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Comprehensive Medication Reviews Associated with Lower High-Risk Medication Use

By Krystal Ngo, PharmD; Reviewed by Janet Kim, PharmD & Shannon Clarke, PharmD, BCACP

Key Points:

- A study demonstrated that Medicare Advantage Part D (MAPD) plans with higher Comprehensive Medication Review (CMR) completion rates had lower high-risk medication use.
- KPWA clinical pharmacists deliver CMRs to eligible members and offer recommendations to providers.
- Encouraging eligible KPWA Medicare members to participate in their annual CMR can help identify and reduce the use of high-risk medications, ultimately improving member quality of care.

Background¹

- Centers for Medicare and Medicaid Services (CMS) utilizes a 5-point star rating system to assess the quality and efficacy of services provided by Medicare plans.
- The use of high-risk medications in the elderly (HRM) and CMR completion rates are two quality metrics measured by CMS.
- Several studies suggest that interventions resulting from medications therapy management programs (MTM), including CMRs, can produce positive medication changes, significant cost savings, and reduced use of high-risk medications in patients 65 years and older.

Relationship between Medication Reviews and High-Risk Medication Use¹

- A study based on 2014 and 2015 performance data found that MAPD plans had significantly lower high-risk medication use and higher CMR completion rates (**Table 1**).

Table 1. Completing More Comprehensive Medication Reviews Correlated to Lower High-Risk Medication Use in MAPD members¹

Year	HRM Use, Median (25 th , 75 th percentile)	CMR Completion Rate, Median (25 th , 75 th percentile)	Standardized Beta Coefficients ^a	P-value
2014	7.0 (5.0, 9.0)	28.2 (17.6, 37.8)	-0.088	0.154
2015	5.0 (4.0, 7.0)	44.5 (28.8, 56.8)	-0.221	<0.001

HRM=high-risk medications in elderly; CMR=comprehensive medication review

^a The standardized beta coefficient reflects the strength of the effect of an independent variable on a dependent variable. Negative value reflects inverse relationship.

- For MAPD plans between 2014 and 2015, an inverse correlation was found between CMR completion rates and high-risk medication use. This inverse correlation was significant in 2015 ($p < 0.001$).
- The relationship shown in the data suggests the value of CMRs in improving medication safety in patients.
- Since the launch of the CMS Star metric back in 2016 (based on 2014 performance data), Medicare plans across the nation have been quickly improving their CMR completion rates each year.
- Providers are encouraged to ensure that patients enrolled in MTM services accept the CMR offer to consult with a MTM pharmacist.

MTM at Kaiser Permanente Washington (KPWA)

- KPWA clinical pharmacy services has a MTM program that offers eligible members the opportunity to complete a CMR at no cost.
- CMRs are offered for all KPWA MAPD MTM enrollees, regardless if the provider is KPWA-employed or from an external non-KPWA clinic.
- Through CMRs, clinical pharmacists can resolve drug therapy problems by offering recommendations related to: therapeutic substitution, dose optimization, cost savings, and reduction of adverse events.
- On completion of a CMR, the pharmacist will reach out to providers with medication recommendations. For clinics with Epic as their Electronic Medical Record (EMR) system, the pharmacist's note is documented in Care Everywhere. The CMR recipient will receive a mailing with an accurate medication list and summary of the patient action plan.
- In addition, Medicare members on high-risk medications can receive targeted medication reviews (TMRs) from pharmacists, regardless of whether they accept their CMR offer.

KPWA Patient Case

- A CMR was conducted in April 2018 with a 65-year-old female patient concerned about her dry mouth symptoms and prescription costs. During the MTM interview, the clinical pharmacist identified potential opportunities with the patient's nortriptyline and Estrin® (estradiol). The pharmacist and patient discussed the following to address the patient's considerations:
 1. Discontinue nortriptyline, which is a high-risk medication in older patients due to its highly anticholinergic effects, and switch to duloxetine to reduce dry mouth symptoms.
 2. Change Estrin® to generic estradiol vaginal tablets to reduce cost burden.
- The recommendations were accepted by the patient's PCP and OB/GYN. The implemented changes therefore improved patient care, safety, and member experience.

Conclusion

- A retrospective analysis found that older adults who receive MTM services are more likely to not use high-risk medications.¹
- An additional study found TMRs that identify medication-related problems in MTM-enrolled patients may significantly improve the appropriate use of medications of these patients.^{2,3}

- Overall, the KPWA MTM program provides an opportunity for providers and pharmacists to work collaboratively to reduce the use of high-risk medications, improving patient safety.

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Identifying Gluten-Free Medications

By Krystal Ngo, PharmD; Reviewed by Janet Kim, PharmD & Sophia Swanson, MD

Key Points:

- Medications that contain gluten may cause an immune reaction in patients with celiac disease.
- These patients should avoid medications with excipients containing wheat starch, pre-gelatinized starch, and sodium starch glycolate. Instead, alternative medications without these excipients should be considered.

Background

- Gluten is a protein that can be found in wheat, barley, rye, triticale, and oats.⁴
- Celiac disease is an immune-based reaction to dietary gluten, which primarily affects the small intestinal mucosa and resolves with exclusion of gluten.^{5,7}
- In patients with celiac disease, exposure to gluten can result in signs and symptoms of malabsorption including diarrhea with weight loss, steatorrhea, postprandial abdominal pain, and bloating.
- Untreated celiac disease is associated with micronutrient deficiencies, low bone mineral density, infertility, malignancies, and increased mortality.^{4,7}
- There is no known cure for celiac disease. However, the disease can be managed through lifelong adherence to a gluten-free diet.
- While types of gluten-free foods may be more commonly known, many healthcare providers and patients have a limited understanding of gluten-free medications.

Gluten in Medications⁶

- Oral medications in the form of tablets and capsules are composed of excipients that may contain gluten.
- Excipients can include absorbents, protectants, binders, coloring agents, lubricators, and bulking agents and can potentially cause unwanted reactions in patients with celiac disease.
- The main medication excipient that can cause a reaction in celiac patients is starch, typically derived from potatoes, tapioca, or wheat. Starch derived from wheat is of the greatest concern. It is highly unlikely that any excipient other than starch will contain any measurable amount of gluten.
- All products with wheat starch should be avoided (e.g. aliskiren/hydrochlorothiazide [Tekturna HCT®], doxycycline capsule [Doryx®]).
- Other types of starch that may exacerbate celiac disease include pre-gelatinized starch and sodium starch glycolate.
 - Pre-gelatinized starch: primarily derived from corn but can be derived from any source
 - Sodium starch glycolate: can be derived from any source
- A common misconception is that a product derived from a wheat *source* (note: different from wheat *starch*) will cause a reaction in patients with celiac disease. This is unlikely since the wheat source is most likely a sugar alcohol source, also known as polyols.
 - Polyols are highly processed sugars that contain no wheat gluten and therefore cannot cause a reaction (e.g., mannitol, sorbitol, sorbitan, xylitol).
- Most medications do not use starch but may use other excipients as starting material for drug production.

- It is important to evaluate excipient information to determine whether the patient is at risk of a gluten reaction. Two resources that can be used to find medication excipient information are [Pillbox](#) and [DailyMed](#). These resources allow healthcare providers to make safe medication recommendations and identify appropriate alternatives.

Table 1. Starch Excipients⁶

Contains gluten	May contain gluten	Likely does not contain gluten
Wheat starch	Pre-gelatinized starch Sodium starch glycolate	Excipients derived from a wheat source

Additional considerations⁶

- Olmesartan (Benicar®) does not contain gluten but can cause celiac-like enteropathies. Considering patients can suffer from severe gastrointestinal symptoms from the drug, this medication should be avoided in patients with celiac disease.
- Drug companies will not guarantee that their product is gluten-free due to potential cross contamination in their manufacturing plant. However, cross contamination is extremely unlikely due to the level of air quality control required at the manufacturing plants by the Food and Drug Administration.

Conclusion

- Although the chance that a drug contains gluten is extremely small, it is important to identify potential gluten sources in medication excipients to provide appropriate care for patients with celiac disease.

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Current Literature on Cannabidiol-Containing Products

By Sophia Lai, PharmD; Reviewed by Ryan Caldeiro, MD

Key Points:

- Cannabidiol (CBD) and tetrahydrocannabinol (THC) are both active components of the cannabis plant. However, unlike THC, CBD does not produce psychoactive effects.
- Use of cannabidiol-containing retail products is increasing for a variety of uses, mainly to alleviate pain.
- Due to the lack of conclusive evidence from scientific literature paired with under regulation of the industry, patients should be cautioned against using CBD-containing products.

Background

- Indica* and *Sativa* are two popular strains of commercially available cannabis and an upward of 108 cannabinoids have been isolated from the plant.
- Cannabidiol is a more concentrated component of hemp, which is the fiber and seed portion of the cannabis plant. THC is a more concentrated component of marijuana, which is the flower portion of cannabis, and currently classified as a Schedule I Controlled Substance.
- Different from THC, CBD does not produce psychoactive effects or the “high” and can be purchased without a prescription.⁸
- Products containing CBD is a growing market.

Reported Use of CBD

- A cross-sectional study that collected 2490 responses from October 2017 to January 2018 assessed the underlying reasons and methods of CBD use.⁹
- Most patients stated CBD use was for medical conditions, with the most common conditions being chronic pain, arthritis/joint pain, and anxiety.
- The most commonly reported routes of administration were sublingual, inhalation, oral, or topical.¹⁰

Scientific Evidence for CBD

- Alleged health benefits of CBD use stem from animal or in vitro studies with most data on its pain relief. CBD-based analgesia is potentially associated with its immune-modulatory, anti-inflammatory, and antioxidant activities.⁹
- In vitro studies have shown CBD to have effects directly and indirectly through the endocannabinoid system (ECS), which is important in regulating tissue inflammation and pain.
- This gives CBD the potential to modulate symptoms of pain and inflammation in inflammatory joint disease.¹¹
- CBD also has many non-endocannabinoid targets, which may explain its other medical properties (**Table 1**).
 - This makes CBD popular in research that study conditions such as acne, type 1 diabetes, multiple sclerosis, Alzheimer's disease, and epilepsy.
 - Of note, in June 2018 the U.S. Food and Drug Administration (FDA) approved Epidiolex, the first synthetically purified cannabidiol oral solution to be approved in the U.S., for the treatment of Lennox-Gastaut syndrome and Dravet syndrome, both rare and severe forms of epilepsy.¹²

Table 1. Medical Properties and Side Effects

Medical Properties	Side Effects
• Analgesia • Anti-inflammatory • Anxiolytic • Antiemetic • Sedative • Reduced nicotine craving	• Dry mouth • Euphoria • Hunger • Red eyes • Sedation/Fatigue • Cough/Wheezing (smoked)

- Common patient-reported side effects (**Table 1**) were reversible and studies did not report tolerance, adverse effects, or altered physiological parameters.^{9,13,14}

Drug Interactions

- *In vitro* studies demonstrated that CBD is metabolized by the cytochrome P450 family, specifically CYP3A4, 2C9, and 2C19. The concurrent use with inducers and inhibitors of the enzymes should be avoided. CBD can also inhibit CYP2C9 and CYP2D6, interacting with drugs such as warfarin, diclofenac, omeprazole and risperidone.^{11,15}
- Monitoring may be necessary when concurrent use of CBD and interacting agent is unavoidable.¹⁶

Under-Regulation of the CBD Industry

- Although the side effects of CBD use appear to be benign, the under-regulation of the CBD industry poses a bigger threat to patient safety.
- A content analysis was performed on 84 CBD products purchased in retail stores and result showed a wide range of CBD content (0.10 mg/mL to 655.27 mg/mL) with only 31% of the

products being accurately labeled. Approximately 40% of the products contained active ingredients other than CBD, i.e. THC, cannabidiolic acid, and cannabigerol.¹⁷

- Misbranded and adulterated products may cause intoxication and impairment in consumers.

Conclusion

- The clinical benefit of CBD is unclear with most available literature being poorly designed, having a small sample size, and CBD use being self-reported.
- Despite the volume of published literature on both CBD and cannabis use, the result on health effects is largely inconclusive and requires better study design with long-term follow up.
- Retail CBD-containing products may be misbranded, adulterated, and pose safety concerns.
- The use of CBD-containing products should be avoided due to the lack of evidence and regulation.

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FDA Safety Alert:

Rare Occurrences of a Serious Infection of the Genital Area	
Issue	Recommendation
FDA is warning that cases of a rare but serious infection of the genitals and area around the genitals have been reported with the class of type 2 diabetes medicines called sodium-glucose cotransporter-2 (SGLT2) inhibitors. This serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene.	Patients should: • Seek medical attention immediately if you experience any symptoms of tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, and have a fever above 100.4 F or a general feeling of being unwell. These symptoms can worsen quickly, so it is important to seek treatment right away. Health care professionals should: • Assess patients for Fournier's gangrene if they present with the symptoms described above. If suspected, start treatment immediately with broad-spectrum antibiotics and surgical debridement if necessary. • Discontinue the SGLT2 inhibitor, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

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