Disclosures

I have no financial disclosures.

Objectives

To review pharmacologic management of common women's health conditions for the primary care provider.

Outline

- Health and Wellness
- Diseases and Conditions
- Reproductive Health
- Disorders related to Infertility
- Gynecological Health
- Preconception and Prenatal Care

Health and Wellness

A 36-year-old woman with an active seizure disorder is contemplating pregnancy. Your recommendation to her is:

A. Switch antiepileptic treatment to a medication not known to cause neural tube defects

B. Take folic acid 4 mg daily during the first trimester

C. Take folic acid 400 mcg daily before conception followed by 4 mg daily during at least the first trimester

D. Increase dietary intake of folic acid

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Folic Acid

- FDA approved
- Fortification of corn masa flour
  - Manufacturers voluntarily add up to 0.7 milligrams of folic acid per pound of corn masa flour, consistent with the levels of certain other enriched cereal grains.
  - A staple food for many Latin Americans including individuals of Mexican and Central American descent in the United States. It can be used to make foods such as tortillas, tortilla chips, tamales, taco shells, and corn chips.

Osteoporosis

- Lifestyle measures
  - Calcium
    - Postmenopausal women with adequate calcium from dietary intake alone (approximately 1200 mg daily) do not need calcium supplements
    - Inadequate dietary intake should take supplemental elemental calcium 500 to 1000 mg/day, in divided doses at mealtime
  - Vitamin D
    - Should ingest a total of 800 international units daily
    - Higher doses are required if malabsorption or rapid metabolism of vitamin D due to concomitant anticonvulsant drug therapy
    - Most postmenopausal women with osteoporosis require vitamin D supplementation – difficult to achieve goals with diet alone
  - Diet
    - Celiac disease is a major contributor
      - Gluten-free diet may result in improvement in bone mineral density
      - Conflicting data ; do not recommend modifying protein intake as a strategy for preventing bone loss

Osteoporosis

- Lifestyle measures
  - Exercise
    - At least 30 minutes three times per week
    - Associated with a reduced risk of hip fracture in older women
      - No convincing evidence that high-intensity exercise, such as running, is of greater benefit than lower intensity exercise, such as walking
  - Cessation of smoking
    - Smoking cigarettes accelerates bone loss
      - Smoking one pack per day throughout adult life was associated with a 5 to 10 percent reduction in bone density
      - May also negate the beneficial effect of estrogen therapy in postmenopausal women

Osteoporosis

- Pharmacologic therapy recommended for postmenopausal women with:
  - A history of fragility fracture or with osteoporosis based upon bone mineral density (BMD) measurement (T-score ≤-2.5)
  - T-scores between -1.0 and -2.5
    - Calculate fracture risk using the Fracture Risk Assessment Tool (FRAX). A reasonable cutpoint is a 10-year probability of hip fracture or combined major osteoporotic fracture of ≥3.0 or ≥20 percent, respectively
- Initial therapy
  - Recommend oral bisphosphonates
    - Efficacious, favorable cost, and the availability of long-term safety data
  - Alendronate
    - Prophylaxis: 5 mg once daily **or** 35 mg once weekly
    - Treatment: 10 mg once daily **or** 70 mg once weekly
  - Risedronate
    - Immediate release tablet: Prevention and treatment: 5 mg once daily **or** 35 mg once weekly **or** 150 mg once monthly
    - Delayed release tablet: Treatment: 35 mg once weekly

Osteoporosis

  - Acceptable initial therapy for women with well-controlled gastroesophageal reflux or peptic ulcer disease
- Contraindications
  - Oral bisphosphonates should not be used as initial therapy in patients with esophageal disorders (eg, achalasia, esophageal stricture, esophageal varices, Barrett's esophagus) or with an inability to follow the dosing requirements (eg, stay upright for at least 30 minutes)
  - Should also be avoided after certain types of bariatric surgery in which surgical anastomoses are present in the GI tract (i.e., Roux-en-Y gastric bypass)
  - Oral and IV bisphosphonates should not be used routinely in patients with chronic kidney disease and an estimated glomerular filtration rate (eGFR)<30 to 35 mL/min
    - IV bisphosphonates are acceptable as long as vitamin D has been assessed and is in the normal range

Osteoporosis

- Bisphosphonates are poorly absorbed orally (less than 1 percent of the dose)
  - Take alone on an empty stomach first thing in the morning with at least 8 oz.. of water
    - After administration, the patient should not have food, drink, medications, or supplements for at least one half-hour
    - Should remain upright (sitting or standing) for at least 30 minutes after administration to minimize the risk of reflux
- Should not be given to patients with active upper GI disease.
- Should be discontinued in patients who develop any symptoms of esophagitis
- Enteric-coated, delayed-release risendronate
  - Regimen is different from that of other bisphosphonates
  - Formulation is taken immediately after breakfast with 4 oz. of water
- Patients Compliance is also important for optimal fracture reduction

Osteoporosis

- Duration of therapy
  - For patients taking alendronate or risendronate for five years or who received zoledronic acid once yearly for three years, have a stable BMD, have no previous vertebral fractures, and are at low risk for fracture in the near future, recommend discontinuation
    - There appears to be residual BMD and fracture benefit
  - For women at highest risk for fracture (history of osteoporotic fracture before or during therapy, T-score below -3.5 in the absence of fractures) who are taking alendronate or risendronate, recommend continuing therapy for up to 10 years
    - Clinical trial data show maintenance of BMD and fracture benefits with no increased risk of adverse events

Osteoporosis

- The decision to resume the drug is often based on a combination of factors, including duration of the holiday, decrease in BMD, clinical risk factors for fracture, and increase in markers of bone turnover
  - No data to support one strategy over another for determining when to restart bisphosphonates after a drug holiday
- Typically restart bisphosphonates when there is persistent bone loss (approximately 5 percent) on at least two dual-energy x-ray absorptiometry (DXA) measurements taken at least two years apart, using the same make and model DXA scanner
- Can be restarted after a three- to five-year holiday in women who showed improvement during their initial course of bisphosphonates and did not have a previous fracture
- Recommend not using combination therapy
  - The additional BMD benefits are small and there is no proven additional fracture benefit

Continued vasomotor symptoms in a 52-year-old postmenopausal woman receiving 0.3 mg of oral conjugated equine estrogens can be managed by:

A. Changing to a SERM
B. Increasing the daily estrogen dose
C. Decreasing the daily estrogen dose
D. None of the above

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Which of the following would be the best option to treat moderate hot flushes in a 55-year-old woman with breast cancer?

A. Estrogen
B. Progestogen
C. Paroxetine
D. Tibolone

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Long-term hormone therapy can be routinely prescribed for which of the following conditions?

A. Coronary heart disease
B. Dementia unresponsive to other therapies
C. Prevention of colon cancer
D. None of the above choices is correct

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Menopause

- 95 percent become menopausal between the ages of 45 to 55 years
- Estrogen is the most effective treatment available for relief of menopausal symptoms, most importantly hot flashes
- Menopausal hormone therapy (MHT; estrogen alone or combined with a progestin) is currently indicated for management of menopausal symptoms
- Long-term use for prevention of disease is no longer recommended

Menopause Hormone Therapy (MHT)

- The goal of MHT is to relieve menopausal symptoms, most importantly hot flashes (vasomotor symptoms)
  - Most common indication
- The Women's Health Initiative clearly demonstrated adverse effects of MHT in older postmenopausal women (over age 60 years)
  - The absolute risk of complications for healthy, young postmenopausal women (late 40s or 50s) taking MHT for five years is very low
- Vasomotor symptoms occur most often in the late menopausal transition and early post menopause
  - Estrogen is the most effective therapy

Menopause Hormone Therapy (MHT)

- Indications
  - Hot flashes
  - Mood lability/depression
  - Joint aches and pains
  - Genitourinary symptoms of menopause
- No longer recommended for prevention of chronic disease (CHD or osteoporosis

Menopause Hormone Therapy (MHT)

- Contraindications
  - Breast cancer
  - Coronary heart disease
  - A previous venous thromboembolic event or stroke
  - Active liver disease
  - Unexplained vaginal bleeding
  - High-risk endometrial cancer
  - Transient ischemic attack
- Oral estrogens should be avoided in women with:
  - Hypertriglyceridemia
  - Active gallbladder disease
  - Known thrombophilias such as factor V Leiden (without a personal history of venous thromboembolism [VTE]).
  - Transdermal estrogen is also preferred for women with migraine headaches with auras.

Menopause Hormone Therapy (MHT)

- A safe option for healthy, symptomatic women who are within 10 years of menopause or younger than age 60 years and who do not have contraindications to MHT
- The Endocrine Society guideline suggests calculating cardiovascular and breast cancer risks before initiating MHT
  - Recommend non-hormonal therapies for symptomatic women who are at high risk (>10 percent 10-year risk) for CVD or moderate (1.67 to 5 percent five-year risk) to high risk (>5 percent) for breast cancer
  - For women at moderate risk of CVD (5 to 10 percent 10-year risk), they suggest transdermal rather than oral estrogen, with micronized progesterone for those with a uterus

Menopause Hormone Therapy (MHT)

- Starting estrogen
  - Type and route
    - Oral, transdermal, topical gels and lotions, intravaginal creams and tablets, and vaginal rings
    - All routes of estrogen administration appear to be equally effective for symptom relief (and bone density), but their metabolic effects differ
  - Need for progestin? Regimen?
  - Oral estrogens
    - Increase sex hormone-binding globulin more than transdermal preparations
      - Leads to lower free testosterone concentrations
      - No negative impact on libido and sexual function proven
    - Risks of VTE and stroke appear to be higher with oral when compared with transdermal estrogen
  - The US Food and Drug Administration (FDA) now requires the adding of labels to all estrogen and estrogen-progestin products warning of the possible risk of heart disease, stroke, and cancer

Menopause Hormone Therapy (MHT)

- Recommend
  - Transdermal 17-beta estradiol
    - Lower risk of VTE, stroke, and hypertriglyceridemia than oral estrogens
- Dose
  - All types and routes of estrogen are effective for relieving menopausal symptoms, particularly, hot flashes
    - In a meta-analysis of 24 trials of MHT in 3329 women, the frequency of hot flashes decreased more in those receiving MHT. The severity of hot flashes also decreased more with MHT compared with placebo.
    - In a second meta-analysis, conjugated estrogen 0.625 mg/day and 17-beta estradiol (oral 1 mg/day or transdermal 0.05 mg/day) appeared to be equally effective for the treatment of hot flashes. These doses eliminate hot flashes completely in about 80 percent of women and reduce the frequency and severity in the remainder.

Menopause Hormone Therapy (MHT)

- Standard doses of estrogen given daily
  - Conjugated estrogen 0.625 mg or its equivalent are adequate for symptom relief in the majority of women
  - Exception - younger women after bilateral oophorectomy
    - Often require higher doses (up to 0.1 mg transdermal estradiol) for the first two to three years after surgery; the dose can subsequently be tapered down.
  - Administer continuously
    - Past regimens where estrogen was administered days 1 to 25 of the calendar month are considered to be obsolete
    - Women will often get hot flashes during the days off, and there is no known advantage to stopping for several days each month

Menopause Hormone Therapy (MHT)

- Side effects
  - Breast soreness, which can often be minimized by using lower doses
  - Some women experience mood symptoms and bloating with progestin therapy
  - Vaginal bleeding occurs in almost all women receiving cyclic estrogen-progestin regimens and is common in the early months of a continuous estrogen-progestin regimen
- Progestin
  - Recommend oral micronized progesterone
    - All women with an intact uterus need a progestin in addition to estrogen to prevent endometrial hyperplasia, which can occur after as little as six months of unopposed ET. Women who have undergone hysterectomy should not receive a progestin, as there are no other health benefits other than prevention of endometrial hyperplasia and carcinoma.

Menopause Hormone Therapy (MHT)

- Progestin
  - Women with an intact uterus
    - Recommend oral micronized progesterone
    - Natural micronized progesterone (200 mg/day for 12 days/month or 100 mg daily)
      - Natural progesterone is safer for the cardiovascular system (no adverse lipid effects) and possibly the breast
  - Perimenopausal or newly menopausal
    - Start with cyclic administration of oral micronized progesterone (200 mg/day for 12 days of each calendar month)
      - Continuous administration in this population is associated with irregular, unscheduled bleeding due to the exogenous hormones and the continued endogenous ovarian function
  - Women who are ≥2 to 3 years post menopause
    - Use a continuous regimen (micronized progesterone 100 mg/day)
    - Irregular and breakthrough bleeding is less of a problem once ovarian function has ceased

Menopause Hormone Therapy (MHT)

- Side effects
  - Some women unable to tolerate cyclic progestin administration (with any type of oral progestin) because of mood side effects and bloating
    - Sometimes suggest off-label use of the lower dose levonorgestrel-releasing intrauterine device (IUD)
  - Almost always result in monthly withdrawal bleeding
    - Recommend switching to a continuous regimen to resolve mood symptoms and bloating
    - Note: Newly menopausal women can anticipate breakthrough bleeding

Menopause Hormone Therapy (MHT)

- Duration of therapy
  - Estrogen or combined EPT
    - Short-term use is suggested (generally not more than five years or not beyond age 60 years
    - Hot flashes persist for an average of 7.4 years, and many women continue to have symptoms for more than 10 years
      - Recurrent, bothersome hot flashes after stopping estrogen
        - Recommend non-hormonal options before considering resuming estrogen.
      - Inadequate relief with non-hormonal therapies
        - Consider extended use of hormone therapy

Menopause Hormone Therapy (MHT)

- Routine mammograms and breast exams are recommended in women taking MHT, even when used short-term.
  - In the WHI, the risk of breast cancer with combined EPT did not increase until the fourth year
- Perimenopausal women seeking relief of menopausal symptoms and desire contraception
  - A low-estrogen oral contraceptive is an option
    - An oral contraceptive containing 20 mcg of ethinyl estradiol provides symptomatic relief while providing better bleeding control than conventional MHT
    - Should be avoided in obese perimenopausal women; at greater risk for thromboembolism
  - Contraindications in this population include smoking, hypertension, and migraine headaches
  - Contraception remains important during perimenopause, as women cannot be certain of infertility until they reach menopause (i.e. 12 months without menses)

Menopausal Hormone Therapy (MHT)

- Women are apt to have hot flushes when estrogen is stopped abruptly
  - Recommend tapering the oral contraceptive by one pill per week as described for ET in the following section.
- Stopping hormone therapy
  - Abrupt withdrawal of exogenous estrogen at any age may result in the return of hot flashes and other menopausal symptoms.
  - Tapering MHT has not been proven to be more effective than stopping treatment abruptly
    - Recommend a gradual taper, particularly in women with a history of severe vasomotor symptoms

Diseases and Conditions

Primary Hypothyroidism

- Treatment of choice is synthetic thyroxine (T4, levothyroxine)
- T4 is deiodinated in peripheral tissues to form T3 (active thyroid hormone)
  - Approximately 70 to 80 percent of T4 is absorbed
  - Long half-life (7 days)
    - Once-daily treatment results in nearly constant serum T4 and triiodothyronine (T3) concentrations when a steady state is reached

T4

- Tablet versus soft gel capsule
  - Most patients are treated with a T4 tablet
  - The soft gel capsule is an option for patients with suspected poor absorption of the standard solid tablet, especially in the presence of atrophic gastritis.
  - Cost effective to increase the dose of a generic T4 tablet with monitoring of TSH.
- Generic versus brand name
  - Either is acceptable
  - If pharmacy switches to another manufacturer and you have concerns regarding equivalent efficacy of the preparations, measure a serum TSH for six weeks after changing to document the serum TSH is still within therapeutic target.

T4

- Initial
  - Average full replacement dose of T4 in adults is approximately 1.6 mcg/kg body weight per day
  - Range of required doses vary from 50 to $\geq$ 200 mcg/day
  - T4 requirements correlate better with lean body mass than body weight
- Take on an empty stomach with water, ideally an hour before breakfast
- T4 should not be taken with medications that interfere with its absorption, such as bile acid resins, calcium carbonate, and ferrous sulfate

T4

- Usually begin to improve symptomatically within two weeks, but complete recovery can take several months in those with severe hypothyroidism
- Although symptoms may begin to resolve after two to three weeks, steady-state TSH concentrations are not achieved for at least six weeks
  - Serum thyroid hormone concentrations increase first and then TSH secretion begins to fall because of the negative feedback action of T4 on the pituitary and hypothalamus

Graves' disease

- Therapeutic approach consists of both rapid amelioration of symptoms and decrease thyroid hormone synthesis

- Symptom control
  - Beta blocker should be started in most patients as soon as the diagnosis of hyperthyroidism is made
    - Even before confirming the cause is Graves' disease
  - Atenolol 25-50 mg/day

Graves' disease

- Treatment options
  - Antithyroid drugs (thionamides)
  - Radioiodine
  - Surgery
- The "best" treatment option should consider the patient's values and preferences.
  - In a randomized controlled trial comparing all three therapies, each was equally effective in normalizing serum thyroid hormone concentrations within six weeks; after treatment, 95 percent or more of the patients were satisfied with their therapy

Thionamides

- For patients with significant symptoms of hyperthyroidism to achieve euthyroidism relatively quickly, prior to more definitive therapy with radioiodine or surgery
  - Goal is a euthyroid state within 3 to 8 weeks
- Methimazole is the primary drug to treat Graves' hyperthyroidism
  - Almost exclusively used because of its longer duration of action
    - Once daily dosing and rapid efficacy
- Propylthiouracil (PTU) is preferred during the first trimester of pregnancy
  - More significant teratogenic effects of methimazole
  - Patients who have minor drug reactions to methimazole who refuse radioiodine or surgery

Methimazole (Tapazole)

- Hyperthyroidism
  - Oral: Initial: 15 to 60 mg/day depending on severity of disease; usual maintenance dose: 5 to 15 mg/day
  - The manufacturer suggests dividing the daily dose into 3 equal administrations; however, administration as a single daily dose or in 2 divided doses (for doses>30 mg/day) may be preferred
- Adjust dosage as required to achieve and maintain serum T_3, T_4, and TSH levels in the normal range.
  - An elevated T_3may be the sole indicator of inadequate treatment. An elevated TSH indicates excessive antithyroid treatment

Methimazole (Tapazole)

- Primary drug to treat Graves' hyperthyroidism (Off-label)
  - Almost exclusively used because of its longer duration of action
    - Once daily dosing and rapid efficacy
- Individualize dose based on serum free T_4 and T_3 levels and clinical status

Methimazole (Tapazole)

- The following recommendations may be considered to guide initial dosing based on free T_4 levels:
  - 1 to 1.5 times ULN: 5 to 10 mg/day
  - >1.5 to 2 times ULN: 10 to 20 mg/day
  - >2 times ULN: 30 to 40 mg/day
- Usual maintenance: 5 to 10 mg once daily for a total of 12 to 18 months, then discontinue if thyroid function tests (i.e. TSH, thyrotropin receptor antibody [TRAb]) are normal at that time

Propylthiouracil (PTU)

- Hyperthyroidism
  - Oral: Initial: 300 mg daily in 3 equally divided doses (~8-hour intervals)
  - 400 mg daily in patients with severe hyperthyroidism and/or very large goiters
  - An occasional patient will require 600 to 900 mg daily; usual maintenance: 100 to 150 mg daily in 3 equally divided doses

Propylthiouracil (PTU)

- Treatment of choice when an antithyroid drug is indicated during or just prior to the first trimester of pregnancy

- Hyperthyroidism associated with Graves' disease (off-label)
  - Oral: Initial: 50 to 150 mg (depending on severity) 3 times daily to restore euthyroidism
    - As clinical condition improves, may reduce dosage to usual maintenance dose of 50 mg 2 to 3 times daily for a total of ~12 to 18 months then discontinue if thyroid function tests are normal at that time.

Urticaria

- Diagnosed clinically, based upon a detailed history and physical examination confirming the presence of characteristic skin lesions
- Initial treatment of new-onset urticaria (with or without angioedema) should focus on the short-term relief of pruritus and angioedema, if present.
- Second-generation agents are preferred for both adults and children

Urticaria

- The newer, second-generation H1 antihistamines are recommended as first-line therapy by published guidelines from both allergy and dermatology expert panels
  - Minimally sedating
  - Essentially free of the anticholinergic effects that can complicate use of first-generation agents
  - Few significant drug-drug interactions
  - Require less frequent dosing compared with first-generation agents

Urticaria

- Cetirizine
  - A rapid onset of action and some mast cell-stabilizing activity
  - It can be mildly sedating, in a dose-dependent manner, although less so than first-generation agents
  - The standard dose of 10 mg once daily is appropriate for adults and children aged six years and older (and may be increased to 10 mg twice daily in adults if needed)

Cetirizine (Zyrtec)

- Standard dose of 10 mg once daily is appropriate for adults and children aged six years and older
  - May be increased to 10 mg twice daily in adults, if needed
- Maintenance dose for patients with significant renal and/or hepatic insufficiency should be reduced by one-half

Levocetirizine

- Produces effects equivalent to cetirizine at about one-half of the dose
- For adults and children 12 years and older, the standard dose is 5 mg once daily in the evening
  - Up to 5 mg twice daily in adults, if needed
- Unlikely to be effective as an alternative for patients who did not have an adequate response to cetirizine
- Sedative effects are similar to those of other second-generation antihistamines
- Dose reductions are necessary in renal insufficiency

Loratidine

- A long-acting, selective H1 antihistamine
- Standard dose is 10 mg once daily for ages six years and older
  - Minimally sedating
  - May be increased up to 10 mg twice daily in adults, if needed
- Significant renal and/or hepatic insufficiency
  - Usual dose is administered every other day

Desloratadine

- Produces effects equivalent to loratadine at about one-half the dose
- For adults and children 12 years and older, the standard dose is 5 mg once daily
  - Up to 5 mg twice daily in adults, if needed
- Significant renal and/or hepatic insufficiency
  - Usual dose is administered every other day

Fexofenadine

- Minimally sedating
- Suggested dose is 180 mg daily for ages 12 years and older
  - Up to twice daily in adults, if needed
  - Best taken without food – not with fruit juices
- Significant renal and/or hepatic insufficiency
  - Usual dose is administered every other day

First-generation agents

- Includes diphenyhydramine, chlorpheniramine, hydroxyzine, and others
- Agents are lipophilic and readily cross the blood-brain barrier
  - Cause sedating and anticholinergic side effects that may be dose-limiting in some patients
  - Significant sedation and impairment of performance (eg, fine motor skills, driving skills, and reaction times) occur in more than 20 percent of patients
  - Anticholinergic side effects include dry mouth, diplopia, blurred vision, urinary retention, or vaginal dryness - advise patients
- Low risk patients may find a sedating H1 antihistamine at bedtime helpful, especially when combined with a nonsedating H1 antihistamine during the day

Pregnancy and Lactating Women

- Pregnancy
  - May be treated initially with loratidine (10 mg once daily) or cetirizine (10 mg once daily)
  - There are reassuring human data for each of these drugs in a large number of pregnant patients
  - Chlorpheniramine
    - First-generation agent
    - 4 mg orally every four to six hours may also be safely used in pregnancy

Pregnancy and Lactating Women

- Lactation
  - May be treated with either cetirizine or loratadine (both are dosed at 10 mg once daily), which are minimally excreted in breast milk and should not cause sedation or poor feeding in the infant

H2 Antihistamines

- Very few data examining the use of H2 antihistamines for acute urticarial
  - One randomized trial of 91 adults presenting to an emergency department with acute allergic reactions. Subjects received 50 mg IV diphenyhydramine with either placebo or 50 mg IV ranitidine. At two hours, the number of patients in whom urticaria had resolved was statistically greater in the ranitidine group compared with the placebo group (4 of 29 and 11 of 24, respectively)
- H2 antihistamines include ranitidine, nizatidine, famotidine, and cimetidine, although caution should be used with cimetidine, since it can increase levels of other drugs
- Studies of the use of H2 antihistamines in chronic urticaria are conflicting and are reviewed elsewhere

Glucocorticoids

- Do not appear to be necessary for isolated urticaria
- A brief course (usually a week or less) of systemic glucocorticoids may be added to antihistamine therapy for patients with prominent angioedema or if symptoms persist beyond a few days
- In the largest study, the addition of prednisone to levocetirizine did not speed resolution of acute urticaria

Carpal tunnel syndrome

Nonsurgical Treatment Options

- Wrist splinting
- Glucocorticoid injection
- Oral glucocorticoids

Oral Glucocorticoids

- Appear to be effective for short-term improvement of Carpal Tunnel Syndrome (CTS) symptoms
- A 2003 Systematic Review
  - Two weeks of oral glucocorticoid treatment was associated with a statistically significant reduction in symptoms as measured by the GSS compared with placebo
  - One trial showed that four weeks of oral glucocorticoid treatment was associated with a statistically significant reduction in symptoms

Prednisone

- There are only limited data regarding the long-term effect of oral glucocorticoids for CTS treatment
  - Clinical trial evaluated two to four weeks of treatment with up to 20 mg per day of oral prednisolone, patients showed clinical and electrodiagnostic improvement for up to 12 months
    - Study did not have a placebo control group
  - Another clinical trial, 60 patients treated with oral prednisolone 25 mg daily for 10 days showed symptomatic improvement in CTS for up to eight weeks
    - Oral prednisolone was less effective than glucocorticoid injection
  - A placebo-controlled trial that evaluated 60 patients with mild to moderate CTS, two weeks of oral prednisone (20 mg daily for seven days, followed by 10 mg per day for seven days) was associated with significant improvement in symptoms as measured by the GSS, but the benefit gradually waned over eight weeks of observation

Fibromyalgia

Fibromyalgia

- A chronic pain disorder that is challenging to treat
- Nonpharmacologic and pharmacologic therapies
- Generally respond best to a multidisciplinary, individualized treatment program
  - Physical medicine, rehabilitation, and mental health specialists

Fibromyalgia

- Treatment directed at reducing the major symptoms of this disorder
  - Chronic widespread pain, fatigue, insomnia, and cognitive dysfunction
- Exercise
  - Significant benefit for pain and function, and may be of benefit for sleep
  - Recommend a minimum of 30 minutes of aerobic exercise three times per week in a range near target heart rate
  - Low-impact aerobic activities such as fast walking, biking, swimming, or water aerobics are most successful
    - Type and intensity of the program should be individualized and based upon patient preference/presence of any other cardiovascular, pulmonary, or musculoskeletal comorbidities

Fibromyalgia

- Medications
  - Factors to consider include fatigue, insomnia, and depression; potential adverse effects; patient tolerance of individual medications; and patient cost and regulatory limitations on prescription choice

Initial Treatment

- Tricyclic antidepressants - effective, widely available, and far less costly
  - Amitriptyline 5 to 10 mg one to three hours before bedtime
    - Dose may be limited by adverse side effects, especially in older adults
      - Mild to moderate symptoms - cyclobenzaprine (alternate)
    - Side effects are common (even at low doses)
      - Dry mouth, constipation, fluid retention, weight gain, grogginess, and difficulty concentrating
  - Desipramine 5 to 10 mg one to three hours before bedtime
    - Possible alternative' fewer anticholinergic side effects
  - Increase dose by 5 mg at two-week intervals
  - Final dose should be set by the patient, based upon efficacy and side effects, always keeping the dose as low as possible (20 to 30 mg is adequate for many patients)
  - Do not exceed a dose of 75 mg in most patients

Inadequate response to TCAs

- Does not respond to trials of low-dose tricyclics or who have intolerable side effects
  - Recommend a trial of pregabalin, duloxetine, or milnacipran, depending upon the patient's symptoms
- Duloxetine
  - Use in the morning at breakfast
  - Starting dose: 20 to 30 mg/day
    - Gradual increase to recommended dose of 60 mg/day
- Several trials pain severity was significantly reduced

Inadequate response to TCAs

- Milnacipran
  - An alternative to duloxetine in patients with severe fatigue in addition to pain
  - Start 12.5 mg each morning
    - Gradually titrate as tolerated to 50 mg twice daily (up to to 100 mg twice daily may be needed)
  - Greater efficacy for pain relief, improvement in global wellbeing, and physical function
  - Nausea and headache were the most frequent adverse effects

Inadequate response to TCAs

- Venlafaxine
  - Not recommended
  - More limited data regarding the efficacy of venlafaxine for fibromyalgia, compared with duloxetine or milnacipran
  - Withdrawal symptoms may more readily occur because of the short half-life of this medication if a dose is missed

Anticonvulsants

- Beneficial for the treatment of fibromyalgia and other conditions causing chronic pain
- Pregabalin and gabapentin are the only anticonvulsants for which there is convincing evidence of benefit in fibromyalgia
  - Analgesic effects by blocking the release of various neurotransmitters

Anticonvulsants

- Pregabalin
  - Starting dose: 25 to 50 mg at bedtime before increasing as tolerated
    - Recommended dose: 300 to 450 mg/day
    - Some patients may respond to lower doses, i.e. 100 to 300 mg/day
  - Efficacy and safety of has been evaluated in randomized trials and in systematic reviews and meta-analyses
- Gabapentin
  - Alternative; evidence is more limited
  - Starting dose: 100 mg at bedtime before increasing as tolerated
    - Recommended dose: 1200 to 2400 mg/day

Irritable bowel syndrome

Irritable Bowel Syndrome (IBS)

- Affects 8-20% of US population
  - 14-24% of women
- Classic gastrointestinal symptoms are chronic or recurrent abdominal and/or discomfort and diarrhea and/or constipation
- Among women, IBS is most prevalent during menstruation years, with symptoms being most severe during postovulatory and premenstrual phases
- Studies have found that over 50% of patients seeing a gynecologist for lower abdominal pain have IBS

Irritable Bowel Syndrome (IBS)

- Women with IBS are more likely than women with other bowel symptoms to ultimately be diagnosed with endometriosis
- Women with IBS are three times more likely to receive a hysterectomy than women without IBS
- Many individuals with IBS also suffer from non-GI symptoms
  - 2/3 of IBS patients report rheumatological symptoms (skin rashes, muscle contraction headache and myalgias)
  - Fibromyalgia syndrome occurs in up to 60% of IBS patients; up to 70% of patients with a diagnosis of FM have symptoms of IBS

Irritable Bowel Syndrome (IBS)

- Initial therapy is lifestyle and dietary modifications
  - Exclude gas-producing foods
  - Diet low in fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs)
  - Lactose and gluten avoidance
  - Fiber
  - Physical activity
- There is insufficient evidence to support routine food allergy testing in patients with IBS

Irritable Bowel Syndrome (IBS)

- In patients with IBS with constipation (IBS-C) who have failed a trial of soluble fiber
  - Polyethylene glycol (PEG)
- Persistent constipation despite treatment with PEG
  - Lubiprostone or Linaclotide

Osmotic laxatives (PEG)

- Inexpensive and widely available
- Fewer side effects as compared with other osmotic laxatives
- Initial
  - 17 g of powder dissolved in 8 ounces of water once daily and titrate up or down (to a maximum of 34 g daily) to effect
  - Side effects of bloating and abdominal discomfort limit the use of PEG
- Treatment with PEG improves constipation but not abdominal pain
  - Randomized trials in children have demonstrated that PEG has greater or similar efficacy to lactulose and magnesium hydroxide in treating constipation, but in adults, PEG has not been directly compared with other osmotic laxatives

Lubiprostone

- Enhances chloride-rich intestinal fluid secretion
- Used in women with IBS with persistent constipation despite PEG
- Used for treatment of IBS-C in women 18 years and older
- The approved dose for IBS-C (8 micrograms twice daily) is lower than the approved dose for treatment of chronic idiopathic constipation

Lubiprostone

- Has not been directly compared with other treatment options for IBS-C
  - Long term safety remains to be established
- The efficacy has been demonstrated in two randomized trials in which the majority of patients were women
  - Placebo response in the studies was far lower than expected

Linaclotide

- Stimulates intestinal fluid secretion and transit
- Long-term risks of linaclotide are unknown
  - Role in the treatment of IBS-C is limited to patients with persistent constipation despite treatment with PEG
- Used for treatment of IBS-C at a dose of 290 micrograms daily
- The efficacy in the treatment of IBS-C has been demonstrated in two randomized controlled phase III trials

Irritable Bowel Syndrome (IBS)

- In patients with diarrhea-predominant symptoms, antidiarrheals are the initial treatment and use bile acid sequestrants as second-line therapy

Loperamide

- The only antidiarrheal agent evaluated in randomized trials in patients with IBS-D
- Systematic review included three controlled trials
  - All three trials were of short duration, enrolled a small number of patients, and had methodological limitations
  - Overall, the trials suggested that loperamide was more effective than placebo for treatment of diarrhea by decreasing stool frequency and consistency, but not for the symptoms of bloating, abdominal discomfort, or global IBS symptoms

Loperamide

- Initial: 4 mg, followed by 2 mg after each loose stool (maximum: 16 mg/day)
- Maintenance dose should be slowly titrated downward to minimum required to control symptoms (usual: 4 to 8 mg/day as a single dose or in divided doses; maximum: 16 mg/day)
- If clinical improvement is not observed after at least 10 days of treatment with 16 mg/day, symptoms are unlikely to be controlled by further administration
- Treatment may be continued if diarrhea cannot be adequately controlled with diet or other therapy

Eluxadoline

- Approved for treatment of IBS-D, however, additional studies are needed to identify subpopulations of patient with IBS-D who may best benefit from eluxadoline
- Current FDA guidelines also cite any history of biliary disorders, pancreatitis, severe liver impairment (Child-Pugh Class C) and heavy alcohol use as contraindications to the drug
- Contraindicated in patients who do not have a gallbladder due to a high incidence of severe acute pancreatitis noted in post-marketing surveillance

Eluxadoline

- Initial: 100 mg twice daily; may decrease to 75 mg twice daily in patients unable to tolerate the 100 mg dose
- Dosage adjustment for concomitant therapy
  - Coadministration of OATP1B1 inhibitors (i.e. cyclosporine, gemfibrozil, atazanavir, lopinavir, ritonavir, saquinavir, tipranavir, rifampin, eltrombopag) 75 mg twice daily

Bile acid sequestrants

- Use is limited by associated gastrointestinal side effects including bloating, flatulence, abdominal discomfort, and constipation
- Up to 50 percent of patients with functional diarrhea and IBS-D have bile acid malabsorption. Bile acids cause diarrhea by stimulating colonic secretion and motility
- In a randomized trial in which 24 patients with IBS-D were assigned to treatment with colesevelam (1.875 g twice daily) or placebo, treatment with colesevelam increased colonic transit time with an average delay of four hours as compared with placebo

5-hydroxytryptamine (serotonin) 3 receptor antagonists

- Alosetron
  - Approved for the treatment of severe diarrhea-predominant IBS in female patients whose symptoms have lasted for six months and who have failed to respond to all other conventional treatment
  - Modulates visceral afferent activity from the gastrointestinal tract, thereby decreasing colonic motility and secretion, and may improve abdominal pain
  - In a meta-analysis that included 14 randomized trials, treatment with 5HT-3 antagonists, alosetron or cilansetron resulted in a global improvement in IBS symptoms and relief of abdominal pain and discomfort

5-hydroxytryptamine (serotonin) 3 receptor antagonists

- Side effects of ischemic colitis and complications of severe constipation led to the withdrawal of alosetron from the market in the United States.
- Following evaluation of postmarketing data, alosetron is now available in the United States but can be prescribed under restricted conditions, at a lower starting dose than previously approved, and by physicians enrolled in the alosetron prescribing program.
- In a randomized crossover trial in which 120 patients with IBS-D were assigned to treatment with ondanestron (starting dose 4 mg) or placebo for five weeks, ondansetron significantly improved stool consistency, frequency, and urgency but was not associated with a significant improvement in abdominal pain

Antispasmodics

- Initiate antispasmodics only if the abdominal pain persists despite treatment of constipation
- In patients with persistent abdominal pain despite antispasmodics, we recommend a trial of antidepressants.
- In patients with moderate to severe IBS without constipation, particularly those with bloating, who have failed to respond to other therapies, we suggest a two-week trial of rifaximin

Antispasmodic agents

- Administered on an as-needed basis and/or in anticipation of stressors with known exacerbating effects
- Provide short-term relief in symptoms of abdominal pain in patients with IBS, but their long-term efficacy has not been established

Antispasmodic agents

- Typical doses include:
  - Dicyclomine 20 mg orally four times daily as needed
  - Hyoscyamine 0.125 to 0.25 mg orally or sublingually three to four times daily as needed
  - Sustained release hyoscyamine 0.375 to 0.75 mg orally every 12 hours

Antidepressants

- Have analgesic properties independent of their mood improving effects
- Tricyclic antidepressants (TCAs), via their anticholinergic properties, also slow intestinal transit time, which may provide benefit in diarrhea-predominant IBS
- Given their effect on intestinal transit, TCAs should be used cautiously in patients with constipation

Antidepressants

- For the treatment of abdominal pain in IBS, antidepressants should be started at low doses
- Initial dose should be adjusted based upon tolerance and response
- Due to the delayed onset of action of antidepressants, three to four weeks of therapy should be attempted before increasing the dose

Dosages

- Amitriptyline, nortriptyline, and imipramine can be started at a dose of 10 to 25 mg at bedtime
- Desipramine should be started at a dose of 12.5 to 25 mg at bedtime. If the patient is intolerant of one TCA, another may be tried
- As compared with TCAs, there is less published experience with other antidepressants such as selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), and results of the few published trials (mainly with SSRIs) have been inconsistent

Antibiotics

- Not routinely recommended in all patients with IBS
  - Patients with moderate to severe IBS without constipation, particularly those with bloating, who have failed to respond to other therapies (eg, a diet low in fermentable oligo-, di-, and monosaccharides and polyols [FODMAPs], antispasmodics, and TCAs) recommend a two-week trial of rifaximin
- Rifaximin
  - Oral: 550 mg 3 times daily for 14 days
  - May be retreated up to 2 times with the same dosing regimen if symptoms recur

Probiotics

- Not routinely recommended in patients with IBS
- Associated with an improvement in symptoms
- The magnitude of benefit and the most effective species and strain are uncertain

Migraine

Migraines

- Data from the 2011 National Health Interview Survey
  - Sample of 15,322 adults aged 20 or older
  - Highest prevalence among ages 18-59, 17.1% of women and 5.6% of men
  - More common among whites than blacks and among those with lower income levels
  - Over half (53.7%) endorsed severe impairment or need for bedrest during their attacks

Migraines

- Mild to moderate attacks not associated with vomiting or severe nausea
  - Simple analgesics (NSAIDs, acetaminophen) or combination analgesics are first choice agents
  - Effective, less expensive, and less likely to cause adverse effects than migraine-specific agents such as triptans or ergots
- Mild to moderate attacks are associated with severe nausea or vomiting
  - An oral or rectal antiemetic drug can be used in conjunction with simple or combination analgesics

Simple Analgesics

- Aspirin (650 to 1000 mg)
- Ibuprofen (400 to 1200 mg)
- Naproxen (750 to 1250 mg)
- Diclofenac (50 to 100 mg)
- Diclofenac epolamine (65 mg)
- Tolfenamic acid (200 mg)
- Dexketoprofen (50 mg)
- Parenteral ketolorac (30 mg intravenous or 60 mg intramuscular) was effective for acute migraine in comparison with other agents, including intranasal sumatriptan, IV prochlorperaezine, IV chlorpromazine, and IV dihyroergotamine combined with metocloperamide

Simple Analgesics

- Although the data are limited, benefit may be seen with indomethacin as abortive therapy for migraine. It is a potent NSAID that is also available in suppository form, which may be helpful for nauseated patients
- There are no studies comparing the relative efficacy of different NSAIDs

Migraines

- Moderate to severe attacks not associated with vomiting or severe nausea
  - Oral migraine-specific agents are first-line, including oral triptans and the combination of sumatriptan-naproxen
- Moderate to severe migraine attacks complicated by vomiting or severe nausea
  - Severe migraine attacks can be treated with nonoral migraine-specific medications including subcutaneous sumatriptan, nasal sumatriptan and zolmitriptan, nonoral antiemetic agents, and parenteral dihydroergotamine

Sumatriptan-naproxen

- Oral: Sumatriptan 85 mg/naproxen 500 mg
  - If a satisfactory response has not been obtained at 2 hours, a second dose may be administered (maximum: Sumatriptan 170 mg/naproxen 1,000 mg in 24 hours)
- The safety of treating an average of >5 migraine headaches in a 30-day period has not been established

Sumtriptan

- *Oral*
  - A single dose of 25 mg, 50 mg, or 100 mg (taken with fluids)
  - If a satisfactory response has not been obtained at 2 hours, a second dose may be administered
  - The total daily dose should not exceed 200 mg
  - Results from clinical trials show that initial doses of 50 mg and 100 mg are more effective than doses of 25 mg, and that 100 mg doses do not provide a greater effect than 50 mg and may have increased incidence of side effects. The safety of treating an average of>4 headaches in a 30-day period have not been established
- *Intranasal*
  - A single dose of 22 mg (11 mg nosepiece in each nostril)
  - If headache has not resolved within 2 hours or returns, the dose may be repeated once ≥2 hours after the first dose (maximum: 44 mg [4 nosepieces] per 24 hours or 22 mg [2 nosepieces] and one dose of another sumatriptan product [separated by ≥2 hours] per 24 hours)
  - The safety of treating an average of>4 headaches in a 30-day period has not been established

Sumatriptan

- Intranasal
  - A single dose of 5 mg, 10 mg, or 20 mg administered in one nostril
    - A 10 mg dose may be achieved by administering a single 5 mg dose in each nostril
  - If headache has not resolved within 2 hours or returns, the dose may be repeated once after 2 hours, not to exceed a total daily dose of 40 mg
  - In clinical trials, a greater number of patients responded to initial doses of 20 mg versus 5 or 10 mg. The safety of treating an average of>4 headaches in a 30-day period has not been established

Sumatriptan

- SubQ
  - Alsuma: 6 mg; Imitrex: 6 mg, if side effects are dose limiting, use lower doses 1 to 5 mg
  - Sumavel: 6 mg, if side effects are dose limiting, use 4 mg
    - May repeat if needed ≥1 hour after initial dose (maximum: 6 mg per dose; two 6 mg injections per 24-hour period; or maximum cumulative dose of 12 mg in 24 hours, separated by at least 1 hour)
    - However, controlled clinical trials have failed to document a benefit with administration of a second 6 mg dose in nonresponders
  - Zembrace: 3 mg
    - May repeat if needed (up to 4 injections) with each injection separated by at least 1 hour (may also give following the dose of another sumatriptan product if separated by at least 1 hour)
    - Do not exceed 12 mg in 24 hours

Migraines

- Variable attacks
  - Attacks vary in severity, time of onset, and association with vomiting and nausea
  - May require two or more options for self-management of acute migraine, including oral medications for mild to moderate attacks and non-oral medications (i.e. subcutaneous or nasal triptans) for more severe attacks or those associated with vomiting or severe nausea

Migraines

- Emergency settings
  - Generally have unusually severe attacks, and in many cases their customary acute migraine treatment has failed to provide relief
  - Treatment in the emergency department or other urgent care settings follows the same principles as treatment in nonurgent settings

Migraines

- The following are reasonable options, with evidence of efficacy from randomized trials:
  - Severe migraine accompanied by severe nausea or vomiting
    - Initial treatment: Sumatriptan 6mg SQ or a parenteral antiemetic (i.e. metoclopramide, prochlorperazine, or chlorpromazine)
      - Metoclopramide 10 mg IV
      - Prochlorperazine 10 mg IV or IM
      - Chlorpromazine 0.1 mg/kg IV to a total dose of 25mg IV
    - When giving parenteral antiemetics for migraine, recommend adjunct use of diphenhydramine (12.5 to 25 mg IV every hour up to two doses) to prevent akathisia and other dystonic reactions
    - A more aggressive alternative option, based upon the results of one clinical trial, is high-dose metoclopramide (20 mg IV every 30 minutes up to four doses) given with diphenhydramine

Migraines

- Alternative treatment of intractable severe migraine in the ED
  - Dihydroergotamine (DHE 45) 1 mg IV combined with metoclopramide 10mg IV
    - Can be used if metoclopramide monotherapy is ineffective
  - Should not be used as monotherapy
  - Contraindicated in patients with ischemic vascular disease involving cardiac, cerebrovascular, or peripheral circulations
- Standard abortive therapies
  - Recommend adjunctive treatment with dexamethasone (10 t 25 mg IV or IM) to reduce the risk of early headache recurrence

Migraines - Pregnancy

- Treatment differs because of concerns about adverse fetal drug effects
- First-line therapy
  - Acetaminophen alone (1000 mg) or combination therapy
    - Acetaminophen 650 to 1000 mg and metoclopramide 10mg
    - Acetaminophen and codeine 30 mg
    - Butalbital-acetaminophen-caffeine
      - Caffeine dosages for migraine range from 40 to 50 mg; daily caffeine intake less than 200 mg
      - Butalbital should be limited to only four to five days per month and codeine to no more than nine days per month to avoid development of medication overuse headache
        - Prolonged use of butalbital or codeine near term can cause neonatal withdrawal in the neonate

Migraines - Pregnancy

- Second-line therapy
  - Aspirin or NSAIDS
    - Naproxen, ibuprofen, and ketorolac are safest in the second trimester
      - Limited and weak evidence – possible modest increase in miscarriage and some congenital defects in the first trimester
- Third-line therapy
  - Opioids
    - Habit-forming and can contribute to abuse and chronic daily headaches
    - May worsen the nausea/vomiting and constipation associated with pregnancy
    - Potential for maternal addiction and neonatal withdrawal

Migraines - Pregnancy

- Triptans
  - For moderate to severe symptoms in patients who do not respond to other drugs
  - Highly effective; selectively vasoconstrict brain vessels
  - Other triptans can be used, but are less desirable because of a longer half-life
    - Sumatriptan 100 mg orally, 4 to 6 mg SQ, or 5 to 25 mg intranasally
    - Rizatriptan 5 to 10 mg
      - Repeat after 2 hours if significant relief is not attained; maximum: 30 mg/24 hours

Migraines - Pregnancy

- Drugs to reduce nausea and vomiting
  - Meclizine 25 mg orally
  - Diphenhydramine 25 to 50 mg orally
  - Promethazine 12.5 to 25 mg oral, per rectum, or intramuscularly
- Effective, but maternal dystonic reactions sometimes occur
  - Metoclopramide 10 mg IV, IM, or orally
  - Prochlorperazine 10 mg IV, IM, or orally or intravenously, intramuscularly, or orally) or chlorpromazine 25 to 50 mg intramuscularly
- As an alternative, ondansetron 4 to 8 mg orally or IV may be used to treat severe nausea and vomiting associated with severe migraine headaches

Migraines - Pregnancy

- Contraindications
  - Ergotamine – induce hypertonic uterine contractions and vasospasm/vasoconstriction
  - Isometheptene – no data for use in pregnancy

Migraines - Pregnancy

- Refractory migraine treatment
  - First-line therapy
    - IV hydration, antiemetic, and an intravenous opioid
    - Pretreatment with diphenyhydramine 12.5 mg is suggested to avoid akathisia
  - Second-line therapy
    - Triptan and droperidol (2.5 mg IV every 30 minutes up to three doses)
      - Droperidol associated with maternal QTc prolongation and the development of Torsades de pointes
  - Third-line therapy
    - Magnesium sulfate 1 or 2 mg IV over 10 to 15 minutes
      - No statistically significant benefit in relief from headache or need for rescue analgesic medications

Urinary tract infections

Urinary tract infections

- Women are at higher risk than men
- Selection of an antimicrobial regimen for acute uncomplicated cystitis depends on the risk of infection with a multidrug-resistant (MDR) isolate
  - Low Risk
    - Nitrofurantoin 100 mg orally twice daily for five days
    - Trimethoprim-sulfamethoxazole one double-strength tablet (160/800 mg) orally twice daily for three days
    - Fosfomycin 3 grams of powder mixed in water as a single oral dose
    - Pivmecillinam 400 mg orally twice daily for five to seven days
  - If any factors (such as allergies or concern for resistance) preclude use of the above first-line antimicrobials, oral beta-lactams (other than pivmecillinam) are appropriate options, and if beta-lactams cannot be used, a fluoroquinolone is reasonable

Urinary tract infections

- High risk
  - Empiric treatments
    - Nitrofurantoin 100 mg orally twice daily for five days
    - Fosfomycin 3 grams of powder mixed in water as a single oral dose
    - Pivmecillinam 400 mg orally twice daily for five to seven days
  - Symptomatic therapy
    - For severe dysuria, a urinary analgesic such as over-the-counter oral phenazopyridine three times daily as needed may be useful to relieve discomfort.
      - A two-day course for symptomatic response to antimicrobial therapy and minimize inflammation
      - Should not use chronically; may mask clinical symptoms

Disorders related to Infertility

Primary Ovarian Insufficiency

- Development of primary hypogonadism before the age of 40 years in women who have a normal karyotype
- Presenting symptoms are similar to those of menopause
- Considerations in the management of POI:
  - Estrogen-deficiency symptoms, emotional health, fertility, sexual function, bone health, cardiovascular health, and the risk for developing primary adrenal insufficiency (in women with autoimmune oophoritis)

Primary Ovarian Insufficiency

- Estrogen therapy
  - Estrogen replacement recommended
    - Limited data regarding advantages/disadvantages of different hormone regiments or about efficacy for cardiovascular disease prevention
- Hormone replacement should mimic normal ovarian function
  - Estradiol and micronized progesterone are bioidentical hormones
  - Optimal replacement depends on whether the patient presents with primary or secondary amenorrhea

Primary Ovarian Insufficiency

- Primary amenorrhea
  - Initial: Oral micronized estradiol 0.25 mg/day, or transdermal estradiol 14 mcg/day (the lowest available transdermal dose
    - Goal is to mimic gradual pubertal maturation
- Secondary amenorrhea
  - Initiate full replacement doses of estrogen
    - Transdermal estradiol (100 mcg daily) or an estradiol vaginal ring (100 mcg daily)
      - Dose is also roughly equivalent to 2 mg daily of oral micronized estradiol
      - Dose is higher than what is used for postmenopausal women and is based upon the average daily production of estradiol by the premenopausal ovary

Primary Ovarian Insufficiency

- Recommend transdermal or vaginal delivery of estrogen
  - More physiologic approaches
  - Lower risks of venous thromboembolism and gallbladder disease in older, postmenopausal women
  - For women who do not like or do not tolerate transdermal or vaginal estradiol, oral estradiol is perfectly acceptable
  - Routine monitoring of serum estradiol levels not needed
    - Start with suggested dosing and titrate to alleviate symptoms or use the lowest dose to preserve bone density in patients who experience side effects

Primary Ovarian Insufficiency

- Intact uterus
  - Prevent estrogen-induced endometrial hyperplasia and carcinoma
  - Micronized progesterone (MP) 200 mg per day for the first 12 days of the month

  OR
  - Oral medroxyprogesterone acetate (MPA) (10 mg daily for 12 days per calendar month)
    - Both progestin regimens improve bone mineral density

Primary Ovarian Insufficiency

- Alternative option: Oral contraceptive pill containing ethinyl estradiol and a progestin
  - Provides contraception should spontaneous ovarian activity resume
  - One small trial suggested that lower-dose, physiologic hormone therapy may be more beneficial for bone mineral density than higher-dose estrogen (an oral estrogen-progestin contraceptive)
- When estradiol-progestin hormone therapy is prescribed rather than contraceptive pills, a cyclic regimen that will induce regular monthly menses allows easier recognition of the 5 to 10 percent potential for a spontaneous and unexpected pregnancy
  - Encourage a menstrual calendar
  - Miss a menstrual period →Obtain a pregnancy test and stop the estrogen and progestin therapy, if positive test result

Primary Ovarian Insufficiency

- Abundant indirect evidence from postmenopausal women that hormone therapy would be effective for estrogen deficiency symptoms and bone health in women with POI
- ACOG recommends systemic hormone therapy until age 50 to 51 years to all women with POI (without contraindications) to manage estrogen deficiency symptoms, prevent long-term health risks associated with POI (osteoporosis, coronary heart disease, stroke, overall mortality, cognitive decline, and dementia), improve quality of life, and maintain sexual function (some women may need vaginal estrogen in addition to systemic estrogen)
  - Hormonal contraception options for those in whom pregnancy prevention is a priority
- Young women with POI differ from normally menopausal women in important ways with regard to the risk:benefit ratio of estradiol therapy.
  - In the absence of estradiol replacement, may be at greater risk for later coronary heart disease, overall mortality, cognitive decline, and dementia, presumably due to estradiol deficiency

BB is a 32-year-old female who presents with complaints of irregular menses. She is hirsute around the jaw line, her BMI is 32 kg/m^2, and her waist circumference is 40 inches (101.6 cm). A pelvic ultrasound reveals polycystic ovaries. Which of the following is most appropriate for BB?

A. A combination oral contraceptive containing ethinyl estradiol and drospirenone

B. A combination oral contraceptive containing ethinyl estradiol and levonorgestrel

C. Metformin 850 mg by mouth twice daily

D. Pioglitazone 15 mg by mouth daily

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In women with PCOS as a cause of anovulatory dysfunction, which of the following may result in improved menstrual irregularity and ovulatory function, reduced hirsutism, increased insulin sensitivity, and improved response to fertility treatments?

A. Metformin
B. Rosiglitazone
C. Smoking cessation
D. Weight loss

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A. Metformin
B. Rosiglitazone
C. Smoking cessation
D. Weight loss

Polycystic ovary syndrome (PCOS)

- An important cause of both menstrual irregularity and androgen excess in women
- The goals of therapy of women with PCOS include:
  - Amelioration of hyperandrogenic symptoms (hirsutism, acne, scalp hair loss)
  - Management of underlying metabolic abnormalities and reduction of risk factors for type 2 diabetes and cardiovascular disease
  - Prevention of endometrial hyperplasia and carcinoma, which may occur as a result of chronic anovulation
  - Contraception for those not pursuing pregnancy, as women with oligomenorrhea ovulate intermittently and unwanted pregnancy may occur
  - Ovulation induction for those pursuing pregnancy

Polycystic ovary syndrome (PCOS)

- Lifestyle changes – diet and exercise
- Oral contraceptives
  - Manage hyperandrogenism and menstrual dysfunction
  - Provide contraception
    - Use caution if prescribed to obese women over age 40 years due to increased risk of venous thromboembolism (VTE)
    - Oral estrogen-progestin
    - Cyclic progestin
      - Induce regular withdrawal uterine bleeding and reduce risk of endometrial hyperplasia
    - Progestin-only ("mini-pill") or a progestin-releasing IUD
      - Reduce risk of endometrial hyperplasia

Polycystic ovary syndrome (PCOS)

- Not pursuing pregnancy
  - Menstrual dysfunction
    - Combined estrogen-progestin contraceptives for menstrual dysfunction and endometrial protection
  - Androgen excess
  - Metabolic abnormalities
  - Depression/anxiety

Polycystic ovary syndrome (PCOS)

- Androgen excess
  - Hirsutism
    - Estrogen-progestin contraceptive
    - Antiandrogen is added after six months if the cosmetic response is suboptimal
      - Spirinolactone (off-label): 50 to 200 mg daily in 1 to 2 divided doses
      - Finasteride (off-label): 5 mg once daily or 2.5 mg once daily
        - In an analysis of four trials, the addition of an antiandrogen to an OC was slightly more effective than an OC alone
    - Gonadotropin-releasing hormone (GnRH) agonists are sometimes used to suppress ovarian androgen production
      - "Add-back" estrogen-progestin therapy is necessary to avoid bone loss and estrogen deficiency symptoms
      - Complex and costly

Polycystic ovary syndrome (PCOS)

- Metabolic abnormalities
  - Obesity – weight reduction
  - Insulin resistance/type 2 diabetes
  - Metabolic effects of OCs
    - Dyslipidemia
      - Exercise and weight loss
      - Pharmacotherapy
        - In a meta-analysis of four trials in 244 women randomly assigned to a statin (simvastatin or atorvastatin) or placebo for 6 to 12 months, statin therapy decreased serum low-density lipoprotein (LDL) and triglycerides, but had no effect on high-density lipoprotein (HDL), fasting insulin, or C-reactive protein. A small decrease in serum testosterone was observed, but there were no improvements in menstrual cycle regularity, ovulation, acne, hirsutism, or BMI
    - Obstructive sleep apnea
      - An important determinant of insulin resistance, glucose intolerance, and type 2 diabetes
    - Nonalcoholic steatohepatitis
      - Increased prevalence
        - Weight loss and metformin improve metabolic and hepatic function

Polycystic ovary syndrome (PCOS)

- Depression/anxiety
  - Women have impaired quality of life and higher rates of depression and anxiety
  - Safety of antidepressant therapy has not been established in women with anxiety or depression

Sexually transmitted infections (STIs)

Syphilis

- Early
  - Preferred: Penicillin G benzathine 2.4 million units IM once
  - Alternatives (choose one):
    - Doxycycline 100 mg orally twice daily for 14 days
    - Ceftriaxone 1 to 2 g daily IM or IV for 10 to 14 days
    - Tetracycline 500 mg orally four times daily for 14 days
    - Amoxicillin 3 g **plus** probenecid 500 mg, both given orally twice daily for 14 days

Syphilis

- Late
  - Preferred: Penicillin G benzathine 2.4 million units IM once weekly for three weeks
  - Alternatives (choose one):
    - Doxycycline 100 mg orally twice daily for four weeks
    - Ceftriaxone 2 g daily IM or IV for 10 to 14 days

N. gonorrhoeae

- Antibiotic resistance has rendered the treatment more complex with fewer options than in the past
- Uncomplicated
  - Ceftriaxone 250 mg intramuscular in a single dose PLUS Azithromycin 1 gram in a single oral dose
  - Alternate: Doxycycline 100 mg orally twice daily for seven days PLUS Ceftriaxone 250 mg intramuscular in a single dose
    - Reserved for patients allergic to or intolerant of azithromycin
- Alternate regimens should only be used if the preferred regimen is not available or precluded because of severe allergies or intolerance

N. gonorrhoeae

- Pregnant women
  - Uncomplicated gonorrheal infection should be treated with dual therapy
    - Ceftriaxone plus azithromycin
    - Doxycycline should be avoided during pregnancy
- If a severe IgE mediated allergy to cephalosporins, desensitization procedures should be employed prior to administration.
  - Alternate regimen if desensitization cannot be performed
    - Gentamicin plus azithromycin

C. trachomatis

- Goals of treatment are to:
  - Prevent complicated infections related to chlamydia and their sequelae
  - Decrease the risk of transmission to others
  - Attain resolution of symptoms
- Uncomplicated genital chlamydia infections include urethritis (men) and cervicitis (women)
  - Azithromycin 1 gram single-dose therapy with observed therapy
  - Doxycycline 100 mg twice daily for seven days
    - Delayed release doxycycline (200 mg daily for seven days) appears as effective as and better tolerated than twice-daily doxycycline but is more costly

Trichomonas

- Treatment is indicated for both symptomatic and asymptomatic women and men
- The 5-nitroimidazole drugs are the only class of drugs that provide curative therapy of trichomonas
  - A single 2 gram oral dose of either tinidazole or metronidazole
  - Alternative: Metronidazole 500 mg orally twice a day for seven days

Trichomonas

- Pregnant women
  - Symptomatic pregnant women with confirmed infection are treated
  - A single 2 gram oral dose of metronidazole
- Lactation
  - Breastfeeding women can be treated with the single 2 gram dose
  - Metronidazole is secreted in breast milk; infants receive metronidazole doses that are lower than those used to treat infections in infants

Vaginitis

Bacterial vaginosis

- Most common cause of abnormal vaginal discharge in reproductive-age women
- Treatment is aimed at relieving symptoms, although many women are asymptomatic

Bacterial vaginosis

- Non-pregnant women
  - Metronidazole 500 mg twice daily for seven days
  - Metronidazole single and multiday dosing options for vaginal gel
    - Multiday vaginal gel has similar efficacy to seven days of oral metronidazole
    - Single-dose treatment is superior to placebo gel
      - Not know if the single-day dose is as efficacious as the multiday oral or vagina treatments
    - No ETOH consumption during therapy and for one day after completion of therapy (for or vaginal therapy)
  - Clindamycin 2% cream vaginally for seven days
    - May be less effective than metronidazole, but a reasonable therapeutic choice
    - Alternative regimens not studies extensively and may have lower efficacy
      - Clindamycin 300 mg twice daily for seven days
      - Clindamycin 100 mg intravaginally once daily for three days
    - Clindamycin cream should be used concurrently with latex condoms

Bacterial vaginosis

- Tinidazole 1 gram orally once daily for five days
  - An alternative regimen if metronidazole and clindamycin are unavailable or not tolerated
    - More costly
    - Longer half-life than metronidazole and fewer side effects
- Secnidazole 2 gram oral dose
  - As effective as a seven-day course of 500 mg metronidazole administered orally twice daily, and was well tolerated
- Systemic reviews of trials of probiotics for treatment of BV have not found sufficient evidence for or against efficacy

Bacterial vaginosis

- Pregnant women
  - Metronidazole 500 mg orally twice daily for seven days
  - Metronidazole 250 mg orally three times daily for seven days
  - Clindamycin 300 mg orally twice daily for seven days
- Special considerations for clindamycin
  - Meta-analysis has not found any relationship between metronidazole exposure during the first trimester of pregnancy and birth defects
  - The CDC no longer discourage the use of metronidazole in the first trimester
  - Mutagenic in bacteria and carcinogenic in mice, but there is no evidence of harm in humans

Bacterial vaginosis

- Lactating women
  - Use of vaginal metronidazole has not been studied during breastfeeding
    - After vaginal administration, plasma levels are less than 2 percent of those after a 500 mg oral dose, so vaginal use of metronidazole during breastfeeding is unlikely to be of concern
  - Recommend interruption of breastfeeding during tinidazole or secnidazole treatment for three days after the last dose based on animal data (tinidazole only)

Candida vulvovaginitis

- Treatment is indicated for relief of symptoms
- Ten to 20 percent of reproductive-age women who harbor *Candida* species are asymptomatic; these women do not require therapy
- Criteria for uncomplicated infection include all of the following:
  - Sporadic, infrequent episodes (≤3 episodes/year)
  - Mild to moderate signs/symptoms
  - Probable infection with *Candida albicans*
  - Healthy, nonpregnant woman
  - Immunocompetent woman

Candida vulvovaginitis

- Uncomplicated criteria:
  - Sporadic, infrequent episodes (≤3 episodes/year)
  - Mild to moderate signs/symptoms
  - Probable infection with *Candida albicans*
  - Healthy, nonpregnant woman
  - Immunocompetent woman
- Fluconazole 150 gm single tablet
  - Usually respond to treatment within a couple of days
  - No medical contraindication to sexual intercourse during treatment, but it may be uncomfortable until inflammation improves
  - Treatment of sexual partners is not indicated

Candida vulvovaginitis

- Complicated criteria:
  - Severe signs/symptoms
  - *Candida* species other than *C. albicans*, particularly *C. glabrata*
  - *P*regnancy, poorly controlled diabetes, immunosuppression, debilitation
  - History of recurrent (≥3/year) culture-verified vulvovaginal candidiasis
- Fluconazole 150 mg orally for two to three sequential doses 72 hours apart, depending on the severity of infection

Candida vulvovaginitis

- If the patient prefers topical therapy, observational series report that complicated patients require 7 to 14 days of topical azole therapy rather than a one- to three-day course
- For severe *Candida* vulvar inflammation (vulvitis), low-potency topical corticosteroids can be applied to the vulva for 48 hours until the antifungals exert their effect

Candida vulvovaginitis

- Pregnant women
  - Symptomatic *Candida* vulvovaginitis
    - Apply a topical imidazole (clotrimazole or miconazole) vaginally for seven days rather than treatment with an oral azole because of potential risks with oral azole therapy in pregnancy
    - Treatment is primarily indicated for relief of symptoms
    - Not associated with adverse pregnancy outcomes

Recurrent vulvovaginal candidiasis

- Four or more episodes of symptomatic infection within one year
- Vaginal cultures should always be obtained to confirm the diagnosis and identify less common *Candida* species, if present
- Treatment
  - Fluconazole 150 mg once daily for 10 to 14 days, followed by 150 mg once weekly for 6 months

  or
  - Fluconazole 100 mg, 150 mg, or 200 mg every 72 hours (day 1, 4, and 7) for a total of 3 doses, then 100 mg, 150 mg, or 200 mg once weekly for 6 months

Gynecological Health

Vulvodynia

- A complex, multifactorial pain syndromes with varied etiologies and implied that treatment should be tailored to each individual based upon their clinical presentation
  - Behavior modification
  - Pelvic floor physical therapy
  - Psychological intervention
  - **Medication**
  - **Complementary and alternative treatments**
  - Surgery
  - Laser therapy

Vulvodynia

- Medication
  - Use in conjunction with behavior modification and psychological interventions
  - Numerous topical medications available
    - Few controlled trials to verify efficacy or determine superiority
    - Patient preferred due to low incidence of systemic side effects, ease of use, and ready availability
- First tier
  - Topical lidocaine ointment
    - Episodic use of lidocaine 2% or 5% ointment can mitigate the pain and discomfort associated vulvodynia, particularly prior to bothersome activities or intercourse
      - Recommend 5 percent lidocaine ointment to be applied to only the affected area as needed for symptom control after sex-play
  - Topical estrogen cream
    - Estradiol 0.01% cream or compounded estradiol 0.01% plus testosterone 0.05% to 0.1% cream applied at bedtime to the vulvar vestibule
      - Reduces symptoms in some women with vulvodynia and/or sexual pain
    - Recommend biweekly nighttime dosing of 0.5 g estradiol to the vagina (not just the vestibule) for signs or symptoms of intravaginal atrophy or women who experience deep dyspareunia related to dryness

Vulvodynia

- Second tier
  - Antidepressants
    - Tricyclic antidepressants
      - Most common TCAs used in the treatment of vulvodynia have been amitriptyline or nortriptyline starting at doses between 10 and 25 mg increasing by 10 mg every 7 to 10 days to an average of 50 to 75 mg per day
        - Maximum dose is 150 mg per day
        - Increased risk of sudden cardiac death for doses over 100 mg per day
    - Selective norepinephrine reuptake inhibitors
      - Duloxetine 20 mg oral dose daily and increase to 60 mg daily, if needed for symptom control
      - Milnacipran 50 mg oral dose twice a day, and increase to 100 mg twice a day as needed
        - Selection based on cost and availability
      - SNRIs are efficacious at treating neuropathic pain and typically have fewer side effects than tricyclic antidepressants

Vulvodynia

- Selective serotonin reuptake inhibitors (SSRI)
  - No controlled data on SSRIs in the treatment of vulvodynia
  - Generally not recommended in the treatment of other chronic neuropathic pain syndromes
- Anticonvulsants
  - Based on more than 40 years of data on anticonvulsants for the treatment of chronic pain
  - Gabapentin, pregabalin, and carbamazepine are FDA-approved
    - Gabapentin has been the most studied and utilized in the treatment of vulvodynia
    - Efficacy rates ranging from 50 to 80 percent in small observational studies and case reports
  - Gabapentin
    - Start at 100mg oral dose at bedtime; sleepiness is common side effect
      - At 3 to 4 days, increase dose to 100 mg orally three times a day
      - Able to tolerate the daytime dosing, increase to three divided doses of 300 mg or more per dose every 7 to 14 days
      - If drowsiness with daytime doses, titrate the single bedtime dose up to 300 mg, rather than the three times a day dosing regimen
    - Therapeutic: 100 mg to 3600 mg/day
    - Educate patients once they reach a therapeutic dose, they should be prepared to remain there for at least four to six weeks before assessing efficacy

Vulvodynia

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  - Therapeutic: 100 mg to 3600 mg/day
  - Educate patients once they reach a therapeutic dose, they should be prepared to remain there for at least four to six weeks before assessing efficacy
- Capsaicin cream
  - Expert panel of the 2015 International Consultation on Sexual Medicine advised the use of capsaicin only if other treatments had failed or as an alternative to surgery
  - The rationale for treatment with capsaicin is that women with vulvodynia have been found to have increased vanilloid receptors (VR1) in the peripheral terminals of nociceptor cells

Vulvodynia

- Third tier
  - Botulinum neurotoxin-A
    - High cost and temporary effect
    - Benefits typically last from 3 to 12 months
    - Used for the treatment of multiple chronic pain disorders
    - Deemed a reasonable treatment for vulvodynia; effect is far greater if the BoNT-A is injected into hypertonic pelvic floor muscles rather than into the vestibular ostium
  - Compounded products
    - Limited availability of compounding pharmacies and high cost
    - Gabapentin 4 to 10% topical preparations
      - Used in the treatment of vulvodynia (both localized and generalized) with good tolerability and low incidence of systemic effects
      - Generalized burning pain; prescribe gabapentin compounded in transdermal base to apply three times daily

Vulvodynia

- Compounded topical amitriptyline/ketamine or amitriptyline/baclofen creams
  - An option to avoid untoward side effects of oral tricyclic antidepressants such as fatigue, weight gain, constipation, and drying of mucous membranes
- Cromolyn
  - Topical cromolyn, 5 to 10% in a petrolatum base, helpful for primary symptom of vulvodynia is itching
- Vaginal prasterone (Intrarosa)
  - Used in the treatment of moderate to severe dyspareunia related to vulvar or vaginal atrophy of menopause
  - Efficacy is not yet known studied in women with genitourinary syndrome of menopause

Vulvodynia

- Complementary and alternative treatments
  - A benefit for chronic pain syndromes
  - Specific modalities reported to reduce vulvodynia symptoms include acupuncture, hypnosis, and transcutaneous electrical nerve stimulation

Which of the following medical therapies is considered a drug treatment of first choice for endometriosis?

A. Anastrozole (oral)
B. Danazol (vaginal)
C. Depot medroxyprogesterone (subcutaneous)
D. Nafarelin (nasal spray)
E. Naproxen (oral)

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D. Nafarelin (nasal spray)
E. Naproxen (oral)

Endometriosis

- Medical treatment options include nonsteroidal analgesics, hormonal contraceptives, gonadotropin-releasing hormone (GnRH) agonists, and aromatase inhibitors
- No data supporting one treatment or treatment combination over another
- Treatment choice based upon symptom severity, patient preferences, medication side effects, treatment efficacy, contraceptive needs, costs, and availability

NSAIDS

- First-line treatment for pelvic pain, including endometriosis-related pain
- No high-quality data regarding efficacy
- If pregnancy desired, avoid selective COX-2 inhibitors
  - Prevent or delay ovulation

Suggested nonsteroidal antiinflammatory drug (NSAID) doses in primary dysmenorrhea

Drug	Initial dose	Subsequent dose, as needed	Maximum dose per day in short-term use (≤3 days)
Propionic (phenylpropionic) acids			
Ibuprofen*	400 to 600 mg	400 to 600 mg every 4 to 6 hours	2400 mg
Naproxen base*	500 mg	250 mg every 6 to 8 hours	1250 mg
Naproxen sodium*	550 mg	275 every 4 to 8 hours	1375 mg
Flesoprofen	200 mg	200 mg every 4 to 6 hours	3200 mg
Ketoprofen	50 mg	25 to 50 mg every 4 to 8 hours	300 mg
Fenamates			
Mefenamic acid	500 mg	250 mg every 6 hours	1000 mg
Meclofenamate	100 mg	50 mg every 4 to 6 hours	400 mg
Acetic acids			
Indomethacin	25 mg	25 mg three times daily	150 mg
Tolmetin	400 mg	600 mg three times daily	1800 mg
Diclofenac	75 to 100 mg	50 mg three times daily	150 mg (100 mg beginning on day 2 in some countries)
Diadolac	600 mg	100 to 600 mg every 4 to 8 hours (immediate release)	1000 mg (immediate release)
Salicylates (nonacetylated)			
Diflunisal[†]	1000 mg	500 mg twice daily	1500 mg
Oxicams			
Meloxicam*	7.5 mg	7.5 mg once daily	15 mg
Piroxicam*	20 mg	10 to 20 mg once daily	20 mg

Estrogen-progestin contraceptives

- First-line treatment
- Can be used long-term, are well-tolerated, are relatively inexpensive and easy to use
- Provide contraception
- Decreased the risk of ovarian and endometrial cancers
- Combined estrogen-progestin treatments include combined oral contraceptive pills (COCs), transdermal patches, and vaginal rings
- Recommend starting with a COC containing 20 mcg of ethinyl estradiol given in a continuous dose fashion

Progestins

- For women unable to take or prefer to avoid combined estrogen-progestin contraceptives
  - Medroxyprogesterone acetate (MPA): SubQ: 104 mg every 3 months (every 12 to 14 weeks)
  - Norethindrone acetate: Oral: 5 mg/day for 14 days; increase at increments of 2.5 mg/day every 2 weeks to reach 15 mg/day; continue for 6 to 9 months or until breakthrough bleeding demands temporary termination

Gonadotropin-releasing hormone (GnRH) agonists

- Commonly used drug regimens with demonstrated efficacy
- Medication selection is driven by availability and cost
  - Leuprolide acetate 3.75 mg IM injection given monthly
  - Leuprolide acetate 11.25 mg IM injection every 3 months
  - Intranasal nafarelin acetate 200 mcg given twice daily
- Endometriosis-related pain is likely treated by the induction of amenorrhea and progressive endometrial atrophy

Gonadotropin-releasing hormone (GnRH) antagonists

- Suppress pituitary gonadotropin hormone production and create a hypoestrogenic state
- Effective immediately, do not cause an initial surge in luteinizing hormone and follicle stimulating hormone, and do not require 7 to 14 days for GnRH suppression
- Available in both oral and injectable forms
- Symptom relief and adverse events such as vasomotor phenomena, vaginal atrophy, and bone loss are also dose-dependent
- Provides a treatment option for women who do not respond to NSAIDs, estrogen-progestin contraceptives, or progestins
  - Easier to dose than GnRH agonists (oral versus intramuscular)
- Recommend Elagolix 150 mg once daily or 200 mg twice daily

Danazol

- Not commonly used because of androgenic side effects
- Side effects include acne, muscle cramps, edema, weight gain (5 percent of body weight), spotting, hirsutism, and voice deepening
- Mild disease
  - Initial: 200 to 400 mg/day in 2 divided doses; gradually titrate dosage downward to maintain amenorrhea; continue (uninterrupted) for 3 to 6 months (may extend up to 9 months). If symptoms recur following discontinuation, may reinitiate treatment
- Moderate-to-severe disease
  - Initial: 800 mg/day in 2 divided doses; gradually titrate dosage downward to maintain amenorrhea; continue (uninterrupted) for 3 to 6 months (may extend up to 9 months). If symptoms recur following discontinuation, may reinitiate treatment

Aromatase inhibitors

- For severe, refractory endometriosis-related pain
- Off-label
  - Appear to regulate local estrogen formation within the endometriotic lesions themselves, in addition to inhibiting estrogen production in the ovary, brain, and periphery (eg, adipose tissue)
    - Anastrozole (oral) 1 mg once daily
      - OR
    - Letrozole (oral) 2.5 mg once daily
  - Prescirbed in combination with a GnRH agonist or an oral estrogen-progestin contraceptive to suppress follicular development
- Disadvantages: bone loss (prolonged use) and ovarian follicular cyst development
- For women unable to use GnRH agonists or oral estrogen-progestin contraceptives
  - Norethindrone acetate (oral) 5 mg per day

Neuropathic pain treatments

- Offered to women who continue to have pain despite medical treatment options
- Nonopioid analgesic medications, opioids and adjuvants therapies include:
  - Nonopioid analgesic agents (i.e. aspirin, acetaminophen, NSAIDS, COX-2 inhibitors)
  - Tramadol
  - Opioids
  - Alpha 2 adrenergic agonists
  - Antidepressants (tricyclics and serotonin-norepinephrine reuptake inhibitors [SNRIs])
  - Antiepileptic drugs (gabapentin, pregabalin, and other anticonvulsants)
  - Muscle relaxants
  - N-methyl-d-aspartate (NMDA) receptor antagonists
  - Topical analgesic agents
- Using combinations of drugs that target different metabolic pathways may result in improved analgesia
  - Relatively few studies specifically evaluating combinations of drugs for chronic pain.
- Fewer side effects because lower doses of each drug can be used
- Treatment response differs between individuals, and no one approach is appropriate for all patients

Uterine fibroids

- Anecdotal data suggest medical therapy provides adequate symptom relief in some women, primarily in situations where bleeding is the dominant or only symptom
- In general, 75 percent of women get some improvement over one year of therapy, but long-term failure rates are high
- A systematic review observed that in trials where women were randomly assigned to oral medical therapy, almost 60 percent had undergone surgery by two years

Uterine fibroids

- Hormonal therapies
  - Some texts continue to suggest that estrogen-progestin contraceptive pills are contraindicated
  - Clinical experience suggests some women with heavy menstrual bleeding associated with leiomyomas respond to OC therapy
- Levonorgestrel-releasing intrauterine system
  - No randomized trials evaluating the use of levonorgestrel-releasing intrauterine system for the treatment of heavy menstrual bleeding related to uterine leiomyomas
  - Observational studies and systematic reviews have shown a reduction in uterine volume and bleeding, and an increase in hematocrit after placement of this IUS

Uterine fibroids

- Progestin implants, injections, and pills
  - Cause endometrial atrophy → provides relief of menstrual bleeding-related symptoms
  - Considered for treatment of mild symptoms, especially for women who need contraception
- Progesterone receptor modulators
  - Not approved by the US Food and Drug Administration (FDA) and available in the US

Gonadotropin-releasing hormone agonists

- Gonadotropin-releasing hormone agonists
  - Rapid rebound in symptoms and side effects
    - Primarily used as preoperative therapy
  - Approved for administration for 3 to 6 months prior to leiomyoma-related surgery in conjunction with iron supplementation to facilitate the procedure and enable correction of anemia
  - Severe hypoestrogenism - hot flashes, sleep disturbance, vaginal dryness, myalgias and arthralgias, and possible impairment of mood and cognition
  - Most serious complication - bone loss leading to osteoporosis after long-term (12+ months)

Gonadotropin-releasing hormone antagonists

- Gonadotropin-releasing hormone antagonists
  - Rapid onset of clinical effects without initial flare-up observed with GnRH agonists
  - In the United States, marketed at doses used for ovulation induction and long-acting preparations are not available
    - Daily injections required for treatment of uterine fibroids - cumbersome

Antifibrinolytic agents

- Antifibrinolytic agents
  - Useful in the treatment of idiopathic heavy menstrual bleeding
    - Not well studied
  - Tranexamic acid
    - Used worldwide
    - FDA-approved for the treatment of heavy menstrual bleeding
    - Oral: Lysteda: 1,300 mg 3 times daily (3,900 mg/day) for up to 5 days during monthly menstruation

Nonsteroidal antiinflammatory drugs

- Nonsteroidal antiinflammatory drugs
  - Have not been extensively studied
  - Do not appear to reduce blood loss in women with myomas
    - Decrease painful menses - useful in this population

Danazol

- Danazol and gestrinone
  - Effective treatment
  - Frequent side effects
  - Danazol
    - Progestin-like effects – induces amenorrhea
    - May control anemia; does not appear to reduce uterine volume
    - Side effects are common: weight gain, muscle cramps, decreased breast size, acne, hirsutism, oily skin, decreased high density lipoprotein levels, increased liver enzymes, hot flashes, mood changes, depression
  - Gestrinone
    - Not available in the US

KS is a 15-year-old female who presents to her family practitioner for follow-up after presenting with severe menstrual pain 6 months prior. At that time, she was prescribed a low-dose combined oral contraceptive pill continuously. Today, KS reports that her pain has not improved. Based on this information, which of the following options is most appropriate at this time?

A. Change current oral contraceptive to cyclic dosing.
B. Switch therapy to the levonorgestrel intrauterine system.
C. Switch therapy to subcutaneous leuprolide.
D. Add ibuprofen during menstrual cycles.
E. Refer for laparoscopic evaluation.

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Dysmenorrhea

- The presence of recurrent, crampy, lower abdominal pain occurring during menses and in the absence of demonstrable disease
  - Goal of treatment is to provide adequate relief of pain.
- Treatment
  - Self-care
  - **Drug therapy**
  - Tocolytics

Dysmenorrhea

- Best evidence for achieving pain relief of primary dysmenorrhea is based on randomized trials of drug therapies
  - Strong placebo effect in the first month of treatment; effects of placebo treatment appear to fade quickly
  - NSAIDs and hormonal contraceptives represent the mainstays of drug therapy

Dysmenorrhea

- Nonsteroidal antiinflammatory agents
  - Randomized trials consistently demonstrate NSAIDs effectively treat primary dysmenorrhea
    - Significantly more effective than placebo
  - COX-2 inhibitors can prevent or delay ovulation
- Hormonal contraception
  - Estrogen-progestin contraceptives suppress ovulation and cause the endometrium to become thin over time
  - Pills
    - Oral contraceptive pills can be given in monthly or extended cycles, or continuously
      - In randomized trials, extended or continuous administration provided better relief of menstrual symptoms than cyclic administration, but all regimens appeared effective for symptom relief
      - Cycle selection is determined by patient preference
      - If the conventional 21 days of medication/7 days of placebo oral contraceptive formulation do not provide sufficient relief of dysmenorrhea, change to a formulation with a reduced hormone-free-interval (eg, a 24/4 formulation) or an extended cycle formulation.

Suggested nonsteroidal antiinflammatory drug (NSAID) doses in primary dysmenorrhea

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Etodolac	400 mg	200 to 400 mg every 6 to 8 hours (immediate release)	1000 mg (immediate release)
Salicylates (nonacetylated)			
Diflunisal[¶]	1000 mg	500 mg twice daily	1500 mg
Oxicams			
Meloxicam[Δ]	7.5 mg	7.5 mg once daily	15 mg
Piroxicam	20 mg	10 to 20 mg once daily	20 mg

Dysmenorrhea

- Transdermal patch, vaginal ring
  - Few trials have evaluated their efficacy for treatment of primary dysmenorrhea or compared them to other therapies
    - Among ring users, the proportion of participants reporting moderate or severe dysmenorrhea decreased from 17.4 percent (baseline prevalence) to 5.9 percent; among oral contraception users, dysmenorrhea decreased from 19 percent (baseline prevalence) to 6.4 percent
    - In a randomized trial designed to evaluate contraceptive efficacy and cycle control in contraceptive patch and oral contraceptive users, dysmenorrhea was slightly more common among women assigned to the patch (13.3 versus 9.6 percent)

Dysmenorrhea

- Progestin-only methods
  - Induces the endometrial atrophy that leads to relief of dysmenorrhea, progestin-only contraceptives may be an effective treatment
    - Have not been studied as extensively as estrogen-progestin contraceptives
  - Injectable contraception
    - Depot medroxyprogesterone
      - 50% of users become amenorrheic after one year due to endometrial atrophy
      - Return of fertility may be delayed after discontinuation
        - Choose a different method if the woman wants to become pregnant within the next one or two years

Dysmenorrhea

- Intrauterine contraception
  - Levonorgestrel-releasing intrauterine device that releases 20 mcg daily
  - Nulliparity is not a contraindication to IUD placement
- Implantable contraception
  - Single-rod etonogestrel-releasing contraceptive was associated with a 68 percent reduction of dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia in women with histologically proven endometriosis
- Tocolytics
  - Primary dysmenorrhea is caused by excessive uterine muscle contractions
    - Effective treatment includes agents that block uterine contractility
      - Nifedipine (single oral dose of 20 to 40 mg)

Prenatal Care

Management of common disorders

A 29-year-old woman who is at week 37 is complaining of constipation for the past 3 days despite increasing her dietary fiber and water intake. Which of the following recommendations is *not* appropriate?

A. Polyethylene glycol
B. Castor oil
C. Bisacodyl
D. Senna
E. None of the above is appropriate

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C. Bisacodyl
D. Senna
E. None of the above is appropriate

Which of the following is *not* an appropriate choice for treatment of acute cystitis in a 32-year-old woman at 27 weeks of gestation:

A. Doxycycline
B. Cephalexin
C. Sulfamethoxazole/trimethoprim
D. Nitrofurantoin
E. Amoxicillin/clavulanate

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D. Nitrofurantoin
E. Amoxicillin/clavulanate

Strategies to lower infant exposure to medications through breast milk include all of the following *except*:

A. Recommend a drug with a shorter half-life
B. Recommend a drug with a low bioavailability
C. Recommend a highly protein bound drug
D. Recommend a drug considered safe for use in an infant
E. Recommend a highly lipophilic drug

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D. Recommend a drug considered safe for use in an infant
E. Recommend a highly lipophilic drug

Nausea and vomiting

- Dietary changes and trigger avoidance
- Pharmacotherapy
  - Pyridoxine is 10 to 25 mg orally every six to eight hours; the maximum treatment dose suggested for pregnant women is 200 mg/day
    - Has a good safety profile with minimal side effects, and is easy to obtain
  - When pyridoxine treatment of nausea fails to improve symptoms
    - Doxylamine-pyridoxine
      - Initial: Two extended-release tablets (each tablet contains doxylamine 10 mg and pyridoxine 10 mg) at bedtime
      - Increase to four tablets over the course of the day as needed for more severe nausea (one tablet in the morning, one tablet in the afternoon, two tablets at bedtime).
      - An extended-release tablet containing 20 mg of doxylamine succinate and 20 mg of pyridoxine is also available

Vomiting

- If doxylamine and pyridoxine are ineffective, discontinue before starting a different antihistamine
  - Antihistamines most extensively studies for treatment of nausea and vomiting of pregnancy are:
    - Dimenhydrinate 25 to 50 mg orally every four to six hours, as needed
      - Dimenhydrinate 50 mg is administered intravenously over 20 minutes or 50 to 100 mg is administered rectally (where available) every four to six hours, as needed; the total dose should not exceed 400 mg/day
      - Total dose of should not exceed 200 mg/day
    - Meclizine 25 mg orally every four to six hours, as needed
      - Human data of an association between facial clefts and meclizine have been mixed, but three large studies did not show an increased risk of malformations
    - Diphenhydramine 25 to 50 mg orally every four to six hours, as needed

Gastroesophageal reflux disease

- Most antacids are considered safe in pregnancy and are compatible with breastfeeding
  - Avoid antacids containing sodium bicarbonate and magnesium trisilicate
  - Sucralfate 1 g orally three times daily
    - Likely safe during pregnancy and lactation because it is poorly absorbed

Constipation

- Preferred treatment
  - Increase dietary fiber and fluids or using bulk-forming laxatives
- Refractory cases
  - Occasional use of magnesium hydroxide, lactulose, or bisacodyl is probably not harmful
    - A good safety profile
    - Lactulose and bisacodyl are minimally absorbed.
    - Castor oil can stimulate uterine contractions
    - Excessive use of mineral oil can interfere with absorption of fat soluble vitamins – generally avoid

Hemorrhoids

- Approximately 30 to 40 percent of pregnant women
- Exacerbated by constipation
- Medical management
  - Local application of anti-inflammatory, antipruritic, and local anesthetic preparations

Rhinitis

- First-line therapy
  - Intranasal cromolyn sodium for mild allergic rhinitis in pregnancy
    - Excellent safety profile
    - Intranasal cromolyn one spray per nostril up to six times daily

Difficulty sleeping

- Do not recommend sleep medication for pregnant women

Diarrhea

- Loperamide
  - Oral: Initial: 4 mg, followed by 2 mg after each loose stool (maximum: 16 mg/day)
  - Not teratogenic in animal studies
  - Human data are conflicting
- Antibiotic therapy rarely needed since illness is usually self-limited and most often viral in etiology

References

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