PSYCHIATRIC ISSUES IN ONCOLOGY

by

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DISCLOSURE

 No paid sponsorship from pharmaceutical companies nor other industries in past 10 years



OBJECTIVES

- Have a broad understanding of <u>psychiatric sequelae</u> from cancer and its treatments
- Role of some medical and psychosocial factors in <u>precipitating</u> <u>psychiatric symptoms</u> (focus on depression, anxiety, delirium)
- <u>Tamoxifen-antidepressant interactions</u>
- A model to manage <u>patient resistance to antidepressant medication</u>, especially in the context of psychosocial stress
- Be able to deal with the <u>"tyranny of positive thinking</u>" in oncology settings
- Potential mental health <u>resources</u> for oncology patients



PSYCHIATRIC SYMPTOMS ACROSS CANCER TRAJECTORY AND BY MANY FACTORS:

- Disease....premorbid apathy and depression
- Diagnosis.....significance and impact
- Treatments
 - Surgery
 - Chemotherapy
 - Any medical side-effect can have psychological significance
 - Treatments of side-effects can lead to further psychiatric complications
 - Chemotherapies have various effects on CNS



Continued

- Hormonal factors... Corticosteriods; Gonadotropins
- Organ Toxicities
- Drug Interactions
- Supportive-Medications (Steroids, sedatives, antiemetics, pain medications)
- Chemobrain
- Radiation

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Bone Marrow Transplantation

Survivorship issues....adrift when less monitored Palliative care issues.....fears of loss of control, dying



INITIAL SEQUELAE FROM CHEMOTHERAPY...

May result from the DISCUSSION of TREATMENT MORTALITY and MORBIDITY!

The hospital's need for medical-legal consent for chemotherapy can lead to overwhelming ANXIETY (+/- FEATURES OF PTSD).

Hospital staff usually worry more about giving "false hope," than about "false despair," which can be immobilizing.

How to Break Bad News by Robert Buckman



BASIC PRINCIPLES OF MEDS AND RANGE OF PSYCH EFFECTS

- If a medication has stimulating neuro s/e's to the CNS, (eg. tremor, insomnia), expect possible related excitatory problems: anxiety, panic, irritability, hypomania, excited delirium (eg. cyclosporine; cipro, imipenem)
- If a medication has depressant effects on CNS, (eg. drowsiness), expect possible related slowing effects on cognition, energy, mood (apathy, depression) (eg. amphotericin)



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Seems obvious, but often over-looked!

CHEMOTHERAPY MEDICATIONS: PROCARBAZINE

PROCARBAZINE

- Hodgkin's in MOPP regimen; brain tumors
- Mild MAOI med!: tyramine precautions. Avoid TCA's, Demerol, etc.
- CNS: Delirium, psychosis, depression, somnolence



METHOTREXATE

- Leukemias; lymphomas; breast ca; head and neck ca
- CNS toxicity intrathecally caused by demyelination of nerve fibers
 - dose-related
 - delirium or cerebellar dysfunction
 - increased effect with Ara-C, daunorubicin, salicylates, sulfonamides, vinblastine, vincristine or concurrent cranial radiation
 - if renal dysft, need to lower dose
- Other toxicities: kidney, liver, lung; mucositis and myelosuppression



ANY MEDICAL SIDE- EFFECT CAN LEAD TO PSYCHOLOGICAL SYMPTOMS

Any symptom may have a UNIQUE significance and meaning to the patient, and therefore may have psychiatric significance.

eg. A patient may have had similar pains just prior to the diagnosis, and is now convinced that his iatrogenic myalgias are indicating a recurrence

eg. A relative may have had a similar illness or symptom just before death.



ANY MEDICAL SIDE- EFFECT CAN LEAD TO PSYCHOLOGICAL SEQUELAE cont.

eg. Loss of body hair is not all managed with a wig! There may be issues of sexual attractiveness, relationship strain, looking frighteningly ill to children...

eg. Fatigue and chemo-brain may be inconvenient to an unemployed person, but terrifying to an obsessive, highly skilled professional trying to work,...and who may also secretly worry that he has brain metastases.



CASCADE OF SIDE-EFFECTS, & THEIR TREATMENTS, AND MORE PSYCHIATRIC SYMPTOMS

MYELOSUPPRESSION ("Low blood counts")

>fatigue, lowered energy, and lowered immunity to infections, > anxiety, social isolation, lowered morale >need for prophylactic antibiotics, antifungals, and antivirals

INFECTIONS

> local and systemic effects;

> **CNS effects** (eg. Viral encephalitis from herpes simplex in immune-compromised patient).

MEDICATIONS FOR INFECTIONS can lead to:

emotional lability or anxiety (in CNS- activating antibiotics such as Ciprofloxacin and Imipenem), BC Cancer Agency Charlet (eg. Amphotericin)



SUPPORTIVE MEDICATIONS: MORE PSYCH SYMPTOMS

- Effects on mental status by:
 - Pain medications
 - Remember that outpatients may be "fuzzy" from morphine...and forget appointments!
 - Anti-emetics
 - Sedatives
 - Anti-seizure medications
 - Prophylactic antibiotics, antivirals, antifungals
 - Immunosuppressants in Transplant patients



RX OF SIDE-EFFECTS: MORE PSYCH SYMTPOMS

ANTI-EMETICS FOR NAUSEA AND VOMITING... can cause

- SEDATION (Gravol, ondansetron; lorazepam often used for nausea)
- **AKATHISIA** (prochlorperazine (Stemetil) and metoclopramide (Maxeran), perceived by staff to be anxiety.
 - Rx.: Add benztropine or diphenhydramine (Benadryl) for 2 days; switch to non-akathisic anti-emetic, ...and...



ADD OLANZAPINE TO TREAT NAUSEA!

- Olanzapine 2.5 5.0 mgm TID PRN
- Olanzapine is "safe and highly effective in controlling acute and delayed chemotherapy-induced nausea and vomiting in patients receiving highly and moderately emetogenic chemotherapy."..."the most exciting anti-emetic since ondansetron." (Oncologist Dr. Navari)
- Navari RM et al, Support Care Cancer, 2005, July
- Navari RM et al, Support Care Cancer, 2007, Nov.



HORMONAL THERAPY: CORTICOSTEROIDS

Numerous indications can include:

- Nausea
 - Given pre-chemotherapy infusions
- Brain edema
 - Brain tumors; post- radiation eg. Dexamethasone 4mg. QID
- Chemotherapy regimens
 - (MOPP= Nitrogen Mustard, Oncovin (vincristine), Procarbazine, Prednisone)
- Graft vs. Host Disease
 - eg. Prednisone 60mg. BID



HORMONAL THERAPY: CORTICOSTEROIDS

Psychiatric sequelae include:

- CNS behavioral activation:
 - Euphoria and hypomania can progress to anxiety, extreme agitation and, psychosis ("Like many "extra-large" Starbucks coffees!")
- Increased appetite; decreased sleep
- Depression
 - In prolonged therapy?; dosage fluctuations

Tapering of corticosteroids:

- Flat, apathy, lethargy, fatigue, depression
- May take a number of weeks before energy restabilizes

HORMONAL ISSUES IN CANCER TREATMENT

- ABRUPT ONSET OF MENOPAUSE/ANDROPAUSE
 - Due to chemotherapy, surgery, or total body irradiation.
 - Symptoms of menopause often include mid insomnia, generalized anxiety, concentration difficulties, and word-finding difficulties.
- Abrupt discontinuation of Hormonal Replacement Therapy
 - Can also aggravate mood.
- Estrogen-Blockers (eg. Tamoxifen)



HORMONAL ISSUES IN CANCER TREATMENT

HORMONALLY-MEDIATED DEPRESSIONS

- Not all women develop post-partum depression after pregnancy...some do!
- Not all women develop depression with estrogenblockers...some do!
- Psychiatric history should include past and family histories of menstrual dysphoria and post-partum disorders

THYROID DYSFUNCTION

 May have occurred in association with cancer treatments



ORGAN TOXICITIES: PSYCHIATRIC IMPLICATIONS

RENAL DYSFUNCTION

- Direct effects of renal dysfunction on brain functioning
- ADDITIONAL factor of increased or new medication toxicities affecting mental status,

HEPATIC DYSFUNCTION

- Direct effects of liver dysfunction on brain functioning Increased liver function values associated with increasing apathy lead to increased psychiatric referrals for "depression."
- ADDITIONAL increased toxicities of current medication
- Caution re: prescribing meds that could aggravate liver function, or are metabolized by liver

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ORGAN TOXICITIES: PSYCHIATRIC IMPLICATIONS

ENDOCRINE SYSTEM

- Suboptimal thyroid and gonadotropins
 - After total body irradiation...resulting in fatigue, andropause, menopause

CARDIAC (eg. Daunorubicin)

• Caution re: arrhythmias, (eg. TCA's) and increased BP (eg. Venlafaxine)

GASTROINTESTINAL TOXICITIES/ SYMPTOMS

- Nausea: might avoid SSRI med. Consider olanzapine
- Vomiting: What meds are not absorbed?
- **Diarrhea:** What meds are not absorbed? Very limiting socially and for medical appointments
- Weight loss: Consider mirtazapine. Weight loss is a complicating factor in considering use of stimulants (eg. Ritalin) for treatment of fatigue, as stimulants could increase energy but suppress appetite.



CHEMOBRAIN

- Cannot be attributed solely to psychological effects nor to hormonal/menopausal effects on cognition
- Although most chemotherapies do not cross the bloodbrain barrier, studies of Adriamycin, which does not cross the blood-brain barrier, indicate CNS toxicity by systemic release of cytokines and induction of tumor-necrosis factor, as well as other mechanisms, which lead to altered CNS functioning. Mechanisms are not fully understood. (Taillibert, S, et al., Current Opinion in Oncology, Nov. 2007)



PHASES OF RADIATION EFFECT

ACUTE EFFECTS

Presents hours to days post-radiation

SUBACUTE EFFECTS

Seen weeks to a few months post-radiation

LATE EFFECT PHASE

Can develop years later



RADIATION EFFECTS: ACUTE PHASE

- Depend on
 - size of radiation field,
 - daily radiation dose,
 - number of treatments (may be weeks
- BRAIN RADIATION causes CEREBRAL EDEMA and increased intracranial pressure, with exacerbation of presenting neurological symptoms, such as headache, nausea and vomiting, weakness, seizures, and mental status changes
- Rx Dexamethasone often 4 mgm TID or QID



RADIATION EFFECTS: SUBACUTE PHASE

 Tissues most at risk are brain, heart, kidney, liver, lung, and spinal cord

FATIGUE

- Is cumulative over the course of radiation treatments, and may peak after weeks, but can persist for prolonged periods after treatments are completed.
- Described by patients as exhaustion, weakness, inability to concentrate or to complete normal daily activities. It profoundly impacts on quality of life.



RADIATION LATE EFFECTS IN BRAIN

LEUKOENCEPHALOPATHY

- Usually this occurs in context of postchemotherapy, but can occur post-radiation.
- Multiple, noninflammatory necrotic foci in white matter of brain tissue, with demyelination and reactive astrocytosis.
- Lethargy, seizures, paresis, ataxia
- MRI helpful
- Generally irreversible



RADIATION LATE EFFECTS IN BRAIN

BRAIN NECROSIS

- Peak onset 1-2 yrs post-radiation, but may occur many years later
- Symptoms include headache, somnolence, cognitive deficits, decrease in short and longterm memory, seizures, and focal CNS deficits
- Dx by MRI.
- Rx Surgical debulking of necrosis; orticosterodis
- Progressive and usually fatal



BONE MARROW TRANSPLANTATION

- AUTOLOGOUS: Hematological products removed; toxic levels of chemotherapy given; patient's own products re-infused
 - No Graft vs. Host Disease
- ALLOGENEIC: High dose chemotherapy and total body irradiation to treat hematological condition; donor products infused
 - Major problem of Graft-vs. Host Disease GVHD)



GRAFT VS. HOST DISEASE (GVHD)

- Immunosuppression required to prevent attack by donor cells on recipient's tissues
- Immunosuppression can lead to infections, with increased illness morbidity, chronicity, and discouragement.
- Immunosuppression mainly by:
 - CYCLOSPORINE
 - CNS Activating: Tremor, anxiety, agitation, delirium, psychosis
 - Toxicity can occur even in "appropriate" CSP levels, particularly if serum magnesium levels are low
 - CORTICOSTEROIDS...HIGH DOSES!
 - CNS activating: Anxiety, hypomania, mania, psychosis

BC Cancer Agenc ACROLIMUS...can cause akathisia



FACTORS IN PRECIPITATING PSYCHIATRIC SYMPTOMS/ SYNDROMES

DEPRESSION ANXIETY DELIRIUM



BEYOND DIAGNOSIS: DIAGNOSTIC FORMULATION

- PREDISPOSING FACTORS (Vulnerability, or Risk Factors)
 - Biological,
 - Psychological,
 - Social,
 - Spiritual
- PRECIPITATING FACTORS (Triggers)
 - Biological,
 - Psychological,
 - Social,



DIAGNOSTIC FORMULATION Cont.

PERPETUATING FACTORS

Biological, Psychological, Social, Spiritual

PROTECTIVE FACTORS

Biological, Psychological, Social, Spiritual

Kline, S, Cameron, PM; "Formulation," Can. Psychiatric Assoc Jounral 23: 39-42, 1978



DEPRESSION WITH CANCER DIAGNOSIS

- Incidence of depression in cancer patients ranges from 10-25%, even 58%, depending on severity of depression, population
- At least 25% patients with advanced cancer have significant degree of dysphoria (Massie), when Adjustment Reactions have been included in the context of depression.
- About 4x more prevalent than in general population



DIFFERENTIAL DIAGNOSES of DEPRESSION

- Situational response
- Situational response in context of marked personality features or traits (eg. Axis II diagnosis)
- Adjustment Reaction with depressed and/or anxious mood (not full-blown depressive episode, and time-limited to 3 months)
- Simple Bereavement
- Major Depressive Episode



DIFFERENTIAL DIAGNOSES OF DEPRESSION cont.

- Dysthymic Disorder (chronic fluctuating depressive symptoms of at least 2 years)
- Bipolar Disorder
 - Bipolar I (at least one Manic or Mixed Episode; not due to switch phenomenon or medical condition)
 - Bipolar II (Depressive episodes and at least one Hypomanic Episode)
 - Cyclothymic Disorder



DIFFERENTIAL DIAGNOSES OF DEPRESSION cont.

- Mood Disorder due to a General Medical Condition (formerly called Organic Mood Disorder)
- Substance-Induced Mood Disorder
- Post-Traumatic Stress Disorder (PTSD)
- Generalized Anxiety Disorder
- Panic Disorder


...IN SIMPLISTIC TERMS...

- There is likely a <u>continuum of mood</u> functioning related to a <u>continuum of neurotransmitter levels and</u> <u>functioning</u> at the nerve synapses
- Possibly an Adjustment Reaction is biochemically a milder form of depression
- Antidepressants are effective not only in Depression, but also in Adjustment Reactions, Dysthymia, PTSD, pain, and Panic Disorder



ASSESSMENT OF DEPRESSION

- Somatic symptoms of depression lack specificity in medically ill patients......
 - Loss of appetite, sleep disturbance, low energy
- Psychological symptoms of greater diagnostic value: dysphoric mood, hopelessness, worthlessness, guilt, and suicidal ideation
- Hopelessness that is pervasive, with despair



PREDISPOSING: Biological Risk Factors

- Increased risk of depression in cancer patients who are:
 - Male
 - Younger
 - Past history depression (major risk)
 - Family history of depression
 - Medical conditions, (eg. Endocrine, esp. thyroid, sex hormones; past substance abuse; toxin exposure,...)



PREDISPOSING: Social

- Limited social support
- Strong social support buffers against depression in cancer, esp. in early illness (Chochinov)
- Decreased functional and physical ability







PRECIPITATING: Biological

<u>Pain</u>

- 2-4x depression in high-pain group vs. low-pain (Spiegel, 1994)
- Pain is single most important factor associated with distress (directly and by causing impaired functioning)
- Pain triggers depression;
- Depression amplifies pain.



PRECIPITATING: Biological cont.

Direct tumor effects (CNS tumors or brain metastases)

Indirect tumor effects

- Hypercalcemia
- Toxins secreted by the tumor
- Liver dysfunction
- Renal dysfunction
- Tumor-induced neuroendocrine changes
 - Increased depression in pancreatic adenoca tumors;
 - Mood effects in Carcinoid/Neuroendocrine tumours;
 - Cushing's syndrome in pituitary tumors



PRECIPITATING: Biological cont.

Infections alter mood

- Viral (Hepatitis; CMV; Epstein-Barr;...)
- Urinary tract infections

Nutritional deficits

Treatment-induced

Chemotherapy

Vincristine, vinblastine, asparagines, intrathecal methotrexate, interferon, interleukin,...

- Corticosteroids --esp. after tapered
- Hormonal changes....gonadotropins and thyroid
- Metabolic Hyponatremia; liver dysfunction
- Radiation (causes cumulative fatigue).
- Brain radiation



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PRECIPITATING: Psychological/Social

Psychological

- Losses
- Role changes (affecting self-esteem)

<u>Social</u>

- Relationship turmoil or estrangement
- Financial worries
- Decreased social support (due to a move or change of culture)



PRECIPITATING: Spiritual

- Loss of meaning in life
- Sudden confrontation with mortality (possibly a new idea)
- Feeling abandoned by God
- Feeling punished by God (both cause and effect of depression); feelings of spiritual ineptitude
- Unsure about an after-life
- Fears of facing judgment or Hell
- Fear of separation from loved ones after death due to differing beliefs
- Fear of being forgotten or replaced after death
- Themes may overlap with mood disorders . (Depression can exacerbate guilt and inadequacy).



PERPETUATING

- Biological
- Psychological
- Social
- Spiritual



PERPETUATING: Biological

- Ongoing disease and conditions ("Battle-weary")
- Pain
- Cumulative effects (eg. Radiation fatigue)
- Ongoing drug interactions due to prolonged half-life of drug (eg. Prozac)



TREATMENT

- Biological
- Psychological
- Social
- Spiritual

- Involve the patient actively...teach
- Knowledge is empowering



MANAGING PATIENT RESISTANCE TO ANTIDEPRESSANT MEDICATION

including

in the context of life-threatening illness



THE "DRYSDALE" APPROACH IN TEACHING PATIENTS ABOUT DEPRESSION

OR.....How to get beyond, "I don't want medications because it's my life that's making me depressed and drugs won't fix that."

"I'm just worn down emotionally."

- "What's worn down?
- Perhaps it's more than your psyche. Perhaps there actually is something physical that's worn down: ... The chemicals that maintain our state of well-being."



NEURON











Neurotransmitters: Chemicals that "swim" from one nerve cell to the next, (and back), relaying the message from one nerve cell to the next.

Depression: "As if"not enough chemical(Serotonin and Norepinephrine) in the mood part of the brain. (Limbic Lobe).











... which in turn increases activity at the serotonin and/or norepinephrine receptor sites.

REVIEW SIGNS AND SYMPTOMS OF DEPRESSION

Changes in <u>mood</u> (sadness, emptiness, anhedonia (lack of pleasure), irritability, anxiety, panic, or increased anger.) May feel hopeless and helpless. Vague suicidal ideation or active thoughts of suicide

Changes in daily body rhythms: (Hypothalamus effects)

- Sleep (decreased or increased, and often early am. Awakening); Appetite changes
- Pattern of daily mood fluctuation, and often lowest in early a.m

Psychomotor activity slowed; speech may be quiet, slow, and monotonal

Depressive thought content, with themes of:

increased guilt,

Paranoia of feeling rejected by others,

Focus on health.



BC Canc Decreased sel-esteem (worthlessness)





Psychological (Reactive)

Psychological

Circle of Depression



Biological

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Changes in mood

Decreased

Neurotransmitter

Changes in daily rhythms sleep, appetite, mood

Slowed psychomotor fct.

Concentration low

Depressive themes (guilt,rejection, health)

Loading at Various Stations Social/Situational

BIOLOGICAL

- Genetic tendency for low serotonin levels
- Infections (viral, bacterial)
- Other illnesses (eg. Thyroid)
- Hormones (menopause, tamoxifen)
- Amount of light
- Medications new or changed BC Cancer Agency CARE & RESEARCH Alcohol, drugs, toxins

Neurotransmitter Worn Down!

Psychological

Loading at Various Stations

<u>SOCIAL</u> <u>STATION</u>

- Relationship issues
- Career and work issue
- **Financial stresses**
- Role changes in famil

Biological

Neurotransmitter
Worn Down!

Psychological



Loading at Various Stations

Social/Situational

Neurotransmitter Worn Down!

Biological

PSYCHOLOGICAL STATION

Control issues

Fears (eg. Of recurrence)

Identity and self-esteem issues (eg. Loss career; changed body image)

Losses(plans and dreams; fertility; self-confidence; control)

Conflicts and worries



Loading at Various Stations

Psychological

Social/Situational

Biological

Neurotransmitter

Worn Down!

<u>SPIRITUAL</u> <u>STATION</u>

Feeling abandoned by God

Anger at God; then guilt

Punishment for past

Feeling "lost"

Feeling "unworthy"









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Development of Effects at each Station (Further wearing down the system in vicious cycle)

Social/Situational

Effects further wear down system in vicious cycle

PSYCHOLOGICAL EFFECTS:

Decreased self-esteem

Blame others or self (guilt), or both

Depressive content (inappropr. Guilt; feel rejected; preoccupied with symptoms)

Biological





Development of Effects at each Station (Further wearing down the system in vicious cycle))

Social/Situational

Effects further wear down system in vicious cycle Psychological

<u>ŚPIRITUAL EFFECTS:</u>

Feels further abandoned or alienated from God

Loss of faith

Feels spiritually inadequate

Biological



Stop Circle of Depression by Treatment at each Station



Biological



Neurotransmitter Decreased Changes in mood Changes in daily rhythms sleep, appetite, mood Slowed psychomotor fct. **Concentration low Depressive themes**

Depressive themes (guilt,rejection, health) **Spiritual**

Psychological

Treatment:Boost the neurotransmitters....Directly or indirectly

SOCIAL:

- Change job or relationship
- Boost support system (friends; support groups)



BIOLOGICAL:

- Antidepressants
- Meditation/Relaxation
- Change hormone or med regimens



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<u>PSYCHOLOGICAI</u>

Psychotherapy Empowerment

Acknowledge coping and resiliency

Visual imagery

SPIRITUAL:

12-Step Programs Re-connect with past faith practices, or explore new ones

Pray - L.Dossey,MD

"TYRANNY" OF "POSITIVE THINKING!"

- Often friends and family, when not knowing what else to say, will say, "Just be positive!"
- It can be hard enough to be positive when things are going well, never mind when one has cancer.
- This puts an extra burden on patients, and they feel anxious or guilty about causing a relapse, and resentful of the burden!
- Better to emphasize having a "fighting spirit,"
 - Not necessarily feeling physically vibrant
 - Means having a determination to live, or to seek treatment



CHOOSING AN ANTIDEPRESSANT

- Limited studies of antidepressants in oncology patients: Complex situation with many cancer diagnoses, stages, comorbidities, regimens
- Small number of randomized controlled trials with SSRI's, imipramine, mirtazepine, bupropion, stimulants. Mostly < 100 pts; various cancers and stages
- Can refer to CANMAT Guidelines for Depression, listing many antidepressants as First line or Second line options



CHOOSING AN ANTIDEPRESSANT by Neurotransmitter Effects

- ANXIOUS: Modulate Serotonin (eg.SSRIs)
 Side-effect of high dosage: Blunting
- COGNITIVELY SLOWED: Noradrenaline (eg. Nortripyline; duloxetine (Cymbalta)
 Too much: Anxious
- ANHEDONIC (Lacking pleasure): Dopamine (eg. Bupropion (Wellbutrin) Too much: Anxious; seizures


ANTIDEPRESSANTS: SSRI DRUGS Selective Serotonin Reuptake Inhibitors

- Effective
- Non-lethal (wide safety margin in dose)
- Minimal anticholinergic effects: less likely to cause urinary retention or constipation
- Decreased incidence of orthostatic hypotension
- No significant cardiac conduction changes



SSRI SIDE-EFFECTS

- Due to both central and peripheral effects
- Increased gastro-intestinal motility (Nausea, loose stools)
- Agitation and insomnia
- Headaches
- Sexual dysfunction (esp. decreased libido)
- Tremor, agitation, akathisia
- SUICIDAL RISK, (ESP. TEENS BUT BE ALERT FOR ALL AGES---agitation-related?).
- DRUG INTERACTIONS—Cytochrome P450 isoenzymes competition: concern re: altered levels of other drugs



SSRI's

- Fluoxetine (Prozac)
- Fluvoxamine (Luvox)
- Paroxetine (Paxil)
- Sertraline (Zoloft)
- Citalopram (Celexa)
- Escitalopram (Cipralex)



SSRI: FLUOXETINE (PROZAC)

- Only SSRI to have an active metabolite (Norfluoxetine, with an elimination half-life of 7-14 days)
- Steady state not attained for 5-6 weeks
- Onset: can cause nausea, agitation, and appetite suppression for several weeks
- May cause insomnia or weight loss
- DRUG INTERACTIONS: Cytochrome P450



FLUOXETINE (PROZAC) DRUG INTERACTIONS

- 2D6 +++
 Increased levels of codeine, dextromorphan, antiarrhythmics, beta blockers,tricyclics, trazadone, antipsychotics, and others. Decreased effectiveness of tamoxifen
- 3A4 ++
 Increased levels of antihistamine (asternizole, terfenadine), antiarrhythmics (lidocaine, quinidine), calcium channel blockers, and other drugs including carbamazepine (Tegretal), erthromycin, cisapride, tamoxifen, cyclosporine, and others
 - Increased anxiolytics, (diazepam, barbiturates), dilantin, tolbutamide
- 1A2 +
 Low to min. increase of various drugs, including warfarin and theophylline



• 2C ++

DRUG INTERACTIONS: FLUOXETINE

- Drug interactions complicated by fact that Prozac is CLINICALLY ACTIVE FOR 6-8 WEEKS after steady state has been achieved; thus DRUG INTERACTIONS can occur weeks after it has been discontinued.
- Avoid starting if interactions could be problematic.
- Discontinuation of fluoxetine mid-treatment protocols could alter levels of protocol drugs



SSRI: FLUVOXAMINE (LUVOX)

- Very sedating; take at bedtime
- Dose 25 -300 mgm.
- CyP 1A2 +++, resulting in elevated blood levels of warfarin by as much as 200%
- interacting with other drugs as well.



SSRI: PAROXETINE (PAXIL)

- Can be sedating
- Very potent inhibitor of 2D6 +++, causing increased levels of codeine, dextromorphan, methadone, antiarrhythmics, beta blockers, and others.
- Due to 2D6 inhibition, it also reduces effectiveness of tamoxifen
- It inhibits hepatic enzymes that metabolize itself, so small dose increases can cause marked rise of Paxil serum levels



SSRI: CITALOPRAM (CELEXA)

- One of least of SSRI's to cause Cyt P450 drug interactions
- Can be slightly sedating
- Start at 1 or ½ of 10 mgm tab, at bedtime, and titrate to 20-30 mgm usually
- QTc interval on EKG increased. (Caution QTc ≥ 450)



SSRI: ESCITALOPRAM (CIPRALEX)

- "Purified form of Citalopram"
- Dosage is ½ of Citalopram (Celexa)
- Activating....give in a.m.
- Dosage: Start 10 mgm tab, ¹/₂ 1 tab qam
- Can cause sensation of pressure in the head after several days
- Can prolong QTc interval.



QTc PROLONGATION

- QRS and T waves represent electrical depolarization and repolarization of the ventricles
- Occurs with many meds: chemo, antiemetics, psychotropic
- Increased risk of arrhythmias and death
- Monitor with baseline EKG and repeat with med changes
- May need to change tmt, esp if $QTc \ge 450$



SSNRIs

- Venlafaxine (Effexor)
- Desvenlafaxine (Pristiq) is the active metabolite of venlafaxine, and preferable in liver dysfunction
- Duloxetine (Cymbalta)
 - Dosage 30 mgm 60 mgm (max 120 mgm)
 - Used in diabetic peripheral neuropathy
 - Do not use if taking a potent CYP 1A2 inhibitor (eg. Luvox) or some antibiotics (eg. Ciprofloxacin, or enoxacine)



SSNRI: VENLAFAXINE (EFFEXOR)

- Selective Serotonin and Norepinephrine Re-uptake Inhibitor
- Least drug interactions of SSRI/SSNRI drugs
- Used for Generalized Anxiety Disorder, as well as Depression
- May cause nausea at onset for several days, and loose stools. Nausea minimal if start with tiny dose and take with food.



SSNRI: VENLAFAXINE (EFFEXOR)

- Activating
- Can cause insomnia. Take med no later than noon, and be aware of possible increased insomnia.
- Can cause modest increase in BP
- My dosage recommendation:
 - 37.5 mgm tab (least dosage), 1 tab at breakfast, for one week
 - May then increase to 2 tabs at breakfast (75 mgm) Often good response with 75 mgm, but can be titrated to 225 or higher.
- If stopping, taper gradually to prevent Discontinuation Syndrome



SSRI AND SSNRI: DISCONTINUATION SYNDROME

- Occurs in short-acting SSRI's or in Effexor, when drug stopped abruptly or delayed
- Dizziness, "spaciness", subtle balance problems, headache, dry mouth, insomnia, nervousness, sweating
- Symptoms abate with small dose.
- If stopping med, taper gradually.



TRICYCLIC ANTIDEPRESSANTS: WHY USE?

- Other antidepressants poorly tolerated: nausea, agitation, insomnia, hypertension, etc.
- Benefits of sedation, improved sleep, increased pain threshold
- Possible weight gain may be desirable for palliative pt.
- Can use tiny doses effectively
- Past response to a specific tricyclic
- Clomipramine (Anafranil) is extremely good for obsessive symptoms, but very sedating and anticholinergic.

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TCA Simplistic Schematic (Pezzot)

Tertiary amines (serotonin)	A Amitriptyline	I Imipramine	D Doxepin	Clomipramine
Secondary amines	N	D	P	
(Norepineph rine)	Nortriptyline	Desipramine	Protriptyline	



TRICYCLICS: SIDE-EFFECTS

Anticholinergic:

- Constipation, dry mouth, urinary retention, and increased risk anticholinergic delirium with other anticholinergic meds (eg. Gravol, Benadryl)
- Amitriptyline (Elavil) and imipramine (Tofranil) worse than Nortiptyline or Desipramine
- Alpha-Adrenergic Blockade:
 - Orthostatic hypotension and falls
 - Nortriptyline safer



TRICYCLICS: SIDE-EFFECTS cont.

- H1 Histamine blockade (sedation):
 - Amitriptyline and clomipramine
- Tachycardia
- Arhythmias due to quinidine-like effects
- Weight gain
- Can be lethal in overdose



TRICYCLICS: TIPS

- Dose: Start small at 10 mgm and titrate by 10 mgm. Medically ill often require smaller doses (25-125 mgm) than gen pop.
- Amitriptyline 10-25 mgm to improve sleep
- Nortriptyline if concern for orthostatic BP drops
- Most activating are desipramine and then nortriptyline
- Clomipramine for obsessive rumination
- All are lethal in overdose



OTHER ANTIDEPRESSANTS

Mirtazapine (Remeron)

- Noradrenergic/Specific Serotonergic Antidepressant (NaSSA)
- Stimulates appetite and weight gain
- Reduces anxiety, even at ¹/₄ ¹/₂ of 15 mgm pill
- Sedating (Take at night)
- Dosage generally 15-45 mgm.



OTHER ANTIDEPRESSANTS

Buproprion (Wellbutrin) (NDRI)

- Activating: insomnia, seizure risk. Good cardiac and sexual profile, but caution if brain disorder
- Sometimes 100 mgm added to SSRI drugs to improve sexual problems due to SSRI's

Trazodone (Desyrel)

- Used for sedation. Minimal anticholinergic
- Problematic orthostatic BP and possible arrhythmias. Increased mammary tumors in rodents.
- Priapism and erection changes in men



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TAMOXIFEN and ANTIDEPRESSANT INTERACTIONS

- Tamoxifen (inactive) requires cytochrome P 2D6 activity to convert it into its active metabolites
- Efficacy of tamoxifen varies due to:
 - Genetic variation of metabolism by CYP2D6
 - Suspected CYP2D6 interactions modulating the drug activity
- Drugs that are strong 2D6 inhibitors can reduce the effectiveness of Tamoxifen, as the tamoxifen is not converted into its active metabolites



2D6 INHIBITORS PREVENT TAMOXIFEN ACTIVATION

TAMOXIFEN 2D6 ACTIVE METABOLITES
 4- hydroxy-tamoxifen
 Endoxifen,

2D6 Inhibitors prevent

activation of Tamoxifen

Prozac, Paxil, bupropion (Wellbutrin), duloxetine (Cymbalta), clomipramine, desipramine, imipramine, trazadone



TAMOXIFEN and ANTIDEPRESSANT CYP2D6 INTERACTIONS (V. Kyritsis, Oct. 2009)

Strong CYP2D6 Inhibitors: Probable interactions

AVOID:

- Paroxetine (Paxil)
- Fluoxetine (Prozac)
- Buproption (Wellbutrin)



TAMOXIFEN and ANTIDEPRESSANT CYP2D6 POSSIBLE INTERACTIONS

- Moderate 2D6 Inhibitors: Possible interactions. Avoid or use caution
 - Duloxetine
 - Tranylcypromine (MAOI)
 - Clomipramine
 - Desipramine
 - Imipramine
 - Trazodone



TAMOXIFEN and SAFER OPTIONS: Weak 2D6 Inhibitors

Weak 2D6 Inhibitors: "Not likely" to have Tamoxifen Interaction

- SSRIs
 - Citalopram
 - Excitalopram
 - Sertraline
 - Fluvoxamine
- SNRIs
 - Venlafaxine
- TCAs
 - Amitriptyline
 - Nortriptyline
- Other
 - Mirtazapine
 - Gabapentin



TAMOXIFEN and SAFER OPTIONS: 2D6 SUBSTRATES

- "Not likely" to have Tamoxifen Interactions
 - Doxepin (Major substrate)
 - Trimipramine (Major substrate)
 - Buspirone (Minor substrate)
 - Of most common and useful, recommend:
 - Venlafaxine (Effexor)/ Desvenlavfaxine
 - Mirtazapine (Remeron)

C Cancer Agency RE & RESEARCH Citalopram/ Escitalopram



PSYCHOSTIMULANTS

Improve psychomotor slowing, concentration, well-being, and fatigue in depression or opiates

Rapid onset

Methylphenidate (Ritalin) onset 5 mgm bid am + noon (1/2 of 10 mgm tab bid); then titrate to 20-30 mgm usually, possibly to 60 mgm Side-effects of anxiety, insomnia, tics, paranoia



GENERAL DOSAGE TIPS

- Palliative or geriatric patients, start low, go slow, resulting in:
 - Minimal side-effects
 - Increased compliance and sense of control



ANXIETY: DIFFERENTIAL DIAGNOSIS

- •Situational eg. Anticipatory anxiety
- Symptom of depression
- Phobias
 - •Specific phobias (eg. Needle phobia)
 - Agarophobia (eg. Avoidance of places or situations)

•Social phobias (Embarassment re: appearance)

ANXIETY: DIFFERENTIAL DIAGNOSIS cont.

- **Panic attacks** (like a misfiring of fight-or-flight mechanism)
- Obsessive-Compulsive Disorder
- Acute Stress Reaction (symptoms last 2 days to 4 wks posttrauma)
- **PTSD** (symptoms last beyond 4 weeks post-trauma) ...can be iatrogenic
- Generalized Anxiety Disorder
- Anxiety due to General Medical Condition ("Organic Anxiety Disorder")
- Anxiety due to Substance Use, Withdrawal, and Medications



ANXIETY DIFFERENTIAL DX cont.: ANXIETY DUE TO MEDICAL CONDITION

- Endocrine
 - Thyroid disorders
 - Hypoglycemia
 - Menopause / Estrogen-blockers/ D/C HRT or depot hormones
 - Hyperadrenocorticism; pheochromocytoma
- Cardiovascular
 - CHF, arhythymias
- Respiratory
 - Pulmonary embolism
 - COPD; pneumonia
 - Hyperventilation
- Metabolic
 - Vit B12 deficiency; porphyria
- Neurological

BC Cancer Agence phalitis, vestibular dysfunction, neoplasms)



ANXIETY: DIFFERENTIAL Dx cont.:

- Substance- Induced Anxiety Disorder. Examples include:
 - Intoxication
 - Alcohol, amphetamines and caffeine, cannabis, hallucinogens,...
 - Withdrawal
 - Alcohol, cocaine, sedatives and hypnotics, anxiolytics, alprazolam (Xanax); also cannabis withdrawal syndrome
 - Side-effects
 - Antiemetics causing akathisia (motor restlessness), (Stemetil and Maxeran
 - Anesthetics and analgesics
 - Sympathomimetics or other bronchodilators; CVS meds
 - Insulin, oral contraceptives
 - Steroids
 - Heavy metals and toxins (volatile substances, insecticdies, carbon monoxide, CO2)
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ANXIETY: TREATMENT MEDICATIONS

- Multiple approaches to treatment, as in Depression
- Antidepressants beneficial in Generalized Anxiety Disorder and in preventing Panic Attacks (
- Anxiolytic medications for short-term or situationspecific use (eg. Pre-procedure) (eg. Ativan)
- Atypical antipsychotics (eg. Quetiapine (Seroquel); Olanzapine



ANXIETY: MEDICATIONS cont.

- Benzodiazepines: eg. Lorazepam (Ativan) .5-1 mgm TID PRN Clonazepam 0.5 mgm ¹/₂ - i BIDand ii QHS for neuropathic pain
- <u>Neuroleptics</u>: Use Atypical Antipsychotics Risperidone .25-.5 mgm TID PRN Olanzapine 2.5-5 mgm TID PRN Quetiazpine (Seroquel) 12.5 - 25 mgm QID PRN
- Antihistamines Benadryl 25-50 mgm TID PRN
- Antidepressants
 Effexor, Celexa, tricyclics



Buspirone (Buspar) (May not feel less anxious, but cope better)
ANXIETY: TREATMENT PSYCHOLOGICAL

- Psychotherapy, Cognitive, and Behavioural strategies
- Relaxation sessions can lower baseline anxiety and give sense of mastery over a new skill
- Mindfulness-based Stress Reduction (MBSR) and Mindfulness-based Cognitive Therapy
- Hypnosis: An effective and time-efficient technique. Annual course in Feb. by Can. Society of Clinical Hypnosis: B.C. Division.



DELIRIUM DSM-IV DIAGNOSIS

Disturbance of consciousness with reduced ability to focus, sustain, or shift attention (ie. Reduced awareness of environment)

<u>Change in cognition</u>, or devt of perceptual disorder, not accounted for by ...dementia

Develops over <u>short period of time</u> and tends to fluctuate during the day

Evidence from history, physical exam, or lab tests that it is caused by <u>medical condition</u>, substance intoxication or withdrawal, med use, multiple etiologies, or not specified.



DELIRIUM: ASSOC. FEATURES

- Disorder of arousal / attention is central to diagnosis; fluctuates
- Disorientation to time, place, or person
- Disturbance sleep-wake cycle (awake at night)
- Disturbed psychomotor behaviour
- (eg. Restless, hyperactive; lethargic, hypoactive)
- Thinking disorganized
- Perceptual disturbance
- (misinterpretations, illusions, hallucinations esp. visual; delusions)
- Emotional disturbance (anxiety, apathy: labile)
- Nonspecific neuro abnormalities (eg. Tremor): EEG: diffuse slowing



DELIRIUM: ETIOLOGY

- Often **multifactorial**;
 - may be global cerebral dysfunction
 - Hypoxia, sepsis, ...
 - or due to specific neurotransmitter system
 - eg. Suppressed cholinergic system
- Predisposing factors
 - eg. Poor functional or cognitive functioning; older; dehydration,...
- Precipitating factors
 - eg. With medications, remember to consider:
 - Side-effects
 - Drug interactions causing increased serum levels and toxicities
 - Decreased hepatic metabolism, decreased renal clearance



DELIRIUM: MEDICAL CONDITIONS

CNS

Metabolic Disorder



- Head trauma
- Seizure (ictal or post-ictal)
- Vascular disease (eg. Stroke, hypertensive encephalopathy)
- Degenerative disease
- Infection (eg. Herpes; HIV)
- Neoplasm or metastases
- Renal or <u>hepatic</u> disease
- Electrolyte imbalance (eg. Dehydration, <u>hyponatremia</u>, potassium imbalance)
- Anemia
- <u>Hypoxia</u>
- Thiamine deficiency
- Hypoalbuminemia
- Endocrine disorder
- Acid-base imbalance

DELIRIUM: MEDICAL CONDITIONS

- Cardiorespiratory
- Myocardial infarction
- Congestive Heart Failure
- Arrhythmia
- Shock
- Respiratory failure

• Systemic Illness

- Infection (Sepsis, pneumonia, urinary)
- Cancer
- Severe trauma and fractures
- Sensory deprivation
- Temperature dysregulation
- Postoperative states



MEDICATIONS CAUSING DELIRIUM

Anesthetics Antibiotics

Acyclovir Amphotericin B. Cephalosporins

Anticholinergics Antihistamines, Gravol,

Anticonvulsants

Antiparkinson drugs

Cardiac drugs

Beta-blockers Clonidine Digitalis Lidocaine and Quinidine

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• Chemotherapy and assoc. meds

Asparaginase, 5-FU, Tamoxifen, Vincristiine, Fludarabine, Methotrexate, IL-2, Interferon; cyclosporine,

Cranial radiation; steroids

- **Opioids** (Demerol>MS>Oxy)
- Psychiatric
 Tricyclics, MAOI, Lithium, Clozapine
- Sedatives
 Barbiturates, Benzodiazepines
- Sympathomimetics
- Others

DELIRIUM CAUSED BY SUBSTANCE INTOXICATION & WITHDRAWAL

Intoxication:

eg. Alcohol: +/- less obvious if genetically predisposed Street drugs; inhalants; <u>opioids</u>; sedatives

• <u>Withdrawal</u>:

eg. Alcohol; sedatives

• <u>Toxins</u>:

eg. carbon monoxide, organic solvents, organophosphates



DELIRIUM: PHARMACOLOGICAL TREATMENT

- Typical Antipsychotics:
 - 1. <u>Haloperidol</u> po. Iv, im, sc
 - Hypoactive: 0.5-2 mg QHS
 - Hyperactive: Typically 0.5-1.0 mgm po, iv, im, sc q 45 60 min. (Breitbart)
 - Parenteral dose 2x as potent as oral
 - iv more rapid onset; sc often in palliative
 - Often combined with Ativan 0.5-1.0 mgm q1-2h, po/iv



DELIRIUM: MANAGEMENT Typical Antipsychotics cont.

2. Loxapine (po, elixir, IM; not iv)

- More sedating and less prone to Extra-Pyramidal symptoms (may develop akathisia)
- Dosage often given at 1600 and hs, to promote sleep (eg. 2.5-5 mgm at 1600, and 5-15 at HS.)
 Also prn doses 2.5-5 mgm q1h
- Can combine with Ativan on TID basis or with PRN's



DELIRIUM: MANAGEMENT ATYPICAL ANTIPSYCHOTICS

- Lower risk of E.P.S. and tardive dyskinesia
- 1. Risperidone (Risperdal) po, IM

eg. 0.5 – 1 mgm BID po.

- 2. Quetiapine (Seroquel) po
 - eg. 25-50 mgm q4h PRN or 25-300 mgm q 12 h
 - Typically at VGH: 12.5-25 mgm BID or at 1600, and 25 100 mgm QHS
 - Can also order 12.5-25 mgm TID PRN doses

Caution re: orthostatic hypotension Weight gain or metabolic syndrome Diabetes Mellitus aggravated or triggered



DELIRIUM MANAGEMENT: ATYPICAL ANTIPSYCHOTICS

- 2. Quetiapine cont.
 - Recently marketed for mood-stabilizing properties and for anti-depressant adjunct properties
- 3.. Olanzapine (Zyprexa) po, IM

eg. 2.5-10 mgm BID or 2.5-20 mgm QHS

- <u>Strong anti-emetic</u> properties
 - Navari at Hoosier studied 5 mgm TID, but 15 mgm/day very sedating. "Best since ondansetron!"
 - 5 mgm/day gave best quality of life (2.5 5 10 mgm options).
- Calming, sedating



DELIRIUM: PSYCHOSOCIAL MANAGEMENT

Tell pt. that he is "having a 'wide-awake dream'...that it is common...it is caused by medical factors, and he is not losing his mind...his thinking will become clear again."

Use calm, quiet voice to reassure pt. that the situation is under control, even if he feels "out of control."

Quiet but lit room, with clock and calendar visible, to help orient pt.Ask permission to touch patient, to decrease risk of assault.



RESOURCES for PATIENTS

- BC Cancer Agency Centres
 - Patient and Family Counseling Departments in centres
 - Vancouver: 604-877-6000, ext 2194
 - Psychiatric Consultation
 - Pamphlets from BCCA on diseases, coping
 - Patient symposiums and education days
 - Support groups eg. Prostate Cancer, Young Women's support Group, Relaxation groups, Mindfulness-Based Stress Reduction Groups,...
 - BCCA Annual Conference in Nov. sponsors a day program for patients and general community
- Internet: Cancer Chat Canada
- Books:

BC Car MeO/GGC

50 Essential Things to Do When the Doctor Says It's Cancer (Greg Anderson)

Fear of dying: Life after Life (Moody); Closer to the Light



RESOURCES for PHYSICIANS

- Google Scholar
- <u>www.azcert.org</u> (Arizona Centre for Education and Research in Therapeutics)...."very helpful"
- Epocrates Program for drug interaction
- Lexicomp Drug interaction app is very helpful
- Medscape Free. Drug interactions
- Phone Pharmaceutical company and speak to Medical Scientific Officer re: info in their files from clinical trials or studies with patients that had co-morbid medical illness

S. Abbey at CPA, 09/ 2012



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