MANAGING SIDE EFFECTS OF COMMON MEDICATIONS

Side Effects and Interactions of Common Medications in Primary Care

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Introduction: drug-related issues more common and more problematic in elderly than in nonelderly; 2011 study — used National Electronic Injury Surveillance System data to look at hospital visits for drug-related issues; >100,000 hospitalizations recorded over 2 yr of study; most hospitalizations occurred among individuals ≥80 yr of age; two-thirds of hospitalizations related to unintentional overdose; medications responsible for most hospitalizations included 1) warfarin (Coumadin), 2) insulin, 3) oral hypoglycemic agents, 4) oral antiplatelet agents, and 5) digoxin; 3 of these medications not included in Beer’s criteria 2012 iteration lists 53 medications or medication classes to avoid; 3 classes include medications to avoid due to side-effect profile, medications to avoid in older adults with specific diseases, and medications to be used with caution in older adults (ie, risks may outweigh benefits); criteria mostly evidence based; among Beers medication classes, anticholinergics and sedatives most problematic in elderly; 53-item list may be cumbersome to use in practice

Drug burden index: simplified for everyday use; assigns number from 1 to 3 based on degree of burden (with 3 indicating highest burden); takes into account anticholinergic and sedative burden of medications, cumulative exposure to these medications, and impact on physical and mental functioning; also takes into account minimum recommended daily dose

Anticholinergics and sedatives: anticholinergic effects of medications — include precipitation of acute angle-closure glaucoma, urinary retention, nausea, vomiting, decline in cognitive functioning, dry mouth, and tachycardia; drugs with anticholinergic effects — include tricyclic antidepressants (anticholinergic burden of 3), furosemide (Lasix), and nifedipine; drugs with anticholinergic and sedating effects — include first-generation antihistamines (but not second-generation antihistamines); drugs with sedating effects — include zolpidem (Ambien); eszopiclone (Lunesta) recommended over zolpidem and chemically related to zolpidem; eszopiclone approved for daily use, whereas zolpidem should be used no more than 3 times/wk and for no longer than 2 wk

Other high-risk medications: include warfarin and insulin; oral hypoglycemic agents — metformin not recommended in patients ≥80 yr of age due to increased risk for lactic acidosis; exercise caution when prescribing sulfonylureas; oral antiplatelet agents — monitor to ensure that appropriate doses taken; antihypertensive agents — avoid atenolol, which has anticholinergic effect

Recommendations: avoid polypharmacy (ie, >5 medications); consider new symptoms in elderly patients as possibly drug related; avoid cascades (ie, prescribing new medication to treat side effect of existing medication, in turn leading to additional side effects); adjust medications for renal insufficiency; attempt nondrug approaches

Herbal medicine: ≤75% of elderly use complementary and alternative medicine (CAM); CAM use highest in most educated and wealthiest individuals; less regulated than prescription medication; survey — 60% of respondents did not inform their physician about use of herbal supplements (main reason being physician’s failure to ask); 88% believed that manufacturer should provide safety information; 60% unaware that herbal preparations not well regulated

Sympathomimetic agents: ephedra — banned in 2004; increases metabolic rate; used in weight-loss products; bitter orange — replaced ephedra in weight-loss products; synephrine active ingredient (similar to phenylephrine and ephedra); associated with serious cardiac side effects; banned by National Collegiate Athletic Association; increases incidence of elevated blood pressure and heart rate when combined with caffeine (to potentiate weight loss)

Indian ayurvedic herbal preparations: may contain impurities; heavy metal toxicity commonly reported

Ginseng and licorice: instances of overdose common; action of licorice similar to that of aldosterone (increased blood pressure, decreased potassium, and salt and water retention), which inhibits effects of antihypertensive medications; ginseng associated with Stevens-Johnson syndrome and insomnia

Interactions with other drugs: most common issue with herbal preparations; warfarin — number 1 drug for interactions with herbal preparations; interacts with coenzyme Q10 (antioxidant), cranberries (used to treat urinary tract infection), saw palmetto (used to treat benign prostatic hypertrophy), feverfew (used to treat colds), garlic (used to lower cholesterol), green tea (antioxidant), and ginger (antiemetic); St John’s wort — has serotoninergic properties (associated with serotonin syndrome when combined with other agents, particularly antidepressants); black cohosh — used to treat menopausal symptoms; associated with liver toxicity; evening primrose oil — anticancer agent; reportedly interacts with seizure medications; saw palmetto — associated with

Educational Objectives

The goal of this program is to prevent adverse outcomes associated with common medications and improve management of metformin-induced lactic acidosis. After hearing and assimilating this program, the clinician will be better able to:

1. Choose appropriate medications for elderly patients.
2. Counsel patients about potential drug interactions with herbal supplements.
3. Evaluate the association between angiotensin-converting enzyme inhibitors and serum creatinine levels.
4. Explain the mechanism by which metformin causes lactic acidosis.
5. Identify the risk factors for metformin-associated lactic acidosis.

Faculty Disclosure

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failure of oral contraceptives; goldenseal — used to treat colds; reportedly interacts with antipsychotic agents

Drug interaction checker: available online; patient handouts listing interactions and potential side effects available from National Center for Complementary and Alternative Medicine Surgery: patients advised to stop all herbal preparations ≥2 wk before surgery

Antihypertensive agents

Ankle swelling: associated with vasodilative effect of dihydropyridine (DHP)-type calcium channel blockers (CCBs; eg, amiodopine, nifedipine); addition of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) recommended (eg, amiodopine and benazepril [Lotrel]; speaker cautions against combination of ACE inhibitor or ARB and diuretic, which may increase risk for acute renal failure); patients may also switch to non-DHP CCB (either verapamil type [associated with constipation] or diltiazem type [probably best tolerated and associated with less edema and constipation])

Hyperkalemia: associated with spironolactone and ACE inhibitors; spironolactone — hyperkalemia can present within first month of use; monitoring of serum potassium recommended; ACE inhibitors — risk for hyperkalemia increased in patients with underlying renal disease or volume depletion

Hypokalemia: associated with diuretics; incidence and degree of hypokalemia and hypernatremia higher with chlorthalidone than with hydrochlorothiazide (rate of hospitalization with chlorothalidone 3%); vigilance recommended; measure serum potassium 1 to 2 wk after starting chlorthalidone or after increasing dose

Increased levels of serum creatinine (SCR): associated with initiation of ACE inhibitors; not usually worrisome; caused by mechanism of action on arteriole in kidney; initial increase of 10% to 20% expected; reduce dose or discontinue if 50% decline in renal function observed (ie, increase of 0.5 mg/dL if initial SCR <2 mg/dL; increase of 1.0 mg/dL if initial SCR >2 mg/dL); 50% decline in renal function more common if patient has underlying kidney disease, >55 yr of age, or taking nonsteroidal anti-inflammatory drugs (NSAIDs)

Statins: liver function — present recommendation to check liver function tests upon initiation and on as-needed basis; data show that rate of elevated liver transaminase 0.4%; liver toxicity uncommon and dose related; review by Journal of American Geriatric Society found that overall benefit appeared to outweigh risk, even in patients >85 yr of age (based on Cochrane review showing benefit for primary prevention and dose-related benefit for secondary prevention); diabetes — statins associated with increased risk of 0.5%, but risk outweighed by reduction in mortality

NSAIDs and gastrointestinal (GI) toxicity: etodolac (Lodine) least toxic to GI tract; ibuprofen second least toxic to GI tract; ketorolac — highly potent and highly toxic to GI tract, therefore do not use for >7 days per course; effective in patients who cannot take narcotics; naproxen — long acting (12 hr) Proton pump inhibitors: more effective than misoprostol (Cyotec) at managing GI side effects; nonresponse rate for relieving GI side effects 10%; use lowest effective dose for shortest period of time; take with meals; avoid other medications that may compound GI toxicity

NSAIDs and cardiovascular (CV) toxicity: increased CV risk can occur in first month of use; naproxen has lowest CV risk; etodolac has high risk; evidence-based review found that low-dose aspirin associated with decreased risk for CV disease in patients on long-term therapy with NSAIDs

Weight-loss agents

Phentermine and topiramate (Qsymia): most effective preparation for weight loss and maintenance of weight loss; phentermine sympathomimetic (use with fenfluramine associated with CV toxicity); topiramate antiseizure agent; highly fetotoxic (only available through restricted access; proof of contraceptive use and negative pregnancy test required); associated with some CV toxicity (significant elevation of heart rate); not recommended in overweight patients with CV issues

Olistat: Xenical (prescription) or Alli (over the counter); technically safest weight-loss agent; taken with meals; prevents absorption of fat; side effects include diarrhea and upset stomach; can result in decreased absorption of fat-soluble vitamins, but not documented in clinical setting; use of multivitamin recommended

Lorcaserin (Belviq): associated with inhibition of serotonin; appetite suppressant; best-tolerated side effects; nausea most common side effect (reason for discontinued use in 30%-40% of cases); risk for serotonin syndrome possible if combined with serotonin-active drugs

Naltrexone and bupropion (Contrave): naltrexone (opioid antagonist) potentiates effect of bupropion (appetite suppressant); weight loss double that of orlistat; not a controlled substance

Liraglutide (Victoza): approved for diabetes and weight loss; associated with thyroid C-cell hyperplasia in mice

Metformin: associated weight loss (5 lb); only antidiabetic agent to specifically decrease morbidity and mortality in overweight patients; top choice for overweight patients <80 yr of age who meet SCR restrictions

Duration of use: each agent has its own guidelines (typically 1-2 yr), but discontinue if ≥5% of body weight not lost in 12 wk

Suggested Reading


Metformin: Friend or Foe?

Steven C. Borkan, MD, Associate Professor of Medicine, Boston University School of Medicine, Boston, MA

Introduction: metformin (eg, Fortamet, Glucophage, Glumetza) highly effective biguanide agent for treatment of type 2 diabetes; typical dose 500 to 1000 mg twice daily; maximum dose 2500 mg/day; mechanism of action — decreases intestinal absorption of glucose, increases cellular glucose uptake by increasing body’s sensitivity to insulin, and reduces hepatic breakdown of glycogen; metformin 90% to 100% renally excreted

Metformin-associated lactic acidosis (MALA): although 2006 Cochran analysis concluded that metformin does not increase risk for lactic acidosis (if prescribed under study conditions), case reports suggest that MALA not uncommon; accumulation of metformin causing lactic acidosis — accumulation
of metformin inhibits mitochondrial respiratory chain, specifically complex I; anaerobic metabolism then takes place, which results in reduced hepatic gluconeogenesis from lactate and increased pyruvate (substrate for lactate); side effects of metformin may explain why some patients predisposed to volume depletion; patients can develop anorexia, nausea, vomiting, diarrhea, and abdominal pain even if metformin at nontoxic levels; these side effects predispose individuals to acute kidney injury, particularly those with chronic kidney disease (CKD), because renal failure of any severity plus volume compromise lowers tolerance; any further reduction in renal perfusion compromising glomerular filtration rate (GFR) lends itself to accumulation of metformin and potential toxicity; metformin black-box warning — lactic acidosis rare, but risk of mortality 50%; lactic acidosis often occurs with renal impairment; insults decreasing GFR progressively increase risk for lactic acidosis; summary — look for situations in which drop in GFR likely to occur, and hold metformin in those situations

Management of metformin toxicity: hemodialysis — effective; removes lactic acidosis, increases serum HCO₃, restores euvoemia in volume-depleted patients, and removes metformin easily and rapidly (metformin highly water soluble) Clinical challenges: identify risk factors for MALA; educate patients about risk for volume depletion, particularly in those with mild CKD; instruct patients when to hold or reduce dose of metformin

Risk factors for MALA: severe hepatic failure; acute heart failure; any condition that decreases tissue perfusion or causes shock; hypoxic state or serious acute illness; suicide attempts; history of lactic acidosis; low GFR

Metformin and CKD: evidence supports metformin use even in mild to moderate CKD (defined by estimated GFR), with appropriate dose reduction and careful follow-up of kidney function; elderly patients with CKD at risk for MALA

Glomerular filtration rate: evaluate in patients >65 yr of age before initiating drug; if normal, use full dose; use low dose if GFR 30 to 50 mL/min/1.73 m² or CKD stage 3; avoid if GFR <30 mL/min/1.73 m² (corresponds to SCR >1.5 mg/dL in men and >1.4 mg/dL in women)

Suggested Reading

Acknowledgments
Dr. Cheng was recorded at the 38th Annual Eastern Shore Medical Symposium, held June 22-26, 2015, in Rehoboth Beach, DE, and jointly sponsored by Sidney Kimmel Medical College at Thomas Jefferson University and the University of Delaware, with promotional assistance provided by the Medical Society of Delaware. For information about upcoming CME activities from Sidney Kimmel Medical College at Thomas Jefferson University, please visit library.jefferson.edu/jeffcme. Dr. Borkan was recorded at Controversies in Internal Medicine, held May 4-8, 2015, in Hilton Head, SC, and presented by the Boston University School of Medicine and the Hofstra North Shore-LIJ School of Medicine. For information about upcoming CME activities from the Boston University School of Medicine, please visit www.bumc.bu.edu/cme. The Audio Digest Foundation thanks the speakers and the sponsors for their cooperation in the production of this program.

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1. According to a 2011 study, which of the following medications is responsible for the most hospitalizations?
   (A) Digoxin  (B) Metformin  (C) Warfarin  (D) Insulin

2. Which of the following herbal supplements is associated with Stevens-Johnson syndrome?
   (A) Bitter orange  (B) Licorice  (C) Ginseng  (D) St John’s wort

3. Patients are advised to stop all herbal preparations at least _______ before surgery.
   (A) 3 days  (B) 5 days  (C) 10 days  (D) 14 days

4. Increased levels of serum creatinine are associated with the initiation of:
   (A) Diuretics  (B) Angiotensin-converting enzyme inhibitors  (C) Spironolactone  (D) Calcium channel blockers

5. Which of the following nonsteroidal anti-inflammatory drugs (NSAIDs) is least toxic to the gastrointestinal tract?
   (A) Etodolac  (B) Ketorolac  (C) Ibuprofen  (D) Naproxen

6. Which of the following NSAIDs is associated with the lowest cardiovascular risk?
   (A) Etodolac  (B) Ketorolac  (C) Ibuprofen  (D) Naproxen

7. Which of the following weight-loss agents is the most highly fetotoxic?
   (A) Orlistat  (B) Phentermine and topiramate  (C) Naltrexone and bupropion  (D) Lorcaserin

8. The daily dose of metformin should not exceed:
   (A) 1500 mg  (B) 2000 mg  (C) 2500 mg  (D) 3000 mg

9. The accumulation of metformin specifically inhibits complex _______ of the mitochondrial respiratory chain.
   (A) I  (B) II  (C) III  (D) IV

10. Evidence supports the use of metformin in which of the following cases?
    (A) 32-yr-old man with moderate chronic kidney disease
    (B) 68-yr-old woman with low glomerular filtration rate
    (C) 51-yr-old man with acute heart failure
    (D) 46-yr-old woman with hypoxia

Answers to Audio Digest Internal Medicine Volume 62, Issue 39: 1-B, 2-D, 3-A, 4-C, 5-A, 6-B, 7-B, 8-C, 9-D, 10-A

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