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METABOLIC SYNDROME

Goal

To review the pathophysiology and clinical relevance for using niacin to treat the metabolic syndrome.

Objectives

After reviewing this article, the reader should be able to:

1. describe the pathophysiology of the metabolic syndrome and the alterations commonly described in serum lipids and lipoproteins;
2. identify the criteria used by the NCEP ATP III for the diagnosis and treatment of metabolic dyslipidemia;
3. understand the rationale for using niacin in patients with the metabolic syndrome;
4. differentiate between the various formulations of niacin in terms of metabolism, adverse effects, and cost.

Test Questions

1. Which one of the following is *not* a common alteration seen in serum lipids or lipoproteins in patients with the metabolic syndrome?
 - (a) low HDL-C
 - (b) high LDL-C
 - (c) elevated triglycerides
 - (d) small, dense LDL-C particles
 - (e) elevated non-HDL-C
2. Which of the following statements concerning the metabolic syndrome is *false*?
 - (a) An estimated 24% (~47 million) of US adults aged 20–70 years have the metabolic syndrome.
 - (b) Prevalence increases dramatically with age.
 - (c) Prevalence is higher among African American women and Mexican Americans.
 - (d) The presence of metabolic syndrome increases the risk of developing diabetes by more than sixfold.
 - (e) In one study, subjects with the metabolic syndrome defined by NCEP ATP III criteria were 4.2 times more likely to die of CHD than those without the syndrome.
3. A clustering of risk factors, including abdominal obesity (waist circumference >40 inches in men, >35 inches in women), hypertriglyceridemia (>150 mg/dL), low HDL-C (<40 mg/dL in men, <50 mg/dL in women), hypertension ($\geq 135/80$ mm Hg), insulin resistance, and hyperglycemia (fasting blood glucose ≥ 110 mg/dL) act synergistically to increase cardiovascular risk. The NCEP ATP III diagnosis criteria for the metabolic syndrome is the presence of:
 - (a) any of the above risk factors.
 - (b) any 2 of the above risk factors.
 - (c) any 3 of the above risk factors.
 - (d) any 4 of the above risk factors.
 - (e) all 5 of the above risk factors.
4. In the HATS, the greatest reduction in stenosis progression was seen in patients randomized to receive:
 - (a) placebo.
 - (b) niacin plus simvastatin.
 - (c) antioxidant vitamins alone.
 - (d) niacin/simvastatin plus vitamins.
 - (e) niacin alone.
5. Of the 160 patients in HATS, what percent of patients had the metabolic syndrome?
 - (a) 12%
 - (b) 24%
 - (c) 36%
 - (d) 48%
 - (e) 60%
6. Which of the following statements concerning the VA-HIT is *true*?
 - (a) Gemfibrozil reduced the risk of the primary endpoint (nonfatal MI or coronary death) by 42% relative to placebo.
 - (b) In a subsequent analysis, the clinical benefit of gemfibrozil correlated most strongly with the change in non-HDL-C.
 - (c) The incidence of CHD events was predicted by the achieved LDL-C, but was unrelated to triglyceride levels.
 - (d) Almost all of the subjects had either diabetes or hyperinsulinemia, and many were obese.
 - (e) This was the first major trial to show that reducing triglycerides and increasing HDL-C without significantly affecting LDL-C significantly reduces cardiovascular events.
7. Which of the following statements concerning small, dense LDL-C particles is *false*?
 - (a) are not particularly susceptible to oxidation
 - (b) may cause an increased expression of cell-adhesion molecules
 - (c) cholesterol core is depleted and the apolipoprotein B/lipid ratio is increased
 - (d) are part of a lipid triad known as atherogenic dyslipidemia
 - (e) are less buoyant than larger LDL-C particles
8. According to NCEP ATP III, treatment of the metabolic syndrome starts with:
 - (a) fish oils.
 - (b) plant stanols.
 - (c) niacin.
 - (d) fibrate.
 - (e) weight reduction and increased physical activity.
9. A patient with coronary disease who meets criteria for the metabolic syndrome should have a non-HDL-C level below:
 - (a) 100 mg/dL.
 - (b) 130 mg/dL.
 - (c) 160 mg/dL.
 - (d) 190 mg/dL.
 - (e) 200 mg/dL.
10. Which of the following medications are available as a fixed-dose combination product?
 - (a) niacin plus pravastatin
 - (b) niacin extended-release plus lovastatin

- (c) ezetimibe plus simvastatin
- (d) niacin extended-release plus simvastatin
- (e) ezetimibe plus lovastatin

11. Which of the following statements concerning niacin is false?

- (a) Niacin inhibits fatty acid release from fat cells and inhibits fatty acid and triglyceride production in liver cells.
- (b) Niacin reduces the uptake of HDL-apolipoprotein A1 particles by the liver without affecting uptake of HDL esters, thus increasing circulating levels of HDL particles and improving the efficiency of reverse cholesterol transport between HDL particles and vascular tissue.
- (c) Niacin is an attractive choice for patients with atherogenic dyslipidemia because it increases HDL particles and HDL-C levels, lowers triglycerides, and increases LDL particle size.
- (d) Niacin IR is usually completely absorbed within 3–4 hours; therefore, it quickly saturates the high-affinity, low-capacity metabolic pathway.
- (e) Niacin SR products are not FDA approved for treating dyslipidemia.

12. Which of the following statements concerning niacin ER is false?

- (a) Niacin ER was developed as a once-daily formulation to be taken at bedtime, with the goal of reducing the incidence of flushing without increasing the risk of hepatotoxicity.
- (b) It has an absorption rate of 8–12 hours, intermediate to niacin IR and SR, and therefore balances metabolism more evenly over the 2 pathways.
- (c) In clinical studies, 4–9% of patients discontinued niacin ER therapy due to flushing.
- (d) Because niacin ER is taken once daily, patient adherence is likely to be improved over IR formulations taken 3 times daily.
- (e) Niacin ER is one of 3 long-acting niacin products approved by the FDA for dyslipidemia.

13. Which of the following statements concerning the ADMIT is false?

- (a) Niacin IR at doses to 3000 mg/day for up to 60 weeks increased HDL-C by 29% and reduced triglycerides and LDL-C by 23% and 8%, respectively.
- (b) Glucose levels increased by 8.7 mg/dL, and glycosylated levels were unchanged from baseline but differed from placebo by 0.3% ($p = 0.04$).
- (c) Although increases in fasting blood glucose levels were seen, they returned to baseline by study's end, in part due to adjustments in hypoglycemic therapy.
- (d) Results suggest that niacin can be used safely in virtually all patients with diabetes.
- (e) ADMIT is 1 of several recent randomized trials demonstrating that

niacin can be used in patients with diabetes.

14. Which of the following statements concerning the Coronary Drug Project is true?

- (a) It is still the largest trial to date to evaluate the long-term effects of niacin in patients with CHD.
- (b) After 5 years of follow-up, niacin significantly reduced the risk of nonfatal MI by 11% relative to placebo ($p < 0.05$).
- (c) Flushing was the most common adverse event, reported by 10% of niacin-treated patients.
- (d) A significant number of patients developed serious hepatotoxicity on niacin compared with placebo-treated patients.
- (e) The benefits of niacin in nonfatal MI and total mortality were similar regardless of baseline glucose levels, including patients with diabetes and impaired fasting glucose.

15. Which of the following statements concerning the cost-effectiveness of treating patients with the metabolic syndrome is false?

- (a) There are limited data on the cost-effectiveness of treating patients with the metabolic syndrome.
- (b) VA-HIT offers some insight since obesity, diabetes, and hyperinsulinemia were prevalent in this study, suggesting that many had the metabolic syndrome and gemfibrozil was shown to be cost-effective.
- (c) Based on average wholesale price for a 30-day supply, niacin IR is less expensive than niacin ER, but the cost implications of increased adverse effects and assumed discontinuations have not been evaluated in clinical studies.
- (d) Gemfibrozil appears to be more cost-effective than niacin in raising HDL-C.
- (e) Based on clinical trial data of statin therapy, it is cost-effective to intervene in patients with CHD or diabetes, as well as in anyone with an annual CHD risk $>1\%$.

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TERIPARATIDE

Goal

To review the pharmacology, toxicology, pharmacokinetics, pharmacodynamics, efficacy, safety, therapeutic controversies, and dosing and administration of teriparatide. The practicing pharmacist is provided with the current clinical trial data available and formulary placement recommendations for teriparatide that will aid in the proper care and treatment of patients with osteoporosis.

Objectives

After review of this article, the reader should be able to:

1. describe the pharmacology, toxicology, pharmacokinetics, and pharmacodynamics of teriparatide therapy;
2. apply appropriate dosing and administration strategies for teriparatide therapy;
3. determine which patients are appropriate candidates for teriparatide therapy.

Test Questions

1. Which of the following agents is considered to be an anabolic agent for treatment of osteoporosis?

- (a) risedronate
- (b) salmon calcitonin
- (c) teriparatide
- (d) Both a and c are correct.
- (e) Both b and c are correct.

2. Teriparatide is indicated for:

- (a) glucocorticoid-induced osteoporosis.
- (b) postmenopausal women with a high risk of fracture.
- (c) men with osteoporosis.
- (d) All of the above are correct.
- (e) Both b and c are correct.

3. Which of the following statements is true?

- (a) Teriparatide does not bind to PTH receptors with the same affinity as endogenous PTH.
- (b) Teriparatide's pharmacologic actions are similar to those of endogenous PTH except that teriparatide does not stimulate syntheses of vitamin D.
- (c) Teriparatide does not alter serum calcium concentrations as does endogenous PTH.
- (d) Teriparatide appears to work by similar mechanisms of action as endogenous PTH.
- (e) Teriparatide differs from endogenous PTH in all of its pharmacologic actions.

4. Which statement best describes teriparatide's pharmacologic activity?

- (a) Daily injections result in new bone formation by favoring osteoclastic activity over osteoblastic activity.
- (b) Daily injections result in new bone formation by favoring osteoblastic activity over osteoclastic activity.
- (c) Continuous infusions result in new bone formation by favoring osteoclastic activity over osteoblastic activity.
- (d) Continuous infusions result in new bone formation by favoring osteoblastic activity over osteoclastic activity.
- (e) Both continuous infusions and daily injections result in new bone formation by favoring osteoclastic activity over osteoblastic activity.

5. An important finding of great concern in animal studies using teriparatide was:

- (a) loss of cortical bone.
- (b) increase in fracture risk.

- (c) osteosarcoma.
(d) hypercalcemia.
(e) gain in trabecular bone.
6. When do peak elevations in serum calcium concentrations occur following a therapeutic dose of teriparatide?
(a) 0.5–1 hour
(b) 1–2 hours
(c) 4–6 hours
(d) 8–10 hours
(e) 16–24 hours
7. Pharmacodynamic effects of teriparatide include elevations of all of the following *except*:
(a) urinary calcium excretion.
(b) serum calcium levels.
(c) urinary deoxyribonucleic acid levels.
(d) serum 25-hydroxyvitamin D levels.
(e) bone-specific alkaline phosphatase levels.
8. Based on clinical trials, which of the following statements regarding teriparatide therapy in postmenopausal women is *true*?
(a) Teriparatide reduced the rate of vertebral fracture but not hip fracture.
(b) Teriparatide reduced the rate of hip fracture but not vertebral fracture.
(c) Teriparatide reduced the rate of both hip and vertebral fractures.
(d) Teriparatide did not affect the fracture rate, but significantly increased bone density.
(e) Teriparatide did not affect the fracture rate, but significantly decreased vertebral pain.
9. A patient recently started on teriparatide calls you complaining of muscle weakness, nausea, constipation, and fatigue. She is asking what she should do about these symptoms. Which of the following is the *most appropriate response* to this patient's complaints?
(a) These adverse effects may be secondary to hypercalcemia and could be serious. She should contact her physician immediately.
(b) These adverse effects should be expected and may fade over time.
(c) These adverse effects are unlikely due to teriparatide therapy but may be another medication that she is taking.
(d) These adverse effects may be secondary to hypercalcemia. They are unlikely to be serious, and the patient should do nothing.
(e) These adverse effects are likely due to the woman's supplemental calcium, and she should cut the calcium dose by half.
10. The black box warning in the approved labeling for teriparatide regards which of the following?
(a) increased incidence of osteomalacia in rats
(b) increased incidence of significant hypercalcemia in clinical trials
(c) increased incidence of hypoparathyroidism in rats
(d) increased incidence of hypophosphatemia in clinical trials
(e) increased incidence of osteosarcomas in rats
11. A 68-year-old woman is being started on teriparatide therapy. The patient has a history of congestive heart failure that is well controlled with digoxin 0.125 mg/day. The physician asks whether there is a problem with digoxin and teriparatide therapy when used together. Which of the following is the *most appropriate response*?
(a) Teriparatide therapy is contraindicated in patients taking digoxin. Continue digoxin and choose another therapy for her osteoporosis.
(b) Caution should be used in patients receiving teriparatide and digoxin concomitantly, but the combination has not been shown to be detrimental in healthy volunteers. Continue digoxin and begin teriparatide.
(c) Change the digoxin to another agent so the woman can start teriparatide therapy.
(d) There are no potential interactions between teriparatide and digoxin.
(e) No data are available regarding concomitant digoxin and teriparatide therapy.
12. The recommended dose of teriparatide in this patient is:
(a) 10 µg/day.
(b) 20 µg/day.
(c) 40 µg/day.
(d) 80 µg/day.
(e) 100 µg/day.
13. For how long should the patient be treated with teriparatide?
(a) up to 6 months
(b) up to 12 months
(c) up to 18 months
(d) up to 24 months
(e) up to 36 months
14. A patient on teriparatide is planning a trip to Europe. What is the *best explanation* for how she should transport her teriparatide pen injection device?
(a) She can keep it out of the refrigerator for up to 48 hours; therefore, no special precautions are needed.
(b) She should freeze it prior to traveling so it will defrost by the time she gets to her final destination.
(c) She should use the cooler bag provided with her starter kit to store the pen.
(d) She should not travel so far from home while on teriparatide.
(e) She should keep the pen device in a pressurized compartment on the airplane during flight.
15. A patient states that he has drug left in the pen device after 28 days of teriparatide therapy. He confirms that he has been taking a dose every day. The patient wants to know what to do with the remaining drug. The *best response* is to:
(a) ensure the patient knows how to set the pen device to receive the proper daily dose.
(b) finish all of the remaining drug in the pen device so as not to waste medication.
(c) discard any remaining medication after 28 days of using the pen device.
(d) Both a and b are correct.
(e) Both a and c are correct.

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ATYPICAL ANTIPSYCHOTICS FOR SCHIZOPHRENIA

Goal

To review the evidence for selecting an atypical antipsychotic agent for management of schizophrenia.

Objectives

After reviewing this article, the reader should be able to:

- compare the atypical antipsychotic agents with respect to efficacy;
- compare the unique toxicity profiles of the atypical antipsychotic agents;
- identify limitations of the current literature that compares atypical antipsychotics for management of schizophrenia;
- select the most appropriate atypical antipsychotic for a given clinical scenario.

Test Questions

- Which of the following statements regarding antipsychotic-induced hyperglycemia is *true*?
(a) Olanzapine causes more hyperglycemia than other antipsychotics.
(b) Risperidone has not been associated with hyperglycemia.
(c) Ziprasidone is more likely than other antipsychotics to cause hyperglycemia.
(d) There is no difference between antipsychotics causing hyperglycemia.
(e) More research on antipsychotic-induced hyperglycemia is needed to determine the relative risk for hyperglycemia among antipsychotics.
- A 36-year-old woman is being started on olanzapine for the treatment of schizophrenia. What patient counseling points are important to cover

when dispensing this prescription for the first time?

- (a) possibility of weight gain
- (b) case reports of hyperglycemia associated with this medication
- (c) case reports of diabetes associated with this medication
- (d) potential to cause movement disorders
- (e) All of the above are correct.

3. Based on indirect comparisons of atypical antipsychotics, which of the following statements about antipsychotic-induced weight gain is true?

- (a) Quetiapine may be associated with weight gain less frequently than other atypical antipsychotics.
- (b) Risperidone may be associated with weight gain more frequently than other atypical antipsychotics.
- (c) Olanzapine may be associated with weight gain more frequently than other atypical antipsychotics.
- (d) Ziprasidone may be associated with weight gain more frequently than other atypical antipsychotics.
- (e) Aripiprazole may be associated with weight gain more frequently than other atypical antipsychotics.

4. Which of the following combinations would not cause potentially significant pharmacokinetic drug interactions?

- (a) olanzapine and fluvoxamine
- (b) quetiapine and paroxetine
- (c) ziprasidone and carbamazepine
- (d) aripiprazole and paroxetine
- (e) risperidone and fluoxetine

5. In the Tran et al.¹⁸ study:

- (a) significantly more patients taking olanzapine completed the study compared with patients on risperidone.
- (b) significantly more patients taking olanzapine experienced EPS compared with patients on risperidone.
- (c) significantly more patients taking olanzapine experienced a greater change in the PANSS score compared with patients taking risperidone.
- (d) patients on olanzapine experienced a significantly larger mean change in the PANSS score than those on risperidone.
- (e) patients on olanzapine experienced a clinically significant improvement in negative symptoms compared with patients on risperidone.

6. In the Conley and Mahmoud²¹ study:

- (a) significantly more patients taking risperidone completed the study than patients taking olanzapine.
- (b) significantly more patients taking risperidone experienced EPS than patients taking olanzapine.

- (c) significantly more patients taking risperidone experienced a greater change in the PANSS score than patients taking olanzapine.
- (d) patients taking risperidone experienced a significantly larger mean change in the PANSS score than patients taking olanzapine.
- (e) patients taking risperidone experienced a statistically significant improvement in positive symptoms and anxiety compared with those taking olanzapine.

7. Which of the following most likely contributed to the differences seen in the results of the Conley and Mahmoud²¹ and Tran et al.¹⁸ studies?

- (a) differences in dosing regimens
- (b) differences in attrition rates
- (c) differences in adherence rates
- (d) differences in study funding
- (e) differences in study duration

8. Based on published studies that directly compare risperidone and olanzapine, we can conclude that:

- (a) olanzapine is more effective than risperidone for controlling both positive and negative symptoms.
- (b) risperidone is more effective than olanzapine for controlling positive symptoms.
- (c) available data do not suggest any difference in efficacy between these 2 agents.
- (d) risperidone induces more EPS than olanzapine.
- (e) olanzapine induces more weight gain than risperidone.

9. The economic analysis authored by Edgell et al.²⁶ suggests that olanzapine reduced overall medical costs compared with risperidone. This conclusion:

- (a) was based on results of the Conley and Mahmoud²¹ study.
- (b) was from a patient perspective.
- (c) may be limited due to the low doses of olanzapine used in the study.
- (d) may be limited due to the high doses of risperidone used in the study.
- (e) is generalizable to the majority of patients with schizophrenia.

10. Studies that indirectly compare atypical antipsychotics for schizophrenia can most appropriately be used to:

- (a) form hypotheses for future research directions.
- (b) draw conclusions regarding an agent's efficacy or toxicity.
- (c) choose an antipsychotic for a patient based upon efficacy.
- (d) make formulary decisions.
- (e) None of the above is correct.

11. The meta-analysis authored by Davis et al.²⁷:

- (a) only compared atypical antipsychotics directly.

- (b) only compared atypical antipsychotics with conventional agents.
- (c) included only published data.
- (d) found that risperidone was more effective than aripiprazole.
- (e) found that there may be a difference in efficacy among the atypical antipsychotics compared with conventional agents, which needs to be clarified further.

12. Limitations of studies comparing olanzapine and risperidone for treatment of schizophrenia include:

- (a) excessive doses of risperidone.
- (b) high attrition rates.
- (c) small sample size.
- (d) short duration.
- (e) All of the above are correct.

13. The most efficient way to compare several therapeutic agents for efficacy and toxicity is:

- (a) open-label study.
- (b) randomized head-to-head trial comparing active treatments.
- (c) randomized nonblind study.
- (d) meta-analysis of randomized placebo-controlled studies.
- (e) None of the above is correct.

14. A 42-year-old woman is receiving quetiapine for schizophrenia. Increasing doses have not led to control of her symptoms. She has been treated with loxapine and zuclopenthixol in the past, which have both induced dystonic reactions. Which of the following would be most appropriate for this patient?

- (a) risperidone
- (b) ziprasidone
- (c) clozapine
- (d) olanzapine
- (e) All of the above would be appropriate.

15. A 52-year-old man has a history of nonadherence with his schizophrenia therapy. He is currently admitted to the hospital and refusing to take ziprasidone 40 mg orally twice daily. When adherent, he has experienced relief of his schizophrenia symptoms with olanzapine, risperidone, and ziprasidone in the past. He has not been previously treated with aripiprazole or quetiapine. Which of the following may be most appropriate for this patient?

- (a) Continue with ziprasidone twice daily.
- (b) Change to olanzapine orally dissolving tablet once daily.
- (c) Change to risperidone liquid once daily.
- (d) Change to aripiprazole once daily.
- (e) Change to quetiapine once daily.