References

Randomised controlled trials

1. Moretti R, Torre P, Antonello RM, et al. Frontotemporal Dementia: Paroxetine as a Possible Treatment of Behavioural Symptoms. European Neurology 2003;49:13-19.
2. Lebert F, Stekke W, Hasenbroekx C and Pasquier F. Frontotemporal Dementia: A Randomized, Controlled Trial with Trazodone. Dementia and Geriatric Cognitive Disorders 2004;17(4):355-359.
3. Jesso S, Morlog D, Ross S, et al. The effects of oxytocin on social cognition and behaviour in frontotemporal dementia. Brain 2010;134:2493-2501.
4. Vercelletto M, Boutoleau-Bretonnière C, Volteau C, et al. Journal of Alzheimer's Disease 2011;23:749-759.

Guidelines

National Institute for Health and Care Excellence (2006) Dementia. Supporting people with dementia and their carers in health and social care. CG42. London: National Institute for Health and Care Excellence. http://www.nice.org.uk/nicemedia/live/10998/30318/30318.pdf

Results

Randomised controlled trials

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Moretti et al. (2003)	*Participants:* Men and women aged 60-70 years with a diagnosis of dementia according to DSM-IV, who satisfied the criteria for probable fronto-temporal dementia according to Lund and Manchester criteria. Patients with a history of significant head trauma, alcoholism, movement disorder, or any other condition known to impair frontal lobe function were excluded. *Intervention:* Paroxetine 20 mg/day (titrated from 10 mg/day over the first two weeks). *Comparator*: Piracetam 1,200 mg twice a day. *Outcomes:* Global cognitive function (MMSE), executive and planning function (TPC, Proverb Interpretation Tasks and the Stroop Test), behavioural performance (NPI, CIR, Cornell Scale for Depression in Dementia, BEHAVE-AD) and caregiver's stress (RRS).	n=16 (paroxetine n=8, piracetam n=8)	No clear statement of a research objective was provided. The study compared treatment with paroxetine to treatment with piracetam over a period of 14 months; participants in both groups were allowed to continue with any previous treatments. There were no apparent differences between the groups, at baseline, in age, gender distribution, level of education, measures of cognitive and behavioural function, or neuroleptic intake. The study included 10 women and 6 men, with a mean age 64.6 ± 4.6 years and a mean educational level of 8.5 ± 2.5 years. The mean duration of symptoms was 8.6 ± 2.6 months. *Behavioural measures which include a measure of agitation:* At 14 months, participants in the paroxetine group showed a statistically significant improvement from baseline in Neuropsychiatric Inventory (NPI) score (-8.25 ± 1.6), where as patients in the piracetam group showed a deterioration (5.0 ± 1.0), $p < 0.01$. Similar results were seen for the Behavioural Pathology in Alzheimer's Disease rating Scale (BEHAVE-AD), where participants in the paroxetine group showed an	No details of the randomisation procedure or allocation concealment were reported. No details of blinding of study personnel, participants, or outcome assessors were reported. No patient withdrew from either group before the end of the study

			improvement from baseline of -2.5 ± 0.2, compared with a deterioration of 13.075 ± 2.12 for patients in the piracetam group, $p < 0.01$. Data were not reported for the individual items of the two scores; 50% of patients in the piracetam groups reported increasing agitation and aggressiveness throughout the study.	and outcomes data appear to have been reported for all participants. Results were reported for all specified outcome measures.
Lebert et al. (2004)	*Participants:* Frontotemporal dementia according to the Lund and Manchester group criteria, with a total score of >3 on the Frontal Behavioural Dysfunction Scale and a total score of >8 on the NPI. Exclusion criteria were: major depression; evidence of addiction; neuroleptics or antidepressants taken in the previous four weeks; poorly controlled concomitant illness. *Intervention:* Trazodone 150 mg/day for 3 weeks (titrated from 50 and 100 mg/day over 6 days), dose increased to 300 mg/day if no side effects were reported at 3 weeks. *Comparator:* Placebo *Outcomes:* Behavioural disturbances (NPI),	n=31 (crossover trial)	The study aimed to assess the effectiveness of trazodone for the treatment of behavioural and cognitive symptoms in people with frontotemporal dementia. The study was a randomised, double-blind, crossover trial. Outcome assessments were conducted on the last day of each six weak treatment period. There was no washout period because of the relatively short half-life of trazodone. Sixteen men and 15 women were included in the study. The mean age of participants was 61.7 years. The mean baseline NPI score was 53 ± 17.9 and the mean Mini Menatl State Examination (MMSE) score was 20.8 ± 8.3. *Behavioural measures which include a measure of agitation:* There was a statistically significant decrease in total NPI score after trazodone treatment compared with placebo, $p = 0.028$;	No details of the randomisation procedure or allocation concealment were reported. The study was described as 'double-blind' and assessment of side-effects was described as 'recorded

	clinical impression (CG-I) and MMSE.		in the placebo-trazedone group the mean total NPI score was 55.9 at baseline, 48.64 and 6 weeks and 34.6 at the end of the trial, and in the trazedone-placebo group the mean total NPI score was 55.7 at baseline, 30,4 at 6 weeks and 39.1 at the end of the trial. When individual items of the NPI were considered, significant treatment effects were observed for the agitation (p = 0.04), irritability (p = 0.04), appetite modification (p = 0.002), and depression (p = 0.02) items.	blindly'. All analyses were conducted on an intention-to-treat basis. Results were reported for all specified outcome measures.
Jesso (2010)	*Participants:* Frontotemporal dementia according to the Neary criteria for diagnosis of behavioural variant FTD and MRI, CT or single-photon emission CT imaging consistent with the diagnosis. All had emotional blunting features. Exclusion criteria: comprehension deficits or language impairment that would preclude task completion; history of stroke, tumour or other focal brain lesion; history of other neurological or psychiatric disorder; uncontrolled hypertension; current use of prostaglandins or use of any investigational or experimental drug or device within the previous 60 days. *Intervention:* Oxytocin, one dose of 24 IU,	n=20 (crossover trial)	The study aimed to assess the effects of a single dose of intranasal oxytocin on neuropsychiatric behaviours and emotion processing in patients with behavioural variant frontotemporal dementia. The study was a randomised, double-blind, crossover trial. Outcomes were assessed 20 minutes after administration of nasal solution and patients returned after two weeks to receive the alternate medication and the same outcome assessments administered in the same order. Twenty participants, with a mean age of 64.4 ± 7.4 years (gender distribution not reported) were included in the study. The mean duration of education was 12.9 ± 3.3 years and the mean duration of illness was 5.0 ± 3.2 years. The mean NPI score at baseline was 32.0 ± 2.9 and the mean	No details of the randomisation procedure or allocation concealment were reported. The study was described as 'double-blind', but no details of blinding of outcome assessors were

	intra-nasally. *Comparator:* Placebo *Outcomes:* Emotional recognition (The Facial Expression Recognition and Intensity task, vocal affect recognition task, the Mind in the Eyes task), behaviour (NPI, the Frontal behavioural Inventory).		Frontal Behaviour Inventory (FBI) score was 37.7 ± 9.8. *Behavioural measures which include a measure of agitation:* There was a statistically significant difference in total NPI score between oxytocin and placebo, -2.70 (95% CI: -5.29 to -0.11) $p < 0.05$, on day 1 (8 hours after administration); there was no significant difference between oxytocin and placebo at 1 week post-administration. There was a trend towards improved FBI score for oxytocin compared to placebo on day 1 (-1.85), however, the difference did not reach statistical significance; there was no significant difference between oxytocin and placebo at 1 week post-administration. Data were reported for the individual items on both the NPI and FBI score, but no statistically significant differences between oxytocin and placebo were reported for any single item.	reported. There were no dropouts from the study and all patients completed behavioural outcome assessments. Results were reported for all specified outcome measures.
Vercelletto et al. (2011)	*Participants:* Ambulatory patients aged 45-75 years who met Neary's criteria for behavioural variant frontotemporal dementia (evolving for at least one year) and had an MMSE score of ≥19, Frontotemporal Behavioural Scale score >3, and Montogomery Depression Assessment Rating Scale <20. Patients with the tvFTD (semantic dementia or progressive non-fluent aphasia) or motoneuron disease involvement and patients treated with an	n=49 (n=23 memantine, n=26 placebo)	This study aimed to assess the efficacy and tolerability of one year treatment with memantine for behavioural variant frontotemporal dementia. There were no apparent differences between the groups, at baseline, in age, gender distribution, level of education, or measures of cognitive and behavioural function. The mean age of study participants was 65.6 years and mean MMSE score was 25.0 (range 19–30). *Behavioural measures which include a measure of agitation:* There were no statistically significant differences between	Randomisation used a list of random numbers. Mementine and placebo were identically packaged to ensure blinding of

	acetylcholinesterase inhibitor were excluded. *Intervention:* Memantine 10mg (bid) *Comparator:* Placebo *Outcomes:* Global change (CIBIC-Plus), behaviour (NPI, FBI, MDRS, DAD, ZBI)		memantine and placebo, at one year compared to baseline, on either total NPI score or total FBI score. There was no significant interaction between time and treatment group for total NPI score, but the mean FBI score increased more rapidly in the placebo group than in the memantine group (p=0.0417). No data were reported for the individual items of the two scores.	participants and personnel throughout the study. Outcome assessments were conducted blind to other aspects of the trail and to other outcome measure. All effectiveness analyses were conducted on an intention-to-treat basis. Results were reported for all specified outcome measures.

Risk of Bias

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
Moretti et al. (2003)	?	?	?	?	☺	☺
Lebert et al. (2004)	?	?	☺	☺	☺	☺
Jesso (2010)	?	?	☺	?	☺	☺
Vercelletto et al.(2011)	?	?	☺	☺	☺	☺

☺ Low Risk ☹ High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Dementia	73	1
DARE	MeSH DESCRIPTOR Violence EXPLODE ALL TREES 161 Delete 2 MeSH DESCRIPTOR Aggression EXPLODE ALL TREES 51 Delete 3 MeSH DESCRIPTOR Psychomotor Agitation EXPLODE ALL TREES 33 Delete 4 MeSH DESCRIPTOR Frontotemporal Dementia EXPLODE ALL TREES 3 Delete 5 (dement*) IN DARE 550 Delete 6 MeSH DESCRIPTOR Frontotemporal Lobar Degeneration EXPLODE ALL TREES 3 Delete 7 (ftd OR ftld) IN DARE 1 Delete 8 (aggress* Or violen* OR agitat*) IN DARE 470 Delete 9 #1 OR #2 OR #3 OR #8 599 Delete 10 #4 OR #5 OR #6 OR #7 551 Delete 11 #9 AND #10	59	0
Primary studies			
CENTRAL	#1 "frontotemporal dementia" 95 #2 "picks disease" 5 #3 "frontal lobe dementia" 8 #4 #1 or #2 or #3 102 #5 MeSH descriptor: [Frontotemporal Lobar Degeneration] explode all trees 14 #6 MeSH descriptor: [Frontotemporal Dementia] explode all trees 9 #7 #4 or #5 or #6 107 #8 MeSH descriptor: [Drug Therapy] explode all trees 116511 #9 medication 39567	4	

	#10 #8 or #9 146425 #11 #7 and #10 28 Central only 4		
PsycINFO	1. PsycINFO; PICKS DISEASE/; 248 results. 2. PsycINFO; "frontotemporal dementia".ti,ab; 1980 results. 3. PsycINFO; FRONTOTEMPORAL DEMENTIA/; 851 results. 4. PsycINFO; "frontal lobe dementia".ti,ab; 120 results. 5. PsycINFO; 1 OR 2 OR 3 OR 4; 2684 results. 6. PsycINFO; DRUG THERAPY/; 105999 results. 7. PsycINFO; medication.ti,ab; 44407 results. 8. PsycINFO; PHARMACOLOGY/ OR DRUGS/ OR PSYCHOPHARMACOLOGY/; 39952 results. 9. PsycINFO; NOOTROPIC DRUGS/; 540 results. 10. PsycINFO; 6 OR 7 OR 8 OR 9; 160730 results. 11. PsycINFO; 5 AND 10; 125 results. 12. PsycINFO; CLINICAL TRIALS/; 7431 results. 13. PsycINFO; random*.ti,ab; 128162 results. 14. PsycINFO; groups.ti,ab; 363350 results. 15. PsycINFO; (double adj3 blind).ti,ab; 17726 results. 16. PsycINFO; (single adj3 blind).ti,ab; 1389 results. 17. PsycINFO; EXPERIMENTAL DESIGN/; 9004 results. 18. PsycINFO; controlled.ti,ab; 79731 results. 19. PsycINFO; (clinical adj3 study).ti,ab; 7852 results. 20. PsycINFO; trial.ti,ab; 67492 results. 21. PsycINFO; "treatment outcome clinical trial".md; 26531 results. 22. PsycINFO; 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21; 562130 results. 23. PsycINFO; 11 AND 22; 41 results.	41	
Embase	12. EMBASE; PICKS DISEASE/; 999 results.	20	

	13. EMBASE; "frontotemporal dementia".ti,ab; 4505 results. 14. EMBASE; FRONTOTEMPORAL DEMENTIA/; 6934 results. 15. EMBASE; "frontal lobe dementia".ti,ab; 175 results. 16. EMBASE; 12 OR 13 OR 14 OR 15; 8605 results. 17. EMBASE; DRUG THERAPY/; 282330 results. 18. EMBASE; medication.ti,ab; 185222 results. 19. EMBASE; PHARMACOLOGY/ OR DRUGS/ OR PSYCHOPHARMACOLOGY/; 93113 results. 20. EMBASE; NOOTROPIC DRUGS/; 0 results. 21. EMBASE; 17 OR 18 OR 19 OR 20; 508909 results. 22. EMBASE; 16 AND 21; 110 results. 23. EMBASE; random*.ti,ab; 857840 results. 24. EMBASE; factorial*.ti,ab; 22365 results. 25. EMBASE; (crossover* OR cross-over*).ti,ab; 67336 results. 26. EMBASE; placebo*.ti,ab; 194043 results. 27. EMBASE; (doubl* ADJ blind*).ti,ab; 138491 results. 28. EMBASE; (singl* ADJ blind*).ti,ab; 13991 results. 29. EMBASE; assign*.ti,ab; 232265 results. 30. EMBASE; allocat*.ti,ab; 81122 results. 31. EMBASE; volunteer*.ti,ab; 172148 results. 32. EMBASE; CROSSOVER PROCEDURE/; 38388 results. 33. EMBASE; DOUBLE BLIND PROCEDURE/; 112516 results. 34. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 339246 results. 35. EMBASE; SINGLE BLIND PROCEDURE/; 18063 results. 36. EMBASE; 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35; 1373179 results. 37. EMBASE; 22 AND 36; 20 results.		
Medline	12. MEDLINE; PICKS DISEASE/; 368 results. 13. MEDLINE; "frontotemporal dementia".ti,ab; 3412 results.	20	

	14. MEDLINE; FRONTOTEMPORAL DEMENTIA/; 910 results. 15. MEDLINE; "frontal lobe dementia".ti,ab; 142 results. 16. MEDLINE; 12 OR 13 OR 14 OR 15; 3944 results. 17. MEDLINE; DRUG THERAPY/; 27823 results. 18. MEDLINE; medication.ti,ab; 131614 results. 19. MEDLINE; PHARMACOLOGY/ OR DRUGS/ OR PSYCHOPHARMACOLOGY/; 78004 results. 20. MEDLINE; NOOTROPIC DRUGS/; 3430 results. 21. MEDLINE; 17 OR 18 OR 19 OR 20; 234385 results. 22. MEDLINE; 16 AND 21; 35 results. 23. MEDLINE; "randomized controlled trial".pt; 370214 results. 24. MEDLINE; "controlled clinical trial".pt; 88117 results. 25. MEDLINE; randomized.ab; 290114 results. 26. MEDLINE; placebo.ab; 152726 results. 27. MEDLINE; "drug therapy".fs; 1685874 results. 28. MEDLINE; randomly.ab; 210334 results. 29. MEDLINE; trial.ab; 301241 results. 30. MEDLINE; groups.ab; 1340667 results. 31. MEDLINE; 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30; 3307708 results. 32. MEDLINE; 22 AND 31; 20 results.		
Summary	**NA**	**NA**	

Disclaimer

BEST in MH answers to clinical questions are for information purposes only. BEST in MH does not make recommendations. Individual health care providers are responsible for assessing the applicability of BEST in MH answers to their clinical practice. BEST in MH is not responsible or liable for, directly or indirectly, any form of damage resulting from the use/misuse of information contained in or implied by these documents. Links to other sites are provided for information purposes only. BEST in MH cannot accept responsibility for the content of linked sites.

© Best Evidence Summaries of Topics in Mental Health 2013