Updates in Therapeutics®2013:
Ambulatory Care Pharmacy Preparatory Review and Recertification Course

Psychiatric Disorders

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Conflict of Interest Disclosures

- Nothing to disclose

Learning Objectives

- Describe the DSM-IV, TR (*Diagnostic and Statistical Manual of Mental Disorders,* Text Revision) criteria, etiology, risk factors, and disease course for the anxiety disorders, sleep disorders, major depression, bipolar disorder, attention-deficit /hyperactivity disorder, schizophrenia, and substance use disorders.
- Relate common drug and nondrug therapy for the psychiatric disorders, including drug, dose, frequency, adverse effects, drug interactions, and monitoring parameters.

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Learning Objectives

- Recommend appropriate initial and maintenance treatment for psychiatric disorders, including duration of therapy.
- Assess treatment regimens for significant drug interactions and appropriateness of therapy, including use of polytherapy.

Discussion topics will include a review of therapeutic principles for the above disorders. These learning objectives and a more thorough discussion can be found in the Ambulatory Care Preparatory Review Course Psychiatric Disorders chapter.

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Principles of Psychiatric Drug Therapy

- Drugs used to treat psychiatric disorders may be used for several different conditions.
- Treatment is often symptom-driven, no drug therapy is “curative” for mental illnesses.
- Adverse effects are common and can be significant reasons for medication non-adherence.
- Never assume that you know what the drug is being used for – always question the patient about their disease states.

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Anxiety Disorders Case

- MP is a 39 year old woman with a 10 year history of GAD, who presents to clinic with worsening symptoms over the past 2 weeks, including difficulty concentrating at work, insomnia related to worry, and increasing restlessness. Her 19 year old daughter told her 3 weeks ago that she is having problems at school, and is considering dropping out. MP’s current medications include paroxetine 40 mg orally at bedtime (taken for 2 years) and lorazepam 0.5 mg orally three times daily as needed for anxiety symptoms. She has not generally used the lorazepam, but has been taking two to three doses daily for the past 7 days. Laboratory results are within normal limits, but MP has gained 40 pounds since initiating paroxetine therapy. She is concerned about this, as well as increasing symptoms although she has been adherent to her medication regimen. She smokes cigarettes ½ PPD, does not use alcohol or other drugs.

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Anxiety Disorders Case Questions

- What is the most likely reason for MP's exacerbation of symptoms?
- What changes, if any, should be made in MP's routine anxiolytic drug therapy?
- How do you respond to MP's increasing use of PRN lorazepam?
- What other therapies are available for MP?

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Anxiety Disorders Overview

- Anxiety disorders are the most commonly diagnosed psychiatric disorders, with a 1-year prevalence rate of ~ 15%.
- Diagnosis of anxiety disorders often comes after the patient has suffered symptoms for a long period.
- Drug therapy often includes a serotonergic drug, combined with "bridge" therapy with a benzodiazepine.
- Expectations of treatment include a significant reduction in symptoms, not necessarily complete resolution.
- Serotonergic drugs should be initiated at low doses and increased slowly to minimize the irritability and agitation that are common side effects of these drugs.
  - Paroxetine 10 mg orally at bedtime.
  - Fluoxetine 5 mg or 10 mg orally once a day.

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Generalized Anxiety Disorder

- Excessive and uncontrolled worrying often for months, about nearly all events in the patient's life.
- Difficulty with concentration, sleep, and functional level, as well as restlessness and irritability.
- Benzodiazepine anxiolytics are very effective as initial therapy, SSRI or SNRI medications are useful long-term treatment.
- The onset of action for SSRI/SNRIs is ~4 weeks.
- Increased use of PRN benzodiazepines can signal increasing symptoms, often related to a recent life event.
- For all anxiety disorders – psychotherapy is a common and often necessary component of treatment.

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Social Anxiety Disorder

- Many people suffer "stage fright" when confronted with situations like public speaking
- Social anxiety disorder reaches the level of fear in most situations of being humiliated by others or fear of interactions with others.
- Symptoms are physical in nature, including sweating, tachycardia, GI upset.
- SSRI medications are commonly used, several weeks are needed for onset of action.
- Propranolol or lorazepam may be used as needed for specific situations or events.

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Obsessive-Compulsive Disorder

- Recurrent thoughts or impulses that lead to behaviors that reduce anxiety.
- Compulsive behaviors may or may not coincide with the recurrent thoughts.
- SSRIs or clomipramine (TCA) are used for long-term treatment.
- Treatment results in ~ 50% resolution of symptoms for most patients.
- Cognitive behavioral therapy targeted at reducing time spent in behaviors or diverting the patient to more useful behaviors may further reduce symptoms.

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Panic Disorder

- A single panic attack does not indicate panic disorder.
- Panic disorder is defined by recurrent panic attacks that limit functionality.
- Physical symptoms of chest pain, shortness of breath, and sweating commonly accompany psychological symptoms such as fear of losing control or dying.
- SSRIs are used for long-term therapy, benzodiazepines may be used PRN to minimize specific attack symptoms.
- Psychotherapy or immersion therapy (subjecting the patient to fearful situations) may be useful to reduce symptoms and improve functionality.

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Post-Traumatic Stress Disorder

- Current focus of the VA system – returning combat veterans.
- May be combat-related or civilian.
- Civilian trauma is easier to treat – likely one-time event versus recurrent.
- Triad of symptoms – reexperiencing, hyper-arousal, avoidance
- SSRIs are first-line therapy, mirtazapine, topiramate, and atypical antipsychotics have been studied as augmenting agents.
- Use of benzodiazepines should be avoided where possible, due to the increased risk of abuse of these agents.
- Combination drug therapy is common with an SSRI agent as the building block – symptomatic treatment follows:
  - Atypical antipsychotic – reexperiencing, hyperarousal, prominent psychosis
  - Adrenergic antagonist (prazosin) – nightmares associated with reexperiencing

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Anxiety Case Question

What changes, if any, should be made in MP's routine anxiolytic drug therapy?

- A. Continue paroxetine.
- B. Directly switch to sertraline.
- C. Cross-taper paroxetine to sertraline.
- D. Decrease paroxetine dose.

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Anxiety Case Answers

- What is the most likely reason for MP's exacerbation of symptoms?
  - The recent information received from patient's daughter, increased worry about outcome of that situation.
- What changes, if any, should be made in MP's routine anxiolytic drug therapy?
  - MP is complaining of weight gain since initiation of paroxetine. Can consider switch to another SSRI medication that would not exacerbate weight gain. Must plan for discontinuation of paroxetine (anticholinergic rebound). Antidepressant withdrawal will be minimal if cross-titrate medications.
- How do you respond to MP's increasing use of PRN lorazepam?
  - Discuss use with MP, if use is not outside prescribed dosing, continue lorazepam and monitor. Ensure that 0.5 mg dose is adequate for symptoms experienced by MP. Will likely need to continue if switching MP's long-term treatment.
- What other therapies are available for MP?
  - Psychotherapy

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Sleep Disorders Case

- JJ is a 56 year old man who states that he has not ever slept very well, but complains of worsening of symptoms for the past 4 weeks. He has difficulty falling asleep and wakes up several times per night. His other medical conditions include asthma and hypertension. His current medications are lisinopril 10 mg orally once a day, atenolol 100 mg orally once a day, and an albuterol inhaler, 2 puffs every 6 hours as needed for shortness of breath (added to drug regimen one month ago). JJ weighs 275 pounds and is 6'0" tall. His BMI is 37. He has smoked 1 PPD cigarettes for 25 years. He occasionally drinks alcohol, but has begun to have a drink before bed to "help him sleep".

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Sleep Disorder Case Questions

- What questions should be asked of JJ?
- What other testing should be done?
- What questions should be asked regarding JJ's medication regimen?
- What sleep medication is the best choice for JJ, if appropriate?

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Sleep Disorders

- 30% of adults complain of sleep difficulties, 10% suffer from insomnia.
- Weight, medical conditions, medications, and substance use can contribute to disordered sleep.
- Evaluation of conditions, such as sleep apnea or restless leg syndrome, should be performed, if appropriate.
- Drug therapy includes benzodiazepines, non-benzodiazepine hypnotics, and novel sleep medications.
- Use of medications for sleep should be used for short periods of time (10 – 14 days), but is used much longer clinically.
- Cognitive behavioral therapy in combination with short-term medication use has been shown to be more effective long-term than use of medications alone.

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Sleep Disorders – Non-Drug Therapy

- Patients should be counseled on stimulus control and sleep hygiene:
  - Stimulus control – go to bed and wake up at the same time every day, avoid daytime naps, use the bedroom for sleep and intimacy only, schedule "worry time".
  - Sleep hygiene – exercise routinely, avoid caffeine, nicotine, and alcohol prior to bedtime, reduce the use of these if possible, have a comfortable sleeping environment, relaxation therapy

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Sleep Apnea

- Obstructive sleep apnea is most common.
- Obesity is a common cause of OSA.
- Treatment of sleep apnea can significantly improve symptoms, including:
  - Weight loss
  - Surgical correction of obstruction
  - Continuous positive airway pressure (CPAP)
- Avoid use of sedative/hypnotic agents in patients with sleep apnea.

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Restless Leg Syndrome

- RLS is defined as undesirable sensations in the legs before sleep and the urge to move with resolution of symptoms upon moving.
- Iron deficiency can contribute to RLS – evaluation of the CBC, serum iron, and serum ferritin is suggested.
- Dopamine agonists are considered first-line therapy.
- Other agents used include opiates, clonazepam, and anticonvulsants (carbamazepine).

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Shift Work Sleep Disorder

- SWSD is considered a circadian rhythm disorder that occurs in people who work the night shift or a frequently changing work shift.
- Functional impairment is caused by insomnia during the major sleep period or excessive sleepiness during the major awake period.
- Environmental factors similar to those for insomnia should be evaluated.
- Short-acting benzodiazepines or Z-hypnotics can be considered to improve sleep time.
- Modafinil and armodafinil are FDA-approved to treat the daytime sleepiness associated with SWSD.
- Dosing of these agents is once daily with the dose taken 1 hour before starting shift work.

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Sleep Disorders Case Question

What sleep medication is the best choice for JJ, if appropriate?

- A. Diphenhydramine 50mg
- B. Zolpidem 5 mg
- C. Temazepam 15mg
- D. Mirtazapine 30mg

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Sleep Disorders Case Answer

- What questions should be asked of JJ?
  - How close to bedtime do you have a drink or smoke a cigarette? What is your bedtime ritual? Has anything changed in the past few weeks?
- What other testing should be done?
  - Epworth Sleepiness Scale, polysomnography for sleep apnea
- What questions should be asked regarding JJ's medication regimen?
  - At what time of day do you take your medications or use your inhaler?
- What sleep medication is the best choice for JJ, if appropriate?
  - If JJ does not have sleep apnea and you are not concerned for alcohol use at bedtime, short-term use of a Z-hypnotic may be considered. A novel sleep agent, such as ramelteon or trazodone, may be used.

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Major Depression Case

- ED is a 31 year old woman with a 5 year history of major depression, with 2 previous episodes. She presents to clinic today with symptoms of fatigue, irritability, and difficulty sleeping. She is in otherwise good health. When questioned, ED endorses feeling hopeless about her life, she is unemployed and is having difficulty finding a job because she is staying in bed most of the day. Her current medication is citalopram 20 mg orally once daily, which she has taken for 2 years. You ask her to fill out a PHQ-9 questionnaire, her score is 17.

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Major Depression Case Questions

- How long have you been experiencing these symptoms, are they similar to your previous episodes?
- Have you taken any other antidepressant medications?
- Are you experiencing any pain?
- Do you have thoughts of suicide?

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Major Depression Overview

- It is estimated that only 30% of people with depression seek treatment, of those only 30% are adequately treated.
- The lifetime prevalence is ~16%.
- Individuals with depression often present to primary care providers with non-specific symptoms of fatigue and pain.
- Risk factors include being female, middle-aged, life stresses, chronic medical conditions, being widowed or divorced, and having a lower income.
- Some patients have concomitant substance use.

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Major Depression Treatment Principles

- The effectiveness of individual antidepressants is similar in clinical trials.
- Drug therapy should be chosen based on adverse effect profiles, doses per day, cost, and patient choice.
- Ascertaining history of antidepressant use may also guide choice of therapy, including history of use in family members.
- Patient counseling regarding onset of effect and duration of treatment will improve adherence.

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Major Depression Pharmacotherapy

- The STAR*D trials are effectiveness trials that focused on the progression of treatment.
- Results suggested that many patients will require several treatment trials and possibly combination medication therapy.
- The goal of treatment with antidepressants should focus on remission of symptoms, not simply response.
- That said, for some patients, a reduction in symptoms will be the maximal response.

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Dose and Duration of Antidepressant Therapy

- Dose and duration are two important factors in treatment success.
- Initial onset of action may be within the first 2 weeks, maximal improvement for a specific dose may take 4 to 6 weeks.
- The dose should be increased based on response and tolerability of side effects.
- Moderate doses may be required.
  - Fluoxetine 40 mg orally once daily
  - Citalopram 40 mg orally once daily (max dose)
  - Sertraline 200 mg orally once daily

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If the first trial fails…..

- A switch to a 2nd SSRI is reasonable if the patient tolerated the first one, but didn't respond to therapy.
- SNRIs can be chosen if the patient is complaining of pain.
- TCAs and MAO inhibitors are generally reserved for prior treatment failures.
- Novel antidepressants can be used as first-line therapy or for subsequent therapy
- Recent trials have suggested that combination therapy that accounts for mechanism of action may have a greater remission rate, even with initial treatment.
- May consider augmentation therapy – atypical antipsychotics, thyroid supplementation, lithium

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What to monitor for antidepressants

- Response – patient report and the PHQ-9
- Suicidal thinking – all antidepressants have a boxed warning for patients younger than 24 years for new onset or worsening suicidal thinking – this should be monitored closely in the first few months of treatment.
- Adverse effects – especially those the patient may not talk about, but may cause lack of adherence.
  - Sexual dysfunction – serotonergic
  - Gastrointestinal side effects
- Antidepressant withdrawal syndrome may present as increased symptoms, including irritability, but will also likely include GI effects.
- Serotonin syndrome
- Pregnancy

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Major Depression in Primary Care

- Ambulatory care settings are a primary place for identifying depression.
- Consider this in a differential diagnosis for patients who present with non-specific symptoms.
- Obtain thyroid function tests for any patient with mood symptoms.
- If combination therapy is considered, ensure that there are not overlapping MOAs.

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Major Depression Case Question

What is the most appropriate drug therapy intervention for ED?

- A. Switch to fluoxetine 20mg.
- B. Increase to citalopram 40mg.
- C. Add mirtazapine 15mg.
- D. Add thyroid supplementation.

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Major Depression Case Answers

- How long have you been experiencing these symptoms, are they similar to your previous episodes?
  - Patients with previous episodes can often express whether the symptoms are similar, leading you to a differential diagnosis of a recurrent episode.
- Have you taken any other antidepressant medications?
  - This will aid in deciding on the need for drug therapy change, including medications that should not be considered. A family history of antidepressant use and response will be useful in guiding drug therapy, as there is some evidence that there is a familial response to treatment.
- Are you experiencing any pain?
  - If the patient is having pain, you may consider using a SNRI as treatment, as the SNRIs are FDA-approved for pain conditions, including fibromyalgia (duloxetine, milnacipran)
- Do you have thoughts of suicide?
  - While these are hard questions to ask, they are appropriate and not generally offensive to a person with depression. The clinician should ascertain the safety of the patient and the need for referral to psychiatric services.

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Bipolar Disorder Case

- KW is a 24 year old woman who presents to clinic for follow up and refill of medications used for bipolar disorder. She has a 3 year history of treatment and has had 2 previous hospitalizations, but has been followed successfully by primary care for 1 year. Her current medications are lithium 600 mg orally twice daily and aripiprazole 30mg orally once a day. Her most recent lithium level was 0.8 mEq/L. She states that she has only been sleeping 3 hours per night, but is not fatigued. She exhibits no other symptoms. No other laboratory monitoring has been done for the past year.

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Bipolar Disorder Case Questions

- What symptoms were experienced in previous episodes?
- What laboratory monitoring is needed?
- What adverse effects of atypical antipsychotics should be monitored?
- At what point should a referral be made to psychiatric services?

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Bipolar Disorder Overview

- The estimated prevalence of bipolar disorder is ~ 1%.
- The average age at onset is 21 years.
- Patients with bipolar disorder spend more of their life in the depressive pole than in the manic or hypomanic pole.
- Misdiagnosis of bipolar disorder is common, many patients will present with depressive symptoms that are considered to be unipolar depression – the delay in diagnosis has been estimated to be an average of 10 years for some patients.
- Careful questioning is necessary to ascertain a past experience of mania or hypomania.
- Suicide attempts may occur in either mood pole.

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Bipolar Disorder – Mood Stabilizers

- Mood stabilizer drug therapy is considered to be the maintenance treatment in bipolar disorder.
- Lithium and valproic acid are generally first-line treatment.
- Many atypical antipsychotics are FDA-approved for the treatment of bipolar disorder, either as monotherapy or in combination with another mood stabilizer.

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Bipolar I Disorder

- In bipolar I disorder, manic or mixed episodes are intermingled with depressive episodes.
- Lithium and valproic acid have shown efficacy as initial monotherapy in bipolar I disorder.
- If the patient is in a manic episode, any antidepressant therapy should be discontinued.
- Combination therapy with lithium and valproic acid or either of those with an atypical antipsychotic is common.

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Bipolar II Disorder

- In bipolar II disorder, depressive episodes are intermingled with hypomanic episodes.
- This is commonly thought of as bipolar depression.
- Lithium and lamotrigine are good first-line choices for treatment, with the atypical antipsychotic quetiapine.
- Lamotrigine dosing should follow a slow dose titration and take into account drug interactions to minimize the risk of Stevens-Johnson syndrome.
- Antidepressant treatment is common, it is controversial whether or not this treatment is effective, as well as the risk of a “switch” into a manic episode.

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Bipolar Disorder – Treatment Considerations

- Take into account the type of bipolar disorder that is diagnosed.
- Pregnancy
  - Most mood stabilizers are Category D.
  - Most atypical antipsychotics are Category C.
  - Recent studies of anticonvulsant mood stabilizers has suggested that valproic acid not only has a risk of neural tube defects, but also negative effects on the IQ of the offspring.
  - Lithium is useful for reducing suicidal thinking in bipolar disorder, but can be fatal in overdose.
- Antidepressant treatment is controversial
  - Most time is spent in depression
  - Antidepressants may not be effective
  - Antidepressants may cause a manic “switch”

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Bipolar Disorder Case Question

What is the most appropriate drug therapy intervention for KW?

- A. Increase to lithium 600mg three times daily.
- B. Repeat lithium level and ascertain adherence.
- C. Switch to divalproex and maintain aripiprazole.
- D. Add zolpidem 10mg.

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Bipolar Case Answer

- What symptoms were experienced in previous episodes?
  - Knowledge of previous symptoms helps the clinician ascertain the level of concern for current symptoms. The patient says that she is only sleeping 3 hours per night and is not fatigued, which could be a sign that she is beginning a manic episode.
- What laboratory monitoring is needed?
  - Laboratory monitoring for lithium includes lithium serum concentrations, electrolytes, renal function, and thyroid function testing. For aripiprazole, the patient should have routine monitoring of the total lipid profile and either fasting blood glucose or a HgbA1c.
- What adverse effects of atypical antipsychotics should be monitored?
  - Movement side effects should be evaluated, including drug-induced Parkinson's and akathisia. Specific to aripiprazole, akathisia is a common side effect. The Barnes Akathisia Scale can monitor this side effect.
- At what point should a referral be made to psychiatric services?
  - If the clinician is concerned about the lack of need for sleep and a manic episode.

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Schizophrenia Case

- MC is a 24 year old man with a 2 year history of schizophrenia. He presents to the clinic today for medication follow up. He is with his mother, who reports that MC hasn't eaten much in the past 3 weeks, hasn't been showering, and is focused on "spirituality" more lately. He is repetitive in his speech, repeating his answers to your questions three times. His current medications are quetiapine XR 600 mg orally once daily and lorazepam 0.5 mg orally three times daily as needed. MC has been otherwise well since beginning at the primary care clinic 1 year ago. He has a history of 2 hospitalizations, but none in the past year. He smokes 1 PPD of cigarettes, but claims no use of alcohol or other substances. His past psychiatric medication history includes paliperidone, risperidone, olanzapine, and haloperidol, with either no effect or significant side effects. He has had no recent laboratory monitoring.

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Schizophrenia Case Questions

- Is the patient taking his medication?
- What are MC's previous symptoms that led to hospitalization?
- At what point should MC be referred to psychiatric services?
- What monitoring should be done for MC?

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Schizophrenia Overview

- The incidence of schizophrenia is ~1%.
- The lifespan of people with severe mental illness is on average 25 years shorter than the general population.
- The average age at onset is the late teens to early 20s for men and ~ a decade later for women.
- Tobacco smoking, poor lifestyle habits, and social isolation likely contribute to this.
- Antipsychotic agents used to treat this condition have significant side effects that exacerbate or cause chronic medical conditions.
- People with severe mental illnesses are often portrayed to have consistent violent tendencies. The reality is that fewer than 1% of people with schizophrenia are ever violent, with most of that violence being self-injurious.

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Principles of pharmacotherapy in schizophrenia

- Antipsychotics are the mainstay of treatment.
- These agents represent symptomatic control, not a "cure".
- Antipsychotics are more effective for the "positive" symptoms.
- Clinical trials suggest that all antipsychotics are similarly effective (with the exception of clozapine).
- Choice of antipsychotic is driven by side effect profile, cost, and patient choice.
- While polytherapy is common, clinical trials suggest that this is no more effective than monotherapy with an increased side effect burden.
- Finding an effective antipsychotic is often a matter of trial and error.
- Adherence to medications can be problematic, this can be improved by consistent and thorough patient counseling.

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How to choose an initial antipsychotic?

- The goal of treatment is full remission of symptoms and a return of the patient to their previous functional level.
- First-line therapy consists of an atypical or a typical antipsychotic.
- Doses per day and side effect profile should be considered, as well as the payor source for the patient.
- Risperidone, quetiapine IR, and olanzapine IR tablets are atypical antipsychotics that are currently available as generics.
- Typical antipsychotics generally cause more EPS than atypical antipsychotics.
- Atypical antipsychotics are associated with more weight gain and metabolic syndrome and less EPS.
- While clozapine is generally reserved for patients who fail several trials of antipsychotic medications, it has been shown in clinical trials to be the most effective antipsychotic.

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Monitoring of antipsychotic therapy

- The response to treatment is a primary monitoring parameter.
  - The clinician often sees "response" as a reduction in positive symptoms of hallucinations or delusions.
  - The patient may feel that "response" is related to daily life activities, such as improving ability to concentrate allows the return to previous activities.
- EPS – Movement side effects occur commonly.
  - Drug-induced Parkinson's is easier to evaluate – tremors
  - Evaluation for akathisia requires the clinician to ask the patient if they feel restless or the need to constantly move.
- Metabolic side effects – Hyperglycemia, hypertension, and hyperlipidemia have been associated with the antipsychotics, especially the atypicals.
  - Monitor weight and blood pressure at each visit, if possible.
  - Obtain labs, including fasting blood glucose or HgbA1c and total lipid profile routinely.

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Engaging the patient in treatment

- Patients who are referred from psychiatry to primary care for follow-up are generally more stable in their illness.
- Engaging the patient by providing consistent and thorough patient counseling regarding their medications, expectations of treatment, and side effects is the best way to ensure adherence to treatment.
- Clinicians often feel (or are taught) that patients with schizophrenia can't understand patient counseling or will feel overwhelmed by it.
  - Most patients with schizophrenia understand what their condition is and are willing to tolerate significant side effects if the drug therapy will minimize their symptoms.

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Schizophrenia Case Question

What is the most appropriate drug therapy intervention for MC?

- A. Increase to quetiapine XR 900mg.
- B. Add paliperidone 6mg.
- C. Evaluate adherence to quetiapine XR.
- D. Switch lorazepam to routine dosing.

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Schizophrenia Case Answer

- Is the patient taking his medication?
  - This is important to ascertain, as this will inform drug therapy changes. If the patient is not taking their medications, an increase in dose could exacerbate side effects. Nonadherence to medication could signal the reason for symptom increase, as well as a lack of tolerability to side effects.
- What are MC's previous symptoms that led to hospitalization?
  - The patient in this case is clearly experiencing an exacerbation in symptoms of schizophrenia. It is important for the clinician to understand what the patient's baseline symptoms are and how severe this exacerbation is.
- At what point should MC be referred to psychiatric services?
  - Since MC is clearly symptomatic, a communication to his psychiatrist should be done at this point, with an appointment scheduled as early as possible or the direction of the psychiatrist followed.
- What monitoring should be done for MC?
  - Metabolic monitoring, EPS rating scales.

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Attention Deficit Disorder Case

- DL is a 7 year old boy who returns to the primary care clinic with his mother for follow up of attention deficit disorder. He was diagnosed 3 months ago after his teacher and parents noticed that he was not completing his work and was acting out in class. DL is currently taking methylphenidate 10 mg orally two times daily in the morning and afternoon (after school). He is able to complete his work in the morning at school, but continues to struggle in the afternoon. He has lost 2 pounds in 12 weeks. DL is currently exhibiting no other adverse effects. His current weight is 50 pounds and he is 74 inches tall. He has no chronic medical conditions and takes no other medications. He has a family history of heart disease and tic disorders. Blood pressure, heart rate, height, and weight were normal prior to initiating methylphenidate therapy.

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Attention Deficit Disorder Case Questions

- What baseline information should be obtained prior to initiating stimulant therapy?
- Do you consider methylphenidate to be effective for the patient in this case?
- What medication changes might be considered?
- What is your concern regarding DL's family history of tic disorders?

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Attention Deficit Disorder Overview

- The prevalence of ADD is thought to be ~6%.
- Many children diagnosed with ADD will continue symptoms into adulthood.
- Risk factors for the development of ADD include family history of ADD or bipolar disorder, low birth weight, maternal smoking, and perinatal stress.
- Modified diets and dietary supplementation have not been shown to be effective.
- Other psychiatric disorders are common comorbidities, including conduct disorders, mood disorders, anxiety, and Tourette's syndrome.
- Treatment of ADD with stimulant medications does not increase the risk of substance use, may actually protect against this.

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Principles of Stimulant Use in ADD

- The goal of treatment is to reduce or eliminate symptoms of ADD so that the patient is able to engage and be functional in all environments.
- Hyperactive symptoms are predominant in childhood, inattention in adults.
- ADD should be considered a chronic condition that may persist into adulthood.
- The effectiveness of stimulant medication in the treatment of inattention is not "diagnostic" for ADD.
- Stimulant monotherapy is preferred, may have to use long-acting and short-acting doses of the same agent.

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Which stimulant to choose?

- Methylphenidate, dextroamphetamine, and mixed amphetamine salts are first-line therapy.
- Provider choice is the primary factor in which drug is used first.
- If the first stimulant is not effective, it is reasonable to switch to another, which may result in adequate effect.
- Onset of action is within 30 minutes of an immediate release dose, drug therapy can be re-evaluated every few weeks.
- Clinically, initial stimulant dosing begins with a sustained release dosage form, immediate release formulations may be added to improve efficacy at specific times.

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Stimulant Adverse Effect Management

- Baseline information should include the family history of heart disease and the child's history of cardiac structural defect, as well as the family history of psychiatric disorders, including psychotic and tic disorders.
  - If family history of cardiac disease or concern for structural abnormality, the patient should have an EKG, with consideration for reading by a pediatric cardiologist.
  - If family history of psychotic disorder – monitor patient closely for psychotic side effects – hallucinations.
  - If family history of tic disorders – monitor for onset of motor/vocal tics
- Common side effects include insomnia, weight loss, decreased appetite, increased BP/HR, and growth suppression.
  - Insomnia – give last dose by 4pm or switch to long-acting agent.
  - Growth suppression – drug holiday, if possible.
  - Decreased appetite/weight loss – give after a meal, if possible.
  - Increased BP/HR – monitor closely, may require discontinuation.

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Use of Alternative Treatments

- Atomoxetine may be useful in patients with a concern for substance use or history of non-adherence.
  - Onset of action is 2 to 4 weeks, must monitor LFTs and suicidal thinking.
- Adrenergic antagonists
  - Clonidine and guanfacine commonly used for the impulsivity associated with ADD, may also be useful for insomnia secondary to stimulant use.

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ADHD Case Question

What is the most appropriate drug therapy intervention for DL?

- A. Switch to methylphenidate OROS long-acting 36mg.
- B. Switch to methylphenidate CD long-acting 20mg.
- C. Add clonidine 0.05mg and evaluate appetite.
- D. Increase methylphenidate to 10 mg orally three times daily.

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Attention Deficit Disorder Case Answers

- What baseline information should be obtained prior to initiating stimulant therapy?
  - Family history of cardiovascular disease is important to have, as there is a boxed warning for sudden cardiac death if stimulants are used in children with a cardiac structural defect. History of psychosis or tic disorders may help to ascertain the risk of those side effects.
- Do you consider methylphenidate to be effective for the patient in this case?
  - Yes, DL has symptom improvement in the morning during school after his morning dose, which wears off by the afternoon.
- What medication changes might be considered?
  - Consider adding an immediate release dose after lunch or a switch to a longer-acting methylphenidate dosage form to cover the afternoon school period. May be able to discontinue afternoon immediate release dose.
- What is your concern regarding DL's family history of tic disorders?
  - Stimulant agents may exacerbate an existing tic disorder or promote the emergence of tics in the patient. Those with a family history may be at greater risk of this side effect.

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Substance Dependence Case

DF is a 35 year old man who presents to the psychiatric emergency room with belligerent behavior and acute psychosis, including visual and auditory hallucinations. He has a past psychiatric history of schizophrenia and alcohol, nicotine, and cocaine abuse. DF has a history of delirium tremens during past alcohol detoxifications, but has not had seizures associated with this. His current medications include naltrexone 380 mg intramuscularly every 4 weeks, paliperidone palmitate 117 mg intramuscularly every 4 weeks, and sodium valproate ER 1500 mg orally at bedtime. Adherence to IM injections is confirmed, he has not refilled sodium valproate at the pharmacy for 3 months. He has NKDA and smokes 1 PPD cigarettes. The urine toxicology screen is positive for cocaine, BAL is 0.25. DF is admitted to the inpatient psychiatric unit with PRN orders for lorazepam 2mg PO/IM every 2 hours as needed for agitation/withdrawal and haloperidol 5mg PO/IM every 4 hours as needed for agitation, in addition to his usual routine medications. Routine CIWA rating scale performance is ordered per nursing staff.

Substance Dependence Case Questions

- What is the timeframe for the onset of DTs or seizures for DF?
- What oral supplement should be given to DF? Why?
- What are the advantages and disadvantages of routine versus PRN dosing of benzodiazepines for DF?

Tobacco Dependence

- Patients with mental health disorders are considered to smoke tobacco at a greater rate than the general population, with more use associated with a more chronic disease.
- These patients are as likely to stop smoking as those with other medical conditions.
- Nicotine replacement therapy, bupropion, and varenicline, as well as substance abuse psychotherapy, is used successfully in this population.
- Treatment of tobacco dependence in psychiatric disorders is similar to the strategy used in the primary care setting, although patients may be more successful if not asked to set a quit date and are able to use these treatment for a longer period of time than the usual 3 to 6 month window.

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Alcohol Dependence

- Patients with a positive blood alcohol level (BAL) upon presentation to the emergency department should be assessed for the risk of delirium tremens (DTs) during alcohol withdrawal.
- Those with a past history of DTs or several past withdrawals should be considered at higher risk and monitored closely using the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar) routinely.
- Treatment for withdrawal should be either as-needed or routine dosing of a benzodiazepine.
- Thiamine is an important supplement to be given to patients in alcohol withdrawal to avoid the risk of Wernicke's encephalopathy.
- FDA-approved treatments for alcohol dependence include disulfiram, naltrexone, and acamprosate.
- Successful treatment of alcohol dependence should include group and/or individual therapy in a substance dependence treatment setting.

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Opiate Dependence

- Prescription drug dependence has become a national epidemic, with many states enacting legislation and prescription monitoring programs to combat this. Use of illicit substances, including heroin, continue to be problematic.
- Opiate withdrawal is not generally a life-threatening condition, but symptomatic treatment is available and includes the use of clonidine, loperamide, NSAIDs, antiemetics, and dicyclomine as-needed.
- The Clinical Opiate Withdrawal Scale (COWS) is commonly used to evaluate the severity of withdrawal symptoms.
- Methadone, buprenorphine, and naltrexone are FDA-approved for the treatment of opiate dependence and can be used in the outpatient setting.
- Methadone maintenance treatment is available in structured, federally-regulated treatment settings and includes psychosocial treatment, as well as drug therapy.
- Buprenorphine may be prescribed by physicians in outpatient settings as set out by the Drug Abuse Treatment Act of 2000 (DATA 2000)

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Cocaine/Stimulant and Marijuana Dependence

- Symptoms of cocaine and stimulant withdrawal are similar, including craving, dysphoria, depression, somnolence, and agitation.
- Significant depression, requiring a consideration for antidepressant treatment, may result and last for several months.
- There are no FDA-approved medications for the treatment of cocaine or stimulant dependence, other than symptomatic treatment of withdrawal.
- Urine toxicology screens in for patients with mental health disorders are commonly found to contain marijuana.
- Acute affects of cannibis abuse can include psychosis and hallucinations, the continued use of marijuana is a risk factor for earlier onset of schizophrenia in at-risk individuals.
- There are no FDA-approved treatments for marijuana dependence, although clinical trials include the use of dronabinol, fluoxetine, lithium, and rimonabant.

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K2/Spice and Bath Salts

- K2 and Spice are synthetic cannabinoids with effects similar to marijuana with the addition of psychosis, aggression, and electrolyte imbalances, specifically hypokalemia.
- Federal and state legislation has recently focused on these “designer drugs” in an attempt to decrease use, although with difficulty in assigning illegality to specific substances and including similar new chemical versions.
- Treatment of K2/Spice abuse acutely includes supportive care, antipsychotics have not been shown to be effective in the acute setting.
- Bath salts are structurally similar to amphetamines and the naturally-occurring substance cathinone.
- The use of bath salts has reached epidemic proportions in some areas of the country, legislation to counter use of K2/Spice has often included bath salt chemicals.
- The acute effects of bath salts include cardiac and CNS adverse events, as well as psychosis and violent behavior.

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Substance Dependence Case Question: What is the most appropriate outpatient medication intervention for DF?

- A. Switch to disulfiram 250 mg orally once daily.
- B. Continue naltrexone IM 380 mg every 4 weeks.
- C. Continue naltrexone IM 380 mg every 4 weeks and ensure psychosocial counseling.
- D. Add acamprosate 666 mg orally three times daily

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Substance Dependence Case Answers

- What is the timeframe for the onset of DTs or seizures for DF?
  - Delirium tremens and/or seizures onset is generally within 96 hours after the discontinuation of alcohol ingestion. Patients may seem fine prior to this with sudden onset of symptoms, requiring diligence in monitoring.
- What oral supplement should be given to DF? Why?
  - Oral thiamine supplementation should be given during the hospitalization to correct thiamine deficiency and decrease the risk of Wernicke’s encephalopathy, especially if there is consideration for IV fluids containing dextrose.
- What are the advantages and disadvantages of routine versus PRN use of benzodiazepines during the withdrawal period?
  - Routine dosing of the benzodiazepine can ensure a reduced risk of withdrawal symptoms, but often causes an increased overall dosing of the drug. PRN dosing based on the CIWA-Ar scale score can more appropriately symptoms and lower the overall dosing burden.

Questions?

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2013 UPDATES IN THERAPEUTICS®
AMBULATORY CARE PHARMACY PREPARATORY REVIEW AND RECERTIFICATION COURSE

Oncology

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Disclosures

- Speakers bureaus for Pfizer and Merck

3

Objectives

- Develop a patient-specific care plan for the treatment and monitoring of a patient with cancer of the breast, lung, or prostate
- Develop a patient-specific drug therapy care plan for the supportive care needs for a patient with cancer, including nausea/vomiting, anemia, myelosuppression, and other adverse effects
- Describe the practice management challenges unique to oral anticancer drug therapies, including specialty distribution systems, Risk Evaluation and Mitigation Strategies (REMS) programs, and adherence and toxicity monitoring
- Describe the screening guidelines for breast and prostate cancer

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4

Overview

- General Cancer Patient Assessment
- Example Cancers
  - Lung Cancer
  - Breast Cancer
  - Prostate Cancer
- Supportive Care
  - Chemotherapy-induced nausea/vomiting (CINV)
  - Anemia
  - Neutropenia/Febrile Neutropenia
- Oral chemotherapy

5

General Cancer Patient Assessment

- Start with practice guidelines from American Society of Clinical Oncology (ASCO) or National Comprehensive Cancer Network (NCCN) for patient's disease, stage, and treatment history
- Assess co-morbidities, concomitant medications, other psychosocial factors that may necessitate off-guideline treatment and conduct literature review
- New cancer patient: focus on education – risks/benefits of treatment, management of AE, monitoring, follow-up
- At follow-up – tolerance to previous course; ROS/side effect assessment and management
- Remember that these patients often also have non-cancer medications, too

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EXAMPLE CANCERS

Lung, breast, prostate

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EJ

- EJ is a 72 year-old male who is newly diagnosed with stage IV non-small cell lung cancer with squamous cell histology. He has a 55 pack-year history of smoking and has co-morbid emphysema managed with ipratropium. He has good performance status (ECOG PS = 1) and has no known drug allergies. What is the best initial chemotherapy treatment for EJ?

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Lung Cancer

- 2nd most common malignancy in the U.S.
- Most common cause of cancer-related death
  - 28% of all cancer-related deaths
- Peak incidence between age 50-70 years
- Overall 5-year survival
  - 17% non-small cell lung cancer (NSCLC)
  - 6% small cell lung cancer (SCLC)

American Cancer Society. Cancer Facts and Figures. Available at www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf. Accessed 9/30/2012

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Pathogenesis - mutations

- *K-ras*
  - Frequency 10-30%
  - Mutants generally nonresponsive to anti-EGFR therapies
- Epidermal growth factor receptor (EGFR)
  - Frequency 13%
- Echinoderm microtubule-associated protein-like anaplastic lymphoma kinase (EMLA-ALK) mutations
  - 2 – 7% of NSCLC, especially nonsmokers
- Other mutations
  - *C-kit*; *BCL2*; p53; phosphatase and tensin homolog (PTEN)

National Cancer Institute. What you need to know about: lung cancer. Available at www.cancer.gov/cancertopics/wyntk/lung/page6. Accessed 9/30/2012

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Risk Factors

- Tobacco abuse
- Asbestos
- Radon
- Other chemicals
- Diet
- Genetics
- Coexisting lung disease

National Cancer Institute. What you need to know about: lung cancer. Available at www.cancer.gov/cancertopics/wyntk/lung/page6. Accessed 9/30/2012

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Screening/Prevention

- No effective chemoprevention
- Smoking cessation
- Low-dose computed tomography (CT) screening controversial
  - USPSTF – evidence insufficient
  - NCCN – baseline recommended for high-risk patients
  - None recommend routine CT screening for low-moderate risk individuals

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Non-small cell lung cancer, version 3.2012. Most recent version of the guidelines available at www.nccn.org. Accessed 9/30/2012.

U.S. Preventive Services Task Force. Lung Cancer Screening. Available at www.uspreventiveservicestaskforce.org/uspstf/uspslung.htm. Accessed 9/30/2012

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12

Pathophysiology

SCLC

- 14% of lung cancers
- Clear relationship to tobacco use
- Most aggressive pulmonary tumor
- Very sensitive to chemotherapy and radiation

NSCLC

- 85% of lung cancers
- Nonsquamous
  - Adenocarcinoma- most common overall and most common in nonsmokers
  - Large cell
  - Other types
- Squamous – clear relationship to smoking
- Less aggressive, slower growing
- Moderate sensitivity to chemotherapy and radiation

National Cancer Institute. What you need to know about: lung cancer. Available at www.cancer.gov/cancertopics/wyntk/lung/page6. Accessed 9/30/2012

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Signs / symptoms

- Lung symptoms
  - Cough (most common)
  - Dyspnea
  - Wheezing
  - Hemoptosis
  - Hoarseness
  - Dysphagia
  - Chest pain
  - Pneumonitis
  - Pleural effusion
- Constitutional symptoms
  - Anorexia
  - Weight loss
  - fatigue
- Paraneoplastic syndromes
  - Hypercalcemia
  - Anemia
  - Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
  - Other rare syndromes

National Cancer Institute. What you need to know about: lung cancer. Available at www.cancer.gov/cancertopics/wyntk/lung/page6. Accessed 9/30/2012

Page 1-80 and 1-81

14

Diagnosis

- Chest x-ray or chest CT
- Tissue diagnosis
- Transthoracic needle biopsy
- Metastatic disease work-up

National Cancer Institute. What you need to know about: lung cancer. Available at www.cancer.gov/cancertopics/wyntk/lung/page6. Accessed 9/30/2012

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Staging

SCLC	NSCLC

• Limited Stage
  • 30-40% of cases
  • Only 1 side of chest involved
• Extensive Stage
  • 60-70% of cases
  • More than one hemothorax
	• TNM system
	• Stage 0 - noninvasive
	• Stage 1 – up to 5 cm, no lymph nodes
	• Stage 2 – up to 5 cm and invades adjacent tissue or 5-7 cm with lymph nodes
	• Stage 3 – any size with distant lymph nodes
	• Stage 4 – distant metastasis, both lungs, or malignant cells in pleura

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Non-small cell lung cancer, version 3.2012. Most recent version of the guidelines available at www.nccn.org. Accessed 9/30/2012.

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Treatment

SCLC	NSCLC
• Sensitive to chemo and radiation • Responses can be dramatic but often not durable • Limited role for surgery • Platinum-based • Prophylactic cranial irradiation • No role for maintenance chemo	• Surgery preferred stage I, II, IIIA • Adjuvant chemo stages II and IIIA • Platinum-based • Histology guides therapy • Role for maintenance therapy in patients who respond

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Non-small cell lung cancer, version 3.2012. Most recent version of the guidelines available at www.nccn.org. Accessed 9/30/2012.

Pages 1-81 through 1-85

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SCLC Treatment

Limited stage	Extensive Stage
• Goal: cure • 2-year survival: 40% • Surgery for single nodule • Cisplatin-etoposide standard first-line • Radiation added to chemo • Prophylactic cranial irradiation if good PS and CR/PR • NO MYELOID GROWTH FACTORS	• Goal: palliation • 2-year survival <5% • No role for surgery • Cisplatin-etoposide standard first line • Cisplatin-irinotecan also used (often 2nd line) • Radiation only palliative • Cranial irradiation for brain mets • Prophylactic cranial irradiation if response in chest

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Non-small cell lung cancer, version 3.2012. Most recent version of the guidelines available at www.nccn.org. Accessed 9/30/2012.

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Cisplatin, Etoposide, Irinotecan

- Cisplatin
  - Highly emetogetic
  - Myelosuppressive
  - Renal function
  - Once every 21-28 days
- Etoposide
  - Given days 1 – 3 every 21-28 days
  - Days 2 – 3 can be oral (50% bioavailable)
  - Oral is moderately emetogetic
  - Oral stored in refrigerator
- Irinotecan
  - Acute and delayed diarrhea
  - Significant myelosuppression, including febrile neutropenia
  - Liver function tests
  - Various regimens – verify dose/schedule

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Treatment: Stage I, II, III NSCLC

- Surgery preferred when possible
- Radiation if localized disease but inoperable
- Adjuvant chemotherapy
  - Cisplatin/vinorelbine preferred
  - Other cisplatin combinations: etoposide, vinblastine, docetaxel
  - Carboplatin and placlitaxel for lower PS or unable to tolerate cisplatin
- Neoadjuvant for stage IIIA
  - Cisplatin with vinorelbine or docetaxel

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Non-small cell lung cancer, version 3.2012. Most recent version of the guidelines available at www.nccn.org. Accessed 9/30/2012.

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Treatment: Stage IV NSCLC

- Cisplatin doublets preferred
- Chemotherapy reserved for ECOG PS 0 -2
- No specific regimen better than another
- Treat 4 – 6 cycles, then assess for maintenance
- Histology guides drug therapy
  - Squamous cell
    - Cisplatin + gemcitabine preferred
    - No bevacizumab – bleeding
    - EGFR and *ALK* testing not generally recommended
  - Non-squamous cell (e.g., adenocarcinomas)
    - Cisplatin + pemetrexed improved survival vs. cisplatin + gemcitabine
    - Cisplatin/vinorelbine/cetuximab if EGFR positive and no brain mets
    - EGFR positive and poor performance status – erlotinib
    - *ALK* positive - crizotinib

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Non-small cell lung cancer, version 3.2012. Most recent version of the guidelines available at www.nccn.org. Accessed 9/30/2012.

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Maintenance Therapy

- If response or stable disease after 4-6 cycles
- Continuation maintenance
  - Continue 1 or more drugs from first-line
  - Bevacizumab (category 1), cetuximab (category 1), pemetrexed, gemcitabine
- Switch maintenance
  - Start drug that was not part of first-line regimen
  - Pemetrexed after cisplatin doublet for nonsquamous
  - Erlotinib after cisplatin doublet for any histology, EGFR-mutation positive
  - Docetaxel after cisplatin doublet for any histology

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Non-small cell lung cancer, version 3.2012. Most recent version of the guidelines available at www.nccn.org. Accessed 9/30/2012.

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Recurrent disease

- Single-agent docetaxel, pemetrexed, erlotinib
- Platinum doublet with or without bevacizumab (only if nonsquamous and erlotinib or crizotinib given as first line)
- Best supportive care or erlotinib for poor performance status (PS 3 – 4)

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Non-small cell lung cancer, version 3.2012. Most recent version of the guidelines available at www.nccn.org. Accessed 9/30/2012.

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Gemcitabine, vinorelbine, pemetrexed

- Gemcitabine
  - Neutropenia, thrombocytopenia
  - Often given day 1 and day 8 every 21 days
- Vinorelbine
  - Vesicant; avoid intrathecal administration
  - Diarrhea, neuropathy
- Pemetrexed
  - Folic acid 1 mg daily and cyanocobalamin 1000 mcg IM once every 3 cycles (start 1 week before first treatment)
  - Rash, GI, myelosuppression

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EJ

- EJ is a 72 year-old male who is newly diagnosed with stage IV non-small cell lung cancer with squamous cell histology. He has a 55 pack-year history of smoking and has co-morbid emphysema managed with ipratropium. He has good performance status (ECOG PS = 1) and has no known drug allergies. What is the best initial chemotherapy treatment for EJ?

1. Carboplatin-paclitaxel-bevacizumab
2. Erlotinib
3. Cisplatin-gemcitabine
4. axitinib

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LP

- LP is a 54 year-old female with newly diagnosed ER+/PR+/HER2+ stage IV breast cancer. She has good performance status (ECOG PS=0) and ran her first marathon 2 months ago. She has normal cardiac function and no co-morbidities. What is the best first-line treatment for LP?

26

Breast Cancer

- Most common cancer in women in the U.S.
- Second most common cause of cancer-related death in women
- 5-year relative survival: 90% for all stages; 99% for localized disease; 84% regional; 23% metastatic

American Cancer Society Screening Guidelines for the Early Detection of Cancer in Average-risk Asymptomatic People. Available at www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-031941.pdf. Accessed 9/30/2012.

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Risk factors

- Female sex and increasing age most important
- 60% of women have no other risk factors
- Family history
- Estrogen exposure
- Benign breast disease
- Genetics
- Obesity
- Physical inactivity
- Alcohol
- Radiation (e.g., from previous cancer treatment)

American Cancer Society Screening Guidelines for the Early Detection of Cancer in Average-risk Asymptomatic People. Available at www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-031941.pdf. Accessed 9/30/2012.

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28

Screening

- Controversial
  - USPSTF: biennial mammograms age 50-74 if average risk, individualized decision age 40 – 50; no recommendations for increased risk
- Average risk
  - Both ACS and NCCN generally encourage self-exams and breast awareness at age 20; clinical breast exam every 1 – 3 years age 20-39; annual clinical breast exam and mammography age 40+
- Increased risk
  - ACS recommends mammography + MRI
  - NCCN recommends annual mammography age 25 if previous thoracic radiation or age 35 with other risk factors
  - NCCN recommends adding annual MRI with strong family history or genetic predisposition age 25+

Page 1-88

U.S. Preventive Services Task Force. Breast Cancer Screening. Available at www.uspreventiveservicestaskforce.org/uspstf/uspsbrca.htm. Accessed 9/30/2012. American Cancer Society Screening Guidelines for the Early Detection of Cancer in Average-risk Asymptomatic People. Available at www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-031941.pdf. Accessed 9/30/2012. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: breast cancer screening and diagnosis, version 1.2012. Most recent version of the guidelines available at www.nccn.org. Accessed 9/30/2012.

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Prevention

- Prophylactic mastectomy
  - Decreases risk by 90%
- Bilateral oophorectomy
  - Decreases risk by 50%
- Tamoxifen 20 mg orally daily
  - 34-38% reduction in incidence by no effect on overall mortality
  - Risk of endometrial cancer, VTE, cataracts, MI
- Raloxifene 60 mg orally daily
  - Above same as tamoxifen from STAR trial without risk of AE above

Page 1-88 and 1-89

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Breast cancer risk reduction, version 1.2012. Most recent version of the guideline available from www.nccn.org. Access 9/30/2012.

30

Diagnosis

- Signs/symptoms
  - Unilateral
  - Painless, firm slow-growing mass
  - Hard, irregular, nonmobile
  - Nipple retraction, dimpled skin, ulceration
- History and physical, including clinical breast exam
- Mammogram
- Biopsy

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U.S. Preventive Services Task Force. Breast Cancer Screening. Available at www.uspreventiveservicestaskforce.org/uspstf/uspsbrca.htm. Accessed 9/30/2012. American Cancer Society Screening Guidelines for the Early Detection of Cancer in Average-risk Asymptomatic People. Available at www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-031941.pdf. Accessed 9/30/2012. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: breast cancer screening and diagnosis, version 1.2012. Most recent version of the guidelines available at www.nccn.org. Accessed 9/30/2012.

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Staging

- Stage 0 – in situ
- Stage I
  - A: 2 cm or less, no LN
  - B: 2 cm or less + LN
- Stage II
  - A: 2 cm or less with ipsilateral LN or 2-5 cm and no LN
  - B: 2-5 cm + ipsilateral LN or >5 cm and no LN
- Stage III
  - A: any size, no chest wall or skin involvement, extensive LN
  - B: chest wall involved
  - C: any size with extensive LN
- Stage IV - metastatic

LN – lymph nodes

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National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Breast cancer, version 3.2012. Most recent version of the guidelines available from www.nccn.org. Accessed 9/30/2012.

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Treatment: Early Stage disease

- Lobular in situ
  - Observation – only 21% risk of developing invasive cancer in 5 years
  - Risk reduction with tamoxifen or raloxifene (post-menopausal)
- Ductal in situ
  - Mastectomy or lumpectomy +/- radiation
  - Tamoxifen x 5 years for some patients
- Stages IA – operable IIIA
  - Goal = cure
  - Lumpectomy + radiation or mastectomy +/- radiation
  - Neoadjuvant chemo for some
  - Adjuvant therapy guided by receptor status, menopausal status, nodal status
    - Tamoxifen or aromatase inhibitors
    - Anthracylines, taxanes, cyclophosphamide
    - Trastuzumab if *HER2* positive

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Breast cancer, version 3.2012. Most recent version of the guidelines available from www.nccn.org. Accessed 9/30/2012. Pages 1-90 and 1-91

33

Treatment: Locally Advanced (IIIA-IIIC)

- Neoadjuvant chemo with anthracycline +/- taxane
- Surgery or radiation follows if respond to neoadjuvant therapy
- Same adjuvant therapies as early-stage disease after local treatment

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Breast cancer, version 3.2012. Most recent version of the guidelines available from www.nccn.org. Accessed 9/30/2012. Page 1-91

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Treatment: Metastatic / Recurrent

- Goal: palliative, prolong life, maximize QOL
- Median survival = 3 years
- ER / PR positive tumors and bone/soft tissue mets tend to respond to endocrine therapy
- Visceral mets and ER / PR negative tumors generally require cytotoxic chemotherapy
  - Anthacyclines, taxanes, gemcitabine, vinorelbine, capecitabine, ixabepilone, eribulin
- Targeted agents
  - Trastuzumab, lapatinib (*HER2*/EGFR), bevacizumab (VEGF), pertuzumab (*HER2);* everolimus (*MTOR)*
- Trastuzumab + pertuzumab + docetaxel preferred first-line in metastatic, *HER2* positive disease

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Breast cancer, version 3.2012. Most recent version of the guidelines available from www.nccn.org. Accessed 9/30/2012. Pages 1-91 and 1-92

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Cytotoxic chemotherapy

- Anthracyclines
  - Doxorubicin, epirubicin
  - Lifetime maximum dose
  - Cardiotoxic
  - Baseline MUGA
  - Vesicant
  - Mucositis, urine/fluid discoloration
- Taxanes
  - Docetaxel, paclitaxel
  - Neuropathy, neutropenia, febrile neutropenia, infusion reactions to solvent
- Antimetabolites
  - Capecitabine, 5-flurouracil
  - Diarrhea, hand-foot syndrome
  - Capecitabine multiple pills orally twice daily x 14 days q21 days
- Ixabepilone
  - Microtubule inhibitor
  - Peripheral neuropathy, neutropenia, anemia, myalgia/arthralgia, alopecia, nausea/vomiting, diarrhea, stomatitis, fatigue/asthenia
- Eribulin
  - Microtubule inhibitor
  - Peripheral neuropathy, alopecia, neutropenia, constipation, asthenia, fatigue, nausea

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Targeted Therapies

Anti-*HER2*

- Each can cause left ventricular hypertrophy
- All approved in metastatic setting
- Trastuzumab
  - Also used in adjuvant setting
- Pertuzumab
  - Binds to different epitope of *HER2* than trastuzumab
  - Diarrhea, alopecia, peripheral neuropathy, rash, fatigue, neutropenia
- Lapatinib
  - Also blocks EGFR
  - Oral therapy: five 250-mg tablets once daily in combination with either capecitabine or letrozole
  - Must be taken on empty stomach
  - Hepatotoxicity, rash, fatigue

Other

- Anti-VEGFR: bevacizumab
  - Minimally improves progression-free survival
  - Hypertension; wound dehiscence; proteinuria; epistaxis
- Anti-MTOR: everolimus
  - Oral therapy taken with food
  - For refractory HR+, *HER2-*

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LP

- LP is a 54 year-old female with newly diagnosed ER+/PR+/HER2+ stage IV breast cancer metastatic to the lungs . She has good performance status (ECOG PS=0) and ran her first marathon 2 months ago. She has normal cardiac function and no co-morbidities. She is pre-menopausal. What is the best first-line treatment for LP?

1. Cyclophosphamide, methotrexate, 5-fluororuacil
2. Tamoxifen
3. Lapatinib, doxorubicin, paclitaxel
4. Trastuzumab, pertuzumab, docetaxel

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WE

- WE is a 68 year-old male with metastatic, castration-resistant prostate cancer metastatic to the right hip. He reports persistent lower back pain that is generally well-managed with oxycodone ER 20 mg q8h. He has been treated with docetaxel for 12 cycles and surveillance CT scan shows that he has progressive disease. He had treatment delays 3 times and required g-csf support during the last 5 cycles of docetaxel. He takes medication for NIDDM and hypercholesterolemia, and his absolute neutrophil count today is 1200/dL. What is the best treatment approach for WE?

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Prostate Cancer

- Most common cancer in men in U.S.
- Second leading cause of cancer-related death in men
- 5-year relative survival is almost 100%; 15-year relative survival for all stages is 91%
- Death rates have declined every year since 1992 despite an increase in incidence

American Cancer Society. Cancer Facts & Figures 2013: prostate cancer. Available from: http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-036845.pdf. Accessed 3/14/2013.

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Risk Factors

- Age most significant risk factor
- Race – African Americans at higher risk
- Family history
- Education – higher incidence in college-educated; advanced disease more likely less educated
- *BRCA2* mutation
- Diet
- Occupation – textile workers
- Vasectomy
- Obesity
- Smoking

American Cancer Society. Cancer Facts & Figures 2013: prostate cancer. Available from: http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-036845.pdf. Accessed 3/14/2013.

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Prevention

- Finasteride / dutasteride
  - Neither FDA-approved for chemoprevention
  - Finasteride reduced prevalence by 24.8% in PCPT trial, but treated group had higher Gleason scores
  - Dutasteride reduced incidence by 23% in REDUCE trial
  - ASCO and AUA joint practice guideline- neither recommended but some patients may benefit from risk/benefit discussion
- Selenium / vitamin E
  - SELECT trial – no difference in incidence

Thompson IM, et al. *New Engl J Med 2003*; 349:215-224.
Klein EA. *Cancer Res 2009*; 163: 212-225.
Lippman SM et al. *JAMA 2009*; 301:39-51.
Andriole GL, et al. *New Engl J Med 2010;* 362: 1192-1202
Kramer BS, et al. American Society of Clinical Oncology / American Urological Association 2008 Clinical Practice Guideline. *J Urol 2009*; 181:1642-1657.

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PSA Screening

- Risk – benefit discussion
- American Cancer Society
  - Average risk: start age 50 and life expectancy at least 10 years
  - High risk: age 45 (African Americans; first-degree relative diagnosed at age less than 65)
  - Highest risk: age 40 (several first-degree relatives)
- NCCN
  - Baseline at age 40
  - Annual if baseline is 1 ng/mL or greater
  - Re-screen age 45 baseline less than 1 ng/mL
  - Annual at age 50 regardless of baseline
  - Annual at age 45 if African American; firs-degree relative
  - Not routine at age 75 and older
- USPSTF – recommends AGAINST PSA-based screening

American Cancer Society. Recommendations for the early detection of prostate cancer. Available from: http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-detection. Accessed 3/14/2013. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology – Prostate Cancer Early Detection, version 2.2012. Most recent version of the guideline available at www.nccn.org. Accessed 9/30/2012. US Preventive Services Task Force. Screening for prostate cancer. Available from: http://www.uspreventiveservicestaskforce.org/prostatecancerscreening.htm. Accessed 3/14/2013.

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Diagnosis

Signs / Symptoms	Work- up

• Early disease often asymptomatic
• Advanced disease
  • Alterations in urination
  • Impotence
  • Lower extremity edema
  • Anemia
  • Weight loss
	• Physical exam
	• Biopsy
	• Grading – Gleason score
	  • 2 samples taken from tumor
	  • Score of 1-5 assigned to each sample and added
	  • Scores 2-4 slow-growing; scores 8-10 are aggressive and higher likelihood of metastasis

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology – Prostate Cancer Early Detection, version 2.2012. Most recent version of the guideline available at www.nccn.org. Accessed 9/30/2012.

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Staging

- I – incidentally found, localized tumor
- II – confined to the prostate
- III – tumor extends outside prostate capsule
- IV – tumor is fixed, invades adjacent structures, or metastasis

Pages 1-97 and 1-98

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology – Prostate Cancer Early Detection, version 2.2012. Most recent version of the guideline available at www.nccn.org. Accessed 9/30/2012.

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Treatment – Stages I - III

- Active surveillance
  - Only for Gleason score 6 or less, life expectancy less than 10 - 20 years (details in handout)
  - PSA at least every 6 months, DRE at least every 12 months, biopsy every 12 months
- Radical prostatectomy + LN dissection
- Radiation therapy
- Androgen deprivation therapy
  - LHRH analog with or without antiadrogen

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National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology – Prostate Cancer Early Detection, version 2.2012. Most recent version of the guideline available at www.nccn.org. Accessed 9/30/2012.

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Treatment – Stage IV

- Androgen deprivation therapy
- Denosumab or zoledronic acid if bone metastases
- Once castration-resistant, first-line treatment based on symptoms
  - Symptomatic: docetaxel (preferred); mitoxantrone; abiraterone; palliative radiation; clinical trial
  - Asymptomatic: sipuleucel-T (category 1); antiandrogens; antiandrogen withdrawal; abiraterone; keotconazole; docetaxel; clinical trial
- Second-line: cabazitaxel or abiraterone after docetaxel failure (category 1); docetaxel re-challenge; mitoxantrone; sipuleucel-T; other secondary hormonal therapies (enzalutamide after docetaxel failure)

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National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology – Prostate Cancer Early Detection, version 2.2012. Most recent version of the guideline available at www.nccn.org. Accessed 9/30/2012.

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Hormonal Therapies

- All subject to cause hot flashes, erectile dysfunction, decreased libido, dyslipidemia, weight gain
- AE worse in younger men and attenuate with time
- LHRH analogs
  - Reversible method of castration
  - Survival outcomes equivalent to surgical castration
  - Remain on therapy for duration of life
- Antiandrogens
  - Added to LHRH analog as second-line therapy
  - Once treatment refractory, withdrawal is a treatment
- Enzalutamide
  - Newest and only anti-androgen approved after docetaxel failure

Pages 1-99 through 1-101

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Cabazitaxel, Mitoxantrone

- Cabazitaxel
  - Taxane approved for use after docetaxel failure
  - Side effects similar to docetaxel but significantly more neutropenia, including febrile neutropenia
  - Death related to diarrhea, renal failure, and neutropenia reported
  - Like docetaxel, formulated in polysorbate 80
- Mitoxantrone
  - Anthracycline derivative
  - Cardiotoxic; blue-green discoloration of body fluids; stomatitis
  - Has not been shown to improve survival compared to best supportive care but improves pain symptoms
  - Maximum lifetime dose = 144 mg/m^2 (12 doses of 12 mg/m^2)

Pages 1-101 and 1-102

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Sipuleucel-T

- Autologous cellular immunotherapy
- Made from patient's own peripheral blood mononuclear cells, linked to GM-CSF
- 3 leukapheresis sessions followed by infusion
- Chills, pyrexia, headache
- Used for castration-recurrent patients who are asymptomatic or minimally symptomatic

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WE

- WE is a 68 year-old male with metastatic, castration-resistant prostate cancer metastatic to the right hip. He reports persistent lower back pain that is generally well-managed with oxycodone ER 20 mg q8h. He has been treated with docetaxel for 12 cycles and surveillance CT scan shows that he has progressive disease. He had treatment delays 3 times and required g-csf support during the last 5 cycles of docetaxel. He takes medication for NIDDM and hypercholesterolemia, and his absolute neutrophil count today is 1200/dL. What is the best treatment approach for WE?

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WE (continued)

1. Cabazitaxel
2. Abiraterone
3. Best supportive care
4. mitoxantrone

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SUPPORTIVE CARE

CINV, anemia, neutropenia

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CINV: Prevention is the Goal!

- Acute
  - Occurs within 24 hours of chemotherapy; peak 5-6 hours after chemo
  - Principal cause is serotonin
  - $5HT_3$ antagonists, NK-1 inhibitors, phenothiazines key drug therapies
- Delayed
  - Begins more than 24 hours after chemo; peak onset 48 – 72 hours after chemo, can persist for up to 1 week
  - No clear mechanism
  - Dexamethasone key drug therapy
- Anticipatory
  - Conditioned response
  - Benzodiazepines key drug therapies

Pages 1-103 and 1-104

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Antiemesis, version 1.2012. Most recent version of the guideline available at www.nccn.org. Accessed 9/30/2012.

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CINV Risk

- Patient-specific
  - Women
  - Younger age
  - Infrequent alcohol use
  - History of CINV, pregnancy-induced n/v, motion sickness
  - Anxiety
  - Higher doses; cumulative administration of chemo
- Treatment-related
  - Grunberg scale according to incidence of emesis in clinical trials
  - High – more than 90% risk
  - Moderate – 30-90% risk
  - Low – less than 30%
  - Minimal – no risk

Pages 1-104 and 1-105

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Antiemesis, version 1.2012. Most recent version of the guideline available at www.nccn.org. Accessed 9/30/2012.

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CINV Prevention

- Highly emetogenic chemo
  - NK1 antagonist days 1-3 + 5HT3 antagonis day 1 plus dexaxmethasone days 1-3
- AC regimens
  - Day 1 same as highly emetogenic chemo
  - Days 1-3: NK1 antagonist +/- dexamethasone
- Moderately emetogenic chemo
  - Days 1 – 3 5HT3 antagonist (esp. palonosetron) + dexamethasone +/- NK1 antagonist
- Low emetogenic risk chemo
  - Day 1 dexamethasone or metoclopramide or prochlorperazine or 5HT3 antagonist; no meds days 2-3
- Minimally emetogenic chemotherapy
  - No scheduled prophylaxis

Pages 1-105 and 1-106

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Antiemesis, version 1.2012. Most recent version of the guideline available at www.nccn.org. Accessed 9/30/2012.. ASCO guideline for antiemetics in oncology: update 2006. *J Clin Oncol* 2006; 24: 2932-2947. MASCC/ESMO Antiemetic Guideline 2010. Available at www.mascc.org. Accessed 2/5/2011.

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Anemia

- Erythropoiesis-stimulating agents (ESAs) approved for nonmyeloid malignancies *without* curative intent
  - Hemoglobin must be less than 10 g/dL to initiate/continue ESA
  - Must be receiving concurrent chemotherapy
- Goal is reduction in RBC transfusions (not QOL)
- REMS
  - Patient med guide: "Your tumor may grow quicker and you may die sooner…"
  - APPRISE program
  - Restricted distribution system
  - Based on trials targeting hemoglobin levels over 12 g/dL which led to shorter time to tumor progression, increased death rates, increased rate of venous thromboembolism
- AE: death, MI, stroke, venous thromboembolism, hypertension, allergic reactions

Pages 1-109 and 1-110

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Anemia, version 1.2013. Most recent version of the guideline available from www.nccn.org. Accessed 9/30/2012.

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Neutropenia/Febrile Neutropenia (FN)

- In general, ANC must be above 1500/mm^3 to give chemo
- Colony stimulating factors for nonmyeloid malignancies treated with chemo with 20% incidence of FN
- Consider CSF if risk of FN is 10-20%
- Dose reductions preferred over CSF if intent is palliative
- Patient risk factors
  - ANC <100/mm^3 for 7 days or more
  - Hepatic or renal insufficiency
  - Uncontrolled/ progressive cancer
  - Pneumonia or other complex infections
  - Alemtuzumab
  - Grade 3 -4 mucositis

Pages 1-111 and 1-112

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Myeloid Growth Factors, version 1.2012. Most recent version of the guideline available from www.nccn.org. Accessed 9/30/2012.

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ORAL CHEMOTHERAPY

Please see Appendix A

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Oral Chemo – key points

- Note dosage forms, pill burden, food effects, drug interactions
- Many come from specialty pharmacies
- Challenge with care coordination
- Patient access & parity to IV – Rx versus medical benefits
- Medication reconciliation
- Adherence – to oral chemo & primary care medications
- Side effect management

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Summary

- Cancer is primarily treated in an ambulatory care setting
- Patient assessment for drug-related problems in cancer setting really not that different than other ambulatory care settings
- Requires a vocabulary, knowledge of resources, context for understanding cancer drug therapies