

Pharmacological Interventions in Behavioural and Psychological Symptoms of Dementia

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What are BPSD?

Is it a useful classification?

Behavioral and Psychological Symptoms of Dementia

A Consensus Statement on Current Knowledge and Implications for Research and Treatment

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Clinicians are aware that many patients with dementia, including Alzheimer's disease (AD), experience psychotic, depressive, and behavioral symptoms over the course of the illness, but, until recently, such symptoms have elicited little interest or research support. Further, research has been hampered by the absence of viable measurements and scales developed for this specific population. Before 1992, only seven placebo-controlled, randomly assigned, double-blind, neuroleptic studies on behavioral and psychological symptoms of dementia (BPSD) in this population had been published, and only one of these was in a nursing home setting. Between 1992 and 1997, eight clinical drug trials were conducted or have begun, using a range of measurements and scales developed in recent years. The field has seen an influx of research attention, while struggling to determine exactly what we are measuring and how these symptoms can be measured most effectively.

It was in this context that the International Psychogeriatric Association (IPA), with an unrestricted grant from Janssen Pharmaceutica, convened an international consensus conference in 1996 to begin to develop an operational definition of "the behavioral disturbances of dementia" (renamed "behavioral and psychological symptoms of dementia [BPSD]"), with directions and implications for future research and treatment. The following consensus statement is a product of that meeting.

Behavioral and Psychological Symptoms of Dementia

The behavioral (e.g., repetitive questioning, hitting) and psychological symptoms of dementia can result in suffering, premature institutionalization, increased costs of care, and significant loss in the quality of life



Behavioural and

Depression: 50%

Anxiety: 35%

Psychological

Brittleness: 30%

Symptoms of

Disinhibition: 28%

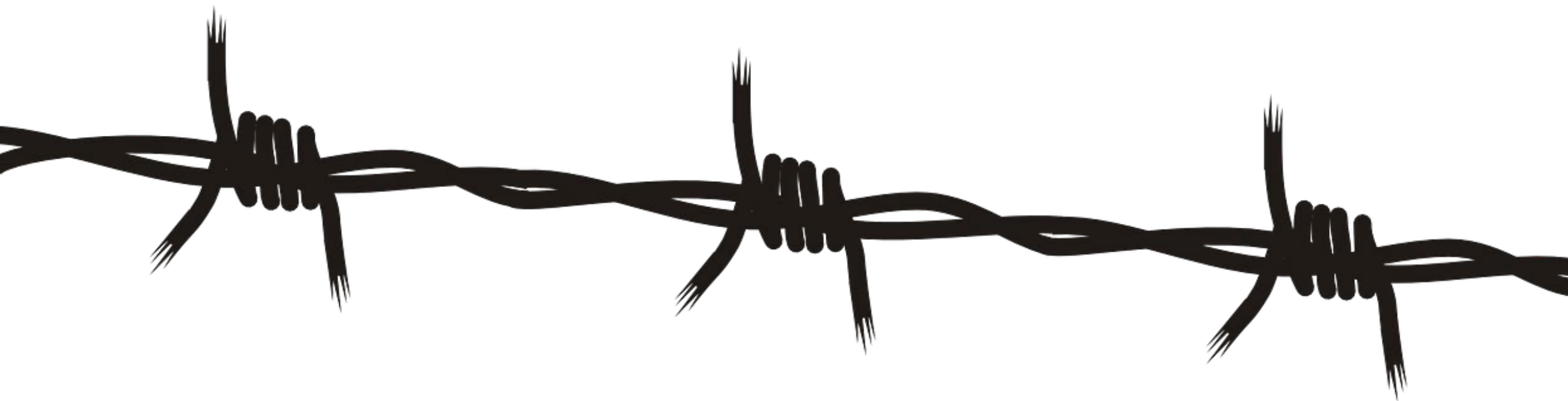
Dementia — 90%

Observed behavior is a normal reaction to an abnormal situation.



Where possible treat the psychological symptoms.....

Treating behaviour.....



What do we want treatment to achieve?

- Maintaining function.
- Improving quality of life.
- Reducing carer stress.
- Reducing patient distress.
- Reducing risk to others or self.

White paper defining optimal palliative care in older people with dementia: A Delphi study and recommendations from the European Association for Palliative Care

Palliative Medicine

2014, Vol. 28(3) 197–209

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Raymond TCM Koopmans⁹ and Ladislav Volicer¹⁰ on behalf of the
European Association for Palliative Care (EAPC)

GOALS OF CARE

**HEALTH PROMOTION AND
PREVENTION/RISK REDUCTION**

PROLONGATION OF LIFE

MAINTENANCE OF FUNCTION

MAXIMIZATION OF COMFORT

BEREAVEMENT SUPPORT

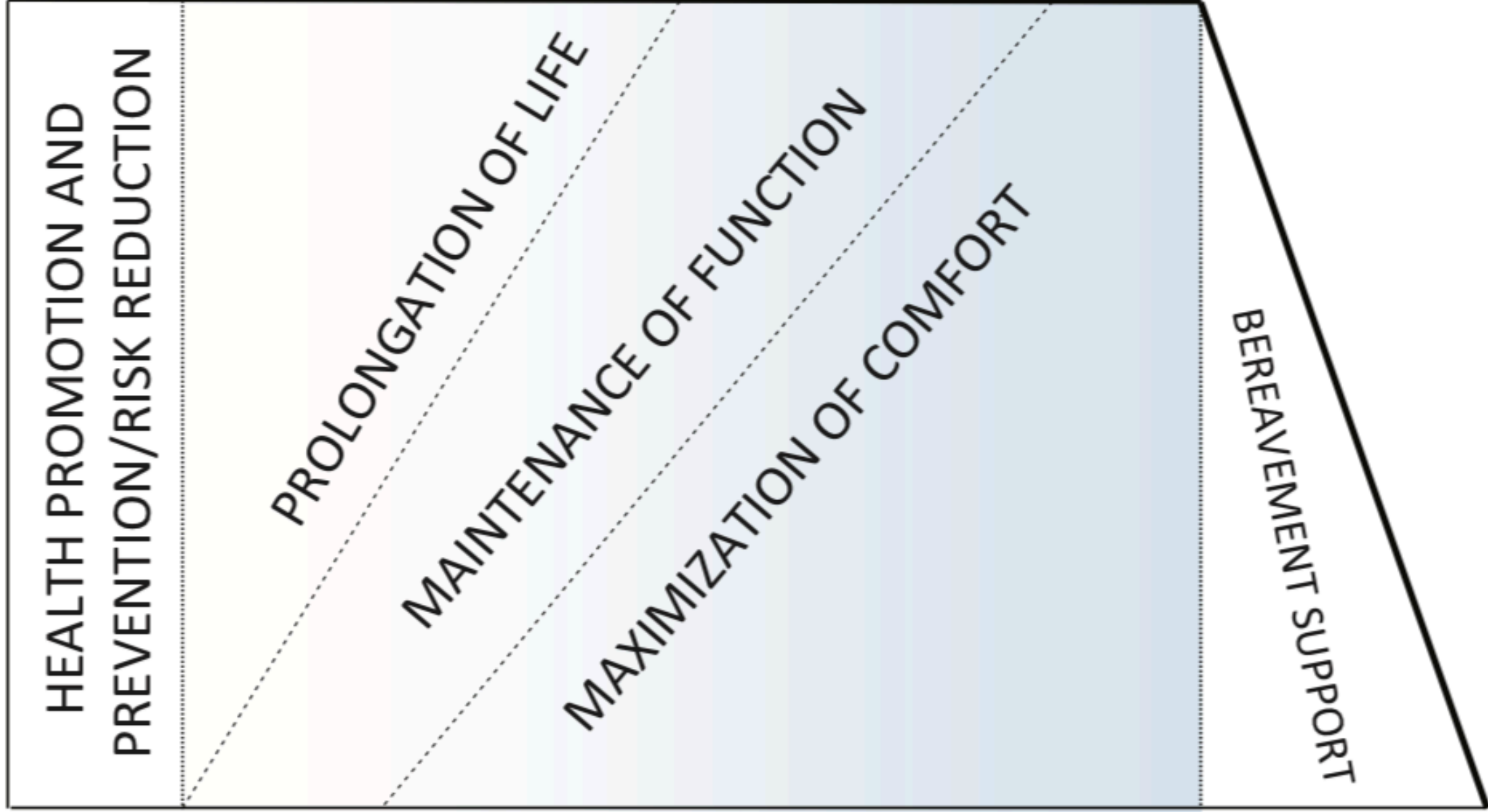
INTACT

MILD

MODERATE

SEVERE

AFTER DEATH



Non- Pharmacological Interventions



Pharmacological Interventions



When to use pharmacological interventions?

- Non pharmacological interventions have failed.
- High levels of risk.
- High levels of distress (patient and carer).
- Clear potential patient benefits.
- ? Non pharmacological interventions are not available.....



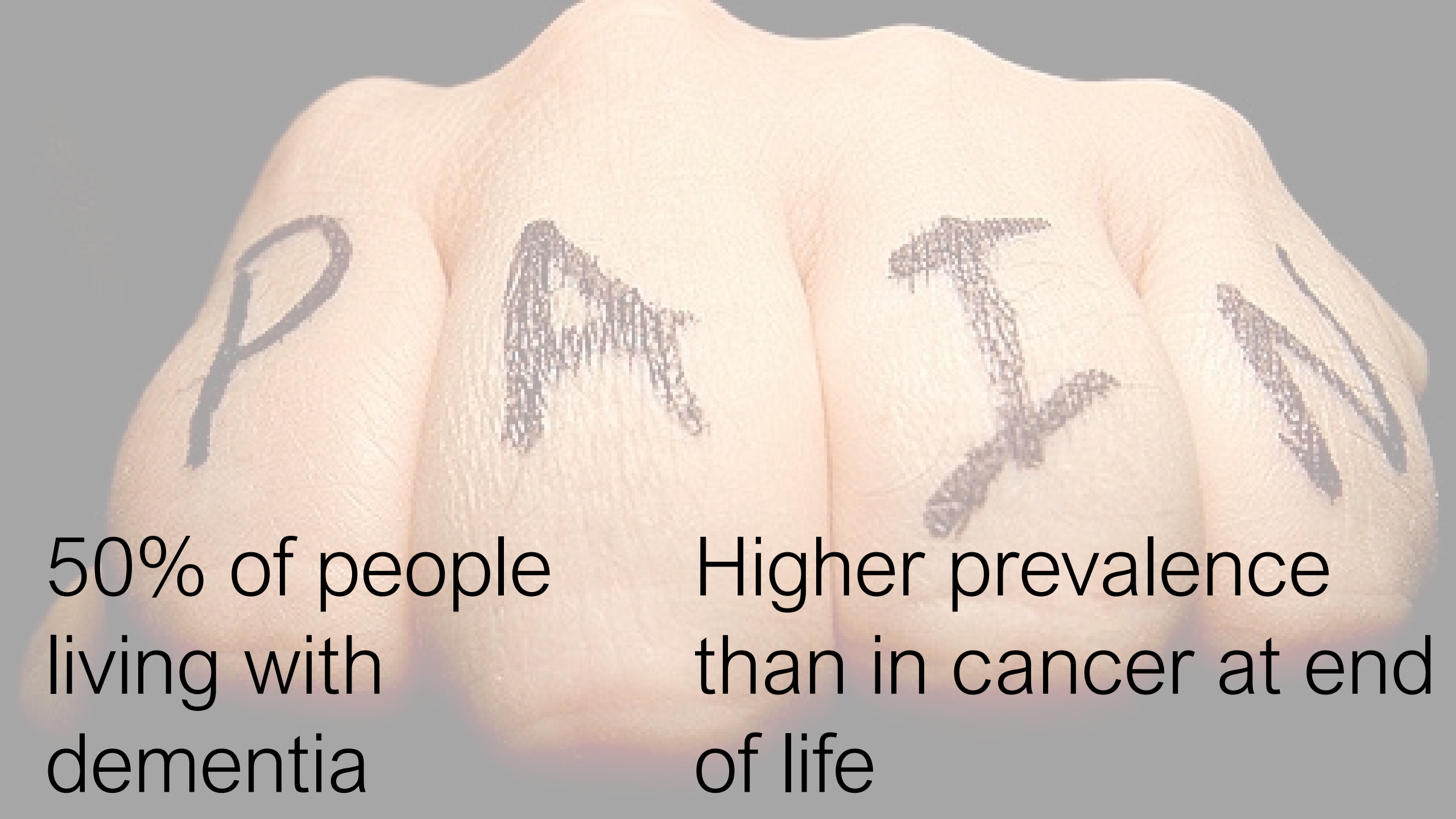
STOP

R

A

T

A



50% of people
living with
dementia

Higher prevalence
than in cancer at end
of life

Nociceptive pain



- Regular paracetamol.
- Remove stimulus – Think constipation, GORD, wind.
- NSAIDS + PPI.
- Opiates.

Neuropathic pain

A close-up, sepia-toned photograph of a man's face in profile, showing a pained expression with his mouth open and teeth bared. The image is used as a background for the text.

- SNRI
- Pregabalin
- ~~Amitriptyline~~

**THINK
DELIRIUM**

Is it indicated?

Contraindications?

Interactions?

Anticholinergic burden

Prescribing considerations

Dosing?

How long to continue?

Assessing impact of the
drug?

Drugs with ACB Score of 1

| Generic Name | Brand Name |
|----------------|------------------------|
| Alimemazine | Theralen™ |
| Alverine | Spasmonal™ |
| Alprazolam | Xanax™ |
| Aripiprazole | Abilify™ |
| Asenapine | Saphris™ |
| Atenolol | Tenormin™ |
| Bupropion | Wellbutrin™, Zyban™ |
| Captopril | Capoten™ |
| Cetirizine | Zyrtec™ |
| Chlorthalidone | Diuril™, Hygroton™ |
| Cimetidine | Tagamet™ |
| Clidinium | Librax™ |
| Clorazepate | Tranxene™ |
| Codeine | Contin™ |
| Colchicine | Colcrys™ |
| Desloratadine | Clarinex™ |
| Diazepam | Valium™ |
| Digoxin | Lanoxin™ |
| Dipyridamole | Persantine™ |
| Disopyramide | Norpace™ |
| Fentanyl | Duragesic™, Actiq™ |
| Furosemide | Lasix™ |
| Fluvoxamine | Luvox™ |
| Haloperidol | Haldol™ |
| Hydralazine | Apresoline™ |
| Hydrocortisone | Cortef™, Cortaid™ |
| Iloperidone | Fanapt™ |
| Isosorbide | Isordil™, Ismo™ |
| Levocetirizine | Xyzal™ |
| Loperamide | Immodium™, others |
| Loratadine | Claritin™ |
| Metoprolol | Lopressor™, Toprol™ |
| Morphine | MS Contin™, Avinza™ |
| Nifedipine | Procardia™, Adalat™ |
| Paliperidone | Invega™ |
| Prednisone | Deltasone™, Sterapred™ |
| Quinidine | Quinaglute™ |

Drugs with ACB Score of 2

| Generic Name | Brand Name |
|-------------------|------------|
| Amantadine | Symmetrel™ |
| Belladonna | Multiple |
| Carbamazepine | Tegretol™ |
| Cyclobenzaprine | Flexeril™ |
| Cyproheptadine | Periactin™ |
| Loxapine | Loxitane™ |
| Meperidine | Demerol™ |
| Methotrimeprazine | Levoprome™ |
| Molindone | Moban™ |
| Nefopam | Nefogesic™ |
| Oxcarbazepine | Trileptal™ |
| Pimozide | Orap™ |

Drugs with ACB Score of 3

| Generic Name | Brand Name |
|------------------|---------------------|
| Amitriptyline | Elavil™ |
| Amoxapine | Asendin™ |
| Atropine | Sal-Tropine™ |
| Benztropine | Cogentin™ |
| Brompheniramine | Dimetapp™ |
| Carbinoxamine | Histex™, Carbihist™ |
| Chlorpheniramine | Chlor-Trimeton™ |
| Chlorpromazine | Thorazine™ |
| Clemastine | Tavist™ |
| Clomipramine | Anafranil™ |
| Clozapine | Clozaril™ |
| Darifenacin | Enablex™ |
| Desipramine | Norpramin™ |
| Dicyclomine | Bentyl™ |
| Dimenhydrinate | Dramamine™, others |
| Diphenhydramine | Benadryl™, others |
| Doxepin | Sinequan™ |
| Doxylamine | Unisom™, others |
| Fesoterodine | Toviaz™ |
| Flavoxate | Urispas™ |
| Hydroxyzine | Atarax™, Vistaril™ |
| Hyoscyamine | Anaspaz™, Levsin™ |
| Imipramine | Tofranil™ |
| Meclizine | Antivert™ |
| Methocarbamol | Robaxin™ |
| Nortriptyline | Pamelor™ |
| Olanzapine | Zyprexa™ |
| Orphenadrine | Norflex™ |
| Oxybutynin | Ditropan™ |
| Paroxetine | Paxil™ |
| Perphenazine | Trilafon™ |
| Promethazine | Phenergan™ |
| Propantheline | Pro-Banthine™ |
| Propiverine | Detrunorm™ |
| Quetiapine | Seroquel™ |
| Scopolamine | Transderm Scop™ |
| Solifenacin | Vesicare™ |

Categorical Scoring:

- Possible anticholinergics include those listed with a score of 1; Definite anticholinergics include those listed with a score of 2 or 3

Numerical Scoring:

- Add the score contributed to each selected medication in each scoring category
- Add the number of possible or definite Anticholinergic medications

Notes:

- Each definite anticholinergic may increase the risk of cognitive impairment by 46% over 6 years.³
- For each one point increase in the ACB total score, a decline in MMSE score of 0.33 points over 2 years has been suggested.⁴
- Additionally, each one point increase in the ACB total score has been correlated with a 26% increase in the risk of death.⁴

Administration challenges

Absorption

Distribution

Pharmacology in older people

Hepatic
metabolism

Renal excretion



Golden rules

1. **Speak to family.**
2. What does the patient with dementia want?
3. Advanced decisions.
4. Advanced statements.
5. Legal framework for drug administration.
6. Low and slow.
7. Titrate to effect.
8. Consider all side effects / contraindications.
9. **Make a plan to review/stop.**

50% prevalence
20-30% Major depression



Accelerated functional decline.
Behavioral disturbance.

Efficacy of Antidepressants for Depression in Alzheimer's Disease: Systematic Review and Meta-Analysis

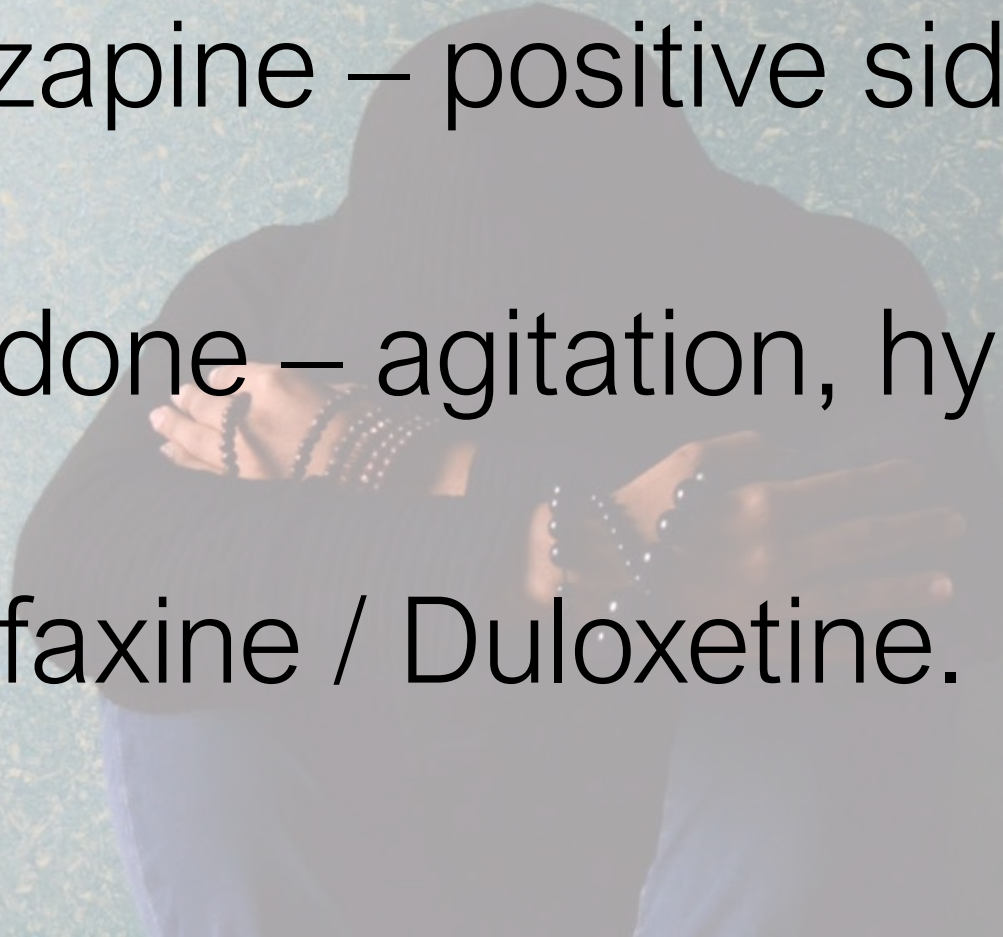
Vasiliki Orgeta^{*}, Naji Tabet, Ramin Nilforooshan and Robert Howard

University College London, Brighton and Sussex Medical School and Surrey and Borders Partnership NHS Foundation Trust, London, UK

Handling Associate Editor: Jeannie-Marie Leoutsakos

‘We found that the overall evidence of effectiveness for antidepressants in people with AD is small, with only a few clinical trials conducted to date. Our pooled meta-analysis (6 RCTs, 297 patients treated with antidepressants and 223 with placebo) failed to show significant differences between antidepressants and placebo for response to treatment. Although the overall difference between antidepressants and placebo failed to reach accepted levels of statistical significance, the analysis trended toward treatment response ($p=0.06$), with the smaller trials contributing a positive effect of antidepressants.’

‘Although our overall analyses were negative, we cannot fully rule out a possible clinical advantage of antidepressants because of the paucity of RCTs.’

- SSRI – Sertraline, Fluoxetine, Citalopram.
 - Mirtazapine – positive side effect profile.
 - Trazadone – agitation, hypnotic.
 - Venlafaxine / Duloxetine.
- 

NICE

National Institute for
Health and Care Excellence

A black and white photograph of a young child covering their eyes with their hands, looking out over a dense city skyline. The child is in the foreground, with their hands pressed against their face. The background is a vast, high-angle view of a city with numerous skyscrapers and buildings, extending to a body of water in the distance. The overall mood is one of anxiety or distress.

Selective serotonin reuptake inhibitor

Mirtazapine

Pregabalin*

Neuropathic pain

Generalised anxiety
disorder

Pregabalin

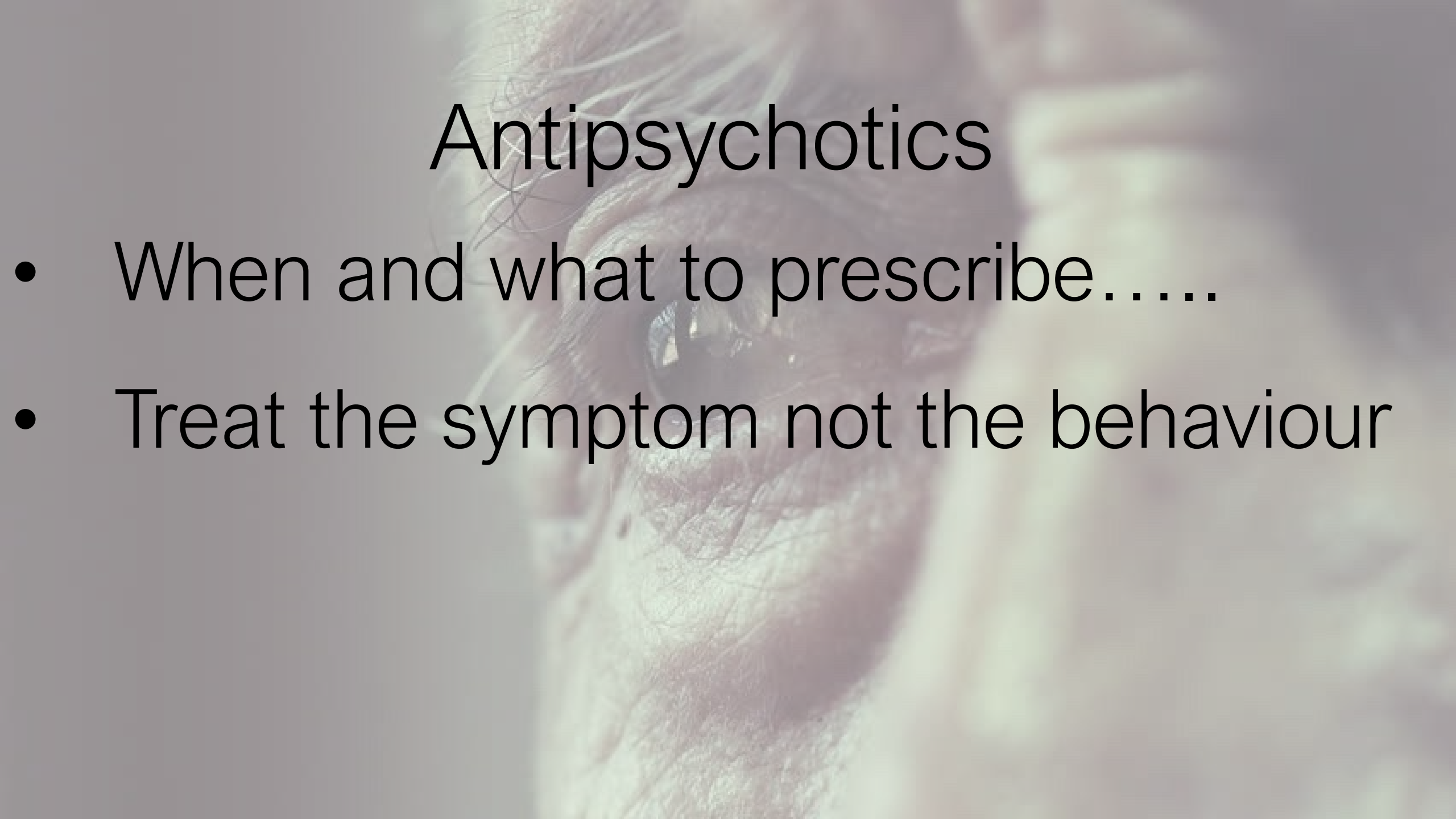
Poor evidence
base, off licence

Low dose 50mg -
100mg

? Treating anxiety
in BPSD

seeing

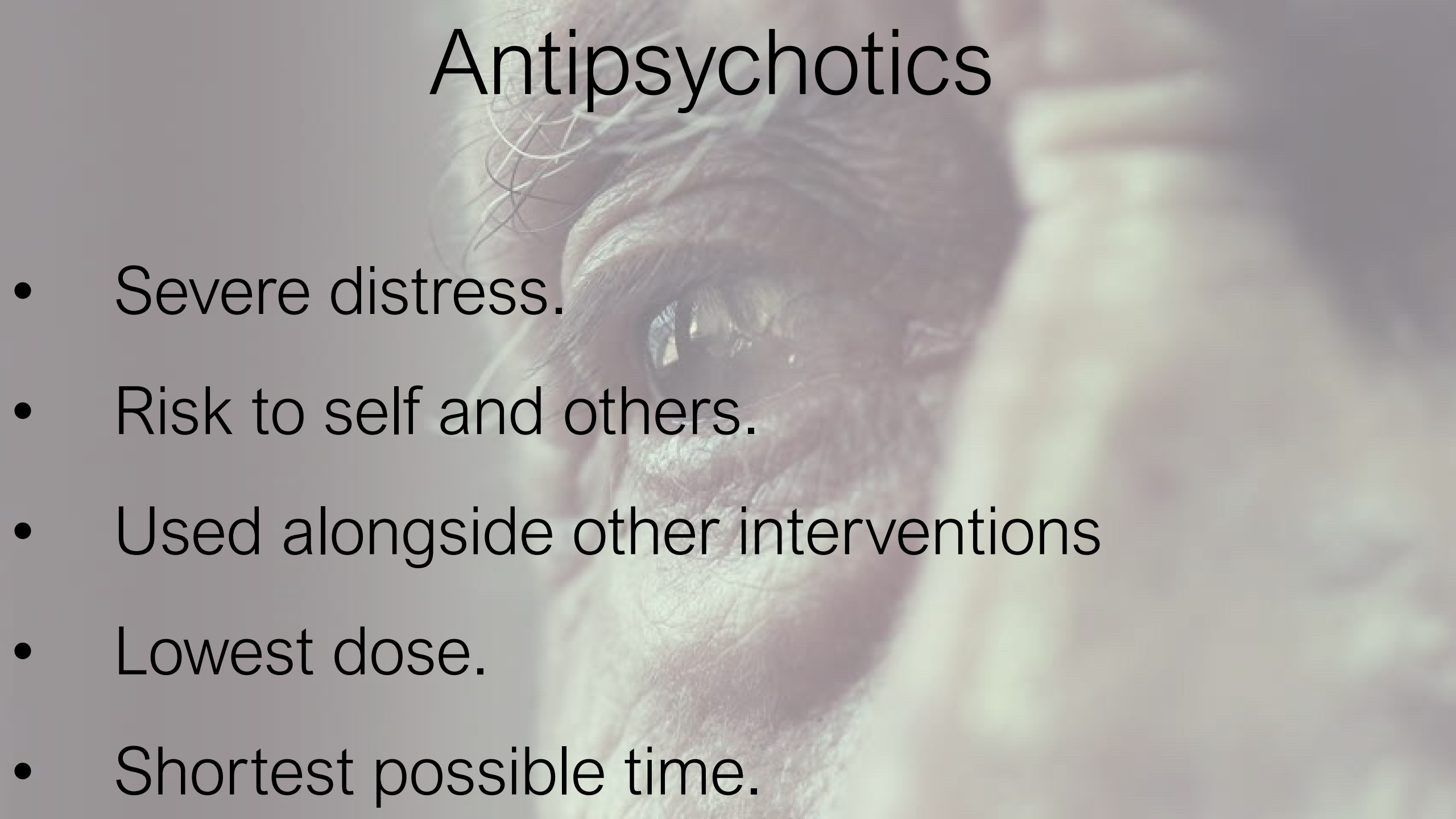
believing

A close-up, slightly blurred photograph of a person's face, showing their eyes and mouth. The person appears to be in a state of distress or discomfort, with their mouth slightly open and a pained expression. The background is out of focus, suggesting an indoor setting with some architectural elements.

Antipsychotics

- When and what to prescribe.....
- Treat the symptom not the behaviour

Antipsychotics



- Severe distress.
- Risk to self and others.
- Used alongside other interventions
- Lowest dose.
- Shortest possible time.

Side effect considerations

A close-up, slightly blurred photograph of an elderly person's face, focusing on the eye and forehead. The skin is heavily wrinkled, and the person has a thoughtful or perhaps slightly distressed expression. The background is out of focus, showing what appears to be a window or a light source.

- Sedation.
- Headache.
- Appetite and weight gain.
- EPSE.
- Stroke and Falls.

'Chemical cosh' drugs given to the elderly triple the risk of stroke

- **The Alzheimer's Society claims antipsychotic drugs can triple the risk of strokes and double the risk of death**
- **National Taiwan University study shows the drugs are most dangerous in high dose and when first taken**
- **Government-commissioned report suggested the drugs kill at least 1,800 dementia patients a year in the UK**



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Antipsychotic drug 'stroke risk'

More people than previously thought could be at higher risk of having a stroke caused by their antipsychotic drugs, say UK scientists.

Previous research suggested only some types of the drug increased the risk, particularly for people with dementia.

However a study published in the British Medical Journal says all forms of antipsychotics boost the risk, in all patients.

A mental health charity said patients on the drugs must be closely monitored.



Antipsychotic drugs are given to people with schizophrenia and dementia

SEE ALSO

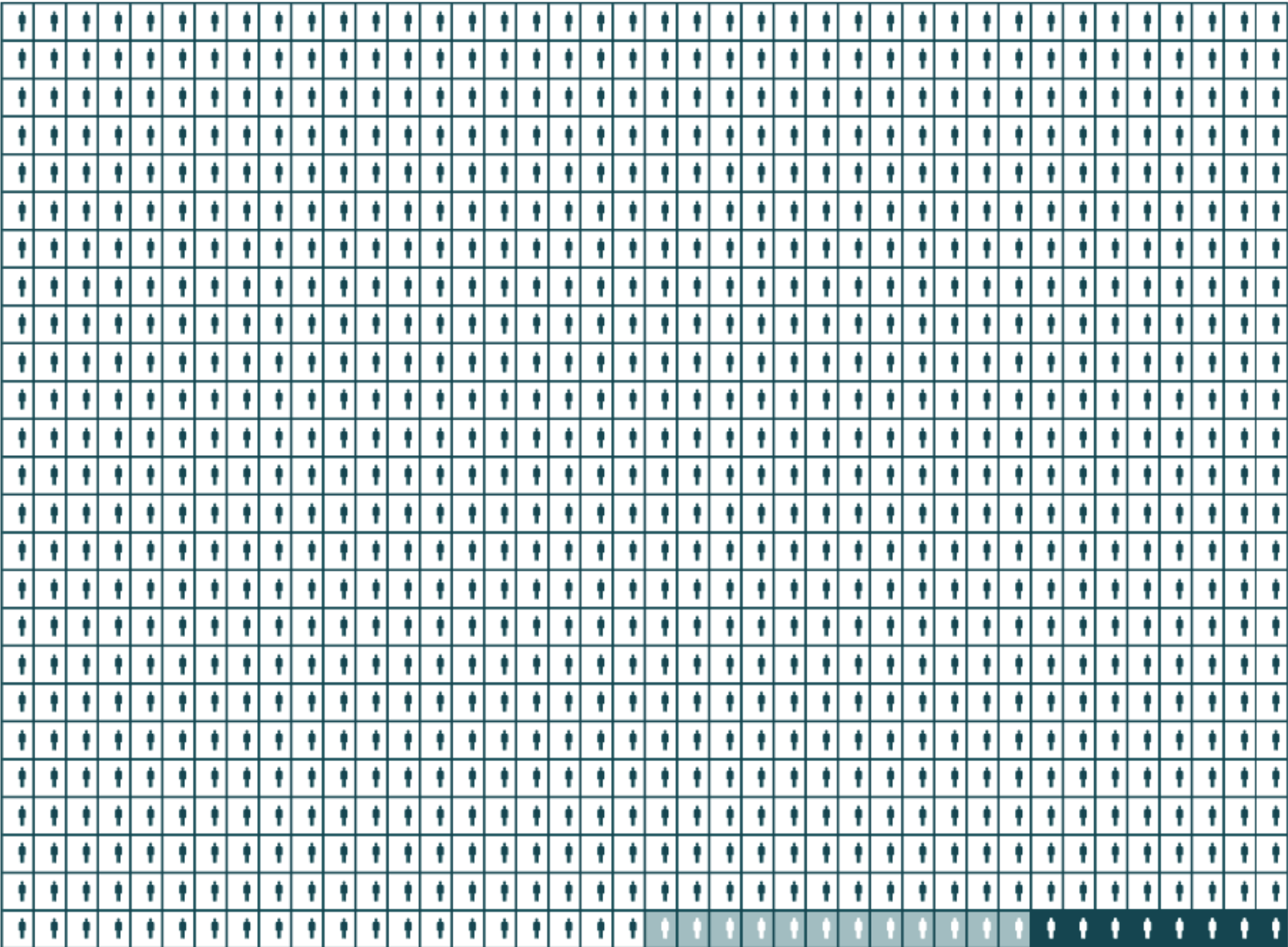
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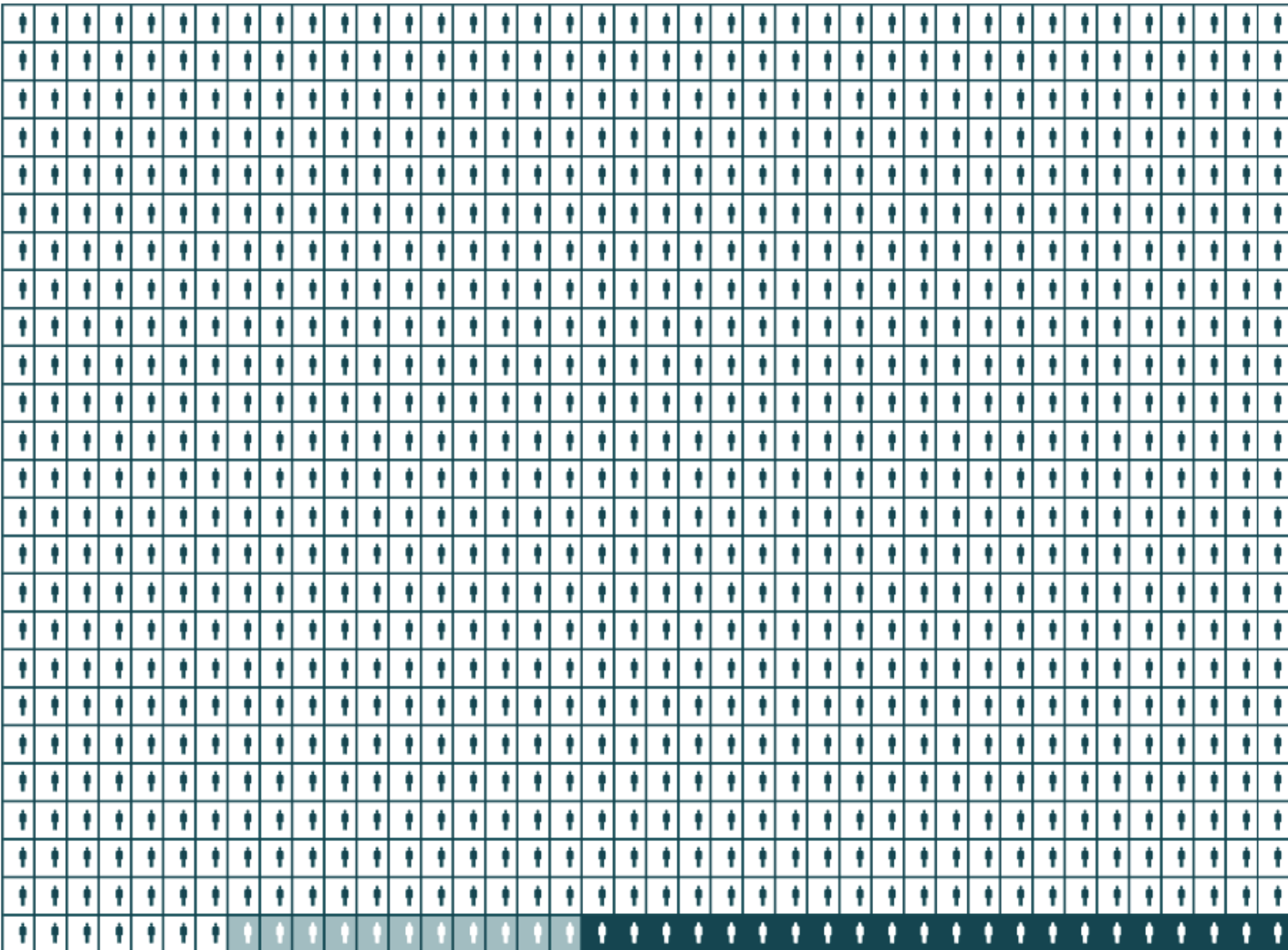
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Effect of antipsychotics on the risk of stroke over 6 to 12 weeks



Effect of antipsychotics on the risk of death over 6 to 12 weeks



NICE

National Institute for
Health and Care Excellence

<https://www.nice.org.uk/guidance/ng97/resources/antipsychotic-medicines-for-treating-agitation-aggression-and-distress-in-people-living-with-dementia-patient-decision-aid-pdf-4852697005>

Antipsychotic choice

- Risperidone - ? The safe (er) option?
- Olanzapine – The all rounder.
- Aripiprazole – Cardiologists friend
- Amisulpride – Diabetologists friend
- Haloperidol – The junior doctors friend
- Quetiapine – Neurologists friend

QTc if possible

Renal function

FBC

Before prescribing

Legal framework

Speak to family

Set a plan to stop the drug



Golden rules

1. Speak to family.
2. What does the patient with dementia want?
3. Advanced decisions.
4. Advanced statements.
5. Legal framework for drug administration.
6. Low and slow.
7. Titrate to effect.
8. Consider all side effects / contraindications.
9. **Speak to family.**

Antipsychotics to manage aggression...

- Olanzapine, Risperidone and Aripiprazole... modest effect on aggression and psychosis in AD over 6-12 weeks.
- Haloperidol: Minor effect controlling aggression. Risks > benefit.
- Quetiapine: No effect – however mixed evidence base.
- Balance risk of mortality.

Ballard CG, Gauthier S, Cummings JL, Brodaty H, Grossberg GT, Robert P et al. Management of agitation and aggression associated with Alzheimer disease. *Nat Rev Neurosci* 2009; 5: 245–55.

Kales HC, Kim HM, Zivin K, et al. Risk of mortality among individual antipsychotics in patients with dementia. *Am J Psychiatry*. 2012;169:71–79

Psychotic symptoms in Parkinson's disease

- Can dopaminergic medication be reduced?
- Rivastigmine
- Quetiapine
- Clozapine

Pimavanserin

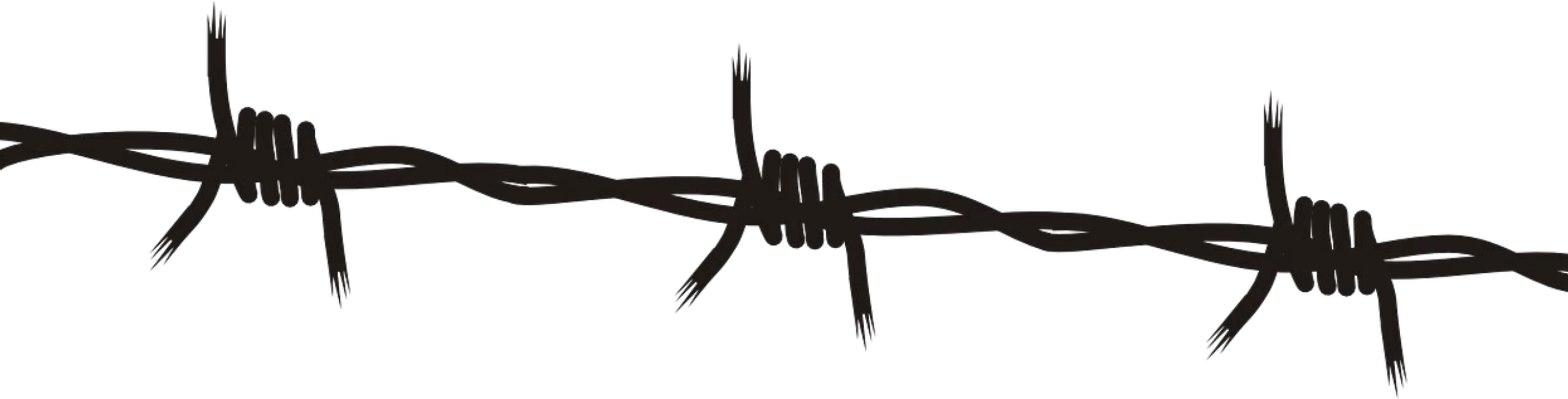
- Inverse agonist and antagonist at 5HT₂ receptors.
- Doesn't interact with dopamine receptors.
- Potentiate the effects of antipsychotics and reduce EPSE related side effects.
- FDA approved not available in the UK yet.
- However.... Evidence base is for short length of time and evidence emerging of high mortality...

Sleep / wake reversal

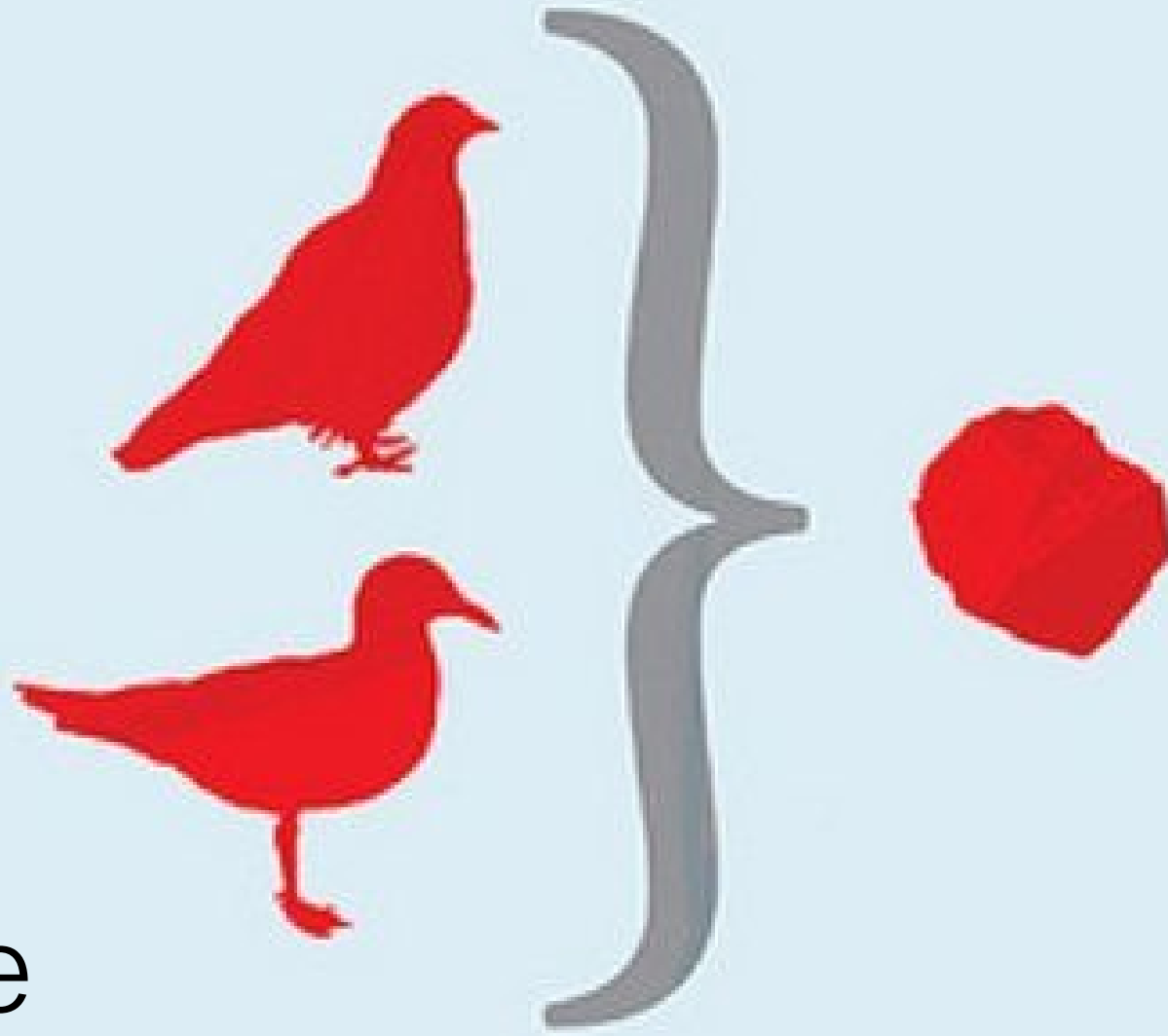


- Zopiclone 3.75-7.5mg
- Melatonin 10mg – mixed evidence, cochrane, no effect and low side effects.
- Trazadone 50mg-100mg – improved time to sleep and time asleep
- Ramelteon 8mg – no effects and poor evidence base.

Treating behavioural symptoms.....



Acetylcholinesterase inhibitors



Memantine

AChIE

- Modest effect size.
- Target depression anxiety and tension.
- Delayed response.

Memantine

- Earlier promising results.
- Targeting agitation, delusions, aggression.
- More recent evidence shows no effect on BPSD.

McShane R, Westby MJ, Roberts E, Minakaran N, Schneider L, Farrimond LE, Maayan N, Ware J, Debarros J. Memantine for dementia. Cochrane Database of Systematic Reviews 2019, Issue 3. Art. No.: CD003154. DOI: 10.1002/14651858.CD003154.pub6

Rodda J, Morgan S, Walker Z. Are cholinesterase inhibitors effective in the management of the behavioral and psychological symptoms of dementia in Alzheimer's disease? A systematic review of randomized, placebo-controlled trials of donepezil, rivastigmine and galantamine. Int Psychogeriatr 2009;21:813-24

5HT2 receptor antagonism and serotonin reuptake inhibition

Good and widely used anecdotal evidence.

Trazadone

Limited evidence base

Fronto Temporal
Dementia

Mood stabilisers

- Valproate – Cochrane - no benefit.
 - Significant adverse event profile.
- Carbamazepine – effective for aggression, agitation, hostility.
 - Significant adverse events – hepatotoxicity, enzyme inducer.

Konovalov S, Muralee S, Tampi RR. Anticonvulsants for the treatment of behavioral and psychological symptoms of dementia: a literature review. *Int Psychogeriatr*. 2008;20:293–308.

Yeh YC, Ouyang WC. Mood stabilizers for the treatment of behavioral and psychological symptoms of dementia: an update review. *Kaohsiung J Med Sci*. 2012;28:185–193

What does the
future hold?



Dextromethorphan/quinidine

- Combination drug containing dextromethorphan, a N-methyl-D-aspartate receptor antagonist and high affinity sigma-1 receptor agonist, and the class I antiarrhythmic agent quinidine.
- FDA approved to treat pseudobulbar affect.
- Significantly improved AD related agitation.

Tetrahydrocannabinol

- Mixed evidence base.
- Initial small trials showed positive effects of reducing agitation.
- More recent larger powered trials (lower doses) more limited effects.

van den Elsen GA, Ahmed AI, Verkes RJ, et al. Tetrahydrocannabinol for neuropsychiatric symptoms in dementia: A randomized controlled trial. *Neurology* 2015;84:2338-46

Walther S, Schuëpbach B, Seifritz E, et al. Randomized, controlled crossover trial of dronabinol, 2.5 mg, for agitation in 2 patients with dementia. *J Clin Psychopharmacol* 2011;31:256-8

Bahji A, Breward N, Duff W, Absher N, Patten SB, Alcorn J, Mousseau DD. Cannabinoids in the management of behavioral, psychological, and motor symptoms of neurocognitive disorders: a mixed studies systematic review. *J Cannabis Res.* 2022 Mar 14;4(1):11.



[Cochrane Database Syst Rev.](#) 2021; 2021(9): CD012820.

PMCID: PMC8446

Published online 2021 Sep 17. doi: [10.1002/14651858.CD012820.pub2](https://doi.org/10.1002/14651858.CD012820.pub2)

PMID: [34532](https://pubmed.ncbi.nlm.nih.gov/34532)

Cannabinoids for the treatment of dementia



Monitoring Editor: Cochrane Dementia and Cognitive Improvement Group, [Dina Bosnjak Kuharic](#), [Domagoj Markovic](#), [Tonci Brkovic](#), [Milka Jeric Kegalj](#), [Zana Rubic](#), [Ana Vuica Vukasovic](#), [Ana Jeroncic](#), and [Livia Puljak](#)[✉]

We found low-certainty evidence suggesting there may be **little or no clinically important effect of cannabinoids on overall behavioural and psychological symptoms of dementia** assessed with the Neuropsychiatric Inventory (or its modified nursing home version) (MD -1.97, 95% CI -3.87 to -0.07; 1 parallel group and 2 cross-over studies, 110 participants).

Citalopram / Escitalopram

- Citalopram for agitation in Alzheimer's disease study - 30mg dose, significant decrease in agitation.
- One trial – as effective as olanzapine and quetiapine.
- QTc prolongation at treatment doses.

Viscogliosi G, Chiriac IM, Ettore E. Efficacy and safety of citalopram compared to atypical antipsychotics on agitation in nursing home residents with Alzheimer dementia. *J Am Med Dir Assoc.* 2017;18:799–802.

Porsteinsson AP, Drye LT, Pollock BG, et al. Effect of citalopram on agitation in Alzheimer disease: The CitAD randomized clinical trial. *JAMA* 2014;311:682-91

Brexpiprazole

- Atypical antipsychotic.
- Mixed evidence base with earlier studies finding no benefit.
- More recent SR evidence showed modest benefit over other second generation antipsychotics.

Lü W, Liu F, Zhang Y, *et al* Efficacy, acceptability and tolerability of second-generation antipsychotics for behavioural and psychological symptoms of dementia: a systematic review and network meta-analysis
BMJ Ment Health 2024;**27**:e301019.

Grossberg, Kohegyi, VMergel, et al. Efficacy and Safety of Brexpiprazole for the Treatment of Agitation in Alzheimer's Dementia: Two 12-Week, Randomized, Double-Blind, Placebo-Controlled Trials, *The American Journal of Geriatric Psychiatry*, Volume 28, Issue 4, 2020, Pages 383-400,



Observed behavior is a normal reaction to an abnormal situation.

Treat the individual.

Communicate treatment decisions.

georgecrowther@nhs.net