Cancer Diagnosis and Mental Health

Kevin Scott Ferentz, MD

Chairman, Department of Family Medicine
Greater Baltimore Medical Center
Clinical Associate Professor
University of Maryland School of Medicine

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

BMJ 2018 April 25

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

Depression: Etiology

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

<u>Genetic factors</u>: family history; polygenic

<u>Psychological and social factors</u>: 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

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

Biopsychsocial 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: _____   DATE: _____

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

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
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	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3

add columns: _____ + _____ + _____

(Healthcare professional: 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?

Not difficult at all	_____
Somewhat difficult	_____
Very difficult	_____
Extremely difficult	_____

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;
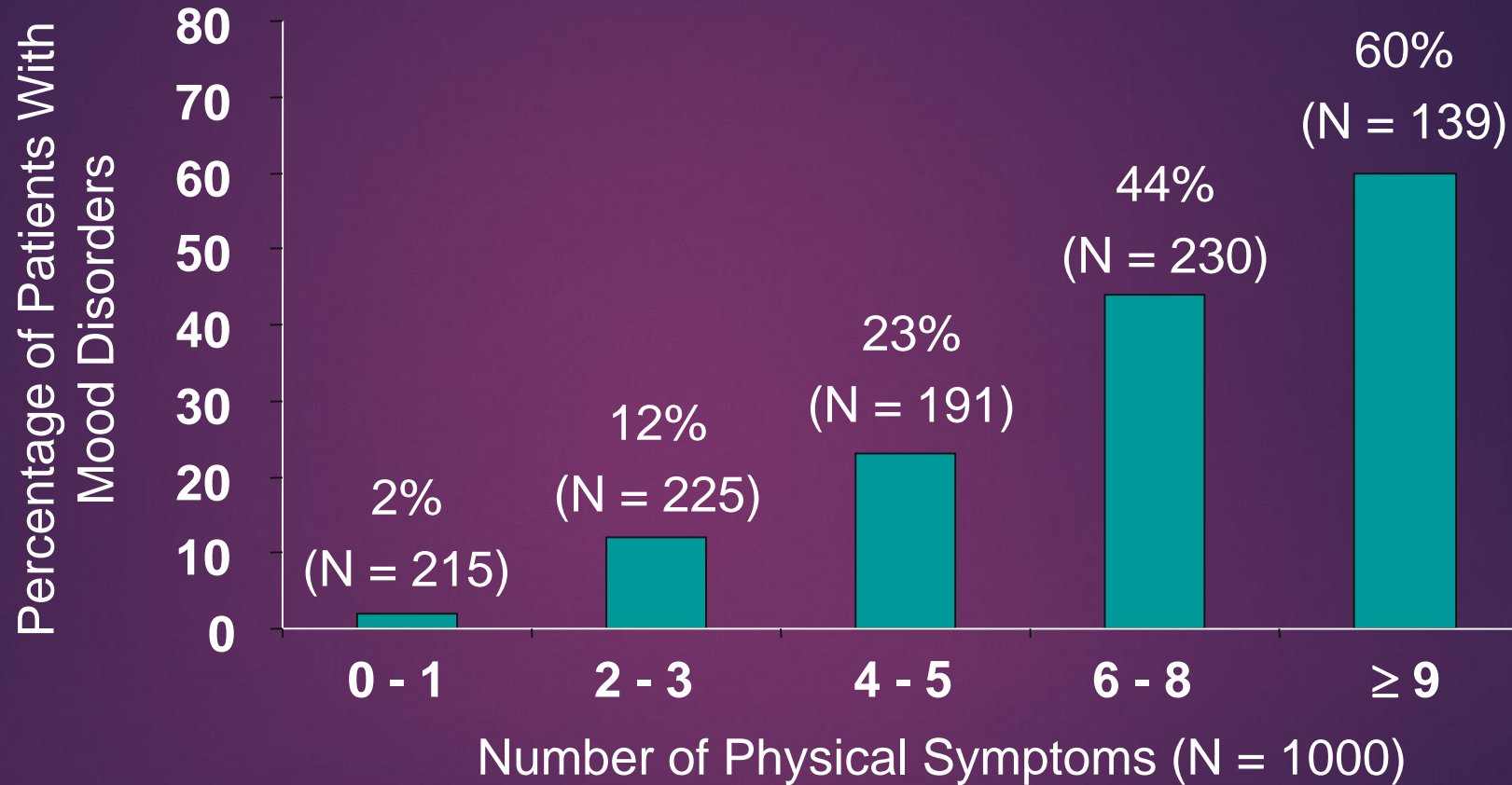More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
0-4	None
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

http://muskie.usm.maine.edu/clinicalfusion/DHHS/phq9.pdf

Relationship Between Physical Symptoms and Depression

Percentage of Patients With Mood Disorders

80
70
60
50
40
30
20
10
0

2%
(N = 215)

12%
(N = 225)

23%
(N = 191)

44%
(N = 230)

60%
(N = 139)

0 - 1   2 - 3   4 - 5   6 - 8   ≥ 9

Number of Physical Symptoms (N = 1000)

The likelihood of depression increases with increasing number of physical symptoms

Kroenke K, et al. *Arch Fam Med*. 1994;3:774-779.

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

Score	Symptom Severity	Comments
5-9	Mild	Monitor
10*-14	Moderate	Possible clinically significant condition
>15	Severe	Active treatment probably warranted

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

- 10th 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

<u>Immediate risk</u>:

someone stay with the patient

call a psychiatrist with admitting privileges

if patient refuses - call police

<u>Risk not imminent</u>:

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
- <u>Feeling Good: The New Mood Therapy</u> 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

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 1st 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[1]

[1]Rush, A. et al. N Engl J Med 2006

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

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
- month-long induction phase: $4700 - $6800.
- $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

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®), Brexpiprazole (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]

[1] JAMA. 2002 Apr 10. [2] Progress in Transplantation. 2001 Jun. [3] Brain Injury. 2002 Apr. [4]American Journal of Medicine. 2002 Apr 15. [5]Anesthesiology. 2002 Apr. [6]Alternative Therapies in Health & Medicine. 2001 Nov-Dec. [7] Pharmacopsychiatry. 2001 Jul. [8]International Clinical Psychopharmacology. 2001 Sep.

PHASES OF TREATMENT

AHCPR Depression in Primary Care. 1993 Stahl. *Essential Psychopharmacology.* 1996 Kupfer. *J Clin Psychiatry.* 1991
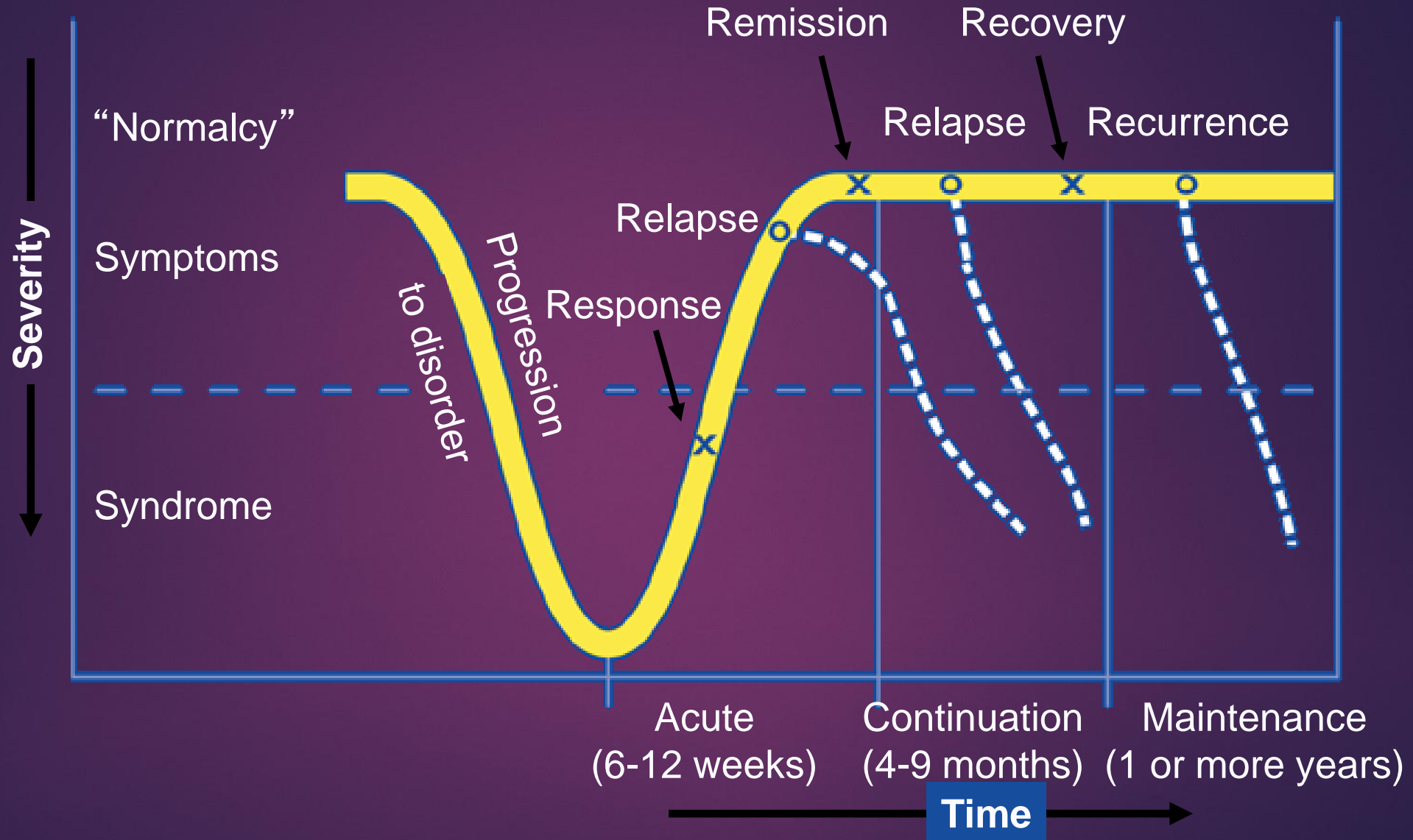
Phases of treatment - acute

- 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

▶ <u>urgent</u> 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

Psychooncology 2017 May

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.

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!