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PRESENT AND FUTURE PROSPECT OF COMBINATION DRUGS THERAPY

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ABSTRACT

A combination therapy is a therapeutic intervention in which more than one therapy is administered to the patient. Examples of combination therapy include treatment regimens that involves administering several separate pills, each containing a particular drug, or single pills that contain several drugs. The aim of this work is to spread the information about the present situation of combination drug therapy and in future what medicinal development we can do with combination therapy. For this work we have visited several hospital such as Anwar khan modern, Square and Samorita hospital in Bangladesh and collected prescription from several department. We have analyzed the prescribe medicine and saw that most of the doctor using 70% single medicine but for some disease such as hypertension, diabetics, cancer, tuberculosis, anti-depression, a little bit in heart disease they used combination drug therapy was 20% and this medicines were more effective than single drug therapy. In future for better medical treatment we have to expand the use of combination drug therapy. In some disease such as ear related disorder, anti-fungal, heart disease there is a little bit using of combination therapy whereas this therapy is more effective than single drug therapy. So combination drug therapy is very essential.

KEYWORD: Combination therapy, prescription, hospital, hypertension, cancer.

INTRODUCTION

Combination drug therapy is defined as the use of two or more pharmacologic agents administered separately or in a fixed-dose combination of two or more active ingredients in a single-dosage formulation. Combination therapy is frequently prescribed by physicians to treat and manage a plethora of medical conditions; however, without thorough monitoring, various problems can arise. In some cases, patients must try several different combinations of drugs before finding the best therapy to successfully treat a medical condition. Pharmacists can be instrumental in ensuring that combination drug therapy is used appropriately by screening for potential drug– drug interactions, contraindications, or both, and by making therapeutic recommendations aimed at achieving optimal response without increasing the potential for adverse drug reactions. Pharmacists also can identify possible cases of poly pharmacy, especially among elderly patients and those with multiple medical conditions. Combination drug therapies can offer additive benefits that target multiple pathologic processes.[1-5] A combination drug is a fixed-dose combination (FDC) that includes two or more active pharmaceutical ingredients (APIs) combined in a single dosage form, which is manufactured and distributed in fixed doses. Terms like "combination drug" or "combination drug product" can be common shorthand for a FDC product (since most combination drug products are currently FDCs), although the latter is more precise if in fact referring to a mass-produced product having a predetermined combination of drugs and respective dosages (as opposed to customized poly pharmacy via compounding). And it should also be distinguished from the term "combination product" in medical contexts, which without further specification can refer to products that combine different types of medical products-such as device/drug combinations as opposed to drug/drug combinations. Note that when a combination drug product (whether fixed dose or not) is a "pill" (i.e., a tablet or capsule), then it is also a kind of "poly pill" or combo pill. Initially, fixed-dose combination drug products were developed to target a single disease (such as with antiretroviral FDCs used against AIDS). However, FDCs may also target multiple diseases/conditions, such as Caduet (atorvastatin/amlodipine) or Exforge (amlodipine/valsartan). In cases of FDCs targeting multiple conditions, such conditions might often be related—in order to increase the number of prospective patients who might be likely to utilize a given FDC product. This is because each FDC product is mass-produced, and thus typically requires having a critical mass of potentially applicable patients in order to justify its manufacture, distribution, stocking etc.[6-9]

Mechanism of combination drug therapy

Mechanism of combination drugs are shown in figure 1.[10]

Advantages of combination drug

Combination drug therapy can be used initially or added gradually if the therapeutic response with mono therapy is not as expected. In addition to using two or more single agents as a treatment for a medical condition, various fixed dose combination formulations may offer several advantages, such as the convenience of fewer pills a patient is required to take daily and reduced potential for medication errors. Research has shown that simpler drug regimens may increase the likelihood of patient adherence, and, depending upon the pharmacologic agent, medication costs may also decrease. Combined agents also may minimize the adverse effects of each individual agent.

- Improved medication compliance by reducing the pill burden of patients. Note that pill burden is not only the number of pills needing to be taken, but also the associated burdens such as keeping track of several medications, understanding their various instructions, etc.
- Ability to compose combined profiles of for example pharmacokinetics, effects and adverse effects that may be specific for the relative dosages in a given FDC product, providing a simpler overview compared to when looking at the profiles of each single drug individually. Such combined profiles can also include effects caused by interaction between the individual drugs that may be omitted in individual drug profiles.
- Since FDCs are reviewed by regulating agencies (such as the Food and Drug Administration in the United States), the active ingredients used in the FDCs are unlikely to exhibit adverse drug interactions with each other. However, FDCs may interact with other drugs that a patient is taking, so the usual medical and pharmaceutical precautions against drug-drug interactions or DDIs remain warranted.
- FDC drug products may be developed by a pharmaceutical company as a way to in effect extend proprietary rights and marketability of a drug product. Since FDCs may be protected by patents, a company may obtain exclusive rights to sell a particular FDC or formulation thereof, even though the individual active ingredients and many therapeutic uses thereof may be off-patent.[11-14]

Disadvantages of combination

Some concerns about using fixed-dose combination drugs include the lack of flexibility in altering the dosing of individual components and the exposure of patients to unnecessary

therapy. The FDA's policy on fixed-dose drug combinations states that two or more drugs may be combined in a single-dose form when each component makes a contribution to the claimed effects, and the dosage of each component is such that the combination is safe and effective for a significant patient population requiring concurrent therapy as defined in the labeling for the drug.

- There may not be an FDC available with the appropriate drugs and/or in the most appropriate respective strength(s) for a given patient, which can lead to some patients getting too much of an ingredient and others getting too little, as the AAO notes that FDCs "limit clinicians' ability to customize dosing regimens. In such cases an alternative possibility (instead of FDC) is to utilize custom-compounded poly pills prepared by a compounding pharmacist according to a prescription. (Pharmaceutical compounding is the practice of preparing individualized drug products for individual patients, which can aid with poly pharmacy.)
- If an adverse drug reaction occurs from using an FDC, it may be difficult to identify the active ingredient responsible for causing the reaction. This problem might be alleviated by starting the medications individually and monitoring for reactions, and then switching to an FDC when no problems have been observed (assuming of course that it's the active ingredient causing the problem).[15-18]

Usefulness in Various Medical Conditions

Combination drug therapy is considered the standard of care in the treatment of several medical conditions. In conjunction with lifestyle modifications, combination drug therapy is often considered to be the best tool in the prevention and delay of the morbidity and mortality associated with cardiovascular disease (CVD) and its risk factors, especially for high-risk patients. Various studies have demonstrated that this approach also may be beneficial in the treatment and management of chronic medical conditions, such as diabetes mellitus, Alzheimer's disease, rheumatoid arthritis, malignancies, pain disorders, neurologic disorders, pulmonary disorders, as well as HIV and other infectious diseases. Chemotherapeutic agents in various combinations comprise regimens for treating specific cancers.[19-20]

Hypertension

According to The Seventh Report of the Joint National Committee (JNC 7) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, results from recent trials demonstrate that effective blood pressure control can be achieved in some patients with

hypertension. To meet the target goal of <130/80 mm Hg, however, the combine- 48n 01.10 | Pharmacy Times www.PharmacyTimes.com Rx focus Monitoring Combination Drug Therapy Yvette C. Terrie, BS Pharm of 2 or more drugs is often necessary. 6 Several antihypertensive combination regimens are now available, including beta-blocking agents with diuretics, angiotensin-converting enzyme inhibitors (ACEIs) with diuretics, angiotensin II receptor blockers (ARBs) with diuretics, or calcium channel blockers (CCBs) with ACEIs or ARBs. Results from studies have demonstrated that the use of pharmacologic agents such as thiazide diuretics, beta-blockers, ACEIs, ARBs, and CCBs have been beneficial in decreasing the incidence of CVD and stroke in hypertensive individuals with diabetes. In addition, the combination of an ACEI and a thiazide diuretic has been shown to decrease the rate of recurrent strokes among some individuals. Because hypertension is a multifactorial condition, studies show that the combination of two antihypertensive agents with different mechanisms of action, such as a di-hydro pyridine CCB plus an ACEI or ARB, may provide additional benefits, and many studies have demonstrated that combination therapy increases the capacity to lower blood pressure compared with mono therapy. Results from clinical trials report that only 30% of hypertensive patients achieved and maintained adequate blood pressure control with mono therapy. Many patients with hypertension tend to require more than a single agent, especially if they have comorbid conditions. Some studies suggest that combination therapy for initial management offers the potential to achieve blood pressure goals sooner and with fewer adverse effects, because lower doses of each agent may be used. Results from a study by Jameson et al evaluated the efficacy and safety of initial combination therapy versus that of mono therapy in patients with stage 2 hypertension who, according to the JNC 7 recommendations, met the criteria for the use of initial antihypertensive combination drug therapy. The results concluded that combination therapy was well-tolerated and resulted in greater reductions in blood pressure.[21-24]

Diabetes

Combination drug therapy is often used to treat diabetes. Some of the advantages of using combination drug therapy in diabetes include the following:

1. Better glycemic control with 2 drugs that work at different sites.
2. Fewer side effects with lower doses of 2 drugs than a large dose of 1 drug
3. When combined in the same pill or capsule, the likelihood of patient adherence to therapy may increase and the cost may be lower, depending on the agent.

Patients with type two diabetes may also require other medications to treat or prevent disease associated complications. Aspirin and statins are often used for cardio protection, and ACEIs/ARBs are used for renal protection.[25-27]

Effectiveness in other conditions

Additional studies point to the effectiveness of combination therapy for Alzheimer's disease, arthritis, and breast cancer. The results from a clinical trial published in the Journal of the American Medical Association demonstrated that individuals with Alzheimer's disease treated with a combination of the N-methyl-D-aspartic acid receptor antagonist, meantime hydrochloride, and the cholinesterase inhibitor, donepezil, showed a slower rate of decline in cognitive function and behavioral changes, compared with those who took only donepezil. A study published in the May 2009 issue of Arthritis and Rheumatism reported that using a combination of disease-modifying ant rheumatic drugs compared with using just 1 agent to treat early rheumatoid arthritis results in higher long-term remission rates. In breast cancer, docetaxel, doxorubicin, and cyclophosphamide are often used together in one chemotherapy regimen. Results from a study published in 2009 state that combination therapy with exemestane and celecoxib has shown promising results in treating advanced breast cancer.[28-29]

MATERIALS AND METHODS

Study design and data analysis

We visited my nearby hospital of Anwar khan modern hospital, Square hospital and Samorita hospital and collected prescription from various department such as medicine, cardiology, orthopedic etc. We analyzed all of prescription and see that 80% doctors use single drug in there prescription, 20% doctor use combine drug in there prescription.[30]

List of single drug, combination drug and related informations are shown below in table 1, 2 and 3.

Cost-effectiveness of combination therapy

It is well established that the treatment of chronic diseases is a burden on the financial health of a society and great efforts have been made to try reducing the costs related to the treatment of these diseases. Previous studies confirmed that the economic burden of PAH is substantial, with direct healthcare costs per patient per month in the range of $2576–$11,875 (excluding indirect cost). However, few studies have evaluated the cost-effectiveness of PAH drugs.

Cost effectiveness is frequently assessed by estimating the incremental cost per quality-adjusted life years (QALYs), with values generally less than US$50,000 but up to US$200,000 being considered cost-effective. A recent cost-effectiveness analysis suggested that first-line mono therapy was associated with cost higher than CAN$140,000 and CAN$350,000 for PDE5i and ERA, respectively. It is noteworthy, however, that although many clinical trials reported measured quality of life, none have reported the impact of treatment in a format that would allow precise estimation of QALYs. These calculations generally rely on utility estimates based on WHO FC that are derived from a single cohort and few studies evaluated the cost-effectiveness of combination therapy. More importantly, the available economic evaluation studies are likely country-specific and have merely concentrated on certain PAH treatments, and the lack of head-to-head comparison studies covering all comparable medications limit the validity cost-effectiveness comparisons. Nonetheless, the emergence of novel drug therapies will necessitate the assessment of their cost effectiveness, especially when it comes to combination therapy. Further studies addressing this issue and weighting against the efficacy, tolerability, availability, and patient preference will thus be needed.[31-32]

Future prospect of combination therapy

The use of antifungal combination therapy is a new clinical approach for combating fungal infections. Although few conclusive clinical studies have been performed to date, data exist that strongly suggest that combination therapy would benefit specific patient subgroups (e.g. stem cell transplant recipients). This paper examines the evidence available from in vitro, experimental, and clinical studies, and seeks to discover viable clinical strategies for this promising new therapeutic approach.[33-34]

RESULT AND DISCUSSION

In the Figure 2 which are shown at the end implied total prescription 100. In which doctor uses 80% single drug and 20% combine drug therapy.

From this observation, we found that almost all doctors prescribed single drug, On the other hand very few doctor prescribed combinations drug among those renowned hospitals in Bangladesh.

In drug therapy, doctors use combine drug 10% in hypertension, 4% for diabetic, 4% in cancer and 2% in others disorder. [Figure 3]

Combination drugs are used mostly in hypertension, diabetes, cancer, tuberculosis, alzheimer's disease and other disease in that hospitals.

Table 1: List of single drug with brand name, Generic name and unit price.

Brand name	Generic name	Unit price
Omidon10mg	Domperidon	2
Zimax 500mg	Azithromycin	35
Ceevit 250mg	Vitamin C	1.3
DON-A 10mg	Domperidon	2
Emistat 8mg	Ondansetron	11
Pantonix 20mg	Pantoprazole	5
Disopan 0.mg	Clonazepam	3
ACE 500mg	Paracetamol	0.8
Alcet 5mg	Levocetirizine dihydrochloride	4.5
Seasonix5mg	Levocetirizine dihydrochloride	3.5
Alatrol 10mg	Cetirizine hydrochloride	3
Revotril o.5mg	Clonazepam	7
Riboson	Reboflavin	0.3
Solas 10mg	Mebendazole	1.5
Albe 10mg	Albendazole	5
Motigut 10mg	Domperidon	3.5
Nexum20mg	Esomeprozole	10
Indomet 25mg	Indomethacin	4
Omep 20mg	Omeprazole	5
Easipum 5mg	Diazepum	3
Cef-3 DS 500mg	Cefixime trihydrate	50
Inh Brodil levo	Levosalbutamol	250
Precodil 5mg	Prednisolone	4
Doxiva 200mg	Doxophylline	6

Table 2: List of combine drug with brand name and generic name with unit price.

Brand name	Generic name	Unit price
D-Rise 40000IU	Cholecalciferol	35
Remood10.5mg	Flupentixol+melitracen	4
Cora-D	Calcium carbonate +VitaminC	15
Pevitin cream	Econazole nitrate +_Triamcinole acetonid	60
Methasol N	Bemethasone + Neomycin sulphate	30
Solvit	Vitamin B complex	2
Cyclopam	Diclomine + paracetamol	4.5
Fimoxyclav625mg	Amoxicillin + Clavulanic acid	50
Kefuclav 625mg	Cefuroxime axetil + Clavulanic acid	50
Bontiv	Diacerin + glucasamine sulphate	12
Napa extra625mg	Paracrtanol + caffeine	2.5
Metivol	Flupentixol + melitracen	3.5
Ostomax -D	Alendronic + vitaminD3	25
EC plus	Vitamin C + vitamin E	6

Table 3: List of single and combination drug with unit price.

Single drug	Combination drug	Unit price
Losectil 20mg	Omeprazol	5
Levoxin 250mg	Levofloxacin	10
Dicaltrol 0.25mg	Calcitriol	10
Zymet 325mg	Pancreatin	5
Mucomist	Acetylcysteine	30
Inj cortef	Hydrocortisone	50
Inj cefiron	Ceftriaxone	160
Inj roxadex	Dexamethasone	50
Inj esotid	Esomeprazole	30
Xovir 250mg vial	Acyclovir	400
Rofixim200mg	Cefixime trihydrate	35
Syp napa	Paracetamol	50
Rabe 20mg	Rabeprazole sodium	5
Omastin 150mg	Fluconazole	22
Reset500mg	Paracetamol	0.8
Acefix 20mg	Rabeprazole	5
Fexofast 120mg	Fexofenadine hydrochloride	7
Recipro 400mg	Ciprofloxacin	80
M –kast10mg	Montelukast	12
Myolax 50mg	Tolperison hydrochloride	7
Zolfin 100mg	Aceclofenac	3
Sergel 20mg	Esomeprazole	7
Reversair	Montelukast sodium	8
Neofloxim 500mg	Ciprofloxacin	14
Betanol 100mg	Atenolol	1.37

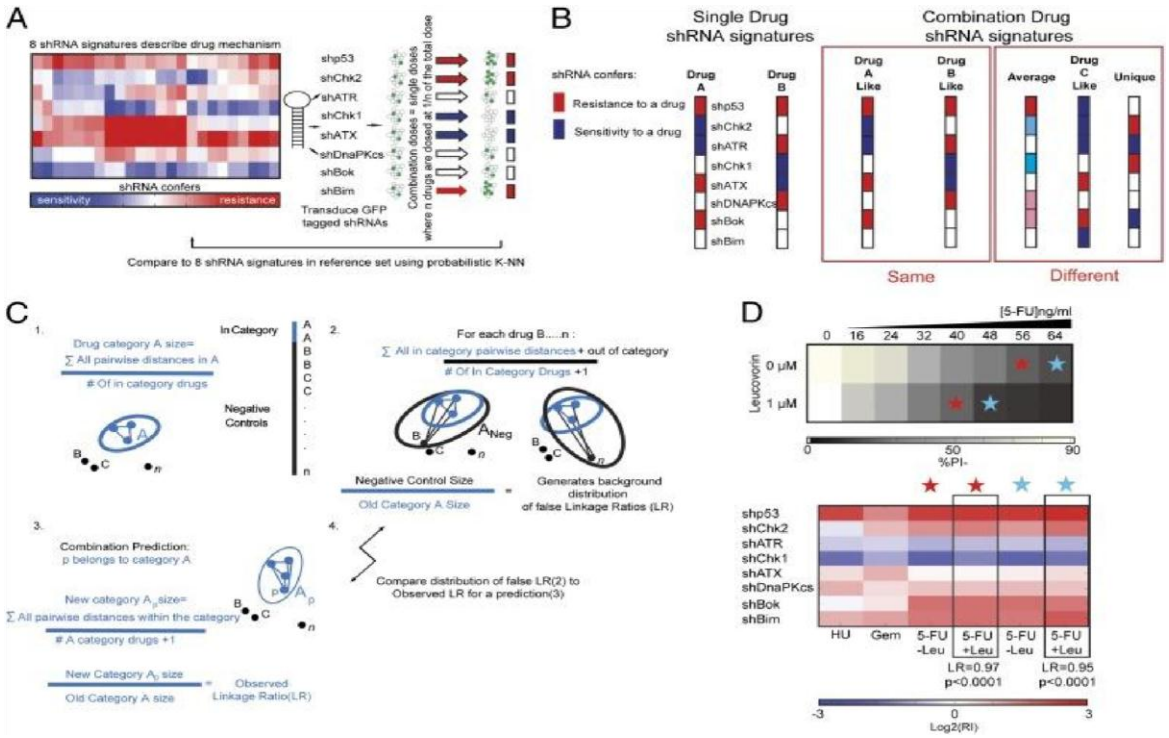

Figure 1: Mechanism of combination therapy.

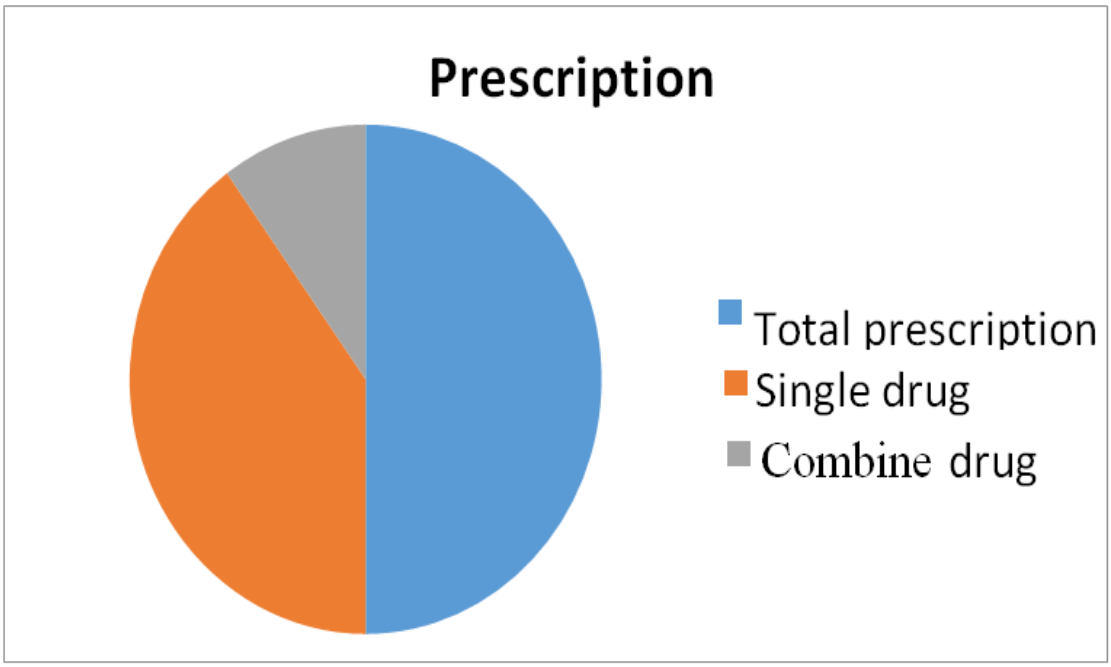

Figure 2: Total prescription.

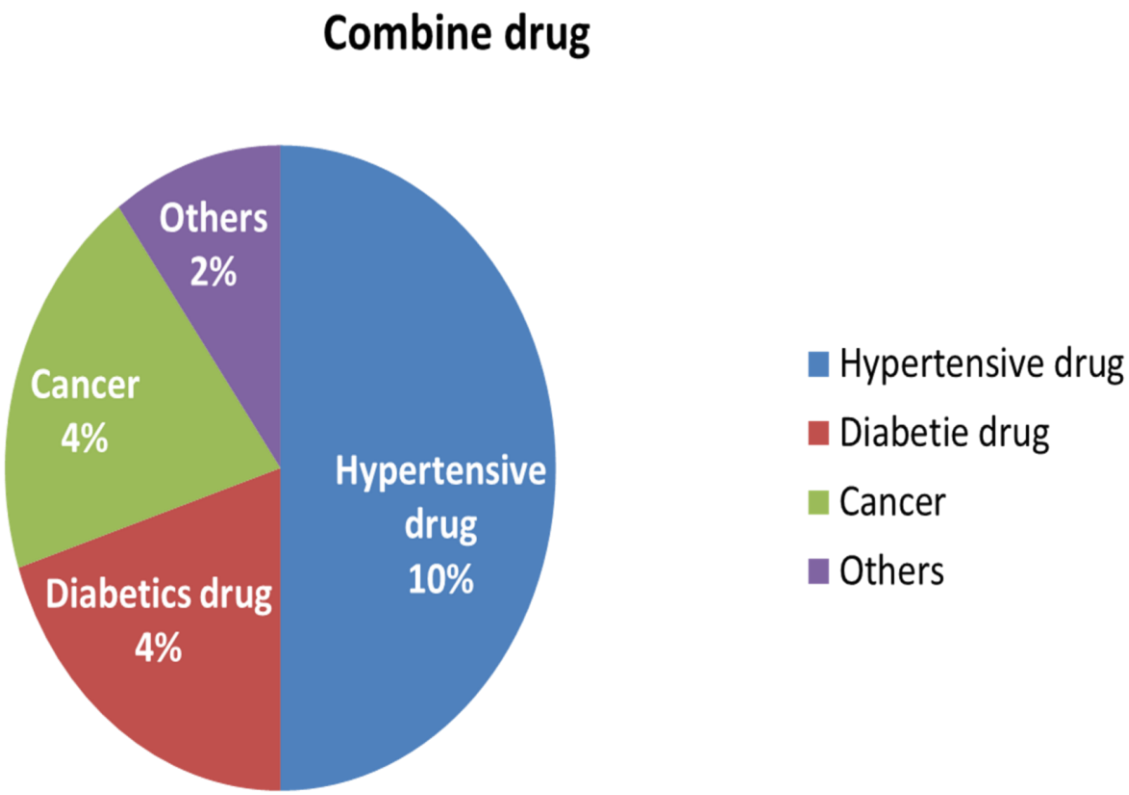

Figure 3: Uses of Combine drug.

CONCLUSION

Combination drug therapy is often necessary for the management and treatment of various chronic medical conditions, including CVD, hypertension, and diabetes. As more fixed-dose

combination formulations become available, they should be considered for use with the aims of improving patient adherence, simplifying drug regimens, and optimizing care. Patients should be encouraged to maintain routine visits with their primary health care provider so they can be properly monitored. Although studies have shown that combination drug therapy is often beneficial for the treatment of many patients, pharmacists are vital to ensuring that these agents are used appropriately by screening for potential drug–drug interactions, contraindications such as hepatic or renal problems, and unnecessary drug use. But it is not beneficial for all kind of disease and most of the doctor prescribe single drug in there prescription. Looking forward to future developments in drug combination therapies, it should be noted that future research will be needed to be able to patient-specific properties that parameterize the different drug combinations. Being able to accurately estimate variations in different patients' synergistic effects, or variations of rates associated with the underlying chemical reaction equations, or the different subpopulations that might exist in a patient will be essential to driving the application of drug combinations models for personalized therapies.

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