Management of Neuropsychiatric Symptoms in Dementia: A Best Practice Guide

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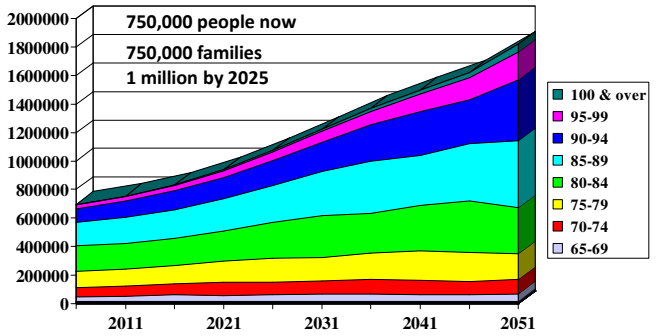
Exploring new directions



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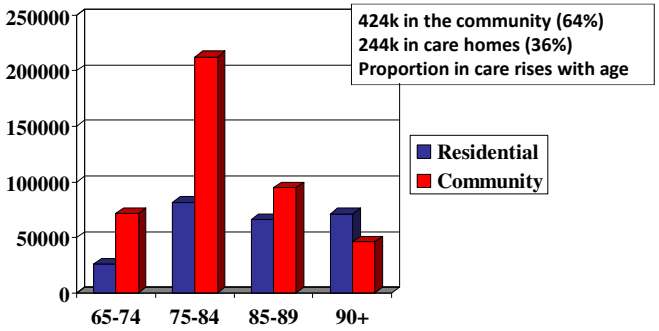
Dementia UK results

Where are people with dementia?



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Non AD dementias

- Vascular dementia (VaD) – Some VaD patients in 2 risperidone* studies, but no separate analysis and no specific trials of VaD. Cochrane review of memantine* in VaD indicates modest but significant benefit on NPI.
- DLB/PDD – only 1 RCT (with quetiapine**), showing no significant benefit. Serious potential concerns re neuroleptic sensitivity. Several trials suggesting some benefit in DLB/PDD with rivastigmine.
  One poster of RCT indicating benefit of Pimavanserin*** in PD psychosis
- Marked need for treatment studies examining treatment of neuropsychiatric symptoms in non-AD dementias

*Memantine, risperidone are not licensed for VaD,** quetiapine is not licensed in DLB/PDD.
***Pimavanserin is an investigational product

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Risperidone* Efficacy: BEHAVE-AD

Ballard & Howard 2006 Nature Neuroscience Reviews

	Target symptom	Mean Difference from placebo	p value	95% CI
Risperidone 1mg	Psychosis	-0.79	p=0.03	-1.31 to -0.27
Risperidone 1mg	Aggression	-0.84	p=0.0002	-1.28 to -0.40
Risperidone 2mg	Aggression	-1.50	p<0.0001	-2.05 to -0.95

*Risperidone is licensed for the short term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non pharmacological interventions and when there is a risk of harm to self or others

Ballard & Howard 2006. Nature Neuroscience Reviews

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STAR TRIAL: Zhong et al 2007

	Quetpiapine* 200mg (N=114)	Quetiapine 100mg (N=120)	Placebo (N=92)	Evaluation
PANSS-EC	-5.7 (0.9)	-4.9 (0.8)	-3.9 (0.9)	NS
NPI (total)	-9.7 (2.2)	-8.9 (2.1)	-8.2 (2.4)	NS
NPI (agitation)	-1.1 (0.5)	-0.9 (0.5)	-1.2 (0.5)	NS
NPI (psychosis)	-2.5 (0.9)	-1.8 (0.8)	-2.5 (0.9)	NS
CGIC	3.0 (0.2)	3.2 (0.2)	3.6 (0.2)	NS

*Quetiapine is not licensed for use in dementia

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Adverse events with Risperidone

Ballard & Howard 2006, Nature Neuroscience Reviews

Adverse events	Dose / day	Risperidone	Placebo	Odds Ratio	95% CI	P Value
Extra pyramidal symptoms	1mg	32 / 500	20 / 571	1.78	1.00 to 3.17	p<0.05
	2mg	35 / 165	12 / 163	3.39	1.69 to 6.80	p=0.0006
Gait	1mg	21 / 402	1 / 408	7.47	2.21 to 25.28	p=0.001
Somnolence	1mg	138 / 665	72 / 685	2.36	1.71 to 3.24	p<0.00001
	2mg	46 / 165	13 / 163	2.36	2.30 to 8.64	p<0.00001
Respiratory tract infection	1mg	15 / 149	6 / 163	2.93	1.11 to 7.76	p=0.03
fever	2mg	24 / 165	12 / 163	2.14	1.03 to 4.44	p=0.04
Peripheral oedema	0.5mg	24 / 149	9 / 163	3.29	1.47 to 7.32	p=0.004
	1mg	32 / 315	15 / 333	2.43	1.29 to 4.59	p=0.006
	2mg	30 / 165	9 / 163	3.80	1.74 to 8.29	p=0.0008

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Major Adverse Outcomes with antipsychotics over 6-12 weeks (Schneider et al 2005,Ballard et al 2009)

- Parkinsonism
- Sedation
- Gait disturbance
- Increased respiratory infections
- Oedema
- Accelerated cognitive decline
- Stroke (>3 fold)
- Other thrombo-embolic events
- Mortality (1.5-1.7 fold)

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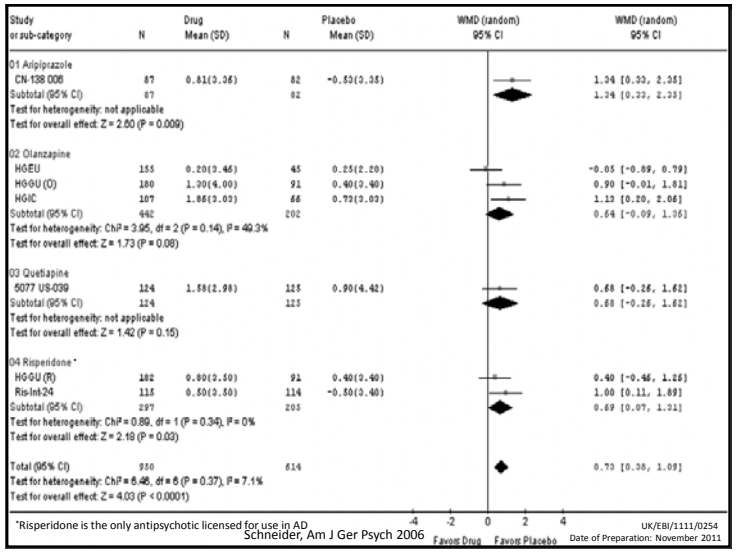

*Risperidone is the only antipsychotic licensed for use in AD

Schneider, Am J Ger Psych 2006

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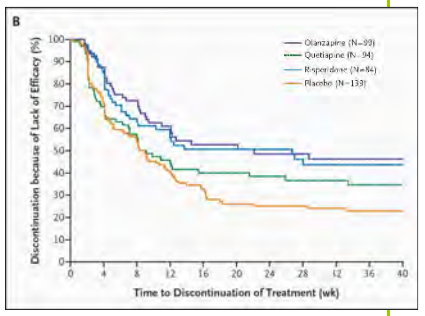
Responses to atypical antipsychotics

- Response** based on CGIC score at 12 weeks:
  - 32% Olanzapine group
  - 26% Quetiapine group
  - 29% Risperidone group
  - 21% placebo group
- Overall comparison: p=0.22



** A response was defined as continued treatment with the original phase 1 study drug and at least minimal improvement on the CGIC.

Schneider L et al. New England Journal of Medicine 2006; 355:1525-38

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Change from Baseline to 6 months

Total NPI	(n=56) 1.3 (15.5)	(n=53) 4.5 (17.6)	-2.4 (-8.2 to 3.5)[3]	0.4
MUPDRS	(n=41) 0.8 (4.1)	(n=43) -0.4 (3.2)	1.3 (-0.4 to 3.0)[4]	0.1
Bristol ADL	(n=54) 1.8 (8.9)	(n=52) 0.2 (7.2)	1.7 (-1.2 to 4.6)[3]	0.2
Change in FAST[5] **-2** **-1** **0** **1** **2**	(n=53) 0 3 34 12 4	(n=53) 1 4 32 8 8		0.9
CGIC[5] **Very much improved** **Much improved** **Minimally improved** **No change** **Minimally worse** **Much worse** **Very much worse**	(n=48) 1 (2%) 3 (6%) 7 (15%) 18 (37%) 9 (19%) 7 (15%) 3 (6%)	(n=48) 0 0 14 (29%) 14 (29%) 10 (21%) 10 (21%) 0		0.9

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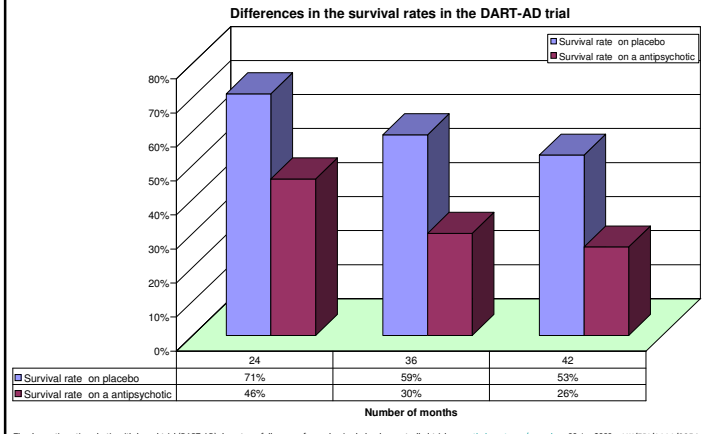
Differential Survival



The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. www.thelancet.com/neurology 09 Jan 2009

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Why do people die?

- Causes of death (Ballard et al 2010)
  - Pneumonia
  - Stroke
  - Pulmonary embolism
  - Sudden cardiac arrythmias
- Likely Mediating Factors
  - Dehydration
  - Chest infection
  - Over sedation
  - Q-T prolongation

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Impact of Antipsychotics on Quality of Life (QOL)

	% with poor QOL (Il-being)
No Antipsychotics	5%
Atypical antipsychotics	10%
Typical Antipsychotics	22%

Ballard et al 2001 BMJ: On average a resident with dementia in a care home Only spent 13% of waking day engaged in social interaction or a positive activity

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FITS: Stopping Neuroleptics: Impact on Quality of Life

n=42	Baseline (sd)	Follow-up		Evaluation (Baseline v Follow-up)
		FITS (sd)	Control (sd)	
Social Withdrawal	6.64 (8.96)	-5.24 (13.56)	-1.29 (5.42)	T 2.1 p=0.04
Daytime sleep	-20.69 (23.24)	-6.20 (24.58)	-1.29 (24.38)	T 1.1 p=0.27
Type 1 Behaviours	+34.74 (19.53)	+13.44 (23.73)	+1.47 (24.29)	T 2.3 p=0.03
Wellbeing	0.65 (0.69)	+0.34 (0.59)	+0.15 (0.98)	T 2.2 p=0.03
CMAI	42.88 (14.57)	+0.75 (22.35)	+5.29 (12.74)	T 0.83 p=0.41

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Standardized tailored psychological treatment

- Cohen-Mansfield 2007 (n=167) Placebo controlled trial of personalized non-pharmacological interventions for 4 hours over days resulted in significant reduction in agitation (p=0.002)
- Cohen-Mansfield 1997 (n=58) Placebo controlled trial of "social interaction", music or simulated presence resulted in significant 25% reduction in abnormal vocalizations over 6 weeks

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Efficacy improves with severity of agitation

BPSD **"tool Box"** intervention from CALM-AD STUDY

N= 200	CMAI baseline	CMAI week 4	Evaluation (paired sample t test)
Overall	62.2±14.3	55.6±17.2	T=5.6 P<0.0001
Baseline CMAI <53	47.1±3.8	48.6±15.9	T=-0.7 P=0.46
Baseline CMAI 53-70	61.2±4.8	54.7±16.2	T=4.1 P<0.0001
Baseline CMAI >70	82.4±12.7	67.1±18.9	T=5.3 P<0.0001

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Intervention by a Clinical Psychologist

- **Bird et al 2009:** 44 consecutive referrals for challenging behaviour (2/3 in residential care). Assessment and interventions were undertaken in collaboration with family carers and care staff. Outcomes Measures taken pre-intervention and up to 5-month follow-up. Psychotropic medication was used with a minority of participants but, overall, antipsychotic use was reduced. Psychosocial methods predominated, with 77% of cases judged as mainly or entirely psychosocial by expert panel. There were significant improvements in behaviour and carer distress. Using conservative criteria there was a 65.9% clinical success rate.
- **Bird et al 2007:** 33 residential care clients with BPSD referred to a community psychogeriatric service (intervention group) received treatment with focus on causes of behavior (ABC). Cases were managed primarily by psychosocial means with psychopharmacology as an adjunct. A control group was made up of 22 referrals to an adjacent service, which used primarily psychopharmacology with psychosocial methods as an occasional adjunct. Measures of behavior showed significant improvement in both groups at two- and five-months' follow-up. Antipsychotic use in the intervention group decreased over time while in the control group it increased. Five control group participants spent extended periods as inpatients in a psychogeriatric unit.

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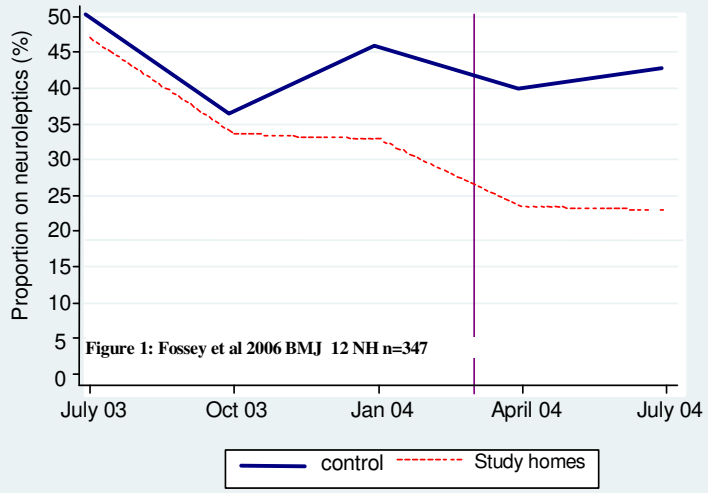

Figure 1: Fossey et al 2006 BMJ 12 NH n=347

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Chenoweth et al 2009 Lancet Neurology Person Centred Care: CADRES Study

- Two interventions: Person Centred Care Training and Dementia Care Mapping (DCM)
- 4 month cluster trial , 15 care homes, 289 residents with dementia
- Significant mean difference of 10.9 on CMAI (95% CI 0.7-21.1; p=0.04) was achieved with DCM and a difference of 13.6 on the CMAI (95% CI 3.3-23.9; p=0.01) with Person Centred Care Training
- Standardized Effect size of 0.55
- Neither intervention reduced antipsychotic use

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Neuropsychiatric Symptoms in AD: Potential Alternative Pharmacological Therapies

Sodium valproate*	Konovalov S *et al.* (Int Psychogeriatr 2008; 20:293-308). Systematic review identified 5 RCTs of valproate, none with significant benefit.
Carbamazepine*	2 small studies (73participants in total) 4-6 week RCT focusing on agitation/aggression, both with positive outcomes (Tariot et al 1998, Olin et al 201). Meta-analysis shows significant benefit on CGIC and BPSD (Ballard et al 2009). The Tariot trial does not discuss psychosis. The Olin trial describes the presence of "mild psychosis" and reports a significant improvement in hallucinations. Somner et al 2009 (n=103) trend to improvement of agitation with oxycarbazepine (p=0.07) . Hollis 2007 – no ↑ mortality.
Trazadone*	Meta-analysis (Martinon-Torres et al 2008): 2 trials, 1 parallel group, 1 cross-over. Insufficient evidence to recommend as a treatment
Citalopram*	In a 17-day trial of psychiatric inpatients with severe BPSD related to AD, Pollock and colleagues reported that citalopram was superior to placebo, with greatest efficacy for agitation/aggression, an effect not seen with perphenazine. In a later study, citalopram was found to be comparable in efficacy to risperidone, differentiated by its significant effect on agitation symptoms, and superior tolerability.

* not licensed for use in AD

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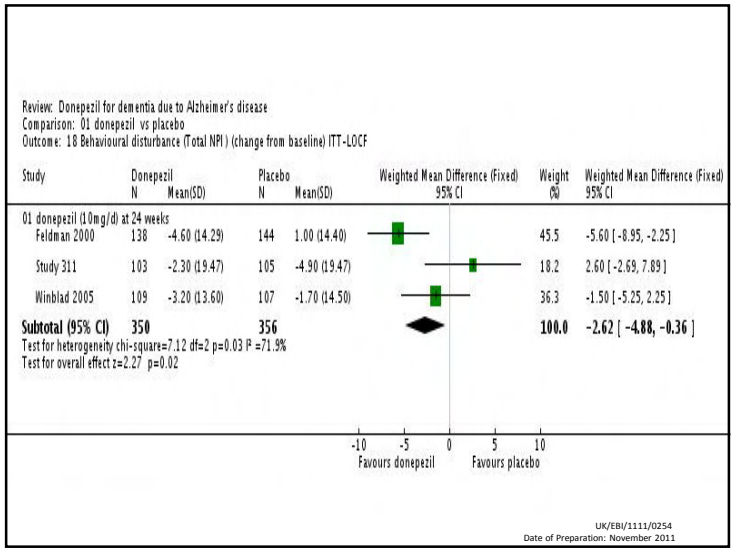

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CALM-AD NEJM 2007

Analysis of change in outcome from baseline to 12 weeks

Outcome (complete at T0 & T+12)	Mean change (standard deviation)[1]		Estimated Mean Difference in Change[2,v] (95% Confidence Interval)	p-value
	Placebo (n=131)	Donepezil (n=128)		
CMAI (all 29 items)	n=108 (82%) 4.99 (18.98)	n=113 (88%) 6.34 (20.35)	-0.064 (-4.35 to 4.22)[3] 0.18 (-4.22 to 4.59)[4]	0.98 0.94
NPI(S-12) (all 12 items)	n=97 (74%) 3.78 (17.75)	n=104 (81%) 3.56 (17.73)	-0.13 (-4.06 to 3.80)[3] 0.099 (-3.79 to 3.99)[4]	0.95 0.96
Carer Distress NPI(D-12) (all 12 items)	n=95 (73%) 1.29 (7.65)	n=105 (82%) 1.53 (7.44)	-0.20 (-1.86 to 1.47)[3] -0.45 (-2.06 to 1.15)[4]	0.82 0.58
SIB (all 51 items)	n=33 (25%) -4.82 (8.80)	n=27 (21%) 1.93 (11.14)	6.45 (1.07 to 11.83)[3] 7.26 (1.27 to 13.26)[4]	0.020 0.019
SMMSE (all 20 items)	n=57 (44%) -0.96 (3.86)	n=56 (44%) 0.54 (3.47)	1.55 (0.23 to 2.88)[3] 1.49 (0.14 to 2.84)[4]	0.022 0.031

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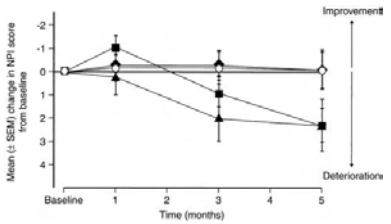
A 5-month, randomized, placebo-controlled trial of galantamine in AD
Tariot, P. N et al Neurology 54, 2269-2276, 2000



At 5 months, both the 16- and 24-mg/day groups had significantly better NPI total scores than placebo (OC and ITT analyses;$p < 0.05$, all comparisons).

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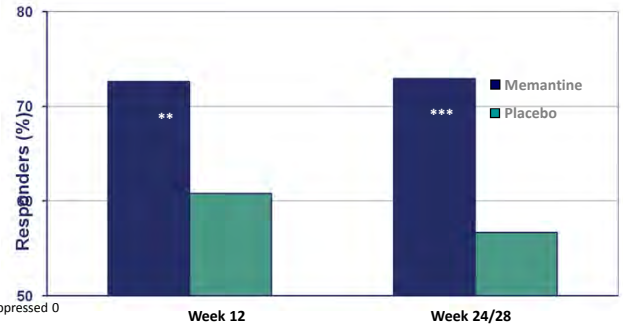
Behaviourally disturbed population (LOCF)

Percentage of patients with moderate to severe AD showing improvement or stabilisation on the NPI cluster at 12 and 24/28 weeks (mean NPI 22.9-24.2)



**p<0.01 ***p<0.001

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Memantine – Emerging Behavioural Symptoms

- Analysis of NPI data from key studies showed a significant reduction in the emergence of agitation/aggression by week 24/28 ($p<0.05$)[44]
- Pooled analysis of 3 trials showed significantly reduced emergence of behavioural symptoms in patients without symptoms at baseline[46]:
  - 20.3% versus 31.9% on placebo at week 12 (p=0.010)
  - 24.2% versus 37.0% on placebo at week 24/28 (p=0.007)
- Results consistent with meta-analysis of all NPI data[45]:
  - significantly fewer patients with symptoms of agitation/aggression at both week 12 and week 24/28 compared with placebo (p=0.002)
  - significantly fewer patients with emergent disinhibition and delusions at week 12 (p=0.011 and p=0.047, respectively)
  - significantly fewer patients with emergent irritability/lability and night-time behaviour at study end (p=0.004 and p=0.050, respectively)

44. Gauthier S, Wirth Y, Mobius HJ. Effects of memantine on behavioural symptoms in Alzheimer's disease patients: an analysis of the Neuropsychiatric Inventory (NPI) data of two randomised, controlled studies. *Int J Geriatr Psychiatry* 2005;**20:** 459–464.
45. Gauthier S, Loft H, Cummings JL. Improvement in behavioural symptoms in patients with moderate to severe Alzheimer's disease by memantine: a pooled data analysis. *Int J Geriatr Psychiatry* 2008:23/537-545
46. Wilcock GK, Ballard CG, Cooper JA, Loft H. Memantine for Agitation/Aggression and Psychosis in Moderately Severe to Severe Alzheimer's Disease: A Pooled Analysis of 3 Studies. *J Clin Psychiatry* 2008: 69:341-348

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BMJ

BMJ 2011;343:d4065 doi: 10.1136/bmj.d4065 Page 1 of 10

RESEARCH

Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial

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RESEARCH

Table 3 **Comparison of Cohen-Mansfield agitation inventory (CMAI) total score between control and intervention (stepwise protocol for treatment of pain) groups using repeated measures analysis of covariance (ANCOVA)***

	Mean (SD) CMAI total score		Effect of intervention on CMAI total†		Intracluster correlation coefficient‡
Week	Control group	Intervention group	Estimate (95% CI)	P value	
0	56.2 (16.1), n=177	56.5 (15.2), n=175	—	—	0.162
2	53.9 (17.0), n=161	52.0 (19.5), n=158	−3.6 (−0.5 to −6.7)	0.022	0.261
4	52.5 (16.3), n=160	49.4 (19.0), n=148	−4.1 (−0.9 to −7.4)	0.012	0.231
8	52.8 (16.8), n=157	46.9 (18.7), n=147	−7.0 (−3.7 to −10.3)	<0.001	0.226
12	52.5 (16.0), n=152	50.3 (20.3), n=142	−3.2 (0.1 to −6.4)	0.058	0.253

*Baseline score as covariate and least squares weighted by number of patients within cluster; P value from multivariate test of intervention was 0.002, and cross effect between week and intervention was <0.001.
†Variable estimate by week of effect of intervention on CMAI score from estimated model.
‡Proportion of total variance between clusters, and measured within framework of ANCOVA.

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Letter to Minister of State Professor Sube Bannerjee

- Some people benefit from these medications (eg where there is severe and complex risk) where trials have not been completed but there may be particular value in using these medications.
- I estimate that we are treating 180,000 people with dementia with antipsychotic medication across the country per year. Of these, up to 36,000 will derive some benefit.
- Negative effects that are directly attributable to the use of antipsychotic medication at this level equates to
  - 1,620 cerebrovascular adverse events, around half of which may be severe
  - an additional 1,800 deaths per year on top of those that would be expected in this frail population
- I estimate that we can reduce the rate of use of antipsychotic medication to a third of its current level over a 36 month period.

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A best practice guide for optimising treatment and care for people with behavioural and psychological symptoms of dementia (BPSD)

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Why do we need the guide?

- Numerous documents set out good principles for practice:
- But these are:
  - lengthy and impractical
  - don't enable implementation
- The BPSD best practice guide:
  - Provides an easy stepped-care approach based on a colour-coded traffic light system
  - Has been designed to aid BPSD management between primary and secondary care
  - Will increasingly be adopted for use in care homes
  - Will help to reduce inappropriate antipsychotic prescribing for people with dementia
  - Has been endorsed by numerous professional bodies

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- For access to the guide and to download, go to: http://www.alzheimers.org.uk/bpsdguide
- To access the reference list that supports the recommendations, go to: http://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=1675

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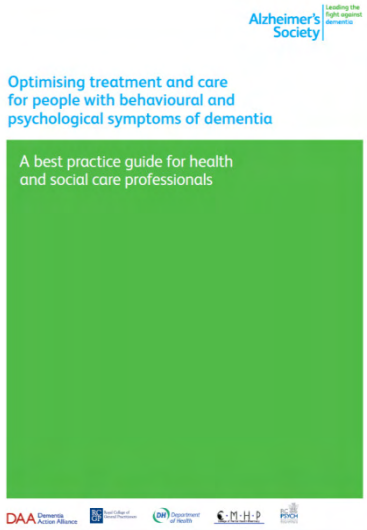

Stepped-care traffic light system

Green – No symptoms. Simple preventative measures	Prevention
Amber – Mild or moderate symptoms. Low intensity, general interventions	Watchful waiting
Red – Severe symptoms. Specific interventions and guidance for antipsychotic use	Specific interventions Antipsychotic prescription

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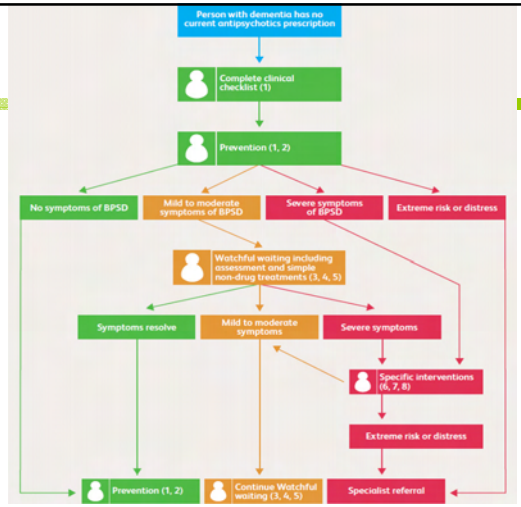

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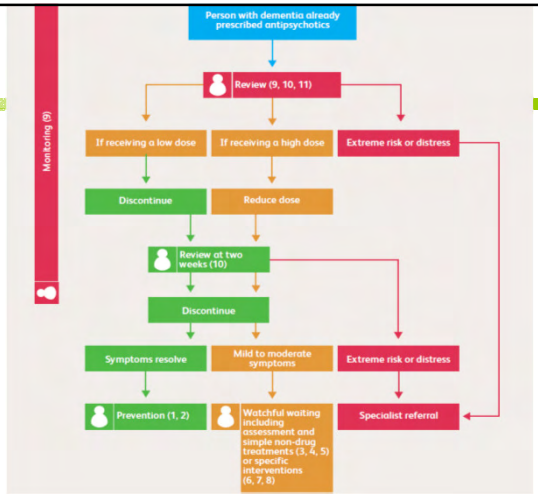

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Format of each section of the guide

1. Clinical checklist
2. Guidance
3. Clinical care plan

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Clinical checklist

Name: | Current diagnosis:

General symptoms
Include known symptoms and information based on person-centred care
(see 4: Watchful waiting guidance)

A recommended rating scale is the Clinical Global Impression of Change (CGIC) Scale (Appendix 1). If completed, enter score here:

Other Symptoms
Note any other significant symptoms in the relevant box. Optional rating scales are suggested for information (see 'Resources' on page 24).

Pain (Scale: Pain Rating Chart)

Depression (Scale: Cornell Scale)

Neuropsychiatric symptoms (Scale: Neuropsychiatric Inventory)

Delirium and confusion (Scale: Confusion Assessment Method)

Other relevant health problems

Signed: | Date:

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2 Prevention Guidance

- Understanding of dementia
- Medical review & recognition of triggers
- Person-centred care
- Physical environment
- Pharmacological treatment

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2 Prevention Guidance

- Medical review & triggers
  - Pain
  - UTI
  - Dehydration
  - Constipation
  - Malnourishment
  - Physical illness
  - Boredom
  - Neglect
- Person-centred care
  - Based on appreciation for the person with dementia:
    - Preferences, lifestyle, culture, history
    - Opportunity for stimulation, enjoyment and interaction
    - Viewing care from the patient perspective
    - Consultation with family/carer
    - Care plan to reflect to communication needs & ability
    - Dignity and respect

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2 Prevention Guidance

- Physical environment
  - Does the person recognise their immediate surrounding as 'home'
  - If the person is mobile, can they move around freely?
  - Is it too hot or cold?
  - Is there access to a radio or television?
  - Bed or chair care – is the person comfortable?
  - If the person has glasses or a hearing aid, are they clean and turned on/working correctly?
  - Is there access to assistive technology to improve safety?
- Pharmacological treatments
  - Acetylcholinesterase inhibitors (AChEIs); donepezil, galantamine and rivastigmine are licensed for mild to moderate Alzheimer's disease (AD)
  - The NMDA receptor antagonist, memantine is licensed for moderate to severe AD
  - There is some evidence that both groups may delay the onset of BPSD, providing additional benefit to using these currently available treatment options

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4 First line interventions, ongoing assessment and **watchful waiting** Guidance

- Medical review (as for prevention)
- Person-centred care (as for prevention)
- Soothing and creative therapies
- Simple non-drug treatments
- Sleep hygiene

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4 First line interventions, ongoing assessment and **watchful waiting** Guidance

- Soothing therapies & simple non-drug treatments
  - Music
  - Massage
  - Aromatherapy
  - Photographs / life story book
  - Singing
  - Dancing
  - Craft
  - Pets
  - Social interaction
  - Conversation
  - Exercise
- Sleep hygiene
  - Reduce daytime napping
  - Increase daytime activity
  - Promote regular eating intervals
  - Agree expectations for sleep duration
  - Create a calming environment conducive for sleep (darkened room free from noise)

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7 Specific interventions Guidance

- Medical review (as for prevention & watchful waiting)
- Psychosocial interventions (eg. ABC approach)
- Pharmacological treatment

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7 Specific interventions Guidance

- Pharmacological treatment
  - **Severe depression**
    - citalopram
  - **Sleep disturbance**
    - Hypnotic for short-term treatment such as zopiclone or zolpidem
  - **Agitation, aggression and psychosis**
    - Only very preliminary evidence for the benefit of non-antipsychotic drugs, though they may have a better safety profile (see reference 14)
  - **Analgesic**
    - paracetamol
  - **Alzheimer's treatments**
    - Donepezil, galantamine, rivastigmine and memantine may improve cognition in people with agitation.
  - **Antipsychotics**
    - Risperidone* for no longer than 6 weeks before review or specialist referral. NICE gives similar advice with a maximum treatment time of 12 weeks but recommends a cardiac risk assessment prior to treatment initiation
    - Evidence shows that quetiapine is ineffective in treating BPSD and cholinergic side-effects may be a particular concern
    - Antipsychotics should not be used in Lewy Body Dementia (LBD)

* Risperidone is indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.

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10 Antipsychotics prescription
Review guidance

- All antipsychotics should be reviewed at 6 and/or 12 weeks
- Unless there is severe risk or extreme distress, the recommended default management is to discontinue the antipsychotic and monitor/assess using watchful waiting or specific interventions (steps 3-8)

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10 Antipsychotics prescription
Review guidance

- Discontinuation of antipsychotics
  - 70% of people have no worsening of symptoms when antipsychotics are discontinued
- If receiving a low dose antipsychotic
  - Proceed directly with discontinuation and monitoring
- If receiving a higher dose antipsychotic
  - Taper the dose over 1 month
    - Reduce to half the dose for 2 weeks
    - GP to review
    - Discontinue immediately after a further 2 weeks

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Summary

- It is better to start treating dementia early
- BPSD is common and can occur at any point through disease progression
- Management of BPSD is clinically significant
- Policy developments provide clarity on what needs to be done
- NICE guidance has changed
- BPSD best practice guide available for your use and reference

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