PHARMACOLOGY AT THE END OF LIFE: HIGH-RISK PRESCRIBING AND CLINICAL JUDGMENT IN SERIOUS ILLNESS

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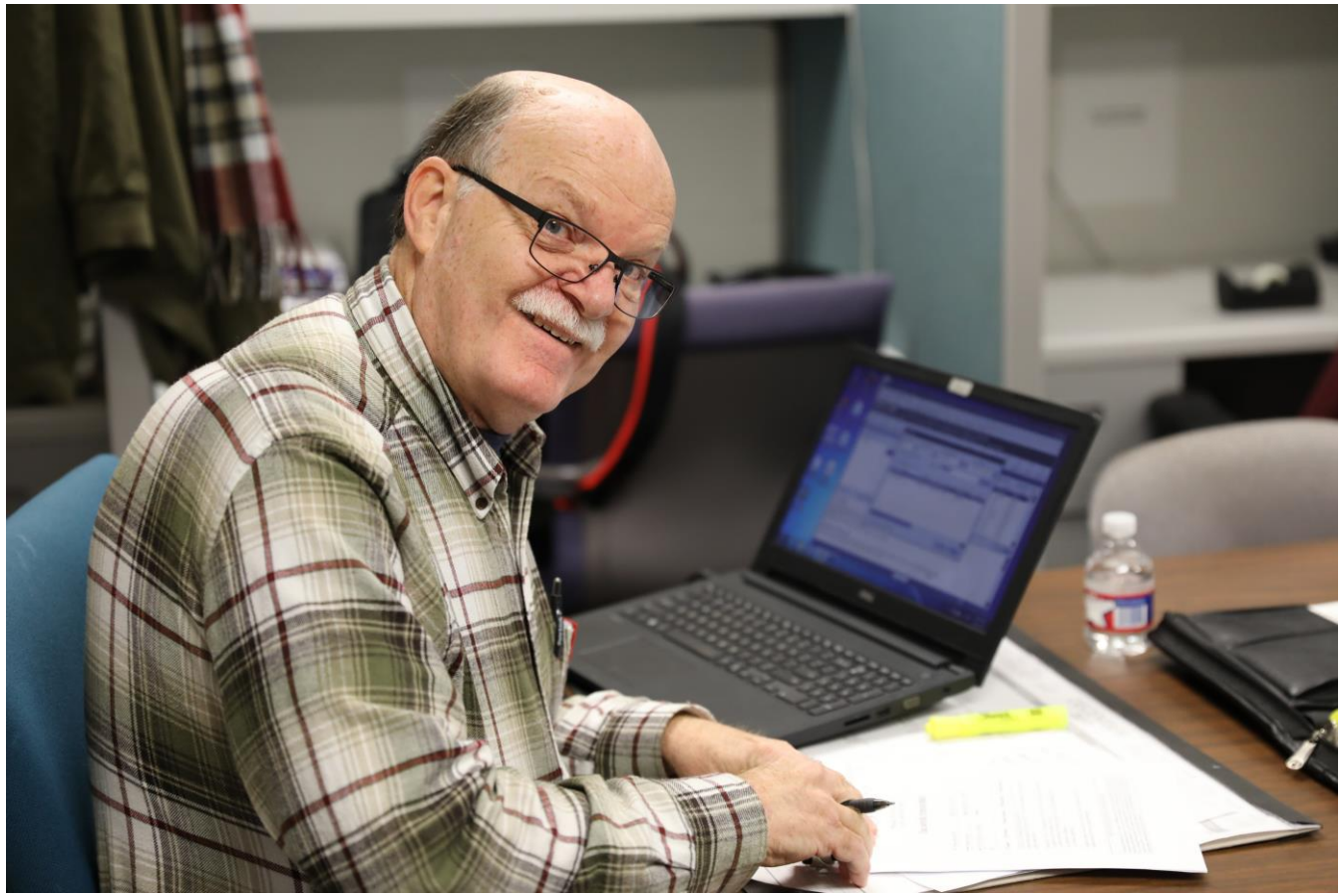
Objectives

1. Describe how physiologic changes in advanced serious illness alter medication response and increase the risk of adverse drug effects.
2. Identify common high-risk prescribing patterns at the end of life, including opioid metabolite accumulation, anticholinergic burden, QTc prolongation, and sedative stacking.
3. Apply palliative-informed deprescribing and dose-adjustment strategies to optimize comfort while minimizing medication-related harm.
4. Integrate clinical judgment and patient-centered goals of care into high-risk pharmacologic decision-making in serious illness.



Mrs. Ramirez

- 74-year-old with metastatic lung cancer
- CKD stage 4, heart failure, diabetes
- Lives at home with daughter
- **Current medications (14 total)**
  - *Morphine ER and IR*
  - *Lorazepam*
  - *Gabapentin*
  - *Sertraline*
  - *Lisinopril*
  - *Metoprolol*
  - *Furosemide*
  - *Atorvastatin*
  - *Insulin*
  - *Ondansetron*
  - *Diphenhydramine (as needed for sleep)*
- **Current symptoms**
  - *Increasing fatigue*
  - *Confusion over the past week*
  - *Myoclonus noted by family*
  - *Pain described as “worse,” despite higher opioid doses*

What is driving her symptoms?

Why Medications Behave Differently at End of Life

- Kidney function declines
- Liver metabolism slows
- Lower protein and weight loss change drug effect
- The brain becomes more sensitive to medications

The same medication and dose can have a very different effect as illness progresses

(Holmes et al., 2020)

Pharmacokinetic Changes

- Medications may stay in the body longer
- Effects can build up over time
- Kidney function declines
- Morphine and gabapentin can accumulate and cause sedation or confusion
- Liver function slows
- Benzodiazepines like lorazepam may last longer than expected
- Changes in weight and nutrition affect response
- Patients may feel stronger effects from usual doses

Medications often last longer and feel stronger as illness progresses

(Twycross et al., 2023; Holmes et al., 2020)

Pharmacodynamic Changes

- The body becomes more sensitive to medications
- Effects may occur at lower doses

- Opioids may cause sedation before pain relief
- Benzodiazepines may cause confusion instead of calming

- Diphenhydramine may cause delirium instead of sleep
- Antihypertensives may lead to dizziness or lightheadedness

- The brain is often the most sensitive organ

“In serious illness, medications are not more dangerous. They are more responsive.”

(American Geriatrics Society, 2023; Holmes et al., 2020)

Examples of Pharmacodynamic Changes

- **Opioids**
  - *May cause sedation at lower doses*
  - *Still first-line for pain and dyspnea*
- **Benzodiazepines**
  - *Can be very helpful for anxiety and dyspnea*
  - *May worsen confusion in some patients*
- **Anticholinergic medications** (e.g., diphenhydramine)
  - *Can contribute to confusion, especially in older adults*
- **Antihypertensives**
  - *May lead to dizziness or lightheadedness as illness progresses*

Most adverse effects are predictable and manageable with dose adjustment and reassessment."

(American Academy of Hospice and Palliative Medicine, 2023; Scott et al., 2015)

Clinical Implications

- Normal doses become high-risk
- Slower titration required
- Monitoring becomes clinical, not lab-based
- Standard dose problems: Lorazepam 1 mg can lead to paradoxical agitation
- Titration adjustments: Start opioids at 25–50% usual dose and extend dosing intervals
- Monitoring: Mental status and function are more important than lab values.

Response to medications becomes the most important data point

(American Academy of Hospice and Palliative Medicine, 2023; Twycross et al., 2023)

Red Flags for Medication-Related Harm

- New or worsening confusion
- Increasing sedation
- Myoclonus or twitching
- Unsteady gait or falls
- Sudden functional decline
- Symptoms that worsen after a medication change

When something changes quickly, review the medication list first

(American Geriatrics Society, 2023; Scott et al., 2015)

Polypharmacy and Risk Amplification

- Patients with serious illness are often on ***10 or more medications***
- Each additional medication increases risk
- Medications do not act in isolation
- Effects combine and build on each other
- One medication change can shift the entire balance
- What was stable can quickly become harmful
- Multiple prescribers and transitions in care increase complexity

Risk is not from one medication. It is from the combination

(American Geriatrics Society, 2023; Centers for Disease Control and Prevention, 2022)

Opioid Metabolite Accumulation

- **Why this matters**
  - *In renal dysfunction, opioid metabolites can build up*
  - *This can cause toxicity even at usual doses*
- **Watch for**
  - *Increasing sedation*
  - *New confusion*
  - *Myoclonus or twitching*
  - *Pain that worsens despite higher doses*
- **Common culprits**
  - *Morphine*
  - *Hydromorphone (less, but still possible)*
- **What to do**
  - *Pause before increasing the dose*
  - *Consider switching opioids*
  - *Reduce dose or space dosing*

(Twycross et al., 2023; American Academy of Hospice and Palliative Medicine, 2023)

Opioid Selection in Organ Dysfunction

- **Why this matters**
  - *Organ dysfunction changes how opioids are processed*
  - *Choice of opioid can reduce risk of toxicity*
- **Higher risk in renal dysfunction**
  - *Morphine*
  - *Codeine*
  - ***Use with caution:*** *Hydromorphone*
- **Lower risk options**
  - *Fentanyl*
  - *Methadone (with experience)*
- **What to do**
  - *Match the opioid to the patient's organ function*
  - *Reassess frequently*
  - *Adjust based on response, not habit*

The safest opioid depends on the patient, not provider preference.

(American Academy of Hospice and Palliative Medicine, 2023; National Comprehensive Cancer Network, 2024)

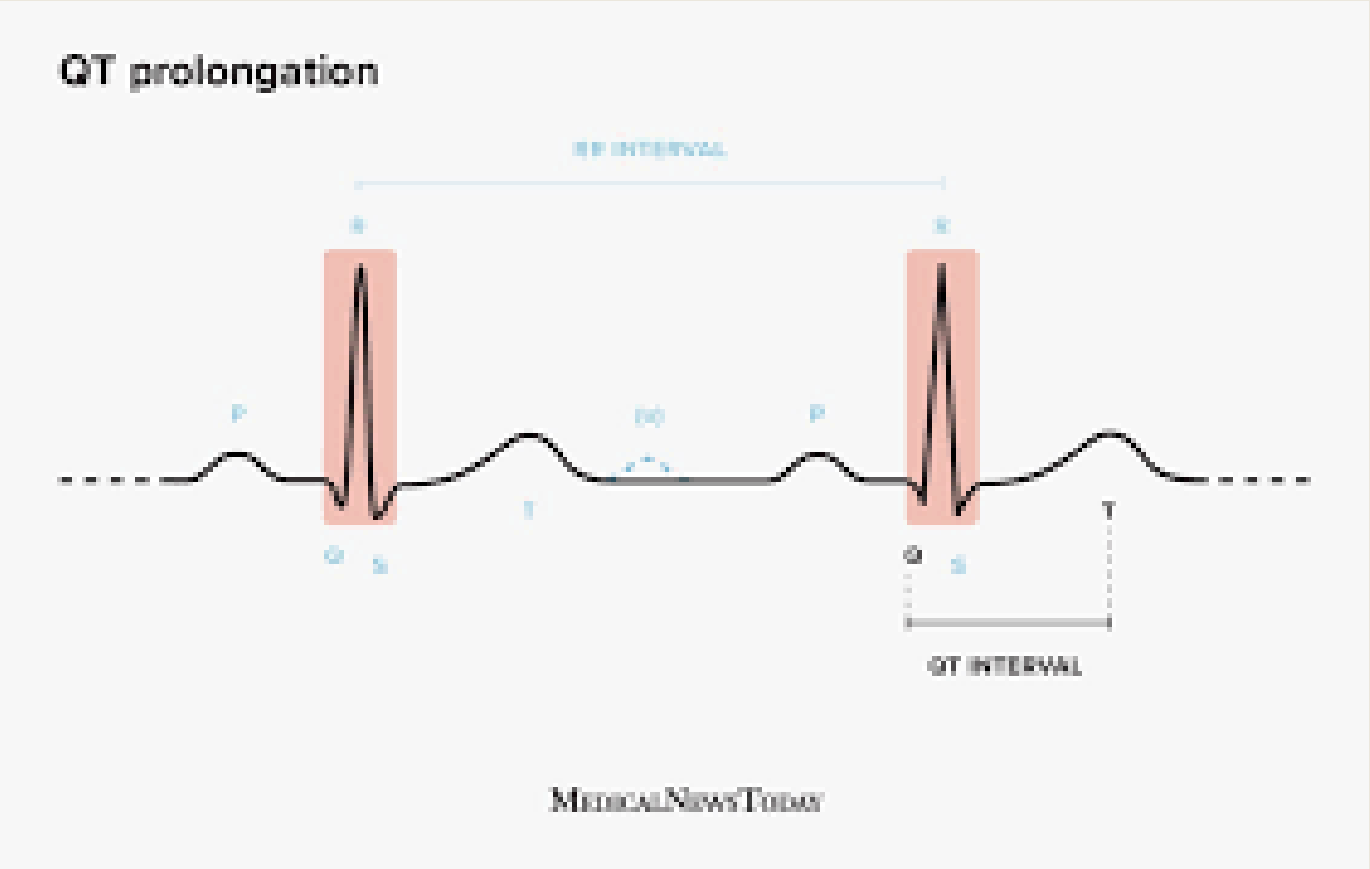
Anticholinergic Burden

- **Why this matters**
  - *Multiple medications can have anticholinergic effects*
  - *Effects add up and increase risk*
- **Watch for**
  - *New confusion or delirium*
  - *Dry mouth*
  - *Constipation*
  - *Urinary retention*
- **Common contributors**
  - *Diphenhydramine*
  - *Amitriptyline*
  - *Oxybutynin*
  - *Promethazine*
- **What to do**
  - *Review the medication list*
  - *Reduce or stop contributing medications*
  - *Choose lower-risk alternatives when possible*

Delirium is often medication-related until proven otherwise

(American Geriatrics Society, 2023; Ruxton et al., 2021)

QTc Prolongation



- Medications:
  - *Methadone*
  - *Haloperidol*
  - *Ondansetron*
  - *Citalopram*
- Risk factors:
  - *Electrolyte imbalance*
  - *Polypharmacy*
  - *Malnutrition or advanced illness*
- What to do
  - *Be aware of combinations*
  - *Correct electrolytes when appropriate*
  - *Reassess if clinical status changes*

Be aware of combinations, especially in frail patients.

(Beach et al., 2020; U.S. Food and Drug Administration, 2023)

Sedative Stacking

- **Common combinations**
  - *Opioid + benzodiazepine*
  - *Opioid + gabapentin*
  - *Opioid + antipsychotic*
  - *Antihistamines added for sleep or nausea*
- **Watch for**
  - *Increasing drowsiness*
  - *Slowed breathing*
  - *Confusion or delirium*
  - *Falls*
- **What to do**
  - *Review the full medication list*
  - *Start low and adjust gradually*
  - *Reassess after each change*

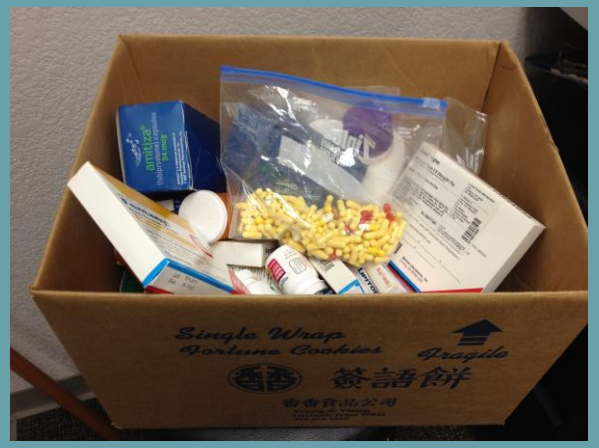
These combinations can be appropriate but require intentional dosing and monitoring

(Centers for Disease Control and Prevention, 2022; Gomes et al., 2022)

When Prescribing Becomes Harmful

- **How it happens**
  - *Medications are added without reassessment*
  - *Side effects are treated with more medications*
  - *Regimens continue after goals have changed*
- **Common patterns**
  - *Escalating opioids without evaluating response*
  - *Adding medications to treat side effects*
  - *Continuing preventive medications in advanced illness*
- **What to watch for**
  - *Increasing fatigue or sedation*
  - *New confusion*
  - *Functional decline*
  - *Growing medication burden*
- **What to do**
  - *Pause and reassess the full medication list*
  - *Ask what is still helping*
  - *Remove what is no longer beneficial*

(Scott et al., 2021)



Practical first step: Have patients bring in all medications, including OTC and PRN.

Deprescribing is Active Treatment

- Reduces harm
- Improves cognition and function
- Aligns with goals

- **Example:**
  - *Stopping statin can lead to an improved appetite, less pill burden*

(Reeve et al., 2022)

Time-to-Benefit vs Time-to-Harm

Statins → years

Bisphosphonates → years

Anticoagulants → months to years

Opioids → hours

(Kutner et al., 2015; Holmes et al., 2020)

Deprescribing Framework

1. Clarify goals
2. Identify non-beneficial meds
3. Evaluate withdrawal risk
4. Stop/taper
5. Monitor

- Gradual steroid taper vs abrupt stop

(Scott et al., 2021; Reeve et al., 2022)

Dose Adjustment Principles

- Start low, go slow
- Adjust for renal/hepatic decline
- Reassess frequently

- **Examples:**
  - *Reduce opioid dose by 25–50% in frailty*
  - *Extend gabapentin dosing interval*

(American Academy of Hospice and Palliative Medicine, 2023; Twycross et al., 2023)

Communication Language

"We are focusing on what helps you feel better now"

"This medication is no longer helping your body"

"These medications are designed to help people live longer over many years. They don't help someone feel better day to day."

"Right now, these medications are more likely to cause harm than help."

"We are not stopping care"

"We are focusing care where it matters most"

(Back et al., 2020; VitalTalk, 2023)

Clinical Judgment vs Guidelines

Guidelines are designed for:

- Stable populations
- Long-term disease prevention
- Single-disease focus
- Assume time and stability

Serious illness requires:

- Individualized risk–benefit decisions
- Shortened time horizon
- Focus on symptom relief and function
- Serious illness requires flexibility and shorter time horizons

(Holmes et al., 2020; American Academy of Hospice and Palliative Medicine, 2023)

Ethical Considerations

- **Primary ethical principles**
  - ***Beneficence:*** *relieve suffering*
  - ***Nonmaleficence:*** *avoid harm*
  - ***Autonomy:*** *honor patient values and preferences*

- **Principle of double effect**
  - *Intention: relieve suffering*
  - *Foreseen but unintended risk: possible life-shortening*
  - *Ethically permissible when proportional*

- **Common tensions in serious illness**
  - *Symptom relief vs medication side effects*
  - *Sedation vs maintaining alertness*
  - *Preventive care vs present-focused care*
  - *Safety vs respecting patient goals*

- **Clinical reality**
  - *Inaction can also cause harm*
  - *Under-treatment of symptoms is an ethical issue*

(Sulmasy et al., 2021; American Academy of Hospice and Palliative Medicine, 2023)

CNS Role

- **Clinical expert in complex pharmacology**
  - *Recognizes medication-related harm early*
  - *Anticipates risk in serious illness*
  - *Applies advanced pharmacologic reasoning*
- **Translator of complexity**
  - *Bridges guidelines to real-world patient context*
  - *Integrates physiology, goals, and symptom burden*
  - *Makes complex decisions understandable to teams and families*
- **Leader in deprescribing and risk reduction**
  - *Identifies non-beneficial medications*
  - *Prevents prescribing cascades*
  - *Promotes safer, goal-concordant regimens*
- **Interdisciplinary influencer**
  - *Guides physicians, APPs, nurses, and pharmacists*
  - *Advocates for patient-centered prescribing decisions*
  - *Shapes team culture around thoughtful medication use*

(National Association of Clinical Nurse Specialists, 2023)

CNS Role

- **Ethical and clinical anchor**
  - *Balances relief of suffering with risk*
  - *Supports families through complex decisions*
  - *Aligns care with patient values*

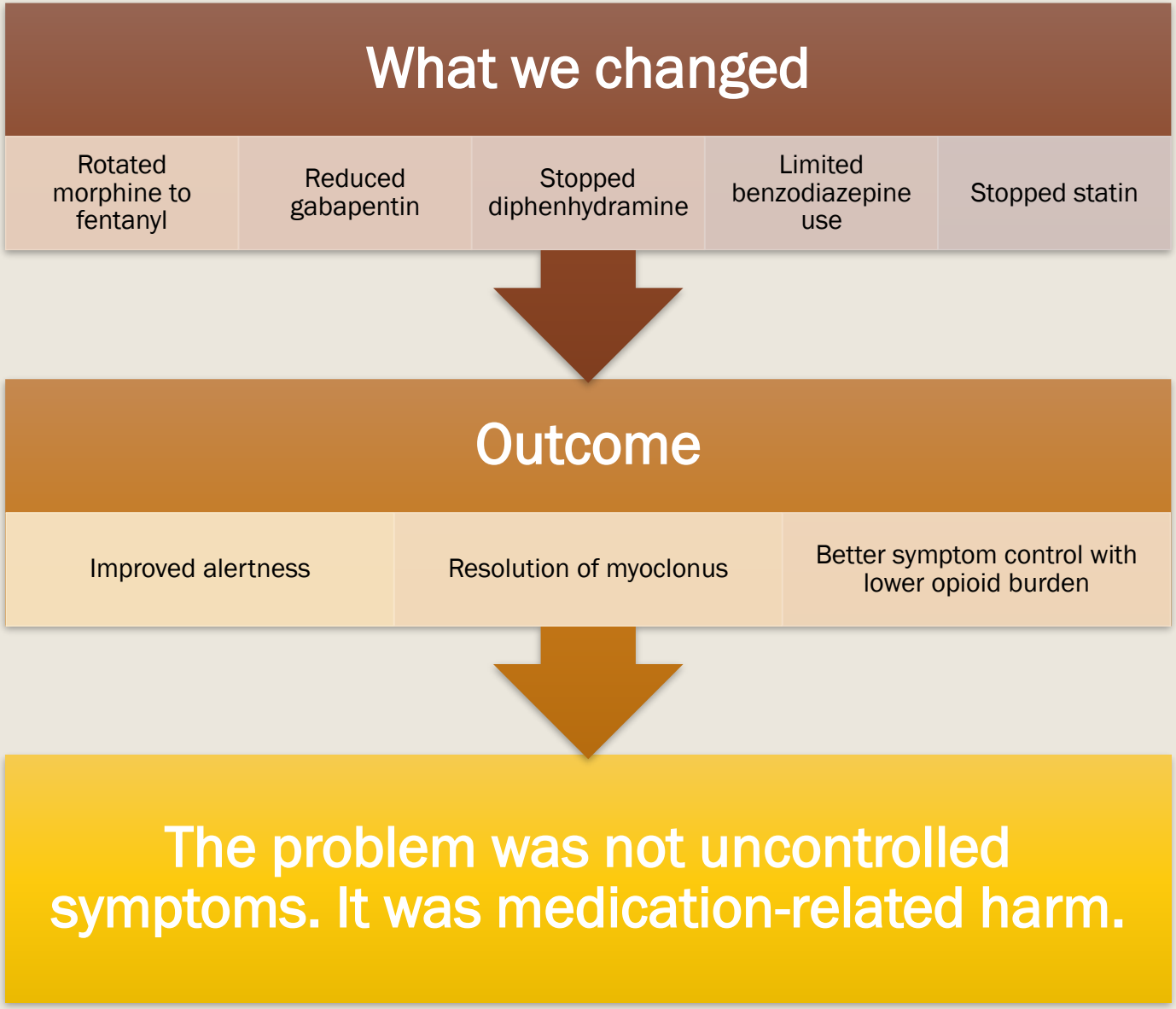
CNSs do not just manage or prescribe medications. They shape how medications are used.

Return to Case

- What would you stop?
- What would you prioritize?
- What risk is acceptable?

(National Comprehensive Cancer Network, 2024; American Academy of Hospice and Palliative Medicine, 2023)

Case Application



Key Takeaways

- Medication response changes in serious illness
- High-risk patterns are common and recognizable
- Worsening symptoms may reflect medications, not disease
- Deprescribing is an essential part of care
- Guidelines inform decisions
- Clinical judgment guides them
- CNSs recognize patterns and lead safe prescribing

Intentional prescribing improves safety, comfort, and quality of life

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