INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Combination Drugs & Adherence***
-November 2024-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a comprehensive review of Combination Medications & Adherence at the Fall 2024 NPTC Meeting. Combination medication(s) listed on the National Core Formulary (NCF) are too numerous to name in their entirety but include common drugs like amoxicillin-clavulanate, carbidopa-levodopa, sacubitril-valsartan, etc. Agency data regarding utilization/trends were insightful regarding the current and historical use of these products across the IHS. Following the comprehensive review, the NPTC voted to **ADD** (1) **Lisinopril-hydrochlorothiazide (any dose, any tablet)** and **ADD** (2**) Losartan-hydrochlorothiazide (any dose, any tablet)** to the NCF.

Discussion:

Combination medications first became available in the 1950s with a medication called Ser-Ap-Es®. This product combined reserpine, hydralazine, and hydrochlorothiazide for the treatment of hypertension. In the 1970's, combination therapies were widely accepted due to the complexity of managing hypertension. However, the introduction of guidelines like JNC III-IV in the 1980s shifted the treatment concept towards "stepped care" (individualized, singular medications) to avoid potential adverse effects and overtreatment. Recent updates to these guidelines showcased the necessity for multidrug initial therapy. C. Everett Koop, MD, former US Surgeon General famously stated, "Drugs don't work in patients who don't take them." In 2017, the US Centers for Disease Control and Prevention (CDC) published a document focused on medication adherence, stating adherence to prescribed medications improves clinical outcomes and reduces mortality for chronic diseases. Conversely, nonadherence leads to higher hospital admissions, suboptimal health outcomes, and increased healthcare costs. As such, single-pill combinations have re-emerged, particularly in managing cardiovascular risks, as a potential solution to increase adherence and improve outcomes.[1,2]

A 2016 retrospective cohort study of 484,493 patients compared the persistence of initiating single-pill combination (SPC) with multi-pill combination therapy, and single therapy. Persistence was determined if the patient was still taking a medication at the end of a study period. Adherence was determined by the proportion of days covered (PDC), which is defined as days covered (not days supplied) divided by the number of days in the period. Authors found that SPCs for hypertension led to a 9% higher persistence (RR 1.09, 95% CI: 1.08-1.10) and 13% better adherence compared to single therapies (RR 1.13, 95% CI: 1.11-1.14). However, the authors noted slightly worse adherence and persistence when single-pill combination was compared to multi-pill combination therapy, which is contrary to findings from other studies.[3]

A recent meta-analysis published in 2024 examined persistence and adherence as measured by PDC and medication possession ratio (MPR), which is the days' supply of medication divided by the days in the period, of SPC compared with equivalent multi-drug combination therapy. SPCs were associated with significantly improved adherence compared with equivalent multi-drug combination therapy, as assessed through MPR ≥80% (OR 0.42, p<0.01) and proportion of days covered ≥80% (OR 0.45, p<0.01). SPC also improved persistence (OR 0.44, p<0.01).[4]

In 2017, the Cochrane Group conducted a meta-analysis to determine the efficacy of SPC therapy vs. placebo or an active comparator for the prevention of atherosclerotic cardiovascular disease (ASCVD). The meta-analysis included 13 trials with a total of 9059 participants. The following outcomes were statistically significant: adverse events (RR 1.16, 95% CI: 1.09 to 1.25, moderate-quality evidence), systolic blood pressure (mean difference: -6.34 mmHg, 95% CI: -9.03 to -3.64, moderate-quality evidence) total cholesterol (mean difference: -0.61 mmol/L, 95% CI: -0.88 to -0.35, low-quality evidence), LDL cholesterol (mean difference: -0.70 mmol/L, 95% CI: -0.98 to -0.41, moderate-quality evidence), and improved adherence (RR 1.44, 95% CI: 1.26 to 1.65, moderate-quality evidence). The effect on all-cause mortality or ASCVD events are uncertain due to low event rates and indirectness of evidence. Authors concluded that, compared to placebo or an active comparator, SPCs are associated with slight increases in adverse events, and may improve adherence, blood pressure, LDL, and total cholesterol.[5]

A retrospective, observational real-world analysis was conducted to analyze adherence and healthcare resource utilization among approximately 7 million patients in Italy. Researchers compared adults receiving perindopril and bisoprolol (PER/BIS) as SPC or multi-pill combination therapy. Adherence was reported to be higher in the SPC group (45.5%) compared to the multi-pill combination therapy group (38.6%), p<0.001, drug discontinuation was lower in the SPC group (35.8%) compared to the multi-pill combination therapy group (41.7%), p<0.001, cardiovascular hospitalizations were fewer in the SPC group (5.3%) compared to the multi-pill combination therapy group (7.4%), p<0.001, and there were lower mean annual total healthcare costs in the SPC group compared to the multi-pill

combination therapy group, $p<0.001$. The authors concluded that patients treated with PER/BIS SPC showed higher adherence, lower risk of drug discontinuation, reduced risk of cardiovascular hospitalization, and lower healthcare costs compared to those on multi-pill combination therapy of the same drugs.[6]

Meta-analyses on the utility of SPCs can be difficult to conduct due to significant heterogeneity among included studies. Paoli et al. conducted a systematic literature review in 2024 and instead of combining an outcome into an aggregate, they looked at whether clinical trials, real-world evidence, health-related quality of life studies, and economic evaluations favored SPCs or multi-pill combination therapy. They found that adherence was higher in patients receiving SPCs in 12 of 13 real-world evidence studies and in 3 of 13 clinical trials, persistence was higher in all 18 real-world evidence studies with SPCs, positive clinical outcomes in 14 of 17 real-world evidence studies (including reduced need for add-on medication, blood pressure control, and improved hemoglobin A1C), health-related quality of life studies were similar among the groups, and all 6 cost-effectiveness or cost-utility analyses found SPCs were less expensive and more efficacious than multi-pill combination therapy. Authors concluded that SPCs are associated with improved patient adherence, persistence, and clinical outcomes while also offering economic advantages. Additionally, differences between real-world evidence and clinical trials are likely due to clinical trial procedures, which maximize adherence in a controlled environment.[7]

Benefits of SPCs are not just with dual therapy but is also evident with triple combination therapy. A 2023 article sought to compare Italian patients prescribed perindopril/amlodipine/indapamide as SPC vs. an angiotensin inhibitor/calcium channel blocker/diuretic as a two-drug SPC plus a third drug, given separately. The researchers found higher adherence among SPC users (59%) vs. two-pill combination users (25%), (RR 2.38, 95% CI: 2.32-2.44, $p<0.001$). Only 8% of SPC users had adherence classified as “low” compared to 23% of two-pill combination users (RR 0.33, 95% CI: 0.31-0.34, $p<0.001$), discontinuation was lower with the SPC group (31% vs. 53%; RR 0.59, 95% CI: 0.57-0.60, $p<0.001$), higher adherence associated with lower risk of hospitalization for CV events (HR 0.74, 95% CI: 0.68-0.80, $p<0.001$), and SPC users had lower mean healthcare costs ($p<0.001$). The authors concluded that the SPC of three antihypertensive drugs significantly improved adherence to drug therapy compared to the two-pill combination. Higher adherence was associated with a lower risk of hospitalization for CV events and lower healthcare costs. The benefits of SPC were consistent across different demographic and clinical subgroups.[8]

Findings:

Combination medications offer a practical solution for improving adherence and reducing cardiovascular risks, particularly in hypertension management. As additional combination products become available, individual sites should explore the option of adding products to the local formulary to further improve adherence and outcomes for multiple disease states.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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