



Pharmacological Management of Dementia

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Overview

Management of **cognitive** symptoms

Management of **non-cognitive** symptoms (BPSD)

Medication to avoid in dementia



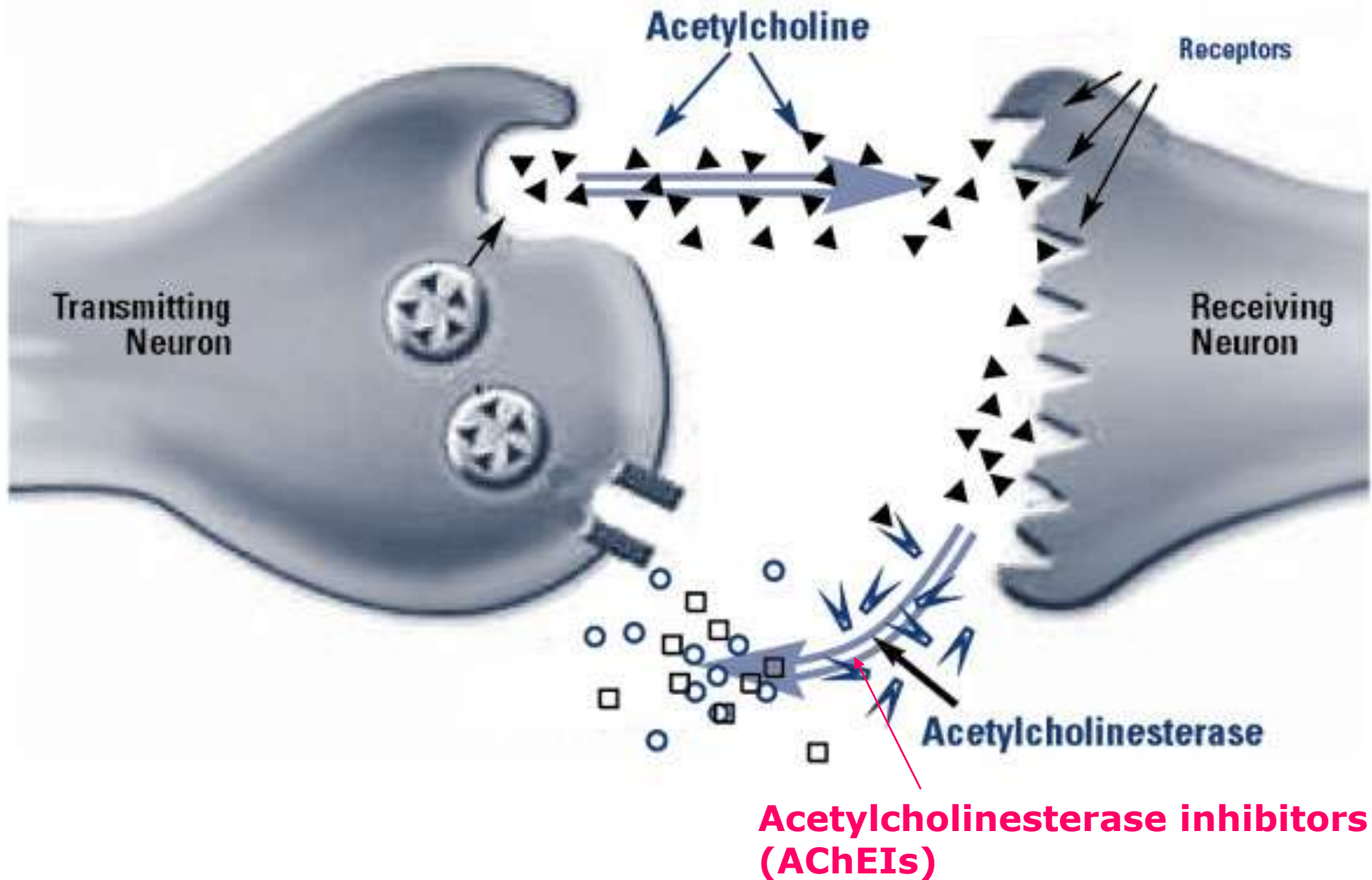
Licensed Treatment

- Acetylcholinesterase inhibitors (AChEIs):
 - Donepezil
 - Rivastigmine
 - Galantamine
- NMDA receptor antagonists:
 - Memantine



AChEIs

- If a response to one agent is not seen then another may be tried.
- Response declines with reducing acetylcholinesterase production, until the agent has little clinical effect.
- Available in a variety of formulations.



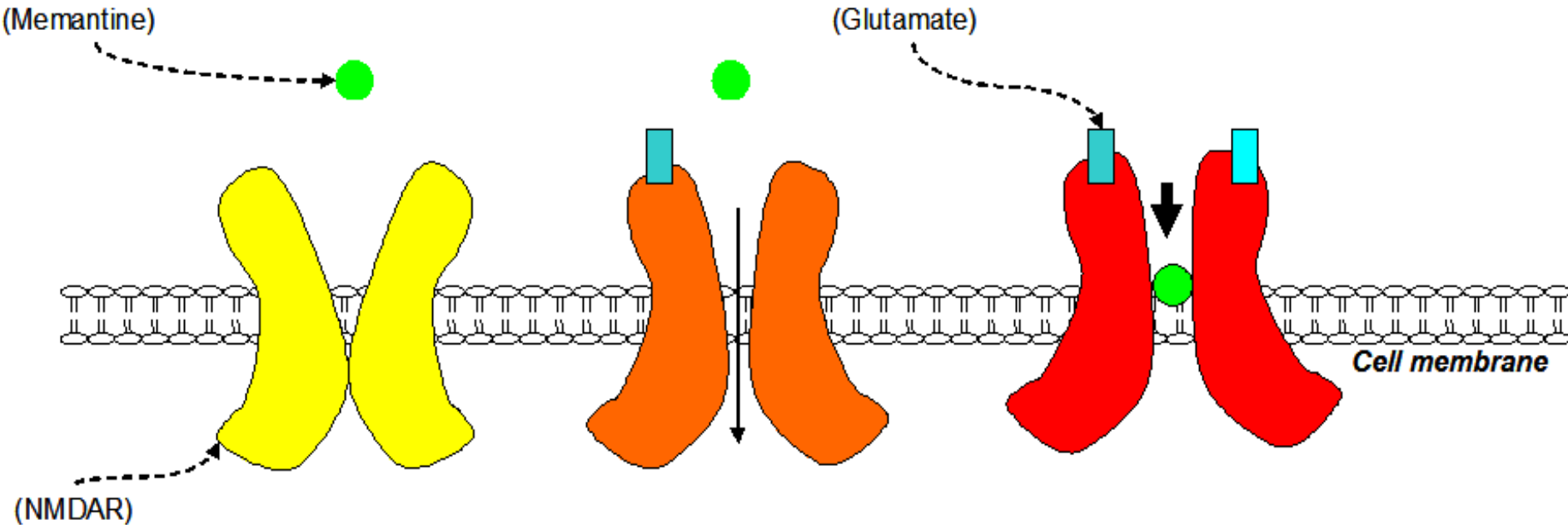
AChEIs

- Caution use in:
 - Supraventricular cardiac conditions
 - Asthma or COPD
 - Peptic ulcer disease
 - Renal/hepatic impairment
- Side-effects:
 - Diarrhoea, fatigue, nausea, vomiting, insomnia and dizziness



Memantine

- Caution use in:
 - History of convulsions
 - Renal/hepatic impairment
- Side-effects:
 - Constipation, hypertension, dyspnoea, hallucinations, drowsiness and dizziness



1. Inactive NMDAR: No memantine effect.

2. Physiological NMDAR activation. Normal ion flux, no memantine effect.

3. Pathological (persistent) NMDAR activation. Massive ion influx and excitotoxicity result. Memantine blocks this channel state.

NICE/Postcode prescribing/AChEIs

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Alzheimer's victory for the Mail: Now just £2.50 can buy a life after U-turn on drugs banned by NICE

By JESSIE HOPE
Last updated at 9:41 AM on 7th October 2010

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Hundreds of thousands of people in the early stages of Alzheimer's will no longer be denied crucial drugs that slow the devastating disease.

A three-year campaign by the Daily Mail ended in victory yesterday when the NHS drug rationing body reversed a ban that had been universally condemned by doctors, patients and their families.

Patients diagnosed with Alzheimer's - who know they are losing their minds - faced the scary situation of waiting for their condition to deteriorate before being prescribed the three drugs.



How the Mail has led the way in fight for victims

ALZHEIMER'S BETRAYAL

Terrible waste **Do not blame** **My husband**
OCT 2006 A coalition of doctors, charities and campaigners announce they will take Nice to court

FOR THE SAKE OF JUST £2.50! **FEB 2007** The Mail launches its own campaign

NICE first allowed the drug, then it did not, and now it says it may only be given to patients in the middle stage. It is the belief of the Alzheimer's Society that this decision was taken simply to save money. That is why it is seeking a judicial review. This is a fight that must be won.

FEB 2007 Daily Mail Comment on the day campaign begins

A decision that beggars belief

FEB 2007 Eminent support pours in as the campaign gathers pace

200,000 thanks
 How your generosity has cleared the way for legal challenge to ban on Alzheimer's drugs

MAR 2007 Generous Mail readers give £230,000 to help Alzheimer's Society pursue its legal challenge



AREN'T OUR LIVES WORTH £2.50 A DAY?

JUNE 2007 The unprecedented case begins at the High Court

Campaigners suffer Alzheimer's setback

AUG 2007 Campaigners lose the legal challenge despite a record 11,000 protests from patients

This issue won't go away. The magnificently generous response of Mail readers shows the depth of national concern. On behalf of Alzheimer's patients and their struggling families, we thank you all. And we promise the fight will go on.

AUG 2007 Daily Mail Comment from the same day pledging to continue the battle

Victory in fight to end Alzheimer's drugs ban

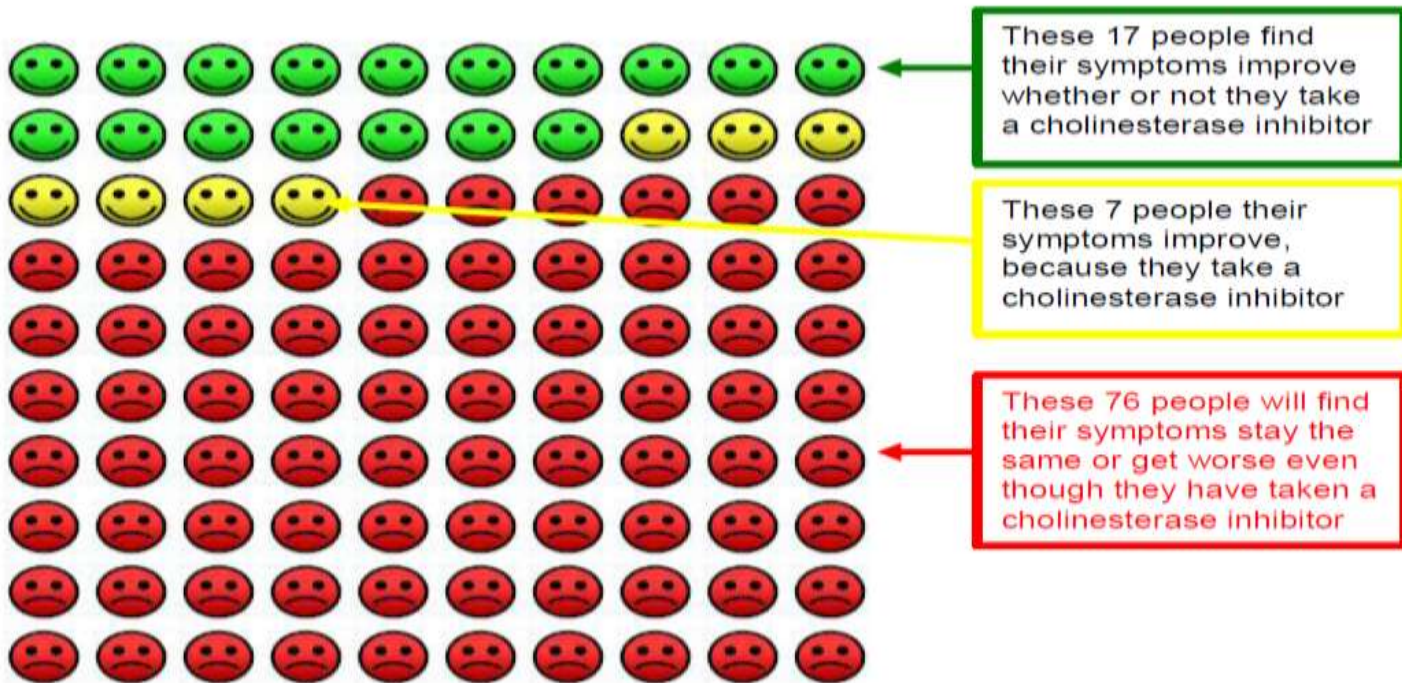
MAY 2008 Court rules Nice acted unfairly

Setback as NHS keeps ban on drug for dementia

JUNE 2009 But Nice refuses to lift ban

Why the fuss?

- All 100 people will have to take a cholinesterase inhibitor for six months.





CURRENT NICE Guidance

- Recommends specialist use of **AChEIs** for mild to moderate Alzheimer's Disease
- **Memantine** approved for use in moderate (where intolerance of anticholinesterase) and severe Alzheimers Disease



Alternative Therapies

- Aromatherapy
- Omega-3
- Ginkgo biloba
- Vitamin E
- Folic acid
- Ginseng
- Vitamin B
- Regular exercise

BPSD

'Behavioural and Psychological Symptoms of Dementia'

e.g. psychosis, agitation, mood disorders, wandering, hallucinations, delusions, anxiety, depression, eating disorders, personality changes, irritability, nocturnal waking, aggressive or resistive behaviour and restlessness.



Medication for BPSD

- Only medicate as a last resort.
- Identify symptoms and review regularly
- Use ABC approach
- Consider associated risks/benefits.
- Record rationale for treatment and medication choice.

“START LOW AND GO SLOW!”



Antipsychotics for BPSD

Psychotic presentations are historically treated first-line with antipsychotics.

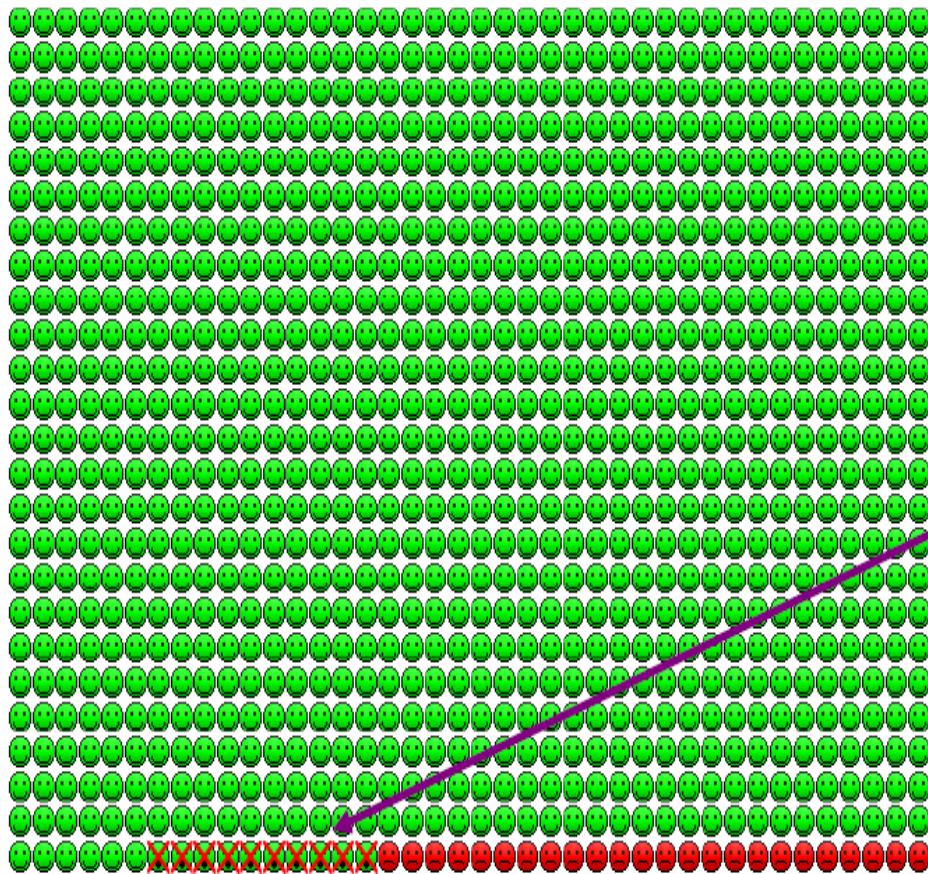
Avoid in dementia due to:

- CNS side-effects
- Increased risk of falls
- Accelerated rate of cognitive decline
- Increased risk of stroke

Controversy

- “Time for Action” report published late 2009
 - Each year, 180,000 people with dementia receive antipsychotics in England.
 - Up to 36,000 of these people benefit to some degree from the treatment.
 - Around 1,620 additional cerebrovascular adverse events (such as stroke), about half of which will be severe, will result from the treatment.
 - Each year, about 1,800 additional deaths will be caused by the treatment in this frail population.

Antipsychotics and death

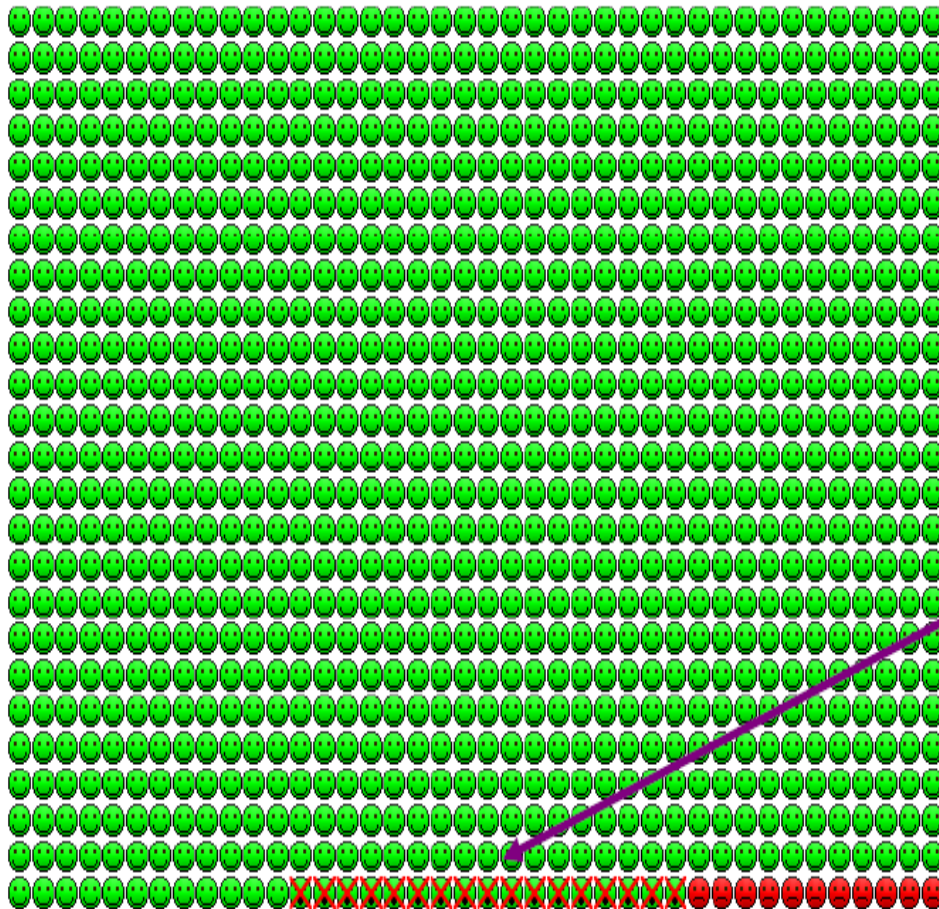


These 966 people do not die in those 6-12 weeks whether or not they take an antipsychotic. Some may suffer other side effects associated with antipsychotic use.

These 10 people die in those 6-12 weeks because they take an antipsychotic.

These 24 people die in those 6-12 weeks whether or not they take an antipsychotic.

Antipsychotics and CVAE



These 972 people do not suffer a CVAE in those 6-12 weeks whether or not they take an antipsychotic. Some may suffer other side effects associated with antipsychotic use.

These 17 people suffer a CVAE in those 6-12 weeks because they take an antipsychotic.

These 11 people suffer a CVAE in those 6-12 weeks whether or not they take an antipsychotic.

Antipsychotics for BPSD

Risperidone is the only antipsychotic with significant evidence for managing aggression and agitation.

500mcg to 2mg daily for maximum 6 weeks

Risperidone treatment exceeding 6 weeks:

- Monitor every 3 months for changes in symptoms and cognition.
- Monitor regularly for the adverse effects.
- Specialist use only

Antipsychotics for BPSD

Off-license use if prescribed for dementia/ BPSD

Alternative options if risperidone inappropriate/not tolerated:

- Olanzapine
- Aripiprazole
- Amisulpiride

AVOID First generation (typical) antipsychotics e.g. haloperidol, chlorpromazine.

Increased risk of extra-pyramidal side effects (with high-potency drugs), postural hypotension and anti-cholinergic side effects (with low potency drugs) in addition to increased risk of CVE and increased mortality.

AChEIs for BPSD

Off-license use if prescribed for BPSD

| Behaviour | Donepezil | Rivastigmine | Galantamine |
|-------------------------|------------------|---------------------|--------------------|
| Agitation/aggression | + | + | - |
| Irritability | + | + | - |
| Anxiety | + | - | + |
| Abnormal motor function | - | + | + |
| Apathy | - | + | - |
| Depression | - | - | - |
| Delusions | + | + | - |
| Disinhibition | + | - | + |
| Hallucinations | - | + | + |
| Euphoria | - | - | - |

+ statistically significant improvement

- no significant effect

Memantine for BPSD

Off-license use if prescribed for BPSD

- Systemic meta- analysis suggested that memantine decreases NPI scores and may have a role in BPSD (reducing agitation/ aggression) but effect size small.
Maidment et al (2008).
- Could be considered for severe agitation/ aggression/psychosis when other medication has failed/is ineffective.

Antidepressants for BPSD

Off-license use if prescribed for dementia/ BPSD

Citalopram: for co-morbid depression/anxiety.

Mirtazapine: for co-morbid depression and SSRI ineffective/tolerated OR first line if increased sedative effect appropriate.

Trazadone: for co-morbid depression and SSRI/mirtazapine ineffective/not tolerated AND increased sedative effect appropriate.

Benzodiazepines for BPSD

Off-license use if prescribed for dementia/ BPSD

- Short term use ONLY for acute AND severe distress where sedation is required.
- Paradoxical disinhibition may occur.
- May cause/ hasten cognitive decline.
- Contribute to falls and hip fractures.
- Accumulation leading to excessive adverse effects/tolerance over time.

Anti-convulsants for BPSD

Off-license use if prescribed for dementia/ BPSD

Valproate and Carbamazepine

ONLY consider when other medication is inappropriate/ineffective.

Side effects include GI disturbances, blood dyscrasias and hepatotoxicity (monitor FBCs and LFTs).

The role of analgesia?

- Norwegian study
 - Stepwise protocol
 - Disturbed behaviour reduced over 8 week period (17% reduction in rating scores)
 - Increased after study ended and analgesia stopped

(BMJ 2011; 343:d4065)



Medication to avoid in dementia

| | |
|--|--|
| Benzodiazepines <i>e.g. Temazepam, nitrazepam</i> | Antihistamines <i>e.g. Chlorpheniramine</i> |
| Tricyclic antidepressants <i>e.g. Amitriptyline, trazodone</i> | Diuretics <i>e.g. Furosemide</i> |
| Antiparkinsonian agents <i>e.g. Levodopa, procyclidine</i> | Anticonvulsants <i>e.g. Phenytoin, carbamazepine</i> |
| Analgesics <i>e.g. NSAIDs, opiates</i> | Oral hypoglycaemics <i>e.g. Tolbutamide, glibenclamide</i> |
| Steroids <i>e.g. Prednisolone</i> | Cytotoxic agents <i>e.g. Methotrexate, flurouracil</i> |
| Antihypertensives <i>e.g. Alpha-blockers, beta-blockers</i> | Antipsychotics <i>e.g. Chlorpromazine, haloperidol</i> |

Health News

Drug danger: how worried should patients be?

Patients should be aware that all medication has side effects and only take medicines that are really required.



Patients should not panic and continue taking their medicines as usual | Photo: ALAMY

By Ian Maidment, Senior Pharmacist with research team
6:00AM BST 24 Jun 2011

We examined the medication records of over 13,000 people aged 65, or over, and found that the use of medicines with anticholinergic activity – meaning they blocked a chemical in the nervous system called acetylcholine- was linked with an increased risk of both mental impairment and death.

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Drugs to avoid in Dementia

ACB Score 1 (mild)

- Alimemazine
- Alprazolam
- Alverine
- Atenolol
- Beclometasone dipropionate
- Bupropion hydrochloride
- Captopril
- Chlorthalidone
- Cimetidine hydrochloride
- Clorazepate
- Codeine
- Colchicine
- Dextropropoxyphene
- Diazepam
- Digoxin
- Dipyridamole
- Disopyramide phosphate
- Fentanyl
- Fluvoxamine
- Furosemide
- Haloperidol
- Hydralazine
- Hydrocortisone
- Isosorbide preparations
- Loperamide
- Metoprolol
- Morphine
- Nifedipine
- Prednisone/Prednisolone
- Quinidine
- Ranitidine
- Theophylline
- Timolol maleate
- Trazodone
- Triamterene
- Warfarin

ACB Score 2 (moderate)

- Amantadine
- Belladonna alkaloids
- Carbamazepine
- Cyclobenzaprine
- Cyproheptadine
- Loxapine
- Meperidine
- Methotrimeprazine
- Molindone
- Oxcarbazepine
- Pethidine hydrochloride
- Pimozide

ACB Score 3 (severe)

- Amitriptyline**
- Amoxapine
- Atropine
- Benztropine
- Chlorpheniramine**
- Chlorpromazine**
- Clemastine
- Clomipramine**
- Clozapine
- Darifenacin
- Desipramine
- Dicyclomine
- Diphenhydramine
- Doxepin
- Flavoxate
- Hydroxyzine
- Hyoscyamine
- Imipramine**
- Meclizine
- Nortriptyline
- Orphenadrine
- Oxybutynin
- Paroxetine
- Perphenazine
- Procyclidine**
- Promazine**
- Promethazine
- Propentheline
- Pyrilamine
- Scopolamine
- Thioridazine (withdrawn)
- Tolterodine
- Trifluoperazine
- Trihexyphenidyl
- Trimipramine

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