Depression, Anxiety & Delirium at the End of Life

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Disclosures

• I do not have anything to disclose.
Terms identifying both symptoms and disorders

Symptoms ≠ disorder
- Psychological distress (uncomplicated grief)
- Result of the underlying medical condition
- Effect of medications/treatment
- Delirium

Prevalence (Kolva 2011):
- Mixed anxiety and depressive symptoms 16%
- Anxiety 15%
- Depression 13%
Grief vs. Depression

• Grief
  – Distinct entity
  – Adaptive, universal and highly personalized response
  – May overlap with major depression

• Depression:
  – Pervasive hopelessness, helplessness
  – Worthlessness, excessive guilt
  – Lack of pleasure (anhedonia)
  – Suicidal ideation
Demoralization vs. Depression

• Demoralization (Kissane, 2001) – existential distress, loss of morale and hope
• Over a period of two weeks or more:
  – Meaninglessness, hopelessness, helplessness
  – Difficulty in coping with and meeting the expectations of self or others
  – Feelings of failure or pointlessness
  – Often associated with the desire to die or commit suicide (because the worthwhile future is inconceivable)
• Heightened risk – socially isolated, reduced social functioning, poorly controlled physical symptoms, poorly treated anx/dep, substance abuse
• Can be “contagious” (decision-making processes are greatly influenced by the views of team members)
Interventions:

- Enhance more adaptive coping – perception of the meaning, value, and worth of life (spirituality is protective)
- Helping patients to engage in life rather than passively accept death (rediscovering the meaning)
- Affirmation of each person’s creativity, success and accomplishments (emphasis on person’s inherent sources of strength and resilience)
- Meaning centered psychotherapy, Dignity therapy
Anxiety

- Natural response to suffering, uncertainty, disability, and impending death
- 10% rising to the level of a psychiatric disorder
- Patients may not self-identify as anxious but rather “worried” or “scared”
- Physical symptoms are the most common presenting symptoms of anxiety in advanced illness
- Autonomic hyperactivity, insomnia, or dyspnea often overshadow the psychological or cognitive sx/o anxiety
Anxiety – Differential Diagnosis

- Psychosocial & spiritual concerns (finances, family, dying)
- Uncontrolled pain, dyspnea, hypoxia or cardiac arrhythmia
- Hyperthyroidism, hyperthermia, hypoglycemia, hypocalcemia
- Medications: corticosteroids, bronchodilators
- Akathisia (inner sense of intense restlessness) - antiemetics w/dopamine blocking effects (metoclopramide, prochlorperazine),
- Delirium
- Substance withdrawal (alcohol, opiates, benzodiazepines, nicotine, cannabis)
Anxiety - Treatment

- Should be based on the patient’s subjective level of distress
- Etiology, presentation, and setting
  - Benzodiazepines:
    - Very short acting: midazolam (critical care setting)
    - Short acting: lorazepam, alprazolam, oxazepam
    - Long acting: diazepam (can be administered rectally), clonazepam
  - Antipsychotics:
    - Typical: haloperidol, chlorpromazine
    - Atypical: olanzapine, quetiapine, risperidone
    - When benzodiazepines are not sufficient or concern for respiratory depression
    - Patients at risk for delirium or with symptoms of delirium
  - Antihistamine: hydroxyzine (mild anxiolytic, sedative, and analgesic properties)
  - Antidepressants: (delayed effect)
Depression

- Common yet often undiagnosed and untreated
- Prevalence in terminally ill cancer patients 3 x that of general population (Li, 2012)
- Range increases with higher levels of disability, advanced illness, and pain
- Higher rates reported in patients with pancreatic, gastric, lung, and oropharyngeal cancers

- **Diagnostic challenge** (presence of neuro-vegetative symptoms)
  - Inclusive approach
  - Presence of *hopelessness, helplessness, worthlessness, excessive guilt, and suicidal ideation* – strong indicators of a depressive disorder
  - Certain degree of disengagement is to be expected in advanced disease but pervasive anhedonia may indicate clinically significant depression

- **Untreated depression:**
  - Diminishes quality of life, results in significant existential distress, complicates symptom control
  - Poorer treatment compliance and increased desire for hastened death
Major Depressive Disorder Criteria – DSM-5

- 5 or more symptoms have been present during the same 2 week period and at least one symptom is either depressed mood or loss of interest or anhedonia
- Depressed mood (can be irritable mood in children and adolescents) and/or
- Markedly diminished interest or pleasure
- Weight loss/gain or change in appetite
- Insomnia/hypersomnia
- Psychomotor agitation/retardation
- Fatigue
- Feelings of worthlessness or excessive guilt (not mere self-reproach about being sick)
- Diminished ability to concentrate or indecisiveness
- Recurrent thoughts of death (not just fear of dying)
Barriers to diagnosis:

- Clinic time
- Focus on physical sx (reluctance to “talk about feelings”)
- Confidence in diagnosing and treating depression
- Fear of psychotropic medications and drug-drug interactions
- Stigma
- Pressure to maintain the “fighting spirit”
Depression – Differential Diagnosis

- Normal grief (preparatory)
- Demoralization
- Hypoactive delirium
- Medications (opiates, hormonal agents)
- Chemotherapy (tamoxifen, vincristine, vinblastine)
- Metabolic/endocrine/nutritional disorders (hypothyroidism, B12/folate deficiency)
Treatment

- Significant distress or QoL impact or functioning
- Individually tailored (medical condition, prognosis, frailty, ability to participate in treatment)
- Relieve uncontrolled symptoms, especially pain
- Pharmacotherapy
- Psychotherapy
- Integrative therapies (hypnotherapy, aromatherapy, massage, music therapy)
- Patient and family education
Antidepressants – General Principles

- Start at a lower dose
- Therapeutic action takes 2-4 weeks (for some even longer)
- If it’s not working within 6-8 weeks, it may require a dosage increase (continue to titrate every 2-4 wks) or it may not work at all
- Provide regular follow-up (office, phone-call)
- Symptoms may recur after medicine is stopped
- Different class agents may be combined for complimentary/augmenting effect (e.g. SNRI + bupropion)
- Not addicting
- Failure of one SSRI agent does not preclude the use of another SSRI
- Taper off gradually (risk of discontinuation syndrome with paroxetine and venlafaxine)
- Common SE of SSRIs: nausea, diarrhea, headache, tremor, anxiety, insomnia, sedation, sexual side effects
- Hyponatremia or bleeding abnormalities - uncommon
Antidepressants, cont.

SSRIs:

- Low drug-drug interactions potential (except fluoxetine/paroxetine – both potent 2D6 inhibitors)
- Side effects (SIADH/hyponatremia, platelet dysfunction, Serotonin syndrome)
- Citalopram (QTc prolongation) → escitalopram
- Fluoxetine – once a week dosing (prolonged NPO, intermittent bowel obstruction), rectal administration also available
- Dose formulations (pill vs capsule vs liquid)
Antidepressants, cont.

SNRIs:

- duloxetine (mid-potency 2D6 inhibitor) – avoid in patients with hepatic and renal dysfx
- venlafaxine – also effective for both fibromyalgia and neuropathic pain – unimportant 2D6 inhibitor – appropriate choice in patients on tamoxifen
- desvenlafaxine (active metabolite of venlafaxine) – unimportant 2D6 inhibitor – only ER tabs – generic since 2017
- levomilnacipran (approved in US in 2013 for fibromyalgia) – reportedly most noradrenergic of the SNRIs – unimportant 2D6 inhibitor – once-daily ER tab – generic not available

* SNRIs are a reasonable choice for depressed cancer patients with pain incompletely responsive to opioids (potential co-analgesic benefit).
“Atypical” AD:

- bupropion (N&D reuptake inhibitor) – multiple pill formulations – fatigued and apathetic ca patient – significant 2D6 inhibitor – lowers seizure threshold (avoid in primary brain TU or mts)
- mirtazapine (N&S AD) – pill/sublingual tab – sedating + antiemetic and appetite stimulating – case reports of neutropenia
- TCAs (amitriptyline, nortriptyline) – use with caution, rarely 1st line agents in medically complex adults
Other Agents For Treatment Of Depression

**Stimulants:**
- methylphenidate
- dextroamphetamine
- Rapidly acting for fatigue, apathy, depression
- More appropriate for a depressed dying patient with < 3 weeks to live
- Generally safe but pay attention to CV effects (ionotropic and chronotropic effect)
- modafinil (wakefulness agent) – 2nd line agent (dopamine enhancing effect)

**Ketamine** (general anesthesia) – NMDA antagonist
- Low dose IV administration can rapidly relieve treatment resistant depression
- Widely varying duration of the effect (attenuating over weeks or days)
- No published data on maintenance IV ketamine for depression in cancer patients undergoing systemic chemotherapies
- *May* be helpful in depressed terminally ill with severe pain
Psychotherapy

- Brief supportive psychotherapy (effective for crisis-related and existential issues)
- Behavioral interventions (relaxation, guided imagery)
- Cognitive-behavioral therapy
- Meaning-centered psychotherapy
- Dignity therapy
- Psycho-education
- Hypnosis
- Other alternative therapies (massage therapy, music therapy, aromatherapy, pet therapy)
Latin origin (*delirare*)
- *De* - away from
- *Lira* – furrow in a field

- Going off the line of the furrow (going off the track - becoming a mad person)

- Initially described by Celsus in the 1st century CE
- Thomas Sutton (19th century physician) coined the term ‘delirium’
- Formal clinical definition in DSM III (1980)
Terminology

**Same syndrome – different names:**
- “ICU psychosis”
- Metabolic encephalopathy
- Critical brain failure
- **Acute brain failure (dysfunction)**
- Reversible toxic psychosis
- “Acute dementia”
- Terminal restlessness
Prevalence

- 85% of terminal cancer patients (Massie, 1983)
- 20-42% on admission to palliative care unit
- 32-45% developing delirium post admission to palliative care unit
- 88% during at least last 6 hours of life (Lawlor, 2000)
- Reversible complication or an integral element of dying?
5 key features:

A. Disturbance in attention and awareness (disorientation)

B. Disturbance develops over a short period of time, represents a change from baseline and tends to fluctuate.

C. An additional disturbance in cognition (e.g. memory, language, perception, visuospatial)

D. The A and C are not better explained by another pre-existing or evolving neurocognitive disorder and do not occur during coma.

E. Evidence of direct consequence of another medical condition, substance intoxication/withdrawal, toxins or multiple etiologies
DSM-5 Diagnostic Definition, cont.

**Timing:**
- Acute (few hours – days)
- Persistent (weeks – months)

**Motor subtypes:**
- Hyperactive (e.g. agitated patient)
- Hypoactive (e.g. lethargic patient)
- Mixed (unpredictable alteration between hyper- and hypoactive)

- **Diagnosis of privilege (no other psychiatric diagnosis should be made)**

*Subsyndromal: one or more symptoms that never progress to a full diagnosis of delirium as described by the DSM-5 criteria
- Superimposed on dementia
- “The great imitator” (misdiagnosis is common)
Delirium Subtypes

- Hyperactive Delirium
  - Combative
  - Agitated
  - Restless

- Hypoactive Delirium
  - Lethargic
  - Sedated
  - Stupor

- Mixed Delirium
# Predisposing Factors

## Non-modifiable:
- Age > 65
- Cognitive impairment/dementia
- History of delirium
- Functional dependence
- History of falls
- History of alcohol or drug abuse
- **Co-existing medical conditions:**
  - Chronic liver or kidney disease
  - History of stroke
  - Fracture or trauma
  - Terminal illness
  - HIV infection
  - Multiple co-existing medical conditions

## Modifiable:
- Malnutrition
- Dehydration
- Infection
- **Reduced functional performance status**
- Organ dysfunction/failure
- Illness severity
- **Visual impairment**
- Hearing impairment
- Polypharmacy
Precipitating Factors

**Non-modifiable:**
- Stroke
- IC bleeding
- Meningitis/encephalitis
- Surgery
- Required multiple procedures
- Required bladder catheter

**Modifiable:**
- Medications: Sedative hypnotics, opiates, anticholinergic drugs
- Infections
- Severe acute illness
- Hypoxia
- Shock
- Fever or hypothermia
- Anemia
- Dehydration
- Metabolic derangement
- Use of physical restraints
Assessment

- Bedside assessment
- Interview (Inattention? Perseveration? Slow processing?)
- Mini-Cog (orientation, clock drawing, 3 words recall)
- Neurological signs (frontal release sings)

- Routine nursing assessment
- E.g. Confusion Assessment Method (CAM)
Laboratory & Imaging Work-up

- Mindful of risk (discomfort to patient) and benefit (may be dubious at the end of life)
- Head imaging (CT vs MRI)
- CXR
- EEG (negative result does not rule out delirium)
- EKG
- Laboratory (to identify contributing factors) – needs to be tailored
  - CBC
  - CMP
  - Ammonia level
  - Oxygen saturation
  - Blood Cx/Uricalysis + Cx
  - Thyroid panel
  - B12/folate
  - HIV/RPR
  - Toxicology screen
  - Drug levels (e.g. Li)
Management

Pre-terminal Delirium
Reverse etiology
Reversible

Terminal Delirium
Control symptoms
Irreversible
Treatment

- **Identify and treat reversible precipitants**
- Be mindful of the interference of delirium with assessment and management of pain

- **Non-pharmacological interventions**
  - Oxygen delivery, hydration, electrolyte correction
  - Ensuring bowel and bladder function
  - Visual/hearing aids
  - Frequent orientation
  - Environmental modification (keep the room well lit during the day, minimize nighttime interruptions)
  - **PT/OT** (mobilization – sitting up in bed or chair better than lying down)

- **Pharmacological interventions**
  - Pharmacy (help identify/eliminate deliriogenic agents)
  - Antipsychotic medication (symptomatic management)
Pharmacologic Symptom Management

- No FDA approved medications for treatment of delirium
- “Black box” warning by the FDA: increased risk of death associated with the use of antipsychotics in elderly patients with dementia-related psychosis
- American Psychiatric Association (Workgroup on delirium, 2010):
  - Low dose haloperidol (1-2 mg Q 4 hrs or 0.25-0.5 mg Q 4 hrs for the elderly) remains the “gold standard” therapy for delirium
  - Many years of use in ICU setting with proven efficacy and safety
  - Few anticholinergic effects
  - Lack of active metabolites
  - Availability of different routes of administration (PO, IM, SC, IV)
- Not enough RCTs to provide solid evidence for the benefit and safety of antipsychotics
- Methylphenidate – hypoactive delirium (?)
- Avoid benzodiazepines and anticholinergic agents, if possible
References

- Trzepacz, P et al: Practice guideline for the treatment of patients with delirium. APA Work group on delirium. 2010