의학석사 학위논문

Exploration of relationship between drug prescribing patterns and therapeutic drug monitoring practice based on electronic medical records

전자 의무 기록을 기반으로 한 약물 처방 패턴과 치료적 약물 모니터링 수행 간의 관계에 대한 탐색적 연구

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서울대학교 대학원
협동과정 임상약리학전공

이 상 미

Exploration of relationship between drug prescribing patterns and therapeutic drug monitoring practice based on electronic medical records

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본 논문을 의학석사 논문으로 제출함

2022년 4월

서울대학교 대학원
협동과정 임상약리학전공
이 상 미

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ABSTRACT

Exploration of relationship between drug prescribing patterns and therapeutic drug monitoring practice based on electronic medical records

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Introduction: Therapeutic drug monitoring (TDM) is performed for drugs with narrow therapeutic indices. At Seoul National University Hospital (SNUH) and Seoul National University Bundang Hospital (SNUBH), TDM services are provided for various drugs including vancomycin, amikacin, gentamicin, tobramycin, valproate, phenytoin, phenobarbital, carbamazepine, digoxin, theophylline, and lithium. This study aimed to identify prescription patterns over time using electronic medical records and analyze their relationship with TDM practice.

Methods: Data were collected from the Clinical Data Warehouse (CDW) from January 1, 2007, to December 31, 2020, and the

number of patients, total number of drug administration days, serum level tests, and TDM were calculated. The ratio was calculated as the number of serum level tests or TDM to the total number of drug administration days.

Results: A total of 136,427 patients in SNUH and 162,927 patients in SNUBH who were prescribed the drugs at least once were included in this study. The 11 drugs were divided into three groups: antibiotics (vancomycin, amikacin, gentamicin, tobramycin), antiepileptics (valproate, phenytoin, phenobarbital, carbamazepine), and other drugs (digoxin, theophylline, lithium). Each drug showed a different prescription pattern over time, and the serum level test and TDM also changed with the prescription pattern changes.

Conclusions: The prescription patterns, number of serum level tests, and TDM were analyzed for SNUH and SNUBH. The use of some drugs and testing for drugs have decreased as newly developed drugs are replacing old drugs. It is recommended that TDM services include these new drugs for effective and safe drug therapy.

Keywords: antibiotics, antiepileptics, electronic medical records, real-world data, therapeutic drug monitoring,

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LIST OF ABBREVIATION

AMK	Amikacin
CBZ	Carbamazepine
DGX	Digoxin
EMR	Electronic Medical Records
GTM	Gentamicin
LTM	Lithium
PBT	Phenobarbital
PNT	Phenytoin
SNUBH	Seoul National University Bundang Hospital
SNUH	Seoul National University Hospital
TBM	Tobramycin
TDM	Therapeutic Drug Monitoring
TPL	Theophylline
VCM	Vancomycin
VPA	Valproate

INTRODUCTION

Therapeutic drug monitoring (TDM) of narrow therapeutic index (NTI) drugs has been conducted for optimal pharmacotherapy since the 1970s.[1,2] NTI drugs have a narrow range between the effective doses and doses with toxic effects.[3] Thus, small changes in systemic concentrations can lead to significant changes in drug effect or toxicity.[3–5] Aminoglycoside, lithium, digoxin, phenytoin, and carbamazepine are representatives of NTI drugs.[3] By performing TDM, the dosage and usage can be adjusted so that the drug concentration is within the therapeutic window to maximize the therapeutic effect and minimize adverse events.[1, 4, 6]

Vancomycin is a drug that requires TDM. Vancomycin drug concentration has been evaluated and an optimal dosage regimen could be suggested.[7] Trough concentration has been widely used, and recently, area–under the curve of concentration (AUC) has also been recommended for vancomycin TDM.[8–10] For aminoglycoside TDM, peak and trough concentrations are used because toxicity is related to peak level and efficacy is related to trough level.[11] Most psychiatric drugs are taken for a long time, and some drugs require evaluation of drug concentrations. One study evaluated the prescription pattern and TDM of psychiatric

drugs. According to this study, even though TDM did not have a great impact on the prescribed doses of psychiatric drugs, it can be a tool to confirm patient adherence.[12]

Electronic medical record (EMR) data have been widely used in retrospective studies.[13] There have been several studies on infections in the bloodstream, errors in antibiotic prescription, and monitoring of antibiotic usage using data from the clinical data warehouse (CDW).[14, 15]

TDM for several drugs has been conducted for more than a decade at Seoul National University Hospital (SNUH) and Seoul National University Bundang Hospital (SNUBH). The drugs studied include vancomycin, amikacin, gentamicin, tobramycin, digoxin, valproate, carbamazepine, phenytoin, phenobarbital, theophylline, and lithium.

In this study, we used data from the CDW to evaluate the drug prescription patterns and analyze its relationship with the practice of TDM.

MATERIALS AND METHODS

Ethics approval and study population

The protocol was reviewed and approved by an Institutional Review Board (IRB) of SNUH and SNUBH (SNUH IRB No. H-2103-153-1206, SNUBH IRB No. B-2104-680-402) under the premise that the anonymity of the patient is guaranteed. In consideration of the large number of patients and the fact that this is a retrospective study, obtaining informed consent was exempted by IRB of SNUH and SNUBH. Our research involving human data has been performed in accordance with the Declaration of Helsinki.

This study included patients who took the following drugs that required TDM: antibiotics (vancomycin, amikacin, gentamicin, tobramycin), antiepileptics (valproate, carbamazepine, phenytoin, and phenobarbital), and other drugs (digoxin, theophylline, and lithium).

Data collection

Data were extracted from the CDW from January 1, 2007, to December 31, 2020. Patients who were prescribed the drug at least once were included in the study, regardless of age or sex.

In this study, we included the drugs which require TDM in practice. For example, ophthalmology formulations or investigational products were excluded, and drugs that did not require TDM were also excluded due to the characteristics of the drug. The capsule formulation of vancomycin does not require TDM because it is used to control infection in the gastrointestinal tract.

In the case of demographics, sex and age were analyzed, and descriptive statistics were presented based on the age at the time of drug description.

The total number of drug administration days and the number of prescriptions were calculated for each patient group prescribed the following drugs: vancomycin, amikacin, gentamicin, tobramycin, valproate, carbamazepine, phenytoin, phenobarbital, digoxin, theophylline, and lithium. The total number of drug administration days for each drug were calculated by adding the number of drug administration days for each patient.

The number of serum level tests and cases of TDM were counted in patients who were prescribed the drugs. In this study, TDM refers to services including serum level tests and dosing recommendations. For reference, it is necessary to interpret the aminoglycoside data considering that serum level tests are

performed twice to check the peak and trough levels in patients who were prescribed aminoglycoside.

Data analysis

In this study, data were collected for 11 drugs and classified into three groups. The first was the use of antibiotics, including vancomycin, amikacin, gentamicin, and tobramycin. The second category was antiepileptics, which included valproates, phenytoin, carbamazepine, and phenobarbital. The third category included other drugs, including digoxin, theophylline, and lithium. Total number of drug administration days were calculated to compare prescription patterns because each drugs has different usual administration days. To evaluate the relationship between the number of drug administration days and the number of tests, total number of drug administration days were divided by the number of serum level tests and TDM tests, which represents how often the tests were conducted.

RESULTS

Patient demographics

This study included patients who had been prescribed drugs at least once. There were no significant differences in the average age and sex between SNUH (136,427 patients) and SNUBH (162,927 patients) (Table 1).

The average age was 40 to 60 years for most drug groups, but for lithium, it was 37.4 years old in SNUH and 37.6 years old in SNUBH. The average age of patients who were prescribed gentamicin in SNUBH was 39.0 years old, while it was 52.3 years old in SNUH.

Differences were observed in the sex ratios of some drugs between the two hospitals. In SNUH, among the patients prescribed gentamicin, the proportion of women (63.2%) was higher than that of men (36.8%). In SNUBH, carbamazepine was prescribed more frequently in women (58.7%) than in men (41.3%), and in the case of lithium, the proportion of women (63.1%) was higher than that of men (36.9%).

Table 1. Demographics of patient population

	Seoul National University Hospital			Seoul National University Bundang Hospital		
	Age* (mean ± SD)	Sex		Age* (mean ± SD)	Sex	
		Male (%)	Female (%)		Male (%)	Female (%)
Vancomycin	59.9 ± 17.0	16660 (58.5)	11817 (41.5)	58.1 ± 23.2	8995 (51.0)	8655 (49.0)
Amikacin	52.9 ± 20.2	3727 (63.7)	2128 (36.3)	45.5 ± 28.1	3666 (57.4)	2720 (42.6)
Gentamicin	52.3 ± 19.7	12357 (36.8)	21238 (63.2)	39.0 ± 28.8	12936 (52.1)	11886 (47.9)
Tobramycin	53.7 ± 16.4	4521 (50.4)	4449 (49.6)	49.1 ± 17.7	7183 (37.7)	11880 (62.3)
Valproate	47.3 ± 18.2	7573 (52.6)	6817 (47.4)	46.9 ± 23.0	9748 (47.0)	10979 (53.0)
Phenytoin	48.4 ± 17.3	2013 (57.8)	1472 (42.2)	42.7 ± 28.3	1346 (57.7)	985 (42.3)
Carbamazepine	54.4 ± 16.1	7322 (44.4)	9184 (55.6)	52.7 ± 18.0	2110 (41.3)	2999 (58.7)
Phenobarbital	51.6 ± 17.0	1433 (50.6)	1401 (49.4)	40.6 ± 26.5	1004 (43.8)	1288 (56.2)
Digoxin	65.0 ± 13.5	7019 (55.8)	5556 (44.2)	68.0 ± 16.2	4418 (57.5)	3264 (42.5)
Theophylline	64.8 ± 13.2	3014 (55.0)	2465 (45.0)	59.5 ± 21.3	1806 (55.3)	1459 (44.7)
Lithium	37.4 ± 15.9	1849 (43.4)	2412 (56.6)	37.6 ± 15.1	1564 (36.9)	2673 (63.1)

*The age was calculated to average. It was rounded to the first decimal place.

Total number of drug administration days, serum level tests, and therapeutic drug monitoring

In SNUH and SNUBH, the number of patients who were prescribed each drug and the number of patients who underwent a serum level test or TDM was evaluated (Figure 1).

In the case of antibiotics (vancomycin, amikacin, gentamicin, and tobramycin), serum level tests were performed on average approximately once every 6–8 days, and for TDM, once every 16–21 days (Figure 2, Table 2). Among the antibiotics, vancomycin had the highest number of total number of drug administration days, serum level tests, and TDM.

In the case of antiepileptics (valproate, phenytoin, carbamazepine, and phenobarbital), serum level tests were performed once every 1–2 years on average, but TDM was not performed frequently in either hospital. Carbamazepine was the drug with the highest number of total number of drug administration days, whereas valproate was the drug with the highest number of serum level tests and TDM in SNUH. In SNUBH, valproate had the highest total number of drug administration day, serum level test, and TDM.

The results for other drugs (digoxin, theophylline, and lithium) are shown in Table 3. TDM for lithium was not performed at SNUBH.

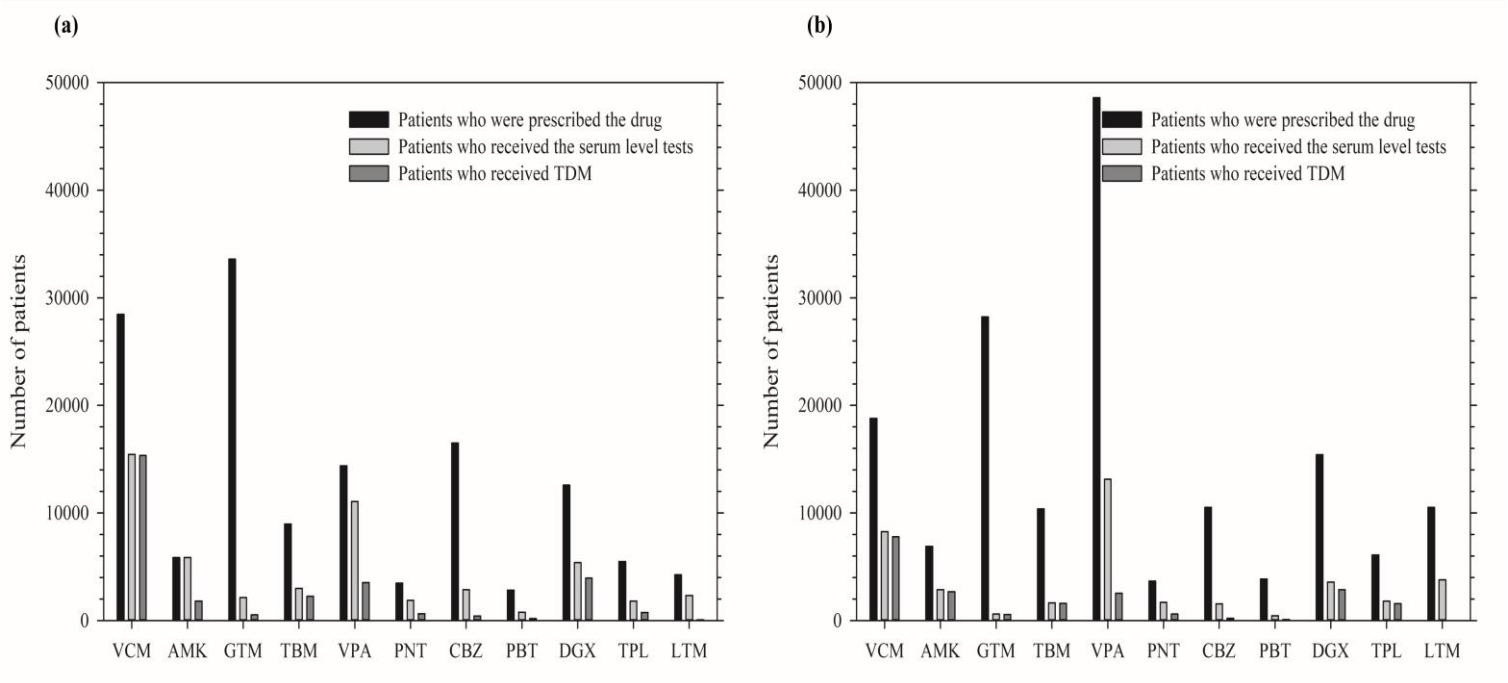
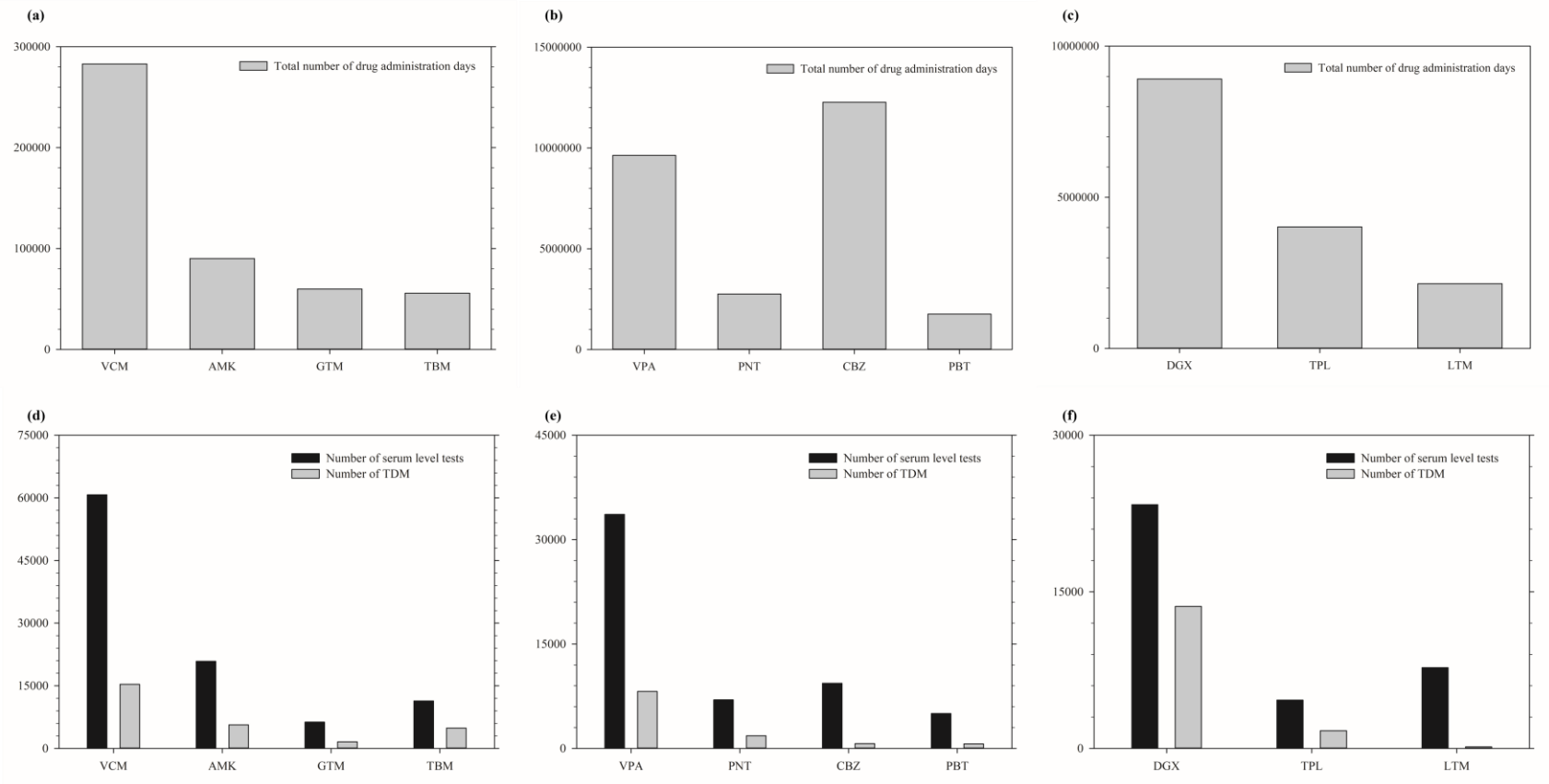


Figure 1. Patients who were prescribed drugs, patients who received serum level tests or received therapeutic drug monitoring (a) Number of patients in Seoul National University Hospital and (b) Number of patients in Seoul National University Bundang Hospital

Abbreviation: VCM, vancomycin; AMK, amikacin; GTM, gentamicin; TBM, tobramycin; VPA, valproate; CBZ, carbamazepine; PNT, phenytoin; PBT, phenobarbital; DGX, digoxin; TPL, theophylline; LTM, lithium;


(a)
Total number of drug administration days
300000
200000
100000
0
VCM
AMK
GTM
TBM
(b)
Total number of drug administration days
15000000
10000000
5000000
0
VPA
PNT
CBZ
PBT
(c)
Total number of drug administration days
10000000
5000000
0
DGX
TPL
LTM
(d)
Number of serum level tests
Number of TDM
75000
60000
45000
30000
15000
0
VCM
AMK
GTM
TBM
(e)
Number of serum level tests
Number of TDM
45000
30000
15000
0
VPA
PNT
CBZ
PBT
(f)
Number of serum level tests
Number of TDM
30000
15000
0
DGX
TPL
LTM

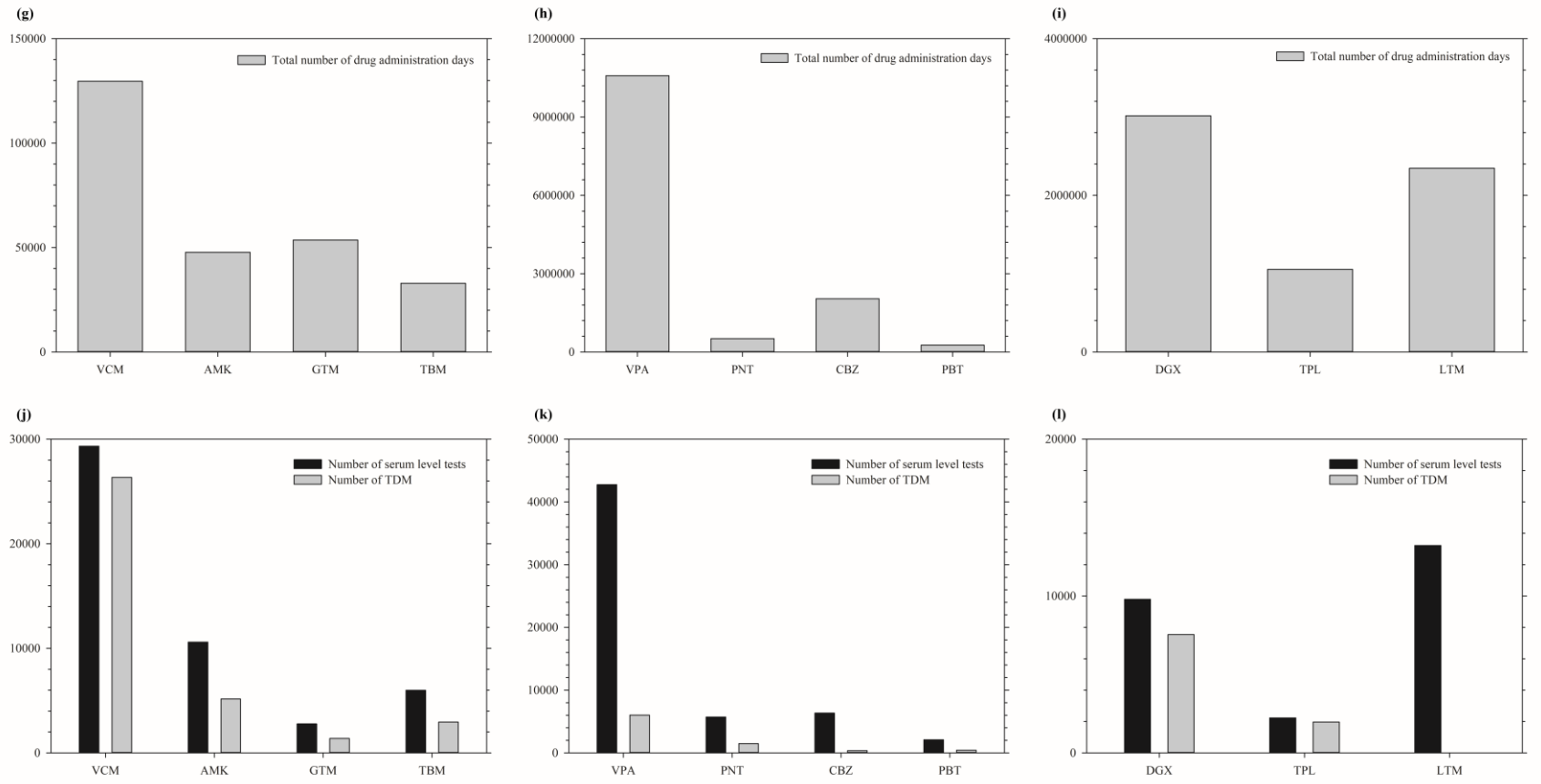

(g)
Total number of drug administration days
150000
100000
50000
0
VCM
AMK
GTM
TBM
(h)
Total number of drug administration days
12000000
9000000
6000000
3000000
0
VPA
PNT
CBZ
PBT
(i)
Total number of drug administration days
4000000
2000000
0
DGX
TPL
LTM
(j)
Number of serum level tests
Number of TDM
30000
20000
10000
0
VCM
AMK
GTM
TBM
(k)
Number of serum level tests
Number of TDM
50000
40000
30000
20000
10000
0
VPA
PNT
CBZ
PBT
(l)
Number of serum level tests
Number of TDM
20000
10000
0
DGX
TPL
LTM

Figure 2. Number of the total number of drug administration days, serum level tests or therapeutic drug monitoring

(a), (g) Total number of drug administration days of antibiotics, (b), (h) total number of drug administration days of antiepileptic drugs, (c), (i) total number of drug administration days of other drugs, (d), (j) number of serum level tests and therapeutic drug monitoring of antibiotics, (e), (k) number of serum level tests and therapeutic drug monitoring of antiepileptic drugs and (f), (l) number of serum level tests and therapeutic drug monitoring of other drugs

Figure (a)~(f) for Seoul National University Hospital and figure (g)~(l) for Seoul National University Bundang Hospital

Abbreviation: VCM, vancomycin; AMK, amikacin; GTM, gentamicin; TBM, tobramycin; VPA, valproate; CBZ, carbamazepine; PNT, phenytoin; PBT, phenobarbital; DGX, digoxin; TPL, theophylline; LTM, lithium;

Table 2. Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average serum level test or therapeutic drug monitoring per administration days

Seoul National University Hospital						
	Total number of Drug administration days (day)	Number of serum level tests (N)	Number of TDM (N)	Average serum level test per drug administration days* (day)	Average TDM per drug administration days* (day)	Number of serum level tests / Number of TDM
Vancomycin	283,030	60,767	15,326	4.7	18.5	4.0
Amikacin	90,148	20,855	5,635	4.3	16.0	3.7
Gentamicin	59,899	6,295	1,605	9.5	37.3	3.9
Tobramycin	55,762	11,384	4,885	4.9	11.4	2.3
Valproate	9,632,245	33,631	8,188	286.4	1176.4	4.1
Phenytoin	2,754,477	6,978	1,818	394.7	1515.1	3.8
Carbamazepine	12,271,882	9,361	693	1311	17708.3	13.5
Phenobarbital	1,760,982	5,015	650	351.1	2709.2	7.7
Digoxin	8,915,373	23,360	13,610	381.7	655.1	1.7
Theophylline	4,019,776	4,625	1,701	869.1	2363.2	2.7
Lithium	2,141,764	7,731	147	277.0	14569.8	52.6

Seoul National University Bundang Hospital

	Total number of Drug administration days (day)	Number of serum level tests (N)	Number of TDM (N)	Average serum level test per drug administration days* (day)	Average TDM per drug administration days* (day)	Number of serum level tests / Number of TDM
Vancomycin	129,635	29,335	26,346	4.4	4.9	1.1
Amikacin	47,723	10,595	5,151	4.5	9.3	2.1
Gentamicin	53,618	2,772	1,376	19.3	39	2
Tobramycin	32,930	5,992	2,941	5.5	11.2	2
Valproate	10,585,806	42,750	6,022	247.6	1757.9	7.1
Phenytoin	514,699	5,719	1,477	90	348.5	3.9
Carbamazepine	2,039,616	6,337	361	321.9	5649.9	17.6
Phenobarbital	261,700	2,091	428	125.2	611.4	4.9
Digoxin	3,016,601	9,795	7,539	308	400.1	1.3
Theophylline	1,055,304	2,233	1,965	472.6	537.1	1.1
Lithium	2,346,433	13,229	–	177.4	–	–

*It was rounded to the first decimal place.

Table 3. The number of patients who were prescribed the drug, received serum level tests and therapeutic drug monitoring

Institution	Seoul National University Hospital			Seoul National University Bundang Hospital		
	Number of patients who were prescribed the drug (N)	Number of patients who received serum level test (N)	Number of patients who received TDM (N)	Number of patients who were prescribed the drug (N)	Number of patients who received serum level test (N)	Number of patients who received TDM (N)
Vancomycin	28,477	15,442	15,326	18,788	8,265	7,784
Amikacin	5,855	5,863	1,816	6,890	2,436	2,353
Gentamicin	33,595	2,137	531	28,233	550	529
Tobramycin	8,970	2,980	2,251	10,363	1,553	1,516
Valproate	14,390	11,065	3,532	48,594	21,298	2,455
Phenytoin	3,485	1,870	637	3,657	2,089	560
Carbamazepine	16,506	2,875	427	10,501	3,432	147
Phenobarbital	2,834	769	192	3,863	775	92
Digoxin	12,575	5,388	3,962	15,419	3,852	3,021
Theophylline	5,479	1,817	756	6,108	1,097	978
Lithium	4,261	2,339	82	10,511	6,620	-

Comparison of the number of patients, serum level tests, and therapeutic drug monitoring

Changes in the number of patients, serum level tests, and TDM over time are shown in Figures 3, 4, 5.

Among the antibiotics analyzed, vancomycin showed no significant changes over time in the number of patients, serum level tests, or TDM for 14 years in both hospitals. The number of patients prescribed amikacin has been continuously decreasing in SNUH. However, in SNUBH, the number of patients decreased until 2014 but then increased again, and the number of serum level tests and TDM also increased. For gentamicin, the total number of drug administration days and number of patients decreased in both hospitals. The number of serum level tests and TDM did not change significantly over time. For tobramycin, the total number of drug administration days and number of serum level tests decreased in SNUH. The number of TDM did not change significantly until 2014 but has decreased since 2014.

The results for antiepileptics (valproate, phenytoin, carbamazepine, and phenobarbital) were as follows. The valproates showed different trends between the two hospitals. In SNUH, the number of patients who were prescribed valproate and the total

number of drug administration days increased by 2010 and decreased thereafter. In contrast, the number of patients and total number of drug administration days increased in SNUBH. The number of serum level tests and TDM remained unchanged in both hospitals. Additional analysis was conducted to identify trends for two main indications of valproate: epilepsy and mood disorders (Figure 6). SNUH and SNUBH showed different trends for each valproate indication. In the case of epilepsy, the number of patients and the total number of drug administration days did not change significantly over time in either hospital. In the case of mood disorders, the number of patients and total number of drug administration days have increased in the past two years in both hospitals, especially in SNUBH. We assumed that these changes influenced the overall pattern of the change in valproate.

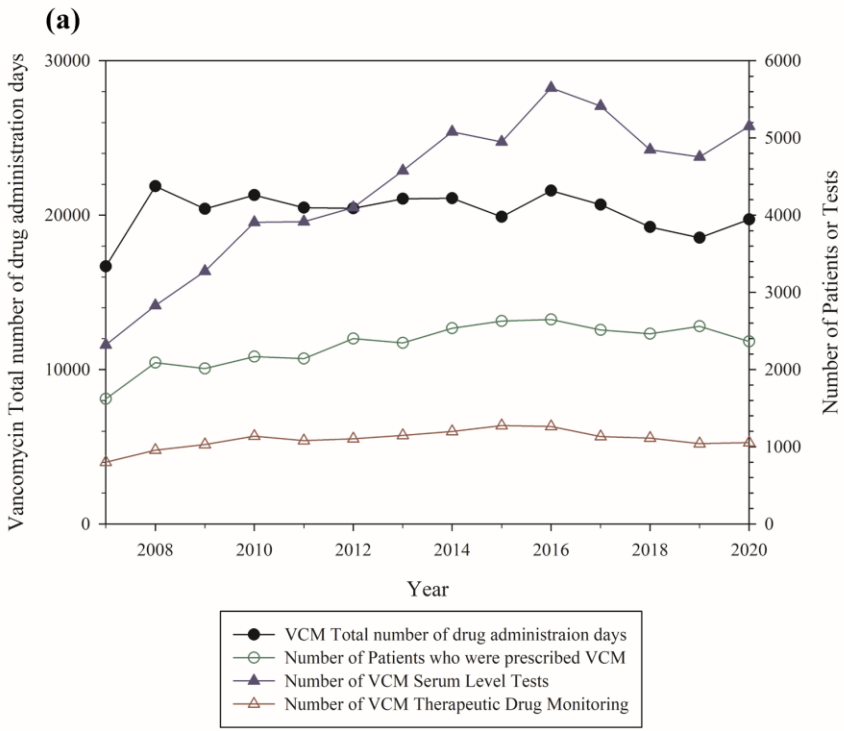
The number of patients and total number of drug administration days of phenytoin decreased continuously in SNUH. The number of serum level tests and the TDM of phenytoin have also decreased since 2016. In SNUBH, the number of patients, serum level tests, and TDM have decreased since 2014. Carbamazepine showed no significant changes in the number of patients or the total number of drug administration days. The number of serum level tests and TDM has decreased in both hospitals. The number of patients and

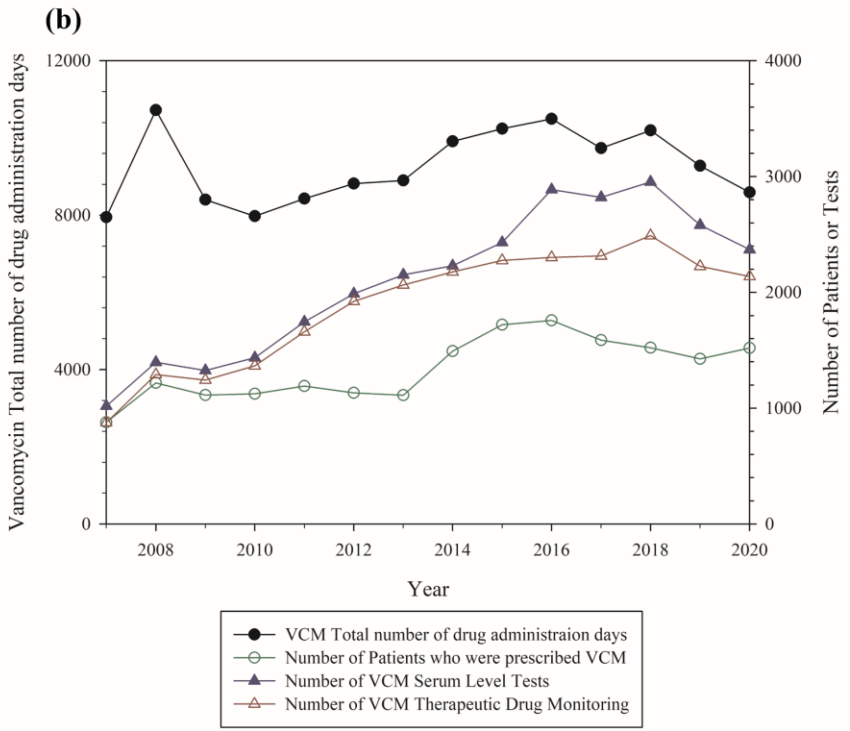
total number of days of phenobarbital administration decreased in SNUH. The number of serum level tests decreased until 2013 and then increased again. However, the number of TDM did not change. In SNUBH, the number of patients showed declining trends, whereas the total number of drug administration days showed some fluctuation. The number of serum level tests and TDM of phenobarbital showed no significant changes.

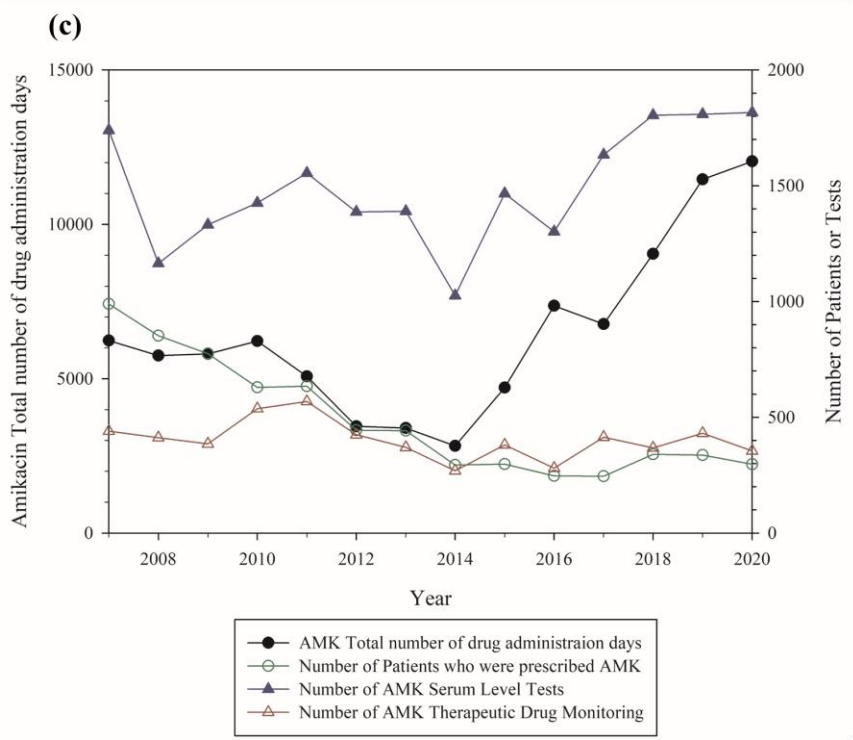
Digoxin showed a gradual decrease in the number of patients and the total number of drug administration days. The number of serum level tests showed no significant changes since 2012. No significant changes were observed in the number of TDM. In SNUBH, the number of patients has increased continuously, and the total number of drug administration days has decreased since 2015. The number of serum level tests and TDM results showed little change.

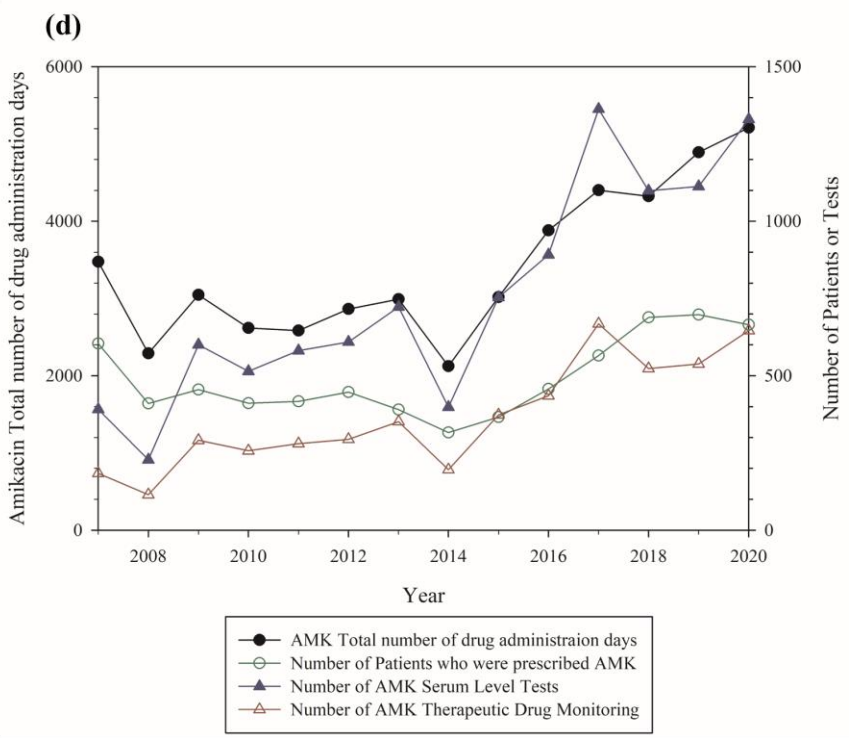
Theophylline use decreased steadily in both hospitals. Serum level tests and TDM also decreased with a decrease in prescription.

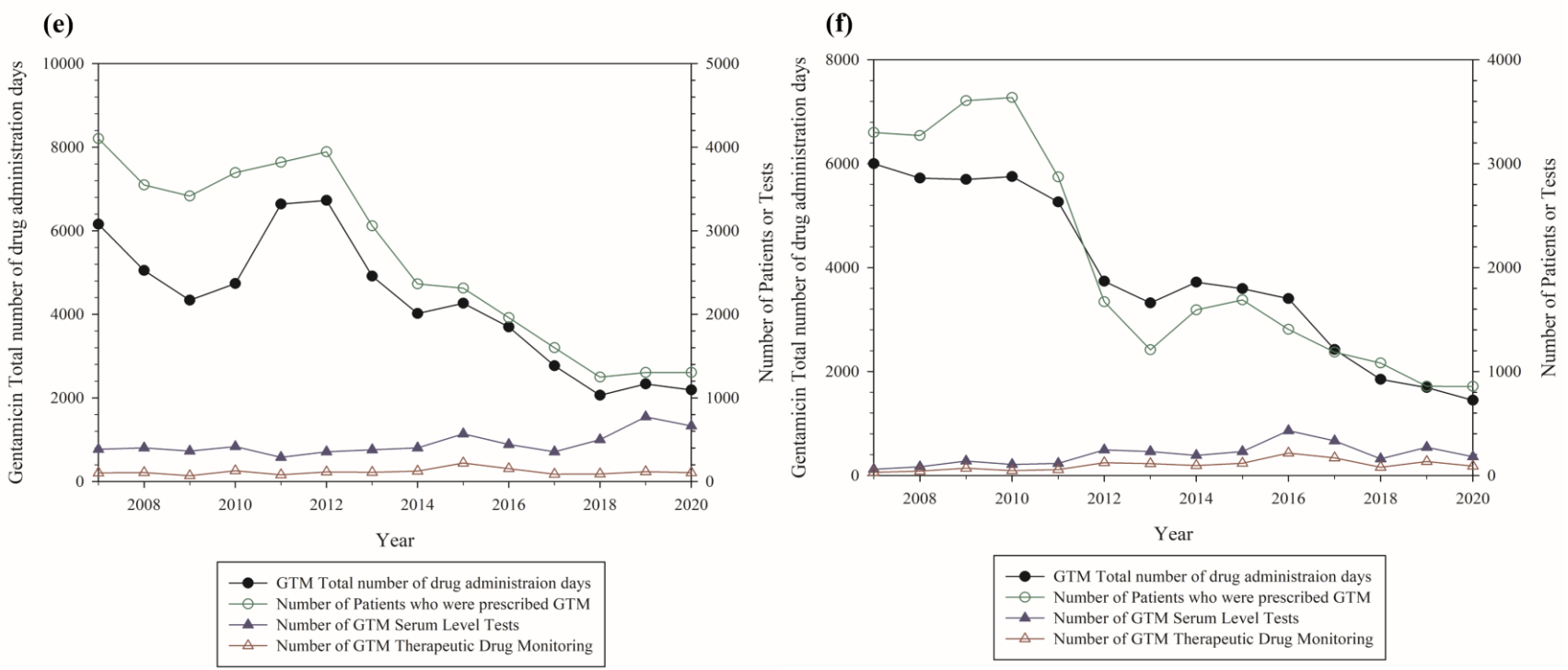
For lithium, the number of patients, total number of drug administration days, and serum levels were analyzed in both hospitals. The number of TDM has rarely been performed in SNUH, and there was no significant change. Lithium TDM has not been performed in SNUBH.


(a)
Vancomycin Total number of drug administration days
Number of Patients or Tests
Year
VCM Total number of drug administraion days
Number of Patients who were prescribed VCM
Number of VCM Serum Level Tests
Number of VCM Therapeutic Drug Monitoring


(b)
Vancomycin Total number of drug administration days
Number of Patients or Tests
Year
VCM Total number of drug administraion days
Number of Patients who were prescribed VCM
Number of VCM Serum Level Tests
Number of VCM Therapeutic Drug Monitoring


(c)
Amikacin Total number of drug administration days
Number of Patients or Tests
Year
AMK Total number of drug administraion days
Number of Patients who were prescribed AMK
Number of AMK Serum Level Tests
Number of AMK Therapeutic Drug Monitoring


(d)
Amikacin Total number of drug administration days
Number of Patients or Tests
Year
AMK Total number of drug administraion days
Number of Patients who were prescribed AMK
Number of AMK Serum Level Tests
Number of AMK Therapeutic Drug Monitoring


(e)
Gentamicin Total number of drug administration days
Number of Patients or Tests
Year
GTM Total number of drug administraion days
Number of Patients who were prescribed GTM
Number of GTM Serum Level Tests
Number of GTM Therapeutic Drug Monitoring
(f)
Gentamicin Total number of drug administration days
Number of Patients or Tests
Year
GTM Total number of drug administraion days
Number of Patients who were prescribed GTM
Number of GTM Serum Level Tests
Number of GTM Therapeutic Drug Monitoring

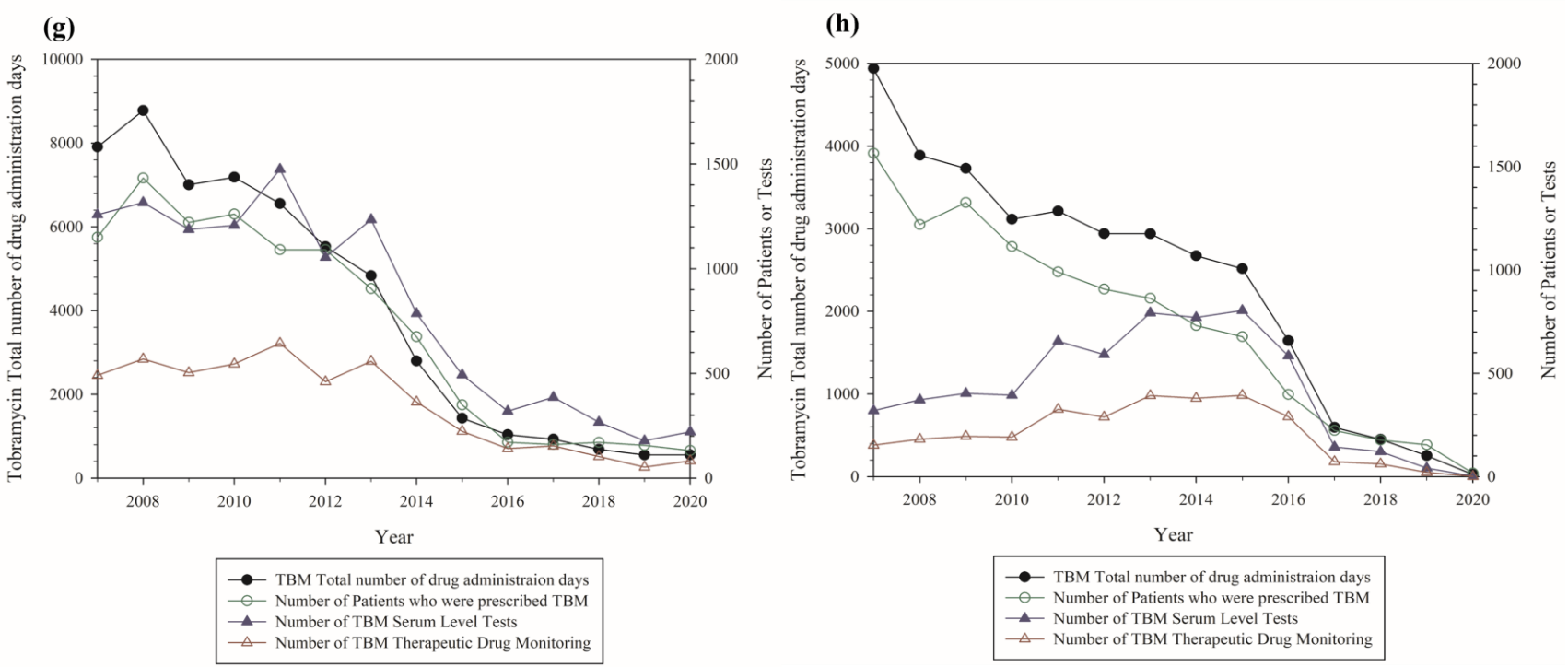
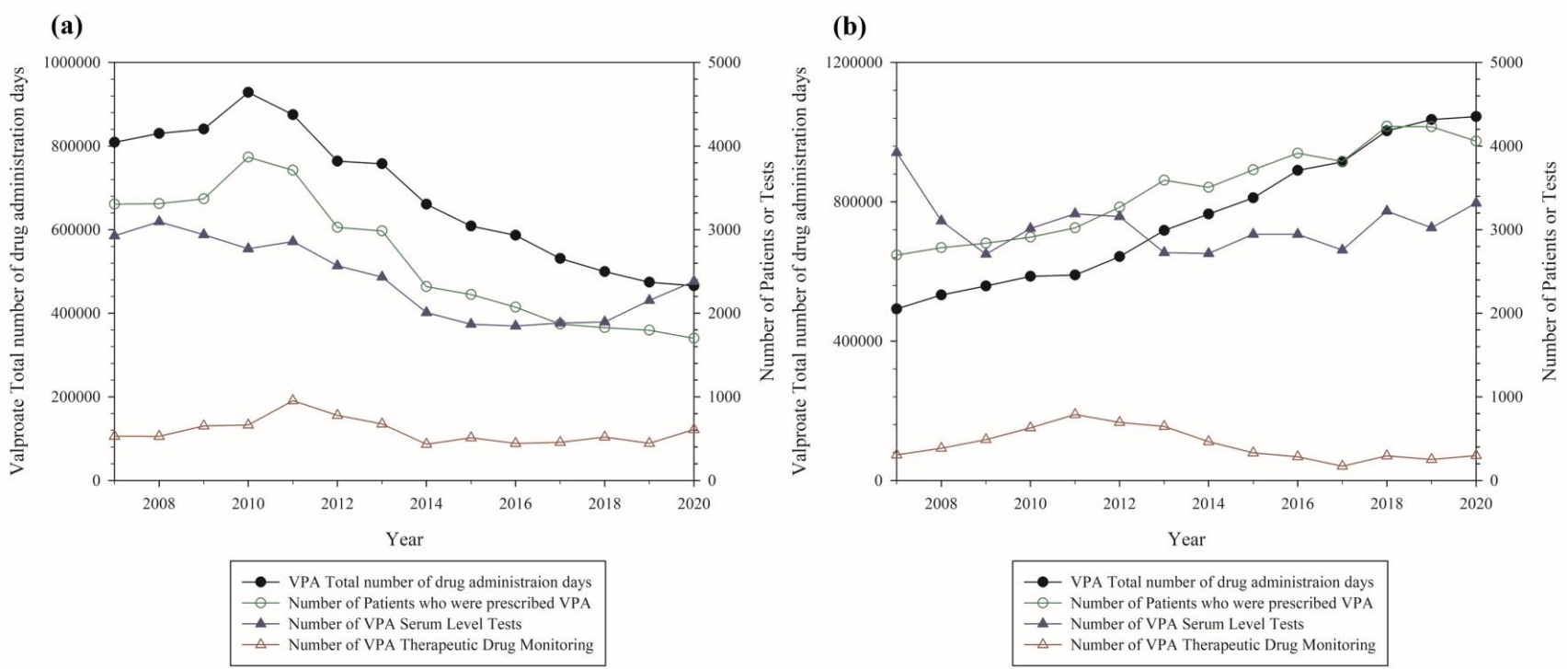


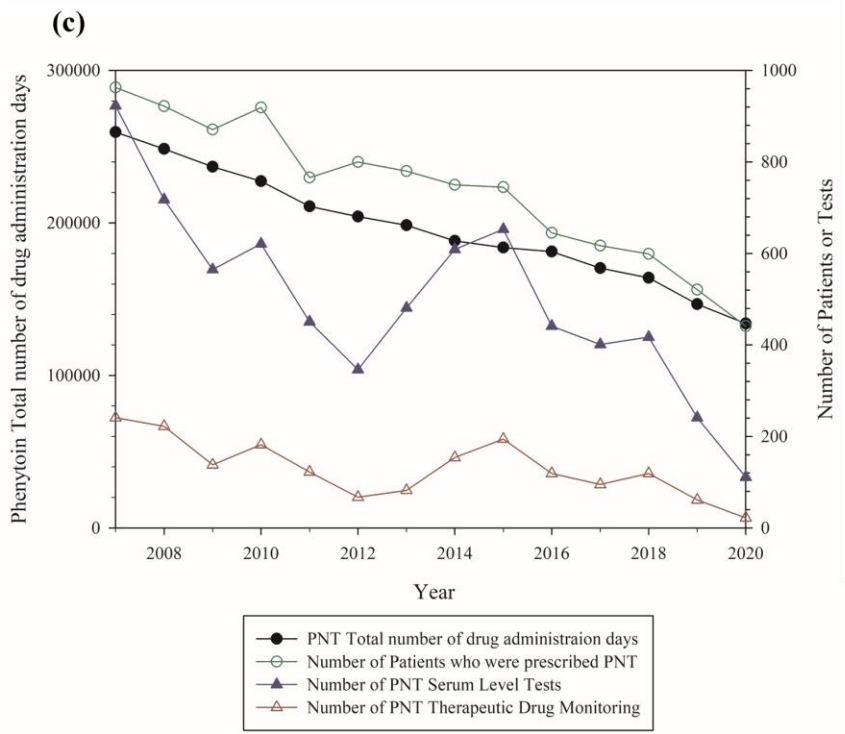
Figure 3. Analysis of total number of drug administration days and the cases of serum level tests and therapeutic drug monitoring by year in Seoul National University Hospital or Seoul National University Bundang Hospital (Antibiotics: Vancomycin, Amikacin, Gentamicin and Tobramycin)

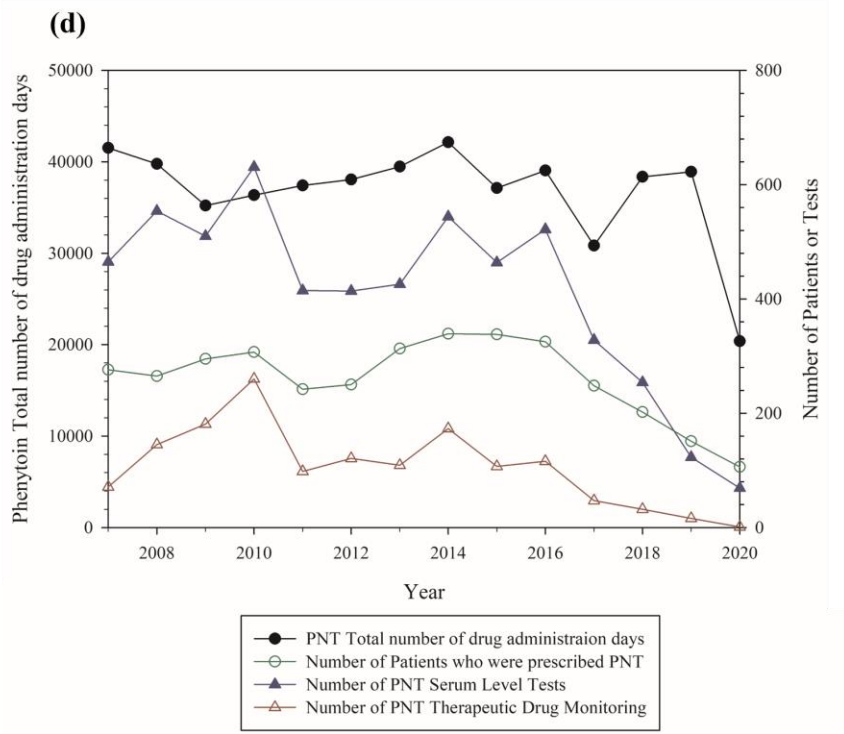
(a), (c), (e), (g) for Seoul National University Hospital and (b), (d), (f), (h) for Seoul National University Bundang Hospital

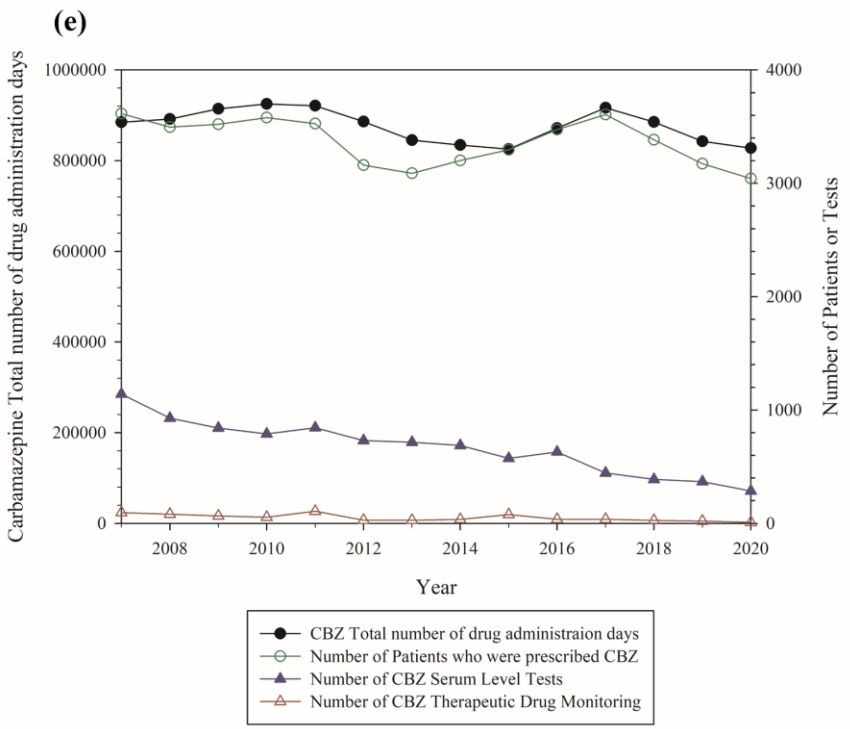
Left y-axis means the total number of drug administration days and right y-axis means number of patients who were prescribed drugs and number of serum level tests or therapeutic drug monitoring.

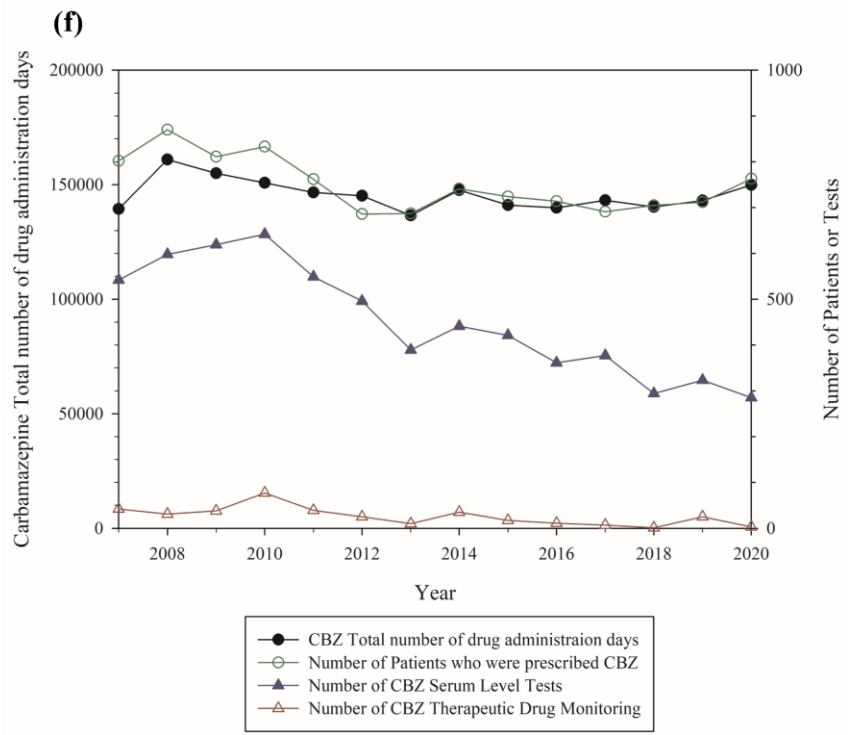
Abbreviation: VCM, vancomycin; AMK, amikacin; GTM, gentamicin; TBM, tobramycin;

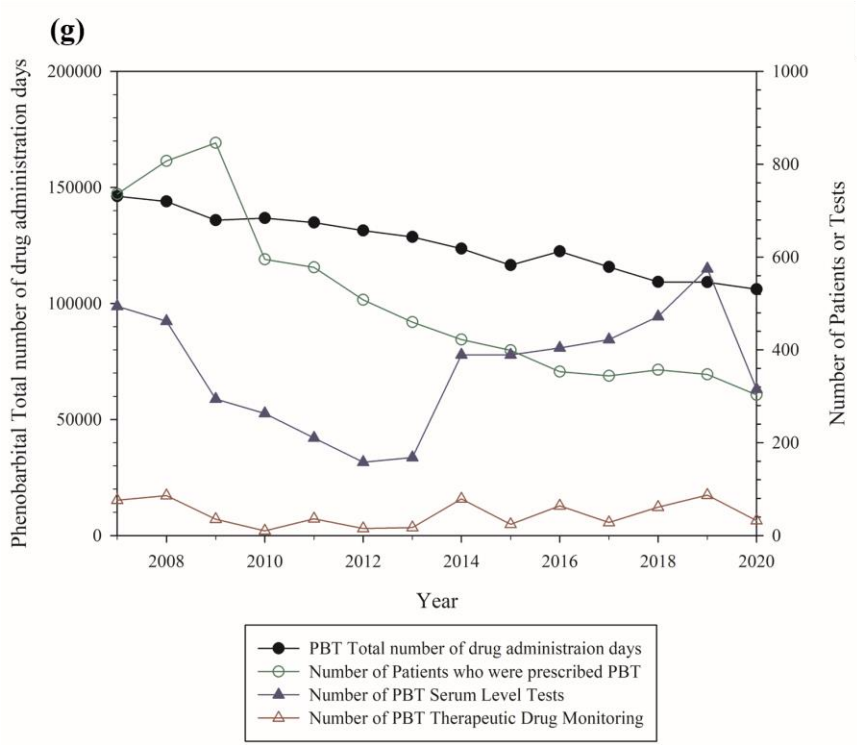

(a)
Valproate Total number of drug administration days
Number of Patients or Tests
Year
VPA Total number of drug administraion days
Number of Patients who were prescribed VPA
Number of VPA Serum Level Tests
Number of VPA Therapeutic Drug Monitoring
(b)
Valproate Total number of drug administration days
Number of Patients or Tests
Year
VPA Total number of drug administraion days
Number of Patients who were prescribed VPA
Number of VPA Serum Level Tests
Number of VPA Therapeutic Drug Monitoring


(c)
Phenytoin Total number of drug administration days
Number of Patients or Tests
Year
PNT Total number of drug administraion days
Number of Patients who were prescribed PNT
Number of PNT Serum Level Tests
Number of PNT Therapeutic Drug Monitoring


(d)
Phenytoin Total number of drug administration days
Number of Patients or Tests
Year
PNT Total number of drug administraion days
Number of Patients who were prescribed PNT
Number of PNT Serum Level Tests
Number of PNT Therapeutic Drug Monitoring


(e)
Carbamazepine Total number of drug administration days
Number of Patients or Tests
Year
1000000
800000
600000
400000
200000
0
4000
3000
2000
1000
0
2008
2010
2012
2014
2016
2018
2020
CBZ Total number of drug administraion days
Number of Patients who were prescribed CBZ
Number of CBZ Serum Level Tests
Number of CBZ Therapeutic Drug Monitoring


(f)
Carbamazepine Total number of drug administration days
Number of Patients or Tests
Year
200000
150000
100000
50000
0
1000
500
0
2008
2010
2012
2014
2016
2018
2020
CBZ Total number of drug administraion days
Number of Patients who were prescribed CBZ
Number of CBZ Serum Level Tests
Number of CBZ Therapeutic Drug Monitoring


(g)
Phenobarbital Total number of drug administration days
Number of Patients or Tests
Year
PBT Total number of drug administraion days
Number of Patients who were prescribed PBT
Number of PBT Serum Level Tests
Number of PBT Therapeutic Drug Monitoring

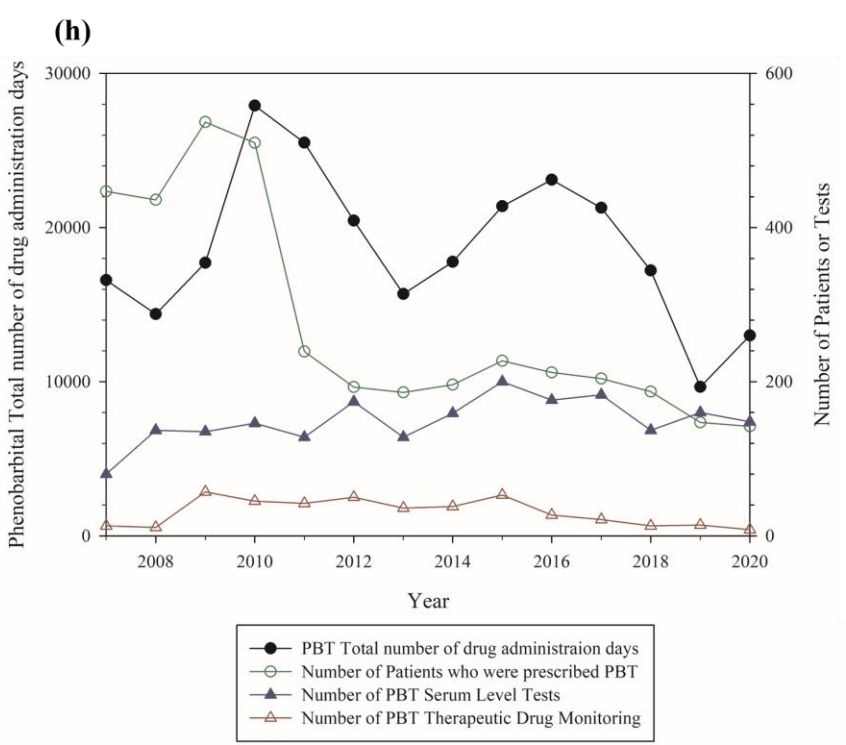
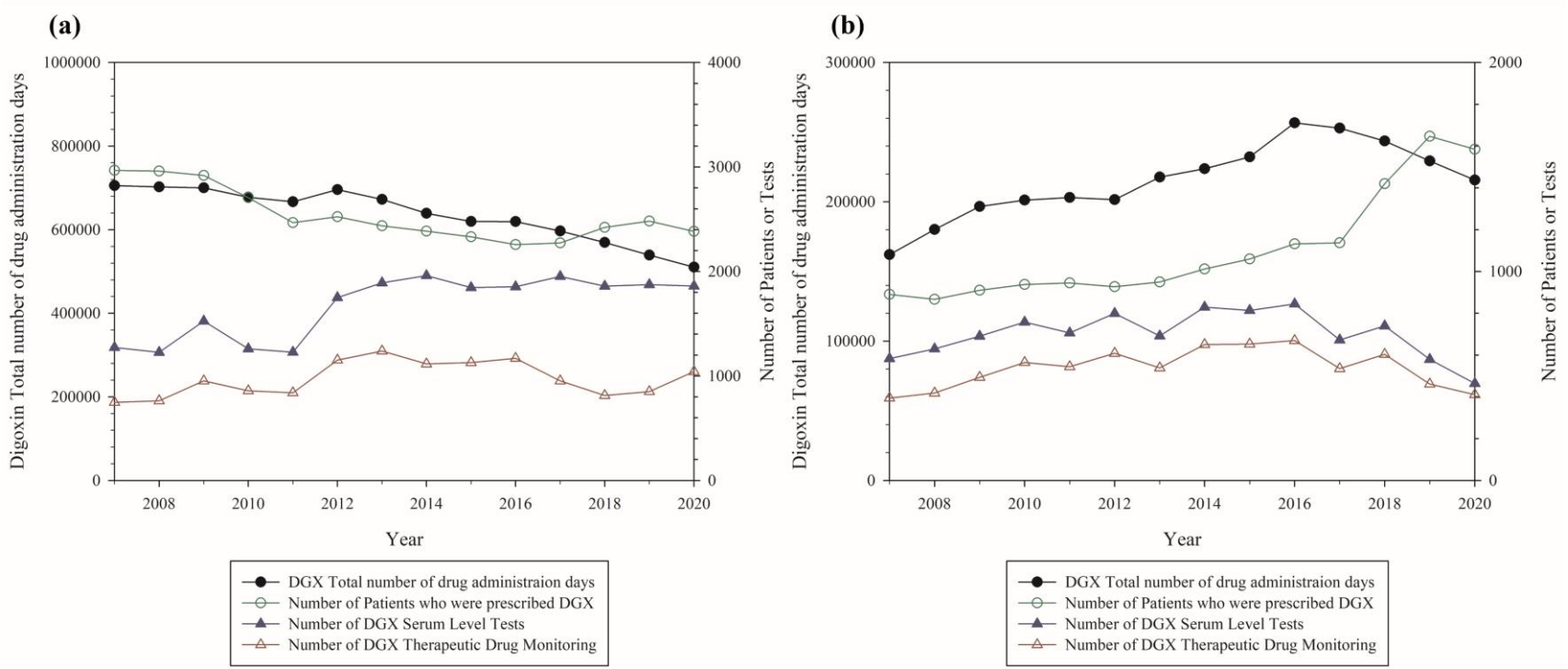

(h)
Phenobarbital Total number of drug administration days
Number of Patients or Tests
Year
PBT Total number of drug administraion days
Number of Patients who were prescribed PBT
Number of PBT Serum Level Tests
Number of PBT Therapeutic Drug Monitoring

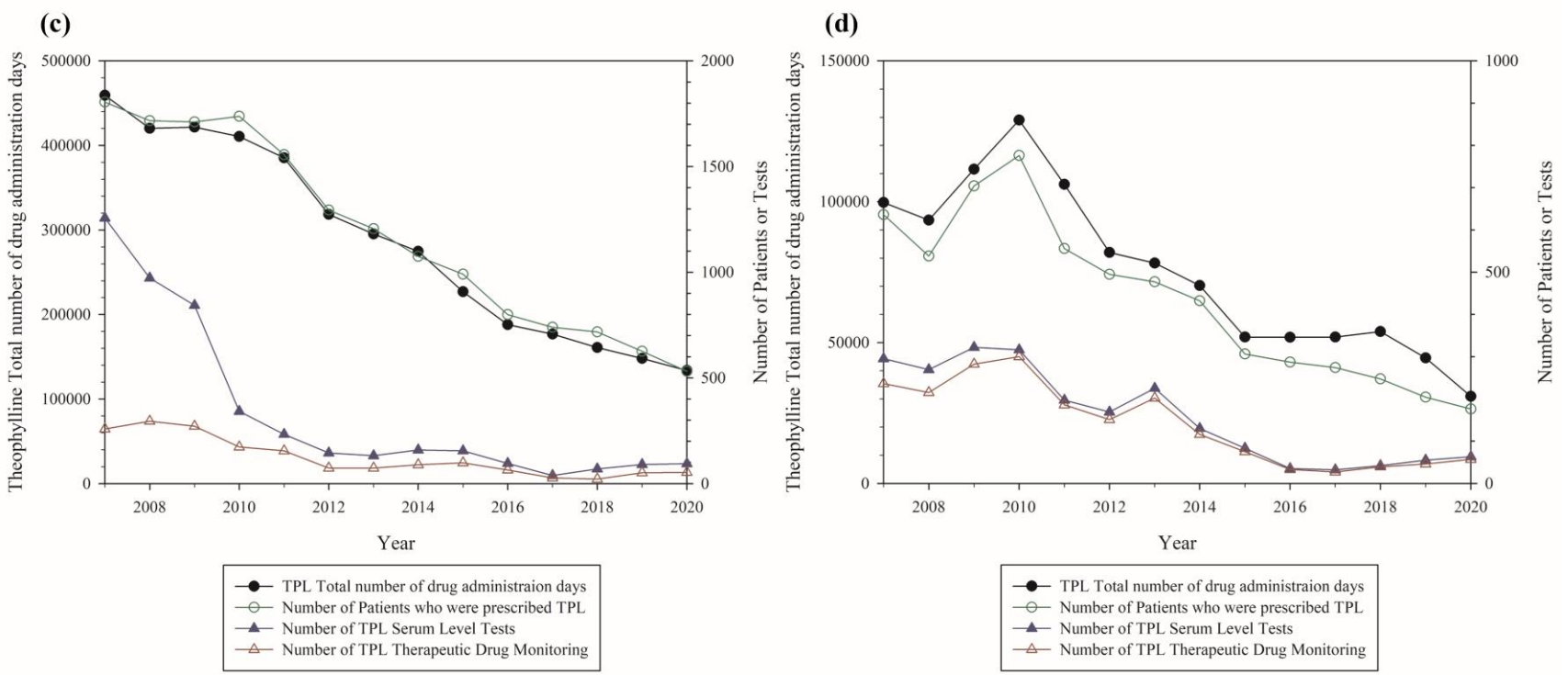
Figure 4. Analysis of total number of drug administration days and the cases of serum level tests and therapeutic drug monitoring by year in Seoul National University Hospital or Seoul National University Bundang Hospital (Antiepileptic drugs: Valproate, Phenytoin, Carbamazepine and Phenobarbital)

(a), (c), (e), (g) for Seoul National University Hospital and (b), (d), (f), (h) for Seoul National University Bundang Hospital

Left y-axis means the total number of drug administration days and right y-axis means number of patients who were prescribed drugs and number of serum level tests or therapeutic drug monitoring.

Abbreviation: VPA, valproate; CBZ, carbamazepine; PNT, phenytoin; PBT, phenobarbital;


(a)
Digoxin Total number of drug administration days
Number of Patients or Tests
Year
DGX Total number of drug administraion days
Number of Patients who were prescribed DGX
Number of DGX Serum Level Tests
Number of DGX Therapeutic Drug Monitoring
(b)
Digoxin Total number of drug administration days
Number of Patients or Tests
Year
DGX Total number of drug administraion days
Number of Patients who were prescribed DGX
Number of DGX Serum Level Tests
Number of DGX Therapeutic Drug Monitoring


(c)
Theophylline Total number of drug administration days
Number of Patients or Tests
Year
TPL Total number of drug administraion days
Number of Patients who were prescribed TPL
Number of TPL Serum Level Tests
Number of TPL Therapeutic Drug Monitoring
(d)
Theophylline Total number of drug administration days
Number of Patients or Tests
Year
TPL Total number of drug administraion days
Number of Patients who were prescribed TPL
Number of TPL Serum Level Tests
Number of TPL Therapeutic Drug Monitoring

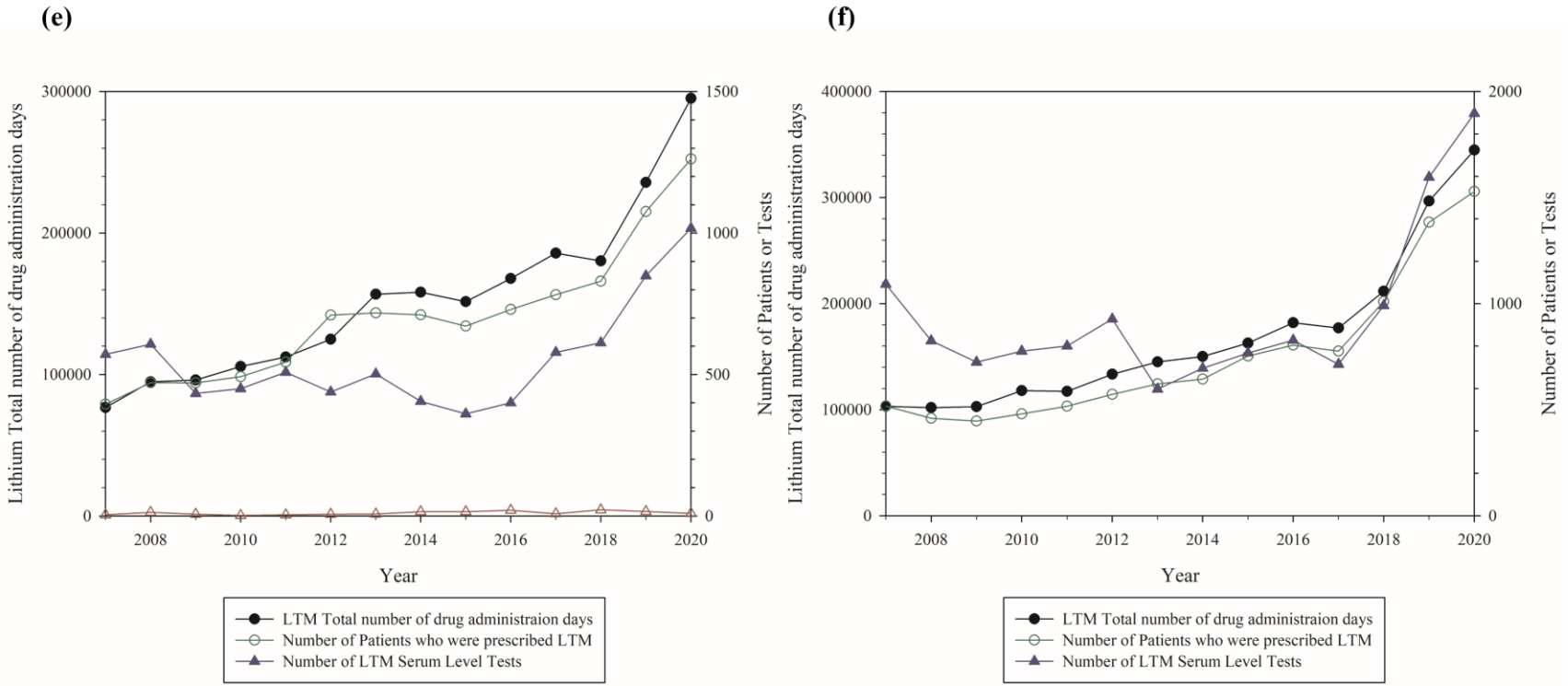

(e)
Lithium Total number of drug administration days
Number of Patients or Tests
300000
200000
100000
0
1500
1000
500
0
2008
2010
2012
2014
2016
2018
2020
Year
LTM Total number of drug administraion days
Number of Patients who were prescribed LTM
Number of LTM Serum Level Tests
(f)
Lithium Total number of drug administration days
Number of Patients or Tests
400000
300000
200000
100000
0
2000
1000
0
2008
2010
2012
2014
2016
2018
2020
Year
LTM Total number of drug administraion days
Number of Patients who were prescribed LTM
Number of LTM Serum Level Tests

Figure 5. Analysis of total number of drug administration days and serum level tests and therapeutic drug monitoring by year in Seoul National University Hospital or Seoul National University Bundang Hospital (Other drugs; Valproate, Theophylline, and Lithium)

(a), (c), (e) for Seoul National University Hospital and (b), (d), (f) for Seoul National University Bundang Hospital

Left y-axis means the total number of drug administration days and right y-axis means number of patients who were prescribed drugs and number of serum level tests or therapeutic drug monitoring.
There was no case of lithium TDM in Seoul National University Bundang Hospital.

Abbreviation: DGX, digoxin; TPL, theophylline; LTM, lithium;

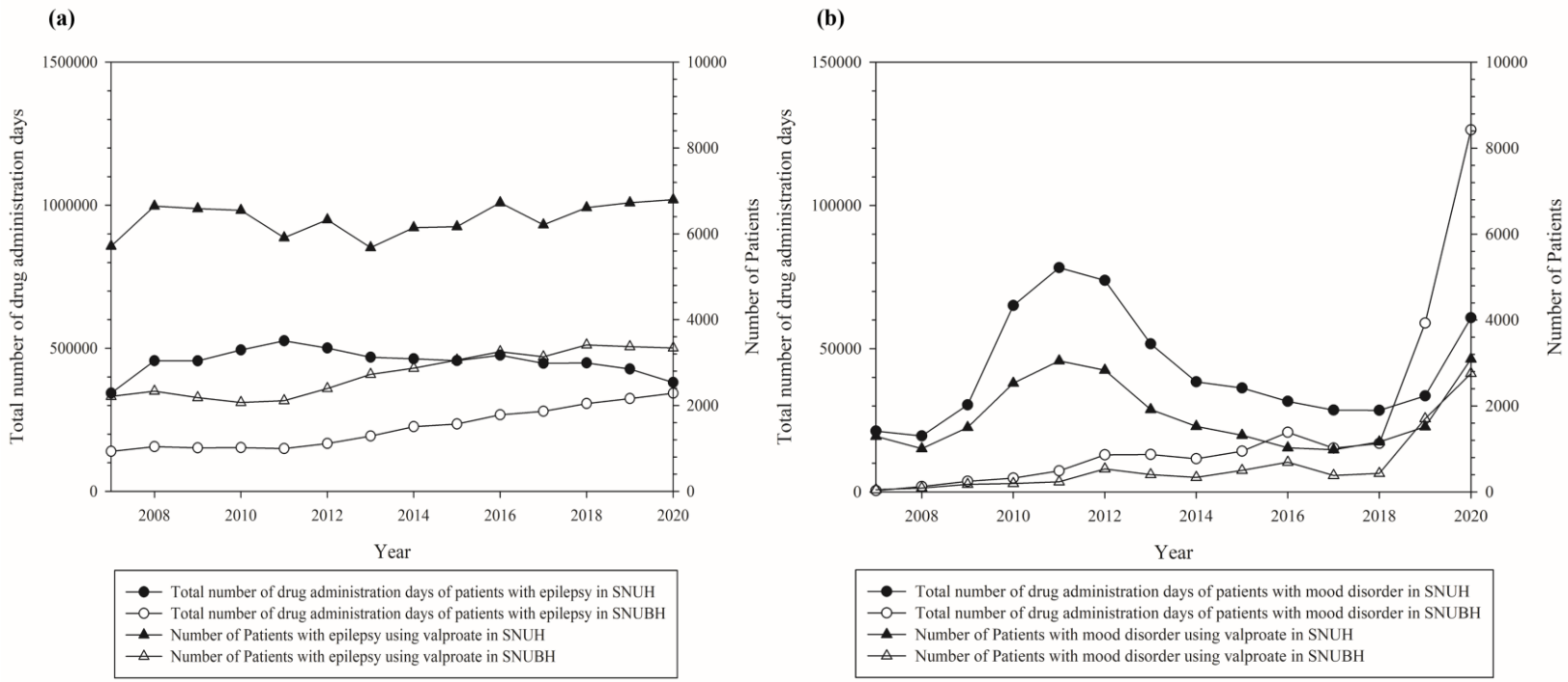


Figure 6. Total number of drug administration days and number of patients who were prescribed valproate for mood disorder or epilepsy by year in Seoul National University Hospital and Seoul National University Bundang Hospital

(a) for epilepsy and (b) for mood disorder

Left y-axis means the total number of drug administration days and right y-axis means number of patients who were prescribed valproate.

DISCUSSION

We calculated the number of patients, total number of drug administration days, serum level tests, and TDM of 11 drugs in the SNUH and SNUBH. Through this, we tried to find a relationship between prescription pattern (number of patients and total number of drug administration days) and TDM practice (number of serum level tests and TDM), and also suggest a future direction for TDM services.

For some drugs, the number of TDM changed with an increase or decrease in the number of patients and the total number of drug administration days, but for others it did not. For gentamicin, antiepileptics (valproate, phenytoin, carbamazepine, phenobarbital), theophylline, and lithium, a serum level test was performed, and then the dosage regimen was adjusted at the discretion of clinicians in most cases. Although there is small pharmacodynamic (PD) variability in antibiotics [16], there could be significant differences in drug response even at the same drug concentration in the case of antiepileptics or digoxin; thus, the evaluation of effectiveness is important for these drugs. [17] Therefore, some physicians prefer to decide the drug regimen for these drugs only with serum level

tests, and the number of TDM cases is small for these drugs compared to other drugs.

It seems that TDM for antibiotics is more frequently performed than for other drugs because these drugs are mostly used in hospitalized patients. TDM for vancomycin is known to prevent adverse events, such as nephrotoxicity or ototoxicity.[7] Vancomycin showed no significant difference in the number of patients, total number of drug administration days, serum level test, and TDM in this study. This might be because there was no change in the use of empirical antibiotics, and the rate of MRSA infection was similar or slightly decreased. [18–20]

Prescription patterns for tobramycin and amikacin changed around 2014 in both hospitals, which was presumed to be due to changes in drug recommendations in clinical practice. Before 2014, a combination of piperacillin–tazobactam and tobramycin was recommended as empirical antibiotics for the first neutropenia with an unknown infection site and causative agent.[21, 22] However, due to the discontinuation of the supply of piperacillin–tazobactam in 2014, the empirical antibiotic recommendations were changed as follows: piperacillin–tazobactam alone or in combination with amikacin at SNUH and a combination of ceftizoxime and amikacin in SNUBH were recommended regimens.[23, 24] It appears as if

these changes in practice also influenced an increase in amikacin usage. Although there were no changes in the drug usage recommendations for gentamicin, its usage continuously decreased. Gentamicin is rarely prescribed, except for infective endocarditis, as the number of referrals and consultations to the Department of Infectious Diseases has increased.[25]

Antiepileptic drugs (AEDs) are mainly prescribed to control seizures. Because the antiepileptics have large interindividual variability, sometimes patients could have a drug concentration not within the known therapeutic range.[17] Due to differences in the effectiveness of drugs between individuals even at the same drug concentrations, some clinicians prefer to evaluate drug efficacy and control the dosage for each patient rather than depending on TDM consultation.

At SNUH, the number of serum level tests and TDM of valproate decreased as drug use decreased. The increase in the use of levetiracetam, lacosamide, and topiramate could be one of the reasons for the decrease in valproate use. The number of patients and total number of drug administration days increased, whereas the number of serum level tests and TDM showed no significant change in SNUBH. While the number of patients prescribed valproate for epilepsy did not change significantly, the number of

patients in SNUBH showed a steady increase. On the other hand, the number of patients with mood disorders has shown an increasing trend since 2018, and this trend was more evident in SNUBH. Despite the increase in the number of patients, the number of serum tests and TDM remained similar. In the case of phenytoin, its usage decreased continuously because it was replaced with other drugs, such as lacosamide. Although carbamazepine is being replaced by oxcarbazepine in epilepsy patients, it is frequently prescribed in patients with neuralgia.[26, 27] However, serum level tests or TDM are rarely performed in these patients because a low dose of carbamazepine is prescribed for the indication.

Digoxin is used to treat heart failure and atrial fibrillation, and patients need to take the drug for a long time.[28] Thus it seems that serum level tests and TDM are performed approximately once every 1−2 years to check if the drug concentrations are within the therapeutic range.

The number of patients, total number of drug administration days, serum level tests, and TDM decreased in both hospitals. Theophylline is prescribed for patients with respiratory diseases such as chronic obstructive pulmonary disease (COPD) and is administered for a long time.[29] Because it has some adverse

reactions that lead to poor medication compliance; therefore, it is being replaced by inhaled long-acting beta2 agonists.[30]

Lithium is an effective antipsychotic drug for manic disorder or depression.[31-33] The number of patients, total number of drug administration days, and serum level tests increased in both hospitals. Only a few cases of lithium TDM were performed in SNUH, and none in SNUBH. Some physicians prefer lithium to valproate for bipolar disorder, and there is a trend for the spectrum of mood disorders to broaden. This phenomenon has led to an increase in lithium use.[34]

As shown so far, it has been confirmed that the number of patients or total number of drug administration days were different in the SNUH and SNUBH due to various factors.

This study has some limitations. First, fewer serum level tests of TDM could be performed in an outpatient setting than in inpatients. As inpatient and outpatient prescriptions were not analyzed separately, we could not distinguish the differences between the settings. Second, there might be differences in prescription patterns for each indication; however, differences for each indication were not analyzed separately. However, valproate, which showed different tendencies in the two hospitals, was further analyzed to

determine whether there was a difference according to the indications.

CONCLUSION

We analyzed the prescription patterns of 11 drugs, number of serum level tests, and TDM at SNUH and SNUBH over 14 years and tried to understand the relationship between them. The changes in the number of TDM differed among the drugs. As new drugs are continuously being developed to replace existing drugs, the use of some drugs and tests for the drugs has decreased. For effective and safe drug therapy, we need to expand TDM services for newly developed drugs.

REFERENCES

1. Touw, D.J., et al., *Cost-effectiveness of therapeutic drug monitoring: a systematic review.* Therapeutic drug monitoring, 2005. **27**(1): p. 10-17.
2. Blix, H.S., et al., *Drugs with narrow therapeutic index as indicators in the risk management of hospitalised patients.* Pharmacy practice, 2010. **8**(1): p. 50-55.
3. Drug, U.S.F., *FY2015 Regulatory Science Research Report: Narrow Therapeutic Index Drugs*. 2017.
4. Burns, M., *Management of narrow therapeutic index drugs.* Journal of thrombosis and thrombolysis, 1999. **7**(2): p. 137-143.
5. Benet, L.Z. and J.E. Goyan, *Bioequivalence and narrow therapeutic index drugs.* Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 1995. **15**(4): p. 433-440.
6. Lesosky, M., J. Joska, and E. Decloedt, *Simulating therapeutic drug monitoring results for dose individualisation to maintain investigator blinding in a randomised controlled trial.* Trials, 2017. **18**(1): p. 1-4.

7. Rybak, M., et al., *Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists.* American Journal of Health-System Pharmacy, 2009. **66**(1): p. 82-98.

8. Rybak, M.J., et al., *Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists.* American Journal of Health-System Pharmacy, 2020. **77**(11): p. 835-864.

9. Craig, W.A., *Basic pharmacodynamics of antibacterials with clinical applications to the use of β-lactams, glycopeptides, and linezolid.* Infectious Disease Clinics, 2003. **17**(3): p. 479-501.

10. Holmes, N.E., et al., *Vancomycin AUC/MIC ratio and 30-day mortality in patients with Staphylococcus aureus bacteremia.* Antimicrobial agents and chemotherapy, 2013. **57**(4): p. 1654-1663.

11. Burton, M.E., *Applied pharmacokinetics & pharmacodynamics: principles of therapeutic drug monitoring*. 2006: Lippincott Williams & Wilkins.

12. Castberg, I. and O. Spigset, *Prescribing patterns and the use of therapeutic drug monitoring of psychotropic medication in a psychiatric high-security unit.* Therapeutic drug monitoring, 2008. **30**(5): p. 597-603.

13. Murphy, E.C., F.L. Ferris, and W.R. O' Donnell, *An electronic medical records system for clinical research and the EMR-EDC interface.* Investigative ophthalmology & visual science, 2007. **48**(10): p. 4383-4389.

14. Karami, M., A. Rahimi, and A.H. Shahmirzadi, *Clinical data warehouse: an effective tool to create intelligence in disease management.* The health care manager, 2017. **36**(4): p. 380-384.

15. Wisniewski, M.F., et al., *Development of a clinical data warehouse for hospital infection control.* Journal of the American Medical Informatics Association, 2003. **10**(5): p. 454-462.

16. Cars, O., *Efficacy of beta-lactam antibiotics: integration of pharmacokinetics and pharmacodynamics.* Diagnostic

microbiology and infectious disease, 1997. **27**(1-2): p. 29-33.

17. Harivenkatesh, N., et al., *Therapeutic drug monitoring of antiepileptic drugs in a tertiary care hospital in India.* Clinical neuropharmacology, 2015. **38**(1): p. 1-5.

18. Klevens, R.M., et al., *Invasive methicillin-resistant Staphylococcus aureus infections in the United States.* Jama, 2007. **298**(15): p. 1763-1771.

19. Peterson, L.R. and D.M. Schora, *Methicillin-resistant Staphylococcus aureus control in the 21st century: Laboratory involvement affecting disease impact and economic benefit from large population studies.* Journal of clinical microbiology, 2016. **54**(11): p. 2647-2654.

20. Prevention, C.f.D.C.a. *What CDC is doing to combat MRSA*. 2019 [cited 2021 23rd, JULY]; Available from: https://www.cdc.gov/mrsa/tracking/.

21. Harter, C., et al., *Piperacillin/tazobactam vs ceftazidime in the treatment of neutropenic fever in patients with acute leukemia or following autologous peripheral blood stem cell transplantation: a prospective randomized trial.* Bone marrow transplantation, 2006. **37**(4): p. 373-379.

22. De Pauw, B.E., et al., *Ceftazidime compared with piperacillin and tobramycin for the empiric treatment of fever in neutropenic patients with cancer: a multicenter randomized trial.* Annals of internal medicine, 1994. **120**(10): p. 834-844.

23. Group*, E.I.A.T.C., *Ceftazidime combined with a short or long course of amikacin for empirical therapy of gram-negative bacteremia in cancer patients with granulocytopenia.* New England Journal of Medicine, 1987. **317**(27): p. 1692-1698.

24. Cordonnier, C., et al., *Cefepime/amikacin versus ceftazidime/amikacin as empirical therapy for febrile episodes in neutropenic patients: a comparative study.* Clinical infectious diseases, 1997. **24**(1): p. 41-51.

25. Habib, G., et al., *2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM).* European Heart Journal, 2015. **36**(44): p. 3075-3128.

26. Panday, D., et al., *Therapeutic drug monitoring of carbamazepine.* Int J Neurorehabilitation Eng, 2017. **4**(245): p. 2376-0281.

27. Killian, J.M. and G.H. Fromm, *Carbamazepine in the treatment of neuralgia: use and side effects.* Archives of neurology, 1968. **19**(2): p. 129-136.

28. Iisalo, E., *Clinical pharmacokinetics of digoxin.* Clinical pharmacokinetics, 1977. **2**(1): p. 1-16.

29. Boulet, L.-P., et al., *The global initiative for asthma (GINA): 25 years later.* European Respiratory Journal, 2019. **54**(2).

30. Virchow, J.C., et al., *Importance of inhaler devices in the management of airway disease.* Respiratory Medicine, 2008. **102**(1): p. 10-19.

31. Shorter, E., *The history of lithium therapy.* Bipolar disorders, 2009. **11**: p. 4-9.

32. Pisanu, C., et al., *Understanding the molecular mechanisms underlying mood stabilizer treatments in bipolar disorder: Potential involvement of epigenetics.* Neuroscience Letters, 2018. **669**: p. 24-31.

33. Cade, J.F., *Lithium salts in the treatment of psychotic excitement.* Medical Journal of Australia, 1949.

34. Shulman, K.I., et al., *Changing prescription patterns for lithium and valproic acid in old age: shifting practice without evidence.* Bmj, 2003. **326**(7396): p. 960-961.

APPENDICES

Supplementary Table 1 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with vancomycin in Seoul National University Hospital

Seoul National University Hospital					
VCM	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	16,681	814	800	20.5	20.9
2008	21,878	1,040	1,030	21	21.2
2009	20,413	1,127	1,114	18.1	18.3
2010	21,301	1,264	1,260	16.9	16.9
2011	20,483	1,221	1,213	16.8	16.9
2012	20,447	1,252	1,235	16.3	16.6
2013	21,064	1,284	1,275	16.4	16.5
2014	21,099	1,379	1,376	15.3	15.3
2015	19,898	1,425	1,419	14	14
2016	21,588	1,460	1,445	14.8	14.9
2017	20,680	1,328	1,314	15.6	15.7
2018	19,234	1,291	1,282	14.9	15
2019	18,542	1,235	1,223	15	15.2
2020	19,722	1,236	1,229	16	16

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: VCM, vancomycin;

Supplementary Table 2 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with amikacin in Seoul National University Hospital

Seoul National University Hospital					
AMK	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	6,234	683	270	9.1	23.1
2008	5,749	429	230	13.4	25
2009	5,804	474	199	12.2	29.2
2010	6,218	460	238	13.5	26.1
2011	5,072	413	219	12.3	23.2
2012	3,456	438	175	7.9	19.7
2013	3,400	411	133	8.3	25.6
2014	2,822	311	74	9.1	38.1
2015	4,710	360	82	13.1	57.4
2016	7,364	326	54	22.6	136.4
2017	6,771	422	65	16	104.2
2018	9,047	503	77	18	117.5
2019	11,460	461	96	24.9	119.4
2020	19,722	1,236	1,229	16	16

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: AMK, amikacin;

Supplementary Table 3 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with gentamicin in Seoul National University Hospital

Seoul National University Hospital					
GTM	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	6,158	172	59	35.8	104.4
2008	5,051	162	57	31.2	88.6
2009	4,337	163	36	26.6	120.5
2010	4,738	163	50	29.1	94.8
2011	6,640	113	32	58.8	207.5
2012	6,728	125	35	53.8	192.2
2013	4,915	116	33	42.4	148.9
2014	4,018	123	40	32.7	100.5
2015	4,263	156	54	27.3	78.9
2016	3,697	139	44	26.6	84
2017	2,768	131	24	21.1	115.3
2018	2,063	141	23	14.6	89.7
2019	2,334	247	36	9.4	64.8
2020	2,189	217	30	10.1	73

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: GTM, gentamicin;

Supplementary Table 4 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with tobramycin in Seoul National University Hospital

Seoul National University Hospital					
TBM	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	7,906	408	286	19.4	27.6
2008	8,776	427	333	20.6	26.4
2009	7,003	380	304	18.4	23
2010	7,186	400	336	18	21.4
2011	6,555	414	316	15.8	20.7
2012	5,527	297	235	18.6	23.5
2013	4,834	331	285	14.6	17
2014	2,795	196	165	14.3	16.9
2015	1,428	123	92	11.6	15.5
2016	1,035	53	34	19.5	30.4
2017	926	79	50	11.7	18.5
2018	685	53	32	12.9	21.4
2019	551	39	13	14.1	42.4
2020	555	45	20	12.3	27.8

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: TBM, Tobramycin;

Supplementary Table 5 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with valproate in Seoul National University Hospital

Seoul National University Hospital					
VPA	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	809,191	1,360	255	595	3173.3
2008	830,319	1,510	247	549.9	3361.6
2009	840,739	1,523	363	552	2316.1
2010	928,547	1,554	373	597.5	2489.4
2011	874,992	1,651	540	530	1620.4
2012	764,005	1,510	400	506	1910
2013	757,685	1,381	326	548.6	2324.2
2014	660,889	1,200	203	550.7	3255.6
2015	608,692	1,133	248	537.2	2454.4
2016	586,642	1,140	177	514.6	3314.4
2017	530,976	1,046	169	507.6	3141.9
2018	499,623	1,137	196	439.4	2549.1
2019	474,193	1,100	169	431.1	2805.9
2020	465,752	1,211	193	384.6	2413.2

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: VPA, valproate;

Supplementary Table 6 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with phenytoin in Seoul National University Hospital

Seoul National University Hospital					
PNT	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	259,528	362	80	716.9	3244.1
2008	248,562	325	71	764.8	3500.9
2009	236,878	301	56	787	4230
2010	227,415	374	98	608.1	2320.6
2011	210,841	265	56	795.6	3765
2012	204,198	251	32	813.5	6381.2
2013	198,493	263	30	754.7	6616.4
2014	188,236	242	46	777.8	4092.1
2015	183,851	268	55	686	3342.7
2016	181,220	237	46	764.6	3939.6
2017	170,439	183	36	931.4	4734.4
2018	164,053	196	48	837	3417.8
2019	146,758	149	22	985	6670.8
2020	134,005	93	14	1440.9	9571.8

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: PNT, phenytoin;

Supplementary Table 7 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with carbamazepine in Seoul National University Hospital

Seoul National University Hospital					
CBZ	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	884,569	653	51	1354.6	17344.5
2008	891,879	579	42	1540.4	21235.2
2009	914,237	610	36	1498.7	25395.5
2010	925,004	652	41	1418.7	22561.1
2011	921,200	693	88	1329.3	10468.2
2012	885,987	622	24	1424.4	36916.1
2013	845,284	578	21	1462.4	40251.6
2014	834,363	547	23	1525.3	36276.7
2015	825,449	489	63	1688	13102.4
2016	871,599	483	22	1804.6	39618.1
2017	916,491	388	24	2362.1	38187.1
2018	885,403	346	22	2559	40245.6
2019	842,623	318	16	2649.8	52663.9
2020	827,794	262	8	3159.5	103474.3

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: CBZ, carbamazepine;

Supplementary Table 8 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with phenobarbital in Seoul National University Hospital

Seoul National University Hospital					
PBT	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	146,213	127	17	1151.3	8600.8
2008	143,998	132	17	1090.9	8470.5
2009	135,883	132	14	1029.4	9705.9
2010	136,821	125	8	1094.6	17102.6
2011	134,883	145	32	930.2	4215.1
2012	131,432	134	12	980.8	10952.7
2013	128,695	124	7	1037.9	18385
2014	123,675	128	16	966.2	7729.7
2015	116,546	109	15	1069.2	7769.7
2016	122,440	117	11	1046.5	11130.9
2017	115,738	93	11	1244.5	10521.6
2018	109,302	94	24	1162.8	4554.3
2019	109,198	111	25	983.8	4367.9
2020	106,158	73	12	1454.2	8846.5

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: PBT, phenobarbital;

Supplementary Table 9 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with digoxin in Seoul National University Hospital

Seoul National University Hospital					
DGX	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	705,563	556	319	1269	2211.8
2008	702,341	548	337	1281.6	2084.1
2009	700,243	560	336	1250.4	2084.1
2010	677,506	520	339	1302.9	1998.5
2011	666,944	522	323	1277.7	2064.8
2012	695,960	685	402	1016	1731.2
2013	672,500	636	357	1057.4	1883.8
2014	639,155	678	353	942.7	1810.6
2015	619,755	654	378	947.6	1639.6
2016	619,318	663	370	934.1	1673.8
2017	596,901	662	305	901.7	1957.1
2018	569,523	647	280	880.3	2034
2019	539,311	669	314	806.1	1717.6
2020	510,353	605	320	843.6	1594.9

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: DGX, digoxin;

Supplementary Table 10 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with theophylline in Seoul National University Hospital

Seoul National University Hospital					
TPL	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	459,293	866	135	530.4	3402.2
2008	420,158	731	144	574.8	2917.8
2009	421,676	626	128	673.6	3294.3
2010	410,614	254	101	1616.6	4065.5
2011	385,406	160	95	2408.8	4056.9
2012	318,480	98	41	3249.8	7767.8
2013	295,269	58	39	5090.8	7571
2014	274,734	95	45	2891.9	6105.2
2015	226,941	86	33	2638.8	6877
2016	187,932	59	33	3185.3	5694.9
2017	176,804	19	11	9305.5	16073.1
2018	160,765	44	15	3653.8	10717.7
2019	148,031	50	27	2960.6	5482.6
2020	133,673	30	16	4455.8	8354.6

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: TPL, theophylline;

Supplementary Table 11 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with lithium in Seoul National University Hospital

Seoul National University Hospital					
LTM	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	76,568	223	3	343.4	25522.7
2008	94,788	246	5	385.3	18957.6
2009	96,028	226	6	424.9	16004.7
2010	105,595	215	2	491.1	52797.5
2011	112,327	243	4	462.3	28081.8
2012	124,888	226	6	552.6	20814.7
2013	156,808	258	5	607.8	31361.6
2014	158,248	215	9	736	17583.1
2015	151,514	190	8	797.4	18939.3
2016	167,898	208	13	807.2	12915.2
2017	185,855	292	6	636.5	30975.8
2018	180,271	338	6	533.3	30045.2
2019	235,787	375	10	628.8	23578.7
2020	295,189	523	3	564.4	98396.3

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: LTM, lithium;

Supplementary Table 12 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with vancomycin in Seoul National University Bundang Hospital

Seoul National University Bundang Hospital					
VCM	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	7,946	365	346	21.8	23
2008	10,720	493	477	21.7	22.5
2009	8,401	454	443	18.5	19
2010	7,975	478	470	16.7	17
2011	8,427	517	503	16.3	16.8
2012	8,819	566	556	15.6	15.9
2013	8,899	581	574	15.3	15.5
2014	9,911	617	609	16.1	16.3
2015	10,240	648	629	15.8	16.3
2016	10,495	729	637	14.4	16.5
2017	9,736	718	626	13.6	15.6
2018	10,198	759	678	13.4	15
2019	9,277	688	616	13.5	15.1
2020	8,591	652	620	13.2	13.9

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: VCM, vancomycin;

Supplementary Table 13 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with amikacin in Seoul National University Bundang Hospital

Seoul National University Bundang Hospital					
AMK	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	3,476	132	122	26.3	28.5
2008	2,288	79	78	29	29.3
2009	3,047	143	139	21.3	21.9
2010	2,618	142	138	18.4	19
2011	2,584	140	135	18.5	19.1
2012	2,864	135	132	21.2	21.7
2013	2,991	137	134	21.8	22.3
2014	2,122	94	92	22.6	23.1
2015	3,018	146	144	20.7	21
2016	3,883	212	205	18.3	18.9
2017	4,402	266	257	16.5	17.1
2018	4,324	261	250	16.6	17.3
2019	4,894	266	255	18.4	19.2
2020	5,212	283	272	18.4	19.2

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: AMK, amikacin;

Supplementary Table 14 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with gentamicin in Seoul National University Bundang Hospital

Seoul National University Bundang Hospital					
GTM	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	6,000	18	17	333.3	352.9
2008	5,723	30	29	190.8	197.3
2009	5,699	29	29	196.5	196.5
2010	5,753	29	25	198.4	230.1
2011	5,264	25	24	210.6	219.3
2012	3,737	44	44	84.9	84.9
2013	3,319	42	38	79	87.3
2014	3,720	42	38	88.6	97.9
2015	3,595	49	48	73.4	74.9
2016	3,402	67	67	50.8	50.8
2017	2,421	56	54	43.2	44.8
2018	1,848	39	38	47.4	48.6
2019	1,690	46	44	36.7	38.4
2020	1,447	34	34	42.6	42.6

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: GTM, gentamicin;

Supplementary Table 15 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with tobramycin in Seoul National University Bundang Hospital

Seoul National University Bundang Hospital					
TBM	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	4,938	110	106	44.9	46.6
2008	3,888	125	124	31.1	31.4
2009	3,731	130	125	28.7	29.8
2010	3,116	120	115	26	27.1
2011	3,214	168	166	19.1	19.4
2012	2,942	155	150	19	19.6
2013	2,941	178	176	16.5	16.7
2014	2,674	176	173	15.2	15.5
2015	2,517	170	167	14.8	15.1
2016	1,645	135	132	12.2	12.5
2017	595	37	36	16.1	16.5
2018	451	36	34	12.5	13.3
2019	254	12	11	21.2	23.1
2020	24	1	1	24	24

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: TBM, tobramycin;

Supplementary Table 16 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with valproate in Seoul National University Bundang Hospital

Seoul National University Bundang Hospital					
VPA	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	492,391	1,573	128	313	3846.8
2008	532,146	1,443	153	368.8	3478.1
2009	558,456	1,331	214	419.6	2609.6
2010	586,107	1,428	276	410.4	2123.6
2011	590,005	1,431	367	412.3	1607.6
2012	642,601	1,535	328	418.6	1959.1
2013	718,001	1,419	265	506	2709.4
2014	765,087	1,393	145	549.2	5276.5
2015	811,431	1,572	116	516.2	6995.1
2016	890,273	1,610	106	553	8398.8
2017	914,773	1,485	72	616	12705.2
2018	1,003,636	1,744	104	575.5	9650.3
2019	1,036,318	1,660	92	624.3	11264.3
2020	1,044,581	1,674	89	624	11736.9

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: VPA, valproate;

Supplementary Table 17 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with phenytoin in Seoul National University Bundang Hospital

Seoul National University Bundang Hospital					
PNT	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	41,527	174	39	238.7	1064.8
2008	39,777	174	48	228.6	828.7
2009	35,221	186	61	189.4	577.4
2010	36,357	216	85	168.3	427.7
2011	37,415	157	45	238.3	831.4
2012	38,063	156	37	244	1028.7
2013	39,484	175	42	225.6	940.1
2014	42,147	179	61	235.5	690.9
2015	37,138	178	44	208.6	844
2016	39,062	160	50	244.1	781.2
2017	30,849	134	26	230.2	1186.5
2018	38,367	98	13	391.5	2951.3
2019	38,918	63	8	617.7	4864.8
2020	20,374	39	1	522.4	20374

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: PNT, phenytoin;

Supplementary Table 18 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with carbamazepine in Seoul National University Bundang Hospital

Seoul National University Bundang Hospital					
CBZ	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	139,401	289	21	482.4	6638.1
2008	160,993	309	18	521	8944.1
2009	155,004	315	15	492.1	10333.6
2010	150,809	340	19	443.6	7937.3
2011	146,625	272	13	539.1	11278.8
2012	145,158	259	12	560.5	12096.5
2013	136,561	228	6	599	22760.2
2014	147,640	226	11	653.3	13421.8
2015	141,099	224	9	629.9	15677.7
2016	139,886	202	10	692.5	13988.6
2017	143,190	217	5	659.9	28638
2018	140,281	179	1	783.7	140281
2019	143,071	188	4	761	35767.8
2020	149,898	184	3	814.7	49966

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: CBZ, carbamazepine;

Supplementary Table 19 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with phenobarbital in Seoul National University Bundang Hospital

Seoul National University Bundang Hospital					
PBT	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	16,593	47	11	353	1508.5
2008	14,387	49	5	293.6	2877.4
2009	17,721	45	7	393.8	2531.6
2010	27,916	51	7	547.4	3988
2011	25,504	42	9	607.2	2833.8
2012	20,457	52	7	393.4	2922.4
2013	15,693	56	8	280.2	1961.6
2014	17,781	53	7	335.5	2540.1
2015	21,386	70	7	305.5	3055.1
2016	23,107	60	8	385.1	2888.4
2017	21,280	68	4	312.9	5320
2018	17,220	63	3	273.3	5740
2019	9,660	62	5	155.8	1932
2020	12,995	57	4	228	3248.8

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: PBT, phenobarbital;

Supplementary Table 20 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with digoxin in Seoul National University Bundang Hospital

Seoul National University Bundang Hospital					
DGX	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	162,106	272	189	596	857.7
2008	180,117	244	178	738.2	1011.9
2009	196,676	282	203	697.4	968.8
2010	201,200	312	229	644.9	878.6
2011	203,101	283	218	717.7	931.7
2012	201,560	287	238	702.3	846.9
2013	217,708	259	217	840.6	1003.3
2014	223,760	298	238	750.9	940.2
2015	232,240	294	235	789.9	988.3
2016	256,663	306	254	838.8	1010.5
2017	252,892	259	204	976.4	1239.7
2018	243,625	276	227	882.7	1073.2
2019	229,349	261	205	878.7	1118.8
2020	215,604	219	186	984.5	1159.2

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: DGX, digoxin;

Supplementary Table 21 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with theophylline in Seoul National University Bundang Hospital

Seoul National University Bundang Hospital					
TPL	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	99,725	158	128	631.2	779.1
2008	93,455	152	125	614.8	747.6
2009	111,551	158	146	706	764
2010	128,989	138	129	934.7	999.9
2011	106,145	98	95	1083.1	1117.3
2012	81,991	91	85	901	964.6
2013	78,235	100	89	782.4	879
2014	70,268	57	52	1232.8	1351.3
2015	51,939	38	32	1366.8	1623.1
2016	51,837	20	19	2591.9	2728.3
2017	51,918	22	18	2359.9	2884.3
2018	53,861	20	17	2693.1	3168.3
2019	44,517	22	21	2023.5	2119.9
2020	30,873	23	22	1342.3	1403.3

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: TPL, theophylline;

Supplementary Table 22 Total number of drug administration days, number of serum level tests and therapeutic drug monitoring, and average drug administration days per patients who performed serum level test or therapeutic drug monitoring by year with lithium in Seoul National University Bundang Hospital

Seoul National University Bundang Hospital					
LTM	Total number of Drug administration days (day)	Number of patients who performed serum level tests (N)	Number of patients who performed TDM (N)	Average drug administration days per patients who performed serum level test* (day)	Average drug administration days per patients who performed TDM* (day)
2007	103,100	414	–	779.1	–
2008	101,911	362	–	747.6	–
2009	102,808	336	–	764	–
2010	117,867	353	–	999.9	–
2011	117,197	367	–	1117.3	–
2012	133,372	444	–	964.6	–
2013	144,998	350	–	879	–
2014	150,141	415	–	1351.3	–
2015	162,715	434	–	1623.1	–
2016	182,023	491	–	2728.3	–
2017	176,954	403	–	2884.3	–
2018	211,723	567	–	3168.3	–
2019	296,729	852	–	2119.9	–
2020	344,895	832	–	1403.3	–

The ratio was divided total number of drug administration days to serum level tests or TDM.
*It was rounded to the first decimal place.
Abbreviation: LTM, lithium;

국문 초록

서론: 치료적 약물 모니터링은 좁은 치료역을 갖는 약물에 대해서 수행한다. 서울대학교병원과 분당서울대학교병원에서는 반코마이신, 아미카신, 젠타마이신, 토브라마이신, 발프로에이트, 페니토인, 페노바르비탈, 카르바마제핀, 디곡신, 테오필린, 리튬 등 다양한 의약품에 대한 치료적 약물 모니터링 서비스에 대해서 제공한다. 본 연구는 전자 의무 기록을 통해 장기간의 약물 처방 패턴을 확인하고 치료적 약물 모니터링 수행과의 관계를 분석하는 것을 목표로 하였다.

방법: 2007년 1월 1일부터 2020년 12월 31일까지의 임상 데이터를 수집하였으며, 환자 수, 총 약물 투여일 수, 혈청 검사 및 치료적 약물 모니터링을 한 건수에 대해서 조사하였다. 총 약물 투여 일수에 대한 혈청 검사 또는 치료적 약물 모니터링의 횟수로 계산하였다.

결과: 최소 한 번 이상의 각 약물을 처방받은 환자를 선택하여, 서울대학교병원의 136,427명 및 분당서울대학교병원의 162,927명의 환자를 본 연구에 포함하였다. 총 11개의 약물의 경우, 항생제(반코마이신, 아미카신, 젠타마이신, 토브라마이신), 항간질제(발프로에이트, 페니토인, 페노바르비탈, 카르바마제핀) 그리고 다른 약물(디곡신, 테오필린, 리튬) 이렇게 3가지 종류의 약물로 나누어 분석하였다. 각 약물은 서로 다른 처방 패턴의 변화를 보였고 혈청 검사 및 치료적 약물 모니터링 건수의

경우 처방 패턴의 변화에 따라 변화하였다.

결론: 서울대학교병원 및 분당서울대학교병원에 대한 처방 패턴, 혈청 검사 수, 치료적 약물 모니터링의 건수에 대해서 분석하였다. 최근에 개발된 약물이 기존의 약물을 대체하면서, 일부 약의 사용과 이에 따른 검사 수가 줄어 드는 추세를 보이기도 하였다. 효과적이고 안전한 약물 치료를 위해 향후 새롭게 개발된 약물에 대해서도 치료적 약물 모니터링을 수행하는 것이 좋을 것으로 판단된다.

주요어: 항생제, 항간질제, 전자 의무 기록, 실제 임상 데이터, 치료적 약물 모니터링

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