Medication Risk—Take a Number

Background
Identifying and resolving medication-related problems has always been our career goal. One challenge for pharmacists is that traditional medication software systems offer clinicians a binary view of drug interactions, presenting an assessment of one drug against one other drug. These legacy systems are (arguably) adequate to assess the safety of a medication regimen consisting of only one or two medications. However, in our PACE populations, most participants take 10+ different medications a day and the current pharmacy technologies are inadequate to ensure safety and minimize risk.

The Matrix
With our Medication Risk Mitigation Matrix®, we deliver a simultaneous, multi-drug review to identify medication-related risk across a variety of safety factors. The MRM Matrix presents meaningful opportunities to mitigate that risk. We partner with PACE, other health plans and provider groups in comprehensive medication management and care transitions programs to identify and substantially mitigate the risk associated with Adverse Drug Events.

By working with CareKinesis, PACE, health plans and provider groups have reduced their pharmacy spend and hospital admissions rates, in some cases by up to 50%. For these reasons, we were selected to lead a large Enhanced MTM initiative focused on reducing costs and improving therapeutic outcomes across a Medicare Part D population.

What’s new for 2017
Our Clinical Advisory Panel of PACE Medical Directors recently helped us release the ‘Medical Directors Dashboard,’ the first version of medication risk visualization that drills down to individual participant risk.

In 2017, our goal is to continue to build on these innovations.

- We have validated various tools for incorporation into the MRM Matrix, including the risk for sudden cardiac death, a common reason medications are removed from the market or given a black-box warning, e.g., anti-psychotics.
- We will further enhance prescribers’ ability to identify medication risk by providing each participant’s medication regimen with a validated risk score.
- We are presenting at various scientific conferences this year on the visual depiction of side effect risk. The goal is to help identify medication-related risk with a heat-map like diagram of a medication regimen’s contribution to various side effects.

Our pharmacists make recommendations, both at the time of prescribing and in a formal comprehensive medication review format, to help reduce risk. Getting data to those who need it is one of the greatest challenges in healthcare. We are determined to overcome this challenge in collaboration with our clients.

Thank you for your support. Stay tuned, the best is yet to come!
EireneRx Integrations Update

In January, CareKinesis and Mediture (technology provider of the TruChart Electronic Health Record used by PACE organizations across the country) announced the official launch of their collaborative software integration. Now, CareKinesis clients who are TruChart users can access CareKinesis clinical decision support tools at the point of e-prescribing.

“Prospectively identifying medication risk is essential to reducing avoidable adverse drug events, especially in the elderly,” stated CareKinesis CEO, Calvin H. Knowlton, PhD. “According to our PACE clients, our Medication Risk Mitigation Matrix solution, coupled with our geriatric-certified and trained pharmacists, increases prescribing accuracy, shortens time to effective treatment, and reduces total costs. Incorporating prospective Medication Risk Mitigation as a safety strategy in the prescriber workflow is a priority for us.”

Other features of the integration include back-end medication reconciliation and a newly launched PACE staff collaboration feature that securely offers enhanced, real-time communication within TruChart and between prescribers and CareKinesis clinical staff across the two platforms.

CareKinesis EHR integration partners include:

- Cognify
- PACECare
- NextGen
- Mediture

“What a pleasure it has been to have Lindsey here with us at LIFE St. Francis. She has been very professional, pleasant, knowledgeable, and helpful. She has gone out of her way to step in and assist where and whenever needed. We wish she could stay…

Thank you so much for sending us such a wonderful employee!”

Maureen Van Niel & Kim Brancati
LIFE St. Francis
FDA Monitors Drug Safety & Long QT

It is within the scope of the Food and Drug Administration (FDA) to continuously monitor for efficacy and adverse effects of medications that have been approved and are in use in the United States. Adverse events can be reported to the FDA through the MedWatch website or to the manufacturer directly.

If sufficient cumulative evidence exists to establish a public safety concern or a lack of clinical benefit, the FDA may recall or withdraw a medication from the market. In the past 25 years, 30 drugs were withdrawn from the market, the majority (56% n=17) of which were removed due to various cardiac safety issues.

Some non-cardiac reasons for drug removal were for severe allergic reactions, liver toxicity, rhabdomyolysis, and no clinical benefit. Medications removed for cardiac issues were removed due to prolongation of the QTc interval, lack of data on cardiovascular safety, cardiopulmonary events, heart valve damage, and general cardiovascular adverse events.

Drugs Removed due to QT Interval Prolongation

Medications removed from the U.S. market due to QT-prolongation include: terodiline, terfenadine, astemizole, grepafloxacin, cisapride, and ondansetron 32 mg (IV), comprising 23% of the last 30 medications removed. Many of these medications are metabolized via the CYP enzymatic system, and may put our elderly patients with multiple medications at higher risk for drug-drug interactions. Research shows that roughly 35% of 249 patients experiencing Torsade de Pointes (TdP) from non-cardiac drugs had a potential metabolic interaction.1

It is imperative to also consider over-the-counter medications (OTCs) and non-prescription products, including those like cimetidine and grapefruit juice, to understand a patient’s metabolizing enzyme functionality.2

Clinical Implications of Prolonged QT interval

Prolongation of the QT interval may predispose patients to syncopal events and the polymorphic ventricular tachycardia, Torsade de Pointes (TdP), which can lead to sudden death. This progression is more common with long episodes of TdP, but it has also been related to QTc interval length. It has been estimated that each 10 msec increase in QTc corresponds to a 5-7% exponential increase in risk for TdP.3 In general, TdP is rare when QTc is <500ms, accounting for less than 10% of all cases.4

Several studies have shown a positive correlation between increased QTc length and mortality, reinforcing the need to take action when a prolonged QTc is identified.5,6 Specifically, results have shown that the QTc interval length was a significant predictor of mortality with a hazard ratio of 1.13 (1.12-1.14, p<0.001), meaning patients with a prolonged QTc interval are 13% more likely to experience death than those with a normal QTc interval length.5

Summary

While the number of drugs removed from the market due to QT prolongation is relatively low, the percentage they account for out of all drug removals is high (23%) and their clinical implications are deadly. We must be aware of participants’ overall risk for QT prolongation, and get EKGs when indicated. We also must be cognizant of drug-drug interactions that may increase plasma levels of already “risky” drugs. If you identify a drug that prolongs the QTc, and it is not yet documented, report it: www.fda.gov/Safety/MedWatch/default.html.

References

Clinical Analysis:
“Common heartburn drugs may raise stroke risk.”

**Background**

Preliminary results from a study conducted by a Danish group and entitled *Proton Pump Inhibitor Use Increases the Associated Risk of First-Time Ischemic Stroke. A Nationwide Cohort Study* were presented at the prestigious American Heart Association Scientific Meeting in November 2016.¹ Such provoking results may, at first glance, significantly impact clinical practice and drug use. However, are these results yet confirmed by other studies and is the clinical community ready for such changes?

The hypothesis generated by the Danish investigators is based on previous results indicating that administration of Proton Pump Inhibitors (PPIs) could be associated with unfavorable changes in vascular functions. Based on these observations, the investigators decided to assess whether PPIs would increase the risk of *de novo* ischemic stroke. Hence, in this retrospective analysis, records from 244,679 individuals above 30 years of age with no manifestation of cardiovascular diseases at the time they underwent an elective gastroscopy (1997 to 2012) were reviewed and analyzed. During the follow-up period (6 years), patients presenting with a first episode of stroke were identified, and it was then determined whether the stroke occurred while patients were taking PPIs (omeprazole, lansoprazole, pantoprazole or esomeprazole).

The investigators reported that they found a positive association between the use of PPIs and an increased risk of first-time ischemic stroke. Although the PPI user group was older and had more comorbidities, including AF at baseline which *per se* may increase risk of stroke in these patients, the adjusted incidence rate ratio of time-dependent PPI exposure associated with a stroke was significant (IRR of 1.21). Furthermore, a positive dose-response relationship was demonstrated between PPI doses and stroke risk: their results indicated that at the lowest doses of the PPIs, there was little or no increase in stroke risk. However, at the highest doses for these 4 PPIs (omeprazole ≥40mg, lansoprazole ≥60mg, pantoprazole ≥80mg or esomeprazole ≥80mg), risk of stroke increased significantly with an incidence ratio ranging from 1.30 to 1.94 (lansoprazole and pantoprazole, respectively). Based on these results, the investigators concluded that PPIs increase the risk of stroke. They mentioned that at this stage, it appears to be a class effect, as they did not have the power to distinguish the relative risk between agents.

**Other Studies**

One must note that another study reported a similar trend towards unfavorable vascular effects of PPI agents while looking at the risk of myocardial infarction: omeprazole, pantoprazole and lansoprazole were significantly associated with odd ratios of 1.36, 1.34 and 1.24, respectively.² Results from these two studies are then rather puzzling!

Additional information can be gathered by looking at various reports suggesting that PPI use may promote cardiovascular, renal, and neurological morbidities. Ghebremariam *et al.* reported that PPIs elevate the concentrations of ADMA (plasma asymmetrical dimethylarginine), an endogenous inhibitor of nitric oxide synthase (NOS), by inhibiting the enzyme that degrades ADMA.³ This inhibition results in a decrease in NOS activity. It is known that impairment of endothelial NOS (eNOS) is associated with an increase in vascular resistance and promotes inflammation and thrombosis. Moreover, a recent study published in *Circulation Research* found that chronic exposure of human endothelial cells to PPIs accelerated endothelial aging.⁴ Vascular senescence would also provide a potential mechanistic explanation for the accumulating evidence that PPIs increase the risk of cardiovascular morbidity and mortality, as well as renal failure.

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¹personal note: This study was mentioned in a previous issue of *CareKinesis*.
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⁴personal note: This study was mentioned in a previous issue of *CareKinesis*.
Recently, one study examined the association between cardiovascular events and PPI use by looking at subjects excluded from high-risk cohorts. Results showed that PPIs use alone was associated with a greater risk of myocardial infarct in subjects with normal cardiovascular risk. Charlot et al. reported similar results showing that patients treated with aspirin after a first myocardial infarction who also received a PPI have a higher incidence of cardiovascular events. A study from Shah et al. recently found that patients with a gastroesophageal reflux disease exposed to PPIs have an increased risk of myocardial infarction regardless of clopidogrel use. And, a post-hoc analysis of the PLATO trial (Platelet Inhibition and Patient Outcomes) found that PPI use was associated with a higher rate of adverse cardiovascular events in patients treated with ticagrelor, a P2Y12 inhibitor that does not require hepatic biotransformation like clopidogrel. These findings suggest that the risk of PPI may apply to subject independently of the antiplatelet therapy. In contrast, H2 blockers, which induce a similar reduction in gastric pH, were not associated with increased cardiovascular risk.

**Our Assessment**

The aforementioned studies clearly deserve some attention although they have several limitations: most are retrospective in nature or use observational data; most do not account for sicker patients using PPIs; there is a lack of information relating to the over-the-counter use of PPIs; they do not relate drug dosage; and they do not take into account comorbid diseases associated with GERD (e.g., obesity and related metabolic disease), which are also established risk factors for cardiovascular diseases. Furthermore, open-label, cross-over pilot studies such as the one conducted by Ghebremariam et al., in healthy subjects and patients with coronary diseases (n=11 and 10, respectively), could not demonstrate that PPI use was associated with a significant effect on vascular endothelial function.

In conclusion, prospective randomized studies controlling for concomitant confounding conditions (e.g., obesity) are required before a change in clinical practice is advisable. Nevertheless, data obtained so far are useful to generate hypotheses regarding a safer use of PPIs. PPIs are known effective drugs but were never approved by regulatory authorities for long-term use. According to US Food and Drug Administration (FDA) documentation, PPIs have only been approved for a brief use of about 6 weeks per year.

**Focusing on our PACE Population**

In the context of an aging population with increasing polypharmacy, optimal therapy should be selected based on co-medications and co-morbidities. Duration of PPI prescription needs to be individualized, and reassessments to continue long-term PPI therapy should be conducted frequently. Indeed, one must also remember that during the short term use of PPIs, drug-drug interactions with antiplatelet agents should be managed according to potential competitive inhibition on some metabolic pathways used for activation or inactivation of these agents.

**References**

CK News

CK in California
In 2013, St. Mary Prescription Pharmacy in San Francisco was acquired by CareKinesis. Since then, St. Mary’s staff has been providing the same excellent service that they always delivered, from their same “cozy” site. We’re pleased to announce that, in February 2017, St. Mary transitioned to a larger, more technologically advanced location, just a few miles from the former site. With this move, this pharmacy practice location will be doing business as CareKinesis.

“EireneRx is more responsive and quicker… it is taking fewer clicks to get to the things that I am doing the most”

- Dr. David Wensel
Midland Care PACE

EireneRx Improvements
When our clients provide feedback, we listen! Most recently, EireneRx users are benefitting from:
- Security Enhancements
- Browser Compatibility Changes
- Response Time Improvement
- Updates to the MRM Matrix
- Integration Enhancements

If there are changes you would like to see in EireneRx, please let us know: ClientLiaison@CareKinesis.com.

Bring on the CE!
We are rapidly approaching the 100% mark for CK pharmacists with Certifications in Geriatric Pharmacy!

To assist in their learning, and at the request of our clients, we host regular Continuing Education programs focused on medication management. These are also made available on-demand. Contact Learn@CareKinesis.com for more information. CE credits are available for pharmacists, physicians, nurses, and certified pharmacy technicians.

- Deprescribing for Safe Geriatric Pharmacotherapy, presented by Kevin Bain, PharmD, MPH, BCPS, BCGP
- Optimizing Patient Care for Patients with Type II Diabetes, presented by Carlos Perez, MSN, RN-BC

What our partners love about CareKinesis
- “Excellent communication”
- “Customer Support”
- “Consistent high quality service”
- “Promptness”
- “Packaging”
- “Best thing we ever did for PACE”

Our Model of Care

Through total cost reduction

www.CareKinesis.com
888-9-PharmD
Dates to Remember!

**MARCH**
⇒ EireneRx 101—3/9 @ 3pm ET
⇒ PACE Appreciation Reception—NPA 5/20 @ 5:30pm ET
⇒ And, visit us at NPA booths 1-3 during exhibit hours 3/21-3/22

**APRIL**
⇒ EireneRx 101—4/13 @ 3pm ET
⇒ And, visit us at the PACE MI Meet & Greet conference 4/21

**MAY**
⇒ Opioids: Regulatory Perspectives for PACE—5/10 @ 3pm ET
⇒ EireneRx 101—5/11 @ 3pm ET
⇒ Opioids: Clinical Perspectives for PACE—5/24 @ 3pm ET
⇒ And, visit us at the NC PACE conference 5/4-5/5

To register for CareKinesis webinars and events, email RSVP@CareKinesis.com