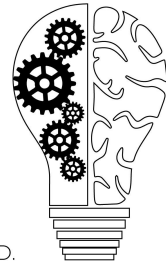


Episode 075: Cancer: Depression, Anxiety, And Hypoactive Delirium - A Dive Into Psycho-Oncology

Shawna Chan, Mona Mojtahedzadeh, M.D., Salman Otoukesh, M.D.,
David Puder, M.D.



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**PSYCHIATRY &
PSYCHOTHERAPY**

This PDF is a supplement to the podcast “Psychiatry & Psychotherapy” found on [iTunes](#), [Google Play](#), [Stitcher](#), [Overcast](#), [PlayerFM](#), [PodBean](#), [TuneIn](#), [Podtail](#), [Blubrry](#), [Podfanatic](#)

There are no conflicts of interest for this episode.

In this week’s episode we sat down with four guests (detailed below) and discussed different aspects of mental health in humans bravely facing cancer. The below notes go beyond the podcast episode in content and depth and hopefully equips you to have more empathy, compassion and knowledge.

Dr. Mona Mojtahedzadeh’s medical career began in Iran, where her passion for public health and service led her to care for refugee patients and mothers and children impacted by HIV. She completed her psychiatry training, including a fellowship in Consultation-Liaison Psychiatry, in the United States, and she is currently a psychiatrist in the Supportive Care Medicine division at City of Hope.

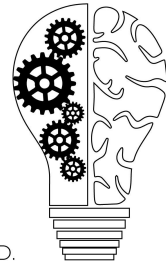
Dr. Salmon Otoukesh began his medical training in Iran and has extensive experience working with international organizations, such as the United Nations. He completed his Internal Medicine residency and Hematology/Medical Oncology fellowship in the United States, and he specializes in Hematopoietic Cell Transplantation at City of Hope.

Shawna Chan is a 4th year medical student at UC Irvine School of Medicine applying to the Psychiatry residency. She hopes to provide empathetic, compassionate care for those living with cancer, and she is interested in psycho-oncology, pain management, and palliative care.

David Puder is the host of the Psychiatry and Psychotherapy Podcast and is the medical director of a day treatment program “[MEND](#)” which treats people with cancer or other medical issues who are struggling with significant depression, anxiety, and other psychiatric issues.

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Mental health in cancer

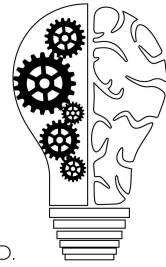
- Nuances of diagnosing depression: normal cancer symptoms that can be confused with depression are somatic symptoms such as anorexia, sleep disturbance and fatigue.
 - “Inclusive approach”: count any of MDD criterion, regardless of whether due to medical or psychological cause, although this may result in falsely elevated rates of depression
 - “Exclusive approach”: excludes anorexia and fatigue, reduced sensitivity
 - “Substitutive approach”: excludes somatic symptoms related to somatic illness (fatigue, weight loss, psychomotor changes, impaired concentration) and replaces with cognitive-affective symptoms (irritability, tearfulness, feeling punished, social withdrawal)
 - Each diagnostic scheme comes with its own set of advantages or disadvantages. Ultimately we must rely on clinical judgement—for example, symptoms that are fixed and nonreactive to environmental factors can help distinguish depression from normal grief ([Koenig et al. 1997](#))

Clinical Pearl: Anhedonia and the inability to enjoy one’s life outside the context of cancer is an important feature in distinguishing depression from adjustment disorder or normal grief.

- Adjustment disorder: the most common psychiatric diagnosis made in cancer patients
 - Meta-analysis of heme/onc patients: 19.4% adjustment disorder, 14.9% major depression, 10.3% anxiety disorder ([Mitchell et al. 2011](#))
 - Psychotherapeutic interventions 1st line, limited research on pharmacotherapy but can temporarily use hypnotics, benzos, antidepressants, etc., to target symptoms
- Depressive disorders: ~16% cancer of patients experienced MDD; if including dysthymia and minor depression, occurs in 22% patients

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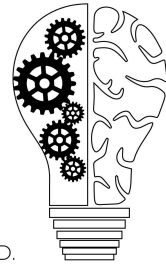
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- Substance/medication-induced depressive disorder following corticosteroids, exogenous cytokines (IFN α , IL-2)
- Differential:
 - Demoralization: affects 13-18% of cancer patients. Presents as hopelessness, helplessness, loss of meaning and purpose to life. ([Robinson et al, 2015](#))
 - Hypoactive delirium mimics depression in the medically ill as patients may appear apathetic or have SI. *Look for disturbances in consciousness, attention, cognition, and perception.*
 - More often in palliative care setting, older vs. younger patients
 - Generally due to hypoxia, metabolic disturbances, and hepatic encephalopathies. Other etiologies more specific to cancer population include: brain tumor, leptomeningeal disease, paraneoplastic syndrome, cerebral edema after brain radiation, hypercalcemia, hyperviscosity syndrome (lymphoma, waldenstrom macroglobulinemia).
 - May be less responsive to pharmacotherapy; also associated with higher risk of mortality
 - Degree of cognitive impairment much more pronounced in delirium than depression. There is also disturbance in level of arousal
 - Poorly organized, abrupt onset delusions; predominantly visual/tactile rather than auditory hallucinations

Clinical Pearl: Consider drug-drug interactions if you suspect hypoactive delirium. Anticholinergic medications (e.g. Benadryl), steroids, and benzodiazepines are common culprits. Concurrent use of CYP2D6 inhibitors (paroxetine, fluoxetine for example) with TCAs can increase serum level of TCAs (which are anticholinergic) and lead to hypoactive delirium.

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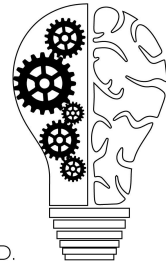


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- Hyperactive delirium: agitated, restlessness, hypervigilance, hallucinations/delusions; more easily recognized and referred to psychiatrists
 - Correlated with alcohol/drug withdrawal, intoxication, medications adverse effects
- Pharmacotherapy for Depression
 - Elements that impact medication choice include: prior response history, medical comorbidities, drug interactions, route of administration, onset of action with regards to patient prognosis, other somatic/physical symptoms such as pain, insomnia, hot flashes
 - SSRIs and SNRIs 1st line for tolerability and safety; SNRIs also help with hot flashes
 - Bupropion: may improve sexual function and fatigue
 - Mirtazapine: cancer-related anorexia, cachexia, nausea/vomiting; rare side effect of reversible neutropenia
 - Trazodone < 100 mg QHS: orthostatic hypotension and dizziness in elderly/fragile
 - Reboxetine: NRI reported to be effective for apathy, fatigue, concentration, anxiety; activating, so be cautious in comorbid cardiac disease
 - Agomelatine: novel melatonergic antidepressant that acts on 5-HT_{2C}, sleep promoting, weight neutral, lacks sexual side effects and DC effects; LFT monitoring required
 - TCAs: seldom 1st line due to side effects, but may be used for comorbid neuropathic pain at lower doses than used for depression
 - Psychostimulants: rapid onset for energizing effects in depressed patients w/ advanced/terminal disease, but unclear efficacy in alleviating depression; prolonged use rarely associated with psychosis, also take caution with cardiac comorbidities
 - Medication adverse effects: osteoporosis, GI hemorrhage, hyponatremia, serotonin toxicity w/ fentanyl, tramadol, ondansetron, metoclopramide

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- Psychotherapy: CBT, relaxation strategies, problem-solving approaches in recently diagnosed; existential, life narrative, dignity conserving, meaning-centered interventions in advanced/terminally ill
- Suicide: patients w/ cancer are at increased risk for suicidal thoughts and behavior compared with general population and other medically ill; 2x risk of suicide vs. general population
 - Fleeting wish to die are often normal in cancer patients, although persistent SI, plan, intent are of great concern.
 - “Wish to hasten death” is a reaction to suffering in the context of a life threatening condition, from which a patient finds no way out other than accelerating death. ([Balaguer et al, 2016](#))
 - Multifaceted, complex, elements of psychosocial, psychological, neurobiological factors, hence suicide risk assessment is crucial

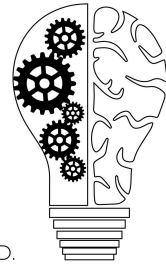
Clinical Pearl: Suicide assessment in this patient population requires a highly individualized approach and differs from patient to patient. Suicidality in a cancer patient who also suffers from clinical depression is highly concerning and must be appropriately addressed.

- Anxiety: 10-30% prevalence in cancer patients, where most often patients report exacerbation of existing problem w/ anxiety due to medical stressor; symptoms persist and remain concern for long-term cancer survivors
 - Primary challenge is to find underlying causes for anxiety
 - Steroids and anti-emetics (prochlorperazine) can cause anxiety
 - Prochlorperazine and metoclopramide are dopamine blockers which can cause akathisia ([Weiden, 1985](#))
 - Medical conditions - CHF, pleural effusion, PE - also present with breathlessness, chest tightness, palpitations

Clinical Pearl: Dopamine blockers may cause akathisia, characterized by inner feelings of restlessness that mimics anxiety.

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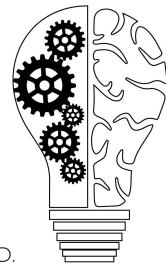


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- Pharmacotherapy: benzos short-term, SSRIs/SNRIs long-term
 - Benzos: alprazolam, diazepam, and lorazepam have the greatest risk for abuse. Lorazepam, oxazepam, and temazepam (remember “LOT for Liver”) are preferable in liver disease because they are not subject to Phase 1 metabolism. Clonazepam has less abuse liability than shorter-onset agents
 - Can use other meds that target symptoms - mirtazapine (some evidence, atypical antipsychotics in patients w/ dementia or at risk for delirium (no clinical trials for APDs)
- Psychotherapy: educational, CBT, supportive therapy, complementary approaches (acupuncture, massage, creative art therapy, although data mostly from non-blinded studies)
 - Cognitive-behavioral interventions have greatest evidence
 - CBT, systematic desensitization, stress management and relaxation ([Hermann et al, 2013](#))
- **PTSD**: difficult to estimate prevalence, but estimated to be 10-20% which is about twice that of the general population; however, full blown PTSD occurs in 5% of cancer patients that must involve sudden or catastrophic events. ([Abbey et al, 2015](#))
 - Cancer experience is a unique type of trauma that doesn't entirely remain in the past. Rather, it is ongoing threat that requires participation in clinical encounters that may reinforce the significance of the threat of cancer
 - Previous trauma increases risk - cancer may not just be independent trauma, but also trigger for existing/dormant traumatic responses
 - Pharmacotherapy: often antidepressant, can add atypical antipsychotic
 - Benzos can help with nausea and PTSD
 - Clonidine and prazosin for nightmares but may be contraindicated with some cancer regimens
 - Psychotherapy: mainstay of treatment in PTSD, most research looks at patients no longer undergoing active cancer treatment

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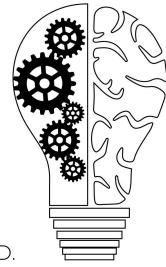


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- CBT effective in cancer setting: psychoeducation about distress and PTSD after cancer, breathing and relaxation training, imaginal and in vivo exposure to cancer-related cues, cognitive restructuring, behavioral activity scheduling—benefits may persist despite re-traumatization
- “Multimodal approach” is recommended by NCI; evidence best for CBT
- **Fatigue:** in 40% of cancer survivors, 100% of those undergoing active treatment, ([Jones et al. 2016](#)). Cancer patients perceive fatigue as more distressing than pain, nausea, or vomiting. Associated with decreased QOL, significant psychological and functional morbidity. Possibly due to inflammatory processes from both tumor burden and treatments that activate pro-inflammatory cytokine network
 - Pharmacotherapy
 - Psychostimulants: methylphenidate (appetite stimulation at lower doses), amphetamine/dextroamphetamine
 - Stimulants can bolster depressed patient in period before antidepressant takes effect
 - Combat sedating effects of narcotics
 - Wakefulness promoting agents: modafinil (low abuse potential, marketed as gentler and less likely than other stimulants to trigger insomnia)
 - In a randomized placebo-controlled trial, Armodafinil did not improve cancer-related fatigue or change the efficacy of CBT ([Heckler et al. 2016](#))
 - Antidepressants: unclear if beneficial for patients w/ cancer-related fatigue in absence of depressive mood d/o
 - Non-pharmacotherapy:
 - NCCN practice guidelines: self-monitoring of fatigue levels, energy-conserving strategies such as setting priorities, structuring daily routine, attending to one activity at a time, limiting naps to < 1 hr
 - Exercise: meta-analysis of randomized control trials with moderate effect size (0.34). American College of Sports Medicine recommends cancer patients and survivors do at least 150 min moderate-intensity exercise/week

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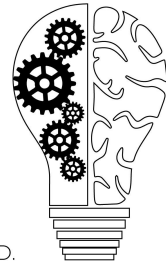


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- **Insomnia:** important to understand etiologies of sleep disturbance for more targeted treatment approach in long-term; in older adults, sleep disturbances can exacerbate certain illnesses and usually don't improve on their own, so it's especially important to treat in these patients
 - Pharmacologic: prescription sleep aids, OTC, herbal supplements; safety and efficacy of sleep medications not yet established in cancer patients!
 - Recommended sequence of medication trial: 1) short-intermediate acting benzo or ramelteon, 2) alternate short-intermediate acting benzo or ramelteon 3) sedating antidepressant (especially in conjunction with treating depression - trazodone, amitriptyline, doxepin, mirtazapine), 4) combined benzo/ramelteon + sedating antidepressant, 5) other sedating agents (gabapentin, olanzapine)
 - Zolpidem can be used in short-term
 - Eszopiclone and Zaleplon have T1/2 of 1 hour = good for patients w/ sleep initiation difficulties
 - Mirtazapine, nortriptyline, trazodone
 - Olanzapine and quetiapine in substance users; APDs also preferred over hypnotics in delirium so as not to exacerbate underlying encephalopathy
 - 2/2 depression/anxiety = antidepressant
 - 2/2 steroids = reduction/cessation
 - 2/2 menopausal symptoms = effexor, gabapentin
 - 2/2 OSA = PEEP
 - 2/2 restless leg syndrome = gabapentin, ropinirole, pramipexole
 - 2/2 pain = analgesia
 - Non-pharmacologic: behavioral therapy, CBT for insomnia (CBTi; best evidence), education, light therapy, exercise, mindfulness, & yoga.
- **Nausea and vomiting:** 2 of the most-feared symptoms among patients with cancer. Antiemetics are better at treating vomiting than nausea.
 - Chemo-induced nausea and vomiting caused by release of free radicals that cause exocytic release of 5-HT from enterochromaffin cells in gut. Chemo also acts directly on vomiting center via 5-HT3 and NK-1 receptors

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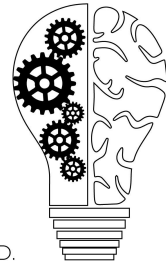


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- High emetogenicity chemos: cisplatin, mechlorethamine streptozotocin, Procarbazine PO, Anthracycline and cyclophosphamide, carmustine, dacarbazine, dactinomycin
- Opioids-induced N/V
- Intestinal obstruction 2/2 tumor progression, adhesions, post-radiation fibrosis
- Radiation-induced N/V - worst with total body irradiation, also moderate risk with upper abdomen irradiation
- CNS-related N/V - increased ICP → meningeal irritation which activates mechanoreceptors that stimulate vomiting center
- Pharmacotherapy
 - D2 antagonists: metoclopramide for constipation, early satiety; haloperidol for anxious, agitated, confused
 - 5-HT3 antagonists (5-HT3R has highest frequency in gut and nucleus solitarius): ondansetron (IV, PO), granisetron (Sancuso) can be given transdermally or IV for patient receiving moderate to high emetogenic chemo
 - NK receptor antagonists: aprepitant, fosaprepitant (water-soluble pro-drug of aprepitant, can be given IV and converted to aprepitant). Greatest impact on delayed N/V from chemo
 - Steroids: dexamethasone, exact mechanism unknown but may decrease 5-HT release, activate glucocorticoid receptor in medulla and increase levels of other antiemetics; tx of choice for N/V 2/2 increased ICP but be careful with side effects
 - Cannabinoids: agonism of CB-1 receptors; dronabinol, nabilone but causes impaired psychomotor function and psychoactive effects especially in older patients
 - Scopolamine - anticholinergic, mgmt of vestibular N/V, nausea related to motion
- Mirtazapine - sedation and appetite stimulation via histamine blockade
- Haloperidol, perphenazine, olanzapine for nausea

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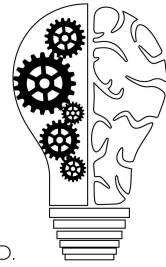


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- Octreotide: somatostatin analog that reduces gastric secretions by inhibiting vasoactive polypeptide activity - decrease in gut fluid volume improves N/V in bowel obstruction
- **Anorexia-cachexia syndrome:** weight loss, anorexia, muscle and fat loss, wasteful increases in energy expenditure; most closely related to inflammation - inflammatory cytokines (IL-1) modulates appetite at hypothalamus and brain stem centers
 - Overriding approach is general symptom control - one won't eat if in severe pain, gasping for breath
 - Appetite agents
 - Corticosteroids: stimulate appetite and mood 2/2 anti-inflammatory
 - Progestational drugs: megestrol, medroxyprogesterone improve appetite and body weight (mostly fat). Caution in hypogonadal pt, concerns about impotence, also increases DVT risk
 - Cannabinoids: likely improves cortical activity related to taste, smell, enjoyment of food. Recent trial in cancer patients was positive and also showed sleep improvement ([Brisebois et al. 2011](#))
 - Non-pharmacologic: consider multimodal therapy
 - Psychosocial therapy: patient and caregivers should be educated that it's okay not to force feed
 - Efficacy of exercise and nutrition unclear
- **Pain:** 70% of patients experience severe pain in the course of illness. Pain may occur as part of "cluster" of physical and psychological symptoms; is both sensory and emotional experience
 - Nociceptive pain results from stimulation of intact nociceptors. Somatic pain from cutaneous or deep tissues - "aching, stabbing, throbbing, pressure-like" while visceral pain involves organs - "gnawing, cramping, aching, sharp" and may be referred
 - Opioids, non-opioid analgesics
 - Neuropathic pain results from stimulation of damaged nerve tissue - "burning, tingling, stabbing, shooting, electric shock"

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- Opioids (used more frequently in cancer-related neuropathic pain because cancer pain often of mixed etiology), anticonvulsants (gabapentin, pregabalin), SNRIs, TCAs, topicals (capsaicin, lidocaine)
- Pharmacotherapy: WHO analgesic ladder - non-opioid → weak opioid → stronger opioid → interventional techniques (nerve blocks, epidurals, PCs, spinal cord stimulators)
 - Mild pain (1-3): NSAID, acetaminophen, consider slow-titration of short-acting opioids if no relief
 - Moderate pain (4-6): give 5-10 mg oral immediate-release morphine with goal of reducing pain by at least 50%. If < 50% reduction, increased dose by 25-50% and reassess in 4 hrs
 - Severe pain (7-10): rapidly titrate short-acting opioids
 - Psychotropic adjuvants: TCAs, SNRIs, mirtazapine, bupropion, trazodone, anticonvulsants

Clinical Pearl: Both the use of opiate medications and insufficiently treated pain may increase the risk of hypoactive delirium.

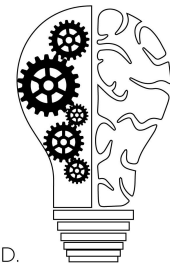
- Psychotherapy
 - Supportive group therapy, CBT - guide patient to sense of control over pain, relaxation, hypnosis, biofeedback, aromatherapy

Effect sizes of treatment modalities

Effect size is the difference between the treatment and control group, expressed in standard deviation units, where an effect size of 1 means that the treatment arm moved 1 standard deviation away from the control group. 0.8 is considered a large effect, 0.5 is a moderate effect, and 0.2 is a small effect.

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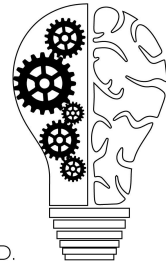


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- Exercise
 - Meta-analysis of 4881 cancer patient found that exercise significantly reduced cancer-related fatigue by mean effect size of 0.32 during cancer tx and 0.38 following cancer tx ([Puetz and Herring, 2012](#))
 - American College of Sports Medicine recommends cancer patient and survivors do at least 150 min moderate-intensity exercise per week
- Psychotherapy
 - CBT: research suggests that CBT for depression and anxiety is efficacious, but most existing trials have been done conducted with patients without known diagnosis of MDD or GAD. Ultimately, CBT interventions may help reduce depression, anxiety, as well as cancer-specific physical symptoms (fatigue, insomnia; interestingly anxiety/depression are often secondary outcomes!) and improve QOL
 - Depression – 1) behavioral activation, 2) correcting negative, automatic thoughts, 3) identify and change core beliefs and schemas
 - In cancer patients: direct tx of distorted cognitions, feelings of helplessness/pessimism about the future. Also CBT identifies, challenges, and attempts to change recurrent negative self-views of worthlessness, inadequacy.
 - Anxiety – identify specific worries and address overestimating of likelihood of negative events and/or catastrophizing
 - CBT > medications for GAD, but it's also compared primarily with benzodiazepines
 - Acceptance and commitment therapy (ACT): CBT variant that aims to change the function of distressing thoughts at the individual level to teach patients to reduce the influence of these thoughts on behavior and goal achievement ([Rost et al, 2012](#))
 - Population: 57 women with stage III or IV ovarian cancer → randomized to TAU or ACT
 - Vs. TAU (treatment as usual - commonly used cognitive and behavioral components): improvement of distress = .89, anxiety = 1.25, depression = 1.69, QOL = 1.35
 - Both groups showed improvement in mood and QOL, but ACT had significantly greater improvements
- Pharmacotherapy (vs. controls)

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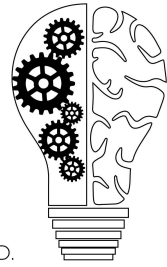
- o Pharmacologic trials: 0.26-0.61, psychotherapeutic trials 0.23-0.95; weighted effect size = 0.43 ([Hart et al, 2012](#))
 - Meds: fluoxetine, paroxetine, desipramine, mianserin
 - Desipramine: 0.26
 - Paroxetine: 0.47
- o Psychosocial interventions (education, relaxation training): 0.46-0.74 (Jacobsen and Jim, 2008)
- o Modafinil for cancer-related fatigue: pharmaceutical intervention weighted effect size = 0.09, exercise + psychological = 0.26, psychological 0.27, exercise = 0.3 ([Mustian et al, 2017](#))

Psycho-Pharmacology

- CYP450 catalyzes Phase I, where oxidation, reduction, and hydrolysis converts inactive compound (prodrug) to active form, or turns non-toxic molecule into a toxic one
 - o Important isoenzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A3/4
 - o CYP2D6 and CYP3A3/4 metabolize most psychotropics
 - o Some anti-neoplastic drugs have pro-drugs that require activation to active metabolites by CYP, or get converted to metabolites with significant toxicity, thus interaction effects crucial
- In oncology patients, psychotropic medications are added to complex regimen of chemotherapy agents, antibiotics, analgesics, antacids, antiemetics, steroids, anticonvulsants, bronchodilators, cardio drugs, hormone replacement..
 - o Most psychotropic drugs (except lithium) undergo primarily hepatic metabolism
- Pharmacokinetics in cancer patients may be impaired due to:
 - o Mucositis - absorption
 - o Edema, lower levels serum-binding proteins - variation in volume of distribution
 - o Renal/hepatic dysfunction - altered excretion

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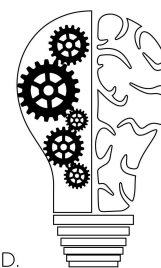
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How common are drug-drug interactions?

- In cancer patients concurrently receiving antidepressants at MD Anderson Cancer Center in 2006, 49% were found to be taking drug combinations with risk for a major drug interaction with antidepressants ([Lal et al, 2011](#))
 - 40% of patients on antidepressants had major drug interaction that could lead to serotonin syndrome
 - 20% of patients on anticoagulants with risk for major drug interaction
 - Potential major drug interactions associated with increased number of hospitalizations and ER visits (OR 2.31, CI 1.37-4.03), where patients found to have major drug interaction had 2.5 mean hospitalizations or ER visits, while patients without major drug interaction had 1.6 mean hospitalizations or ER visits (P = 0.01)
 - Of note, heparin flushes were counted as anticoagulant medications, thus high rates of hospitalization may be due to patients with higher illness severity requiring IV medications rather than actual drug interactions
 - Issue of debate: Antidepressants are already underprescribed, as such this article might lead to even more bias and reluctance to treat mood symptoms in cancer patients.

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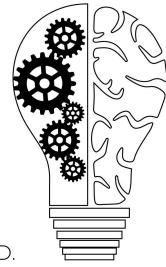
Table 3 Top ten major drug interactions with antidepressants

Antidepressant	Major drug interaction with	Number of interactions	Summary of interaction (substantiation of interaction)
Sertraline HCL	Heparin sodium (porcine)	16	Concurrent use of sertraline and anticoagulants may increase the risk of bleeding. (probable)
Escitalopram oxalate	Heparin sodium (porcine)	12	Concurrent use of escitalopram and anticoagulants may increase the risk of bleeding. (probable)
Escitalopram oxalate	Oxycodone HCL	11	Concurrent use of escitalopram and oxycodone may increase the risk of serotonin syndrome (tachycardia, hyperthermia, myoclonus, mental status changes). (probable)
Sertraline HCL	Oxycodone HCL	9	Concurrent use of sertraline and oxycodone may increase the risk of serotonin syndrome. (probable)
Venlafaxine HCL	Heparin sodium (porcine)	8	Concurrent use of venlafaxine and anticoagulants may increase the risk of bleeding. (probable)
Mirtazapine	Olanzapine	7	Concurrent use of mirtazapine and olanzapine may increase the risk of serotonin syndrome. (probable)
Venlafaxine HCL	ABH (Ativan, Benadryl, Haldol) (lorazepam, diphenhydramine, and haloperidol)	6	Concurrent use of haloperidol and venlafaxine may increase haloperidol serum concentrations and increase the risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest). (probable)
Venlafaxine HCL	Amoxicillin and potassium clavulanate	6	Concurrent use of venlafaxine and amoxicillin/potassium clavulanate may increase the risk of serotonin syndrome. (probable)
Bupropion HCL	Dexamethasone sodium phosphate	5	Concurrent use of bupropion and systemic steroids may lower the seizure threshold. (theoretical)
Duloxetine HCL	Tramadol HCL	5	Concurrent use of duloxetine and tramadol may increase the risk of serotonin syndrome. (theoretical)
Paroxetine HCL	Heparin sodium (porcine)	5	Concurrent use of paroxetine and anticoagulants may increase the risk of bleeding. (probable)

- Psychiatric (52%), psychogeriatric (49%), and geriatric (46%) patient populations have high prevalence of patients treated with at least 1 drug metabolized by CYP2D6, with 62% of these classified as antidepressants, followed by antipsychotics as the next most commonly used CYP2D6 substrate ([Mulder et al, 2007](#))
- Psychostimulants may inhibit metabolism of anticoagulants, antidepressants, anticonvulsants. They may also antagonize hypotensive effects of antihypertensives while increasing hypertensive effect of pressors ([Luigi et al, 2014](#))
 - Faster onset of action for terminally ill and cancer patients
 - May improve attention, concentration, cancer-related fatigue, asthenia
 - Precautions: cardiac (hypertension), psychiatric (hallucinations, delusions, violent behavior)

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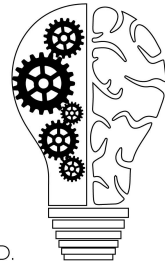


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- Most benzodiazepines are metabolized by CYP450 and have significant potential for interactions. Benzodiazepines metabolized by glucuronidation (lorazepam, oxazepam, temazepam) have fewer drug interactions and are considered 1st line in oncology
- In cancer patients concurrently receiving antidepressants and oral anti-cancer drugs at National Cancer Centre Singapore between 2006 and 2009, 21% were found to have potential drug-drug interactions ([Chan et al. 2011](#))
 - Of 17 pairs of potentially interacting drugs, only 3 were clinically documented to have actually caused interacting effects
 - CYP2D6 inhibition by fluoxetine leads to reduced efficacy of tamoxifen
 - CYP2D6 inhibition by fluvoxamine leads to lower plasma concentration of endoxifen
 - CYP2D6 inhibition by paroxetine leads to reduced efficacy of tamoxifen
 - There may be potential for electronic drug-drug interaction databases to overcall theoretical drug-drug interactions that may not be clinically significant
 - Possible solutions include incorporating upper dose limits (drug-drug interactions are typically dose dependent) or identifying patients at risk for adverse events through individual risk assessments
- Desvenlafaxine is the major active metabolite of venlafaxine after CYP2D6 metabolism and has low risk of variability when co-administered with CYP2D6 substrates or inhibitors ([Low et al. 2018](#))
 - Of note, some of the above authors work for Pfizer (manufacturer of desvenlafaxine)
 - Fluoxetine and paroxetine are strong CYP2D6 inhibitors
 - Fluvoxamine is strong CYP1A2 and CYP2C19 inhibitor → likely to cause drug-drug interactions
 - Sertraline, citalopram, escitalopram less likely to cause significant alterations in CYP450, although these can become clinically significant in renally and hepatically impaired patients
 - Beta-blockers are metabolized by CYP2D6 - antidepressants that inhibit CYP2D6 cause additional HR reduction with given with propranolol, which is both metabolized by and inhibits 2D6 ([Bahar et al. 2017](#))
 - Clinically significant bradycardia has been reported with paroxetine/fluoxetine and metoprolol

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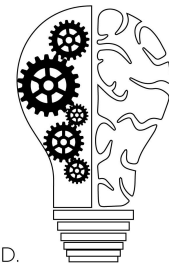
- o Opioids: fentanyl, methadone, oxycodone are major CYP3A4 substrates, thus inhibitors lead to increased effects
 - Tramadol undergoes extensive metabolism via CYP2D6 and CYP3A4, but DES doesn't seem to interfere in major way with CYP-metabolizing pathway of opioids (Pfizer 2016)
 - + risk of serotonin syndrome w/ SSRI or SNRI because tramadol has potential SNRI effect
- o Cancer: pooled prevalence of cancer and comorbid MDD from 31 studies was 10.8% (range 3.7-49%)
 - Lung cancer: antimicrotubule agents (vinca alkaloids - vincristine, vinblastine, vinorelbine; taxanes - paclitaxel, docetaxel) extensively metabolized by CYP3A4
 - PK studies showed that Desvenlafaxine is not extensively metabolized by CYP3A4, or does it measurably alter CYP3A4-mediated metabolism ([Nichols et al, 2013](#))
 - TKIs (erlotinib, gefitinib, osimertinib.. etc) cleared by CYP3A4
 - Breast cancer: cyclophosphamide, ifosfamide major substrates of CYP3A4 and CYP2B6; doxorubicin is major substrate of CYP3A4 and CYP2D6 → given w/ inhibitors increases concentration and clinical effect of anticancer agents
 - Colorectal cancer: irinotecan metabolized by CYP3A4 and competitively inhibitors CYP3A4 and CYP2C9
 - Case report showed potentially fatal rhabdo in patient taking irinotecan and citalopram (CYP3A4 substrate) - speculates theoretical PK interaction between irinotecan and other CYP3A4 substrates such as escitalopram and fluoxetine ([Richards et al, 2003](#))

A Closer Look at Tamoxifen

- In a study of 2430 women living in Ontario treated with tamoxifen for breast cancer between 1993 and 2005 w/ overlapping treatment with single SSRI (paroxetine, fluoxetine, sertraline, citalopram, fluvoxamine, venlafaxine), paroxetine use during

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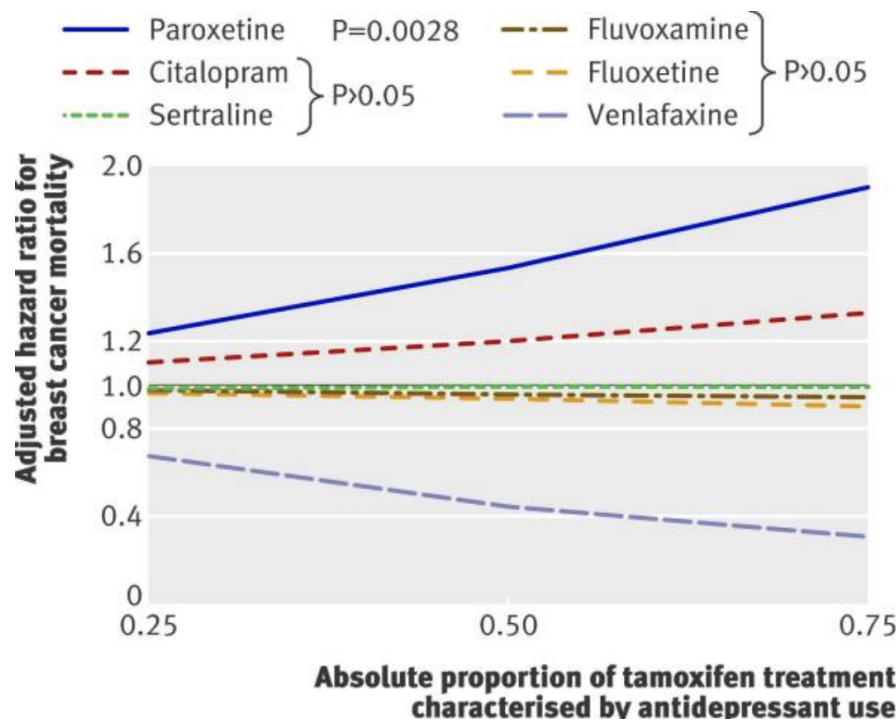
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tamoxifen treatment was associated with increased risk of death from breast cancer. This suggests that paroxetine, a strong irreversible CYP2D6 inhibitor, can reduce the benefit of tamoxifen in women with breast cancer ([Kelly et al. 2010](#))

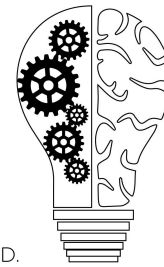
- o “absolute increases of 25%, 50%, and 75% in the proportion of time on tamoxifen with overlapping use of paroxetine (an irreversible inhibitor of CYP2D6) were associated with 24%, 54%, and 91% increases in the risk of death from breast cancer”



- o Tamoxifen is metabolized by hepatic CYP450 to active metabolites 4-hydroxytamoxifen and 4-hydroxy-N-desmethyltamoxifen (endoxifen) that have 100x higher affinity for estrogen receptor than parent compound ([Jin et al. 2005](#))
- o The authors also found a non-significant trend towards reduced breast cancer mortality among venlafaxine users. However, this may reflect the practice of prescribing venlafaxine for hot flashes, which may predict better outcomes in women receiving tamoxifen. Hot flashes are thought to occur when less estrogen is present, and tamoxifene is estrogen receptor blocker ([Mortimer et al. 2008](#))

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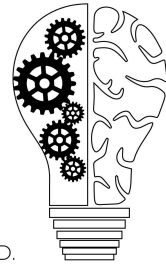
- o Paroxetine also associated with increased relative risk of death from any cause; also in subgroup of 226 women w/ unknown cause of death
- o Interestingly, fluoxetine, a strong CYP2D6 inhibitor, had no association with increased death from breast cancer in this study. Only 10.4% of subjects received fluoxetine while 25.9% received paroxetine.

Clinical Pearl: Strong CYP2D6 inhibitors such as paroxetine and fluoxetine can significantly decrease serum levels of chemotherapy agents, in particular, tamoxifene. Venlafaxine and mirtazapine are weak CYP2D6 inhibitors and may be preferred in patients concurrently receiving chemotherapy.

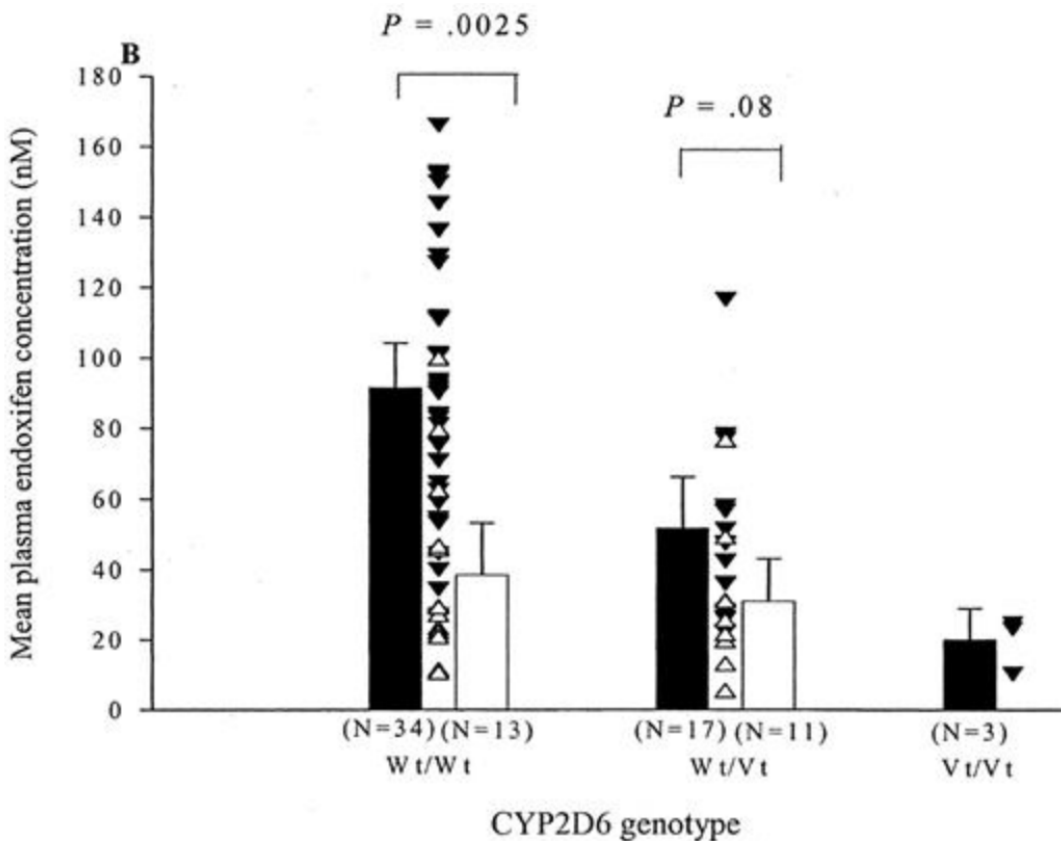
- Interactions between CYP2D6 polymorphisms and coadministered antidepressants that are CYP2D6 inhibitors in women with newly diagnosed breast cancer at Lombardi Comprehensive Cancer Center were found to decrease plasma concentrations of endoxifen, the active metabolite of tamoxifen ([Jin et al, 2005](#))
 - o CYP2D6 homozygous variant or heterozygous had lower plasma endoxifen vs. homozygous WT
 - Wt/Wt patients using CYP2D6 inhibitors found to have 58% less plasma endoxifen compared to those who did not use CYP2D6 inhibitors
 - In patients heterozygous for nonfunctional allele, those taking CYP2D6 inhibitors had 38% lower levels of endoxifen
 - Among those *not* taking CYP2D6 inhibitor, plasma concentration endoxifen associated w/ CYP2D6 genotype (white bars/triangles represent patients taking CYP2D6 inhibitor)

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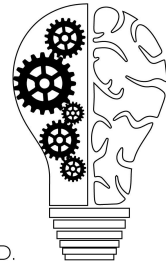
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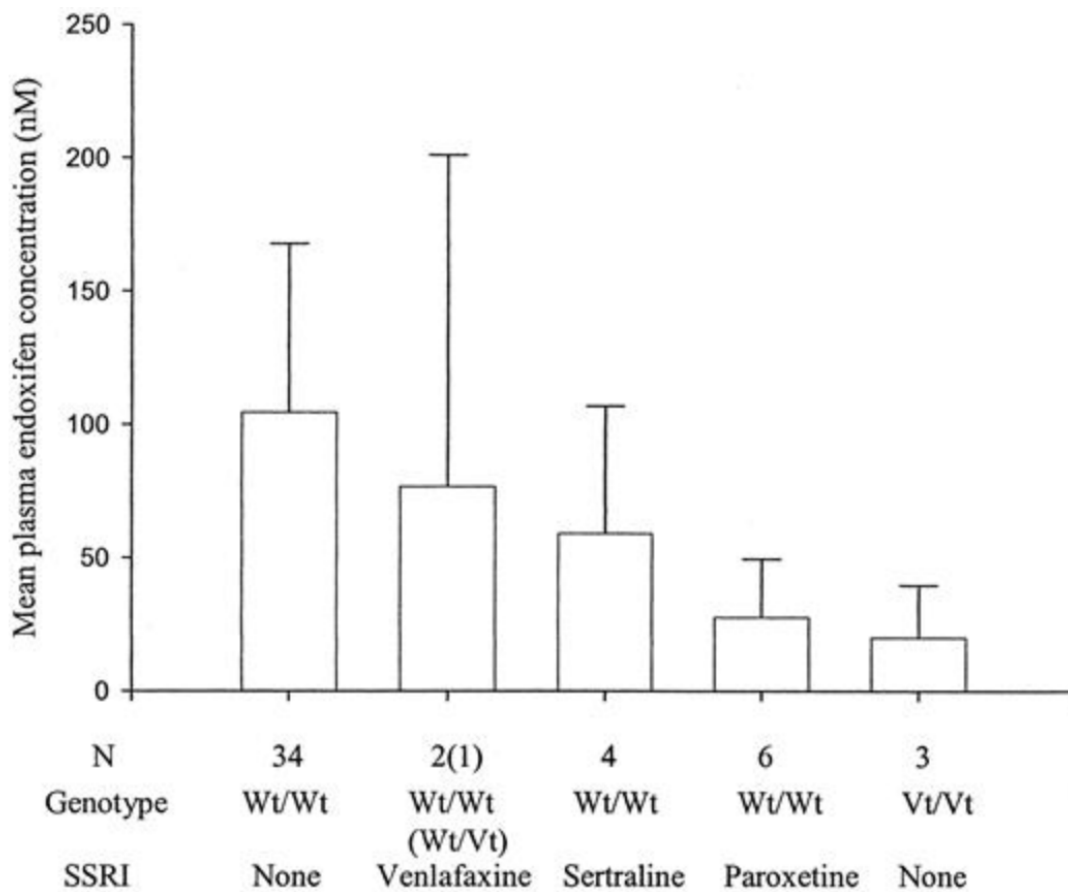
- o Plasma endoxifen was slightly reduced in women taking venlafaxine and substantially reduced in women taking paxil

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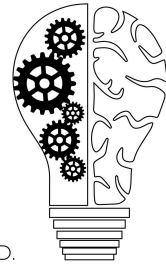


- o The study found the following inhibition constants for CYP2D6 inhibition: paroxetine (0.05 $\mu\text{mol/L}$) > fluoxetine (0.17 $\mu\text{mol/L}$) > sertraline (1.5 $\mu\text{mol/L}$) > citalopram (7 $\mu\text{mol/L}$) > venlafaxine (33 $\mu\text{mol/L}$)

Mental Health and Survivorship/QOL

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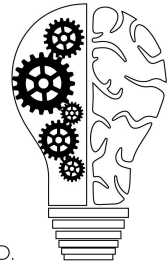


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- Depression Care for People with Cancer (DCPC), which consists of pharmacological and psychological collaborative care, is highly effective in improving depression and quality of life in depressed cancer patients, although it does not have significant effect on survival. However, given evidence for improvements to quality of life, treatment of depression is still strongly indicated ([Mulick et al. 2018](#))
 - SMaRT Oncology-2 trial found that patients with good prognosis cancers who received DCPC had greater treatment response (defined as >50% reduction in Symptom Checklist Depression Scale at 24 weeks); less depression, anxiety, pain, and fatigue; better functioning, health, and quality of life
 - Secondary analysis of survival outcomes found that 69% of the usual care group and 72% of DCPC group survived to 6 yrs with no significant difference in survival
 - SMaRT Oncology-3 trial found that patients with lung cancers who received DCPC had significantly lower average depression severity and better self-rated depression improvement, anxiety, quality of life, and role functioning
 - Secondary analysis of survival outcomes found that 15% of the usual care group and 23% DCPC group survived to 6 yrs
- Major depression comorbid w/ cancer affects ~105 patients w/ cancer and associated w/ worse survival in multiple studies ([Walker et al. 2014](#); [Satin et al. 2009](#); [Barber et al. 2016](#); [Pinquart et al. 2010](#))
 - Previous studies have found that patients on antidepressants prior to breast cancer diagnosis had poorer survival and higher risk of poor quality medical care, suggesting that survival effects of depression may be mediated by quality of medical care
 - Patients with depression and other mental health conditions receive less population preventive screening for cancer ([Mitchell et al. 2014](#)) and diagnosed/treated later ([Iglay et al. 2017](#)) → survival disadvantage in patients w/ poor mental health
 - Depressed cancer patients may be less likely to pursue recommended treatments, have longer hospital stays, higher mortality rates, and higher likelihood of reporting desire for hastened death ([Kruse et al. 2015](#))

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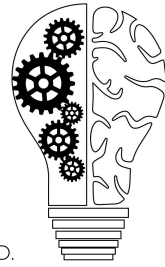
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Commonly used psychotropic medications

Medication	Use(s)	Caution, CYP Interactions
Bupropion	Depressive disorders, adjuvant treatment of pain; may improve sexual function and fatigue	Lowers seizure threshold, be cautious in patients with vomiting, cardiac comorbidities Cyclophosphamide and ifosfamide (CYP2B6 inducers) may cause decreased concentrations of bupropion
Mirtazapine	Depressive disorders, anorexia-cachexia, nausea, insomnia in conjunction with depression, adjuvant treatment of pain	Rare side effect of reversible neutropenia May contribute to QTc prolongation <i>Weak CYP450 inhibitor – preferred</i>
Trazodone	Depressive disorders, insomnia in conjunction with depression, adjuvant treatment of pain	Orthostatic hypotension and dizziness in elderly and/or fragile patients – do not exceed 100 mg QHS

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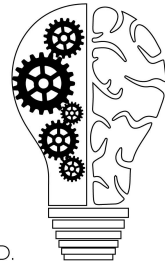


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Psychostimulants (Methylphenidate, Amphetamine)	Rapid onset energizing effects in depressed patients with advanced/terminal disease but unclear efficacy for depression; methylphenidate is appetite stimulant at lower doses	Prolonged use associated with psychosis, be cautious in patients with cardiac comorbidities May inhibit metabolism of anticoagulants, antidepressants, anticonvulsants
Modafinil	Cancer-related fatigue	
SNRIs	Depressive disorders, long-term treatment of anxiety, neuropathic pain; may alleviate hot flashes	- Venlafaxine is <i>weak CYP2D6 and CYP3A4 inhibitor - preferred</i> - Caution with duloxetine in medically ill as it undergoes CYP2D6 metabolism
TCAs	May be used for comorbid neuropathic pain at lower doses than used for depression	Seldom 1 st line due to side effect profile - Amitriptyline (metabolized by CYP2D6, which is available in small quantities) can cause hypoactive delirium if given with CYP2D6 inhibitors

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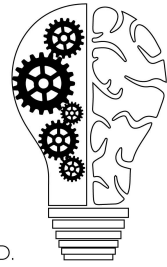


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SSRIs	Depressive disorders, long-term treatment of anxiety	<ul style="list-style-type: none"> - Fluvoxamine not recommended for action as CYP450 1A2, 2C19, 3A4 inhibitor - Avoid fluoxetine and paroxetine for CYP2D6 inhibition - Escitalopram and citalopram are <i>weak CYP450 inhibitors – preferred</i> - Sertraline - Depression + tamoxifen: venlafaxine > escitalopram > citalopram <p>SSRIs have risk of upper GI bleed w/ NSAIDs (metabolized by CYP)</p>
Benzodiazepines	<p>Short-term treatment of anxiety, PTSD</p> <p>Lorazepam, oxazepam, and temazepam preferable in liver disease; clonazepam has less abuse potential than shorter-onset agents</p>	Cognitive impairment, sedation. Risk of disinhibition, irritability, and violence in patients with CNS damage.

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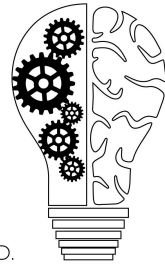


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Antipsychotics (Haloperidol is gold-standard in cancer patients, chlorpromazine is alternative if increased sedation required)	<p>Agitation, paranoia, hallucinations; delirium and hypoactive delirium on case-by-case basis</p> <p>Steroid-induced irritability, sleep disturbance, mood symptoms</p> <p>Olanzapine and quetiapine may be used for insomnia in patients with history of substance use</p> <p>Haloperidol, perphenazine, and olanzapine may be used for nausea</p>	<p>Antipsychotics metabolized by CYP450</p> <p>Phenothiazines may cause cognitive impairment.</p>
Clonidine, Prazosin	Nightmares in PTSD	May be contraindicated with some cancer regimens
Ramelteon	Insomnia	
Zolpidem, Eszopiclone, Zaleplon	Insomnia, particularly for sleep-initiation difficulties	
Gabapentin	Insomnia, hot flashes, anxiety especially if history of substance use	Less drug-drug interactions because primarily excreted by kidneys

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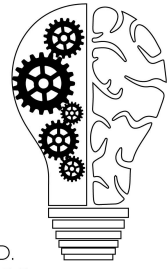


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D2 antagonists	- Metoclopramide: nausea with constipation, early satiety - Haloperidol: nausea with anxiety, agitation, confusion	
5-HT3 antagonists (Ondansetron, Granisetron)	Nausea	
NK receptor antagonists (Aprepitant, Fosaprepitant)	Nausea, in particular delayed onset nausea/vomiting from chemotherapy	
Octreotide	Nausea, in particular in bowel obstruction	
Cannabinoids (Dronabinol, Nabilone)	Nausea, anorexia-cachexia; recent clinical trial also found improved sleep in cancer patients	Causes impaired psychomotor function and psychoactive effects, especially in elderly patients
Steroids	Nausea, in particular secondary to increased ICP; anorexia-cachexia, anti-inflammatory properties may also help with mood	Mood changes, anxiety, insomnia, steroid psychosis
NSAIDs, acetaminophen	Mild pain (1-3/10)	Metabolized by CYP450

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Opioids	Moderate to severe pain (4+/10)	Sedation, nausea, constipation, opioid psychosis Fentanyl, methadone, and oxycodone are major CYP3A4 substrates, thus inhibitors lead to increased effects
Anticonvulsants	Pain	Psychostimulants may inhibit metabolism of anticonvulsants

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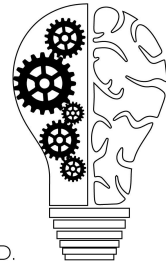
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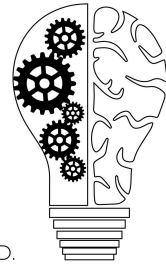
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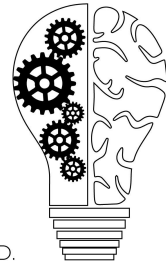
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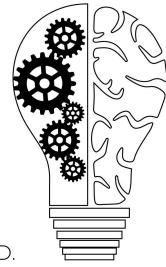
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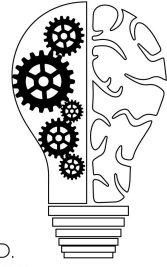
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