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Resident Editors: *Athena Cannon, PharmD; Radhika Patel, PharmD; Colton Sharp, PharmD*
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RESEARCH UPDATES

Association Between Benzodiazepine Use With or Without Opioid Use and All-Cause Mortality in the United States, 1999-2015[1]

Atuobi Nana Yiadom, PharmD
CentraCare Hospital, Paynesville

Background: Benzodiazepines are widely used medications for the management of anxiety and insomnia. It has been reported that about 13% of U.S. adults have used benzodiazepines in the past year, with ambulatory prescriptions of benzodiazepines doubling in the past decade. Additionally, increases in benzodiazepine prescribing and long-term use has been accompanied by falls, cognitive impairment, and life threatening withdrawal. One area of concern has been combined use of benzodiazepines and opioids, which can lead to risk of overdose, suppressed breathing, and death. This study evaluates the association of benzodiazepine use with or without opioid co-prescriptions with long-term all-cause mortality using a large nationally representative data set in the U.S. linked to the National Death Index spanning approximately 15 years of follow-up time (1999-2015).

Objective: To evaluate whether benzodiazepine use, with or without opioid use, is associated with increased all-cause mortality relative to the use of low-risk antidepressants.

Study Design: This study was a retrospective cohort study from 1999 to 2015. Among the eligible participants who were 20 years or older, 43,793 were identified using the National Health and Nutrition Examination Surveys. A total of 5,212 were included in the study who were on either benzodiazepines and opioids, benzodiazepines or opioids, or other comparators such as selective serotonin reuptake inhibitors (SSRIs). There were 38,581 participants excluded from the study who did not participate in face-to-face interviews, had missing data on prescription information or medical conditions, died within one year of follow up, or were not taking SSRIs, benzodiazepines, or opioids. The primary exposure in the study was benzodiazepine and opioid co-prescriptions, with patients taking SSRIs serving as a reference group. SSRIs were chosen as a reference group due to their overlapping indication with benzodiazepines, and diminished morbidity and mortality compared to tricyclic antidepressants and monoamine oxidase inhibitors. The main outcome measure was all-cause mortality from the exposure variable. Cox proportional hazard regression model was used to estimate mortality of participants in the exposure versus reference group, and stratified analyses were performed on follow up time and age (20-65 vs ≥65 years) of participants. All P values were from 2 sided tests and results were statistically significant at $P<0.05$.

Results: The majority of study participants were women, who accounted for 62% of the study population, and 64% were white with a mean age of 54.8 years. Out of the 5,212 participants, 9% were prescribed both benzodiazepines and opioids, 24% were prescribed benzodiazepines only, 37.5% were prescribed opioids only, and 29.4% were

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on neither benzodiazepines or opioids, but were on SSRIs. The median time to death was 6.7 years for all participants. Of the 892 deaths that occured in total, 11.3% occurred in participants receiving benzodiazepines and opioids, 26.4% occured in benzodiazepines only, 37% in participants on opioids only, and 25.4% of deaths occurred in participants using SSRIs only. A Kaplan-Meier survival curve showed that all-cause mortality was significant in the benzodiazepine and opioid group compared to other groups ($\chi 2=0.41$; $P<0.001$). Participants receiving benzodiazepines both with and without opioids showed increased risk of death when compared with participants taking SSRIs only (co-treatment group: hazard ratio [HR], 1.71 [95% CI 1.34 - 2.19]; benzodiazepines without opioids group: HR, 1.36 [95% CI, 1.13 - 1.64]). A subgroup analysis showed increased risk of mortality in younger participants (20-65 years) on benzodiazepine and opioid co-prescriptions compared to participants 65 years and older. There was increased risk of death in participants with longer follow up who were receiving benzodiazepines only (HR, 2.17 [95% CI 1.59 - 2.98] vs 1.17 [95% CI 0.92 - 1.50]), and similar analysis also showed increased risk of death in participants on benzodiazepine and opioid co-treatment regardless of follow up time.

Conclusion: Overall, the results of the study suggest that short- or long-term co-prescriptions of benzodiazepines and opioids may lead to increased risk of death. In addition, all-cause mortality with benzodiazepine and opioid use together increased in younger participants than in participants older than 65 years.

Key Point: Benzodiazepines and opioids may often be prescribed together, and combined use of these medications can lead to death. Long term use of benzodiazepines and opioids should always be reviewed, and targeted interventions are needed to reduce the use of these medications together.

Once-Weekly vs Once-Daily Basal Insulin for Treatment of Type 2 Diabetes[2]

Elizabeth Tupper, PharmD
St. Cloud VA

Background: Current type 2 diabetes treatment guidelines recommend escalation of therapy when individualized glycemic goals are not achieved. Despite known complications of uncontrolled diabetes and recommendations for therapy intensification, clinical inertia exists in the management of type 2 diabetes with the longest delays observed for insulin initiation. Patient and clinician apprehensiveness may be related to discomfort with injections, side effects associated with insulin, and need for adherence to daily basal insulin dosing for optimal glycemic control. Once-weekly insulin may decrease such apprehensiveness, similar to the way literature indicates that treatment with a once-weekly injectable glucagon-like peptide-1 receptor agonist (GLP-1RA) is associated with significantly better treatment adherence and satisfaction compared to once-daily injectable GLP-1RA therapy.

Objective: To compare the glucose-lowering efficacy and the safety profile of once-weekly insulin icodec vs once-daily insulin glargine in patients with type 2 diabetes without previous insulin treatment.

Study Design: Two hundred forty-seven study participants were randomly assigned to once-weekly subcutaneous icodec plus once-daily placebo or once-daily subcutaneous glargine plus once-weekly placebo in this 26-week, randomized, double-blind, double-dummy, treat-to-target, active-controlled, parallel-group, multinational phase 2 trial. Inclusion criteria included patients aged 18 to 75 years who had not previously received long term insulin treatment, who received diagnosis of diabetes at least 180 days prior to screening, who were receiving stable doses of metformin with or without dipeptidyl peptidase 4 inhibitor (DPP4), and whose A1c was 7-9.5%. Baseline characteristics in both groups were similar, although duration of diabetes was slightly longer in the icodec group. The starting dose of icodec was 70 units once weekly and the starting dose of glargine was 10 units once daily. Doses were adjusted weekly to achieve fasting morning glucose of 70-108 mg/dL. The primary endpoint was change in A1c from baseline to week 26. Secondary endpoints included changes in fasting plasma glucose, body weight, and mean of the nine-point self-monitored glucose profile from baseline to week 26, however, the study was not designed to test the statistical significance of secondary endpoints.The key safety endpoint was the number of adverse effects (hypoglycemia, injection-site reactions) from baseline through the follow-up period.

Results: The mean A1c in the icodec group decreased from 8.1 ± 0.7% at baseline to an estimated mean of 6.7% at week 26. In the glargine group, A1c decreased from 8.0 ± 0.7% to 6.9%. The estimated mean treatment difference was -0.2 percentage points [95% CI -0.38 - 0.02; P=0.08). The estimated percentage of patients reaching A1c less than 7% was 72% in the icodec group and 68% in the glargine group (estimated OR 1.20 [95% CI 0.98 - 2.13]). The mean self-monitored glucose was lower in the icodec group at all time points. A lower insulin dose and greater time spent within the tight glycemic range (70-140 mg/dL) was found in the icodec group. Changes in fasting plasma glucose and body weight were similar between groups. Approximately 50% of patients in each treatment group had an adverse event. Level one hypoglycemia incidence was 54% in the icodec group and 38% in the glargine group, and the observed rates of level one hypoglycemia during the treatment period were 5.1 and 2.1 events per patient-year of therapy for icodec and glargine, respectively (estimated RR 2.42 [95% CI 1.50 - 3.88]).

Conclusions: Overall, there are similar effects related to A1c lowering, fasting plasma glucose lowering, and rates of

hypoglycemia when comparing once-weekly insulin icodec to once-daily insulin glargine. Patients treated with icodec did spend a greater amount of time in the tight glycemic range compared to those treated with once-daily glargine. The mean weekly insulin dose was higher in the glargine group; however, no difference in change in body weight was observed between groups. While no statistical differences were seen, aforementioned findings may hold clinical significance. Future areas of research may involve studies powered to detect statistically significant differences between treatments, compare adherence to weekly vs daily regimens, and assess treatment satisfaction.

Key Point: The once-weekly basal insulin analogue, insulin icodec, provided similar glucose-lowering effects and a similar safety profile to once-daily insulin glargine; however, this study was not powered to detect significant differences between treatments for any end point and further studies are needed to determine significance.

THERAPEUTIC THOUGHT

Clinical Impact of Removing Race from Estimates of Kidney Function[3-4]

Paige Behrend, PharmD
Park Nicollet Health Services

Background: Race-based adjustments are still present in various clinical algorithms used for disease risk assessment and therapeutic guidance, despite a lack of evidence that race is a reliable predictor of genetic difference. Many medical centers across the U.S. have begun the process of removing race from these clinical tools and algorithms due to mounting concern that race-based medicine may be perpetuating disparities and biases in healthcare. For example, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) equations for estimating kidney function include a race-based adjustment to account for hypothetical higher serum creatinine concentrations in patients that identify as Black. When used within these equations, the adjustment suggests a higher estimated kidney function that may not accurately represent the patient's true renal function. A recent study by Diao et. al aims to quantify the impact of removing race from kidney function estimators on CKD diagnosis, CKD stage reclassifications, nephrologist referrals, and more.

Evidence and Discussion: The study utilized laboratory measurements and demographics from adult National Health and Nutrition Examination Survey (NHANES) participants from 2001 to 2018. In total, the study cohort included 9,522 non-Hispanic Black adults with a median age of 45 years. The CKD-EPI equation was utilized to calculate estimated glomerular filtration rate (eGFR) with and without the race coefficient. After removal of the race coefficient, the median eGFR decreased from 102.9 mL/min/1.73m2 to 88.8 mL/min/1.73m2. Based on this data, removing race from the CKD-EPI equation may increase the prevalence of CKD among Black adults in the U.S. from 14.9% to 18.4%. Additionally, 29.1% of Black adults with pre-existing CKD may be reclassified to a more severe stage. This overestimation of eGFR may have significant pharmacological implications, such as necessitating a dose adjustment for metformin or the emergence of an indication for an angiotensin-converting enzyme inhibitor to protect renal function and delay CKD progression.

In addition to the implications on CKD diagnosis and staging, access to kidney care and services is impacted by the overestimation of eGFR in Black adult patients. Computing eGFR without race would allow 0.36% of Black adults to receive kidney disease education instead of 0.22%. Currently Medicare covers medical nutrition therapy for 5% of Black adults, but this increases to 5.5% with removal of race coefficient. Increasing access to both kidney disease education and medical nutrition therapy can help delay CKD progression and help improve overall health outcomes among Black patients. Additionally, computing eGFR without race may increase the proportion of Black adults qualified for kidney transplant by 0.05%, which equates to an additional eight patients eligible for transplant among the 9,522 non-Hispanic Black adults included in the NHANES sample population.

Clinical Impact: Removal of race-based adjustments from kidney function estimators may increase CKD diagnoses and severity of CKD staging within adult Black patients, as the inclusion of race coefficients can result in false estimates of actual kidney function. Overestimation of eGFRs in adult Black patients perpetuates racial healthcare inequalities by delaying access to nephrologists, medical nutrition therapy, kidney disease education, and kidney transplantation.

Digoxin, Dig-ya think I was gone? Not yet![5-8]

Ann K. E. Nagle, PharmD
Pharmaceutical Care Leadership PGY1 Resident

Background: The 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guideline for the Management of Heart Failure (HF) describes a strong correlation between HF and atrial fibrillation (AFib). These conditions often perpetuate one another by reducing cardiac function, worsening scarring of cardiac tissue, and activating the renin-angiotensin and vasopressin systems. While beta blockers

are first-line therapy for both AFib and HF, digoxin also has a place in therapy for both conditions. Despite this, digoxin is only used when all other medications have been exhausted or optimized in patients with HF.

Digoxin has been a treatment option for many years, yet remains understudied both clinically and in patient-reported outcomes, especially in patients with comorbid HF and Afib. The only significantly powered study examining the morbidity and mortality benefit of digoxin in HF (DIG trial) found that while it lacked mortality benefit, digoxin did significantly reduce hospitalizations in patients with HF. Patients in the DIG trial had normal sinus rhythm; however, this may not be applicable to all patients with HF and AFib. Notably, the DIG Trial was conducted before treatment guidelines included beta blockers. Other observational studies have shown mixed results for digoxin and mortality, therefore its clinical benefit is inconclusive.

Patient-reported outcomes, such as symptom improvement and quality of life, are also important considerations for choosing therapies. However, patient experience measures have not been well-researched in patients where Afib and HF overlap. The recently published RATE-AF trial focuses on these patients and evaluates the place of digoxin in therapy.

Evidence: The RATE-AF trial is the first trial to exclusively study patients with AFib and HF comorbidities. It is a randomized, open-label, blind endpoint study that examined 160 patients in the UK. Participants were 60 years of age or older and had diagnoses of both AFib and HF (New York Heart Association [NYHA] class II or above). Baseline characteristics of patients included: average age 76 years, 46% female, heart rate 100 bpm with a majority having moderately troubling Afib symptoms (European Heart Rhythm Association [EHRA] class 2b), 19% had left ventricular ejection fraction (LVEF) of <50%, and median N-terminal pro b-type natriuretic peptide (NT-proBNP) was 1,057 pg/mL. Patients were randomized 1:1 into digoxin and bisoprolol with the average dose of digoxin being 161 mcg (average serum level 0.78 ng/mL) and average bisoprolol dose of 3.2 mg.

Primary endpoints were patient-reported quality of life improvements using the 36-Item Short Form Survey (SF-36) physical component summary (Physical Function, Role-Physical, Bodily Pain and General Health) at 6 months. Secondary endpoints at 6 and 12 months included mental and general health status, symptom and functional capacity, and NT-proBNP levels.

No statistical difference was reported in the primary outcomes; however, secondary outcomes did show some benefit to the digoxin group. At 12 months, those patients randomized to digoxin had significant improvement in vitality (P=0.01), general health (P=0.05), physical function (P=0.05) and role limitations due to physical health problems (P=0.05). AFib Effect on Quality of Life scores were not statistically different between digoxin and bisoprolol groups at 6 or 12 months. Post hoc analysis found that daily activities and treatment satisfaction were higher in the digoxin group and symptomatic improvement (EHRA class) was found to be substantially better in the digoxin group. LVEF improved similarly in both groups, but NT-proBNP levels were significantly improved at 12 months with treatment of digoxin. Post hoc analysis also found NYHA class improvement at 6 and 12 months in the digoxin group, with fewer adverse events.

Discussion & Clinical Impact: Beta blockers remain as a Class I, Level A recommendation to reduce mortality for patients with HF. The only significant clinical improvement in the RATE-AF trial was reduction in NT-proBNP levels in the digoxin group. While patient-reported outcomes (general health, treatment satisfaction, and physical limitation improvement) in the RATE-AF trial were significant, these findings are not clinical outcomes that would suggest digoxin be prioritized in treatment algorithms. Though secondary outcomes of the RATE-AF trial were significant, they should be interpreted with caution. A major limitation of these secondary endpoints is that this was a small cohort and multiple hypotheses were tested at once, which increases the risk of incorrectly detecting a difference between digoxin and bisoprolol groups. In practice, the results of this trial can only be used to consider digoxin as similar to beta blockers in patients with AFib and HF for improvements in quality of life and satisfaction of treatment. Digoxin may be an important tool for our patients who remain symptomatic after being optimized on guideline-driven therapy.

FROM THE PHARMACY PRESS

Analysis of Provider-Generated Revenue and Impact on Medication Reconciliation from a Pharmacist-Led Chronic Care Management Service[9]

Alexandra Vecchia, PharmD
M Health Fairview

Background: The Centers for Medicare and Medicaid Services (CMS) allows pharmacists to utilize incident-to-billing in order to be reimbursed for providing chronic care management (CCM) services to covered patients. CCM services aim to bridge gaps in care and to help patients manage their chronic conditions. CMS not only allows for face-to-face time with the patient to be submitted for reimbursement, but also time spent on activities, such as reviewing labs and communicating with other healthcare

providers. There are few data on direct and indirect revenue generated by community pharmacies that offer these services.

Objective: This study of CCM services provided by a chain of community pharmacies aims to calculate the direct and indirect revenue generated by this service, and to analyze discrepancies found when completing medication reconciliations.

Practice Description: This practice is a small chain of independent community pharmacies, Realo Drugs, located in North Carolina. The pharmacies offer many services including comprehensive medication review (CMR), medication packaging, diabetes education, and transition of care management.

Practice Innovation: Realo Drugs began offering CCM services to their patients in coordination with a local patient-centered medical home in 2018. The CCM services are run by one pharmacist and one post-graduate year one (PGY-1) pharmacy resident. Patients are enrolled in the program by their provider. After receiving the referral, the clinical pharmacist contacts the patient to complete a health risk assessment and CMR. Thereafter, the pharmacist provides CCM services on an ongoing basis including performing medication reconciliation, coordinating referrals, identifying community resources, requesting appointments, communicating medication refill requests, providing vaccine recommendations, and conducting clinical screenings. These services are submitted to CMS for reimbursement every month using incident-to-billing under the referring provider. The referring provider is reimbursed for the services and a percentage of the reimbursement is passed on to the pharmacy.

Evaluation Methods: A retrospective analysis was conducted on CCM services provided from April 1, 2018 through June 30, 2019. Direct revenue to both the pharmacy and patient-centered medical home consisted of reimbursement from CMS for the CCM services. Indirect revenue included in-office visits with the provider resulting from a referral from the pharmacist. Medication changes made during medication reconciliation were tracked using the electronic health record.

Results: The study identified 112 patients that received CCM services, 18% of whom were patients of Realo Drugs. The direct and indirect revenue generated from these patients over the 15 month analysis was $26,148, equaling about $15.56 per patient per month. The vast majority (92%) of the revenue was directly from CCM services as opposed to indirect revenue from in-office appointments resulting from pharmacist referrals. The analysis discovered 609 medication discrepancies identified during medication reconciliation. The most common discrepancy involved patients no longer taking a medication that was still on the medication list (67%). Other discrepancies included patients taking a medication that was not on the list (23%) and incorrect strengths or doses (10%).

Limitations: Due to the retrospective design of this study, there were limitations in the data collection and results. There was no pre-specified way to determine if an in-office provider visit was made as a result of a pharmacist's recommendation. Similarly, medication reconciliation visits were not prospectively tracked or documented. The only way to determine that a medication reconciliation occurred was to identify changes to the medication list under the pharmacist's username in the electronic health record. Therefore, if a medication reconciliation visit was completed and no changes were made to the medication list, this visit would not have been included in the analysis.

Conclusion: This retrospective study of CCM services provided in a chain of community pharmacies demonstrated $26,148 in direct and indirect revenue over 15 months. It also highlights the importance of pharmacist-driven medication reconciliation in order to identify and resolve discrepancies.

Assessment of Racial Differences in Pharmacotherapy Efficacy for Smoking Cessation[10]

Katherine Anderson, PharmD
Cash Wise Clinic Pharmacy/Carris Health

Background: Tobacco consumption in the U.S. is the leading cause of preventable morbidity and mortality. With more than 480,000 deaths and more than 34% of all cancer deaths annually. Racial/ethnic differences in quitting are not well understood. Non-Hispanic Black individuals (referred to as Black) have a prevalence of smoking that is comparable to non-Hispanic White individuals (White), smoke fewer cigarettes per day, smoke fewer days per month, but have higher rates of smoking related morbidity and mortality. Results of randomized clinical trials (RCTs) have shown mixed results with about half showing no difference in cessation rates between Black and White smokers, half showing higher cessation rates with White smokers, and only one study showing a higher cessation rates for Black smokers. Though no study has examined the variables with race and smoking cessation. Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) is the largest and most comprehensive smoking cessation study to date. The study found that Black smokers were significantly less likely than White smokers to quit across all treatments, but did not explore the reason for this difference. A secondary analysis of the EAGLES trial was designed to examine why Black smokers achieved lower quit rates compared to White smokers when given the same treatment and smoking cessation counseling.

Methods: EAGLES was a randomized 1:1:1, double-blind, triple-dummy, placebo-controlled and active controlled (Nicotine Replacement Therapy (NRT): 21 mg per day with taper), varenicline (1 mg twice daily), bupropion (150 mg twice daily for 12

12-week no treatment follow up. The trial recruited from 16 countries including the U.S. from November 2011-January 2015. A total of 8,144 male and female smokers aged 18-75 years with or without prespecified current or lifetime psychiatric diagnoses and who smoked 10 or more cigarettes per day were included. The study analyzed total participants and divided the results into participants with psychiatric conditions and non psychiatric conditions. Of the participants, 95.9% were either self-identified as Black or White and 53.2% of participants were from the U.S. (71.5% White vs. 25.0% Black participants compared to non-U.S. of 92.8% White vs 2.5% Black). Continued cigarette abstinence rate (CAR) for 9-24 weeks was the primary endpoint because longer periods of abstinence are more strongly associated with lifetime abstinence. Statistical analyses were performed using SAS statistical software version. Tests and 95% CI's are 2-sides and used a 5% level of significance, which invoked a nominal P<0.1 rule.

Results: The study included 1,065 U.S. Black participants (255 varenicline, 259 bupropion, 286 NRT, and 265 placebo) and 3,044 U.S. White participants (788 varenicline, 769 bupropion, 738 NRT and 759 placebo). Nine hundred and ninety-eight participants discontinued from the study after starting treatment. Only treatment and race were associated with CAR for weeks 9-24; 12.5% for White participants and 7.0% for Black participants. The absolute difference in CAR for weeks 9-12 was 6.6% less for Black vs. White participants [95% CI 0.45 - 0.69; P<0.01]. Comparing the relative efficacy of treatments with race, White smokers had a significantly higher odds of CAR with varenicline compared to bupropion. Black participants showed higher odds of continuous abstinence rates using a smoking cessation agent compared to placebo. There was no significant difference when compared to varenicline vs. bupropion or NRT, bupropion and NRT vs. placebo and bupropion vs. NRT for Blacks. Post baseline differences demonstrated that Black participants were less likely to discontinue treatment, had greater compliance, increased days of exposure to the drug studied, had greater reduction in depression, and fewer psychiatric and non-psychiatric adverse effects over the study period.

Discussion: This study does confirm prior Black-White differences in abstinence reported in RCTs. Black participants were significantly less likely to quit overall though differences do not appear to be from a pharmacological interaction. Socioeconomic variables were not measured in the EAGLES trial and cannot be speculated about that impact. All smoking cessation therapy had a greater efficacy compared to placebo for White smokers. Varenicline had greater efficacy compared to placebo but not other therapies for Black smokers. Lower rates of abstinence is likely due to inclusion of a large psychiatric cohort, lower-intensity behavioral counseling, and the use of more stringent continuous abstinence.

Clinical Impact: The EAGLES study suggests that varenicline is the most successful smoking cessation agent regardless of race and Black smokers are less likely to quit than White smokers. Clinicians need to be aware that race is a proxy for powerful social and contextual factors that affect all aspects of life. Further studies should be conducted to examine the variables associated such as socioeconomic and biologic variables for Black smokers. In practice, clinicians shall consider all smoking cessation therapies, and select an agent for the patient that is best suited to help them successfully quit with minimal adverse events.

Pharmacists: Essential Partners in Shared Decision-Making for Schizophrenia and Schizoaffective Disorder[11-12]

Tim Isdahl, PharmD
Minnesota Community Care

Background: Schizophrenia and schizoaffective disorder are diagnoses that require significant understanding and collaboration between patients and their care team for optimal treatment. Medications used to treat schizophrenia and schizoaffective disorder often require frequent monitoring of drug levels, and have side effect risks including metabolic syndrome, akathisia, and tardive dyskinesia.

The American Society of Health System Pharmacists (ASHP) recently published a Therapeutic Position Statement on schizophrenia and schizoaffective disorder to serve as a resource for pharmacists participating in shared decision-making processes with patients. Shared decision-making, a clinical approach that emphasizes empowering patients to participate in their own care, is designed to give autonomy back to patients. Past research has found that shared decision-making typically leads to better outcomes than coercive treatments in mental health care.

Discussion: Early recognition and treatment of schizophrenia and schizoaffective disorder have been found to slow neurodegeneration and decrease all-cause mortality. Past research by Ringen et al. has noted that people living with schizophrenia have a life expectancy that is 20 to 25 years shorter than those without this diagnosis. This shortened life expectancy, along with studies demonstrating that over half of persons with schizophrenia are non-adherent to prescribed treatment at some point, demonstrates a space for pharmacists to step in to help patients receive optimal treatment. Shared decision-making, which involves open and honest discussions about potential treatment options and probable outcomes, can help increase patient buy-in and respect patients' views about their own ideal care. Pharmacists are able to support this process in the ambulatory setting by providing comprehensive medication management and working under collaborative practice agreements with providers.

Practical Impact: The pharmacist's role in patient care is no longer confined to traditional retail and hospital settings. Pharmacists are

increasingly a frontline resource and provider for patients with mental illnesses, whether they are leading medication education classes in inpatient psychiatric units or seeing patients independently in an ambulatory care setting. This position statement and the guidelines contained within will allow pharmacists to practice at the top of their licenses and provide information to patients to allow for informed consent in treatment.

MISCELLANEOUS NEWS

FDA Warning on Male Enhancement and Weight Loss Products Sold Online[13]

Ashton Forst, PharmD
Hennepin Healthcare

The Director of the Office of Compliance with the Food and Drug Administration (FDA), Donald D. Ashley, stated "Protecting the health and safety of Americans is the FDA's highest priority, and we will remain vigilant and communicate about products and companies that place U.S. consumers at risk." This statement was made after a December 2020 warning released by the FDA for consumers to not use about 50 weight loss and male enhancement supplements due to the products containing potentially harmful, hidden ingredients. Of these products, 26 were purchased on Amazon and 25 were purchased on eBay. Laboratory testing of these products indicated that all 26 products from Amazon and 20 of the 25 products from eBay contained active pharmaceutical ingredients that were not listed on the product labels. Some of the active pharmaceutical ingredients detected included sildenafil, tadalafil, vardenafil, sibutramine, desmethylsibutramine, phenolphthalein, and fluoxetine. Nearly all of these active ingredients are FDA-approved only for use under the supervision of a healthcare professional as a prescription medication due to potentially significant health risks associated with use.

Although this specific warning is recent, this is not the first time the FDA has released warnings regarding weight loss and male enhancement products. Over the past decade, the FDA has released several warnings on similar products sold through online marketplaces such as Amazon and eBay. The FDA's tainted products database includes nearly 1,000 products identified as potentially harmful and can be used as a resource for consumers when purchasing products online. Despite the FDA's effort to capture all products that are misbranded, they do not have the bandwidth to test every product sold online or in retail stores. Consumers are encouraged to use caution when purchasing products or supplements online, especially those marketed for sexual dysfunction, weight loss, bodybuilding, sleep aids, or pain relief. Buyers are encouraged to consult with a healthcare professional before purchasing products online to ensure safety of the product as some ingredients may interact with prescription medications or may be unsafe in certain medical conditions. If a consumer is unable to contact a healthcare professional, it is advised that they research product information from sources other than the seller to help differentiate between questionable information.

Due to the increased prevalence of hidden ingredients in products sold through online marketplaces, the FDA encourages reporting of adverse events to the MedWatch Adverse Event Reporting program by both healthcare professionals and consumers; this allows the agency to take action on potentially harmful products on the market.

FDA tainted products database:
https://www.fda.gov/drugs/buying-using-medicine-safely/medication-health-fraud

FDA MedWatch Adverse Event Reporting:
https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program

Amazon Launches a New Online Pharmacy Service[14]

Ashton Forst, PharmD
Hennepin Healthcare

In November 2020, Amazon launched an online pharmacy dedicated to delivering prescription medications to patients within the United States called Amazon Pharmacy. This new online service offers Amazon users a quick and easy way to purchase both prescription and non-prescription medications in one location. In addition to the accessibility of this service, Amazon is also offering significant discounts on medication prices for Prime members. Prime members get up to 80% off generic and up to 40% off brand name medications when they pay without insurance. Customers also will have the opportunity to compare co-pay prices with discounted Amazon prices at checkout. This business move builds off Amazon's purchase of PillPack, an online pharmacy that lets user's buy medications in pre-made doses. CEO of PillPack and vice president of Amazon Pharmacy stated that the pharmacy service intends to bring "customer obsession to an industry that can be inconvenient and confusing."

Although this service appears to be an advantage for patient accessibility, Amazon's entry into the highly competitive pharmacy market is not necessarily welcomed with open arms. A professor from Northwestern University's Kellogg School of

Management, Craig Garthwaite, stated "Amazon's launch of an online pharmacy is a meaningful threat to brick and mortar pharmacies. These retail pharmacies must now offer more than just easy access to a prescription". In addition to Amazon Pharmacy's online services, similar discounts on non-insurance products apply at more than 50,000 retail pharmacie, such as CVS and Walgreens, for those customers who are Prime members and desire to buy their products in-person.

Since the purchase of PillPack in 2018, Amazon has secured Board of Pharmacy licensure to ship prescription medications to nearly all 50 states. Currently, Amazon's online pharmacy is not available to residents of Illinois, Minnesota, Louisiana, Kentucky, and Hawaii, but this won't be the case for long. Online purchasing of medications will likely increase in the coming years.This new service will impact pharmacies and pharmacists as it will likely drive more patients to purchase their medications online. It is important as healthcare professionals to stay informed on online platforms for purchasing medications in order to provide accurate guidance for safe online buying of medicines.

Minnesota Board of Pharmacy Approves Protocol for Pharmacist Prescribing of Self-administered Hormonal Contraceptives[15]

Brianna Ferrell, PharmD
Essentia Health

The Minnesota Board of Pharmacy approved a protocol in December 2020 that pharmacists must follow when independently prescribing self-administered hormonal contraceptives. The protocol was developed in accordance with Minn. Stats. §151.37, subd. 1, several professional agencies, the commissioner of health, and professional associations, including the Minnesota Board of Medical Practice. It contains pertinent definitions, general information, procedures, and the Minnesota Hormonal Contraceptive Self-Screening Questionnaire. Before a pharmacist is authorized to independently prescribe contraceptives under this protocol, they must first complete an approved training program accredited by the Accreditation Council for Pharmacy Education and provide proof of completion to the Board of Pharmacy.

As a first step in this protocol, the pharmacist must determine the patient's age and date of the most recent clinical visit with a physician, advanced practice registered nurse (APRN), or physician assistant (PA). If the patient is under the age of 18, the pharmacist may only utilize this protocol if the pharmacist confirms that the patient has previously been prescribed a contraceptive by a licensed physician, APRN, or PA. The patient then completes the Minnesota Hormonal Contraceptive Self-Screening Questionnaire at least once every 12 months. After reviewing the self-screening tool answers with the patient, the pharmacist then measures and records the patient's seated blood pressure if combined hormonal contraceptives are requested or recommended. Next, the pharmacist completes the Minnesota Board of Pharmacy Standard Procedures Algorithm for Prescribing of Contraceptives and evaluates the health and history of the patient using the United States Medical Eligibility Criteria for Contraceptive Use developed by the Centers for Disease Control and Prevention. Finally, before prescribing, the pharmacist must ensure the patient is appropriately trained in the administration of the recommended contraceptive. Prior to dispensing, the pharmacist must perform appropriate counseling as required in Minn. Rules 6800.0910. In addition to verbal counseling, the pharmacist must supply a fact sheet and a written record to the patient about the prescribed contraceptive medication. Prescribing of a self-administered hormonal contraceptive cannot be delegated to any other person other than the pharmacist authorized under this protocol. A registered pharmacist intern may prepare a prescription for the contraceptive, but prior to processing and dispensing, the authorized pharmacist must review, approve, and sign the prescription. The pharmacist must generate a written or electronic prescription for any self-administered contraceptive prescribed and dispensed pursuant to Minn. Stats. §151.01, subd. 16a. The prescription must be kept on file for a minimum of two years.

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