Cancer Diagnosis and Mental Health

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Who is this guy?

- Family Physician for 35 years (not an oncologist)
- Recovering Academic – 25 years at the University of MD School of Medicine
- Academic Interest: treatment of Depression in Primary Care
- Primary care physicians diagnose cancer and refer
- But we still take care of patients and their families – during and after treatment
- Had a thin melanoma when graduating med school in 1983
- Friends with Linda Hollander…
Recent Cancer Patients of Mine

- 34 year old male with hepatocellular carcinoma
  - Care for his wife and two children, his sister (delivered her kids)
  - MRI every 6 months, no effective treatment if recurrence

- 64 year old male with recurrence of cancer of base of tongue
  - Care for his wife, brother and sister-in-law
  - He doesn’t want to do follow-up studies

- Mother of 10 year old with rhabdomyosarcoma
  - No further treatments being offered
Epidemiology of Depression and Bipolar disorder

- In 2017
  - estimated 17.3 million adults in US had at least one major depressive episode (7.1% of all U.S. adults)
  - The prevalence higher among females (8.7%) - males (5.3%)
- Lifetime prevalence depression: 16.2%
- Lifetime prevalence bipolar I: 0.4 - 1.6%
- Lifetime prevalence Bipolar II: 0.5%
Epidemiology of Anxiety disorders

- 40 million adults in US (18.1% of the population)
- Generalized Anxiety Disorder - 6.8 million (3.1%)
- Panic Disorder – 6 million (2.7%)
- Social Anxiety Disorder - 15 million (6.8%)
- Specific phobias - 19 million (8.7%)
- Obsessive-Compulsive Disorder - 2.2 million (1.0%)
- Post-Traumatic Stress Disorder - 7.7 million (3.5%)
Depression and Anxiety in Cancer Patients

- 20% of patients with cancer have Depression, 10% have anxiety disorder
- 2/3's of patients with depression also have significant anxiety symptoms
- Depression incidence varies by cancer type:
  - Pancreas – 70% (arises months before diagnosis)
  - Lung – 13%  GYN – 11%  Breast – 9%  Colorectal – 7%  GU – 6%
- May relate to prognosis, pain, body image disruption
- Many depressed cancer patients do not receive effective treatment
- Poor recognition of depression and anxiety is associated with reduced quality of life and survival
On Death And Dying – Dr. Kubler-Ross

- Classic work written in 1969
- 5 Stages patients go through:
  - denial and isolation
  - anger
  - bargaining
  - depression
  - acceptance
- Generally fallen out of favor
Other issues

- Patient who blame themselves for their cancer diagnosis more likely to become depressed
- Patients with pre-existing PTSD may be re-traumatized with pelvic, breast, or rectal exams
- Depression in cancer patients receiving end-of-life care is no more prevalent than in patients living actively with cancer
When does depression present?

- At cancer presentation
- Acute treatment phase – highest prevalence
- Discharge – can represent sudden cessation of regular support
- End of life – prevalence no different than at other times
- Survivorship – fear of recurrence
Depression and Cancer mortality

- Meta-analysis - 76 prospective studies
- Depression diagnosis and higher levels of depressive symptoms predicted elevated mortality
- true in studies that assessed depression before and after cancer diagnosis
- Associations between depression and mortality persisted after controlling for confounding medical variables
- Screening for depression should be routinely conducted in the cancer treatment setting. Referrals to mental health specialists should be considered
- Research needed on whether treatment of depression could, beyond enhancing quality of life, extend survival of depressed cancer patients

Psychol Med. 2010; 40
Depression: Etiology

**Biochemical**: noradrenergic +/or serotonergic dysfunction; decreased levels in blood, CSF; mechanisms of antidepressants

**Genetic factors**: family history; polygenic

**Psychological and social factors**: stressful events within six months of depression
Neurotrophic hypothesis

- atrophy of prefrontal cortex areas and hippocampus
- decreased levels of nerve growth factors (NGF)
- BDNF – Brain Derived Neurotrophic Factor - regulates neuronal development and plasticity
  - increases survival of neurons, stimulates growth of dendrites
  - involved in maturation of excitatory synapses
  - expression of BDNF halted by chronic stress, normal levels after successful treatment with antidepressants.
- Treatment takes weeks because of neurogenesis

J Depress Anxiety 2017, 6:1
Biology of depression in Cancer

- prevalence of depression in cancer pts exceeds that in gen’l population
- increased prevalence not solely explained by psychosocial stress
- Pro-inflammatory cytokines - biomarkers of inflammation in cancer pts
- Some cancers can release chemicals thought to cause depression, and certain cancer treatments, such as chemotherapy and corticosteroids, are associated with depression
  - Pancreas (elevated cytokine IL-6)
  - Lung (paraneoplastic syndromes)
- Chronic inflammatory processes may also underlie depression symptoms
- Therapeutic modalities used in treatment of cancer cause inflammatory reactions
Biopsychosocial factors

- Psychological reactions to diagnosis, treatment, relapse, end of life care, or survivorship
- Losses – hair, sexual function, organs
- Expectations regarding survival
- Effects on work and social roles
- Side effects of chemo: vomiting, hair loss, mucositis, peripheral neuropathies
Treatments that increase depression

- Androgen deprivation for prostate cancer
- Radiotherapy for head and neck cancers – hypothyroidism
- Bilateral oophorectomies for prophylaxis or treatment
Depression: DSM-5 Criteria

Depressed mood most of the day, nearly every day
Diminished interest or pleasure in activities
Major change in appetite or weight
Insomnia or hypersomnia
Psychomotor agitation or retardation
Fatigue or loss of energy
Feeling worthless, excessive/inappropriate guilt
Decreased ability to think, concentrate, indecisive
Recurrent thoughts of death, dying, or suicide

APA Diagnostic and Statistical Manual of Mental Disorders. 2013.
**PATIENT HEALTH QUESTIONNAIRE (PHQ-9)**

**NAME:**

Over the last 2 weeks, how often have you been bothered by any of the following problems? (use "✓" to indicate your answer)

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Several Days</th>
<th>Most of the Time</th>
<th>Nearly Every Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead, or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

(add columns: 4 4)

(High care professionals: For interpretation of TOTAL, please refer to accompanying scoring card.)

**TOTAL:**

10. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

<table>
<thead>
<tr>
<th></th>
<th>Not difficult at all</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Extremely difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PHQ-9 SCORING CARD FOR SEVERITY DETERMINATION
for healthcare professional use only

Scoring—add up all checked boxes on PHQ-9

For every ✓: Not at all = 0; Several days = 1;
More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Depression Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>None</td>
</tr>
<tr>
<td>5-9</td>
<td>Mild depression</td>
</tr>
<tr>
<td>10-14</td>
<td>Moderate depression</td>
</tr>
<tr>
<td>15-19</td>
<td>Moderately severe depression</td>
</tr>
<tr>
<td>20-27</td>
<td>Severe depression</td>
</tr>
</tbody>
</table>

The likelihood of depression increases with increasing number of physical symptoms.

Anxiety and related disorders

- panic attack/panic disorder
- agoraphobia (+/- panic)
- phobias - specific, social
- generalized anxiety disorder
- obsessive-compulsive disorder
- post traumatic stress disorder
- acute stress disorder
- (adjustment disorder w/ anxious mood)
GAD-7 Questions

Over the last 2 weeks, how often have you been bothered by the following?

1. Feeling nervous, anxious, or on edge
2. Not being able to stop or control worrying
3. Worrying too much about different things
4. Trouble relaxing
5. Being so restless that it's hard to sit still
6. Becoming easily annoyed or irritable
7. Feeling afraid as if something awful might happen

Not at all= 0   Several days= 1   More than half days= 2   Nearly every day= 3

Using threshold of 10, GAD-7 has sensitivity - 89% and specificity - 82% for GAD
GAD-7 Scoring

<table>
<thead>
<tr>
<th>Score</th>
<th>Symptom Severity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-9</td>
<td>Mild</td>
<td>Monitor</td>
</tr>
<tr>
<td>10*-14</td>
<td>Moderate</td>
<td>Possible clinically significant condition</td>
</tr>
<tr>
<td>&gt;15</td>
<td>Severe</td>
<td>Active treatment probably warranted</td>
</tr>
</tbody>
</table>

**MANAGEMENT**
Scores ≥10: Further assessment (including diagnostic interview and mental status examination) and/or referral to a mental health professional recommended.

*For Panic Disorder, Social Phobia, & PTSD, cutoff score of 8 may be used for optimal sensitivity/specificity
Suicide

- 10\textsuperscript{th} leading cause of death in US
- 1999 to 2016 rate increased over 30% in 25 states
- half didn't have known mental health disorder
- Factors: relationship problems, life stressors, health problems, financial difficulties
- 15\% of severely depressed commit suicide
- 41,000 deaths per year; 18 attempts for every suicide
- women attempt, men succeed (20.7 vs 5.8/100,000)
- Rates highest for men > 75
- most see a physician the month before
Suicide and Cancer Patients

- Patients with cancer in the US have nearly twice the incidence of suicide of the general population
- Suicide rates vary among patients with cancers of different anatomic sites
- Cancers of the lung, head and neck, testes, bladder, and Hodgkin lymphoma had the highest rates
- Elderly, white, unmarried males with localized disease are at highest risk
- Among those diagnosed < 50 years of age, most suicides in patient with hematologic and testicular tumors
- Diagnosed > 50 – most in prostate, lung, and colorectal cancer patients

Asking about suicide

• ask!!! - most will talk frankly
• “Have you had thoughts about death or about killing yourself?”
• If yes:
  • are there means? - gun, bullets, poison
  • have you rehearsed?
  • how strong is your intent?
  • can you resist the impulse?
Managing suicidal patients

Immediate risk:
someone stay with the patient
call a psychiatrist with admitting privileges
if patient refuses - call police

Risk not imminent:
involve others - vigilance, remove means
increase contact with patient - call, visits
treat depression, alcohol abuse
benzodiazepines helpful
Role of psychotherapy

- Considered adjunct to drugs, not replacement
- Some data CBT may be as effective
  - “Preventive” CBT decreases recurrence\(^1\)
- Combination of drugs + psychotherapy optimal in severely depressed
- Exercise effective in mild depression
- Internet based CBT
- Feeling Good: The New Mood Therapy by David Burns

\(^1\)The Lancet Psychiatry May 2018
Psychotherapy for Advanced Cancer Patients

- Patients prefer non-pharmacological treatments such as psychotherapy over meds for depression
- Meta-analysis of randomized controlled trials - 12 studies
- Psychotherapy - moderate decrease in depression scores
- Quality of evidence across the studies was rated as low
- Low quality evidence suggests psychotherapy is moderately more effective for the amelioration of symptoms of depression among advanced, incurable cancer patients than controls

Cancer Treat Rev 2017 May
Early generation antidepressants

- Tricyclics
  - amitriptyline
  - imipramine
  - nortriptyline
  - desipramine
  - doxepin

- Monoamine oxidase inhibitors (MAOI’s)
  - phenelzine
  - tranylcypromine
  - transdermal selegiline (Emsam®)
Late generation antidepressants

▸ selective serotonin reuptake inhibitors (SSRI’s)
  - fluoxetine (Prozac)
  - sertraline (Zoloft)
  - paroxetine (Paxil)
  - fluvoxamine (Luvox)
  - citalopram (Celexa)
  - escitalopram (Lexapro)

▸ Venlafaxine (Effexor)

▸ Duloxetine (Cymbalta)

▸ Desvenlafaxine (Pristiq)

▸ Mirtazapine (Remeron)

▸ Levomilnacipran (Fetzima)

▸ Trazodone (Desyrel)

▸ Nefazodone (Serzone)

▸ Bupropion (Wellbutrin)

▸ Vilazodone (Viibryd)

▸ Vorioxetine (Trintellix)
Efficacy

- All anti-depressants are equally effective, assuming reasonable dosing
- 2/3’s get better on 1\textsuperscript{st} drug chosen
- Majority respond to second or third
- Consider prior anti-depressant treatment, including those used by family members
- Patients that failed treatment with citalopram:
  - Switched to bupropion, sertraline, or venlafaxine
- One in four had remission after switching\textsuperscript{1}

Meta-analysis of 12 drugs

- 117 randomized controlled trials (25,928 participants)
- Bupropion, citalopram, duloxetine, escitalopram, fluoxetine, mirtazapine, paroxetine, sertraline, and venlafaxine
- Mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more efficacious than duloxetine, fluoxetine, and paroxetine
- Escitalopram and sertraline showed best acceptability - less discontinuation than duloxetine, paroxetine, and venlafaxine
- Sertraline might be best choice
  - Best balance between benefits, acceptability, and cost

*The Lancet, 373:9665, 28 February 2009*
Ketamine

- NDMA receptor antagonist (glutamatergic system)
- IV, IM, intranasal, oral, sublingual
- Not indicated for treatment of depression
- Single infusion – rapid response (40-120 min)
- At least 50% respond
- Benefits last up to 2 weeks
- May merely be transient intoxicant/euphoriant
- Causes dissociation
- May be used as augmentation

J Clin Psychiatry 2017
Esketamine (Spravato®)

- nasal spray for treatment-resistant depression
- chemical mirror image of ketamine
- must be taken with an oral antidepressant
- significant effect on depression compared with placebo; significantly longer time to relapse.
- Restricted use; boxed warning about risks for dissociation, sedation, and suicidal thoughts
- Pts self-administer in clinician's office, monitored; 2/wk weeks 1–4, q wk weeks 5–8, then q 1-2 weeks
- $590 for a 56-mg dose and $885 for an 84-mg
Marijuana

- Many patients self-medicate
- Intoxicating effects may produce immediate symptom improvement
- 12 longitudinal studies in 11,959 patients with PTSD, panic disorder, bipolar disorder, depression
- Effect of cannabis use in ≤6 months before study entry on later outcomes (f/u 2.5–60 months).
- Cannabis users had more-severe symptoms and lower rates of remission
- Not effective for the treatment of PTSD

Ann Int Med September 2017, J Clin Psychiatry 2018
Augmentation

- Not everyone gets better at maximal doses of a single antidepressant
- Add second medication
- Bupropion (Wellbutrin®)
- Buspirone (Buspar®)
- Mirtazapine (Remeron®)
- Topiramate (Topamax®)
- Aripiprazole (Abilify®), Brexipiprazole (Rexulti®)
- L-methylfolate (15 mg)
St. John’s Wort (hypericum)

- Ineffective in moderate to severe depression\(^1\)
- Reduces cyclosporine levels (CYP450 3A4)\(^2\)
- Can induce hypomania\(^3\), precipitate hypertensive crisis\(^4\), delay emergence from anesthesia\(^5\)
- Highly variable formulations\(^6,7\)
- Probably effective in mild depression, but no better than standard anti-depressants\(^8\)

PHASES OF TREATMENT

Acute (6-12 weeks)

Continuation (4-9 months)

Maintenance (1 or more years)

Remission

Recovery

Relapse

Recurrence

“Normalcy”

Symptoms

Syndrome

Response

Progression to disorder

Time

Phases of treatment - acute

- see patient back within 2 weeks
- Do PHQ9
- If no change increase dose
- If some change – see back in few weeks
- if no better in 4 - 6 weeks: switch
Antidepressants for the treatment of depression in people with cancer

- Depressive symptoms have negative impact in quality of life, compliance with anti-cancer treatment, suicide risk and mortality rate
- meta-analysis (7 studies)
- Acute treatment (6-12 wks) - no difference between antidepressants and placebo
- No difference between SSRI’s and TCAs
- available studies very few and of low quality
- use of antidepressants in people with cancer should be considered on individual basis and choice of agent may be based on the data on antidepressant efficacy in the general population
- data on medically ill patients suggest a positive safety profile for the SSRIs
- urgent need for trials comparing antidepressants versus placebo in people with cancer

Cochrane Database 2018 Apr
Antidepressants in Cancer Patients

- Antidepressants can worsen existing cancer symptoms and interact with chemotherapy agents.
- Sertraline and citalopram tend to have the least interactions and are generally well tolerated as first line agents.
Electroconvulsive therapy (ECT)

- treats severe, resistant depression
- nearly 80% respond
- Short term memory loss common
- 3 sessions/week for 2 weeks then assess
- Can be used prophylactically
Other treatments

- **Transcranial Magnetic Stimulation (TMS)**
  - FDA approved - magnetic pulses stimulate brain cells
  - outpatient, no anesthesia, 5 treatments weekly for 6 wks
  - Up to 50% respond

- **Deep Brain Stimulation**
  - experimental – implants device - “brain pacemaker”
  - approved for essential tremor, Parkinson’s disease
  - not yet FDA approved for treatment of depression

- **External trigeminal nerve stimulation (eTNS)**
  - Increases blood flow to limbic and frontal areas
  - Patches on face for 8 hours while sleeping
  - Not yet FDA approved
Mindfulness-based Therapy

- Meta-analysis of effectiveness of mindfulness-based interventions for improving anxiety and depression in cancer patients (7 studies)
- Mindfulness-based stress reduction and art therapy most common interventions
- Those undergoing mindfulness-based therapy had significantly lower anxiety and depression scores over controls
- Mindfulness-based therapy significantly improved anxiety for ≤12 weeks after start of therapy, but not >12 weeks after start of therapy
- Lack of consistency between studies in type of mindfulness interventions; Patients had different forms of cancer, time since diagnosis, stage
- Bottom line: Mindfulness-based interventions relieved anxiety and depression among patients with cancer. Not sure how long the beneficial effects persist
Collaborative Care

- meta-analysis of newer collaborative care interventions - may include meds and psychotherapy - as well as integrated delivery and follow-up

- collaborative care: multifaceted intervention involving combinations of professionals working collaboratively within primary care setting: case manager, primary care practitioner, and mental health specialist

- collaborative care interventions significantly more effective than usual care (depression reduction maintained at 12 months)

- Collaborative care interventions may result in more long-term depression remission
Does Treatment Effect Survival?

- SMaRT Oncology-2 (good prognosis cancers) and SMaRT Oncology-3 (lung cancer, poor prognosis cancer) used depression treatment program, Depression Care for People with Cancer (DCPC) - effective in reducing comorbid major depression
- pts with cancers and major depression randomly assigned to DCPC or usual care
- obtained long-term data on deaths (all causes)
- no significant effect of DCPC on survival in good or bad prognosis cancers
- Conclusion: DCPC is highly effective in improving depression and quality of life in depressed patients with cancer, but no evidence for significant effect on survival. Despite absence of an effect on length of life, the management of depression remains important for its beneficial effect on quality of life.

*Lancet Psychiatry. 2018*
Depression Care for People with Cancer (DCPC)

- extended form of the collaborative care model
- delivered by a care manager
- receives regular supervision from a psychiatrist
- care manager coordinates the patient's depression management
- Coordinates with both their primary care physician and cancer team
- provides brief talk treatment
Anxiety & Depression in Cancer Survivors

- Some patients experience persisting negative mood, such as cancer-related fears, posttraumatic stress, anxiety, or depression.
- Mood fluctuations may not reach criteria for a clinical diagnosis but subclinical symptoms can interfere with quality of life.
- Women, adolescents, and young adults are particularly at risk.
- CBT and meds are effective treatments.
- Much of the research on managing emotional needs after cancer has been completed with breast cancer survivors and more work is needed with diverse groups of survivors.
Conclusions

- Having cancer increases risk for depression and anxiety
- Combination of cancer and depression worsens cancer prognosis
- Medications treat the depression but don’t effect cancer survival
- Sertraline may be the best choice
- Interdisciplinary models help relieve symptoms of depression
- The state of the literature in this area is woeful deficient!
- Thanks for listening!