Pathways to Success
Live Webinar Series

Drugs and Dementia in the Hospice Patient

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Outcome Resources

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Drug Therapy: Targeted at Symptoms

Cognitive:
- Impaired abstract thinking
- Impaired ability to focus or maintain interest or a thought
- Impaired memory
- Impaired judgment & decision-making ability
- Impaired language and communication abilities

Behavioral/Emotional:
- Agitation
- Psychotic symptoms
- Wandering
- Repetitive speech, yelling
- Insomnia
- Depression

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Cognitive Enhancing Agents

Goal of therapy: **Delay** decline in cognition and function

Cholinesterase inhibitors (ChEI's): increase acetylcholine in brain
- Donepezil (Aricept, Aricept 23)
- Galantamine (Reminyl, Razadyne)
- Rivastigmine (Exelon) oral & transdermal patch

NMDA (n-methyl-d-aspartate antagonist): block NMDA effects in CNS
- Memantine (Namenda, Namenda XR)

Memantine-Donepezil combo (Namzaric)

Miscellaneous:
- Gingko biloba, Vitamin E, NSAIDs, Estrogens
  (insufficient evidence of efficacy- can't be recommended)

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Clinical Trial Findings: Cholinesterase Inhibitors & Memantine

- *Small* but **statistically significant** benefit in cognition and ADL
- Improvements generally classified as "mild"
- Benefits are time limited – may delay decline for 1 to 2 years
- Duration of therapy in trials: 6 months – 2 years
- May delay need for nursing home placement
  (SNF admission delayed in 20% of patients at 2 years of treatment)
- Combination therapy with Memantine and Donepezil shown to be more effective than either drug alone
- Symptoms will inevitably worsen over time despite treatment
- Therapy should be stopped when dementia reaches severe stages

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Duration of Therapy with ChEIs or Memantine

- Cognitive and functional benefits, although modest, have been demonstrated for at least 2 years (UK study with Donepezil)
- Decline in cognition / function is not an indication for D/C *in and of itself* – drugs will not stop decline (just slow it)
- Discontinue when:
  - intolerable side effects are present, or
  - there is a perceived lack of efficacy or benefit, or
  - patient reaches end-stage disease (FAST – 7)
- May re-start if:
  - rapid acceleration in pace of decline is observed within two weeks of stopping drug

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Staging of Dementia with F.A.S.T

- **F**unctional **A**ssessment **ST**aging
- Seven levels based on functioning and ADL
- Level 1 (no difficulties) through Level 7 (severe/end stage)
- Cholinesterase inhibitors & Memantine evidence of efficacy:
  - Stages 3 through 5: Many studies-reasonable benefit
  - Stage 6: Limited efficacy (few studies show marginal benefit)
  - Stage 7: No clinically significant benefit

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Functional Assessment Staging of Alzheimer's Disease (FAST)

STAGE	SKILL LEVEL
1.	No difficulties, either subjectively or objectively. **(Normal)**
2.	Complains of forgetting location of objects. Subjective word finding difficulties. **(Normal older adult)**
3.	Decreased job function evident to co-workers; difficulty in traveling to new locations. Decreased Organizational capacity. **(Early Dementia)**
4.	Decreased ability to perform complex tasks (e.g., planning dinner for guests), handling personal finances (forgetting to pay bills), difficulty shopping, etc. **(Mild Dementia)**
5.	Requires assistance in choosing proper clothing to wear for day, season, occasion. **(Moderate)**

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Functional Assessment Staging of Alzheimer's Disease (FAST)

STAGE	SKILL LEVEL
6a.	Difficulty putting clothing on properly without assistance. **(Moderately Severe)**
b.	Unable to bathe properly (e.g., difficulty adjusting bath water temperature) occasionally or more frequently over the past weeks.
c.	Inability to handle mechanics of toileting (e.g., forgets to flush the toilet, does not wipe properly or properly dispose of toilet tissue) occasionally or more frequently over the past weeks.
d.	Urinary incontinence, occasional or more frequent.
e.	Fecal Incontinence, (occasional or more frequently over the past week).

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Functional Assessment Staging of Alzheimer's Disease (FAST)

STAGE	SKILL LEVEL
7a.	Ability to speak limited to approximately six different words or fewer, in the course of an average day or in the course of an intensive interview (the person may repeat the word over & over). **(Severe Dementia)**
b.	Speech ability limited to the use of a single intelligible word in an average day.
c.	Ambulatory ability lost (cannot walk without personal assistance).
d.	Ability to sit up without assistance lost (e.g., the individual will fall over if there are no lateral rests [arms] on the chair).
e.	Loss of the ability to smile.

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Medicare Hospice Benefit: Dementia Criteria

- FAST level 7 or beyond
- Unable to ambulate without assistance
- Unable to dress without assistance
- Unable to bathe without assistance
- Urinary or fecal incontinence, intermittent or constant
- Speech limited to 6 or fewer intelligible words
- Plus one of the following within past 12 months:
  - aspiration pneumonia
  - pyelonephritis or upper UTI
  - septicemia
  - multiple stage 3 or 4 decubitis ulcers
  - fever that recurs after antibiotic therapy
  - inability to maintain fluid & calorie intake, with 10% weight loss in previous 6 months (very common at FAST - 7)

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Hospice Coverage of Cognitive Enhancing Drugs

- By CMS criteria, a hospice diagnosis of dementia is FAST level 7a or greater
- Cholinesterase inhibitors and Memantine are not effective at this stage
- The drugs have significant potential for side effects (next slide)
- Hospices should not cover these drugs for patients with the hospice diagnosis of dementia

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Side Effects: Cognitive Enhancing Drugs

Clinical Trials Data:

Memantine
- Dizziness (7%)
- Headache (6%)

Cholinesterase Inhibitors
- Headache (10%)
- Insomnia (10%)
- Dizziness (8%)
- Nausea, Diarrhea, Anorexia (6%)
- Bradycardia / syncope*

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*A large population based cohort study of Cholinesterase Inhibitors in dementia patients found increased risk for:
- Bradycardia
- Syncope
- Falls w/ hip fracture

Arch Intern Med. 2009;169(9):867-873:

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Cholinesterase Inhibitor Risk for Cardiac Patients

Patients with pre-existing AV block at risk for:

- Profound sinus bradycardia
- Syncope
- Falls with fracture
- Heart failure

Avoid in patients w/ heart rate < 60 bpm
Bradycardia risk may be enhanced with Digoxin or beta-blockers

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Behavioral and Mood Disorder Symptoms in Dementia

- Agitation (non-specific and danger to self or others)
- Hallucinations/delusions (psychotic symptoms)
- Paranoid and delusional ideation
- Anxiety
- Wandering
- Confusion
- Repetitive continuous speech or yelling
- Sleep disturbance (diurnal rhythms upset)
- Depression and other mood disorders

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Conditions That Often Don't Respond to Drug Therapy

Try Non-pharmacologic Interventions Here:

- Confusion (meds may worsen confusion)
- Wandering (med may increase fall risk for wanderers)
- Continuous repetitive speech/yelling *
  - may be distressing to patient b/c unable to control it
  - may be the only means for patient to communicate distress to others

* **This behavior should prompt further investigation**

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Underlying Causes for Behavior Symptoms?

- Inadequately managed pain
- Constipation
- Urinary retention
- Visual disturbance (blurred vision, dry eyes)
- UTI
- Oral discomfort (dry mouth, dental pain, fungal infection)
- Environmental issues (noise, light, temp, other individuals)

* **Pay attention to increases in volume/frequency of repetitive speech over baseline – may indicate increasing discomfort**

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Drug Therapy May Help These Symptoms

• Agitation (non-specific)	- Antipsychotic, *anxiolytic*?
• Hallucinations/delusions	- Antipsychotic
• Paranoia and delusions	- Antipsychotic
• Aggression/combativeness	- Antipsychotic, antiepileptic
• Anxiety	- SSRI antidepressant, anxiolytic
• Insomnia	- Anxiolytic, sedative-hypnotic, or sedating antidepressant
• Depression	- Antidepressant

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Antipsychotic Dosage Range: Dementia

Traditional (1st generation)

- Haloperidol (Haldol) 0.25mg – 2mg Q12h
- Chlorpromazine (Thorazine) 50mg Q12h

Atypicals (2nd generation)

- Risperidone (Risperdal) 0.25mg – 2mg Q12h
- Quetiapine (Seroquel) 25mg – 100mg Q12h
- Olanzapine (Zyprexa) 2.5mg - 5mg Q24hr

- Implementation strategy: **Start LOW & Go SLOW**
- If needed, increase dose no more frequently once-a-week
- All similar in effectiveness & side effects at this dose range
- Haloperidol > 5mg per day: increased risk of EPS
- Attempt **gradual taper** off at 6 to 12 weeks

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Antipsychotic Drugs Boxed Warning: Increased Risk of Death in Elderly with Dementia

Retrospective review of 17 placebo-controlled trials concluded:

- Risk of death was 1.6X greater with antipsychotic than placebo in elderly dementia patients
- Death rate of 4.5% *vs.* 2.6% over a typical 10-week trial
- Cause of deaths varied but were mostly cardiovascular or infectious in nature
- None of the antipsychotics are FDA approved for dementia-related psychosis

Risk reduction: employ lowest effective dose for limited periods of time – gradual tapers

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Antipsychotic Use: Other Risks for Elderly with Dementia

- Stroke / CVA
- Falls
- Postural hypotension
- EPS (more w/ haloperidol in higher doses > 5mg/day)

Risk reduction: employ lowest effective dose for limited periods of time – gradual tapers

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SNF Antipsychotic Drug Regulatory Exception

F-329 Unnecessary Drug Regulation (Federal law / CMS) Section 483.25

Regulation strictly limits antipsychotic drug use in the SNF patient:

- usage allowed only for certain specific conditions
- criteria for managing specific behavioral issues only
- limited duration of therapy & gradual dose reductions required
- maximum daily dosage limitations

Exception to requirement (spelled out in regulation):

"When antipsychotic medications are used for behavioral disturbances related to adjunctive therapy at end of life."

Location: Under "Intent" section, subsection "Table 1 (Medication Issues of Particular Relevance)"

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Comparative Cost: Antipsychotic Drugs

Drug	Dose (Oral)	Cost of 15-day supply
Olanazpine (Zyprexa)	5mg Daily	$170
Quetiapine (Seroquel)	100mg BID	$190
Risperidone (Risperdal)	1mg Q12h	$130
Chlorpromazine (Thorazine)	50mg Q12h	$190
Aripiprazole (Abilify)	5mg BID	$480
Haloperidol (Haldol)	**1mg Q12h**	**$15 (tab or oral conc. 2mg/ml)**

Cost expressed as Average Wholesale Price (AWP)

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Anxiolytic Dosage Range: Dementia

- Phenobarbital 15mg – 30mg Q8-12h
- Benzodiazepines:
  - alprazolam (Xanax) 0.125 – 0.25mg Q4-6h
  - lorazepam (Ativan) 0.25mg – 0.5mg Q4-6h
  - clonazepam (Klonopin) 0.25mg – 0.5mg Q8 -12h
  - diazepam (Valium) 2mg - 5mg Q12h
  - chlordiazepoxide(Librium) 10mg Q8 -12hr

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Anxiolytic Use: Risks for Elderly with Dementia

- May worsen confusion
- Dis-inhibition effects – may worsen agitation
- Ataxia / Falls
- Lethargy

Risk reduction:

- Use lowest effective dose
- Avoid routine use for extended periods of time
- Avoid long-acting benzodiazepines if possible
- Initiate gradual taper off at 6 to 12 weeks
- Use an SSRI antidepressant instead of anxiolytic or in addition
  - citalopram (Celexa) 10 – 20mg daily

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Common Drugs Used for Insomnia: Dementia

Sedative-hypnotic	
• temazepam (Restoril)	15mg Qhs
• zolpidem (Ambien, Ambien CR)	5mg / 6.25mg Qhs
Antidepressant	
• trazadone (Desyrel)	25 -100mg Qhs
• mirtazapine(Remeron)	15 -30mg Qhs
• amitriptyline (Elavil)*	10 – 25mg Qhs
Antipsychotic	
• quetiapine (Seroquel)	25 -50mg Qhs
Antihistamine	
• diphenhydramine (Benadryl)*	25 -50mg Qhs
• diphenhydramine/APAP (Tylenol PM)*	25 -50mg Qhs

* Drugs not recommended in elderly due to high level of anticholinergic activity and related side effect potential.

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Seditive-hypnotic Use: Risks for Elderly with Dementia

- Increased confusion
- Dis-inhibition effects
- Falls
- Hang-over effect

Risk reduction:
- Use lowest effective dose
- Initiate appropriate sleep hygiene procedures
- Limit usage to 3 nights per week if possible
- Trial of trazadone or mirtazapine, prior to benzo
- Avoid drugs with high anticholinergic activity

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Cost-Effective Alternatives: Hypnotic Drugs

Cost of a 15-day supply of equivalent doses, based on AWP:

Lunesta 2mg	$160
Rozarem 8mg	$180
Ambien CR 6.25mg	$ 90
Zolpidem (Ambien)	$ 40
Trazadone (Desyrel) 50mg	**$ 14**
Temazepam (Restoril) 15mg	**$ 11**

Special case: Temazepam 7.5mg (single source): $150
- alternative is Trazadone 25mg Qhs: $8

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Antiepileptic Drugs (AEDs) for Agitation

Valproate (Depakote)	125 - 250mg Q12h
Carbamazepine (Tegretol)	100 - 300mg Q12h
Gabapentin (Neurontin)	100 - 300mg Q12h

- AEDs are most effective for physical aggression & restlessness
- Not very effective for psychotic symptoms
- Not FDA approved for this use
- Valproate has best response rate of the three (case reports - no head to comparisons available)
- Advantage over antipsychotic drugs: no EPS risk
- Advantage over anxiolytic benzos: less fall risk

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AED Use: Risks for the Elderly with Dementia

- Ataxia
- Sedation (especially with Gabapentin)
- Confusion
- Invasive lab monitoring required for Carbamazepine
  - CBC & liver panel in first 30 days
  - Repeat in 3 months, then Q6 months

Advantage to Valproate (Depakote)
- less sedating than gabapentin
- no invasive lab monitoring necessary
- sprinkle cap available if unable to swallow pills
- more case reports & retrospective reviews suggesting efficacy for agitation

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Antidepressants for Depressive Symptoms in Dementia

- Tricyclic: amitriptyline (Elavil), nortriptyline (Pamelor)
- SSRI:* paroxetine (Paxil), citalopram (Celexa)
- SNRI: venlafaxine (Effexor), duloxetine (Cymbalta)
- Other: mirtazapine (Remeron), Trazadone (Desyrel), bupropion (Wellbutrin)

*SSRIs also effective for treating anxiety symptoms & less likely to be associated anxiolytic adverse effects:
- -Falls
- -Confusion
- -Dis-inhibition

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Antidepressant Use: Risks for the Elderly with Dementia

- Drug interactions
- Sedation
- Confusion
- Anticholinergic effects (tricyclics):
  -constipation, blurred vision, urinary retention, dry mouth, rapid heart rate
- Delayed onset of antidepressant effect (2 – 4 weeks)
- Sedative effects may develop rapidly (mirtazapine, trazadone, amitriptyline, nortriptyline)

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Drugs That Worsen Dementia Symptoms

May worsen behavior, mood, and/or cognitive symptoms:

- Older antihistamines:
  (diphenhydramine, hydroxyzine, OTC sleeping pills)
- All benzodiazepine anxiolytics and sedative-hypnotics:
  (lorazepam, temazepam, diazepam, alprazolam, zolpidem)
- Antispasmodic drugs:
  (hyoscyamine, atropine, scopolamine, Donnatol)
- Older antidepressants:
  (amitriptyline, nortriptyline)

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Drug Interaction: ChEIs vs. Anticholinergic Drugs

Anticholinergic Drugs May Cancel–Out ChEI Beneficial Effects

- Cholinesterase inhibitors (ChEIs):
  - donepezil (Aricept)
  - rivastigmine (Exelon)
  - galantamine (Razadyne)
- Anticholinergics:
  - Atropine, Transderm Scop, Levsin
  - Ditropan, Detrol, Donnatol (other antispasmodics)
  - Benadryl (other older antihistamines)
  - Elavil (other older antidepressants)
  - Anticholinergic activity is ADDITIVE with these drugs

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Conclusion

Pharmacologic management is at directed to 2 areas:
- Cognitive symptoms
- Behavioral /emotional symptoms

Cognitive symptoms respond to ChEI's &/or Memantine
(in mild-to-moderate stages, not for end-stage disease)

Become familiar with FAST staging scale

Some behavioral / emotional symptoms respond to these drugs:
-antipsychotics, anticonvulsants, antidepressants, anxiolytics
(caution with benzodiazepines)
-dosage: Start Low – Go Slow

Always incorporate *non-drug* interventions for behavior management

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