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Design and Implementation of the Prevention System for Side Effects of Polypharmacy Components Utilizing Data Queuing Algorithm

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[Abstract]

In this paper, we designed and implemented the integrated system to prevent adverse drug reactions of polypharmacy components in medicine by supporting component-component information and disease-component information, through data queuing algorithm and vast amounts of pharmaceutical big data. In addition, by providing information for drugs, drug components, prohibited drugs, as well as suppliers and distributors, it could help ease anxiety about taking drugs not only for health-care professionals but also for general users. The representative information provided were side effects between two drugs, main components and effectiveness of particular drugs, drugs manufactured by the same pharmaceutical company, and drug component information for patients with chronic diseases. The future work is to update the database by collecting information on rare & new diseases and new drugs.

▸ **Key words**: Data Queuing Algorithm, Polypharmacy Components, Adverse Drug Reaction, Big Data

[요 약]

이 논문은 데이터 큐잉 알고리즘과 의약품 빅데이터를 통해 약품 성분-성분 간의 정보와 질병-성분 간의 정보를 지원함으로써 의약품 다약제 복용 시 부작용이 발생 가능한 약물 정보를 사용자에게 제공하기 위한 시스템을 제안하고 구현한다. 또한, 의약품 성분에 더하여 복용이 금지된 의약품, 공급업체, 유통업체의 정보 등을 제공함으로써 의료 전문가뿐만 아니라 일반 사용자의 의약품 복용에 대한 불안감을 덜어줄 수 있다. 제공되는 대표적인 정보는 두 가지 약물 사이에서 일어나는 부작용, 특정 의약품의 주성분과 효능, 동일한 제약회사에서 제조된 의약품, 만성 질환 환자가 주의해야 할 약품 성분 정보이다. 앞으로, 희귀병 약이나 신약에 대한 정보를 수집하여 데이터를 업데이트하는 것이 필요하다.

▸ **주제어**: 데이터 큐잉 알고리즘, 다약제 성분, 약물 부작용, 빅데이터

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I. Introduction

1. Introductory Remarks

As the average life expectancy of people has increased with development of the modern medicine, the onset of chronic diseases such as diabetes, dementia and cancers is also skyrocketing [1]. It increases the occurrence frequency of various complicated diseases, leading to situations in which many kinds of doses of drugs are needed. In 2017, the ratio of polypharmacy to patients aged 75 or older in Korea was 68.1 percent, the highest among OECD countries as illustrated in Fig. 1 indicating that Korea's polypharmacy use was serious [2]. According to the Korea National Health Insurance Service [3], the polypharmacy prescription rate continued to increase, and as of 2018 more than 950,000 people had more than one kind of disease and took more than 10 kinds of drugs at the same time [4].

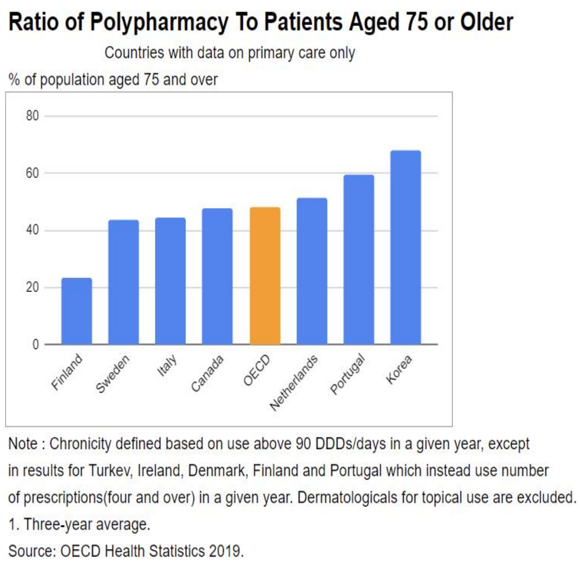


Fig. 1. Ratio of Polypharmacy to Patients Aged 75 or Older in Korea Comparing with OECD

Thus, people with chronic diseases, not only by component-component drug interactions, but also by disease-component drug interactions, can be worsen in the disease. Based on this situation, there has been awareness of the problem against side effects caused by chemical reactions in drugs and adverse side effects caused by negative interactions of polypharmacy component use for diseases in possession [5, 6, 7]. Therefore, the paper analyzed polypharmacy data and the data between disease and drug, and developed the system for preventing side effects caused by chemical reactions in drugs and adverse drug reactions caused by negative interactions of polypharmacy components [8, 9, 10, 11, 12, 13, 14, 15, 16].

This paper is organized as follows: Section I describes introductory remarks, previous research and big data sources. Section II describes system architecture in this research including entity-relationship diagram of the system and composition of its attributes. Section III provides result analysis of the research model and representative useful information against adverse drug reaction. Finally, discussions and contributions are described in Section IV.

2. Related Studies and Big Data Sources

Recently various studies have been underway on side effects caused by drug reactions [7, 17, 18]. There was an existing study focusing on attitude and awareness of healthcare professionals regarding pharmacovigilance and experience for adverse drug reaction from a single university hospital [18]. The study showed that 65% of all respondents among healthcare professionals had confronted incidences of adverse drug reaction and most agreed on the necessities of the promotion and education about adverse drug reaction as well as improvement of the adverse drug reaction reporting. Thus, the integrated system for the adverse drug reactions is eagerly awaited, and even should be upgraded continuously by the reporting of the healthcare professionals and the new drugs.

And, Wang [19] suggested the Data Queuing Algorithm for vital data of reporting, as follows. “After collecting patients' physiological information from the node, various physiological sensors would continuously upload them to the coordinator.” So the key to this research would be how to keep the integrity and effectiveness of each node's information and then how to process it. The general algorithm of the data queuing is as follows:

Define priority function: $f(x, y) = ax + by + \varepsilon$,

x: semantic matching degree, $0 \leq x \leq 1$
y: a request arriving at the serial position, $0 < y \leq 1$
a is defined as the weight of semantic matching degree, $0 < a < 1$
b is defined as the weight of serial position of request arrives, $0 < b < 1$, $a + b = 1$
ε is defined as the disturbance value, $0 \leq \varepsilon \leq 0.1$

With the definitions above, f(x, y) can turn to be:

$$f(x, y) = ax + (1 - a)y + \varepsilon$$

namely, $f(x, y) = y + a(x - y) + \varepsilon$

Generally, a is close to $\mu = 1/2$, $\sigma^2 = 0$

unidimensional normal distribution $N(\mu, \sigma^2)$.

After all the messages in the queue would be calculated according to the above formula, they would be inserted into the existing waiting queue in descending order. This research utilized the Data Queuing Algorithm described above to process the vital data of reporting.

Based on the previously studied theories, this research focused on the system not only for health-care professionals but also for general users, about adverse drug reactions, drug-related information, safety-related drug stores, medication prescription information, and component quality [20, 21, 22, 23, 24].

This research carried out data modeling that could produce a variety of useful information in addition to adverse drug reactions by utilizing drug-related information, data of safety-related drug stores, medication prescription information, and component quality by DUR (Drug Utilization Review) type [20]. For drug information, drug ingredient information, drug manufacturer information, patient information for taking the drug, and prescription information for prescription drugs, it used data from Ministry of Food and Drug Safety, Korea Local Information Research & Development Institute (LOCALDATA), Open Data Portal, and Korea Institute of Drug Safety & Risk Management. [25, 26, 27, 28]. It built data modelling by getting data from the portal described above.

According to Jang [29], who proposed ignoring the regularization of the relational database as one of the design methods in the database system, the research utilized some omitting among the normalization processes of data, for generating a flexible database system with limited memory capacity.

II. System Architecture for the Adverse Drug Reaction Prevention

1. Entity-Relationship Model of the System

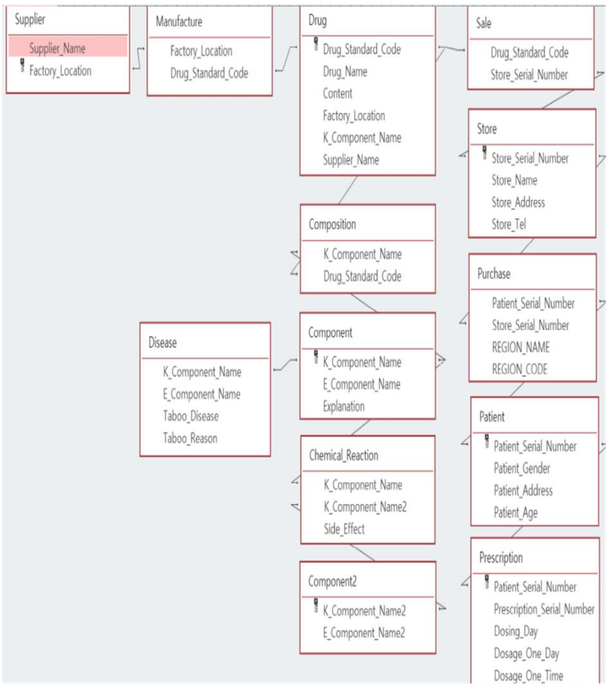


Fig. 2. Entity-Relationship Model of the System for Prevention of Adverse Drug Reaction

The suggested database system designed the entity-relationship diagram (E-R diagram) to provide the users with medical information for adverse drug reaction prevention of polypharmacy components [19, 30]. It used data from The Ministry of Food and Drug Safety (Generic Data obtained through the Drug Bundle Information) [25], the Pharmacy and Safety Drug Store Data of LOCALDATA [26], the Open Data Portals' drug prescription information [27], and the Korea Institute of Drug Safety & Risk Management [28]. Furthermore, it processed the vital data of reporting from the healthcare professionals utilizing the Data Queuing Algorithm.

2. Description of Entity & Relation's Attribute Composition

The E-R Diagram was developed to design a database management system for preventing side effects of drug mixture using the data mentioned in the section 1.2. As shown in Fig. 2, Supplier, Drug, Component, Component2, Disease, Store, Patient, and Prescription were set as entities, and Manufacture, Composition, Chemical_Reaction, Sale, and Purchase were set as relationships. The diagram differentiated itself by adding not only the detailed description of drugs in the entities Drug and Component with basic information on the pharmaceutical company that manufactured it, but also contraindications against concomitant use and contraindications when possessing underlying diseases. In addition, an entity Patient was added to provide useful information so that it could identify characteristics based on gender, age, and region.

The entity Supplier represented pharmaceutical company information, which set the attributes as Supplier_Name and Factory_Location, and the primary key as Factory_Location. The entity Drug represented the drug information, which set the attributes as Drug_Standard_Code, Drug_Name, Content, Factory_Location, K_Component_Name and Supplier_Name, and the primary key as Drug_Standard_Code. And, one-to-many relationship between the Supplier and the Drug entities was established, where the Supplier was a weak entity.

The entity Component represented component information, set the attributes as K_Component_Name, E_Component_Name, and Explanation, and set the primary key as K_Component_Name. And, many-to-many relationship between Drug and Component entities was established. The entity Disease contained disease information for drug use contraindication, and set the attributes as K_Component_Name, E_Component_Name, Taboo_Disease and Taboo_Reason, where the relationship between Component and Disease entities was set to many-to-many.

Component2 is an entity for comparison with the entity Component. In the entity Component2, K_Component_Name2 and E_Component_Name2 were set as attributes except for Explanation, where the primary key is K_Component_Name2. The relation Chemical_Reaction, with the Side_Effect property added between the Component and Component2 entities, was set in many-to-many relationship.

The entity Store contained information on the stores of sale, set the attributes as Store_Serial_Number, Store_Name, Store_Tel and Store_Address, and set the primary key as Store_Serial_Number. A relation Sale had many-to-many relationship between the Drug and Store entities, and Store is a weak entity. The entity Patient represented patient information, set attributes as Patient_Serial_Number, Patient_Gender, Patient_Address, and Patient_Age, and set the primary key as Patient_Serial_Number. Here, Purchase, many-to-many relationship with Region_Name and Region_Code properties added between the Store and Patient entities, was set. As described above, the system schema was created for entities by setting the appropriate attributes and relationships between entities.

III. Representative Information for Prevention of Adverse Drug Reactions

The implemented system provided the users with medical information for side effect prevention of polypharmacy components. The representative information provided were side effects between two drugs, main components and effectiveness of specific drugs, drugs manufactured by the same pharmaceutical company, and drug component information for patients with chronic diseases.

1. Side Effects between Two Drugs

It was not easy for the general consumer to know what side effects occur between two drugs. So, the system was designed and implemented so that consumers could know the chemical reactions between the two drugs that might occur in case they took the ingredients of the two drugs. If an adverse reaction occurred between the drugs entered in Fig. 3, the side effect that might occur was returned to the result set, and if there were no side effects, no value would be returned to the result value.

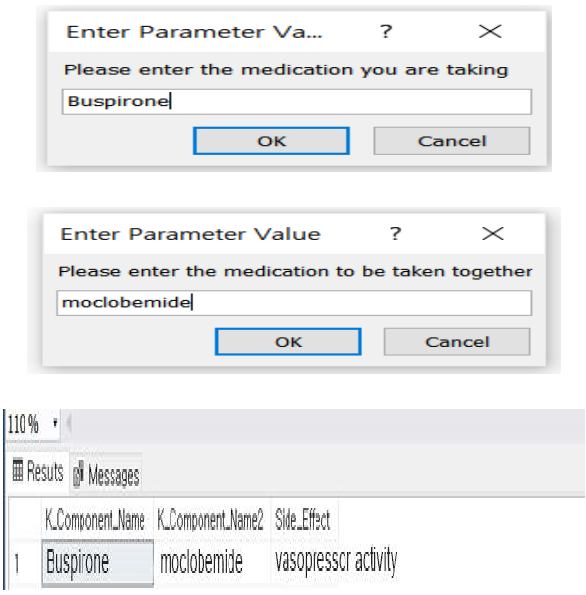


Fig. 3. Side Effects between the Two Drugs

2. Main Components and Efficacy of a Designated Drug

In general, when you took medicine you might know what its component worked for. But if you were prescribed with several kinds of medicine at a time, you might take it without knowing what their effects were. Given this situation, the system searched for the name of the drug and printed out the main ingredients and efficacy of the detected drug. Fig. 4 illustrated the main ingredients and efficacy of the 'Parox CR Tab' by searching for it.

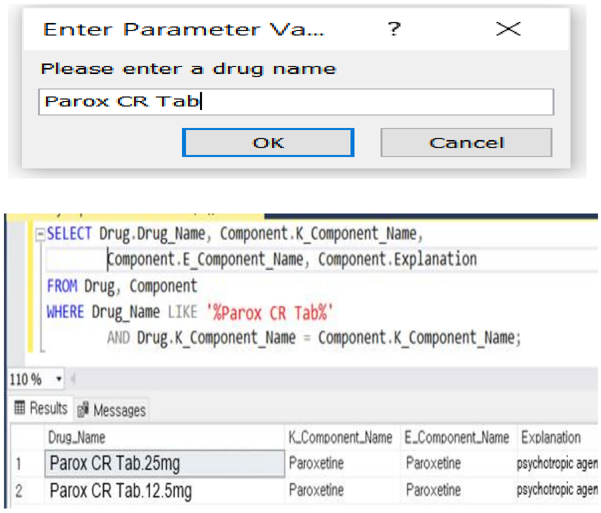
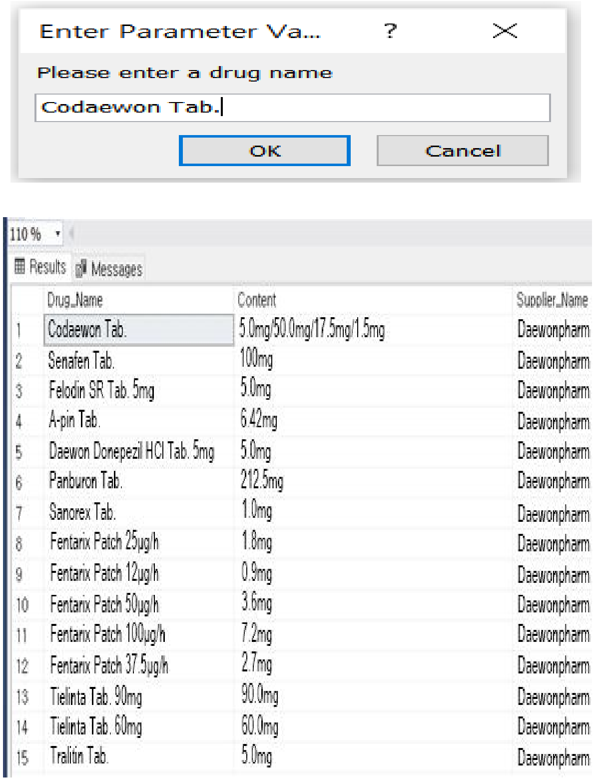


Fig. 4. Component Name and Efficacy of the Detected Drug 'Parox CR Tab'

3. Drugs Manufactured by the Same Pharmaceutical Company

Consumers' perception of the brand has a significant influence on purchasing drugs. Especially, consumers' perception of pharmaceutical companies has a moral standard that discriminates against other business organizations, and awareness that pharmaceutical companies should provide drugs to patients in need is expected or recognized. Consumers who experience positive effects on a drug are more likely to be interested in drugs manufactured by the same pharmaceutical company. Thus, the system was implemented to search for drugs manufactured by the designated pharmaceutical company.

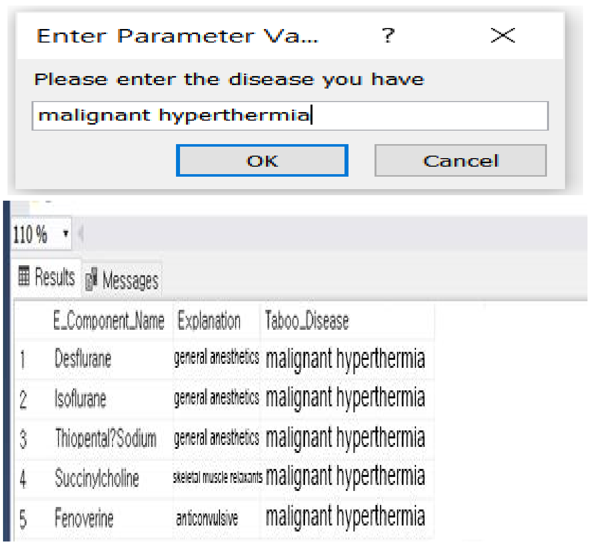
When the user input the drug name, the manufacturer name was compared based on the entered drug, and only drugs with the same manufacturer were displayed as a result value set as illustrated in Fig. 5.



	Drug_Name	Content	Supplier_Name
1	Codaewon Tab.	5.0mg/50.0mg/17.5mg/1.5mg	Daewonpharm
2	Senafen Tab.	100mg	Daewonpharm
3	Felodin SR Tab. 5mg	5.0mg	Daewonpharm
4	A-pin Tab.	6.42mg	Daewonpharm
5	Daewon Donepezil HCl Tab. 5mg	5.0mg	Daewonpharm
6	Panburon Tab.	212.5mg	Daewonpharm
7	Sanorex Tab.	1.0mg	Daewonpharm
8	Fentanix Patch 25μg/h	1.8mg	Daewonpharm
9	Fentanix Patch 12μg/h	0.9mg	Daewonpharm
10	Fentanix Patch 50μg/h	3.6mg	Daewonpharm
11	Fentanix Patch 100μg/h	7.2mg	Daewonpharm
12	Fentanix Patch 37.5μg/h	2.7mg	Daewonpharm
13	Tielinta Tab. 90mg	90.0mg	Daewonpharm
14	Tielinta Tab. 60mg	60.0mg	Daewonpharm
15	Tralitin Tab.	5.0mg	Daewonpharm

Fig. 5. Drugs Manufactured by the Same Pharmaceutical Company on Entering a Specific Drug Name.

4. Drug Component Information for Patients with Chronic Diseases



	E_Component_Name	Explanation	Taboo_Disease
1	Desflurane	general anesthetics	malignant hyperthermia
2	Isoflurane	general anesthetics	malignant hyperthermia
3	Thiopental?Sodium	general anesthetics	malignant hyperthermia
4	Succinylcholine	skeletal muscle relaxants	malignant hyperthermia
5	Fenoverine	anticonvulsive	malignant hyperthermia

Fig. 6. Drug Components Which Patients with ‘Malignant Hyperthermia' should be Careful of.

Patients with chronic diseases are especially susceptible to the possible negative interactions with their medications. If these patients could search the drug components against chronic diseases they currently had, they could check the component name, and the component effectiveness of the medications they should be careful about. In Fig. 6, one of the chronic diseases, ‘malignant hyperthermia', was entered to return the drug components that consumers with malignant hyperthermia should be careful about.

However, the entity Drug in this database mainly covers domestic drug information. Although imports of foreign medicines have been steadily increasing as illustrated in Fig. 7, there is a limitation that it is difficult to check information on imported drugs because mainly domestic drug information exists in the Korean big data sets. Through additional research, it is possible to obtain information on ingredients of the imported drugs.

Division	2019	the component ratio	2018	year on year
Active Pharmaceutical Ingredient	2,123,740	23.59%	2,028,754	104.68%
Medicinal Product	4,707,758	52.30%	4,441,313	106.00%
Sanitary Aid	182,297	2.03%	200,508	90.92%
Medicinal Herbs	145,385	1.62%	146,960	98.93%
	6,817,735	79.53%	6,817,535	105.01%

Fig. 7. Imports of General Drugs in 2019

IV. Conclusions

1. Overall Conclusions

With the development of medical technology, the average life expectancy of people has been increasing, and so the number of patients with chronic diseases has also been increasing. As the desire to live a healthy life may include medical intervention, the number of drugs to be taken and the frequency of adverse reactions between drugs will increase. Clinicians with professional knowledge also have difficulty in identifying clinical trials and all side effects on thousands of drugs.

This research presented the integrated system for drug information that might prevent from generating side effects among diseases and drugs through the data queuing algorithm and vast amounts of pharmaceutical data, not only for health-care professionals but also for general users. In addition, by providing information for drugs, drug components, prohibited drugs, as well as suppliers and distributors, it could help ease anxiety among users about taking drugs. Moreover, because everyone has a different physical structure, public data related to the gender, age, and taboo drugs of patients with chronic diseases were also collected, indicating the validity period of the drug, daily dosage, and a dose of medicine. By utilizing the system provided, users could expect to take the right medication, including current medication users. The system could provide useful information to users through the process of data modeling by integrating the Ministry of Food and Drug Safety, public data and research data.

In addition, the drug entity in this database mainly covered domestic drug information. Although imports of foreign medicines have been steadily increasing, it is difficult to check information on imported drugs because mainly domestic drug information exists in the Korean big data. The future work is to obtain information on the ingredients of imported drugs as well as more reporting from healthcare professionals.

2. Contributions and Limitations

Component-component data and disease-component data as well as the data queuing algorithm can help system users including medicine users who do not have knowledge of components and chemical reactions of polypharmacy components in medicine. Component-component data identify the ingredients of the two drugs to show side effect information, which can prevent ill effects that may appear in the users. In addition, the disease-component data specifies information about the chronic diseases that users have ever had, and about the ingredients of drugs that may have a negative impact on them. It also contributes to providing useful information to users who lack information about drugs. The users can search for drugs that have positive reactions and drugs manufactured by the same pharmaceutical company, and use the drug's main component data to find out what actions they should take.

The system should try to continue to update the database in collecting information on rare diseases, new diseases and new drug information in this database because not all data on medicines and diseases exist nowadays. In particular, as the coronavirus emerged as a new infectious virus in 2019, the world is trembling with fear of disease. In the currently established database, information on prohibited drugs when infected with the coronavirus is not available, nor are the possible adverse reactions of the developed new drug rapidly known. Tamiflu, a flu virus treatment, has become a major social issue leading to suicide cases by hallucinations. However, the specific reasons for these anomalies and side effects are still unknown, which information on side effects is not specified; it should also be considered that the uncertainty of this information results in insufficient knowledge, and more work and reaearch is needed.

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