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Minimization of the Drug and Gene Interactions in Polypharmacy Therapies Augmented with COVID-19 Medications

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Abstract. Medications *Dexamethasone, Remdesivir* or *Colchicine,* used to treat *COVID-19* patients, have significant interactions with other medications and the human genome. The study presented in this paper investigates how to use the *Personalized Medicine Therapy Optimization Method (PM-TOM*) to minimize these interactions in polypharmacy therapies of *COVID-19* patients. We applied *PM-TOM* on the *EMR* database of *Harvard Personal Genome Project (PGP)*, drug database *DrugBank* and *Comprehensive Toxicogenomics Database (CTD)* to analyze polypharmacy therapies augmented with these medications. The main finding is that these *COVID-19* medications significantly increase the drug and gene interactions in partially optimized (or unoptimized) therapies, which is not the case in the fully optimized ones. For example, the test results show that in polypharmacy treatments for patients having between 3 and 8 conditions, the average number of drug and gene interactions in partially optimized therapies ranges from 3 to 18 after adding *Remdesivir*, 4.3 to 20 *Colchicine,* and 4.7 to 23 *Dexamethasone*. On the other hand, these interactions in fully optimized therapies range only 0.6 to 5.2, 1.2 to 7, and 2.7 to 11, respectively. These results suggest that polypharmacy therapies should be carefully examined before adding these medications. This recommendation applies to all other situations when polypharmacy patients may conduct new serious conditions, such as *COVID-19*, requiring additional medications with a high number of drug and gene interactions.

Keywords. *COVID-19*, *PM-TOM*, Clinical Decision Support Systems (*CDSS*), Dexamethasone, Remdesivir, Colchicine, Polypharmacy, Multimorbidity, Drug-Drug Interactions *(DDI)*, Drug-Gene Interactions *(DGI)*.

1. Introduction

The *Medical Guidelines for Treating COVID-19 Patients* [1] of *the US National Institutes of Health (NIH)* recommend drugs for various categories of these patients. For example, high-risk hospitalized patients who do not require supplemental oxygen should be treated with *Remdesivir*. *Dexamethasone* is recommended only for patients who need invasive mechanical ventilation or extracorporeal membrane oxygenation (*ECMO)*. *NIH* also reported several active or completed studies on the benefits of *Colchicine* for *COVID-19* patients. For example, study [2] found that the median hospitalization time was reduced from nine to seven days for the *COVID-19* patients treated with *Colchicine*.

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While these medications could help the *COVID-19* patients to overcome this infection without serious outcomes, they may also pose a significant risk due to their numerous drug-drug interactions and drug-gene interactions (*DDIs*, *DGIs*). For example, the total number of *DDIs* for *Dexamethasone* is 1,211, *Colchicine* 1,297 and *Remdesivir* 442, according to *DrugBank* [3].

Several studies, for example [4], report a high occurrence of adverse drug and gene interactions in polypharmacy cases (66-87% of the patients had *DDIs* and 34-73% *DGIs*). In addition, study [5] found that adverse drug reactions and interactions were between the fourth and sixth causes of death in the US. So, the possible adverse drug and gene interactions of the *COVID-19* medications should be carefully considered before adding them to polypharmacy treatment of multimorbidity patients infected with *SARS-CoV-2.*

This study used the *Personalized Medicine - Therapy Optimization Method* (*PM-TOM*) [6, 7] to optimize *DDIs* and *DGIs* in polypharmacy treatments extended with the *COVID-19* medications. To the best of our knowledge, *PM-TOM* is the only published method for optimizing both the drug-drug and drug-gene interactions in polypharmacy treatments. The results suggest that these interactions can be significantly reduced, thus increasing the chances for multimorbidity patients to overcome *COVID-19* with minimal consequences.

2. PM-TOM Method

The ***PM-TOM* datasets** are a database of Electronic Medical Records (*EMR)*, Drug Repository *(DRG)*, and Gene-Drug Repository *(GDR)*. *PM-TOM* retrieves the patient's conditions, prescriptions and genome from *EMR* (only pharmacogenetic and pathogenic gene variations). The drug repository *(DRG)* offers data about the active medication ingredients (referred to as "drugs" in this paper), commercial drug products (referred to as "drug products") and drug-drug interactions. Gene-Drug Repository *(GDR)* keeps data about drug-gene interactions and their severities. Further information about the *PM-TOM* Data Model can be found in papers [6, 7].

***PM-TOM* inputs** are a patient's: conditions, genome and drug products considered by a physician, clinician or clinical pharmacist for treating these conditions. Several drug products can be provided for each condition, with an indication of the preferred one. The list of preferred drug products forms so-called *Initial Therapy (IT)*.

***PM-TOM* outputs** are *(i) Optimal therapy for considered drugs (OTCD)*, *(ii) Optimal therapy for all drugs (OTAD)* and *(iii)* a *Personalized Therapy Report (PTR)*. *PM-TOM* creates *OTCD* after examining drug and gene interactions in the considered drugs and *OTAD* after looking into all drugs in *EMR* prescribed for the same conditions by other physicians, clinicians or clinical pharmacists. In the rest of this paper, *OTCD* will also be referred to as *partially optimized therapy* and *OTAD* as *fully optimized therapy*. Lastly, *PTR* reports the patient's demographic data, conditions, considered drugs and drug products, partially and fully optimized therapies, along with their *Cumulative Adverse Drug Interactions Indicators* (*CADI*), explained below.

As the number of all combinations of potential medications for a patient's conditions could be rather high, *PM-TOM* implements an **iterative heuristic algorithm** [6] that examines a select set of candidate therapies rather than all possible ones. For finding an *OTCD,* these candidate therapies are derived from the initial therapy *(IT)* by replacing only one drug preferred for a condition with another drug considered for the

same condition. For creating the corresponding *OTAD,* the *PM-TOM* would repeat the same process, starting with *OTCD* rather than *IT* and examining all medications from *EMR* indicated for the same conditions.

For each candidate therapy, *PM-TOM* calculates indicator *CADI* as a weighted sum of its drug-drug and drug-gene interactions [6, 7]. The optimal therapy will be formed by selecting a drug for each condition whose candidate therapy has minimal *CADI* against the candidate therapies formed from other drugs considered for the same condition. In that way, the algorithm evaluates only a small subset of all candidate therapies, which significantly reduces its complexity.

3. Testing Results and Discussion

In this study, we implemented the *PM-TOM* method on 484 *EMRs* from the *PGP* database of the *Harvard Personal Genome Project* [8]. These records include the patient's conditions, drugs prescribed for the treatment of these conditions and genome. In addition, the drug database *DrugBank* [3] was used to find the drug-drug interactions (*DDIs)* and *the Comprehensive Toxicogenomics Database (CTD)* [9] to retrieve drug-gene interactions *(DGIs).*

We added condition *COVID-19* and then medications *Dexamethasone, Remdesivir* or *Colchicine* to the *PGP EMRs*. Then we used *PM-TOM* to calculate the ***CADIs*** of their ***OTCD*** and ***OTAD*** therapies before adding each of these medications and after. Table 1 summarizes information about the groups of examined *EMRs*: the number of conditions before the patient contracted *COVID-19* ***(Conditions#)***, the total number of patients in each group *(**Cases#**),* the average number of patients' pharmacogenetic and pathological genes *(**Genes#**)* and the average number of all drugs from *EMR* indicated for patient's conditions *(**Drugs#**)*. It also shows the average ***CADIs*** of ***OTCDs*** and ***OTADs*** in the original therapies and therapies augmented with each *COVID-19* medication.

Table 1. Testing cases and their drug and gene interaction indicator *(CADI)* before and after applying *COVID-19* medications. *OTCD-Optimal Therapy for Considered Drugs, OTAD-Optimal Therapy for All Drugs.*

Conditions #	Cases #	Genes #	Drugs #	OTCD CADI before COVID	OTAD CADI before COVID	+Remdesivir OTCD CADI	+Remdesivir OTAD CADI	+Colchicine OTCD CADI	+Colchicine OTAD CADI	+Dexameth. OTCD CADI	+Dexameth. OTAD CADI
1	272	5.4	9.6	0.2	**0.03**	0.5	**0.06**	1.0	**0.33**	2.8	**2.2**
2	122	7.4	18.5	1.0	**0.3**	1.7	**0.4**	2.4	**0.7**	4.7	**3.2**
3	49	3.9	28.5	2.1	**0.4**	3.0	**0.6**	4.3	**1.2**	5.5	**2.7**
4	16	4.4	28.7	3.4	**1.1**	4.9	**1.6**	6.1	**2.7**	7. 6	**4.4**
5	13	4.5	41.8	4.9	**2.1**	6.6	**2.7**	8	**3.5**	10.2	**6.1**
6	3	0	49. 7	8.3	**5.3**	10.3	**5.7**	12. 7	**7**	12.3	**7**
7-8	5	6	61.8	15.4	**5**	18	**5.2**	20.4	**7**	23.2	**11**
>8	4	15.5	49.5	24.2	**19.5**	25.2	**21.2**	31.2	**29**	34	**28**

These results confirm previous findings that *PM-TOM* can find polypharmacy treatments with significantly reduced drug and gene interactions. For example, in the

group of three conditions, the average *OTCD's CADI* is 3.0 after adding *Remdesivir,* while the average *OTAD's CADI* is only 0.6. For *Colchicine,* these reductions are from 4.3 to 1.2 and *Dexamethasone* from 5.5 to 2.7. In the group with five conditions, these decreases are even more substantial: 6.6 to 2.7, 8 to 3.5 and 10.2 to 6.1.

The second observation is that these *COVID-19* medications significantly increase the drug and gene interactions in partially optimized therapies and, consequently, unoptimized ones, which is not the case in fully optimized therapies. For example, as shown in Table 1, in polypharmacy patients having 3 to 8 conditions, the *CADIs* of partially optimized therapies including *Remdesivir* would increase from 3 (in 3 conditions) to 18 (in 8 conditions), for *Colchicine* from 4.3 to 20 and *Dexamethasone* 4.7 to 23. On the other hand, the *CADI* of the fully optimized treatments ranges only from 0.6 to 5.2, 1.2 to 7, and 2.7 to 11, respectively.

4. Conclusion

These results further emphasize a need for the minimization of adverse drug and gene interactions in polypharmacy therapies. The above findings also show significant room for further fine-tuning of these therapies should a physician, clinician, or clinical pharmacist opt to modify *PM-TOM* recommendations due to the aspects not currently considered in this method, such as patient's age, gender, ethnicity, etc.

Proper selection of polypharmacy therapies is particularly important when the polypharmacy patients could acquire new severe conditions, such as *COVID-19*, which may need medications with a high number of drug and gene interactions, like *Dexamethasone* or *Remdesivir* or *Colchicine*.

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