# Understanding and Treating Anxiety and Depression in Patients with Families with Advanced Cancer

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## Learning Objectives

- By the end of this discussion, you should be able to:
  - Describe the epidemiology of depression and anxiety disorders in patients with cancer and their family caregivers
  - Recognize the initial pharmacologic and non-pharmacologic treatment strategies for anxiety and depression in cancer
  - Identify the major risk factors for suicide among patients with cancer

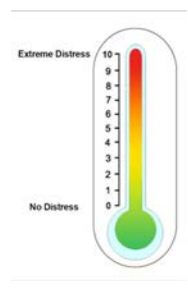
## Anxiety in cancer is . . .

- A normal adaptive response to cancer diagnosis and its treatment (RESPONSE OPTION 1)
- A symptom or disorder leading to disruptions in cancer therapy or impairments in functioning (RESPONSE OPTION 2)

## Symptoms and Syndromes

- Distress (~ 40% of patients and caregivers)*

*** American College of Surgeons Commission on Cancer now requires distress screening for cancer patients treated at comprehensive cancer centers**




Carlson et al, 2003

## NCCN Definition of Psychosocial Distress:

A multifactorial unpleasant experience of a psychological (i.e., cognitive, behavioral, emotional), social, spiritual and/or physical nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment.

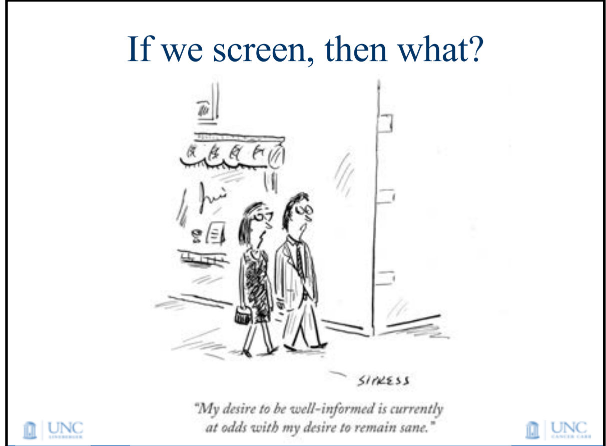
## What Psychosocial Distress is Not

- A single construct
  - It may or may not reflect depression; anxiety, existential dread; worry about finances; embarrassment; etc
- The same in all patients
  - Or in the same patient over time
- Always a cause for intervention…not end of conversation

## Normal response to serious illness and end of life

- Includes anger, sadness, worry, loneliness, fear, hopefulness
- Coping style not associated with mortality risk in cancer
- Most will oscillate between competing styles/outlook
- Significant minority of patients engage in some form of denial

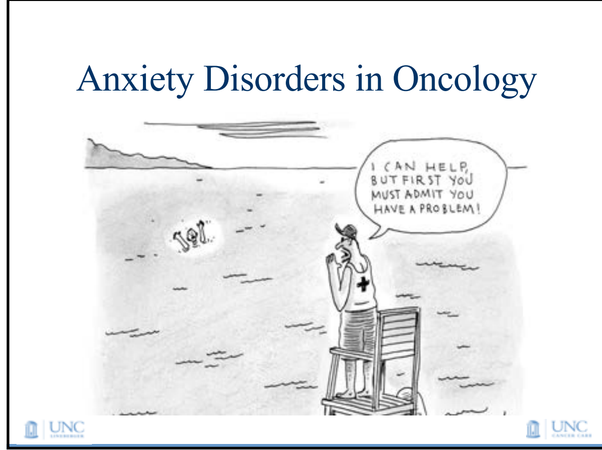
## If we screen, then what?




## Three-tiered clinical pathway

| Brief screen (2 min) | Brief assessment (5-20 min) | Full evaluation (30+ min) |
| --- | --- | --- |
| Identify distress severity | Determine need for clinical intervention<br>Guides next steps | Comprehensive evaluation<br>Establish diagnosis & management plan |

## Anxiety Disorders in Oncology




## Anxiety in cancer

- Common even in non-cancer populations
- Persistent, potentially chronic in some
- Difficulty with adaptation

## Anxiety disorders in context

Lifetime prevalence of anxiety disorders (US)

33%

12-month point prevalence in US population = 10%

Point prevalence of anxiety disorders among cancer patients shows **similar rates** to US population norms

48%

Prevalence of clinically significant (HADS >7) scores among oncology patients

Pozo-Kaderman, 2017; Stark et al, 2002

## What is the prevalence of anxiety for cancer patients?

- Depends on when and how you ask
- Pre-treatment
  - Anxiety more prevalent than depression
  - Anxiety symptoms ranging from 21-54%
  - Clinically significant 10-20%
- During
  - Substantial declines during treatment (rates are half)
- Post-treatment
  - Depression more prevalent, anxiety variable but generally lower

Stiegelis et al, 2004

## Trajectories of anxiety from baseline to 24 months s/p breast cancer surgery

From: Saboonchi F, et al. J Psychosocial Oncology

## Management considerations

- Temporary distress versus manifestations of new or chronic anxiety disorder?
- Symptom severity
- Risk for physiologic contributors
- Risk for substance use disorders
- Life-expectancy
- Willingness to engage in treatment

## Initial treatment for anxiety

- Ongoing/chronic or severe symptoms merit treatment that addresses prevention and long-term management
- Antidepressants
  - SSRIs, SNRIs, mirtazapine
  - Patient education about treatment
- Limited value in patient when life expectancy is only a few days to weeks

## As needed/immediate symptom relief (mostly off-label)

- Benzodiazepines
- Non-benzodiazepine anxiolytics
  - Gabapentin
  - Buspirone
  - Hydroxyzine
  - Propranolol, clonidine, and guanfacine
  - Hydroxyzine
- Neuroleptics (antipsychotics)
  - Quetiapine, risperidone, olanzapine commonly used

## Additional notes re: benzodiazepines

- Benefits
  - Immediate symptom relief for most
  - Multiple routes of administration
  - Helpful for variety of symptoms
- Drawbacks
  - Habit-forming
  - Tolerance and withdrawal
  - Respiratory effects, daytime sedation, cognitive slowing, falls

## Additional notes re: benzodiazepines

- Patient selection and education are key
- Utilize the Prescription Database Monitoring Program
- Lorazepam or clonazepam most commonly used

## Psychotherapies

- Should accompany pharmacologic therapy whenever possible
- Very effective for motivated patients
- Cognitive behavioral therapy best studied
- Mindfulness, guided imagery, relaxation
  - Multiple useful apps to help with this (many are free)

## Depression Disorders in Oncology

"Am I a happy man or just an asymptomatic one?"

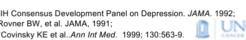
## Depression in cancer patients

- Cancer diagnosis itself is a risk factor for depression
  - Nearly one in five patients who are seriously ill meet criteria for major depressive disorder
  - Prevalence increases as physical symptoms grow
  - Highest in patients with head and neck cancer, pancreatic, breast and lung

Zhao et al, 2014

## Impact of Depression

- Increased morbidity
  - Worsens severity of pain & other symptoms
  - Decreases function
- Health behavior
  - Decreased adherence to cancer treatment
- Worse quality of life
- Increased mortality
  - Suicide and cancer-related mortality
- Increases cost


*NIH Consensus Development Panel on Depression. *JAMA.* 1992;
**Rovner BW, et al. JAMA, 1991;
***Covinsky KE et al..*Ann Int Med.* 1999; 130:563-9.

## Risk Factors for Depression in Serious Illness

- Younger age
- Prior history of depression
- Uncontrolled physical symptoms
- Cancer type
- Treatment
  - CNS involvement, steroid exposure, interferon, endocrine therapies

## DSM-V Criteria

- At least 5 symptoms over 2 week period and represent change in functioning
  - Core sx: Depressed mood or loss of interest (anhedonia)
- Major Depressive Episode checklist (SIGECAPS)
  - **Depressed mood** most of the day, nearly every day
  - **Sleep** disturbance [S];
  - Diminished **interest** or pleasure [I];
  - Feelings of worthlessness, **guilt** [G];
  - Fatigue or loss of **energy** [E];
  - Diminished ability to **concentrate**, or indecisiveness [C];
  - Poor **appetite** or significant weight loss [A];
  - **Psychomotor** agitation or retardation [P];
  - Thoughts of death, **suicidal** ideation/plan [S]

American Psychiatric Association. Diagnostic and Statistical Manual (5th edition) 2013

## Key Features of Depression in the medically ill

- Depressed mood, sadness, grief, and anticipatory feelings of loss *are* appropriate.
- The following *are not*:
  - Persistent guilt
  - Feelings of worthlessness, hopelessness and helplessness
  - Social withdrawal
  - Suicidal ideation

Breitbart et al. Oncology. 1987

## Questions Used to Differentiate

- Are there moments you can still feel joy, despite the the sorrow you have been through?
- What keeps you going on difficult days?
- From what sources do you draw hope?
- Would you do more if you could physically?
- Do you feel you are to blame or deserve your illness?

## Detection of Depression

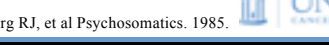
"Are you depressed?"

Single question screening is both sensitive and specific

Chochinov et al. Am J Psychiatry 1997

## Diagnostic and Therapeutic Obstacles

- Fluctuating course of illness
- Shared symptoms with other disorders
- Symptoms seen as "appropriate"
- Reluctance to treat patients w/ limited life expectancy
- Limited life-expectancy before desired results of intervention
- Poor evidence base
- Drug-drug interactions



Goldberg RJ, et al Psychosomatics. 1985.

## Depression, cognitive impairment and delirium

**Shared symptoms**



**Shared risk factors**



Downing LJ, et al., Curr Psychiatry Rep. 2013

## Treatment of depression in outpatients with cancer and MDD



Study of 21151 patients in the U.K. completing the HADS, 1538 diagnosed with MDD and with complete treatment data

Walker et al, Lancet Psychiatry, 2014

## Depression Care for People with Cancer (DCPC)

- Integrated care model
  - Oncology RN + psychiatrist
- SMaRT Oncology 2 (better prognosis cancers) and 3 (poorer prognosis cancers)
- Effectively treats depression and improves QOL
- Cost-effective



Sharpe et al: Lancet 2014

## Does treating depression in cancer patients decrease mortality?

- Probably not
- Follow-up analysis of DCPC intervention vs usual care in Scotland (n= 643)

Mulick et al, 2018

## Before you prescribe…

- Evaluate medications
- Ask about substances
- Consider bereavement/demoralization
- Look for cognitive disorders
- Rule out medical conditions
  - B12 deficiency, Hypothyroidism, Hypercalcemia
  - Neurologic illness

## Pharmacologic considerations

- Know a couple of medications from two different classes well
- Same meds but slower and lower initial dosing (but don't forget to titrate)
- Evaluate for symptom clusters to guide initial treatment selection
- Ask about prior treatment response

## Pharmacologic considerations

- SSRIs are typical first-line choice, except….
- Appetite/stimulation desired…consider mirtazapine
- Existing/expected neuropathy…consider SNRIs (duloxetine, venlafaxine, etc.)
- Appetite reduction and wakefulness desired…consider bupropion

| Drug class | Notable adverse effects |
|---|---|
| SSRIs | GI effects<br>Bleeding risks<br>Fracture risks<br>Hyponatremia<br>QTc effects<br>Drug-drug interactions |
| SNRIs | Hypertension<br>Withdrawal syndromes<br>GI effects |
| Mirtazapine | Nightmares<br>Constipation<br>Appetite stimulant |
| Bupropion | Appetite suppression<br>Stimulant-like effects<br>Seizure-risk |

## Pharmacologic treatment of depression in advanced cancer

- No recent RCTs of primary antidepressant therapy (including ketamine)
- Methylphenidate add-on therapy
  - Methylphenidate + SSRI = SSRI alone
  - Methylphenidate + Mirtazapine > Mirtazapine alone (Day 3-28)

Sullivan, Psycho-oncology, 2016

## Titrating, Switching and Combining Antidepressants

No response 4 weeks or partial response 6-8 weeks

1. Increase dose
2. Switch antidepressants
   - For SSRIs direct switch can be made at usual starting doses without cross-taper or washout
   - Cross taper vs direct switch
3. Combine with antidepressant of another class
4. Augment with another psychotropic agent

## Other pharmacologic treatment options

- Psychostimulants
  - Methylphenidate and Dextroamphetamine preparations
  - Modafanil and Armodafinil
  - T3
- Ketamine
- ECT and TMS

Zanicotti et al.. J Pall Med. 2012
Irwin et al. J Pall Med. 2010.Rozans et al. J. Clin Onc. 2002.

## Antidepressant for co-morbid pain

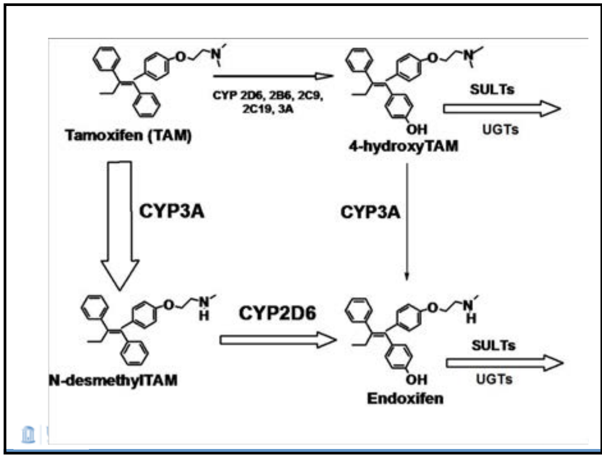
- Effective as adjuvant therapy for pain, especially neuropathic pain
- Tricyclic Antidepressants (TCAs)
  - Analgesic effects occur at lower doses
  - Nortriptyline and Desipramine are best due to lower anticholinergic effects
- SNRIs
  - Venlafaxine (doses > 225mg/day)
  - Duloxetine
  - Desvenlafaxine

Lynch ME. J Psychiatry Neurosci 2001.

## Drug Interactions

- Polypharmacy is the rule
- It's easy to make things worse
- However, truly dangerous drug interactions are less common
- Isoenzyme-drug interaction chart

  http://medicine.iupui.edu/flockhart/




## Tamoxifen, Antidepressants, & Mortality in breast cancer patients

- 16,887 breast cancer survivors (TNM stages 0-II), all treated with tamoxifen
- Exposure = percent of days of overlap with tamoxifen and antidepressants. Follow-up for up to 14 years.
- **No increased risk of subsequent breast cancer** in women concurrently treated with tamoxifen and paroxetine (or other antidepressants)

Haque et al. JNCI 2016

## Combined treatment is usually best

- Multiple modalities are effective
- Individual Psychotherapy
- Group therapy
- Other forms of therapy/counseling:
  - Behavioral activation
  - Motivational interviewing
  - Guided imagery
- Crisis intervention/social support

Anderson T et al.. Palliat Med 2008.
Horne-Thompson A et alJ Palliat Med 2008
Thomas Et al. Curr Psych Rep

## Promoting Resilience

- Assess for prior strengths and life challenges
- What have you overcome previously in life?
- What has helped in the past?
- How do you cope with adversity?
- Engage the family and members of the treatment team.

## Indications for referral

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- Failure to respond to 1st or 2nd line therapy
- Significant co-morbid medical illness
- Suicidality
- Psychotic or bipolar depression
- Co-occurring psychiatric disorders
  - Personality disorders
  - Substance use disorders
- Severe symptoms (e.g. life-threatening reduction in po intake)

## Indications for referral

- Comprehensive care including psychotherapy, group therapy
- Particularly for patients
  - Adolescent/young adult population
  - Low social support
  - Have caregivers with co-occurring depression/anxiety

## Anxiety/Depression in Caregivers

- Rates higher in family members caring for loved ones in advanced cancer and hospice
- 18-46% of caregivers with clinically significant depression
  - Emotional exhaustion and depersonalization
- Psychological symptom burden highly correlated with those of patients
- Caregiver distress warrants attention

*Chentsova-Dutton Y et al. Ann Clinical Psychiat 2000.
**Grunfeld E et al. CMAJ 2004.
***Yilmaz A et al.. Austral J Ageing 2009.

## Suicide in cancer patients

## Suicidality in cancer

- Cancer patients are at elevated risk for completed suicide
- Most patients who complete suicide had contact with medical providers prior to death
- In AYA population, patient-oncologist alliance is stronger protector against suicidality than mental health interventions
- Desire for hastened death fluctuates substantially during final weeks of life

Trevino; Cancer, 2014; Rosenfeld, Soc Sci Med, 2015

## How many cancer patients think they would be better off dead?

- Study of 2,924 UK patients attending cancer clinics
- "Over the last week, how often have you had thoughts of that you would be better off dead or of hurting yourself in some way?" (PHQ-9, Q9)
- 7.8% answered affirmatively

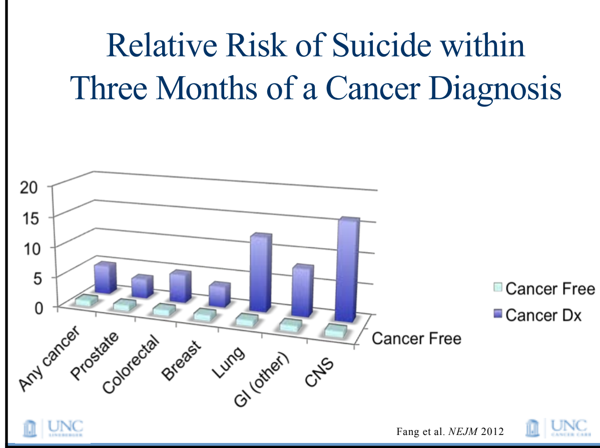
Walker et al, 2008

## How many cancer patients think they would be better off dead?

- Follow-up telephone interview
  - 33% denied SI
  - 33% believed they would be better off dead
  - 33% clear thoughts of attempting suicide

Walker et al, 2008

## Relative Risk of Suicide within Three Months of a Cancer Diagnosis




Fang et al. *NEJM* 2012

UNC

## Key domains of risk assessment: Is the patient at imminent risk?

- Involvement with mental health care
- Cooperating with interview
- Present/past suicidal ideation and behavior
- Psychiatric history
- Psychological traits
- External stressors (immediate)
- Access to lethal means or has plausible plan
- Social supports
- Reasons for living
- Coping mechanisms
- Cognitively intact

***Too close to call? Err on the side of caution***

## Desire for hastened death

**Studied two ways**

Desire for hastened death

Will to live

**Thoughts are not uncommon**

9-17% cancer patients have desire for hastened death

**Thoughts commonly fluctuate**

No variables that clearly distinguish between those who remit vs those who do not

**Risk factors**
Depression
Anxiety
Hopelessness
Low spiritual well-being

Breitbart, 2000; Chochinov 1995; Rosenfeld 2000

## Responding to statements/requests

**Acknowledge their request**
Repeat the patient's words to verify their understanding

**Clarify the underlying cause**
"We haven't talked about this before. Tell me more"
"What is the worst part of your illness right now for you?
"What would make life worth living? What can we do to help?"

**Formal assessment**
Decision-making capacity, depression, suicide

**Suicide screening**
"In your worst moments, do you finding yourself wishing that death would come soon? Does it ever approach the point where you think about killing yourself or asking someone to help you?"

**Plan for follow-up**
Even if referred to someone else

Abrahms, 2008

## Suicide assessment

- An authentic therapeutic alliance is protective
- Refine and personalize the language you use
- We should all stay humble: prediction is poor
- Anxiety, alcohol, drugs, and access to weapons promote impulsivity
- Know your patients and attend to changes

## Questions?

The UNC Comprehensive Cancer Support Program (CCSP) is dedicated to helping patients and their caregivers with cancer treatment, recovery and survivorship.

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