

Painweek.

ADVANCED EDUCATION

CERTIFICATION SERIES



PALLIATIVE CARE

Neuropsychiatric Symptoms

Mary Lynn McPherson, PharmD, MA, MDE, BCPS

Titles and Affiliations

Mary Lynn McPherson, PharmD, MA, MDE, BCPS

Professor and Executive Director,
Advanced Post-Graduate Education in Palliative Care

Executive Program Director, Online Graduate Studies in Palliative Care
(Graduate Certificate, Master of Science, and PhD)

Department of Pharmacy Practice and Science

University of Maryland School of Pharmacy

Disclosures



Learning Objectives

- At the conclusion of this presentation, after being given a simulated patient with one of the targeted symptoms (sleep disturbances/disorder, anxiety, depression, or delirium), the participant will be able to:
 - Assess the complaint
 - Recommend a treatment plan
 - Recommend a monitoring plan and adjust therapy as indicated

Sleep Disturbances in Palliative Care

- Sleep disturbance is defined as “any symptom or condition that interferes with normal sleep”
 - Affects up to 95% of cancer population
 - May be temporary symptom, associated with the cancer, or part of depression/ anxiety
- There are 6 major classifications of sleep disorders:
 - Insomnia
 - Sleep-related breathing disorders
 - Hypersomnia
 - Circadian rhythm sleep disorders
 - Parasomnias
 - Sleep-related movement disorder

Montoya et al. Sleep disturbances in advanced cancer patients. In: Bruera et al. *Textbook of Palliative Medicine and Supportive Care*, 2021.

General Criteria for Insomnia in Adults

- Difficulty initiating sleep, difficulty maintaining sleep, or waking up too early, or sleep that is chronically nonrestorative or poor in quality
- Sleep difficulty occurring despite adequate opportunities, circumstances for sleep
- Patient reports ≥ 1 of the following forms of daytime impairment related to the nighttime sleep difficulty:
 - Fatigue or malaise
 - Attention, concentration, or memory impairment – social or vocational dysfunction
 - Mood disturbance or irritability
 - Daytime sleepiness
 - Motivation, energy, or initiative reduction
 - Proneness for errors or accidents at work or while driving
 - Tension, headache, or gastrointestinal symptoms in response to sleep loss
 - Concerns or worries about sleep

Montoya et al. Sleep disturbances in advanced cancer patients. In: Bruera et al. *Textbook of Palliative Medicine and Supportive Care*, 2021.

Key Etiologic Factors of Insomnia in Cancer Patients

- Predisposing factors
 - Psychiatric disorders, female sex, advancing age, hyperarousability, family history of insomnia, personal history of insomnia, misconceptions about the causes of insomnia
- Precipitating factors
 - Pain, medical illness, mutilating surgery, hospitalization, radiation therapy, bone marrow transplantation, medications (antiemetic drugs, hormonal therapy, chemotherapy), delirium
- Perpetuating factors
 - Poor sleep habits (excessive time spent in bed, napping, irregular sleep schedules)
 - Dysfunctional reactions to sleep (anxiety associated with the act of sleeping)
 - Unrealistic sleep requirements
 - Misattributions of daytime impairment

Montoya et al. Sleep disturbances in advanced cancer patients. In: Bruera et al. *Textbook of Palliative Medicine and Supportive Care*, 2021.

Assessment of Sleep Disorders

- Characterize the sleep difficulty, causes, exacerbating factors, and comorbidities that trigger the sleep difficulty
- Sleep history – ask patient and significant other
- Screening and evaluation tests
 - Self-reports about sleep patency, quality, satisfaction and awakenings
 - Questionnaires on sleep quality, sleep history, sleep diaries, daytime sleepiness
- Laboratory values
- Physical examination
- STOP-BANG questionnaire

Nonpharmacologic Management of Sleep Disorders

- Commonly recommended sleep hygiene measures
 - Maintain a regular bed and wake time schedule including weekends
 - Establish a regular, relaxing bedtime routine (bath, reading book, soothing music)
 - Create a sleep-conducive environment (dark, quiet, comfortable, cool)
 - Sleep on a comfortable mattress and pillow
 - Use your bedroom only for sleep and sex
 - Finish eating at least 2-3 hours before regular bedtime
 - Exercise regularly
(complete at least a few hours before bedtime)
 - Avoid caffeine, nicotine, alcohol close to bedtime

Cognitive behavioral treatment
Progressive muscle relaxation
Hypnosis interventions
Exercise interventions
Regular exercise

Adapted from National Sleep Foundation. Healthy Sleep Tips. American Academy of Sleep Medicine.

Pharmacologic Management of Sleep Disorders

Activity	Medication	Initial Dose (mg)	Considerations
Ultra-short acting	Zaleplon	5-10	Little to no anxiolytic effect, costly
Short-onset brief duration	Triazolam Alprazolam	0.125 0.5-1	Rapid sleep induction; limited effect on sleep maintenance
Short-onset, intermediate duration of action	Zolpidem Zopiclone Eszopiclone	5-10 5-7.5 3	No clear advantage over benzodiazepines; costly; minimal anxiolytic effect
Intermediate onset, duration	Lorazepam Temazepam	0.5-4 7.5-15	Adequate effect on sleep induction and maintenance; risk of daytime drowsiness
Longer latency to onset, prolonged activity	Clonazepam Chlordiazepoxide Diazepam	0.5-2 50-100 5-10	Slow sleep induction with increased risk of accumulation of metabolites; high risk of daytime sedation
Longer latency to onset, prolonged activity (off-label for insomnia)	Amitriptyline Imipramine Doxepin Trazodone Mirtazapine	25-100 25-100 25-100 25-100 15-30	Increased risk of daytime sedation, confusion, constipation and cardiac conduction abnormalities
Variable activity (off-label for insomnia)	Haloperidol Risperidone Olanzapine Quetiapine	0.5-5 0.5-1 5-10 25	Used in sleep disturbance related to psychosis or delirium Other: diphenhydramine, melatonin, ramelteon

Montoya et al. Sleep disturbances in advanced cancer patients. In: Bruera et al. *Textbook of Palliative Medicine and Supportive Care*, 2021.

Depression and Anxiety

- Depression and anxiety are common in cancer and other serious illnesses
- Depression affects 121 million people worldwide
 - 5.8% of men and 9.5% of women experience a depressive episode every year
 - Depression is 2-3 times more common in patients with chronic medical illnesses
 - Depression increases risk of physical decline and long-term mortality in older adults
 - Depression is a risk factor for diabetes, coronary heart disease and stroke
- Depression is defined as...
 - “depressed mood or anhedonia (loss of interest in pleasurable activities) that lasts for at least 2 weeks plus the presence of 3 or 4 other specific psychological or somatic symptoms”
- 50%-60% of cases of depression respond to antidepressants, psychotherapy, or both

“Of course they’re depressed...they’re dying”

- Living with a serious illness such as cancer is a difficult and disappointing way to live
- Cancer patients often have physical symptoms of depression (neurovegetative symptoms) such as sleep disturbance, psychomotor retardation, appetite disturbance, poor concentration, low energy) due to their illness
- Presence of fatigue, pain, lack of energy, weakness and loss of appetite occur in >50% of cancer patients – depression in this context is different from the general population
- Assess risk factors for depression – social and environmental factors, psychiatric factors, cancer-related factors, cancer treatment factors

Common Barriers to Assessing Depression in Cancer

- Overlap of physical symptoms of depression and symptoms of cancer or its treatment
- Clinician's underrecognition of hopelessness, feelings of worthlessness, or suicidal ideation
- Clinician's uncertainty about how to interpret screening instrument cut-offs
- Lack of clinician's routine discussion with patients and family about low mood, not like pain assessment
- Limited understanding by cancer professionals regarding which patients are most at risk
- Time constraints in busy oncology settings

Akechi. Depression/anxiety. In: Bruera, et al. *Textbook of Palliative Medicine and Supportive Care*, 2021.

Common Barriers to Assessing Depression in Cancer

- Cost constraints limiting access to professionals with behavioral health training
- Few mental health programs and specialists connecting with oncology
- Poor continuity of care over the trajectory of illness
- Stigma concerning mental illness or weakness perceived by the patient/family
- Patient/family fear that revealing depression will lead to undertreatment of the cancer

1- or 2-Question Screening Methods

- One question
 - “Are you depressed?”
 - “Please grade your mood during the past week by assigning it a score from 0 to 100, with a score of 100 representing your usual relaxed mood. A score of 60 is considered a passing grade.”
- Two question
 - “Have you often been bothered by feeling down, depressed, or hopeless?”
 - “Have you often been bothered by having a lack of interest or pleasure in doing things?”

Treatment of Depression

- Antidepressant therapy and psychotherapy seem to be equally effective for treating mild-to-moderate depression in the general medical population
- For treating severe depression, antidepressant therapy combined with psychotherapy may be better than psychotherapy alone
- Antidepressants are also effective for treating depression in patients with concomitant physical illnesses
- There are about 40 available antidepressants, that work by at least 8 distinct mechanisms of action
 - No one drug or category of drugs has proved more or less effective for relieving depressive symptoms or treating the syndrome of major depression

Commonly Used Antidepressants

Category/Examples	Comments
Selective serotonin reuptake inhibitors (SSRIs) <ul style="list-style-type: none">• Sertraline• Citalopram• Escitalopram• Fluoxetine	These agents are frequently used. Few anticholinergic or cardiovascular side effects, not fatal in an overdose. Sexual dysfunction, insomnia, headache, or nausea may occur with any of these agents.
Noradrenergic and specific serotonergic antidepressants (NaSSA) <ul style="list-style-type: none">• Mirtazapine	This agent is frequently used for patients with poor appetite and/or insomnia, because it causes sedation and weight gain. For this reason it can be dosed at night to improve sleep and given to patients who have a poor appetite.
Serotonin and norepinephrine reuptake inhibitor (SNRIs) <ul style="list-style-type: none">• Venlafaxine• Duloxetine	In addition to their effect on depression, these agents have been used to decrease the frequency and intensity of hot flashes and neurotoxicity induced by chemotherapy in cancer patients. Dose-related sustained hypertension is an important possible side effect to monitor. These may cause sexual dysfunction, insomnia, headache, constipation or nausea.

Akechi. Depression/anxiety. In: Bruera, et al. *Textbook of Palliative Medicine and Supportive Care*, 2021.

Commonly Used Antidepressants

Category/Examples	Comments
Dopamine and norepinephrine reuptake inhibitor <ul style="list-style-type: none">Bupropion	This agent is also indicated to improve rates of successful smoking cessation. Sometimes used to avoid the sexual dysfunction seen with other agents. Does not treat anxiety. Known to lower the seizure threshold. May cause insomnia, agitation, confusion, headache, or weight loss.
Psychostimulants <ul style="list-style-type: none">MethylphenidatePemolineDextroamphetamine	These agents are known for the rapid onset of action in terms of antidepressant efficacy. They are activating agents and are also used to counteract opioid-induced sedation. Generally given in the waking hours (morning and early afternoon). Should be avoided in patients with unstable ischemia or cardiac arrhythmias. Drug tolerance, abuse, and dependence may occur. May cause nervousness, agitation, insomnia or nausea.

Akechi. Depression/anxiety. In: Bruera, et al. *Textbook of Palliative Medicine and Supportive Care*, 2021.

Commonly Used Antidepressants

Category/Examples	Comments
Tricyclic antidepressants <ul style="list-style-type: none">• Nortriptyline• Amitriptyline• Doxepin• Desipramine	These agents are generally not used because they can cause cardiac arrhythmias, and overdoses are lethal. Baseline electrocardiography is recommended. Often used as adjuvant analgesics at doses subtherapeutic for depression. May cause sexual dysfunction, weight gain, anticholinergic effects or orthostatic hypotension.
Novel antidepressants <ul style="list-style-type: none">• Vortioxetine	This agent is a multimodal antidepressant with two different types of pharmacologic targets: serotonin receptors and transporters including 5-HT _{1a} receptor agonist, 5-HT ₃ , 5-HT ₇ , 5-HT _{1D} receptor agonist, 5-HT _{1B} receptor partial agonist, and inhibitor of 5-HT transporter.

Akechi. Depression/anxiety. In: Bruera, et al. *Textbook of Palliative Medicine and Supportive Care*, 2021.

Unique Issues at the End of Life

- There should be a low threshold for treating depression using short-term therapeutic trials of interventions
- The rapid onset of action of psychostimulants makes this class of drugs appealing in patients very close to the end of life
- Survival time determine susceptibility to pharmacologic treatment
- What to do with the end-of-life patient who expresses desire for death

Anxiety

- Anxiety is a response to threat (serious illness is a serious threat)
- Symptoms uniquely attributable to anxiety include physical symptoms:
 - Tremor, sweating, tachycardia, hyperventilation, restlessness
- Symptoms may also be psychological:
 - Worry, rumination, fear
- In palliative care it may be difficult to distinguish the somatic causes of anxiety from the psychological ones

Common Causes of Anxiety in Palliative Care

Cause	Examples	
Situational	<ul style="list-style-type: none">• Recent diagnoses of serious illness• Impending surgery or chemotherapy• Impending diagnostic imaging	<ul style="list-style-type: none">• Perceived risk for receiving bad news• Fear of death/existential anxiety
Symptom-related	<ul style="list-style-type: none">• Pain• Dyspnea	<ul style="list-style-type: none">• Palpitations• Nausea
Metabolic disturbances	<ul style="list-style-type: none">• Hypercalcemia• Hypoglycemia• Carcinoid syndrome	<ul style="list-style-type: none">• Pulmonary embolus• Paraneoplastic syndrome
Drug-associated	<ul style="list-style-type: none">• Akathisia due to antipsychotics or antiemetics (dopamine-2-agonists)• Steroids• Bronchodilators• Psychostimulants	<ul style="list-style-type: none">• Thyroid replacements• Allergic reactions• Substances or withdrawal from substances
Psychiatric disorders	<ul style="list-style-type: none">• Delirium• Depressive disorders• Panic disorder	<ul style="list-style-type: none">• Posttraumatic stress disorder• Phobias• Generalized anxiety disorder

Akechi. Depression/anxiety. In: Bruera, et al. *Textbook of Palliative Medicine and Supportive Care*, 2021.

Treatment of Anxiety

Category	Examples
Nonpharmacologic	<ul style="list-style-type: none">• Meditation• Cognitive therapies
Benzodiazepines	<ul style="list-style-type: none">• Alprazolam• Diazepam• Lorazepam• Clonazepam• Midazolam
Antidepressant agents	<ul style="list-style-type: none">• SSRI and newer antidepressants
Neuroleptic agents	<ul style="list-style-type: none">• Haloperidol• Atypical antipsychotics
Other drug therapies	<ul style="list-style-type: none">• Buspirone• Beta-blockers (for autonomic symptom relief)• Sedative hypnotics (for relief of insomnia)• Antihistamines

Akechi. Depression/anxiety. In: Bruera, et al. *Textbook of Palliative Medicine and Supportive Care*, 2021.

Self-Assessment!



- Which of the following antidepressants would be useful to treat depression and neuropathic pain, while minimizing the risk for toxicity?
 - A. Amitriptyline
 - B. Duloxetine
 - C. Paroxetine
 - D. Haloperidol

Self-Assessment!



- Which of the following antidepressants would be useful to treat depression and neuropathic pain, while minimizing the risk for toxicity?
 - A. Amitriptyline
 - B. **Duloxetine**
 - C. Paroxetine
 - D. Haloperidol

Delirium

- Defined as a disturbance in attention, awareness, and cognition that develops over a short period of time (usually hours to a few days), represents a change from baseline, and tends to fluctuate in severity throughout the day
- Can take several forms
 - Hyperactive form: patient may be withdrawn, agitated or aggressive
 - Hypoactive form: patient is sluggish with reduced psychomotor activity
 - Mixed form: patient has a normal level of psychomotor activity or rapid switching between forms during the day or even during the episode

Common Causes of Delirium

System	Causes
Brain	Stroke, seizure, head trauma, brain mass or metastases, normal pressure hydrocephalus, infection
Heart, lungs, circulation	Cardiac or pulmonary disease (anything that causes hypoxia), carotid disease, anemia, infection
Digestive, urinary	Hepatic or renal failure, peritonitis, bowel obstruction, fecal impaction, constipation, urinary retention, urinary tract infection
Endocrine	Thyroid, parathyroid, adrenal
Metabolic	Acid-base or electrolyte disturbances, abnormal glucose, dehydration
Toxicity and/or withdrawal	Drugs of abuse, opioids, steroids, benzodiazepines, anticholinergics, immunosuppressants, interferon, histamin-2-blockers (cimetidine and ranitidine)

Cobbs. Recognizing & managing delirium. In: Berger. Principles and Practice of Palliative Care and Supportive Oncology, 5th ed. 2022.

Behaviors/Signs/Symptoms

Behavior/Sign/Sx	Definition
Acute onset	Rapid onset of symptoms over minutes to days, even if symptoms began or occurred in past
Agitation	Unintentional, excessive, and purposeless cognitive and/or motor activity; restlessness
Altered level of consciousness	Clinically differentiable degrees of awareness and alertness, that is, hypervigilant, alert, lethargic, cloudy, stuporous, and comatose
Confusion	Not oriented to person, place, time or situation
Delusion	A fixed and false belief or wrong judgment that opposing evidence does not change. Can be paranoid, grandiose, somatic, and persecutory
Disinhibition	Unable to control immediate impulsive response to a situation
Disorg thinking	Thoughts are confusing, vague, and/or do not logically flow; they are loosely or not connected
Fluctuation, waxing/waning	Intensity changes rapidly; symptoms may come and go
Hallucination	Perception of object that does not exist. May be visual, auditory, olfactory, gustatory, tactile
Inattention	Inability to focus or direct thinking
Irritable	Prone to excessive impatience, annoyance, or anger to get needs met
Labile affect	Rapidly changing and out of context mood symptoms
Psychosis	Loss of contact with reality

Cobbs. Recognizing & managing delirium. *Principles and Practice of Palliative Care and Supportive Oncology*, 5th ed. 2022.

Screening Instruments

- Confusion Assessment Method (CAM)
- Intensive Care Delirium Screening Checklist
- Bedside Confusion Scale

- Diagnosis and Severity Rating Tools
 - Delirium Rating Scale Revised-98
 - Memorial Delirium Assessment Scale



Management of Delirium

- If consistent with patient's diagnosis, prognosis, functional status, and goals of care – attempt to treat the underlying cause of a potentially reversible delirium
- Nonpharmacologic management is KEY
- When necessary, pharmacologic management (safety for the patient, caregivers, and family is of paramount importance)

Nonpharmacologic Management

- Engage patient in mentally stimulating activities to help them with disordered thinking
- Provide orienting and familiar materials to help patients know the time and date, where they are, and which staff are working with them
- Ensure all individuals identify themselves each time they encounter the patient, even if the encounters are minutes apart
- Minimize the number of people interacting with the patient and the quantity of stimulation the patient received (limit loud music and TV)
- Use family or volunteers as constant companions to help reassure and reorient a delirious patient. Encourage staff to sit with patient as they do their documentation

Nonpharmacologic Management

- Provide adequate soft lighting so patients can see without being overstimulated by bright lights
- Manage fall risks
- Provide warm milk, massage, warm blankets, and relaxation tapes to optimize sleep hygiene and minimize sleep disturbances
- Ensure patients use their glasses, hearing aids, etc, to optimize orientation, decrease confusion and promote better communication
- Ensure patients have good nutrition and an effective bowel and bladder management strategy

Nonpharmacologic Management

- Monitor fluid intake; rehydrate with oral fluids containing salt, for example, soups, sport drinks, red vegetable juices, when necessary, infuse fluids subcutaneously rather than intravenously
- Avoid physical restraints unless needed as a last resort to temporarily ensure the safety of both staff and a severely agitated and not redirectable patient and only until less restrictive interventions are possible
- Provide education and support to help family members cope with what they are witnessing

Pharmacologic Management

- There are no medications approved by the FDA for the management of delirium
- There is no consensus among oncologists, geriatricians, psychiatrists, and palliative care specialists on the pharmacologic management of delirium
- Systematic reviews highlight the importance of multicomponent nonpharmacologic strategies
- Guidelines recommend avoiding drug treatment for hypoactive delirium, and the avoidance of benzodiazepines for the treatment of delirium except in cases of alcohol or benzodiazepine withdrawal

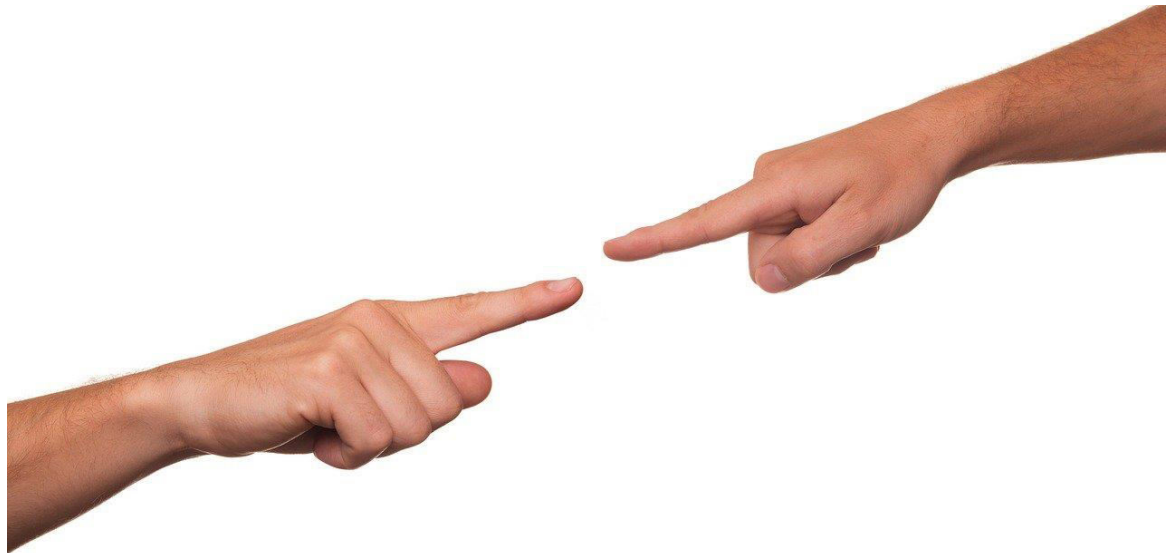
Pharmacologic Management

- Antipsychotic agents

- Haloperidol
- Chlorpromazine
- Olanzapine
- Risperidone
- Quetiapine
- Ziprasidone
- Aripiprazole

- Other agents

- Psychostimulants
- Cholinesterase inhibitors
- Alpha-2-agonists
- Benzodiazepines
- Valproic acid



Self-Assessment!



- True or false: Nonpharmacologic interventions in the management of delirium only provide a small effect; it is best to initiate pharmacologic and nonpharmacologic interventions simultaneously.
 - A. True
 - B. False

Self-Assessment!



- True or false: Nonpharmacologic interventions in the management of delirium only provide a small effect; it is best to initiate pharmacologic and nonpharmacologic interventions simultaneously.
 - A. True
 - B. **False**

Conclusion

- Sleep disturbances are common in the general population, and even more prevalent in serious or advanced illness
- Depression and anxiety often appear in tandem, and presenting symptoms significantly overlap with sickness behavior
- Delirium may have many causes in serious or advanced illness
- Providers should be able to screen for each of these neuropsychiatric symptoms
- Generally speaking, nonpharmacologic interventions should be fully explored before, or concurrently with pharmacologic management

Additional References

- Krystal AD, Prather AA, Ashbrook LH. The assessment and management of insomnia: an update. *World Psychiatry*. 2019;18(3):337-352. doi:10.1002/wps.20674
- Greenblatt HK, Greenblatt DJ. Gabapentin and Pregabalin for the Treatment of Anxiety Disorders. *Clin Pharmacol Drug Dev*. 2018;7(3):228-232. doi:10.1002/cpdd.446
- Bush SH, Tierney S, Lawlor PG. Clinical Assessment and Management of Delirium in the Palliative Care Setting. *Drugs*. 2017;77(15):1623-1643. doi:10.1007/s40265-017-0804-3
- Watt JA, Goodarzi Z, Veroniki AA, et al. Comparative Efficacy of Interventions for Aggressive and Agitated Behaviors in Dementia: A Systematic Review and Network Meta-analysis. *Ann Intern Med*. 2019;171(9):633-642. doi:10.7326/M19-0993
- Agar MR, Lawlor PG, Quinn S, et al. Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative Care: A Randomized Clinical Trial [published correction appears in *JAMA Intern Med*. 2017 Feb 1;177(2):293]. *JAMA Intern Med*. 2017;177(1):34-42. doi:10.1001/jamainternmed.2016.7404

Painweek.

ADVANCED EDUCATION

CERTIFICATION SERIES



PALLIATIVE CARE

Neuropsychiatric Symptoms

Mary Lynn McPherson, PharmD, MA, MDE, BCPS