Henry Brodaty

UNSW AUSTRALIA

BPSD and research

What have we learned?

Do we need new trials?

Never Stand Still | Medicine

- Dementia Centre for Research Collaboration
  www.dementiaresearch.org.au
- Centre for Healthy Brain Ageing
  www.cheba.unsw.edu.au

University of New South Wales (UNSW Sydney)

DCRC Dementia Collaborative Research Centres

CHeBA Healthy Brains Positive Ageing

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Terminology

Avoid language of blame or stigma

Does medicalisation impede quality care

- Challenging → Changed behaviours
- Expressions of unmet needs
- Behavioural expression of need
- Responsive behaviours
- Behaviours of concern
- Behaviours & psychological symptoms of dementia (BPSD)[2]
- Neuropsychiatric Symptoms (NPS)

[1] Markwell, H. (2016) DBMAS Working Group; [2] Cunningham C et al, IJGP 2019

Reconceptualising BPSD[1]

- **PLWD interpret causes as reactive to changing circumstances (eg s*elf-isolate because felt not accepted socially)***
- **CPs interpret behaviours as resulting from cognitive decline (eg *loss interest, motivat^{n}*)**
- **PLWD - feelings of loss and identity changes**
- **Contribution of historic trauma (*stuck in painful memories*)**
- **Differences in language important**
  - **PLWD – CP - clinician**

[1] Burley CV et al, Frontiers in Psychiatry, 2021 doi: 10.3389/fpsyt.2021.710703.

Prevalence of BPSD

- BPSD common in dementia
- ~90% in residential care[1]
- Apathy ~50% AD[2], 100% severe FTDbv[2]
- Delusions, hallucinations, apathy, sleep disturbance ≥ 50% in DLB[2]
- Agitation, sleep disturbance > 50% in moderate-severe in VaD[2]
- Depends on type & severity of dementia
- Depends on context

[1]Edvardsson (2008); [2]Kazui et al. (2016)

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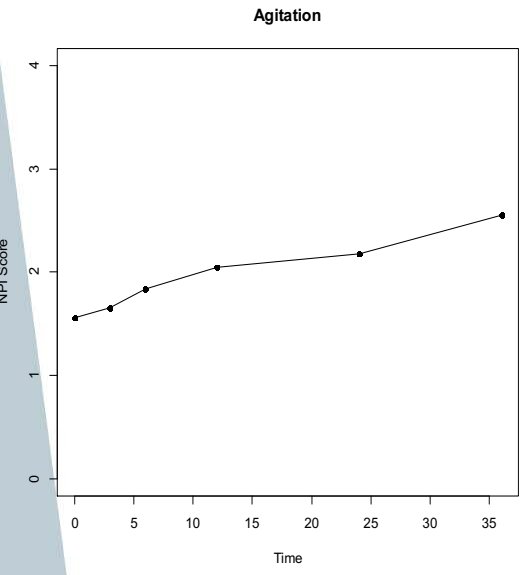
BPSD: Natural History

- Some behaviours become more prevalent with time & severity – apathy, agitation
- Some peak then decrease as dementia progresses – depression, hallucinations

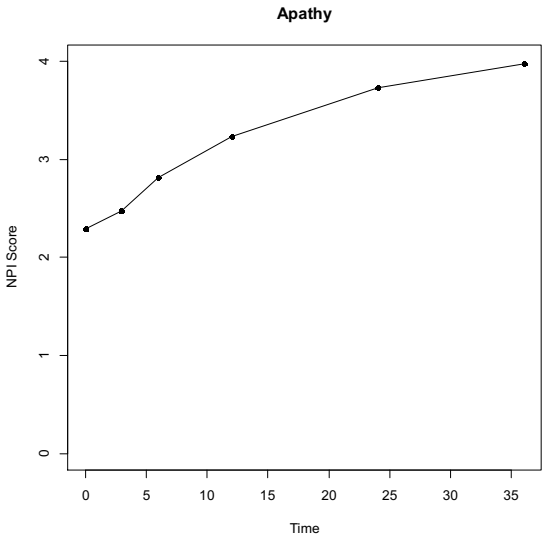
Brodaty, Connors, Woodward et al. (2015) JAMDA, 5: 380-387

Trajectories of behaviours/symptoms

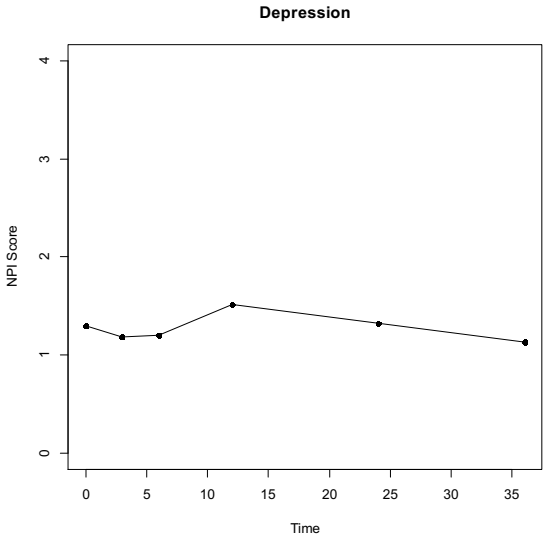
Agitation



Apathy



Depression



Brodaty H, Connors M et al JAMDA 2015

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Before intervening …

1. Is the description accurate?
2. Identification of target behaviour
3. Does behaviour require intervention?
4. Careful diary of behaviours
5. Exclude non-dementia causes eg pain, UTI
6. Correct sensory impairment - hearing, vision

Psychosocial interventions

Family caregivers

- Family carers as therapists for people living in the community
- Systematic review
  - ES 0.34 for decreasing BPSD
  - ES 0.15 for decreasing caregiver “stress”

Brodaty H & Arasaratnam C, Am J Psychiatry, 2012

Nurse led PCC

- **Cluster RCT of nurse-delivered, supervised dementia care management (with GP and specialist consultation)**
- **Intervention = psychosocial management, Mx meds and carer support, education & discussion with a psychiatrist or neurologist; 1 session/month x6**
- **634 PWLD (mean age 80 years) *at home* with a primary carer or alone. Mean MMSE 23, only 38% had a formal diagnosis of dementia; 51% mild dementia, some moderate or severe dementia**

Thyrian JR et al. *JAMA Psychiatry* 2017; 74: 996–1004.

PCC psychosocial intervention

- **Better NPI score −7·5, 95% CI −11·1 to −3·8),**
- **Care as usual group NPI increased: 7·2 to 15·2; intervention group NPI increased: 7·6 to 8·2**
- **Effects on quality of life only for people living with a carer**

Thyrian JR et al. *JAMA Psychiatry* 2017; 74: 996–1004

OT-led Tailored Activity Program[1,2]

- **An 8-session home-based tailored activity program RCT, tailored to PLWD *at home* & to family member vs 8 telephone-based education sessions[1]**
- **160 participants via GPs; 64% follow-up; data imputed**
- **Large reduction in overall NPS immediately after intervention, which were better in group receiving home-based TAP better on NPI (mean diff 24·3, 95% CI 3·1–45·6); & on functional dependence and pain**
- **Not sustained 4 months later.**
- **Non-completers more severe NPS**

[1] **Gitlin L** *J Am Geriatr Soc* 2018; **66:** 339–45

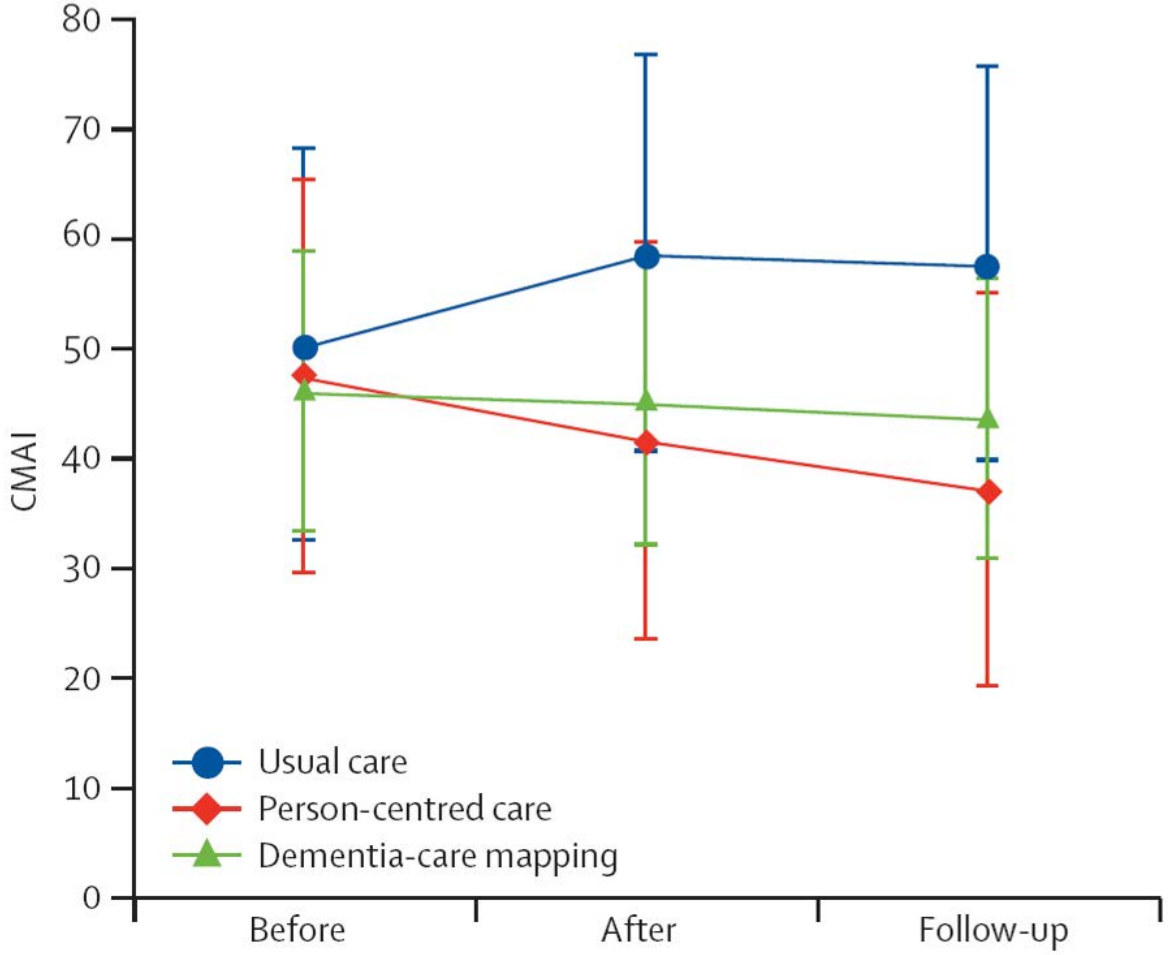
[2] **Gitlin et al.** *Am J Geriatr Psychiatry*; 2008;**16: 229–239**

Agitation in care homes

- **WHELD study[1,2]: multi-component → PCC, improved communication; social and other activities, sensory experiences; antipsychotic educat[n]; physical problems → CMAI ↓**
- **TIME study[3]: manualised comprehensive Ax; structured case conference – staff & doctor, tailored plan → CMAI ↓ and NPI ↓**
- **Multi-component interventions appear effective[4]**

[1] Ballard C Am J Psychiatry 2016; [2] **Ballard C et PLoS Med 2018;**
[3]Lichtwarck B et al, Am J Ger Psych 2018; [4] Livingston et al, Lancet 2020

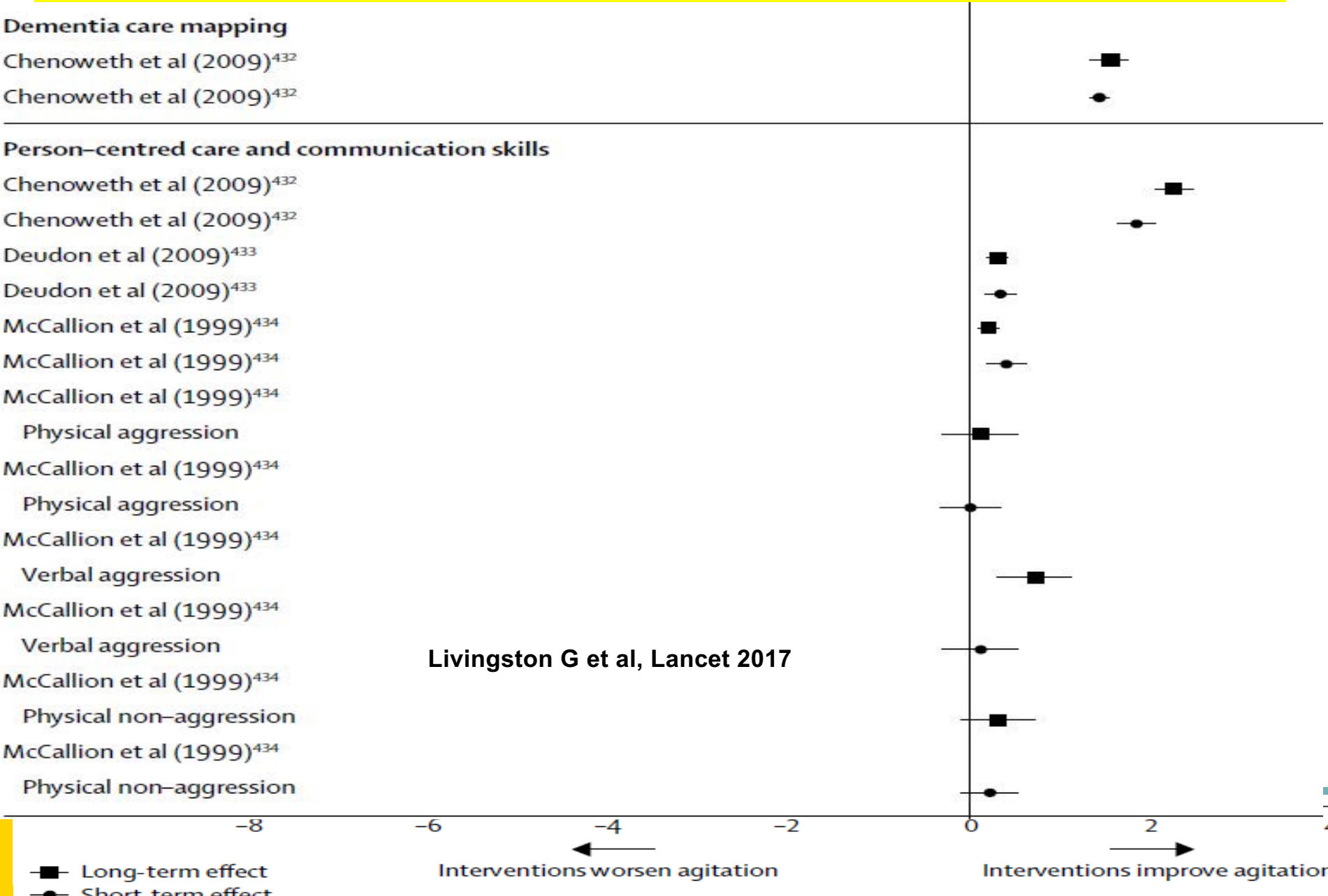
Dementia Care Mapping & Person Centred Care for agitation



Cost for PCC ≈ $6 to reduce a point on CMAI

Chenoweth et al. Lancet Neurology 2009

DCM & PCC for agitation



Livingston G et al, Lancet 2017

STrAtegies for RelaTives

- **Carer distress more related to NPS than dementia Sx & associated with ↑use & ↑ costs of health services[1]**
- **Need to identify, educate & support distressed carers**
- **START[2]: 8 sessions; 6-year follow-up**
- **Manual-based coping intervention delivered by supervised psychology graduates →**
- **Continuing effectiveness for depressive Sx in carers and risk of case-level depression**
- **Patient-related cost ≈ 3 times lower than those who did not receive the intervention**

[1] **Maust DT et al** *Am J Geriatr Psychiatry* 2017; **25:** 1074–82.

2 **Livingston G et al** *Br J Psychiatry* 2020; **216:** 35–42.

Novel strategies

- Humour therapy
- Volunteers
- Music, singing, dance therapy
- Integrating kindergarten/ babies

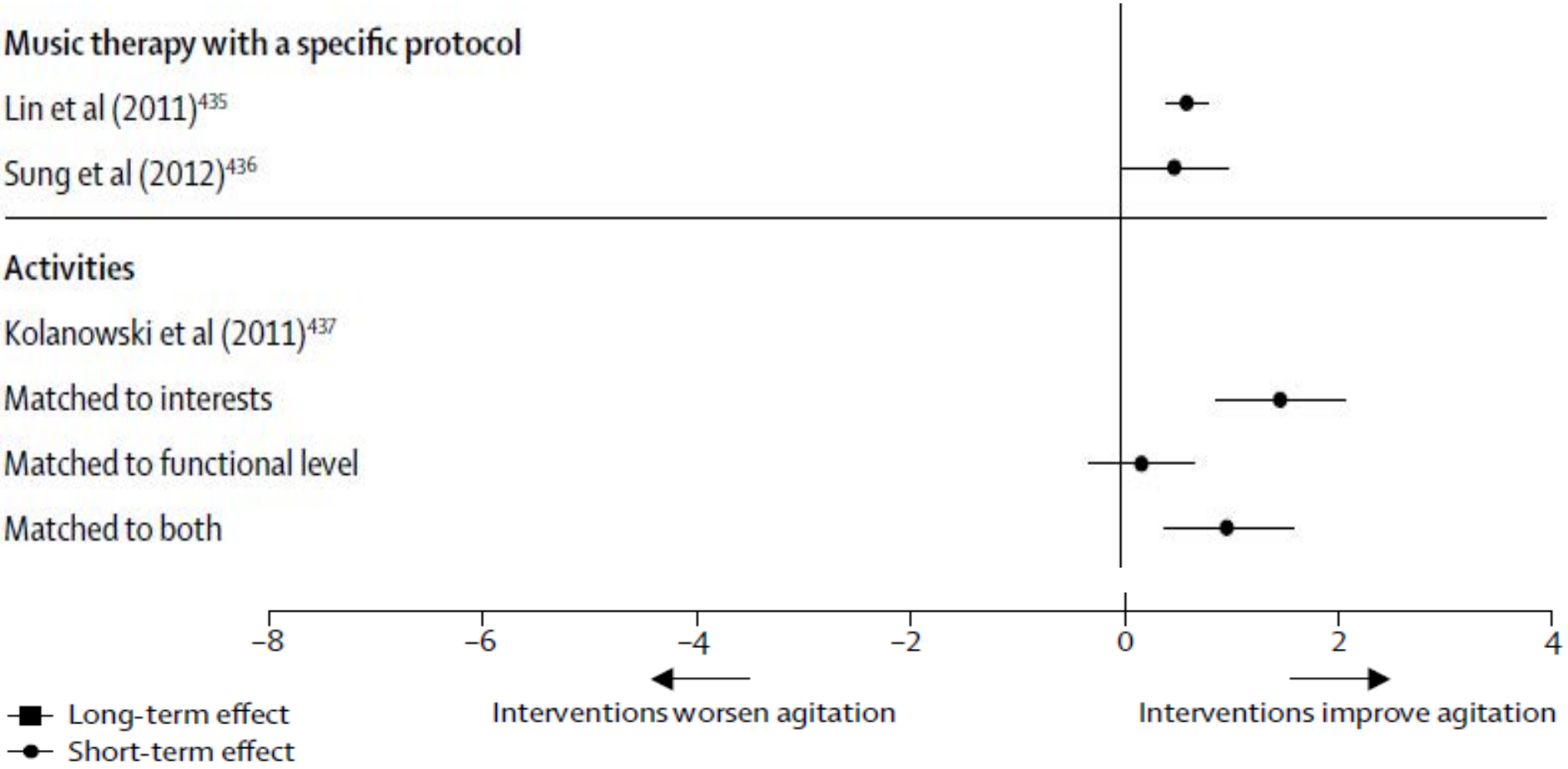
Humor therapy: SMILE study

- 20% reduction in agitation
- Effect size = antipsychotic medications for agitation
- Adjusting for dose of humour therapy
  - Decreased depression
  - Improved quality of life

Low LF et al BMJ Open 2013
Brodaty et al Am J Ger Psych 2014
Low LF et al JAMDA 2014

Music therapy & activities for agitation

Livingston G et al, Lancet, 2017



Pharmacological interventions

Drug Rx for BPSD

- Not first line
- Obtain consent
- Analgesic stepped approach
- Cholinesterase inhibitors – for apathy
- Memantine - ?benefit for agitation/aggression/ delusions/ hallucinations
- Antidepressants – (es)citalopram, sertraline, venlafaxine, mirtazapine – gp data = placebo
- Risperidone 0.5 - 2mg/day; modal = 1mg

ChEIs & BPSD

- **Some benefit, statistically significant in some reviews but questionable clinical significance**

- **Individual Sx may be more susceptible: apathy, hallucinations, aberrant motor behaviour, delusions, anxiety, depression**

- **Trinh N-H et al, 2003**
- **Rodda et al, 2009**
- **Campbell et al, 2008**

www.ipa-online.org

Memantine on BPSD

- **Mixed results**
  - **Several negative results [1-2]**
  - **Some positive results [3-4]**
- **Specific benefits reported for cluster of aggression, hallucinations & delusions**

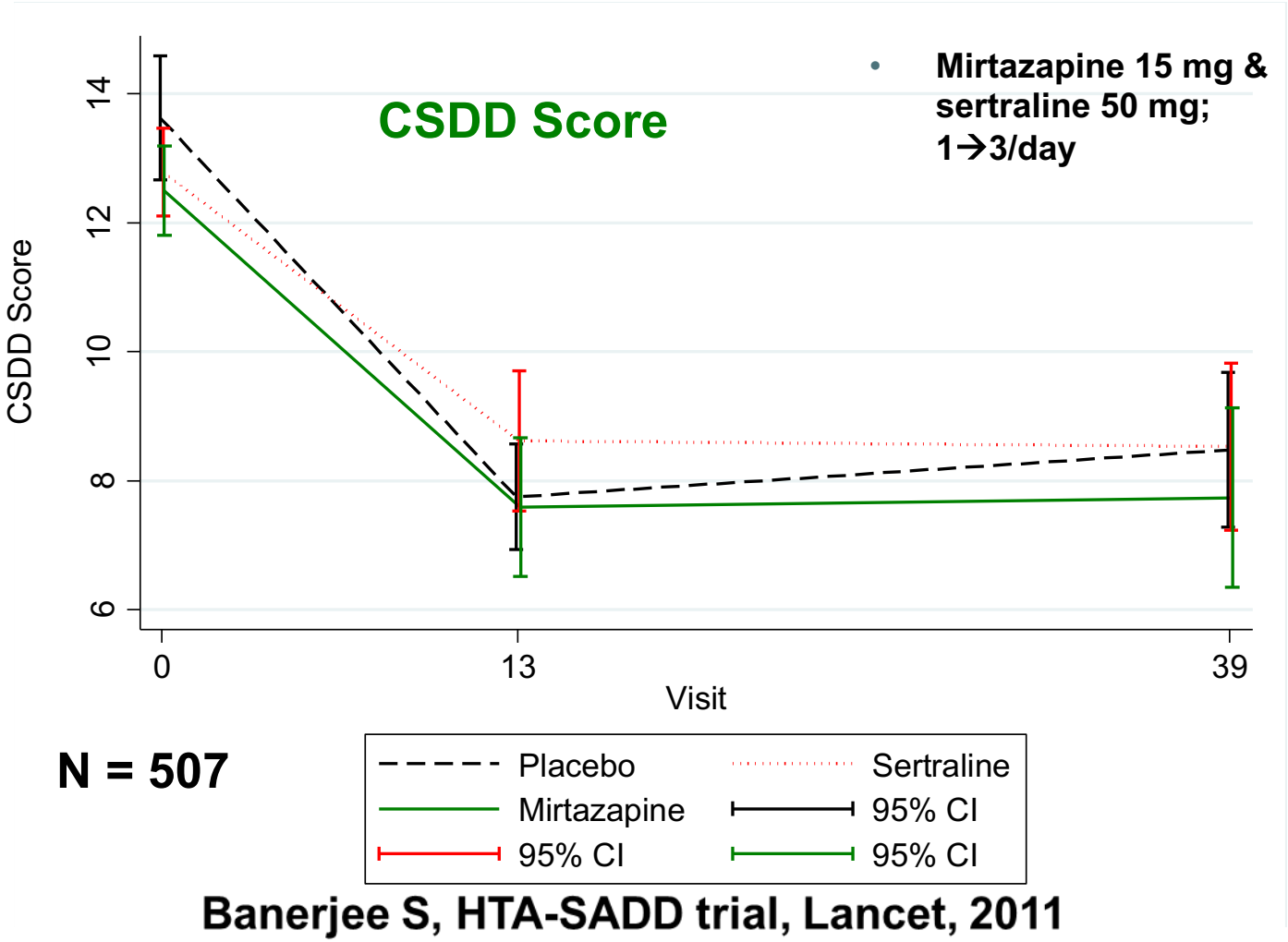
[1] Reisberg B et al, 2003; [2] Van Dyck et al, 2007;
[3] Tariot P et al, 2004 ; [4] Gauthier et al (2005), IJGP, 20, 459-464

Sertraline for treatment of depression in AD: (DIADS-2)

- 67 Sertraline, 64 placebo; 12 wk RCT + 12 wk
- No between-groups diff. in depression response
  - in CSDD score
  - remission rates
  - secondary outcomes
- SSRI associated > adverse events of diarrhoea, dizziness, dry mouth, pulmonary SAE (pneumonia)

Weintraub D et al. Am J Ger Psych, 2010;18:332-340

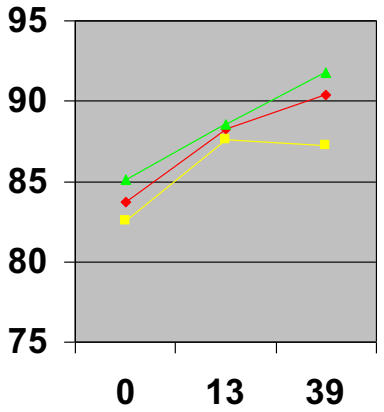
HTA-SADD Trial



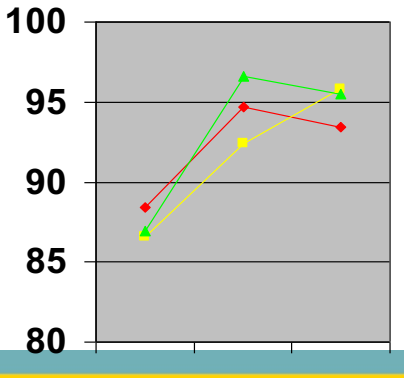
N = 507

Banerjee S, HTA-SADD trial, Lancet, 2011

DEMQOL



DEMQOL-Proxy



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Citalopram in BPSD

- ?benefit hallucinations, delusions (≡ antipsychotics) [1, 2]
- Improve agitation [3, 4]
- Prolong QT interval [4]
- Cognition↓ more than placebo [4]

1. Pollock et al. (2002). Am J Psych 159: 460-465
2. Pollock et al. (2007). Am J Geriatr Psych 15: 942-952
3. Siddique et al. (2009) J Clin Psychiatry 70(6):915-918
4. Porsteinsson et al. *JAMA*. 2014;311(7):682-691. doi:10.1001/jama.2014.93

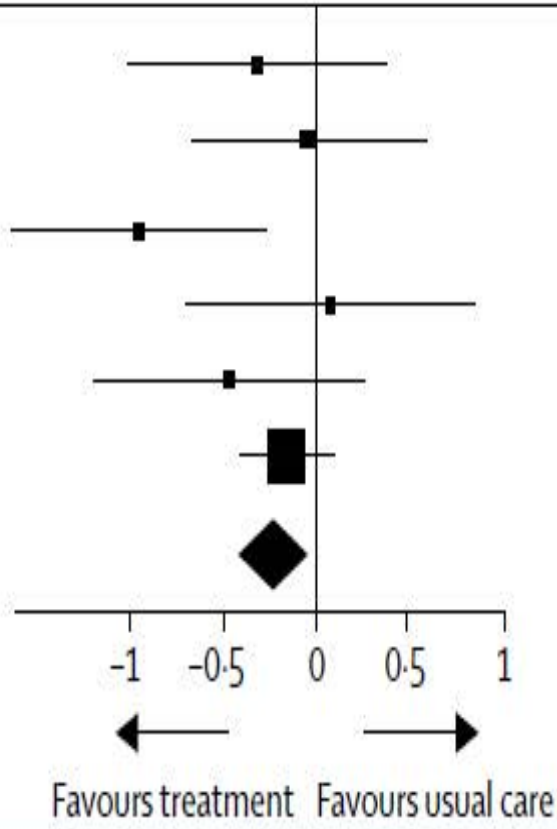
Depression: psychological treatment

Livingston et al, Lancet 2017

Study or subgroup	Experimental		Control		Weight %
	Mean (SD)	N	Mean (SD)	N	
Burgener et al (2008)[474]	3·3 (2·9)	19	4·3 (3·4)	14	7·4
Burns et al (2005)[475]	5·4 (2·6)	20	5·5 (3·1)	20	9·3
Spector et al (2012)[476]	10·38 (5·835)	21	16·72 (7·283)	18	8·0
Stanley et al (2012)[477]	8·2 (2·86)	11	7·8 (5·95)	15	5·9
Tappen et al (2009)[478]	15·13 (9·54)	15	19·13 (7·37)	15	6·8
Waldorff et al (2012)[479]	5·05 (4·61)	130	5·77 (5·07)	141	62·7
Total (95% CI)		**216**		**223**	**100·0**

Heterogeneity: $\chi^2 = 6{\cdot}33$, df = 5 (p = 0·28); $I^2 = 21\%$

Test for overall effect: Z = 2·30 (p = 0·02)



Anticonvulsants for BPSD[1]

- Literature review of 7 RCT
  - 2 carbamazepine & 5 valproate
- Results (treatment vs placebo):
  - 1 study: sig. ⇩ BPSD
  - 5 studies: no sig. difference
  - 1 study: sig. ⇧ BPSD
  - AEs more frequent in treatment groups
- Might be beneficial for some patients
- Not recommended for routine use

[1] Kanovalov et al (2008). Int Psychogeriatr, 20:2

Antipsychotics for …

- Screaming X
- Wandering X
- Intruding into other people's rooms X
- Aggression ?√ (but not 1st line)
- Delusions and hallucinations ?√ (but not 1st)
- BUT AEs, stroke and death!

Cochrane: aim to discontinue antipsychotics [1]

[1] Declercq T et al, Cochrane Review, 2013

Stopping anti-psychotics in dementia patients?

Ballard 2008

- 12 months RCT, continuous use vs placebo
- For most AD patients withdrawal - no detriment
- Continuers: ↓ verbal fluency ($p<.002$); ↑mortality
- Subgroup of pts with more severe symptoms (NPI ≥ 15) might benefit from continued Rx

Devanand 2012

- Pts who responded for psychosis or agitation
- Discontinuation → higher rate of relapse

Ballard et al 2008 PLOS Medicine, 5:587-599; Devanand DP_NEJM, 2012

Deprescribing

- HALT Study
- COSMOS trial
- CHROME Trial

Halting Antipsychotics in Long-Term Care (HALT)

- Single arm 12-month longitudinal study in 24 aged care facilities
- Resident participants assessed ≈1-4 wks prior to deprescribing & at 0, 3, 6 and 12m
- GPs (academic detailing) & Train-the-trainer model → nurse champions → train care staff
- 136 pts started deprescribing → 93 follow-up @ 12 months

HALT Conclusions

- Deprescribing antipsychotics sustained in 75%[1]
  - Without re-emergence of behaviours
  - Without substitution regular medication & with minimal prn benzodiazepine use
- LTC staff are significant drivers of AP prescribing
- Is there subgroup (20-25%) who benefit from Rx?
- Questions remain about identifying who benefits from continuing antipsychotics

[1] Brodaty H et al, JAMDA, 2018: doi: 10.1016/j.jamda.2018.05.002.

[2] Harrison F et al, Int Psychoger 2020; doi: 10.1017/S1041610219002011.

[3] Aerts L et al, Int J Ger Psych. 2019 doi: 10.1002/gps.5167

COSMOS trial (Norway)

- Medication reviews – collegial mentoring & systematic clinical evaluation of psychotropics
- **CO**mmunication & advanced care planning, **S**ystematic pain management, **M**edication reviews with collegial mentoring, **O**rganization of activities adjusted to individuals' needs & preferences, and **S**afety.
- 4m Cluster RCT 67 NH wards, N 428 (64% dementia, mean MMSE 12)
- Reduced ∑psychotropics (**anxiolytics, hypnotics, sedatives; *not*** APs, antidepressants, antidementia)
- No change in NPI-NH, CSDD
- ADL better

Gedde MH et al, Am J Ger Psych 2021:29:304-315

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Chemical Restraints avOidance MEthodology (CHROME)

- Syndrome vs symptom based approach
- Audit psychotropic drug use in 288 residents (77% with dementia) in single nursing home in Spain 2015-17
- Substantial reductions in atypical antipsychotics (42.7% to 18.7%), long-acting benzodiazepines (25.2% to 6.5%) and hypnotics (47.7% to 12.1%)
- Parallel reduction in falls

Muñiz R et al (2020). The "CHROME criteria": *International Psychogeriatrics, 32*(3), 315-324 doi:10.1017/S104161021900111X

Changes in psychotropic prescribing UK 2005-15

Antipsychotics

- **Any**
- **Typical**
- **Atypical**

Anxiolytics

Hypnotics

Antidepressants

Livingston G et al Lancet 2020

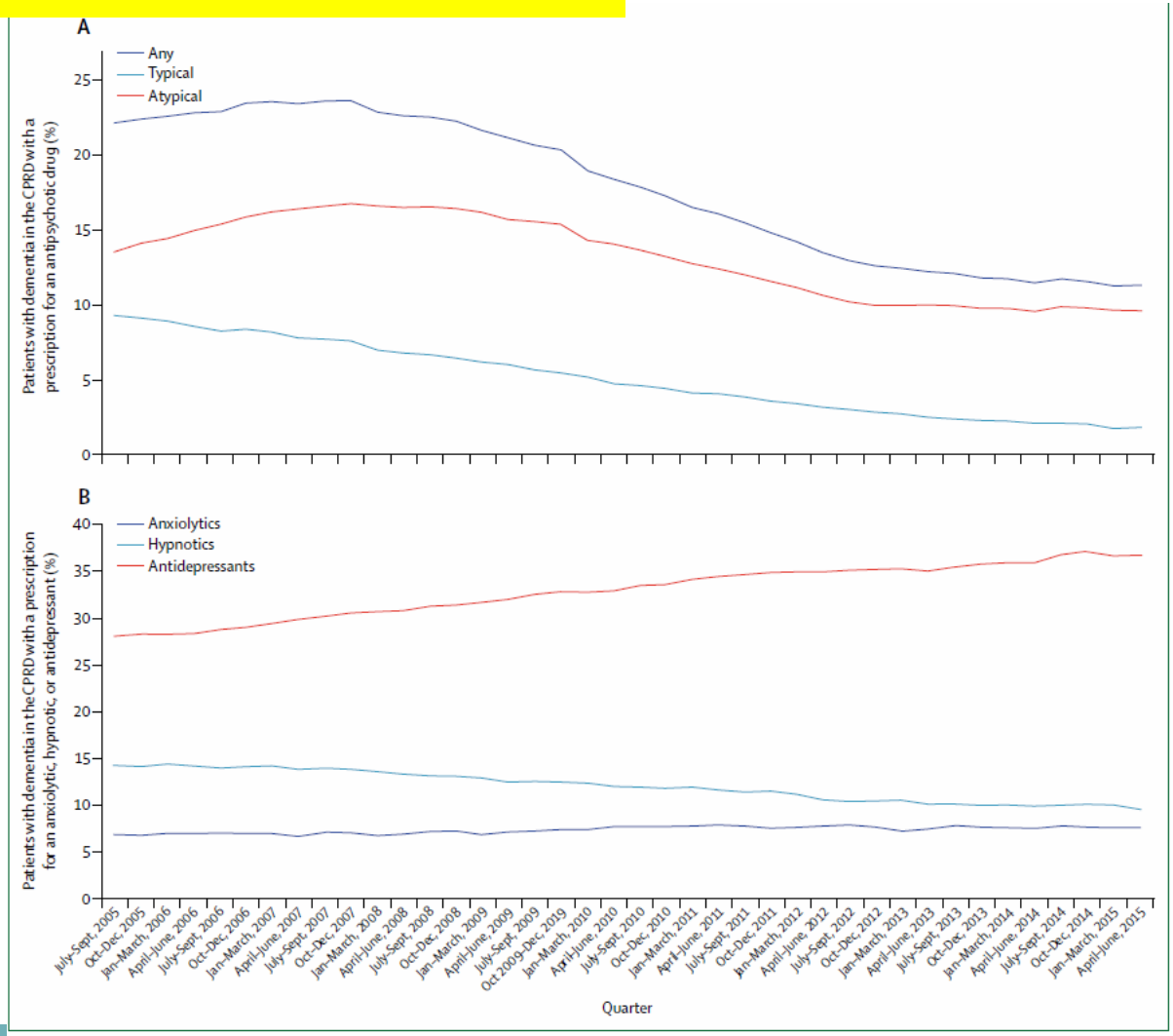

Figure 8: **Proportion of patients with a diagnosis of dementia prescribed an antipsychotic drug (A) and those prescribed an anxiolytic, hypnotic,**

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Decreases in antipsychotic prescribing

- **Medication substitution**
- **Diagnosis substitution**
  - **Rate of schizophrenia doubled**
  - **Winter JD Increased Reporting of Exclusionary Diagnoses Inflate Apparent Reductions in Long-Stay Antipsychotic Prescribing. *Clinical Gerontologist 2019***

doi.org/10.1080/07317115.2017.1395378

Novel Drugs

Dextromethorphan-quinidine

- Used in pseudo-bulbar palsy
- Preliminary 10-week phase 2 randomized clinical trials of pts with probable AD, combination dextromethorphan-quinidine demonstrated clinically relevant efficacy for agitation and was generally well tolerated
- NPI agitat^{n} /agg^{n} ↓ 3.3 on D-Q vs ↓ 1.7 on PBO
- AEs – falls, diarrhoea, UTI
- SAEs 7.9% (PBO 4.7%)

Cummings JL et al_*JAMA* 2015; 314:1242-1254

doi:10.1001/jama.2015.10214

Cannabinoids

- Cannibinoids ↓pain, ↑mood, ↑sleep
- Cannabinoids being researched
- **Dronabinol:** ↓agitation, aberrant motor & night-time behaviours[1]
- **Delta-THC:** ↓ delusions, agitation, aggression, irritability, apathy[2]
- **Nabilone:** improved behaviour (case study)[3]

[1]Walther et al. (2006); [2]Shelef et al. (2016); Passmore (2008)

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Nabilone (synthetic cannibinoid) → improvements in …

- **CMAI:** treatment difference b= - 4.0, 95% CI -6.5 to -1.5, *P*=0.003
- **NPI agitation/aggression score**:
  b= -1.5 (95% CI -2.3 to -0.6, *P*=0.001)
- **Overall neuropsychiatric symptoms**:
  b= - 4.6 (95% CI -7.5 to -1.6, *P*=0.004)
- **Cognition:** b= 1.1 (95% CI 0.1-2.0, *P*=0.026)
- **Nutrition:** b= 0.2 (95% CI 0.02-0.4, *P*=0.03)

Only AE = More sedation in nabilone group …

Hermann N et al, Am J Ger Psych 2019; DOI: 10.1016/j.jagp.2019.05.002

Brexpiprazole for agitation

- Brexpiprazole (Rexulti) – Otsuka/Lundbeck
- Pts with AD and agitation
- Trials N = 433 and 270 across nine & seven countries
- Positive result for 2mg in 1 of 2 trials not for 1mg[1]

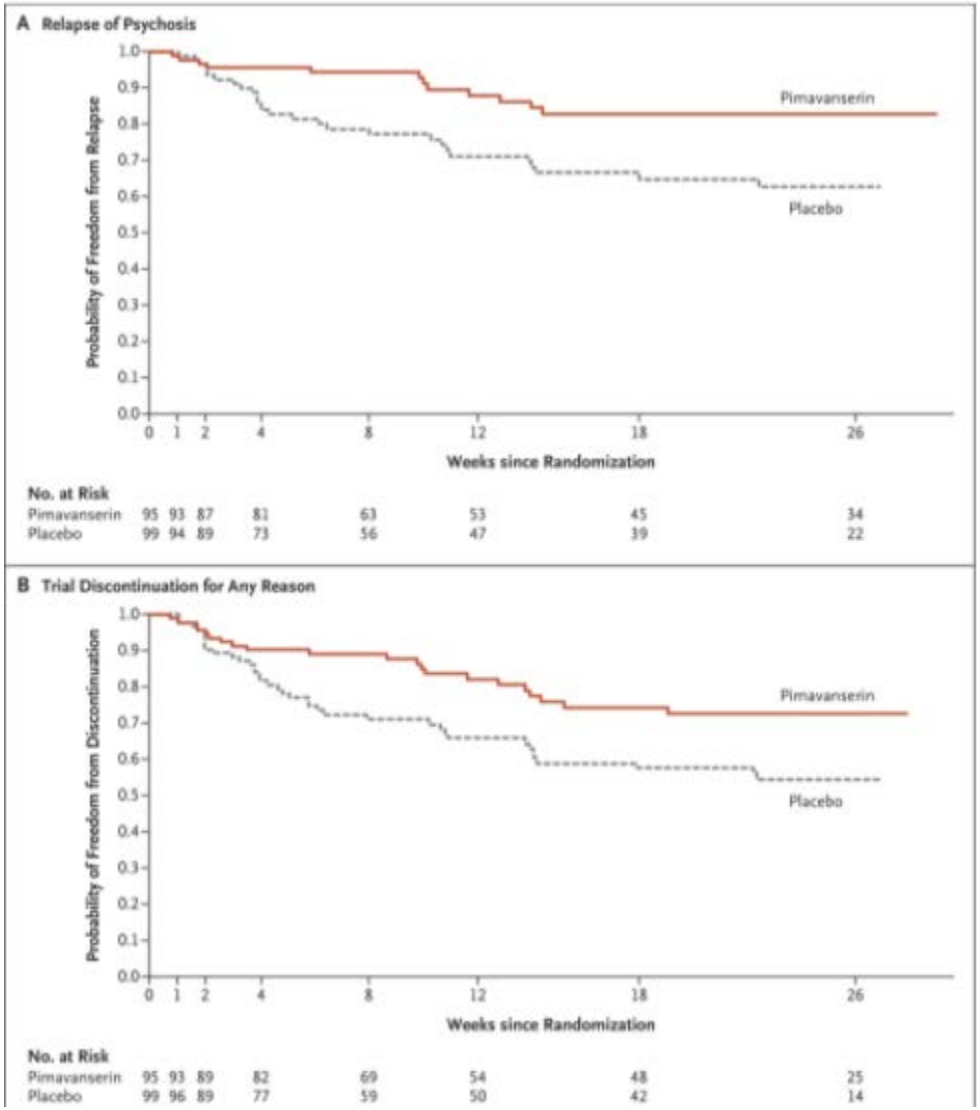
Grossberg GT Am J Ger Psych 2020 doi.org/10.1016/j.jagp.2019.09.009

Pimavensirin for psychosis

- **Pimavensirin: $5HT_{2A}$ receptor inverse agonist, rapidly suppresses Aβ production and related pathology in mouse AD[1]**
- **Significantly less relapse in RCT withdrawal trial for pts with dementia & psychosis who had responded to Rx [2]**

[1] Yuede CM JNC 2020 doi.org/10.1111/jnc.15260

[2] Tarriot PN et al, N Engl J Med 2021; 385:309-319



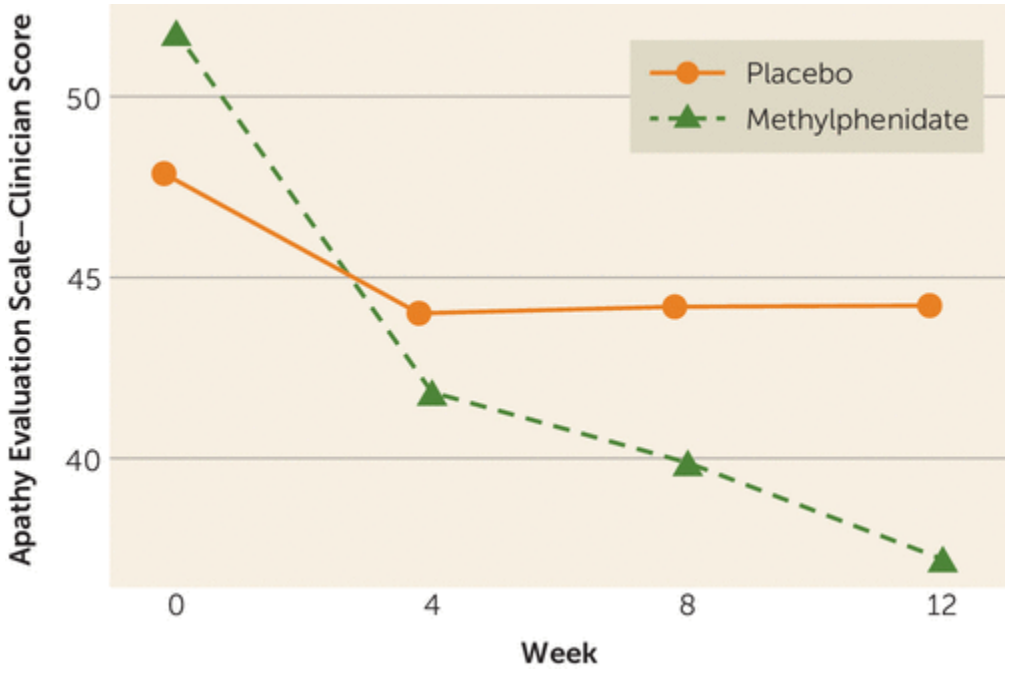
- time to relapse

Pimvansirin

Survival curves over 6 months for Rx-responsive PLWD + psychosis

- time to attrition

Apathy Evaluation Scale – Methylphenidate and Placebo for Apathy in 60 Veterans With Alzheimer's Disease



Padala PR, Am J Psychiatry, 2018

JAMA Neurology | Original Investigation

Effect of Methylphenidate on Apathy in Patients With Alzheimer Disease
The ADMET 2 Randomized Clinical Trial

Jacobo Mintzer, MD, MBA; Krista L. Lanctôt, PhD; Roberta W. Scherer, PhD; Paul B. Rosenberg, MD; Nathan Herrmann, MD; Christopher H. van Dyck, MD; Prasad R. Padala, MD; Olga Brawman-Mintzer, MD; Anton P. Porsteinsson, MD; Alan J. Lerner, MD; Suzanne Craft, PhD; Allan I. Levey, MD, PhD; William Burke, MD; Jamie Perin, PhD; David Shade, JD; for the ADMET 2 Research Group

JAMA Neurol. doi:10.1001/jamaneurol.2021.3356
Published online September 27, 2021.

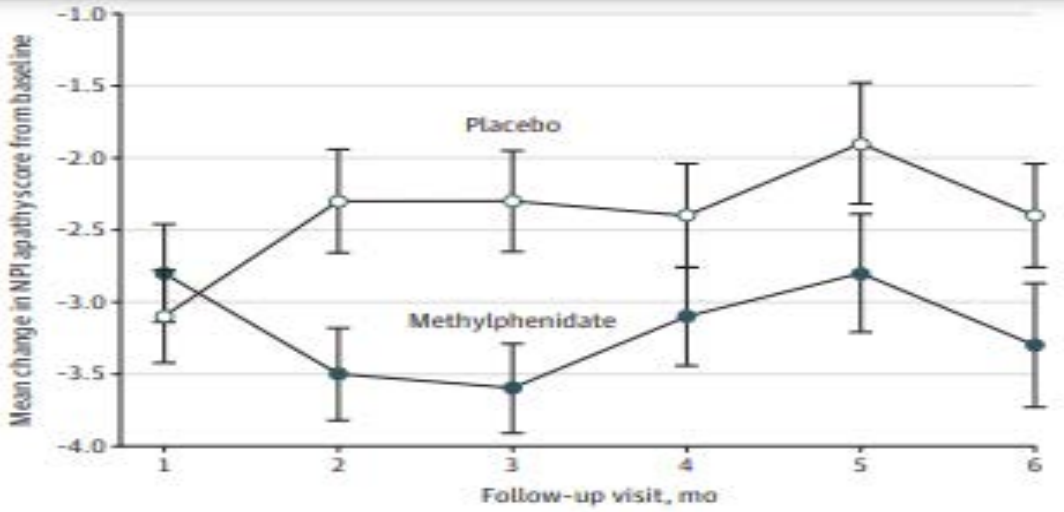
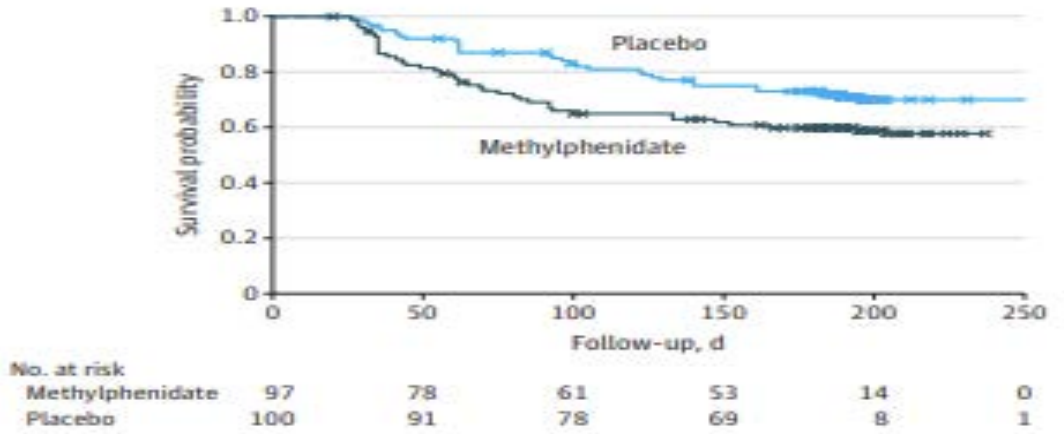


Figure 3. Kaplan-Meier Estimates of Proportion of Participants Achieving a Neuropsychiatric Inventory Apathy Score of 0



Censored events are noted by X's. Over the complete follow-up period of 6 months, the methylphenidate group had a 57% increase in the hazard ratio

ADMET2

Fig 2 – mean NPI apathy score over 6 m

Fig 3 – survival curve time to reach NPI-Apathy = 0

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Services for BPSD

- The Dementia Behaviour Management Advisory Service (DBMAS)
  1- 800 699 799
  https://www.dementia.com.au/
- DBMAS and Severe Behaviour Response Teams (SBRT)
  http://www.sbrt.org.au/
- Flying squads – some hospitals
- Special dementia care units
  - PHNs, rolling out nationally

Behaviour Management Resources

- Behaviour Management–A Guide to Good Practice (currently being updated from 2012)
- A Clinician's Field Guide to Good Practice
- Guide for Family Carers
- BPSD Guide App for clinicians
- BPSD in-service & evaluation training packages
- Care4Dementia App (family carers & direct care)
- BPSD posters for remote Aboriginal Communities

https://www.dementiaresearch.org.au/bpsdguide.html

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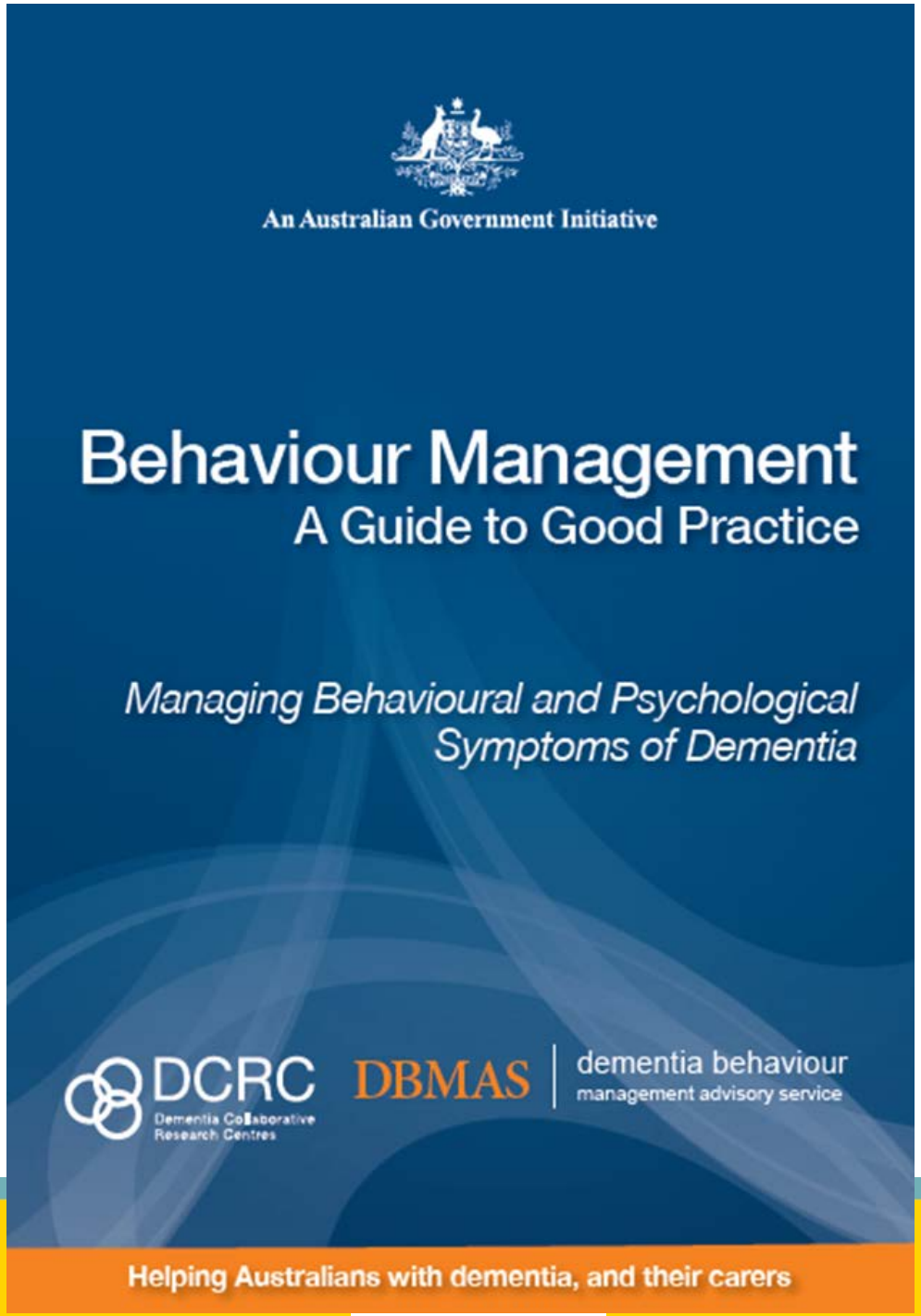
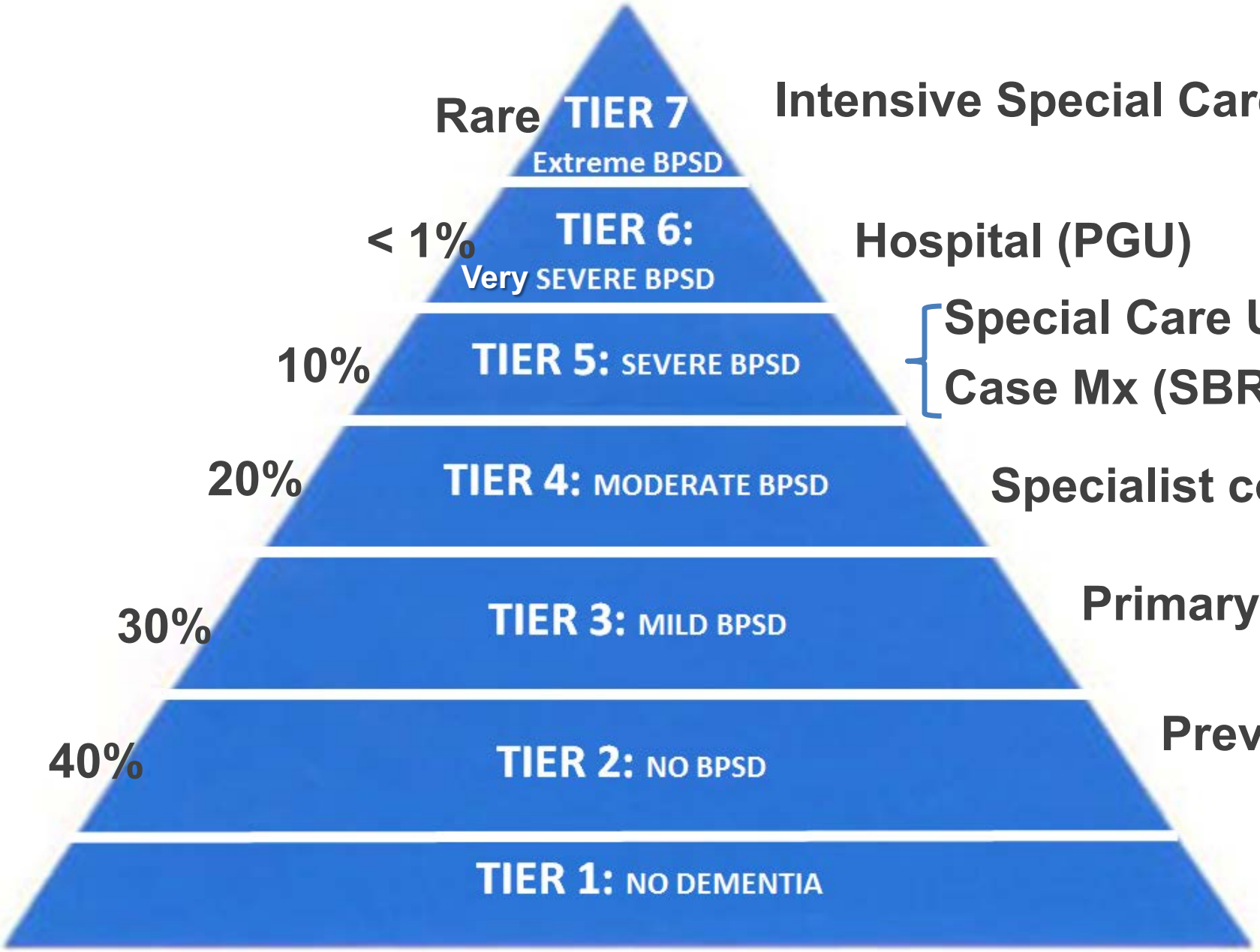

An Australian Government Initiative
Behaviour Management
A Guide to Good Practice
Managing Behavioural and Psychological Symptoms of Dementia
DCRC
Dementia Collaborative Research Centres
DBMAS
dementia behaviour management advisory service
Helping Australians with dementia, and their carers



Brodaty, Draper & Low (2003) Behavioural and psychological symptoms of dementia: A seven-tiered model of service delivery. MJA; 178: 231–234

What have we learned?

- Don't just label the behaviour …..
- …. understand the person
- Different approaches often together
- Be creative, document, monitor outcome
- Partnerships with family/ carers and HCPs
- Drug treatments have AEs and limited benefits
- Care for behaviours makes economic sense[1]
  - ≤ 30% of cost; reduce agitation by $6 per point

[1]Burley CV et al, Int Psychoger 2020 doi.org/10.1017/S104161022000037X

Challenge for helping people experiencing changed behaviours

- Changing attitudes
- Changing culture
- Implementing PCC → Business as Usual
- Changes in rules after Royal Commission
  - Restrictive practices including (chemical)
  - Limits on antipsychotic prescribing

Further trials needed?

- Prevention – education, communication skills, culture change
- Personalised medicine: Match intervention to person and behaviour
- Implementation science trials
- Involve PLWD in deciding how they would like help if their behaviours changed
- All drug trials have run-in period with psychosocial intervention before randomisat^{n}

Thank you

Dementia Centre for Research Collaboration (Assessment & Better Care Hub)

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