Broke in the ER: Pharmacologic Choices for Acute, Non-traumatic Low Back Pain in the Emergency Room

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Background: Acute, non-traumatic low back pain accounts for 2-3% of all emergency department visits. Providers triage serious etiologies (cancer, infection), serious symptomologies (loss of bowel function, saddle anesthesia, sensory loss) and radiculopathies (nerve root involvement) from strain, sprain, and herniation in muscle, ligament, and discs (excluding central discs). Diagnoses in this later group are often a diagnosis of exclusion that represent most incidents. The evidence for their pharmacologic management is derived mostly from the acute care setting, which recommend acetaminophen, benzodiazepines, muscle relaxants, Non-Steroidal Anti-inflammatory Drugs (NSAIDs), opioids and tramadol for primary and adjunctive therapy. Expert opinion, group consensuses, and national and international guidelines mostly recommend acetaminophen and NSAIDs for first or second line therapy and muscle-relaxants or opioids for tertiary or adjunct therapy. Interestingly, one national retrospective study from 2002 to 2006 of 183,633 patients demonstrated that 52% received either a muscle relaxant or opioid in combination with an NSAID, while 61% received an opioid with or without an NSAID. This begs the question if this should be an accepted, regular practice.

Objective: The primary study objective was evaluation of the efficacy of adjunctive cyclobenzaprine and oxycodone-acetaminophen pharmacotherapy in acute, non-traumatic low back pain.

Study Design: This study was a 323-patient, randomized, double-blind, three-arm trial conducted at a New York hospital. The eligible subjects had nontraumatic, nonradicular lower back pain of 2 weeks duration or less and a Roland-Morris Disability Questionnaire (RMDQ, 0-24) score of five or more. Mean RMDQ scores in the three arms were 19-20. The primary outcome was improvement on the RMDQ between emergency department discharge and a 7-day telephone follow-up. Patients received a 10 day supply of naproxen (500 mg) to be taken twice daily and either a placebo (lactose), cyclobenzaprine (5 mg) or oxycodone/acetaminophen (5-325 mg). All study drugs were prepared in identical capsules by a pharmacist to ensure patient blinding. Patients were instructed to take one or two adjunctive capsules every 8 hours as needed, with a minimum of 30 minutes between the first and second capsule to evaluate pain relief.

Results: The one-week RMDQ mean scores and confidence intervals (CI) for placebo, cyclobenzaprine and oxycodone-acetaminophen were 8.9 (95% CI -1.6-3.0), 8.2 (95% CI -1.1-3.4), and 7.8 (95% CI -1.2-2.7), respectively. Mean RMDQ differences between groups at one week were also measured: cyclobenzaprine vs placebo was 0.3 (98.3% CI -2.6-3.2; P = .77), oxycodone/acetaminophen vs placebo...
1.3 (98.3% CI −1.5−4.1; P = .28), and oxycodone/acetaminophen vs cyclobenzaprine, 0.9 (98.3% CI −2.1−3.9; P = .45).

Conclusion: Twenty years of increased opioid prescribing for chronic, non-cancer pain has influenced acute and urgent care practice. An expectant culture has developed for many patients and providers that opioids are an appropriate first-line or regular adjunctive pharmacological choice for pain, without due reflection for appropriateness and potential harms. This study, despite its limitations in size, demonstrates that patients do not receive improvement in functional outcomes or pain with the adjunctive use of cyclobenzaprine or oxycodone-acetaminophen.

Key Point: Pharmacists should continue to recommend against using muscle-relaxants and opioids as adjunctive therapy in mild to moderate acute, nontraumatic low back pain in emergency room settings. Pharmacists should reserve adjunctive use of muscle relaxants and opioids to severe cases with prescriptions of limited amounts for two to three day durations.

Estimating the Impact of Adherence to and Persistence with Atypical Antipsychotic Therapy on Health Care Costs and Risk of Hospitalization

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Background: The Affordable Care Act is projected to increase prescription drug spending due to expanded coverage. This may result in heightened budget concerns for health systems. In the long-term, the Affordable Care Act is projected in increase overall healthcare costs. Because schizophrenia and bipolar disorder impose a great economic burden on the healthcare system, it is important for decision makers to know how adherence and persistence to atypical antipsychotics affect overall healthcare costs. Adherence is defined as proportion of days covered by all atypical antipsychotic prescription fills and persistence is defined as time from initiation to discontinuation of therapy.

Objective: To estimate the impact of adherence and persistence with atypical antipsychotics on healthcare costs and risk of hospitalization when two sources of endogeneity were taken into account. These two sources included: drug use patterns are likely mutually causal with outcomes measures during the same time period, and compliant and noncompliant subjects likely have differences in unobserved characteristics.

Study Design: Pharmacy and medical claims data from the Humana health care insurance plan was obtained between January 2007 and June 2013. A total of 32,374 patients with a diagnosis of schizophrenia or bipolar disorder who had a prescription for a non-injectable atypical antipsychotic (aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, or ziprasidone) were enrolled. Of these patients, 11,643 were adherent (defined as ≥85% of days covered by atypical antipsychotic therapy) and 17,772 were persistent (defined as ≥360 days between initiation and discontinuation of the atypical antipsychotic). The cohort was also restricted to subjects who had a pre-index (prior to the start of the atypical antipsychotic) washout period of at least 180 days during which they did not use any atypical antipsychotics and had a post-index (after initiation of the atypical antipsychotic) period of at least 720 days of continuous enrollment in the database. Outcome measures included: all-cause total healthcare cost, medication costs, medical services costs, and inpatient admissions. Two instrumental variables (IV) were used to account for endogeneity which included the reimbursement rate of atypical antipsychotic and whether the first fill of the medication was filled by a mail order pharmacy.

Results: Estimates of cost using IV measures showed that adherent patients had an $8,194 increase in medication costs (p<0.001), a $27,664 decrease in medical costs (p<0.001), and an overall $19,497 decreased in total costs (p<0.05). Adherent patients also had a 27% reduction in risk of hospitalization (p<0.001). Persistence was associated with an $10,278 increase in medication costs (p<0.001), a $34,178 decreased in medical costs (p<0.001), and an overall $23,927 decrease in total cost (p<0.001) when IVs were accounted for. There was no significant association observed between persistence and hospitalizations. Tests of the validity and endogeneity of the IVs were performed and results showed that the IVs were not weak and were exogenous.

Conclusions: Adherence and persistence to atypical antipsychotic medications generated a net overall healthcare savings when two sources of endogeneity were accounted for. Future efforts should be focused on developing programs to help improve adherence and persistence to medications in these patient populations.

Blacks and Exacerbations on LABA v. Triotropium (BELT) Trial

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Background: For patients with poorly controlled asthma using a low-dose inhaled corticosteroid (ICS), National Heart, Lung, and Blood Institute (NHLBI) Guidelines recommend increasing to a medium-dose ICS or adding
a long-acting β- agonist (LABA). Unfortunately, there are safety concerns surrounding the use of LABAs, including possible increased rates of hospitalization and death. Due to these concerns, researchers have started to explore the potential role of long-acting anticholinergics as an alternative to LABAs for patients with asthma. Most of the research on this topic has involved white patients, however available data suggest that black adults may be at a higher risk of adverse effects and may not obtain the same benefit from LABAs due to genetic variations at the β2-adrenergic receptor.

**Purpose:** The Blacks and Exacerbations on LABA v. Tiotropium (BELT) Trial was designed to compare the safety and efficacy of tiotropium to LABAs in black adults with poorly controlled asthma who are currently using inhaled corticosteroids. The study also examined the effects of allelic variation in the Arg16Gly locus of the β2-adrenergic receptor on treatment response.

**Study design:** This study was an open-label, parallel-group, randomized pragmatic trial conducted at 20 sites between March 2011 and July 2013. The two primary outcomes were time to asthma exacerbation, and the association between Arg16Gly allelic variation and time to first exacerbation. Self-identified black adults, ages 18 to 75, were enrolled in the trial if they had physician-diagnosed asthma and were receiving ICS + LABA therapy, or receiving ICS therapy with an Asthma Control Questionnaire (ACQ) score higher than 1.25. Patients were excluded if they were current smokers, had a less than 10 pack-year history of smoking, had a prebronchodilator FEV1 less than 40% predicted, or had an exacerbation requiring oral steroids within the past 3 months. Patients were randomized to receive their usual ICS dose with either tiotropium 18 mcg once daily, salmeterol 50 mcg twice daily, or formoterol 9 mcg twice daily. Patients were followed for 6-18 months, depending on when they enrolled in the study. Patients were required to complete monthly questionnaires and were scheduled for clinic follow-up at one, six, twelve, and eighteen months. Genomic DNA was collected from saliva and genotyped using a gene expression assay.

**Results:** A total of 1070 patients were included in the trial, with 532 patients assigned to the tiotropium + ICS treatment group and 538 patients assigned to the LABA + ICS treatment group. More than 75% of the patients were women, and the only significant baseline difference between treatment groups was time since initial asthma diagnosis (23.3 years vs. 25.6 years in patients receiving tiotropium + ICS and LABA + ICS, respectively (95% CI 0.3-4.3; P=0.02). There was no difference in time to first exacerbation between the two treatment groups, with

0.42 exacerbations per person-year in LABA + ICS group vs. 0.37 exacerbations per person-year in tiotropium + ICS group (RR 0.9; 95% CI 0.73-1.11; P=0.31). Hazard ratios for time to first exacerbation were stratified according to genotype, and there were no differences in treatment effects between Arg16Gly allelic variations (HR 0.84 for Arg/Arg; 95% CI 0.47-1.51 vs. 0.85 for Arg/Gly or Gly/Gly; 95% CI 0.63-1.15; P=0.97). There were no differences in secondary outcomes such as change in FEV1 at twelve months (-0.68 for LABA + ICS vs. -0.72 for tiotropium + ICS (95% CI -0.021-0.061; P=0.33) or mean change in ACQ scores at 18 months (-0.68 for LABA + ICS vs. -0.72 for tiotropium + ICS (95% CI -0.18-0.27; P=0.70).

**Conclusions:** For black adults between the ages of 18 and 75, adding tiotropium to current ICS treatment was not associated with decreased time to asthma exacerbation compared to LABA + ICS. In addition, genetic polymorphisms did not impact the time to first exacerbation between treatment groups.

**Key Point:** The results of the BELT trial showed no difference in primary efficacy outcomes between tiotropium and LABAs, however there was not enough power to evaluate important safety outcomes such as hospitalizations and deaths between treatment groups. More research is needed to better understand the potential role of tiotropium in this patient population.

**Spironolactone Versus Placebo, Bisoprolol, and Doxazosin to Determine the Optimal Treatment for Drug-resistant Hypertension (PATHWAY-2): A Randomized, Double-blind, Crossover Trial**

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**Background:** Patients with resistant hypertension (as defined by inadequate blood pressure (BP) control with treatment of at least three antihypertensive agents) are at risk for complications of uncontrolled high BP, including end-organ damage. With no treatment guideline recommendation to suggest the optimal fourth-line agent after ACE inhibitors or ARBs [A] plus calcium channel blockers [C] plus diuretics [D] for resistant hypertension, clinicians are left to trial various therapies without clinically significant evidence to support their decision-making.

**Objective:** The primary objective of this study was to assess if spironolactone is overall the most effective add-on treatment for resistant hypertension.

**Study Design:** PATHWAY-2 was a 12-month, multi-center, double-blind, placebo-controlled, crossover phase 4 trial conducted at 14 sites in the United...
Kingdom from May 15, 2009 to July 8, 2014. After one month of a single-blind placebo run-in period, patients went through four 12-week cycles of once daily oral therapy with one of the three study drugs in a pre-designated, randomized order: spironolactone 25-50 mg, doxazosin modified release 4-8 mg, bisoprolol 5-10 mg, and matched placebo. Nine follow-up visits were conducted at six-week intervals to assess efficacy and tolerability. Doses of each study drug were doubled six weeks into each 12 week cycle. There was no washout period between treatment cycles. BP, electrolytes, and adverse effects (AEs) were assessed at each visit.

Patients included in the study were adults aged 18-79 years with a seated clinic systolic blood pressure (SBP) of ≥ 140 mmHg (or ≥ 130 mmHg for patients with diabetes) and a home SBP of ≥ 130 mmHg despite treatment for hypertension with maximally tolerated doses of 3 drugs ([A]+[C]+[D]). Exclusion criteria included secondary or accelerated hypertension, type 1 diabetes, eGFR < 45 mL/min, cardiovascular event requiring hospitalization in the last six months, requirement for a study drug for an indication other than hypertension (e.g. diuretic for heart failure), any NSAID use, any corticosteroid use within 3 months of starting the trial, and less than 70% adherence after the placebo run-in period.

The primary endpoints measured were the difference in averaged home SBP between spironolactone and placebo, between spironolactone and the average of the other two active study drugs, and between spironolactone and each of the two study drugs. Home BPs were measured instead of clinic BPs to negate differences caused by placebo effect and “white coat syndrome.”

314 patients were included in the intention to treat primary endpoint analysis. 285 patients received spironolactone; 282, doxazosin; 285, bisoprolol; 274, placebo. The average reduction in home SBP by spironolactone was superior to placebo –8.70 mmHg (95% CI –9.72 - –7.60; p=0.0001), superior to the average of doxazosin and bisoprolol, –4.26 mmHg (95% CI –5.13 - –3.38; p<0.0001). Spironolactone was also found to be superior when compared with each study drug individually: spironolactone vs. doxazosin –4.03 mmHg (95% CI –5.04 - –3.02; p<0.0001) and spironolactone vs. bisoprolol –4.48 mmHg (95% CI –5.50 - –3.46; p<0.0001). However, the superiority of spironolactone was confined to home SBP readings on the higher dose ranges at the end of each treatment cycle. Additionally, there was no statistical difference in diastolic BP lowering among any of the active treatment groups at any treatment dose of study medication.

Spironolactone, doxazosin, and bisoprolol were all well tolerated, with low rates of AEs being similar between groups.

Conclusions: Home SBP was lowered in a statistically significant manner with spironolactone as compared to doxazosin, bisoprolol, and placebo in most adult patients with resistant hypertension. Use of spironolactone as a fourth-line antihypertensive agent significantly increased the likelihood of achieving BP control (defined as home SBP < 135 mmHg) compared to other active treatments, with a number-needed-to-treat of approximately 7 patients.

Key Point: This randomized, placebo-controlled, double-blind phase 4 crossover trial determined that low-dose spironolactone may be the most effective treatment for resistant hypertension as a fourth-line agent. The results of PATHWAY-2 may impact future evidence-based guidelines for the treatment of resistant hypertension.

The Role of Gastrointestinal Prophylaxis in Dual Anti-Platelet Therapy11,16
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Background: Dual anti-platelet therapy (DAPT) is the standard of care in reducing the risk of myocardial infarction, stroke, and stent thrombus following acute coronary syndrome and percutaneous coronary intervention.11,12 DAPT poses an increased risk of gastrointestinal (GI) bleeding as much as two-fold. The 2010 ACCF/ACG/AHA consensus document recommends the use of PPI therapy for patients receiving DAPT if the patient is considered high risk based on the following risk factors: history of GI bleed, peptic ulcer disease, advanced age, concurrent anticoagulants, NSAID use, steroid use, or Helicobacter pylori infection.13 Although PPIs are generally well tolerated and safe, PPIs possess an increased risk of Clostridium difficile infections, pneumonia, fractures, hypomagnesemia, and the potential drug-drug interaction between PPIs and clopidogrel. Despite the consensus statement from ACCF/ACG/AHA, a 2014 retrospective chart review of patients receiving DAPT
found that only 48% of patients were receiving appropriate GI prophylaxis. Recent studies have reviewed the effectiveness and safety of PPIs in DAPT to prevent GI bleed as well as the potential use of histamine-2 receptor antagonists (H2RA) in DAPT to prevent GI bleed.

**Evidence:** The COGENT trial compared omeprazole and placebo in patients on DAPT with a primary endpoint of patient-reported symptoms of dyspepsia. At both 4 weeks and 24 weeks the omeprazole group had a mean score of pain intensity and non-pain symptoms lower than the placebo group (4 weeks: 5.61+0.17 versus 6.40+0.17; P=0.001 and 10.61+0.07 vs 11.00+0.07; p<0.001 respectively) (24 weeks: 5.91+0.35 vs 7.10+0.37; P=0.0020 and 10.36+0.12 vs 10.93+0.13; P=0.001 respectively). When describing risk factors, one study defined advanced age as >75 years and steroid use as >14 days. In this study only 47% of patients were appropriately prescribed GI prophylaxis. A 2015 meta-analysis reviewed 39 studies, 8 of which were randomized control studies, comparing the outcomes in patients receiving clopidogrel with or without a PPI. This study found that patients showed no significant differences in all-cause mortality (OR 0.91; 95% CI 0.58-1.40; P=0.66) acute coronary syndrome (OR 0.96; 95% CI 0.88-1.05; P=0.35), myocardial infarction (OR 1.05; 95% CI 0.86-1.28; P=0.65) and cerebrovascular accident (OR 1.47; 95% CI 0.66-3.25; P=0.34) between the two groups and the PPI group had a significant reduction in the risk of GI bleeding. This meta-analysis found no difference in risk of MI and mortality between PPIs considered to be high-risk (omeprazole, esomeprazole and lansoprazole) and those considered to be low risk (pantoprazole and rabeprazole). Another 2015 meta-analysis comparing PPIs and H2RAs found that PPIs are superior for the prevention of DAPT associated GI erosion/ulcers (OR 0.28; 95% CI 0.16-0.50) and bleeding (OR 0.28; 95% CI 0.14-0.59).

**Discussion:** Recent studies show that GI prophylaxis is frequently missed in high risk patients on DAPT. Additionally, current evidence has shown the use of PPIs for GI prophylaxis in high risk patients on DAPT not only reduces the risk of a GI bleed/erosion/ulcer but also reduces overall pain and non-pain symptoms. Research has shown little reduction in absolute risk in use of PPIs in DAPT patients without the risk factors described above; therefore PPIs should only be used in patients at high risk for GI bleed.3 Previous concerns surrounding the reduced metabolism of clopidogrel to its active ingredient when in combination with PPIs has been further explored. Although the research has shown that the use of high-risk PPIs versus low-risk PPIs does not change the outcomes of cardiovascular morbidity or mortality, the consensus statement and current experts recommend the use of low risk PPIs (pantoprazole and rabeprazole) when possible in order to reduce this potential interaction.

**Clinical Impact:** PPIs continue to be the mainstay of GI prophylaxis in DAPT patients. Clinicians should review all DAPT patients at risk for GI bleed/erosion/ulcer and prescribe PPIs to reduce this risk, if appropriate. The pharmacodynamic interaction between PPIs and clopidogrel likely has no clinical significance. The benefit of GI prophylaxis, particularly with pantoprazole and rabeprazole, outweighs the risk of the drug-drug interaction between PPIs and clopidogrel in high risk GI bleed patients. Finally, current studies confirm that PPIs are superior to H2RAs for use in DAPT patients at high risk for GI bleed. H2RAs may be a reasonable option in patients at lower risk for GI bleed. Continued use of PPIs is recommended in patients on DAPT and at high risk for GI bleeds, especially if patients have one or more of the following risk factors: history of GI bleed, peptic ulcer disease, advanced age (not well defined), concurrent anticoagulants, NSAID use, steroid use (not well defined), or Helicobacter pylori infection.

**Dual Antiplatelet Therapy After Ischemic Stroke or TIA**

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**Background:** Current treatment guidelines for secondary prevention of stroke or transient ischemic attack (TIA) recommend the use of aspirin monotherapy, dual aspirin and dipyridamole therapy, or clopidogrel monotherapy. The use of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel for secondary prevention of ischemic stroke or TIA has been evaluated in clinical trials and shown no difference in efficacy with an increased risk of bleeding compared to monotherapy. Long-term DAPT is not recommended by current treatment guidelines for secondary prevention of stroke or TIA. A new recommendation to consider dual antiplatelet therapy within 24 hours of minor ischemic stroke or TIA has been included in the 2014 AHA/ASA Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack.

**Evidence:** Results from two clinical trials, FASTER20 and CHANCE,21 led to a new recommendation to consider initiation of DAPT within 24 hours of minor ischemic stroke or TIA for 90 days in the 2014 AHA/ASA Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. Although
discontinued before completion due to slow recruitment, the FASTER trial compared DAPT with aspirin 81 mg daily and clopidogrel 75 mg daily to aspirin monotherapy initiated within 24 hours of a vascular event and continued for 90 days. The data showed a trend toward reduced ischemic stroke with DAPT with a 1% increase in risk for intracranial hemorrhage at 90 days. The CHANCE trial, published in 2013, compared DAPT with aspirin 75 mg daily and clopidogrel 75 mg daily to aspirin alone started within 24 hours of symptom onset. In the DAPT group, dual therapy was used for 21 days followed by clopidogrel monotherapy for the remainder of 90 days. DAPT was found to be superior to aspirin monotherapy for reduction of stroke recurrence (HR 0.68; 95% CI 0.57-0.81) without an increase in risk of hemorrhage at 90 days. Two recent publications provide further data from the CHANCE trial population.

The one-year follow-up results of the CHANCE trial were recently published in Circulation. The primary efficacy outcome of the trial was a new ischemic or hemorrhagic stroke during one year of follow-up. Safety outcomes included moderate-to-severe bleeding events and any bleeding event. Of the 5,170 patients randomized to treatment, 197 were lost to follow-up at one year. The proportion of patients taking antiplatelets remained similar between 90-day and one-year follow-up with approximately 75% of patients on aspirin monotherapy, 5% on clopidogrel monotherapy, and 1.4% on DAPT at the one-year follow-up. The rate of stroke remained lower in the DAPT group at the one-year follow-up (HR 0.78; 95% CI 0.65-0.93). Rates of moderate-to-severe bleeding were similar between the two groups with events occurring in 7 (0.3%) patients in the DAPT group and in 9 (0.4%) patients in the aspirin group (P=0.44).

Using data from one hospital participating in the CHANCE trial, Wang et al. studied whether DAPT therapy increased the number cerebral micro-bleeds (CMB) compared to aspirin monotherapy. CMB has been associated with increased risk for antplatelet-associated intracerebral hemorrhages. All patients had an MRI examination within 24 hours of symptom onset and were classified by severity of CMB. No difference in progression of CMB was found between treatment groups (DAPT 50%, aspirin 32.4%, p>0.05). The authors conclude that the use of DAPT within 24 hours of symptom onset in patients with TIA or minor stroke with CMB does not increase the numbers of microbleeds.

**Discussion:** Treatment guidelines now recommend consideration for use of DAPT if initiated within 24 hours of symptom onset for 90 days. This recommendation was based on trends from the incomplete FASTER trial and 90-day outcomes of the CHANCE trial which utilized DAPT for 21 days followed by clopidogrel on days 22 through 90. One-year outcomes of the CHANCE trial show persistence in benefit of early DAPT without a rebound effect after 90 days. A subgroup of the CHANCE trial showed no difference in the progression of CMB, a possible predictor of hemorrhagic stroke risk, between DAPT and monotherapy with aspirin which is consistent with the lack of difference in rates of hemorrhagic stroke found in the CHANCE trial. These recent publications add to the available data for safe use of DAPT in the acute setting of minor ischemic stroke or TIA. However, generalizability of study results is limited due to use of an entirely Chinese population and extensive exclusion criteria resulting in a low risk for hemorrhage.

**Clinical Impact:** Long-term use of DAPT for secondary stroke prevention is not supported in the literature and not recommended by current guidelines. The short-term use of DAPT for 21 days may be appropriate if initiated within 24 hours of symptom development. It remains important for pharmacists and providers to routinely evaluate the appropriateness of DAPT and continue to assess the risks and benefits in each individual patient.

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**Update in American Geriatrics Society’s Beers Criteria**

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**Background:** The Beers Criteria is a widely used resource that outlines Potentially Inappropriate Medications (PIMs) that should be avoided in adults aged 65 and older, excluding hospice and palliative care patients. The American Geriatrics Society (AGS) adopted the responsibility of updating and maintaining the Beers Criteria in 2011. The AGS then released the first update of the Beers Criteria in 2012. The purpose of the Beers Criteria is to bring awareness to these PIMs and reduce their use in older adults. PIMs have been associated with poor health outcomes in older populations leading to increased confusion, falls, and mortality. The 2015 revision is designed to add two new sections including drugs that need to be adjusted based on renal function and drug-drug interactions while also reviewing and updating the existing criteria.

**Evidence:** An interdisciplinary panel of 13 experts in geriatric care and pharmacotherapy were used to update the guidelines. They used a modified Delphi method to systematically review and grade literature from August 1, 2011 to July 1, 2014. The literature search included systematic reviews, meta-analyses, randomized control trials, and observational studies and was completed using PubMed and the Cochrane Library. The initial searches uncovered over 20,000 articles; however, only
1,188 were ultimately selected and reviewed by the full panel.24

Discussion: There are several notable updates to the 2015 Beers Criteria. There is a new recommendation that non-benzodiazepine, sedative hypnotics (like eszopiclone, zaleplon, and zolpidem) should be avoided without consideration of duration.24 This recommendation comes from a case-crossover study of 15,528 nursing home patients that examined the relationship between non-benzodiazepine sleep medications and the risk of hip fractures. The trial found that the risk of hip fracture was elevated among users of non-benzodiazepine hypnotic drugs (OR 1.66; 95% CI 1.45-1.90).25 These medications have also been included in a list of medications to avoid in patients with dementia or cognitive impairment. The new update also suggests that proton pump inhibitors (PPIs) should be avoided for duration greater than 8 weeks without justification due to their association with Clostridium difficile, bone loss, and risk of fractures.

The new “Drug-Drug Interactions” section is a list of drug-drug interactions that have been highly associated with harmful outcomes in the elderly. For example, the use of three or more CNS-active drugs together increases the risk of falls. This section only includes a few select drug-drug interactions identified to be particularly troublesome in the elderly. Lastly, there is a new section detailing PIMs that need to have dosage adjustments based on kidney function to avoid harm. There are not specific guidelines on how to adjust each medication, but it does have a list of frequently used medications that need renal adjustments.

Clinical Impact: The 2015 AGS Beers Criteria update contains several improvements. It's an important resource to help practitioners appropriately use medications in older adults with the hope to reduce exposure and adverse events related to PIMs. It's also important to note that the AGS does not suggest that these guidelines are entirely comprehensive and cite that prescribing medications needs to be on a case-by-case basis.24

Trends in Prescription Drug Use Among Adults in the United States from 1999-201226-33

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Background: Healthcare costs in the U.S. have continued to rise and medication mismanagement plays a large role. Pharmacist intervention has been proven to improve clinical outcomes and has shown the return on investment (ROI) of pharmacist-led interventions to be as high as 12:1.1 However, a recent meta-analysis found a wide variability in efficacy and cost-effectiveness of medication therapy management (MTM) services in outpatient settings.2 Targeting patients at a higher risk of developing drug therapy problems (DTPs) may be one effective way of maximizing the ROI of the service. Prior studies have looked at developing screening tools to identify patients that have a higher number of DTPs.3-5 The screening tools in these studies were applied to an elderly population, Medicare Part D beneficiaries, and patients at a family medicine clinic. Pammett et al. attempted to evaluate a similar self-administered screening questionnaire for its predictive capabilities for identifying patients at risk for DTPs in a community pharmacy setting.6

Study Design: This questionnaire (Table 1) was self-administered to 52 patients visiting one of three pharmacies in Saskatoon, Saskatchewan, Canada between November 2013 and February 2014. Each pharmacy included patients during a four-week study period who were 18 or older, able to speak and read English that were picking up a refill for a chronic, unchanged medication (defined as no changes to the drug, dose, or directions for the past 6 months). The only exclusion criterion was that pharmacy staff could exclude patients for any reason (examples provided included perceived patient agitation or otherwise deemed inappropriate).

Surveys were returned to the research pharmacist (non-pharmacy staff) in a sealed envelope and then the patient and research pharmacist met for a comprehensive medication assessment. After the visit, the research pharmacist also completed the questionnaire on the patient's behalf.

Patient and pharmacist responses to the survey questionnaire were assessed for interrater agreement using Cohen's κ coefficient7, a statistical tool which produces values from 0-1 in which a result of 0 indicates that similar results occur based on chance alone. DTP’s were categorized by unnecessary drug therapy, inappropriate drug therapy, subtherapeutic dose, supratherapeutic dose, drug therapy required, adverse drug reaction, and non-compliance8. The investigators
also allowed for an “other or unsure” category. It was suspected by the investigators that this occurred most often when the pharmacist could not confirm the DTP due to lack of information. DTPs were also assigned a severity index – mild, moderate, or severe – by the pharmacist; these scores were audited by external, independent pharmacist and physician.

Results: Agreement between questionnaire responses for the patient and pharmacist were high, especially for questions 1,3,5 (see Table 1). The overall questionnaire $\kappa$ coefficient was 0.910, classified as “very good.”

Of the 49 patients who completed both the questionnaire and the medication assessment, 63% (n=31) were categorized as low risk (answered yes to <3 questions in the survey). The remaining 37% (n=18) were categorized as high risk (answered yes to >3 questions in the survey). High-risk patients had a mean of 5.7 DTPs per patient whereas low-risk patients had a mean of 2.0 DTPs per patient (p<0.01). The mean number of moderate or severe DTPs in the high-risk patients was 3.6 as compared to 0.8 in the low-risk patient group (p<0.01).

Conclusions and Potential Applications: The results of the work by Pammett et al. indicate patients answering yes to 3 or more questions on this self-assessment questionnaire administered in a community pharmacy setting may correlate with patients at higher risk for DTPs, as well as DTPs of increasing severity. Responses for patient and pharmacist answered questionnaires were highly agreeable, indicating that patients are able to correctly answer the studied questions.

There are several limitations to this study, notably the pharmacist’s lack of access to the patient’s electronic medical record. There may have been some DTPs categorized as “other or unsure” that were not true DTPs although this accounted for only 10.9% (n=18) of DTPs. Additionally, it is unclear if the pharmacists used the patient care process as outlined by Cipolle and Strand or if they solely borrowed their classifications of DTPs. Finally, the pharmacy team was allowed to exclude patients for any reason, leaving a possibility for selection bias.

The results of this study have potential to aid pharmacists who want to provide enhanced MTM services in community settings. The questionnaire in the survey could be used to identify patients that are in the most need of these services. Additionally, pharmacists practicing in a clinical ambulatory care setting that is affiliated with a retail pharmacy could increase recruitment of patients who may benefit from MTM services by screening in the retail setting.

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<tbody>
<tr>
<td>1. Do you take 5 or more different medications on a regular basis?</td>
<td>0.877</td>
<td>very good</td>
</tr>
<tr>
<td>2. Do you take 12 or more doses of medications each day?</td>
<td>fair</td>
<td></td>
</tr>
<tr>
<td>3. Are you currently taking medications for 3 or more medical conditions?</td>
<td>0.836</td>
<td>very good</td>
</tr>
<tr>
<td>4. Have your medications or the instructions on how to take them changed 4 or more times in the past year?</td>
<td>fair</td>
<td></td>
</tr>
<tr>
<td>5. Do you take any of the following medications? carbamazepine, phenytoin, warfarin, rivaroxaban, dabigatran, apixaban, methotrexate, lithium, digoxin, any drug for chronic pain, insulin (any type), drugs to lower blood sugar</td>
<td>0.912</td>
<td>very good</td>
</tr>
<tr>
<td>Overall questionnaire</td>
<td>0.910</td>
<td>very good</td>
</tr>
</tbody>
</table>

Evaluation of a Pharmacist-Provided Telemonitoring Program for Diabetes Management
Karin Josephson, Pharm.D.
CentraCare Health

Background: Diabetes management can be overwhelming for patients and providers alike. It requires routine education and follow-up to adjust regimens. There are 29 million people in the United States living with diabetes and, of those diagnosed, costs are $245 billion per year. Non-adherence leads to disease complications that lead to more care and increased cost. Studies involving nurse-coordinated telemonitoring programs in diabetes care have shown benefits, but few studies involve pharmacy-coordinated telemonitoring programs. However, pharmacists in the clinic have shown to be important members of an interdisciplinary care team in chronic disease state management.

Objective: To assess the impact on the use of telemonitoring devices coordinated by a pharmacist to expand and improve chronic disease state management in patients with diabetes with or without hypertension. Clinical outcomes assessed included: glycosylated hemoglobin (A1c), blood pressure, and lipids, as well as disease state knowledge, adherence, and self-efficacy.
**Study Design:** This prospective observational study involved 150 patients with uncontrolled diabetes (A1c >7%) with or without hypertension from September 1, 2011 to September 30, 2013 in four community health centers in Utah. Care was led by a pharmacist fluent in English and Spanish, who was certified as a diabetes educator and had collaborative practice agreements in place. Outcomes were assessed pre- and post-intervention in 75 patients managed with telemonitoring through lab work, blood pressure readings, and questionnaires. The control group included 75 patients who did not receive telemonitoring and were identified by retrospective chart review of a registry of patients with diabetes who were seen during the same time frame and had two A1c values approximately six months apart. After enrollment, patients received instruction in clinic on how to use the telemonitoring device and received a phone call later in the day to assess understanding. Patients used the device five days per week with each session lasting approximately five to ten minutes. During the session, patients would enter how they were feeling, confirm they took their medication that day, measure blood pressure, manually enter blood glucose and weight, and receive a series of diabetes education messages. The pharmacist would check a secure website several times daily to assess blood glucose and blood pressure values. Telephone follow-up with patients took place if the blood glucose or blood pressure was out of range, the patient had questions, or no values were submitted for a few days. At discharge, after approximately 6 months, vitals were taken, labs were drawn, and questionnaires were reassessed.

**Results:** Patients who utilized telemonitoring with a pharmacist had a statistically significant decrease in mean A1c of 2.07% from beginning to end of study (p<0.001) as well as statistically significantly greater reduction in A1c versus control, where an A1c reduction of 0.66% was seen (P=0.006). The percent of patients with an A1c less than seven percent was significantly higher in the telemonitoring group versus those who received standard care (34.7% versus 14.7%, p<0.004). Reductions in blood pressure and LDL were significant from the beginning to the end of the study in the intervention group, but neither differed significantly from the comparison group. Patient activation, diabetes knowledge, hypertension knowledge, and hypertension medication adherence improved significantly from baseline (p<0.05 for all), however there was no difference in diabetes medication adherence.

**Conclusion:** Pharmacist-led diabetes management via telemonitoring in community health centers in Utah showed improvement in patients’ A1c, percent of patients at A1c goal, encouraged patient activation, improved diabetes and hypertension knowledge, and improved adherence to hypertension medication. This model could be utilized to help other patients manage their diabetes.

**Key Point:** In this pharmacist-led model, telemonitoring showed improvements in outcomes such as A1c reduction as well as patient understanding and self-efficacy. This model allows for diabetes management in the patient’s home and is another method for pharmacist interventions, education, and medication management.

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**Miscellaneous News**

**Development of a Medication Therapy Management Model Test to Enhance Medicare Part D**

Laura Krasky, Pharm.D.
Park Nicollet Health Services

The Center for Medicare and Medicaid Services (CMS) issued a press release on September 28, 2015 announcing a Part D Enhanced Medication Therapy Management (MTM) Model Test. Part D prescription drug plans (PDPs) are required by CMS to provide MTM programs aimed to improve patient outcomes and drug costs. However, current MTM requirements are thought to incentivize cost efficiency for stand-alone plans over maximization of MTM programs for reduction in overall cost of care. The newly announced model test will be used to assess whether providing stand-alone Part D PDPs with financial incentives and regulatory flexibility will allow for more effective provision of MTM while reducing Medicare expenditures.

Beginning in January 2017, the enhanced MTM model test will operate for five years. In addition to a voluntary application, Part D PDPs interested in participating must meet specific requirements including minimum enrollment of 2,000 patients, existence as a stand-alone plan for at least three years, and no CMS or law enforcement sanctions. This program will be offered in select states (Virginia, Florida, Louisiana, Iowa, Minnesota, Montana, Nebraska, North Dakota, South Dakota, and Wyoming) chosen to represent a broad...
patient population and provide enough power to serve as a comparator to other regions.

The model test consists of four core components. The first is greater flexibility in target populations and MTM benefits offered. This flexibility includes waivers of multiple traditional Part D MTM requirements such as documentation in the standard Comprehensive Medication Review format and provision of MTM services by a pharmacist. The aim is to strengthen communication between plans, prescribers, and pharmacies by allowing electronic exchange of interoperable MTM documentation that can integrate more conveniently into prescribers’ and pharmacy workflow. Enrolled PDPs will be asked to develop internal protocols in place of CMS requirements to improve delivery of MTM by selecting the most appropriate recipients and offering risk-stratified interventions. The second component is a prospective payment offered to each enrolled PDP outside of their annual Part D bid to cover the cost of their interventions for MTM expansion. The third component is a direct premium subsidy offered to enrolled PDPs who reduce projected Medicare Part A and B expenditures by at least 2% and meet pre-specified quality requirements. This subsidy will reduce premiums and is intended to help PDPs gain a competitive edge in the marketplace if they perform well on quality measures in addition to cost reduction. The fourth component implements quality measures which will be established by CMS in mid-2016. They will be identified using Systematized Nomenclature of Medicine (SNOMED) codes to convert MTM interventions and patient outcomes to numeric codes for improved collection and analysis. Regulatory flexibility and financial incentives outlined in the Part D Enhanced MTM Model Test aim to better align the priorities of stand-alone Part D PDPs with Medicare goals to improve quality of patient care while reducing overall healthcare costs.

**The Impact of Dietary Supplements on Emergency Department Visits**

*Chelsea Steffen*

*First Light Health System*

Dietary supplements are commonly used in the United States. Despite this, data regarding their safety and adverse effects is limited, likely because FDA approval is not required. In the United States, about half of the adult population reports having used at least one dietary supplement in the past month. A recent study analyzed emergency department (ED) visits for adverse events related to dietary supplements. Dietary supplements include micronutrients (vitamins and minerals), herbal, and complementary nutritional products.

Nationally representative surveillance data from 63 EDs acquired between 2004 and 2013 were used to analyze ED visits due to adverse events from dietary supplements. There were 3,667 cases identified during this time period, which results in a calculated average of 23,005 annual ED visits. An estimated average of 2,154 of these visits resulted in a hospital stay. Clinicians attributed these adverse events to use of only one supplement in 88.3% of ED visits.

The average age of patients was 32 years, with female patients involved in over half of the ED visits. Patients were more likely to be hospitalized if they were 65 years of age and older. Dietary supplement adverse events due to unsupervised ingestion by children occurred in one fifth of these ED visits and 61.9% of cases involved a micronutrient product. The following averages excluded unsupervised ingestion by children. A single herbal or complementary product was involved in 65.9% of ED visits due to adverse events from dietary supplements and 31.8% involved a single micronutrient. Ten percent of visits were due to an energy product and 25.5% of visits involved a weight-loss product. Weight-loss products were more common among female patients whereas sexual-enhancement or bodybuilding products were more common among male patients. Cardiac effects were the most common symptoms in weight-loss, energy, sexual-enhancement, and bodybuilding products. Mild to moderate allergic reactions and swallowing problems were the most common adverse events from most micronutrients. Swallowing problems were most common with calcium products and abdominal symptoms often involved iron or potassium.

Dietary supplements are marketed and regulated under the presumption of safety, yet an average of 23,000 ED visits and 2,000 hospitalizations annually are a result of adverse events due to dietary supplements. With this data, we can focus on interventions to help reduce the risk of adverse events due to dietary supplements such as safety packaging and education on safe storage.
Newly Approved Praxbind® (idarucizumab)
Manufactured by Boehringer Ingelheim, for the
Reversal of Pradaxa® (dabigatran etexilate)
Miriam Maklad, Pharm.D.
Cub Pharmacy

Teaser Summary: Praxbind® (idarucizumab) is newly approved for the reversal of Pradaxa® (dabigatran etexilate). Idarucizumab is available for intravenous use as a one-time dose in life-threatening bleeding and in emergency surgery and procedures.

Indication: Idarucizumab is a humanized monoclonal antibody fragment (Fab) with an FDA-approved indication for the specific reversal of dabigatran in life-threatening or uncontrolled bleeding and in emergency surgeries and procedures. Of note, idarucizumab received accelerated FDA approval based on findings seen in healthy volunteers.

Mechanism of Action: Idarucizumab is a humanized monoclonal antibody fragment that is derived from an IgG1 isotype molecule, whose target is the direct thrombin inhibitor dabigatran. Idarucizumab binds to dabigatran and its metabolites with a greater affinity than dabigatran's affinity to thrombin, thus reversing the anticoagulant effect.

Dosage and Administration: Idarucizumab is available for intravenous use only. It is available in vials containing 2.5g/50mL with a recommended 5g one-time dose. There is limited data to support additional administration of idarucizumab beyond the recommended 5g dose. Once solution has been removed from vial, idarucizumab must be administered within 60 minutes, usually administered as two consecutive IV infusions or consecutive bolus injections (2.5g each).

Effectiveness: The Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) trial was a prospective cohort study in which 90 patients treated with dabigatran who had uncontrolled bleeding or required emergency surgery or procedures were given 5.0 g idarucizumab. Idarucizumab provided a median maximum dabigatran reversal of 100% of the anticoagulation effect within 4 hours in an interim analysis.

Safety: Specific laboratory monitoring is not recommended for idarucizumab. The most common adverse reactions seen in idarucizumab in frequencies greater than 5% include headache, hypokalemia, delirium, constipation, fever, and pneumonia. It is important to consider restarting antithrombotic therapy when appropriate to prevent thromboembolic events from occurring. Dabigatran may be reinitiated 24 hours after idarucizumab has been administered. Idarucizumab has not been studied in pregnancy or pediatric populations.

Place in Therapy: A concern with novel oral anticoagulants like dabigatran is the lack of reversal agents in the event of a major bleed; however, with idarucizumab's recent approval, providers may be less hesitant to put their patients on this therapy. It is important to note that Idarucizumab will not reverse the effects of other antithrombotic therapies. Idarucizumab’s main place in therapy is for the reversal of dabigatran in life-threatening bleeding and in emergency surgery/procedures.

References


