Original Article

An Extensive Therapeutical Drug Monitoring Repository for Localized Population Pharmacokinetics Research

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Abstract

Aim: The study's long-term goals, such as determining supratherapeutic ranges according to age distributions specific to the country, adjusting dosages for additional drugs used by patients in different disease groups, and providing the opportunity for etiological studies in the light of diagnosis and drug metabolism perspective, are of great importance in defining the study. **Method:** Population pharmacokinetics is a method expressed to evaluate processes such as absorption, distribution, metabolism, and elimination of a drug from an individual's blood-plasma concentration. In drug pharmacokinetic experiments, generating data without considering any pharmacokinetic differences among patients prevents the measurement or observation of variability among individuals in the population as a simple approach. The dose-concentration relationship is crucial for individualized dose adjustment. Additionally, the impact of other drugs used by the individual on metabolite levels and the metabolic interactions between drugs play a critical role in the development of personalized treatments. Population approaches provide a foundation that benefits the observation of these effects. The variability in drug metabolism among individuals forms one of the fundamental building blocks of personalized treatment approaches, specifically through Therapeutic Drug Monitoring (TDM), which plays an important role in determining the therapeutic range of drugs. **Materials**: In this study, drug metabolism findings of patients served at NP Istanbul Brain Hospital between 2010 and 2022 were examined within the repository created along with other patient-specific parameters. **Results and Conclusion**: The analysis results have been followed up longitudinally, partially demographically, and retrospectively. Thanks to the repository of NP Istanbul Brain Hospital, population pharmacokinetic analyses aimed in this study are being conducted for the first time globally and nationally in terms of scope. The repository has been studied with TDM for individualized treatment methods, and within this project, it is anticipated to perform phenotyping with the population pharmacokinetic approach.

Keywords: Pharmacokinetics, Population Pharmacokinetics, Psychiatric Drugs, Statistical Analysis, Therapeutic Drug Monitoring.

Introduction

Therapeutic drug monitoring (TDM) is a method that allows clinicians to maintain patients' drug plasma concentrations in the target range through individual dose adjustment[2]. These methods accelerate the recovery of many patients and reduce medical costs[10]. TDM can be particularly beneficial for children and adolescents in the psychiatry and neurology patient group, pregnant women, the elderly, those with substance use disorders, forensic psychiatry patients, and patients with known or suspected abnormal pharmacokinetic curves[10].

Pharmacokinetics is a method expressed for the evaluation of processes such as absorption, distribution, metabolism and excretion (ADME) of compounds (such as drugs, medicinal biological substances and new chemical entities (NCE)) taken from the blood-plasma concentration of the individual[5, 9]. It is evaluated depending on the time course of concentration. Pharmacokinetics is concerned with what the compound does to the body, on the contrary, while pharmacodynamics (PD) is concerned with explaining the processes that the compound is exposed to by the body after ingestion and excretion[1].

In order to explain the pharmacological activity profile of the compounds, the pharmacokinetic analysis is crucial. While a more common pharmacokinetic profile can be obtained especially in adults, it is rarer to have a certain profile in children, adolescents or the elderly[3]. Considering the fact that there is a certain gap in the literature on the pediatric population, in vivo pharmacokinetic models support appropriate dose and administration functions in order to identify the main metabolites and to have more information about human metabolism[1]. Pharmacokinetics enables the predictions about the absorption, distribution, metabolism and excretion of the compound *in silico*.

Population pharmacokinetics is used in drug studies to make adjustments by including all

How to cite this article: Cakır E. An Extensive Therapeutical Drug Monitoring Repository for Localized Population Pharmacokinetics Research. J Neurobehav Sci 2024; 11: 93-108.

Ethics committee approval: The local ethical approval was obtained from Üsküdar University Non-interventional Research Ethics Board (23.2.2023, 61351432/Feb 2023-20).

Received: 22.10.23
Revised: 18.01.24
Accepted: 04.08.24
Published: 31.12.24

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Access this article online

Website: https://dergipark.org.tr/tr/pub/jnbs/issue/89057/1608197

DOI: 10.32739/jnbs.11.1608197

Quick Response Code:

the features in the body, from organ functions to genetic changes, in order to determine the dose adjustment, dose scaling and correct dose rate for the individual in the population[16]. It is also an approach to make sense of the relationship between pharmacokinetics and pharmacodynamics. Because, as in drug development, the PK-PD relationship has a very important place in population pharmacokinetic studies[17]. The distribution of drug use in the population includes the estimation approaches to be made over this distribution.

Based on the pharmacokinetic method, it evaluates the differences in the processes of absorption, distribution, metabolism and excretion of the drug, which correspond to mathematical values between individuals[4]. It is expected that clinicians will adjust the dose by considering these differences. Pharmacokinetic studies are usually conducted by volunteers or selected by clinicians. However, this study design does not provide an accurate sample of population pharmacokinetic studies. While the most common limitation in population pharmacokinetic studies is the interindividual variability, the study conducted by volunteers or selected individuals prevents the limitation of this diversity[4]. Preventing this restriction is seen as a problem since an accurate population model will not be established.

In addition to demographic variables, measurable pathophysiological variables cause significant differences in therapeutic ranges, which may require re-adjustment of the dose to be administered to the individual[15]. Evaluation of all patients on the same parameters, regardless of environmental or pathophysiological variables in the patient, may lead to deviation from accurate estimates for pharmacokinetic characterization in the relevant population[9].

Population pharmacokinetics are widely used in drug development for precise dose adjustment through therapeutic drug monitoring[8, 9]. While the dose-concentration relationship is an important factor for drug dosing, interactions with other drugs used by the individual have a critical importance in the development of personalized treatments. Population approaches provide a useful basis for observing these effects. The drug metabolizing status that differs between individuals and TDM practice, which plays an important role in determining the therapeutic range of drugs, constitutes one of the basic building blocks of personalized treatment approach.

MATERIALS AND METHODS

The repository construction included the patient data, who received treatment and drug/metabolite blood plasma level tests at NPİSTANBUL Brain Hospital between 2010-2022. The local ethical approval was obtained from Üsküdar University Non-interventional Research Ethics Board (23.2.2023, 61351432/Feb 2023-20).

All patient information was stored in the local database, BİLMED, and the tests were performed in Medical Biochemistry Laboratory, Üsküdar University. The patient identity was hidden in the repository and only the ID number assigned to every patient in the system was included. The raw data included 26,324 patients (8963 inpatients, 20936 outpatients) and 174,387 total entries. Only a portion of the data included repeated entries per patient. Among these, 60.3% of entries belong to inpatients (n=105,194) and 39.7% to outpatients (n=69,193). The tests in the raw data included vitamin D (25-OH(D2+D3)) tests and genotypic profiling, which were omitted in the scope of this study.

The repository organization and descriptive statistical analysis was performed on Python-based protocols. The raw patient data was extracted from the system over 16 different parameters as follows. The descriptive analysis focused only on the Patient ID, Sex, Age, Admission and Test.

- **Patient ID [numerical] :** Unique ID number assigned by the system for every patient.
- **Sex [categorical] :** Sex of the patient. (Female (F), Male (M))
- **Age [numerical] :** Age of patient at the day of test
- **Date [date] :** Date of test
- **Admission [categorical]:** Admission at the day of test (Inpatient, Outpatient)
- **Height [numerical]:** Height of patient further organized in two options as in “m” and in “cm”.
- **Weight [numerical]:** Weight of patient at the day of test in “kg”.
- **Test [categorical] :** The name of the test (usually in the form of “drug” or “drug + metabolite”)
- **Doctor [categorical] :** The name surname of the doctor who entered the patient information.
- **Sample # [numerical] :** The unique ID for each test.
- **Test Result [numerical]:** The test results in the system in the form of “drug + metabolite” in the raw data is further organized into seperate entries as “drug” and “metabolite”.
- **DMIN - DMAX [numerical]:** The reference test result intervals in “ng/ml”.
- **Dose [numerical] :** The drug dose prescribed at the day of test, usually in mg/day.
- **Interaction [categorical] :** Other drugs that are prescribed simultaneously to the patient at the day of test
- **Diagnosis [categorical] :** The diagnosis of the patient at the day of test

RESULTS

The NPİstanbul Brain Hospital TDM database (2010-2022) contains drug/metabolite plasma level tests for 74 drugs and for vitamin D. The drugs organized in the repository grouped by their respective classes is given in Table 1. Genotypic profiling of Cyp1a2 (n=28), Cyp2d6 (n=30) and Cyp3a4 (n=27) enzymes were performed for a smaller portion of the patients in the database.

The drugs with the respective number of patients tested is given in Table 2. The drugs that were tested with the highest number of patients are risperidone (n=5397), olanzapine (n=4967) and valproic acid (n=4046). Further test profiles were obtained by the distribution over age, sex and admission. Among the inpatients, olanzapine (n=3749), risperidone (n=3630), quetiapine(n=2542), valproic acid (n=2039) and aripiprazole (n=1906) was the most commonly tested drugs. Aripiprazole was also the most commonly tested drug for outpatients (n=2598), followed by fluox-

Table 1: Drugs in NPİstanbul Brain Hospital TDM Database. The classes/types of drugs together with metabolizing enzymes and inhibited/induced enzymes are given. AKR: Aldo-keto reductase; CR: Carbonyl reductase; CYP: Human cytochrome P450 (CYP) enzymes; FMO: flavin monooxygenase; UGT: UDP-glucuronosyltransferase. (Hiemke ve ark., 2017)

Drugs	Class / Type	Metabolizing Enzymes	Inhibited enzymes	Inducer enzymes
Alprazolam	Anxiolytic	CYP3A4/5		
Amisulpride	Antipsychotic	More than 90% is excreted unchanged via the kidney		
Amitriptyline	Antidepressant	CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A3, UGT1A4, UGT2B10		
Aripiprazole	Antipsychotic	CYP2D6, CYP3A4		
Atomoxetine	Drug for ADHD	CYP2C19, CYP2D6		
Biperiden	Antiparkinson	Unknown		
Bupropion	Antidepressant	CYP2C19, CYP2B6, CR	CYP2D6	
Carbamazepine	Anticonvulsant	CYP1A2, CYP2C8, CYP3A4/5, UGT2B7, epoxide hydrolase		CYP1A2, CYP2B6, CYP2C9, CYP3A4, UGT
Citalopram	Antidepressant	CYP2C19, CYP2D6, CYP3A4		
Chlorpromazine	Antipsychotic	CYP1A2, CYP2D6		
Clomipramine	Antidepressant	CYP1A2, CYP2C19, CYP2D6, CYP3A4, UGT2B10		
Clonazepam	Anxiolytic	CYP3A4		
Clozapine	Antipsychotic	CYP1A2, CYP2C19, CYP3A4		
Diazepam	Anxiolytic	CYP2B6, CYP2C19, CYP3A4, UGT2B7		
Disulfiram	Substance-related disorders	CYP1A2, CYP2A6, CYP2B6, CYP2E1, CYP3A4	CYP2E1	
Donepezil	Antidementia	CYP2D6, CYP3A4		
Duloxetine	Antidepressant	CYP1A2, CYP2D6	CYP2D6	
Escitalopram	Antidepressant	CYP2C19, CYP2D6, CYP3A4		
Fluoxetine	Antidepressant	CYP2B6, CYP2C9, CYP2C19, CYP2D6	CYP2D6, CYP2C19, CYP3A4	
Flupenthixol	Antipsychotic	CYP2D6		
Fluvoxamine	Antidepressant	CYP2D6, CYP1A2	CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4	
Gabapentin	Anticonvulsant	Not metabolized, renal excretion		
Haloperidol	Antipsychotic	CYP2D6, CYP3A4, AKR, UGT		
Lamotrigine	Anticonvulsant	UGT1A4, UGT3B7		UGT
Levetiracetam	Anticonvulsant	Not metabolized		
Lithium	Mood stabilizer	Renal clearance		

Lorazepam	Anxiolytic	UGT2B15		
Memantine	Antidementia	Scarcely metabolized		
Methylphenidate	ADHD medication	Carboxylesterase 1		
Mirtazapine	Antidepressant	CYP3A4, CYP1A2, CYP2D6		
Modafinil	ADHD medication	Amide hydrolase, CYP3A4		CYP1A2, CYP2B6, CYP3A4
Naltrexone	Substance-related disorders	AKR1C4		
Olanzapine	Antipsychotic	UGT1A4, UGT2B10, FMO, CYP1A2, CYP2D6		
Oxcarbazepine	Anticonvulsant	AKR, UGT2B15		
Paroxetine	Antidepressant	CYP2D6, CYP3A4	CYP2D6	
Pimozide	Antipsychotic	CYP1A2, CYP2D6, CYP3A4		
Piracetam				
Pregabaline	Anxiolytic	Not metabolized, renal excretion		
Quetiapine	Antipsychotic	CYP3A4, CYP2D6		
Reboxetine	Antidepressant	CYP3A4		
Risperidone	Antipsychotic	CYP2D6, CYP3A4		
Sertraline	Antidepressant	CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, UGT1A1		
Sulpiride	Antipsychotic	Not metabolized, renal excretion		
Topiramate	Anticonvulsant	UGT		
Trazadone	Antidepressant	CYP3A4, CYP2D6		
Trifluoperazine		UGT1A4		
Valproic Acid	Anticonvulsant	UGT1A3, UGT1A6, UGT2B7, CYP2A6, CYP2B6, CYP2C9, CYP219		
Venlafaxine	Antidepressant	CYP2C19, CYP2D6, CYP2C9, CYP3A4		
Vit D2 + D3	Vitamin D	CYP27A1, CYP2R1, CYP27B1, CYP24A1		
Vortioxetine	Antidepressant	CYP2D6, CYP3A4, CYP2A6, CYP2C		
Ziprasidone	Antipsychotic	CYP3A4		
Zuclopenthixol	Antipsychotic	CYP2D6		

Table 2. Drug test data available in the database with relevant number of tested patients. The table includes the total number of drugs in the database and the number of patients.

Drug	Number of Patients	Drug	Number of Patients
Risperidone	5397	Alprazolam	433
Olanzapine	4967	Levetiracetam	414
Valproic Acid	4046	Diazepam	355
Aripiprazole	3922	Topiramate	347
Sertraline	3815	Pimozide	301
Quetiapine	3267	Vortioxetine	271
Fluoxetine	2576	Naltrexone	269
Paroxetine	2324	Donepezil	208
Carbamazepine	1832	Memantine	201
Venlafaxine	1824	Piracetam	185
Escitalopram	1764	Amitriptyline	179
Haloperidol	1532	Ziprasidone	157
Oxcarbazepine	1381	Disulfiram	139
Zuclopenthixol	1311	Modafinil	133
Duloxetine	1241	Reboxetine	113
Lithium	1193	Metformin	90
Lamotrigine	1158	Mianserin	81
Methylphenidate	1141	Buspirone	76
Sulpiride	1086	Maprotiline	56
Fluvoxamine	1079	Moclobemide	55
Amisulpride	1030	Lacosamide	46
Gabapentin	957	Rivastigmine	39
Trifluoperazine	879	Acamprosate	34
Clonazepam	847	Buprenorphine	32
Clomipramin	842	Imipramine	29
Mirtazapine	831	Sertindole	21
Biperiden	715	Tianeptine	19
Clozapine	707	Milnacipran	17
Bupropion	691	Fluphenazine	14
Citalopram	675	Agomelatin	11
Chlorpromazine	626	Opipramol	11
Pregabaline	526	Phenobarbital	11
Atomoxetine	502	Zolpidem	7
Lorazepam	501	Pramipexole	2
Flupentixol	459	Dextromethorphan	1
Trazadone	453	Norbuprenorphine	1

Table 3. Drug tests available in the database grouped over admission and sex with respective number of tested patients. Distribution of the drug service received by the patients on the population according to the way of admission and gender, as the patients are subject to more than one drug use. M = male, F= female.

INPATIENT			OUTPATIENT		
TEST	SEX	#PATIENTS	TEST	SEX	#PATIENTS
Acamprosate	M	23	Acamprosate	M	5
	F	5		F	1
Agomelatin	M	1	Agomelatin	M	2
	F	5		F	3
Alprazolam	M	148	Alprazolam	M	77
	F	166		F	66
Amisulpride	M	420	Amisulpride	M	313
	F	275		F	173
Amitriptyline	M	39	Amitriptyline	M	44
	F	55		F	60
Aripiprazole	M	993	Aripiprazole	M	1442
	F	913		F	1156
Atomoxetine	M	127	Atomoxetine	M	284
	F	13		F	91
Biperiden	M	316	Biperiden	M	115
	F	291		F	44
Buprenorphine	M	26	Buprenorphine	M	5
	F	1		F	1
Bupropion	M	163	Bupropion	M	211
	F	103		F	255
Buspirone	M	22	Buspirone	M	18
	F	10		F	27
Carbamazepine	M	449	Carbamazepine	M	549
	F	511		F	552
Chlorpromazine	M	318	Chlorpromazine	M	80
	F	218		F	52
Citalopram	M	143	Citalopram	M	208
	F	99		F	254
Clomipramin	M	123	Clomipramin	M	369
	F	96		F	316
Clonazepam	M	349	Clonazepam	M	96
	F	346		F	86
Clozapine	M	297	Clozapine	M	303
	F	112		F	158
Dextromethorphan	M	1	Diazepam	M	36
				F	20
Diazepam	M	211	Disulfiram	M	70
	F	105		F	11
Disulfiram	M	71	Donepezil	M	37
	F	14		F	56
Donepezil	M	69	Duloxetine	M	423
	F	63		F	642

Duloxetine	M	97	Escitalopram	M	608
	F	141		F	675
Escitalopram	M	242	Fluoxetine	M	858
	F	330		F	1049
Fluoxetine	M	459	Flupentixol	M	100
	F	401		F	78
Flupentixol	M	203	Fluphenazine	M	3
	F	153		F	4
Fluphenazine	M	7	Fluvoxamine	M	450
	F	1		F	368
Fluvoxamine	M	238	Gabapentin	M	177
	F	181		F	206
Gabapentin	M	334	Haloperidol	M	223
	F	346		F	117
Haloperidol	M	853	Imipramine	M	12
	F	513		F	9
Imipramine	M	4	Lacosamide	M	28
	F	4		F	13
Lacosamide	M	6	Lamotrigine	M	276
	F	3		F	536
Lamotrigine	M	146	Levetiracetam	M	183
	F	346		F	160
Levetiracetam	M	49	Lithium	M	478
	F	41		F	408
Lithium	M	283	Lorazepam	M	34
	F	257		F	15
Lorazepam	M	201	Maprotiline	M	13
	F	261		F	26
Maprotiline	M	10	Memantine	M	39
	F	10		F	45
Memantine	M	78	Metformin	M	36
	F	61		F	34
Metformin	M	7	Methylphenidate	M	764
	F	14		F	268
Methylphenidate	M	89	Mianserin	M	18
	F	34		F	21
Mianserin	M	22	Milnacipran	M	3
	F	24		F	4
Milnacipran	M	10	Mirtazapine	M	162
				F	148
Mirtazapine	M	407	Moclobemide	M	32
	F	151		F	13
Moclobemide	M	9	Modafinil	M	47
	F	5		F	32
Modafinil	M	34	Naltrexone	M	44
	F	28		F	5
Naltrexone	M	210	Norbuprenorphine	M	1
	F	30			
Olanzapine	M	2254	Olanzapine	M	1136
	F	1495		F	732
Opipramol	M	2	Olanzapine	M	1136
	F	5		F	732
Oxcarbazepine	M	386	Opipramol	M	1
	F	452		F	3
Paroxetine	M	462	Oxcarbazepine	M	333
	F	334		F	358

Phenobarbital	M	2	Paroxetine	M	824
	F	3		F	902
Pimozide	M	81	Phenobarbital	M	3
	F	141		F	3
Piracetam	M	74	Pimozide	M	59
	F	104		F	56
Pramipexole	M	1	Piracetam	M	2
				F	6
Pregabaline	M	159	Pramipexole	F	1
	F	98			
Quetiapine	M	1533	Pregabaline	M	140
	F	1009		F	184
Reboxetine	M	23	Quetiapine	M	548
	F	19		F	488
Risperidone	M	2465	Reboxetine	M	36
	F	1165		F	51
Rivastigmine	M	12	Risperidone	M	1801
	F	8		F	788
Sertindole	M	1	Rivastigmine	M	9
	F	3		F	11
Sertraline	M	804	Sertindole	M	8
	F	548		F	9
Sulpiride	M	228	Sertraline	M	1260
	F	203		F	1477
Tianeptine	M	8	Sulpiride	M	431
	F	5		F	308
Topiramate	M	43	Tianeptine	M	4
	F	125		F	6
Trazadone	M	104	Topiramate	M	54
	F	125		F	160
Trifluoperazine	M	162	Trazadone	M	90
	F	476		F	152
Valproic Acid	M	1278	Trifluoperazine	M	137
	F	761		F	177
Venlafaxine	M	316	Valproic Acid	M	1721
	F	257		F	1129
Vortioxetine	M	38	Venlafaxine	M	622
	F	20		F	743
Ziprasidone	M	37	Vortioxetine	M	109
	F	53		F	116
Zolpidem	M	3	Ziprasidone	M	36
	F	2		F	57
Zuclopenthixol	M	794	Zolpidem	M	1
	F	322		F	1
			Zuclopenthixol	M	287
				F	131

Table 4: Median and MAD for age of patients per drugs. The median and MAD of age distribution per drug for female and male patients. The drugs with more than 50 patient data were included.

	FEMALE		MALE	
TEST	MEDIAN	MAD	MEDIAN	MAD
Alprazolam	48	15	44	15
Amisulpride	41,5	15	41	16
Amitriptyline	49,5	12,5	36,5	12,5
Aripiprazole	41,5	18,5	40	19
Atomoxetine	17	5	25,5	11
Biperiden	40	13	37	13
Bupropion	44,5	15	42,5	14,5
Carbamazepine	42	19	42	19
Chlorpromazine	42,5	15	39,5	13,5
Citalopram	50	20	44,5	17,5
Clomipramin	41	17	39,5	14,5
Clonazepam	45	18	44,5	18
Clozapine	49	18	42,5	16
Diazepam	43,5	14	43,5	14
Disulfiram	40	7	38,5	10
Donepezil	67,5	11,5	65	11
Duloxetine	49,5	17,5	45	14
Escitalopram	49	20	45,5	20
Fluoxetine	43	19	39,5	17
Flupentixol	37,5	12,5	37,5	12,5
Fluvoxamine	43,5	15,5	39,5	15,5
Gabapentin	46,5	18	43	15
Haloperidol	46,5	20,5	44,5	19,5
Lamotrigine	45	17	40,5	16
Levetiracetam	41,5	18	41,5	17,5
Lithium	43,5	15,5	44,5	16
Lorazepam	45,5	17	39,5	13
Memantine	70	10	65	13
Methylphenidate	26,5	11,5	29,5	12,5
Mirtazapine	49	18	46,5	17
Modafinil	43	12	35	13
Naltrexone	34	10	40	11
Olanzapine	47,5	21	47	21
Oxcarbazepine	40,5	17,5	37,5	17
Paroxetine	48	19	47	18
Pimozide	38,5	13	32,5	9
Piracetam	38	14	32	11
Pregabaline	49,5	16	44	14
Quetiapine	49	20	47	20
Reboxetine	45	12	37,5	11,5
Risperidone	41,5	19,5	43	21
Sertraline	48	21	46,5	20,5
Sulpiride	46,5	17,5	42,5	17
Topiramate	37,5	14	32,5	11,5
Trazadone	46	17	45,5	16
Trifluoperazine	44,5	17,5	39	13
Valproic Acid	41,5	20	43,5	20,5
Venlafaxine	46	17	47	17
Vortioxetine	44	13	42,5	13
Ziprasidone	36	11	34	9
Zuclopenthixol	39	15	38	14

Table 5 : Genotypic profiling of Cyp enzymes in the database per drugs.

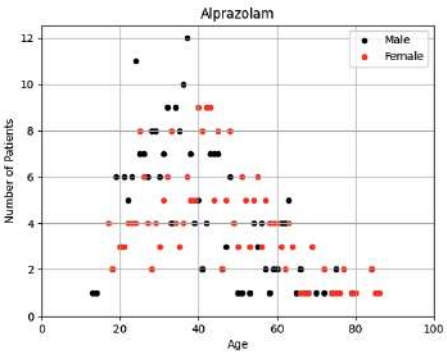
Drug	CYP1A2	CYP2D6	CYP3A4
Alprazolam	3	3	3
Amisulpride	7	7	8
Amitriptyline	3	2	2
Aripiprazole	14	17	17
Biperiden	4	4	4
Bupropion	4	4	2
Carbamazepine	6	7	6
Chlorpromazine	4	1	4
Citalopram	2	2	1
Clomipramin	3	4	2
Clonazepam	4	4	4
Clozapine	8	7	4
Diazepam	4	4	4
Disulfiram	0	1	1
Duloxetine	4	4	3
Escitalopram	5	5	5
Fluoxetine	7	8	7
Flupentixol	2	3	2
Fluvoxamine	9	10	10
Gabapentin	5	5	4
Haloperidol	7	7	6
Lamotrigine	4	3	1
Lithium	9	8	8
Lorazepam	4	4	4
Maprotiline	0	1	1
Metformin	1	1	1
Methylphenidate	2	4	3
Mianserin	1	1	0
Mirtazapine	3	2	2
Moclobemide	1	1	1
Modafinil	2	2	2
Naltrexone	1	1	1
Olanzapine	16	18	16
Oxcarbazepine	3	3	3
Paroxetine	4	5	5
Pimozide	1	0	1
Piracetam	1	0	1
Pregabaline	2	2	2
Quetiapine	13	16	16
Reboxetine	3	3	2
Risperidone	16	18	14
Sertraline	9	7	8
Sulpiride	1	2	2
Tianeptine	1	1	0
Topiramate	1	1	0
Trazadone	2	2	3
Trifluoperazine	1	1	0
Valproic Acid	14	16	16
Venlafaxine	6	6	5
Vit D2 + D3	7	6	6
Vortioxetine	2	1	1
Ziprasidone	0	0	1
Zolpidem	1	0	1
Zuclopenthixol	9	7	7

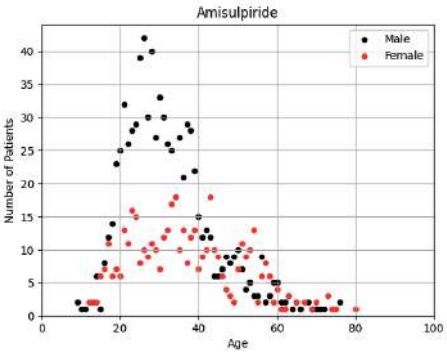
etine (n=1907), olanzapine (n=1868), paroxetine (n=1726) and escitalopram (n=1283). The test profile over the type of admission and sex for each drug is given in Table 3.

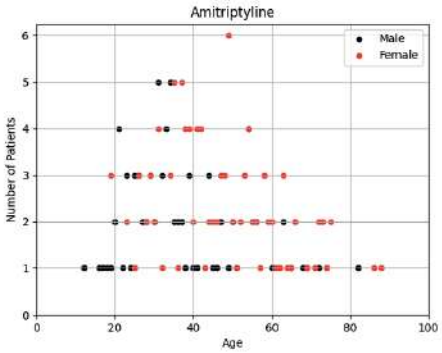
The drug combinations in the repository was evaluated over the the frequency of tests carried on the same patient. The raw combination frequencies were first normalized for each drug by the total number of patients that are tested, and then further normalized over the total sum of frequencies in the combination table. The frequencies are given as percentages in Supplementary Table. The drug pairs that are tested together for the same patient most frequently are risperidone-biperiden (36.4‰), olanzapine-haloperidol (34.3‰), olanzapine-lorazepam (32.5‰), quetiapine-diazepam (32‰), valproic acid-chlorpromazine (31.7‰), risperidone-flupentixol (30.6‰), valproic acid-biperiden (30.6‰), risperidone-disulfiram (30.2‰) and olanzapine-chlorpromazine (30.1‰).

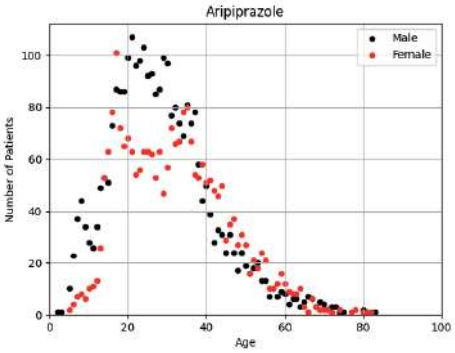
The distribution of genotypic profiling for Cyp1A2, Cyp2D6 and Cyp3A4 over the prescribed drugs at the time of profiling is given in Table 6. Normalization was carried on the same way as described for drug combination frequencies.

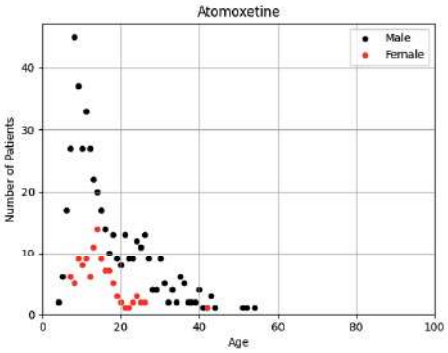
The age profile for each drug is analyzed for the tests with more than 100 patients and was also grouped over sex (Figure 1) and age median for each drug is given in Table 4. The age distribution per drug was similar over sex and there were no statistically significant differences. The age distributions of the drugs are shown alphabetically in Figure 1A, Figure 1B, Figure 1C, Figure 1D, Figure 1E, Figure 1F, Figure 1G, Figure 1H, and Figure 1I. Generally the age distribution was skewed towards 30-40 years interval with heavy-tail distribution for the majority of the tested drugs. However, the distribution was skewed towards younger ages for atomoxetine (Figure 1A) and methylphenidate (Figure 1E), and to older ages for donepezil (Figure 1C) and memantine (Figure 1E). Table 5 presents the genotypic profiling of CYP enzymes in the database per drugs.











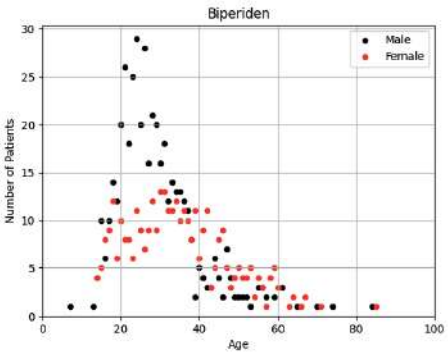
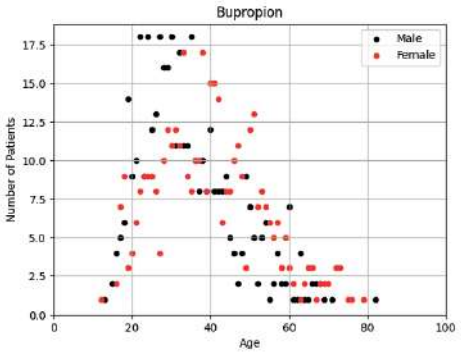
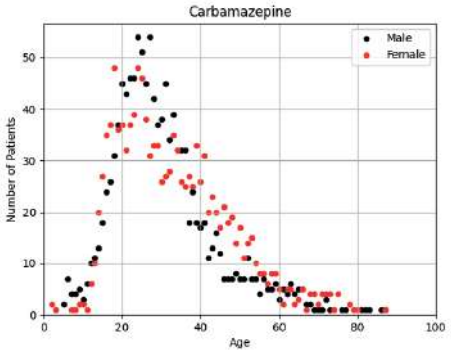
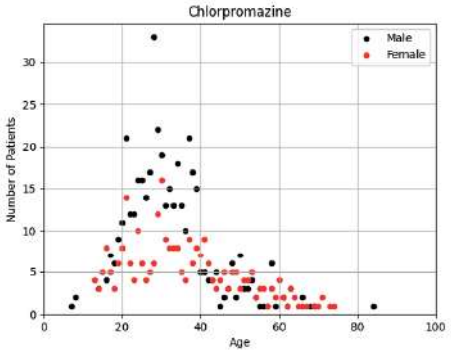
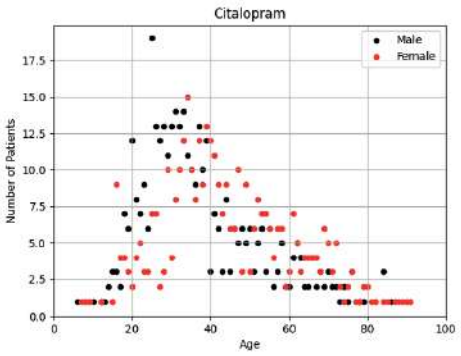


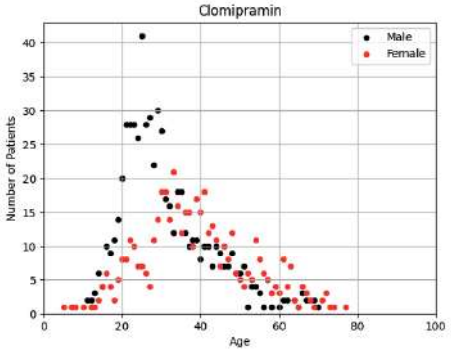
Figure 1.A: Age distribution of alprazolam, amisulpride, amitriptyline, aripiprazole, atomoxetine and biperiden.











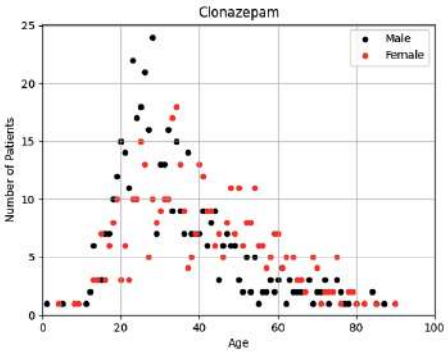
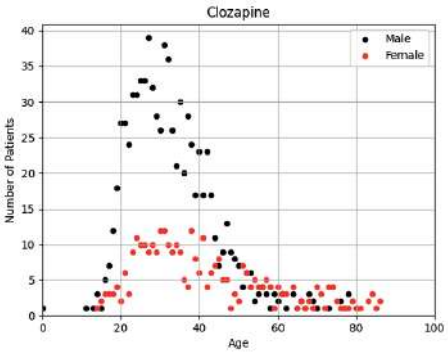
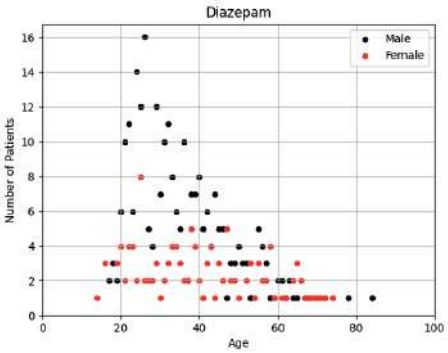
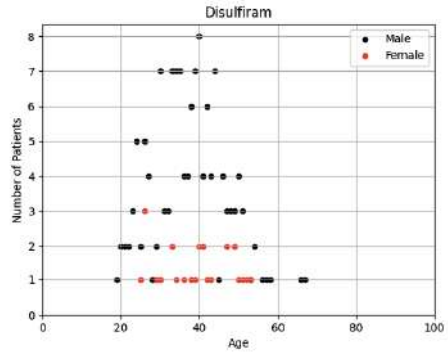
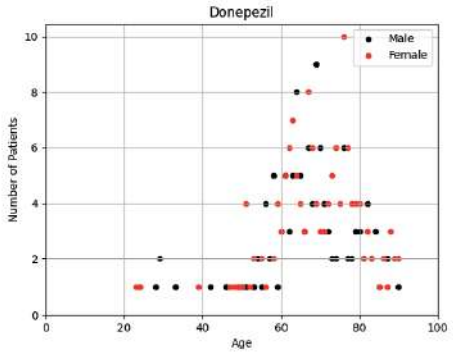


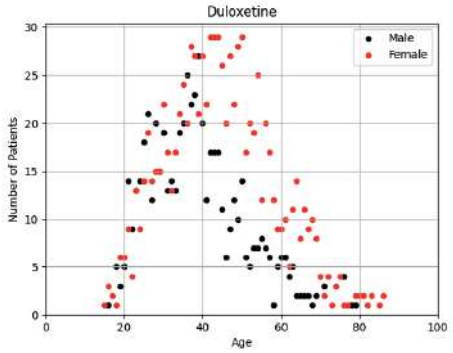
Figure 1.B: Age distribution of bupropion, carbamazepine, chlorpromazine, citalopram, clomipramine and clonazepam.

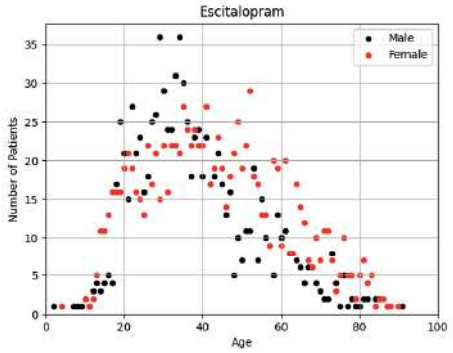


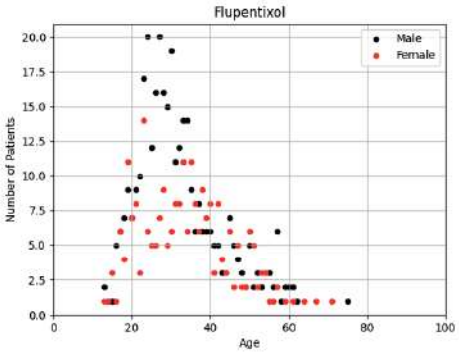


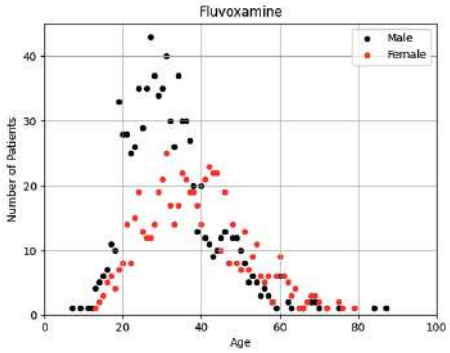












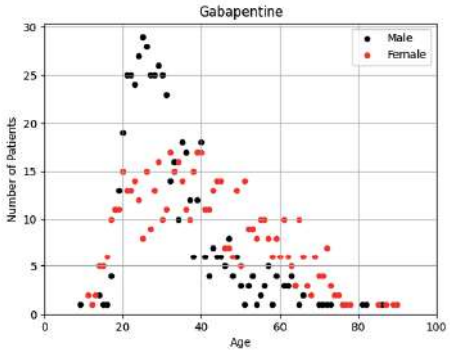
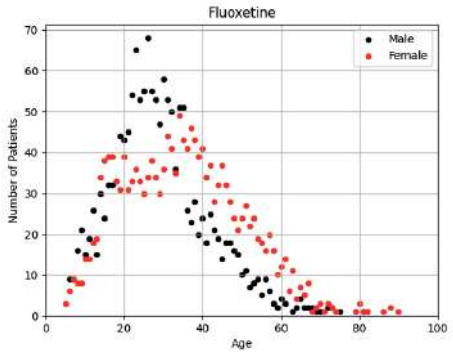
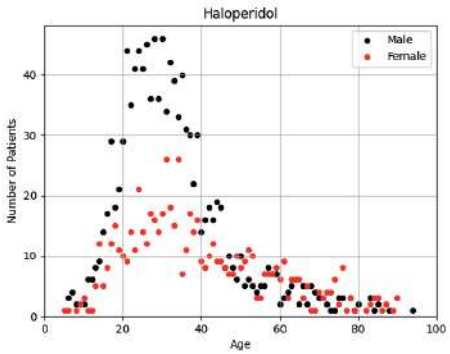


Figure 1.C: Age distribution of clozapine, diazepam, disulfiram, donepezil, duloxetine and escitalopram.





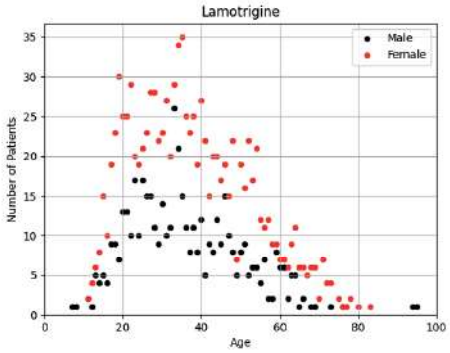
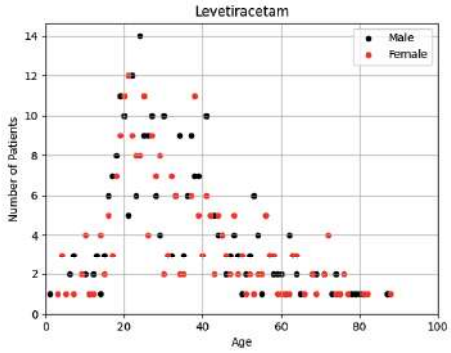
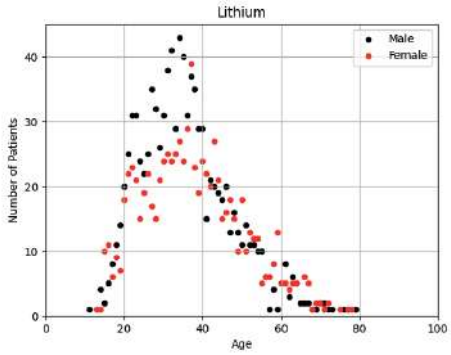
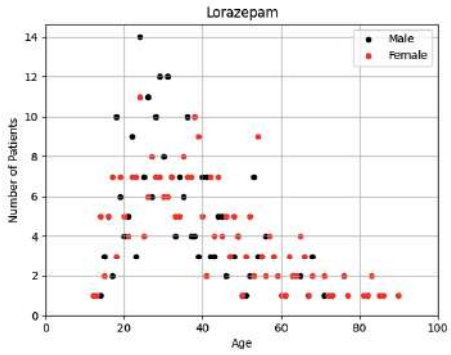
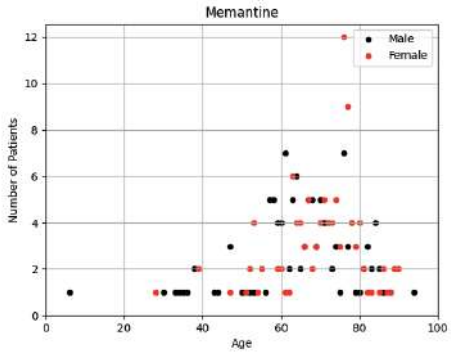


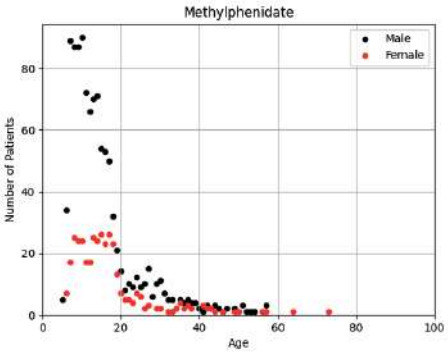
Figure 1.D: Age distribution of fluoxetine, flupentixol, fluvoxamine, gabapentin, haloperidol, lamotrigine.











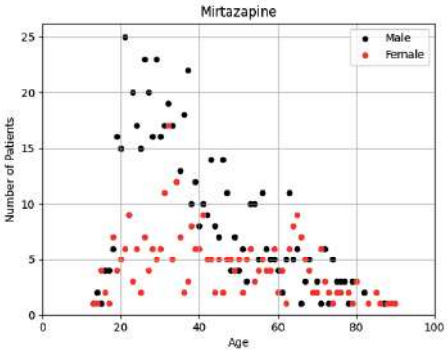
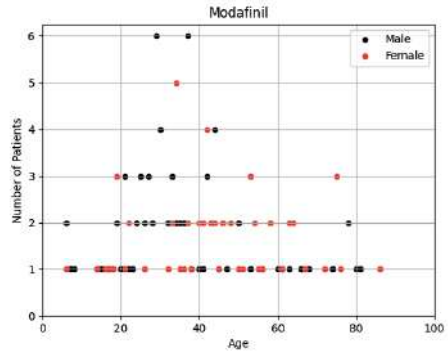
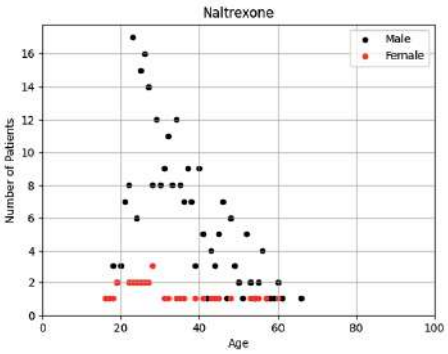


Figure 1.E: Age distribution of levetiracetam, lithium, lorazepam, memantine, methylphenidate and mirtazapine.





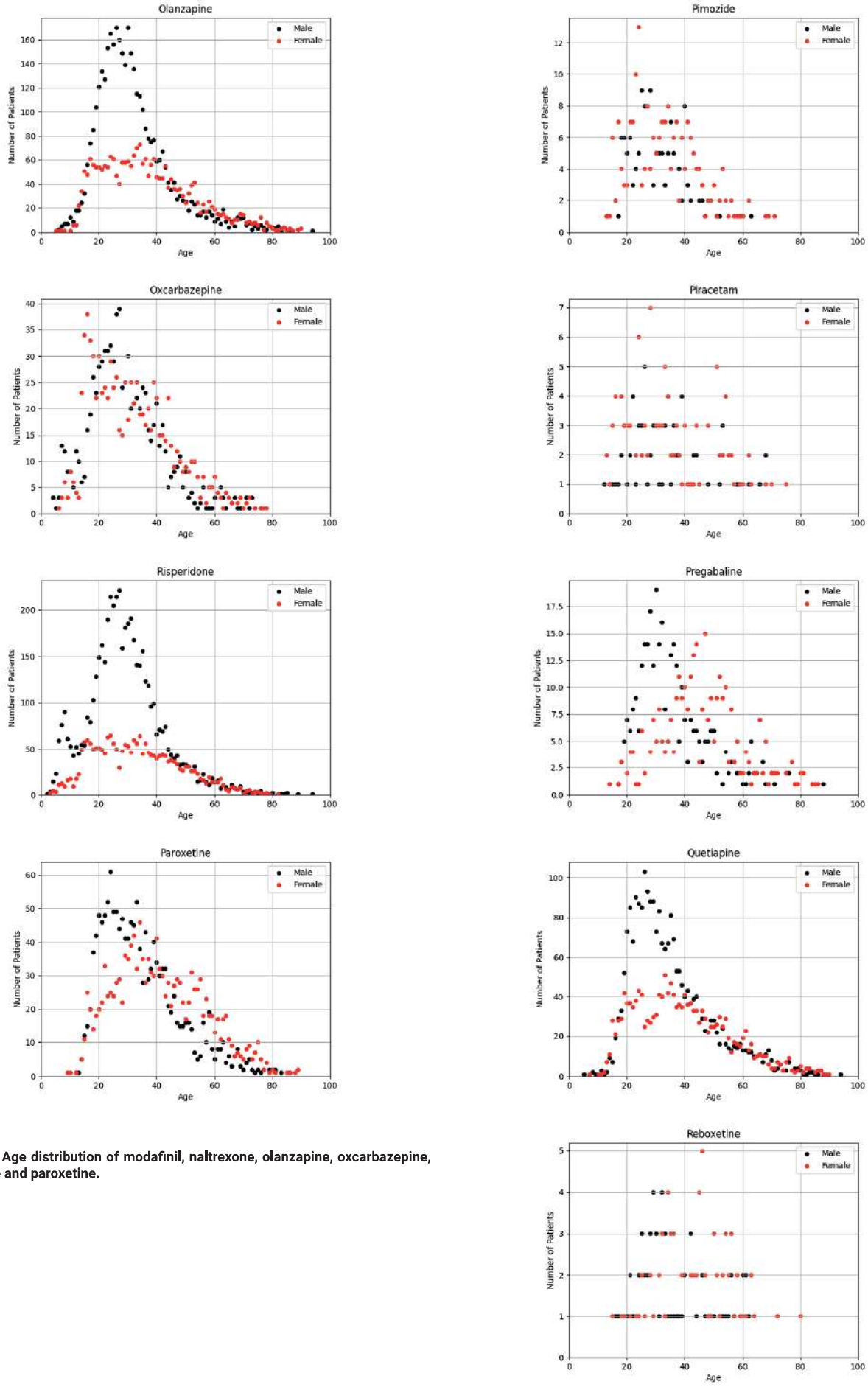


Figure 1.F: Age distribution of modafinil, naltrexone, olanzapine, oxcarbazepine, risperidone and paroxetine.

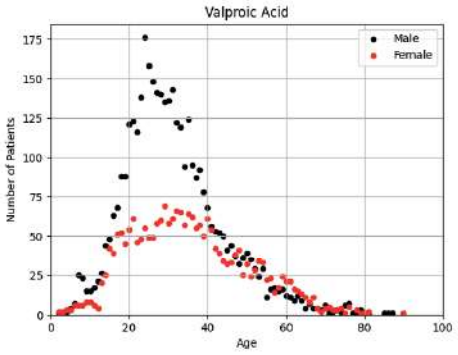
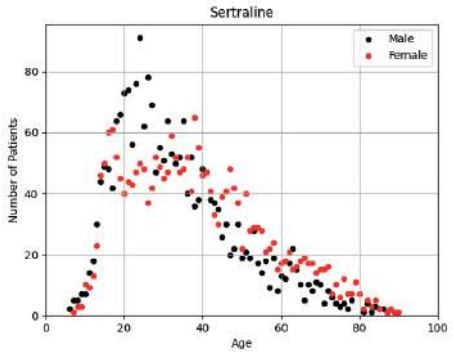
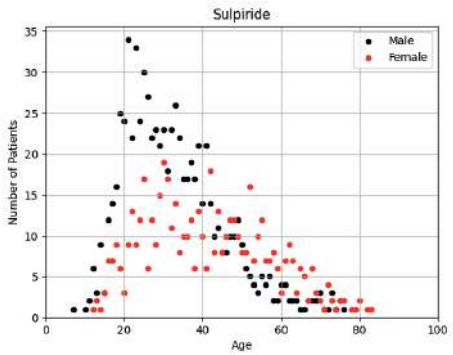
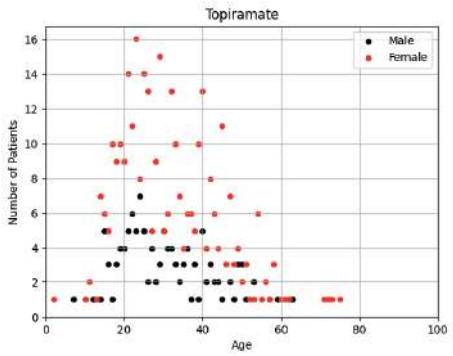
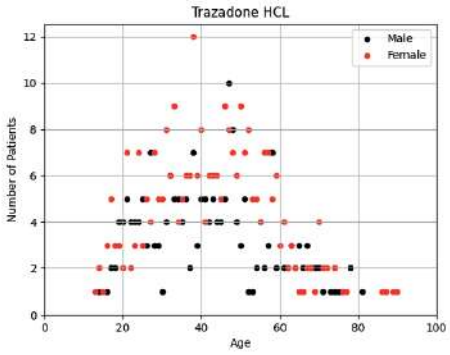


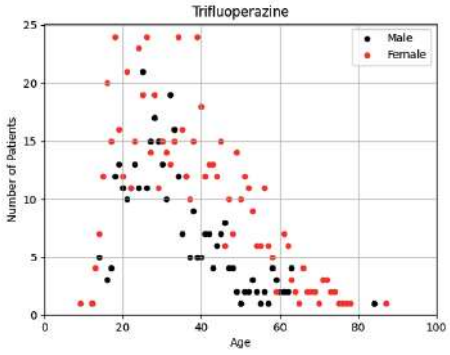
Figure 1.G: Age distribution of pimozide, piracetam, pregabalin, quetiapine, reboxetine and valproic acid.











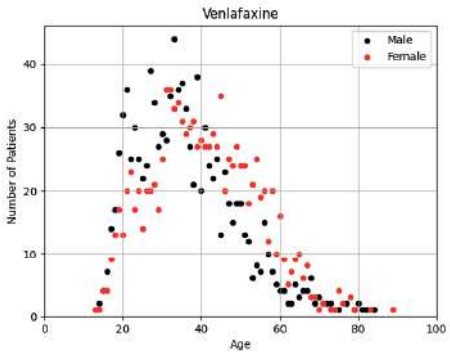
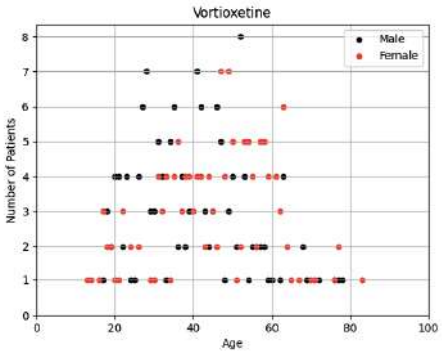


Figure 1.H: Age distribution of sertraline, sulpiride, topiramate, trazodone HCL, trifluoperazine, and venlafaxine.



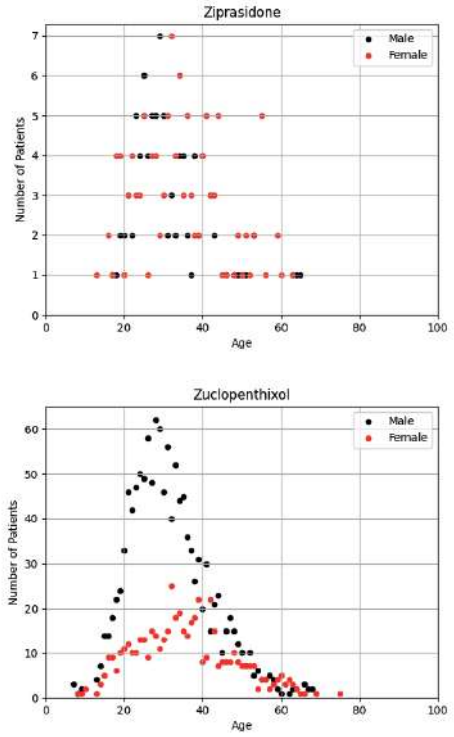


Figure 1.I: Age distribution of vortioxetine, ziprasidone and zuclopenthixol.

DISCUSSION

Population pharmacokinetics in conjunction with TDM enables the progress of personalized medicine. Pharmacokinetics is vital in particular, to demonstrate the demographic, biological, or physiopathological profiles within the population, as individual variability stands as a prominent factor within personalized medicine.

Establishing well-structured data repositories that can reflect and combine patient variability is an essential first step for detail pharmacokinetic analysis in a population. The data repository established with this study enables classification over age, sex and diagnosis. Furthermore, the data from inpatients enable continuous analysis of variations within individual over a period of time, that is more trustable due to being monitored by the experts. Therefore, follow-up studies on population pharmacokinetics for each drug can be incorporated with the existing information on multiple drug use, personal history, genetical variations and electrophysiological data. Detailed repositories enable data elimination due to ,e.g., drug interactions but also outcomes of these drug interactions with respect to population, especially when combined with genotypic profiling.

Another important outcome for the follow-up studies from this repository would be establishing the dosing intervals, i.e. supratherapeutical dosing, with respect to age. While it is possible to locate a PK profile, particularly for adults, within the literature, the likelihood of encountering a PK profile for infants and children is quite low when age ranges are categorized as infants, children, adolescents, adults, and elderly patients. Particularly, the illnesses that manifest during childhood, the drugs administered, or the treatment modalities employed in line with the diagnoses have a lasting impact on an individual's future life. It should also be noted that some drugs might interfere with early neurodevelopmental processes when administered at younger ages, which requires close and careful monitoring to maintain therapeutic levels during childhood. The absence of PK profiles for commonly used drugs in children can potentially lead to neurodevelopmental complications. The inclusion of a pediatric therapeutic range in metabolizer phenotyping would be advantageous for pediatric personalized medicine. In this regard, addressing the literature gap regarding pediatric therapeutic ranges in TDM studies is crucial. This effort can help mitigate the risk of neurodevelopmental disorders resulting from drug use in children. The determination of the supratherapeutic range is of great significance, just as the identification of the therapeutic range within the population is crucial. Overdose exposure in poor metabolizers can lead to various complications or even reach critical levels. Hence, the possibility of an individual's demise is one of the potential scenarios.

Through the repository established in this study, the goal is to elucidate the repository's purpose, allowing patients to access the correct treatment and focus on the objectives of personalized medicine. The repository encompasses various drugs and distinct diagnostic groups. In the TDM-specific treatment process for individuals, there exists a substantial gap in local studies. The aim is to extend the phenotyping study to encompass a larger population in our country in collaboration with the repository maintained by NPİSTANBUL Brain Hospital to enable better and more personalized therapeutical interventions.

FUTURE PERSPECTIVE

The need for a foundation created by genotypic analyses arises in the presence of multiple enzyme contents in drug metabolism. The genotyping conducted in Table 5 serves as an example for prospective studies. It is believed that there should be an intensification of interest in genotyping studies to obtain outputs from metabolic analyses. It is anticipated that enhancing the genetic analysis infrastructure in the design of studies for further development and progression of this research will be beneficial. Extracting individual genetic panels of patients is considered a fundamental requirement for focusing on personalized treatment studies. It is suggested that efforts should be directed towards increasing and contributing to the database for the creation of these panels.

Patient informed consent:

Patient informed consent was obtained.

Ethics committee approval:

The local ethical approval was obtained from Üsküdar University Non-interventional Research Ethics Board (23.2.2023, 61351432/Feb 2023-20).

Conflict of interest:

There is no conflict of interest to declare.

Financial support and sponsorship:

No funding was received.

Author contribution subject and rate:

Elif Çakır (25%) Data curation, software, investigation, formal analysis, writing – original draft

Pınar Öz (30%) Conceptualization, methodology, software, validation, project administration, writing- review and editing

Murat Özdemir (15%) Conceptualization, resources, supervision

Selma Özilhan (15%) Conceptualization, resources, supervision

Nevzat Tarhan (15%) Conceptualization, supervision, funding acquisition

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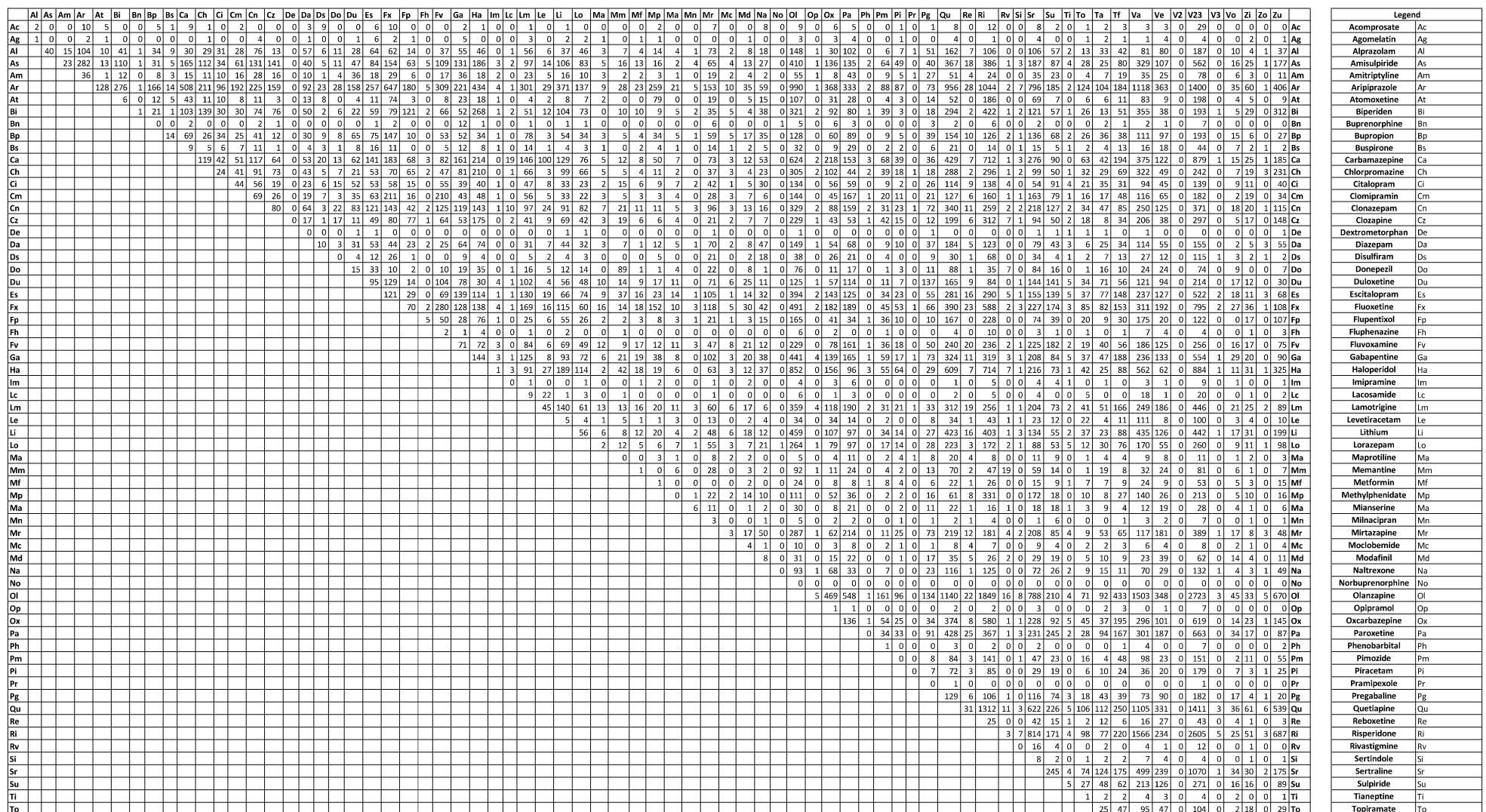

Legend	
Acomprosate	Ac
Agomelatin	Ag
Alprazolam	Al
Amisulpiride	As
Amitriptyline	Am
Aripiprazole	Ar
Atomoxetine	At
Biperiden	Bi
Buprenorphine	Bn
Bupropion	Bp
Buspirone	Bs
Carbamazepine	Ca
Chlorpromazine	Ch
Citalopram	Ci
Clomipramin	Cm
Clonazepam	Cn
Clozapine	Cz
Dextrometorphan	De
Diazepam	Da
Disulfiram	Ds
Donepezil	Do
Duloxetine	Du
Escitalopram	Es
Fluoxetine	Fx
Flupentixol	Fp
Fluphenazine	Fh
Fluvoxamine	Fv
Gabapentine	Ga
Haloperidol	Ha
Imipramine	Im
Lacosamide	Lc
Lamotrigine	Lm
Levetiracetam	Le
Lithium	Li
Lorazepam	Lo
Maprotiline	Ma
Memantine	Mm
Metformin	Mf
Methylphenidate	Mp
Mianserine	Ma
Milnacipran	Mn
Mirtazapine	Mr
Moclobemide	Mc
Modafinil	Md
Naltrexone	Na
Norbuprenorphine	No
Olanzapine	Ol
Opipramol	Op
Oxcarbazepine	Ox
Paroxetine	Pa
Phenobarbital	Ph
Pimozide	Pm
Piracetam	Pi
Pramipexole	Pr
Pregabaline	Pg
Quetiapine	Qu
Reboxetine	Re
Risperidone	Ri
Rivastigmine	Rv
Sertindole	Si
Sertraline	Sr
Sulpiride	Su
Tianeptine	Ti
Topiramate	To
Trazadone	Ta
Trifluoperazine	Tf
Valproic Acid	Va
Venlafaxine	Ve
Vit D2	V2
Vit D2 + D3	V23
Vit D3	V3
Vortioxetine	Vo
Ziprasidone	Zi
Zolpidem	Zo
Zuclopenthixol	Zu

Supplementary Table : Normalized frequency of drug combinations in data repository.

Cakır: An Extensive Therapeutical Drug Monitoring Repository for Localized Population Pharmacokinetics Research