Serotonin Syndrome: What is the Risk When Co-Prescribing a Triptan With a Selective Serotonin Reuptake Inhibitor (SSRI) or Selective Norepinephrine Reuptake Inhibitor (SNRI)?

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Background: Serotonin syndrome (SS) or serotonin toxicity is a potentially life-threatening diagnosis caused by an excessive amount of serotonin in the central nervous system (CNS). Symptoms of serotonin syndrome may include agitation, diaphoresis, muscle rigidity or spasms (clonus), tremor, and hyperthermia. The Hunter Toxicity Criteria and the Sternbach Criteria are diagnostic tools for serotonin syndrome. Serotonin or 5-hydroxytryptamine (5-HT) is a neurotransmitter which may bind with different 5-HT receptors in the body leading to effects on the enteric nervous system, CNS, respiratory function, and cardiovascular system. Triptans are 5-HT1b/1d receptor agonists leading to vasoconstriction and reduced inflammation to aid in migraine relief. The mechanism of SSRI's is to block the reuptake of serotonin leading to increased levels of serotonin available to bind the 5-HT receptors. This is compared to SNRIs which block reuptake of serotonin, norepinephrine, and to a smaller extent dopamine. In 2006, the US Food and Drug Administration (FDA) published an advisory on the risk of serotonin syndrome with the combined use of a triptan with SSRI or SNRI therapy. The alert stated "Potentially Life-Threatening Serotonin Syndrome with Combined Use of SSRIs or SNRIs and Triptan Medications." There is a lack of evidence available to show the specific risk associated with combined medication use.

Objective: To assess the risk of SS with concomitant use of triptans and SSRI or SNRI antidepressants.

Study Design: This was a 14 year, retrospective database study using the Partners Research Patient Data Registry. This data review searched for patients who received prescriptions for both a triptan and SSRI or SNRI from January 1, 2001 to December 31, 2014 in Boston, Massachusetts and surrounding areas. Co-prescription was defined as receiving at least one prescription for a triptan and one for a SSRI/SNRI during the study period. Diagnosis of SS was determined by review of the electronic medical record. Serotonin syndrome does not have its own ICD-9 code but is part of "other extrapyramidal diseases and abnormal movement disorders" (ICD-9 code 333.99). Information regarding medication use was determined from lists of medications prescribed by clinicians in this healthcare network and from clinician notes on the date of the event. Then, cases were reviewed by three individuals to verify accuracy of data abstraction and application of diagnostic criteria.
Those defined as “possible cases” of SS related to co-prescription were those in which SS was suspected but did not meet diagnostic criteria or triptan ingestion did not occur during the same time as the event. For this study, it was assumed that subjects were at risk of serotonin syndrome for one full year during the time that co-prescription occurred.

**Results:** From the search, 47,968 subjects were prescribed a triptan of which 19,017 were co-prescribed a SSRI or SNRI. Of those prescribed both a triptan and SSRI/SNRI, 229 had a reported diagnosis of extrapyramidal symptoms of which 17 cases were suspected SS. Of those 17, seven subjects actually met the criteria for SS. Four of these seven subjects met the Sternbach and Hunter criteria, two met the Sternbach criteria only and, one met the Hunter criteria only. From consideration of 15 possible cases per 30,928 person-years of exposure to co-prescription, the incidence rate was 2.3 cases per 10,000 person-years (95% CI 0.6-3.9). Only two of the seven cases of SS occurred when patients were receiving co-prescriptions at the same time as the event (definite cases), thus providing an incidence rate of 0.6 cases per 10,000 person-years (95% CI 0-1.5). Despite the publication of the FDA risk advisory in 2006, there has been an increasing trend of triptan prescribing and co-prescribing when comparing incidence from 2001 to 2014. However, the increase in triptan prescriptions did not increase the incidence in SS diagnosis.

**Conclusions:** The risk of SS from co-prescription of triptan with SSRI or SNRI was low and the trial showed no life-threatening cases of SS. These results spark doubt regarding the validity of the FDA advisory which should be considered for revision.

**Key Point:** A significant increase in SS events was not seen when triptan therapy was combined with SSRI or SNRI medications.

**Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout**

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**Background:** Patients with a diagnosis of gout have an increased risk of cardiovascular (CV) events making CV safety of medications used for gout a concern. Early febuxostat development trials suggested modestly higher CV event rates when compared with allopurinol and placebo. As an FDA requirement the CARES trial, Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout and Cardiovascular Morbidities, was conducted.

**Objective:** The purpose of this trial was to assess CV safety of febuxostat, a non-purine xanthine oxidase inhibitor, compared to allopurinol, a purine base analogue xanthine oxidase inhibitor, in patients with gout and history of major CV disease.

**Study Design:** This trial was a multicenter, randomized, double-blind noninferiority trial. Takeda Pharmaceuticals funded this trial and participated in trial design, conduct and monitoring along with an independent data safety monitoring committee. Eligible participants were male ≥50 years of age or female ≥55 years of age with history of major CV or cerebrovascular disease defined as at least one of the following: myocardial infarction (MI), hospitalization for unstable angina, coronary or cerebral revascularization procedure, stroke, hospitalized transient ischemic attack (TIA), peripheral vascular disease, or diabetes with evidence of microvascular or macrovascular disease. Participants had a diagnosis of gout according to the American Rheumatism Association (ARA) definition and met additional criteria including serum uric acid level ≥7.0 mg/dL at screening or ≥6.0 mg/dL at screening plus inadequately controlled gout, as pre-defined by the investigators.

At the screening visit, previous gout therapy was discontinued for a 1 to 3 week washout period. Participants were initiated on colchicine 0.6 mg daily. This was given as monotherapy during the washout period and continued concomitantly with study drug for a total of 6 months of colchicine therapy. Participants were randomized and stratified by renal function to received either febuxostat or allopurinol once daily as study drug. Initial allopurinol dose was renal-adjusted and doses for both allopurinol and febuxostat were titrated up based on serum urate levels following a pre-defined protocol.

The primary endpoint was a composite measure including first occurrence of CV death, non-fatal MI, nonfatal stroke, and urgent revascularization for unstable angina. The individual components of the primary composite were measured as secondary endpoints and death from any cause was measured as a safety endpoint. To assess non-inferiority, the CARES trial was designed to accrue a total of 624 primary events. Non-inferiority determination would be made if the upper bound of the hazard ratio (HR) was less than 1.3.

**Results:** A total of 6190 participants were included in the modified intention-to-treat analysis. High rates of discontinuation were noted for both febuxostat and allopurinol groups, 57.3% and 55.9%, respectively. The median duration of exposure and duration of follow-up were 728 days and 968 days for febuxostat and 719 days and 942 days for allopurinol, respectively. The modified intention to treat analysis in this trial included participants who received at least one dose of trial medication. Therefore, patients who discontinued therapy were included in the analysis rates.
The primary composite outcome occurred in 10.8% of patients in the febuxostat group and 10.4% of patients in the allopurinol group. The HR for primary composite outcome was 1.03 [97% CI 0.87 - 1.23] demonstrating non-inferiority of febuxostat. The secondary endpoint of CV death comparing febuxostat and allopurinol was HR 1.34 [95% CI 1.03 - 1.73] and death from any cause was HR 1.22 [95% CI 1.01 - 1.47]. No other secondary endpoints demonstrated statistical significance. Of note, the serum urate levels and gout flares between arms were similar, although not collected or analyzed for statistical significance.

Conclusions: Participants with a history of CV disease and current uncontrolled gout requiring additional serum urate level lowering therapy had similar outcomes with febuxostat compared to allopurinol in regard to the primary composite endpoint of first occurrence of CV death, non-fatal MI, nonfatal stroke, urgent revascularization for unstable angina. However, statistical significance was found showing increased risk for CV death and death from any cause with febuxostat when compared to allopurinol.

Limitations: A significant limitation of this trial was the large discontinuation and loss to follow-up rate. Despite rates between arms being similar, the trial did not provide further information regarding these rates. Discontinuation of treatment may create bias toward the null hypothesis, creating a potential to miss a statistically and clinically significant difference between arms for the primary and other endpoints. It should also be noted that the manufacturer of febuxostat and colchicine, two medications used in the trial, funded and supported the trial presenting a risk of bias. Although doses of both medications were titrated according to urate levels, neither medication was titrated up to the maximum dose.

Key Point: Participants in the CARES trial with gout and history of CV disease treated with febuxostat has similar outcomes in regard to overall major CV events as those treated with allopurinol. Outcomes for CV death and all cause mortality were higher in participants receiving febuxostat therapy.

Primary Literature Review: Effect of Opioid vs Non-opioid Medications on Pain-Related Function in Patients with Chronic Back Pain or Hip or Knee Osteoarthritis Pain – The SPACE Randomized Clinical Trial

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Background: Despite an increasing number of opioid-related deaths and limited efficacy, opioids have become a common treatment for musculoskeletal pain. Opioid prescribing for treating chronic pain is discouraged by many institutions given the high risk/benefit ratio, and there is evidence that non-opioid alternatives can be equally effective.

Objective: This randomized clinical trial aimed to compare opioid therapy vs non-opioid therapy over 12 months for primary care patients suffering from chronic back pain or hip or knee osteoarthritis pain of at least moderate intensity despite analgesic therapy. The hypothesis was that opioids, compared with non-opioids, would result in better pain management and more adverse events.

Design: The primary outcome was pain-related function. In order to maintain the most realistic approach, a variety of patients from primary care (total of 240) were included. Therapies were delivered at varying doses and with flexibility in medication selection based on a stepwise methodology detailed below. All patients were allowed to seek out non-pharmacological options as well. Treatments were adjusted within treatment groups according to participant response. Participants had to be suffering from chronic pain defined as a duration of 6 months or greater. Patients were recruited from 62 Minneapolis Veteran’s Affairs (VA) primary care clinicians from June 2013 to December 2015.

Patients in the opioid group started with immediate release (IR) opioids. Step one was morphine IR, hydrocodone/acetaminophen, and oxycodone IR. Step 2 was sustained action (SA) morphine and oxycodone SA. Step three was transdermal fentanyl. Single opioid regimens were preferred but patients were allowed to use combination of SA and IR opioids if necessary. Opioids were not titrated to doses greater than 100 morphine equivalents (ME) mg. Lower doses were used if adequate pain relief was achieved.

In the non-opioid group, the first step was acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). Step two included nortriptyline, amitriptyline, gabapentin, topical capsaicin or lidocaine. The third step involved pregabalin, tramadol, and duloxetine.

Results:
Of the 265 enrolled patients, 25 withdrew before to randomization mostly due to concerns with substance abuse, or lack of interest in the study. As a result, 240 were randomized (mean age, 58.3 years; women, 32 [13.0%]); 234 (97.5%) completed the trial. In total, 120 patients were enrolled in each arm of the study. There was no reported difference in pain-related function between the two groups over 12 months (P = 0.58). Pain intensity was significantly better in non-opioid group (P = 0.03). The most common treatment in the non-opioid group was non steroidal antiinflammatory agents.
Health related quality of life was not significantly different between the groups. The opioid group experienced significantly more medication related symptoms (overall P = 0.03). There was no difference in adverse outcomes or misuse between the groups.

**Conclusion:** Among patients with chronic back pain or hip or knee osteoarthritis pain, there was no significant difference in pain-related function between treatments with opioids compared with non-opioids over 12 months.

**Key Point:** Opioids are not more effective than non-opioid pain medications when treating chronic back pain or hip and knee osteoarthritis pain, but do pose significantly higher risks.

**Two is Company, but is Three Really a Crowd? Once Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD**

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**Background:** With the recent advancements in inhaler delivery systems there has been new developments for multi-drug options in a single inhaler. This is particularly useful for patients with advanced and symptomatic chronic obstructive pulmonary disease (COPD) who may require up to three classes of inhalation therapy: inhaled corticosteroids (ICS), long-acting B2-agonists (LABA), and long-acting muscarinic antagonists (LAMA). Daily administration of these maintenance medications is vital to avoid COPD exacerbations and hospitalizations. Using multiple inhalers with varying administration mechanisms can be overwhelming and confusing to patients. Thus, the introduction of one inhaler containing all three COPD therapies brings a novel product to the market that has the potential to improve patient adherence and outcomes.

**Objective:** Is single inhaler triple therapy as effective as the current therapy? A recently published study in *The New England Journal of Medicine* sought to answer this question.

**Study Design:** The Informing the Pathway of COPD Treatment (IMPACT) trial was a phase 3 study that analyzed the efficacy and safety of a triple therapy in one inhalation method as compared to dual therapy in a single inhaler. This randomized, double-blind, parallel-group study enrolled 10,355 participants age 40 years of age or older and had symptomatic COPD (COPD Assessment Test [CAT] score, ≥10. These patients had either a forced expiratory volume in one second (FEV1) that was less than 50% of the predicted normal value and a history of at least one moderate or severe exacerbation in the previous year, or an FEV1 of 50 to 80% of the predicted normal value and at least two moderate exacerbations or one severe exacerbation in the previous year. Participants were randomized into one of the three following groups: (1) once daily use of combination fluticasone 100 mcg + umeclidinium 62.5 mcg + vilanterol 25 mcg (triple therapy) (2) fluticasone 100 mcg + vilanterol 25 mcg (dual therapy) (3) umeclidinium 62.5 mcg + vilanterol 25 mcg (dual therapy), which were each administered in a single Ellipta inhaler. These treatments are consistent with recommendations from Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 guidelines. However, because patients were randomized, their assigned treatment study may not match corresponding recommended GOLD 2017 treatment according to FEV1 and patient symptoms. The patients were followed for 52 weeks, and the primary outcome the authors assessed was the annual rate of moderate or severe COPD exacerbations during treatment.

**Results:** The results of the study found that patients taking the triple therapy had an overall lower rate with 0.91 per year of moderate and severe exacerbations during treatment as compared with 1.07 per year with fluticasone-vilanterol dual therapy [95% CI 0.80-0.90; rate ratio with triple therapy, 0.85], and 1.21 per year with umeclidinium-vilanterol [95% CI 0.70-0.81; rate ratio with triple therapy, 0.75] (P<0.001). Safety analysis of the three trial groups showed similar effects, and no new findings were associated with the triple therapy inhaler. Some of the side effects noted by the investigators included anticholinergic side effects, cardiovascular effects (hypertension, arrhythmias), and rates of pneumonia infections. Lung function was measured by mean change in trough forced expiratory volume (FEV1) from baseline. Triple therapy showed improved lung function as compared to both groups [difference of 97 mL between triple therapy and fluticasone-vilanterol group (95% CI, 85-109, P<0.001), and 54 mL difference between triple therapy and umeclidinium-vilanterol groups (95% CI, 39-69, P<0.001)]. The investigators found there were no clinically relevant differences in lab values including ECG, vital signs, or other clinical laboratory values.

**Conclusion:** The authors concluded that once-daily single-inhaler triple therapy with fluticasone, umeclidinium, and vilanterol resulted in significantly lower rates of moderate or severe COPD exacerbations. The results of this head-to-head trial look promising.

**Key Point:** For patients who may require triple therapy, an option that offers all three in one inhaler would be ideal for improved adherence. Future research may demonstrate long-term impacts of this novel therapeutic combination.
A Closer Look at the Updated ADA Standards of Medical Care Recommendations for Patients with Diabetes and ASCVD\textsuperscript{5-11}
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Background: In 2008, the U.S. Food and Drug Administration (FDA) published a Guidance for Industry, which required sponsors of drug trials to conduct cardiovascular outcome trials (CVOTs) in order to demonstrate that their new antidiabetic therapy would not result in an unacceptable increase in cardiovascular risk.\textsuperscript{1,2}

The results of recent CVOTs of antidiabetic medications have influenced the newly updated recommendations in the 2018 Standards of Medical Care in Diabetes. These guidelines suggest adding a second agent with evidence of cardiovascular risk reduction in patients with atherosclerotic cardiovascular disease (ASCVD) who are already on metformin and need additional therapy.\textsuperscript{3}

Evidence: EMPA-REG OUTCOME randomized participants to either empagliflozin 10 mg or 25 mg once daily to placebo.\textsuperscript{4} Over 7,000 patients with established CVD were followed for approximately 3.1 years. The primary endpoint was a composite endpoint of 3-point major adverse cardiovascular events (MACE): cardiovascular death, nonfatal MI, and nonfatal stroke. Use of empagliflozin was associated with reduced risk of the primary composite endpoint and met both non-inferiority and superiority criteria (HR 0.86 [0.74-0.99]; P=0.04).\textsuperscript{4} The significance of the primary composite endpoint was largely driven by reduction in cardiovascular death, which was the only significant individual component of the composite endpoint (HR 0.62 [0.49-0.77]; P<0.001).\textsuperscript{4}

The CANVAS Program randomized participants to canagliflozin 100 mg or 300 mg once daily to placebo. The CANVAS Program included over 10,000 participants: over 4,000 from the CANVAS study and over 5,000 from the CANVAS-R study.\textsuperscript{5} Participants were followed for approximately 2.4 years on average. Interestingly, only 66% of CANVAS Program participants had established CVD at baseline, the remaining 34% participants had multiple risk factors for developing CVD. Canagliflozin use was associated with reduced risk of the primary composite endpoint, and this met non-inferiority and superiority criteria (HR 0.86 [0.75-0.97]; P=0.02).\textsuperscript{5} None of the individual components of the composite endpoint demonstrated a significant risk reduction and the use of canagliflozin was associated with increased risk of bone fracture (HR 1.26 [1.04-1.52]) and amputations (HR 1.97 [1.41-2.75]).\textsuperscript{5}

LEADER randomized participants to liraglutide 1.8 mg once daily or to placebo. Approximately 80% of the participants in LEADER had established CVD, with others having high risk of developing CVD.\textsuperscript{6} Over 9,000 participants were followed for approximately 3.8 years. Use of liraglutide reduced the risk of the primary composite endpoint of 3-point MACE (HR 0.87 [0.78-0.97]; P=0.01).\textsuperscript{6} Similar to EMPA-REG OUTCOME and the CANVAS Program, both non-inferiority and superiority criteria were met. The significance of the primary composite endpoint was driven by reduction of cardiovascular death, which was the only significant individual component of the composite endpoint (HR 0.78 [0.66-0.93]; P=0.007).\textsuperscript{6}

Discussion: EMPA-REG OUTCOME\textsuperscript{4} and the CANVAS Program\textsuperscript{5} demonstrated 14% risk reduction of 3-point MACE, and LEADER\textsuperscript{6} demonstrated a 13% risk reduction of 3-point MACE (NNT 63, 218, and 53 for empagliflozin, canagliflozin, and liraglutide, respectively). However, only EMPA-REG OUTCOME and LEADER demonstrated a lower risk of cardiovascular death (38 and 22%, respectively).\textsuperscript{4,5} Perhaps this is because the CANVAS Program included the lowest percentage of participants with established CVD. Interestingly, none of these CVOTs showed reduced risk of the individual components of nonfatal MI or nonfatal stroke.
Admittedly, EMPA-REG OUTCOME and LEADER defined cardiovascular death in a controversial manner. Protocols for these studies confirm that all death not attributed to the categories of cardiovascular death or non-cardiovascular death was presumed to be cardiovascular in nature, which may have impacted the significance of findings from EMPA-REG OUTCOME and LEADER. A sensitivity analysis that removed non-assessable death from EMPA-REG OUTCOME no longer demonstrated superiority for the primary composite endpoint; however the superiority was maintained for the individual component of cardiovascular death. Thus, the results of EMPA-REG OUTCOME are highly debated between experts. In a sensitivity analysis of LEADER, superiority persisted for the primary composite endpoint.

Clinical Impact: In patients with uncontrolled T2DM and comorbid ASCVD, the addition of empagliflozin, canagliflozin, or liraglutide to metformin is supported by the 2018 Standards of Medical Care in Diabetes. Clinicians should continue to demonstrate patient-centered care when deciding upon an individual medication. It is preferred to use a medication that has been shown to reduce risk of cardiovascular death in addition to 3-point MACE; however more studies are needed to yield robust statistical support for the use of various SGLT-2 inhibitors and/or GLP-1 agonists for risk reduction of cardiovascular disease in patients with T2DM.

Benefit of Adding Ezetimibe to Statin

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Background: Statins are an important therapy used to reduce cholesterol levels and lower risk of cardiovascular (CV) events. Ezetimibe is another medication that can be used to lower cholesterol levels by reducing intestinal absorption of cholesterol. The effect of ezetimibe on risk of CV events when used with statins has been assessed in the IMPROVE-IT trial and was shown to lower LDL cholesterol and improve CV outcomes. The results of a subanalysis of this trial compared use of this combination therapy in patients with or without diabetes, which provides more information about whether adding ezetimibe to statin therapy is beneficial for reducing LDL cholesterol and CV risk.

Evidence: The IMPROVE-IT trial was a randomized, double-blind trial in which subjects with acute coronary syndrome received ezetimibe 10 mg plus simvastatin 40 mg or simvastatin 40 mg plus placebo. Average LDL cholesterol at baseline was 94 mg/dL. Following intervention, LDL cholesterol lowered to 70 mg/dL in the simvastatin plus placebo group versus 54 mg/dL in the ezetimibe plus simvastatin group. The primary endpoint was death from CV disease, major coronary event, or non-fatal stroke. The authors found a two percent risk reduction in the primary endpoint with ezetimibe plus simvastatin, which was statistically significant (0.936 [95% CI 0.89-0.99]; P = 0.016). One subgroup of the IMPROVE-IT trial included individuals with diabetes. At baseline, diabetes patients had a lower median LDL cholesterol than those without diabetes (89 mg/dL and 97 mg/dL respectively). Following intervention, the ezetimibe plus simvastatin group had a lower average LDL cholesterol than simvastatin plus placebo regardless of diabetes status. For patients who had diabetes, the authors found a 5.5% reduction in the primary endpoint with ezetimibe plus simvastatin (0.85 [95% CI 0.78-0.94]). For patients without diabetes, the absolute difference was 0.7% (0.98 [95% CI 0.91-1.04]; p = 0.02). Benefit in the diabetes population was seen most with reduction of acute ischemic events.

Discussion: The IMPROVE-IT trial and the diabetes subanalysis of this trial showed significant reduction in the primary endpoint of death from CV disease, major coronary event, or non-fatal stroke. The results may mean that reducing LDL cholesterol can reduce risk of CV events. Authors considered the benefit of adding ezetimibe to simvastatin to be modest overall for the IMPROVE-IT trial, but patients in the subanalysis who had diabetes benefited considerably more than those without diabetes. The authors note the reason for this is unclear, but suspect it is due to more than just lowering of LDL cholesterol and may be because of effects of ezetimibe on glucose metabolism. The most recent update of the American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce ASCVD Risk do not suggest treating to a target LDL cholesterol. However, the 2017 American Association of Clinical Endocrinologists/American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of CV Disease do suggest treating to a goal LDL cholesterol depending on individual risk of CV disease. They define a goal of less than 55 mg/dL for patients who are at extreme risk of clinical CV disease, which includes individuals with diabetes. These guidelines are important to consider when determining therapeutic options and may help guide whether or not further LDL lowering with addition of ezetimibe may be warranted.

There were several limitations to the IMPROVE-IT studies, including that simvastatin was the only statin assessed, an upper LDL cholesterol limit was set at
entry to the study, and the diabetes subgroup results have limited statistical power.3,4

Clinical Impact: Adding ezetimibe to statin therapy may be a reasonable option to reduce LDL cholesterol and CV risk for patients with acute coronary syndrome who are at an extreme risk for CV disease. This would include patients who have diabetes. A patient-centered risk versus benefit analysis should be done on an individual patient basis and take into consideration current clinical trials and practice guidelines.

Cost of Prescription Drug-Related Morbidity and Mortality16
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Background: The role of primary care in the prevention and management of chronic diseases has become a pillar of healthcare to improve overall population-health outcomes and to address the ongoing growth of healthcare spending. The breadth of medication-related cost beyond baseline drug pricing has become increasingly concerning. Medication morbidity and mortality, including non-adherence to medications, was estimated at approximately 13% of healthcare spending in 2008 as a result of non-optimized medication use. With the significant changes in the healthcare system since this analysis and the increased attentiveness to drug cost, an updated estimation of medication related costs would provide a cornerstone to drive healthcare related reform and help align efforts to reduce costs associated with medication use. This article aimed to update the estimated cost of medication-related morbidity and mortality resulting from non-optimized medication therapy from a third-party payer perspective.

Methods: Total costs of non-optimized prescription drug use and average pathway costs for a patient who experienced a treatment failure (TF), a new medical problem (NMP), or a TF and NMP were modeled based on probability pathways previously published in the literature.

Results: The estimated annual cost of prescription drug–related morbidity and mortality resulting from non-optimized medication therapy was $528.4 billion in 2016 US dollars, ranging from a minimum of $495.3 billion to a maximum of $672.7 billion when utilizing lowest and highest estimations of hospitalization costs, respectively. Based on information gathered from the decision-analytic model used, estimated cost of a physician encounter was an average of $850 (range of $792 to $902) when incorporating costs of patients receiving no drug therapy, successful drug therapy, and downstream costs of non-optimized drug therapy. The average cost of an individual experiencing NMP from non-optimized drug therapy was estimated to be highest at $2610 (range from $2374 to $2848) compared to TF, or a combination of TF and NMP, at $2481 (range from $2233 to $2742) and $2572 (range from $2408 to $2751), respectively.

Conclusions: The updated annual cost of drug-related morbidity and mortality from non-optimized medication use of $528.4 billion is 16% of total US health care expenditures in 2016, compared to 8% and 13% in 1995 and 2008, respectively. Although this estimate does account for overall price inflation, it does not include non-medical or indirect cost, such as caregiver expenses or lost productivity, which have been estimated to be more than the direct medical cost alone for many prevalent chronic diseases.

Factors including the increasing Medicare population and the growing utilization of specialty drugs will continue to drive medication related costs. Costs for prescription drugs for major disease categories, home health services, and medical resources (eg ED visits, hospitalizations, etc) are expected to accelerate between 2018 and 2025.

Study authors conclude that reducing these utilization costs will require a systematic approach to medication management to reduce the number of patients experiencing TF, NMP, or TF and NMP resulting from non-optimized medication therapy. Comprehensive medication management (CMM) focused on achieving optimal clinical and patient centered goals of therapy is becoming recognized as a cornerstone of delivery and payment reform efforts. The collaboration of clinical pharmacists with the rest of the healthcare team will be increasingly relied upon to make real-time drug therapy decisions. Utilizing CMM is an effective way to resolve drug therapy problems with the shortage of primary physicians and support other specialty areas, such as behavioral health, where medications are having a growing role.

Expansion of CMM programs can help reduce the avoidable medical costs associated with non-optimized medication use and improve overall patient care.
A Pilot Study for Antimicrobial Stewardship Post-Discharge: Avoiding Pitfalls at the Transitions of Care

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Background: Antimicrobial stewardship programs (ASP) are well established across the country – predominantly in the inpatient setting. These programs aim at making interventions to ultimately decrease antibiotic resistance and support appropriate antibiotic use including dosing and duration of therapy.

Objectives: The main objectives of this study were to describe the feasibility of expanding ASP and to follow hospitalized patients after discharge and determine its impact on inappropriate antimicrobial therapy 72 hours after inpatient culture data were finalized.

Study Design: This was a prospective cohort study that included all patients discharged on antimicrobial agents with unresulted culture data at hospital discharge between February 3, 2016 and March 2, 2016. These patients were compared to a pre-intervention cohort discharged without any ASP intervention/ follow up between September 18, 2015 and October 18, 2015. Hospital reports were run daily to identify qualifying patients. Once finalized culture data was available, the ASP pharmacist or pharmacy resident would determine regimen appropriateness. Inappropriate antimicrobial therapy was defined as isolation and identification of any organism from available microbiology cultures taken prior to hospital discharge with documented in vitro resistance (or intermediate resistance) to all prescribed outpatient antimicrobial agents. If the ASP pharmacist or pharmacy resident deemed therapy inappropriate after manual chart review, recommendations were made to the on-call infectious disease physician. Criteria for intervention included, but were not limited to: whether the identified organism was a likely pathogen, whether an adequate duration of antimicrobial therapy had been completed. If an intervention was considered necessary by the infectious disease physician, recommendations were then communicated to the provider who had prescribed the outpatient antimicrobial therapy, with questions and follow-up provided via telephone.

Results: 61 patients with culture data finalized after discharge were identified, only 38 of these patients were prescribed oral antimicrobial therapy at discharge and evaluated by the ASP pharmacist. Five (13%) had a suspected pathogen identified as non-susceptible to their prescribed antimicrobial. Therapy modification was accepted for 3 (60%) of 5 patients.

The historical cohort had 63 patients with culture data pending at discharge, 43 of them had antimicrobial therapy prescribed. Five (11%) patients in this cohort had grown pathogens reported as non-susceptible to their prescribed antimicrobial therapy, resulting in therapy modification by the discharging physician for 1 (20%) of the 5 patients.

Conclusions: This outpatient centered ASP program shows potential at improving appropriate antimicrobial therapy selection and ultimately decreasing antimicrobial resistance. Some limitations of the study include a small sample size, and a narrow definition of inappropriate antimicrobial therapy, which limited the potential interventions that could have been made by the pharmacist. These results should only be hypothesis forming, to potentially guide other institutions who want to implement their own transitional care ASP.

Increasing Access to Hepatitis C Medications: A Program Model to Obtain Prior Authorization Approval

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Background: Direct-acting antivirals (DAAs) have been shown to be effective and tolerable in treating hepatitis C virus (HCV) infections. Unfortunately, the high cost of these medications has resulted in insurance companies requiring a prior authorization (PA) in order for patients to receive access to these medications. Many insurers, including Medicaid, can limit access of DAAs to patients with liver fibrosis. The PA process includes a health insurance provider determining if a specific medication treatment is necessary for a patient, and approving or denying the medication to be covered by insurance. This process is time consuming for providers and can cause the patient to be in an uncertain waiting period without access to their antiviral medication. Each individual insurer may have different policies for determining which patients qualify for oral DAA treatments, which is why obtaining approval efficiently and successfully requires expertise. The Respectful and Equitable Access to Comprehensive Healthcare (REACH) program, which is based in Mount Sinai Hospital, uses an interprofessional team model to provide a variety of services to reduce barriers to successful treatment (such as mental health and social work) for HCV-infected patients. The PA process is managed by a nurse and a specialty pharmacy, to lessen physician and patient burden.
**Objective:** The aim of this study is to analyze the number of successful PA approvals for DAA hepatitis C medications by analyzing specific factors that may predict a PA’s approval success.

**Study Design:** A retrospective chart review of program databases and medical records of all patients in the REACH program whose DAA HCV medications were ordered between November 1, 2014, and October 31, 2015 was performed. A total of 197 patients were followed for 180 days, or until PA approval was obtained. Patient clinical characteristics, number of steps in the PA process, and time until medication approval were analyzed. The steps involved in the process included a program nurse, specialty pharmacy and patient navigators.

**Results:** The primary outcome measured was the number of steps in the medication approval process required to obtain PA approval, while the secondary outcome was the time needed to obtain approval of the medication in number of days. The main medication applied for was ledipasvir/sofosbuvir (84.3%). The program obtained HCV medication approval for 93% of the prescriptions (95%CI 88%-96%). The mean time to approval was 59.8 days (SD=64.5). When analyzing the time to approval, 37% were approved on first submission with a mean of 30.7 days to approval, while approval after internal appeal (2 steps) was around 45% with 66.8 mean days. It was determined that Medicare or Medicaid/Medicare compared to Medicaid solely resulted in fewer steps in the PA cascade. A P value <0.200 determined independent predictors of time to approval by 180 days. The statistically significant predictors of time in relation to fewer steps in the process were comorbid hypertension, comorbid diabetes, older age, being domiciled and HCV genotype 1. Lastly, those with highest fibrosis scores (FIB-4 range >3.25) had slower medication approval than those with midrange fibrosis (P=0.005).

**Conclusions:** The REACH program demonstrated the role of patient navigators, nurses and specialty pharmacies coordinating PA approvals. Insurance status was found to be a factor determining the amount of work required, as was time required to obtain PA approval. Medicaid insurance and HCV genotype 2 were associated with increased steps to PA approval, while Medicare insurance and mid-range fibrosis were associated with less time to PA approval.

**Key Point:** This study demonstrates a collaborative model used to increase PA approvals for DAA medications for HCV infections in an urban primary care clinic. Patient specific factors such as insurance type, co-morbid conditions, and HCV genotype were found to decrease time to PA approval in this study.

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**Improving Medication Adherence Through Smartphone Apps**

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Medication nonadherence is a common and costly problem, occurring in about 50% of patients on chronic medication therapy and accounting for $100 billion in annual healthcare costs. Various methods to improve adherence have been studied, with most attempting to change patient behavior by using traditional reminders. While traditional reminders such as weekly pill boxes are helpful, they only passively remind patients to take their medications and can be cumbersome for complex regimens.

Smartphone adherence apps present a novel approach to improving adherence. Apps can easily be implemented as they are inexpensive, accessible to anyone with smartphones, and do not require separate devices or packaging. Features of adherence apps include reminders that can be set for consumption and refills, doses that can be logged, and data logs that can be shared with providers. Although there are limited studies on the efficacy of apps on adherence, text messaging, which uses similar prompts to apps, have been shown to improve adherence and behavior.1

One study evaluated the features of medication adherence apps across the operating systems Apple, Android, and BlackBerry during August to September 2012.2 A total of 147 unique apps were identified. To identify apps with the most utility for patients, the authors created a list of desirable features and ranked them by perceived importance to user desirability. Desirable features included online data entry, scheduling of complex medication instructions, cloud data storage, searching and entering medications using auto-population, syncing, exporting, and printing capabilities, tracking of missed and taken doses, provider input, availability on more than one operating system, free-only apps, generation of reminders with no connectivity, statement of HIPAA compliance, multiple profile, and multilingual capabilities. The 10 highest-rated apps were...
installed and tested by two authors using a standard medication regimen. A total of six apps met or exceeded manufacturer claims, with the majority being intuitive, easy to use, and providing satisfactory medication reminders. Among all apps, MyMedSchedule, MyMeds, and RxmindMe (no longer available) rated highest due to enhanced levels of functionality.

Apps with functionality beyond a simple reminder system, such as maintaining medication regimens through “pushing” to patients’ devices and the ability to export taken and missed doses, offer advantages for pharmacists and providers. The biggest limitation to medication adherence apps is that they can only be used by individuals who have access to a smartphone. In addition, very few apps are interconnected with information systems such as electronic medical records. This prevents pharmacists from customizing reminders for patients with adherence difficulties and ensuring the accuracy of manually inputted prescription data. Medication adherence apps have the potential to improve patient adherence during medication therapy management in community and ambulatory care settings.

Reducing Nicotine Content of Cigarettes- Public Health Implications

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Tobacco is the leading cause of preventable death not only in the United States but worldwide. The initiation of tobacco use is disproportionally high during one’s youth, starting with experimentation and leading to addiction due to the nicotine content of tobacco products. While smoking may be the cause of harm, addiction to nicotine sustains use and leads to a great burden on public health. Due to this, in July 2017, the FDA released an advanced notice of proposed rulemaking (ANPRM) to gain insight and opinions on requiring a reduced nicotine level in combustible tobacco products to discourage future addiction in our nation’s youth and to promote smoking cessation.

To lend expert opinion to the ANPRM, a simulation model analysis published in the New England Journal of Medicine assessed the risk and benefits of reducing the nicotine content of combustible tobacco. Utilizing data from the 2015 Census estimates, National Health Interview Survey estimates, and the National Youth Tobacco Survey, the use of cigarettes and effect on tobacco-related mortality and life-years gained was assessed. The analysis also included the opinion of eight experts on the potential implications of reduced nicotine content over an 80 year span from 2020 to 2100.

The results of the expert opinion and simulation model analysis showed a substantial positive impact on reduction of both smoking initiation and continued use. The distributions of the expert opinions on reduced cigarette use varied, yet all estimated a reduction in cigarette use with a median reduction of 2% [12.8% to 10.8%] in the first year. By 2060, the median estimate of smoking prevalence dropped to 1.4%. It was also estimated by 2060, 16 million people who would have initiated smoking with current nicotine levels would not become addicted to smoking, which increases to 33.1 million by 2100. This equates to the prevention of 8.5 million tobacco-related deaths and 134.4 million life-years by 2100. While these are results are based off estimates of current baseline trends and expert opinion, they point towards the potential positive effects of this intervention.

The FDA is currently accepting comments on this topic until June 14th, 2018. Current literature, including the above analysis, point to the potential positive implications of reducing the nicotine content of combustible cigarettes. If enacted, maximum nicotine limits for combustible cigarettes may ultimately become a polarizing topic for smokers and non-smokers alike. The FDA decision remains to be seen, but will likely have a monumental impact on public health and millions of lives in the United States.

References


