Using a pharmacogenetic clinical decision support system to improve psychopharmacotherapy dosing in patients with affective disorders

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Drug Metab Pers Ther. 2020 Sep 1;35(4). doi: 10.1515/dmpt-2019-0033.

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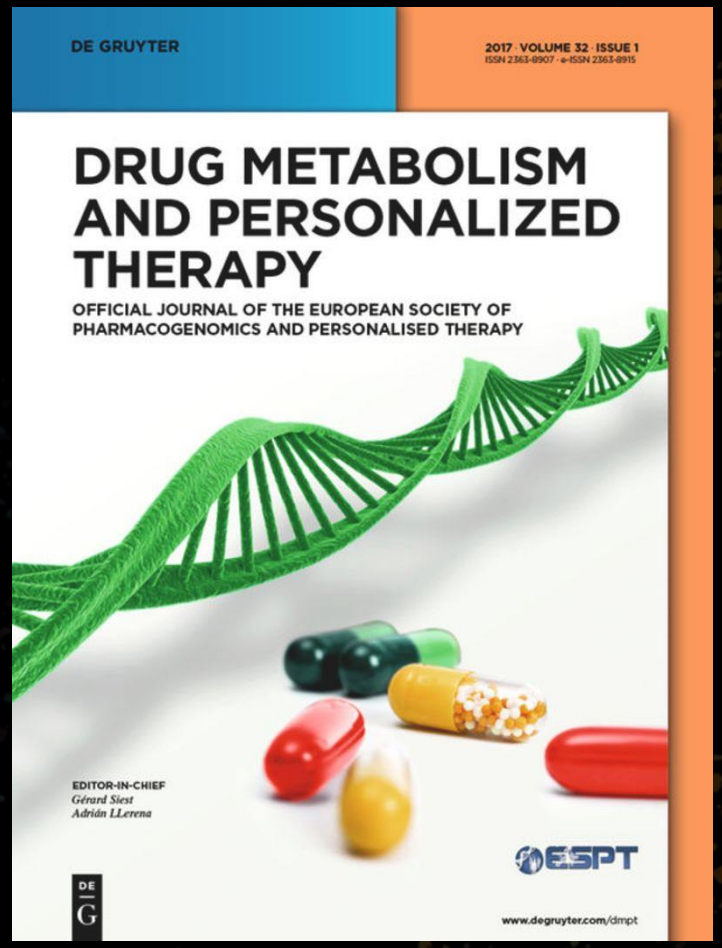
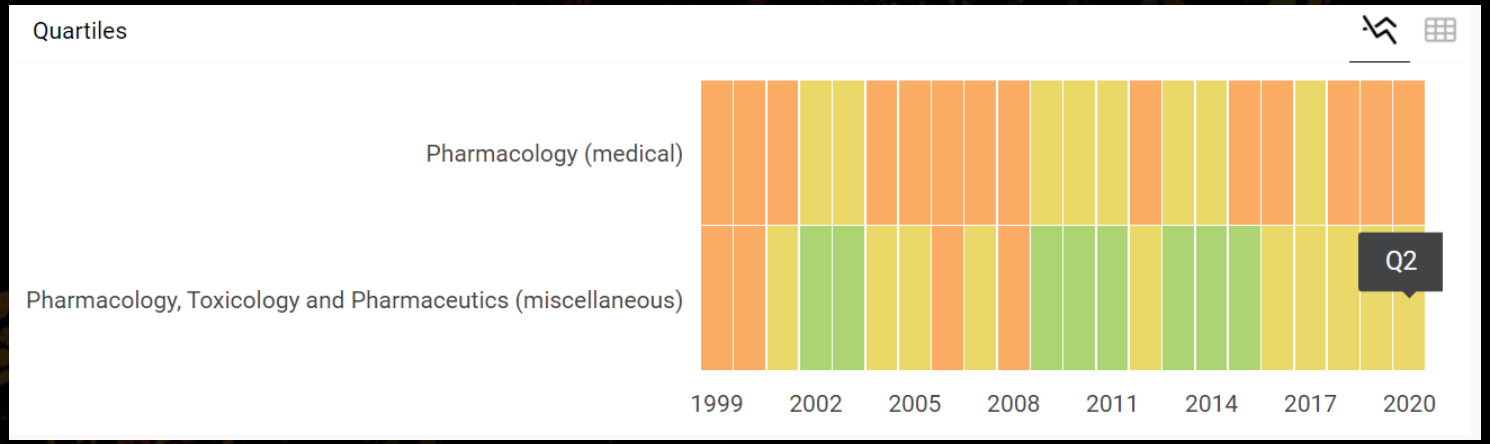


Editor-in-Chief: Adrián Llerena

ISSN: 2363-8915 | Online ISSN: 2363-8915 | 4 Issues Annually

Scopus CiteScore 2020: 2,5

Official journal of the European Society of Pharmacogenomics and Personalised Therapy



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What is pharmacogenetics?

- **Pharmacogenetics** (or pharmacogenomics) is the study of variability in drug response due to genetic factors.
- Pharmacogenetics is an important part of **precision** (or personalized) **medicine**, which aims to tailor medical treatment to each person or to a group of people.
- Data on the polymorphisms of genes implicated in pharmacokinetics and pharmacodynamics of the specific drug is a basis of pharmacogenomic **clinical decision support systems** (CDSSs).

*All pics are taken from «The Chemical Brothers – The Darkness That You Fear" Music Video. Dir. by RUFFMERCY, 2021

Roden DM, McLeod HL, Relling MV, Williams MS, Mensah GA, Peterson JF, Van Driest SL. Pharmacogenomics. Lancet. 2019 Aug 10;394(10197):521-532. doi: 10.1016/S0140-6736(19)31276-0. Epub 2019 Aug 5.

Why do we need CDSSs?

- **30-50%** of patients with depression do not respond to the first course of antidepressant treatment.
- It can take **several months** (even years) of clinical **trial and error** before an effective tolerable antidepressant and its dosage are found for an individual patient.
- During this time patients **remain exposed** to the handicapping effects of their symptoms.
- If affordable practical treatment biomarkers of sufficient effect size emerged, some of the trial and error in antidepressant prescribing **could be eliminated.**

Singh AB. Improved Antidepressant Remission in Major Depression via a Pharmacokinetic Pathway Polygene Pharmacogenetic Report. *Clin Psychopharmacol Neurosci*. 2015;13(2):150-156. doi:10.9758/cpn.2015.13.2.150

What genes affect drug response?

Genes affecting **both pharmacokinetics and pharmacodynamics** are associated with drug response. Polymorphisms of genes encoding enzymes involved in drug biotransformation have a direct impact on its blood levels and, therefore, its **efficacy and safety**.

For most psychotropic medications these genes are:

- Genes of cytochrome P450 family isoenzymes:
  - ***CYP2D6***
  - ***CYP3A4***
  - ***CYP3A5***
  - ***CYP2D19***
- ***ABCB1*** (encodes P-glycoprotein which transports a wide variety of substrates across extra- and intracellular membranes).

Allele variants of *CYP* genes are associated with corresponding isoenzyme activity: functional (**extensive** metabolizers), low functional (**intermediate** metabolizers), nonfunctional (**poor** metabolizers) and enhanced (**ultrarapid** metabolizers).

Results of pharmacogenetic tests

- Although pharmacogenetic tests provide the information on a genotype and the predicted phenotype, these tests do not themselves provide **the interpretation of data** for a health practioner.
- There are currently **more than 20** pharmacogenomic CDSSs used in psychiatry.
- Meanwhile, only part of such systems has shown evidence of effectiveness.
- In particular, a double-blind, randomized study showed that patients with depression receiving genetically guided prescribing had a **2.52-fold** greater chance of remission (Singh et al., 2015).
- A prospective double-blind randomized controlled trial of a combinatorial, five gene pharmacogenomic test and interpretive report (GeneSight) showed that patients with depression had **greater than double** the likelihood of response and remission at week 10 (Winner et al., 2013).

Bousman CA, Hopwood M. Commercial pharmacogenetic-based decision-support tools in psychiatry. Lancet Psychiatry. 2016 Jun;3(6):585-90. doi: 10.1016/S2215-0366(16)00017-1. Epub 2016 Apr 25.
Singh AB. Improved Antidepressant Remission in Major Depression via a Pharmacokinetic Pathway Polygene Pharmacogenetic Report. Clin Psychopharmacol Neurosci. 2015;13(2):150-156. doi:10.9758/cpn.2015.13.2.150
Winner JG, Carhart JM, Altar CA, Allen JD, Dechairo BM. A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. Discov Med. 2013 Nov;16(89):219-27.

Aim of the study

- Implementation of the CDSSs capable of forming the recommendations on drug and dose selection according to the results of pharmacogenetic testing **is an actual task.**

- **The aim** was to study the effect of implementing the decision support system to optimize the drug dosage regimen, based on pharmacogenetic biomarkers, on the efficacy and safety of the therapy for patients with affective disorders and comorbid alcohol addiction.

Design

- A **prospective cohort, randomized, double-blind** study.
- Recruitment took place among inpatients of Moscow Research and Practical Center on Addictions.

- Inclusion criteria:
  - a diagnosis of “Major depressive disorder, single episode (**F32.X**)” or “Cyclothymic disorder (**F34.0**)” with comorbid “Alcohol dependence in remission (**F10.21**)”;
  - signed informed consent;
  - treatment with either **fluvoxamine**, **mirtazapine** or **carbamazepine** for at least **16 days**.

- Exclusion criteria:
  - presence of any other mental disorders;
  - presence of severe somatic disorders (except alcoholic hepatitis and toxic encephalopathy);
  - use of any other psychotropic medications in the treatment regimen except fluvoxamine, mirtazapine, or carbamazepine (with the exception of benzodiazepine Phenazepam® [Cayman Chemical, Ann Arbor, MI, USA] administered during the treatment of the alcohol withdrawal syndrome);
  - creatinine clearance values <50 mL/min, creatinine concentration in plasma ≥1.5 mg/dL (133 mmol/L);
  - body weight less than 60 kg or greater than 100 kg;
  - age of 75 years or more.

Genotyping

- Real-time polymerase chain reaction (**RT-PCR**) was used for single-nucleotide polymorphisms (SNP) detection. DNA was extracted from patients' venous blood samples.

- SNP set:
  - CYP2D6*4 (1846G>A, rs3892097)
  - CYP2C19*2 (681G>A, rs4244285)
  - CYP2C19*3 (636G>A, rs4986893)
  - CYP2C19*17 (−806C>T, rs12248560)
  - CYP3A5*3 (6986A>G, rs77646)
  - ABCB1*6 (3435C>T, rs1045642)

All these SNPs are associated with poor metabolic activity.

Interpretation of genetic data

- Pharmacogenetic test results were interpreted using software **PGX2** (www.pgx2.com).
- This software allows creating the report on results of pharmacogenetic testing instantly, with recommendations **understandable to a health practioner**.
- Algorithms for preparing the recommendations were based on systematic reviews and studies of Clinical Pharmacogenetics Implementation Consortium (**CPIC**) the Dutch Pharmacogenetics Working Group (**DPWG**) Guidelines.
- PGX2 was developed by the **authors' scientific team.**
- PGX2 is a **free** software.

Example: in patients carrying homozygous polymorphism 1846G>A of CYP2D6 gene (genotype AA), it was recommended to reduce an initial fluvoxamine and mirtazapine dose by 25–50% from the one intended by the physician according to the clinical presentation of the patient.

Psychometric scales

- To evaluate the efficacy of therapy, several international psychometric scales were used:
  - Penn Alcohol Craving Scale (**PACS**),
  - Clinical Global Impression (**CGI**),
  - Hospital Anxiety and Depression Scale (**HADS**),
  - Hamilton Rating Scale for Depression (**HAM-D**),
  - Beck Depression Inventory (**BDI**).
- The safety profile was evaluated using the UKU Side-Effect Rating Scale (**UKU**).

Statistics

- Statistical analysis was performed using Microsoft **R Open** (Microsoft Corp., Redmond, Washington, USA), a statistical programming language, through Microsoft R Application Network (R version 3.3.2 [2016-10-31]).
- Sample size calculating has been performed using the “pwr” package (a basic library for R). A power analysis showed that **110** patients are sufficient to minimize type 2 errors (<0.2).
- The normality of sample distribution was evaluated using the **Shapiro-Wilk test** and taken into account when choosing a method.
- The differences were considered statistically significant at **$p<0.05$** (power in excess of 80%).
- To compare two independent groups, the **Mann-Whitney U test** or **Students t-test** (with **Welch’s correction** for unequal variances) was used with **Benjamini-Hochberg multiple testing correction**.
- Research data are presented as the median and interquartile range (Me [IQR1; IQR3]) or, in case of a normal distribution, as the arithmetic mean and standard deviation (mean ± SD).
- **Pearson’s $\chi 2$-test** was used to compare the frequencies of genotypes and undesirable side effects.

Sample and randomization

- The study included **118 Russian male patients** (average age – 36.95 ± 8.92 years).
- All patients were **primary** (diagnosis of affective disorder was exhibited for the first time).
- Among them, 48 patients started treatment with either fluvoxamine or mirtazapine or carbamazepine in doses recommended by the results of pharmacogenetic testing performed through special software www.pgx2.com (**main group**).
- When prescribing drugs to the remaining 70 patients and to exclude the factor of knowledge or ignorance of the physician about the use of pharmacogenetic testing, treating physicians received a report containing information that patients had normal genotypes with regard to all of the studied markers and regardless of the patient's real genotype (**control group**).
- Randomization was performed by assigning random numbers generated using "=RANDBETWEEN()" function in Microsoft Excel 2016.
- Patients were examined on days **1**, **9**, and **16** of the therapy.

Sample characteristics

Table 1: Distribution of patients by diseases and prescribed treatment.

Parameter	Main group (n=48)	Control group (n=70)	p[a]
Patients with depression who received fluvoxamine, n (%)	30 (62.5%)	45 (64.3%)	>0.999
Dose of fluvoxamine, mg/day	121.7 ± 40.9	136.8 ± 43.2	0.134
Patients with depression who received mirtazapine, n (%)	12 (25%)	16 (22.9%)	>0.999
Dose of mirtazapine, mg/day	25.9 ± 9.7	33.8 ± 11.6	0.067
Patients with cyclothymia who received carbamazepine, n (%)	6 (12.5%)	9 (12.9%)	>0.999
Dose of carbamazepine, mg/day	100 ± 44.7	155.6 ± 46.4	0.038

[a]p-Value adjusted by the Benjamini-Hochberg procedure (based on results of the Student's t-test for independent samples with Welch's correction for quantitative variables and the two-tailed Fisher's exact test for qualitative data).

Table 2: Clinical and demographic characteristics of the patients.

Parameter	Main group (n=48)	Control group (n=70)	p[a]
Age, years	36.7 ± 9.5	38.2 ± 8.6	>0.999
Weight, kg	80.4 ± 14.5	83.8 ± 16.8	>0.999
Height, cm	174.1 ± 26.1	178.4 ± 30.3	>0.999
Body mass index, kg/m^2	24.2 ± 6.05	25.7 ± 5.14	>0.999
Nationality (Russian), n (%)	48 (100%)	70 (100%)	>0.999
Alcoholic steatohepatitis, n (%)	47 (97.9%)	67 (95.7%)	>0.999
Toxic encephalopathy, n (%)	37 (77.1%)	56 (80%)	>0.999
Toxic polyneuropathy of the upper extremities, n (%)	12 (25%)	18 (25.7%)	>0.999
Toxic polyneuropathy of the lower extremities, n (%)	6 (12.5%)	5 (7.1%)	>0.999
Viral hepatitis C, n (%)	3 (6.3%)	4 (5.7%)	>0.999
Peptic ulcer disease, n (%)	2 (4.2%)	1 (1.4%)	>0.999
Duodenal ulcer, n (%)	4 (8.3%)	1 (1.4%)	>0.999
Arterial hypertension, n (%)	7 (14.6%)	11 (15.7%)	>0.999
Active smoking, n (%)	45 (93.8%)	64 (91.4%)	>0.999
Duration of comorbid alcohol dependence, years	7.4 ± 3.5	8.7 ± 3.9	>0.999
Age on onset, year	18.4 ± 3.6	17.6 ± 3.4	>0.999
Amount of alcohol daily use, standard drinks	36.7 ± 15.6	38.4 ± 16.9	>0.999

[a]p-Value adjusted by the Benjamini-Hochberg procedure (based on results of the Student's t-test for independent samples with Welch's correction for quantitative variables and the two-tailed Fisher's exact test for qualitative data).

Genotyping results

Table 3: Genotyping results in patients of the guided and unguided groups.

Allelic variant	Polymorphism	rs	Group	"Wild-type" allele (AA)	Heterozygotes (AB)	Homozygous mutants (BB)	Hardy-Weinberg Equillibruim	
							Chi^2	p^a
CYP2D6*4	1846G>A	rs3892097	Guided	40 (83.33%)	8 (16.67%)	0 (0.00%)	0.40	0.53
			Unguided	56 (80.00%)	13 (18.57%)	1 (1.43%)	0.06	0.81
CYP2C19*2	681G>A	rs4244285	Guided	43 (89.58%)	5 (10.42%)	0 (0.00%)	0.14	0.70
			Unguided	64 (91.43%)	6 (8.57%)	0 (0.00%)	0.14	0.70
CYP2C19*3	636G>A	rs4986893	Guided	46 (95.83%)	2 (4.17%)	0 (0.00%)	0.02	0.88
			Unguided	65 (92.86%)	5 (7.14%)	0 (0.00%)	0.10	0.76
CYP2C19*17	−806C>T	rs12248560	Guided	25 (52.08%)	20 (41.67%)	3 (6.25%)	0.14	0.70
			Unguided	39 (55.71%)	26 (37.14%)	5 (7.14%)	0.05	0.81
CYP3A5*3	6986A>G	rs77646	Guided	0 (0.00%)	3 (6.25%)	45 (93.75%)	0.05	0.82
			Unguided	0 (0.00%)	6 (8.57%)	64 (91.43%)	0.14	0.71
ABCB1*6	3435C>T	rs1045642	Guided	24 (50.00%)	20 (41.67%)	4 (8.33%)	0.01	0.95
			Unguided	38 (54.29%)	27 (38.57%)	6 (8.57%)	0.15	0.70

[a]p-Value based on the results of Pearson's chi-squared test.

There is no statistically significant difference between the frequencies of the genotypes in the main group and the comparison group.

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[a]p-Value based on the results of Pearson's chi-squared test.

There is no statistically significant difference between the frequencies of the genotypes in the main group and the comparison group.

HAM-D scores dynamics

- Day 1: groups were **comparable** in HAM-D scores (main: 14.0 [12.0; 15.0] vs. control: 14.0 [12.5; 15.0], **p>0.05**).
- Day 9: HAM-D scores were statistically significantly **different** between the compared groups (main: 9.0 [8.0; 10.0] vs. control: 11.0 [10.0; 12.0], **p<0.001**).
- Day 16: this **difference remained** (main: 4.0 [2.0; 6.0] vs. control: 14.0 [13.0; 14.0], **p<0.001**).

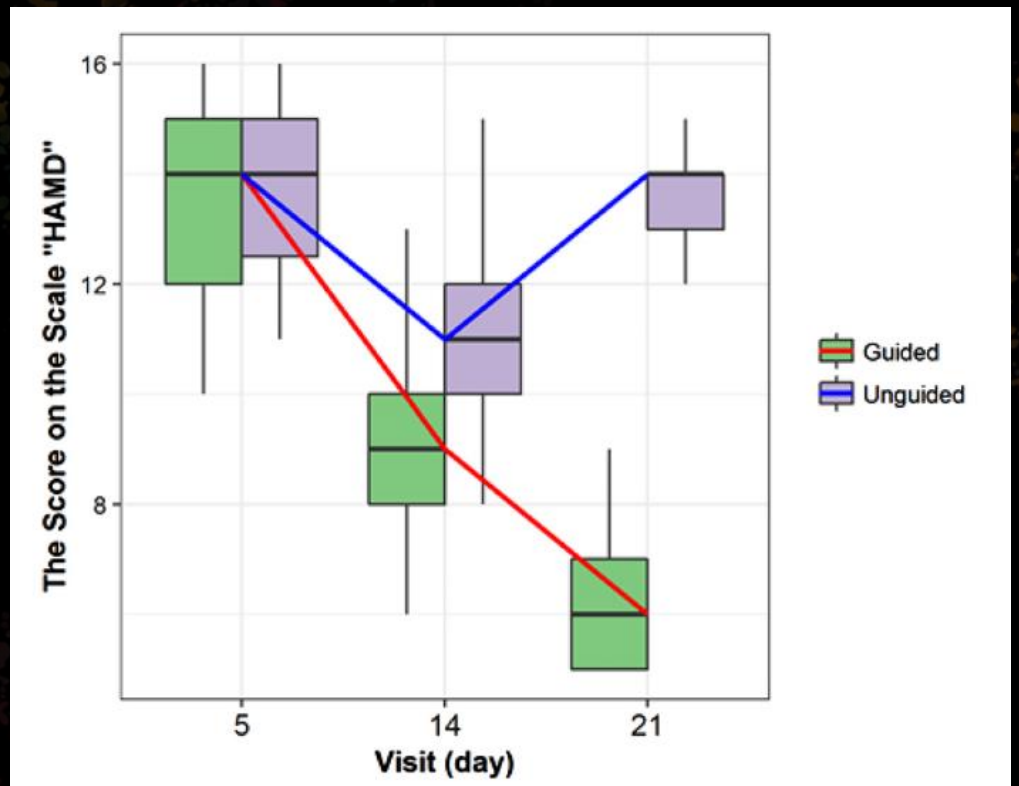
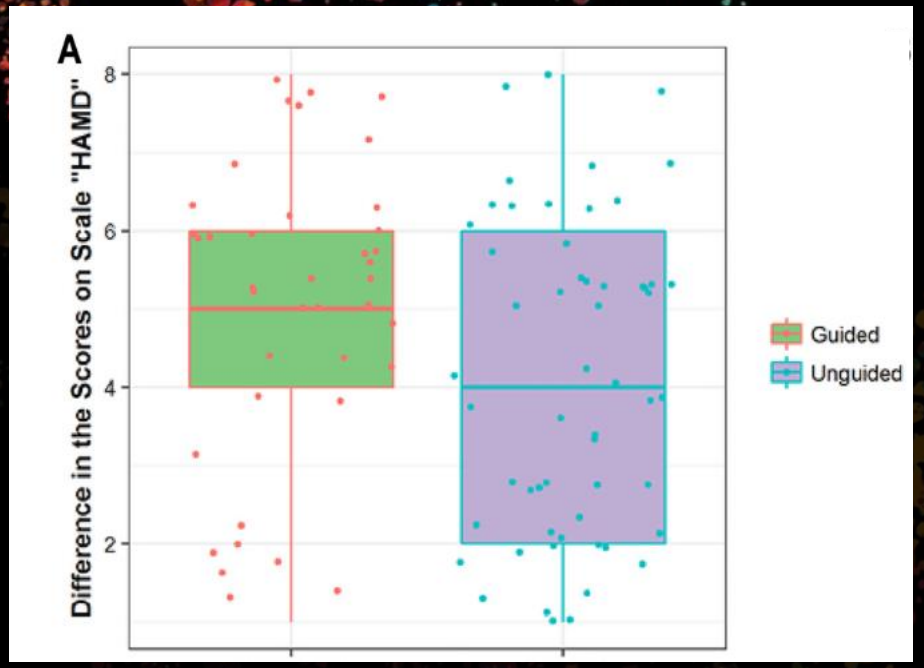


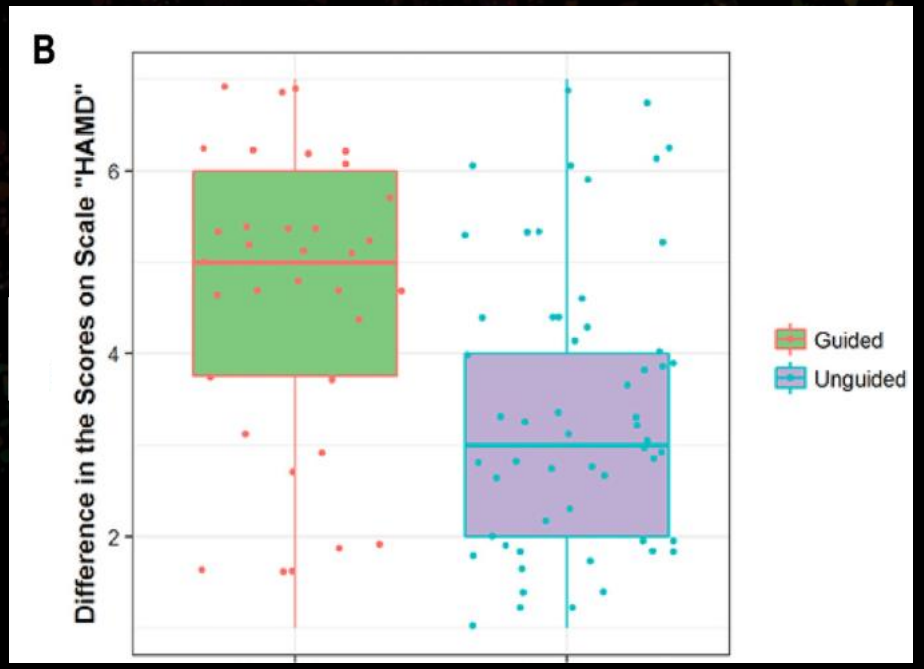
Figure 1: Dynamics of changes in Hamilton Rating Scale for Depression (HAM-D) scores across patients with different genotypes (data are presented as median and IQR).
IQR, interquartile range.

HAM-D scores dynamics

- A. The differences between groups in the HAM-D scores decrease from day 1 to day 9 were statistically **significant**: 6.0 [4.0; 7.2] in the main group and 3.5 [2.0; 5.0] in the control group (**p<0.001**).



- B. The differences between groups in the HAM-D scores decrease from day 9 to day 16 were also statistically **significant**: 5.0 [3.0; 6.2] in the main group and 3.0 [1.0; 4.0] in the control group (**p<0.001**).



UKU scores dynamics

- Day 1: groups were **comparable** in UKU scores (main: 1.0 [1.0; 1.0] vs. control: 1.0 [1.0; 1.0], **p>0.05**).
- Day 9: UKU scores were significantly **different** between the compared groups (main: 4.0 [4.0; 5.0] vs. control: 5.0 [5.0; 6.0], **p<0.001**).
- Day 16: this **difference remained** (main: 3.0 [0.0; 4.2] vs. control: 9.0 [7.0; 11.0], **p<0.001**).

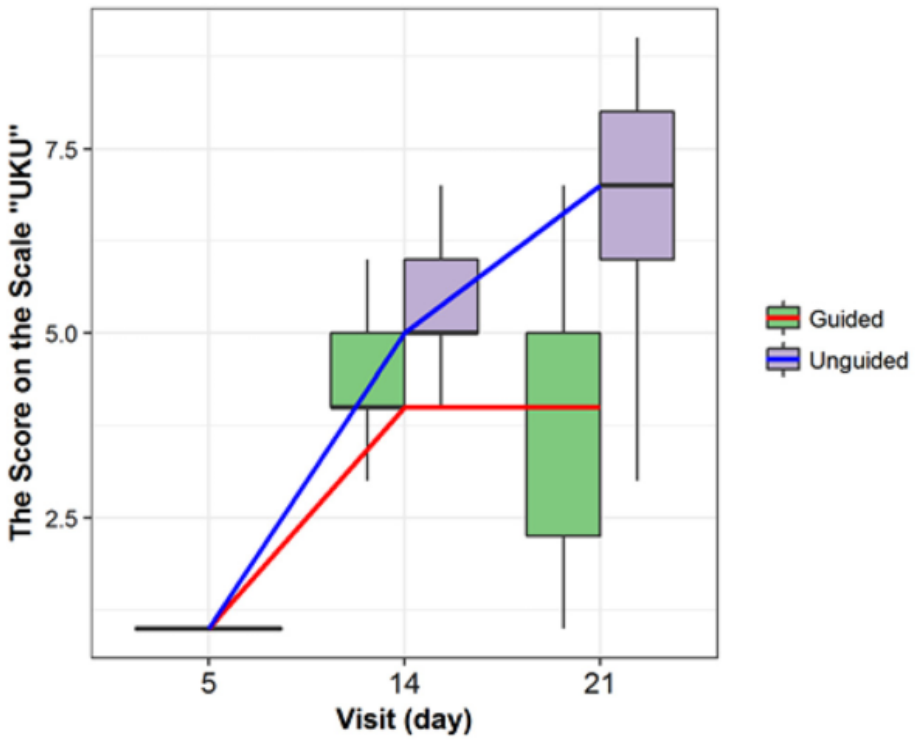
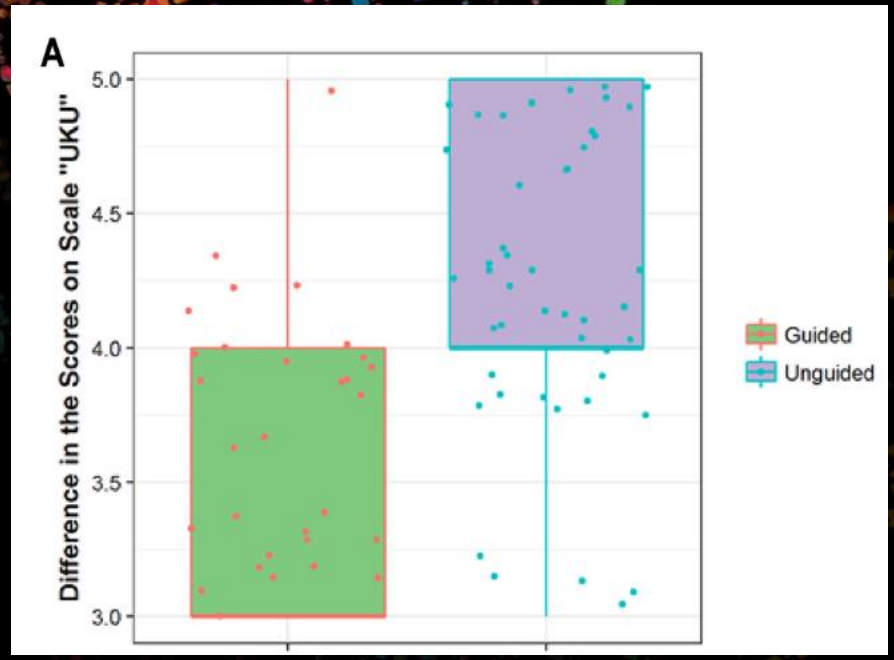


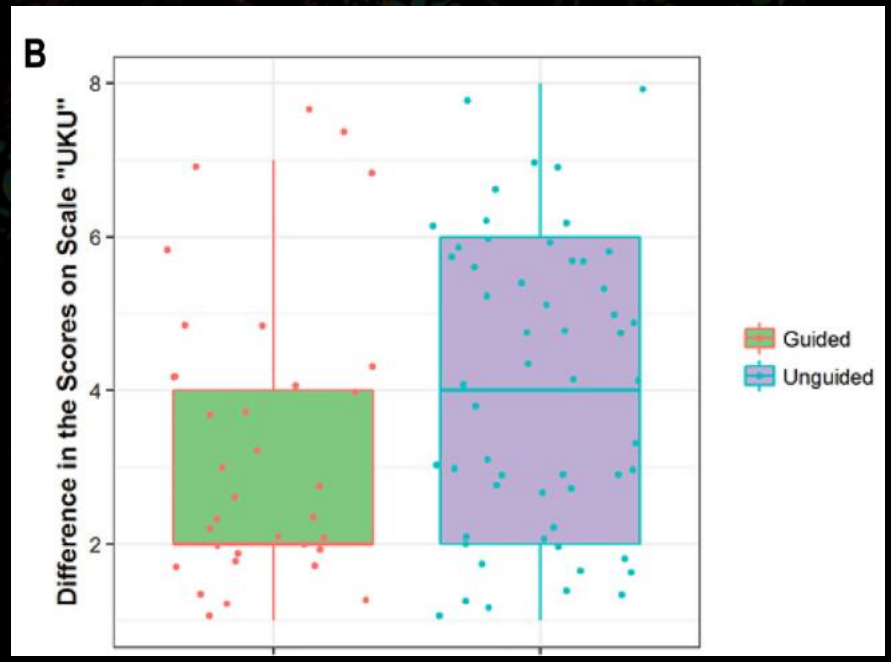
Figure 2: Dynamics of changes in UKU Side-Effect Rating Scale scores across patients with different genotypes (data are presented as median and IQR).
UKU, UKU Side-Effect Rating Scale IQR, interquartile range.

UKU scores dynamics

- A. The differences in the UKU scores increase from day 1 to day 9 and were **significant**: 3.0 [3.0; 4.0] in the main group and 4.0 [3.0; 4.0] in the control group (**p<0.001**).



- B. The differences in the UKU scores increase from day 9 to day 16 and were **significant**: 3.0 [3.0; 4.0] in the main group and 4.0 [3.0; 4.0] in the control group (**p<0.001**).



Other scales scores dynamics

Same patterns were observed for other scales (PACS, CGI, HADS and BDI).

Table 4: The results of psychometric scales and side effect rating scale data analysis (scores) in patients from the main (guided) and control (unguided) groups on the first day of therapy.

Parameter	Unguided	Guided	p[a]
PACS	7.00 [6.00; 7.00]	7.00 [6.00; 8.00]	>0.999
CGI	3.00 [3.00; 3.00]	3.00 [3.00; 3.00]	>0.999
HADS	23.00 [21.00; 26.00]	22.00 [21.00; 24.00]	0.440
HAMD	14.00 [13.00; 16.00]	15.00 [13.00; 16.00]	>0.999
BDI	37.00 [34.00; 41.00]	36.00 [31.75; 40.25]	>0.999
UKU	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	>0.999

Table 5: The results of psychometric scales and side effect rating scale data analysis (scores) in patients from the main (guided) and control (unguided) groups on day 9 of therapy.

Parameter	Unguided	Guided	p[a]
PACS	6.000 [5.000;6.000]	5.000 [4.000;5.000]	<0.001
CGI	3.000 [3.000;3.000]	2.000 [2.000;2.000]	<0.001
HADS	20.000 [18.000;21.000]	14.500 [14.000;15.000]	<0.001
HAMD	11.000 [10.000;12.000]	9.000 [8.000;10.000]	<0.001
BDI	30.000 [28.000;32.000]	24.500 [22.000;26.000]	<0.001
UKU	5.000 [5.000;6.000]	4.000 [4.000;5.000]	<0.001

Table 6: The results of psychometric scales and side effect rating scale data analysis (scores) in patients from the main (guided) and control (unguided) groups on day 16 of therapy.

Parameter	Unguided	Guided	p[a]
PACS	5.00 [5.00; 6.00]	1.00 [1.00; 2.00]	<0.001
CGI	3.00 [3.00; 3.00]	1.00 [1.00; 1.00]	<0.001
HADS	19.00 [17.25; 20.00]	5.00 [4.00; 6.00]	<0.001
HAMD	14.00 [13.00; 14.00]	4.00 [3.00; 5.00]	<0.001
BDI	28.00 [26.00; 29.00]	8.00 [7.00; 10.00]	<0.001
UKU	9.00 [7.00; 11.00]	3.00 [0.00; 4.25]	<0.001

Strengths

- This study is the **first** in the field of pharmacogenetics that takes into account the doctor's knowledge about the use of pharmacogenetic testing and is **truly double blinding** (previously the doctor knew which patients underwent pharmacogenetic testing and which did not).

- The recommendations were elaborated through free software PGX2 (www.pgx2.com). Its calculation algorithms are based on recommendations of the pharmacogenetic consortiums CPIC and DPWG.

- This is the first study conducted on the **Russian** population.

- This study was conducted on patients with affective disorders and comorbid alcohol use disorder who were **not studied before**.

Limitations

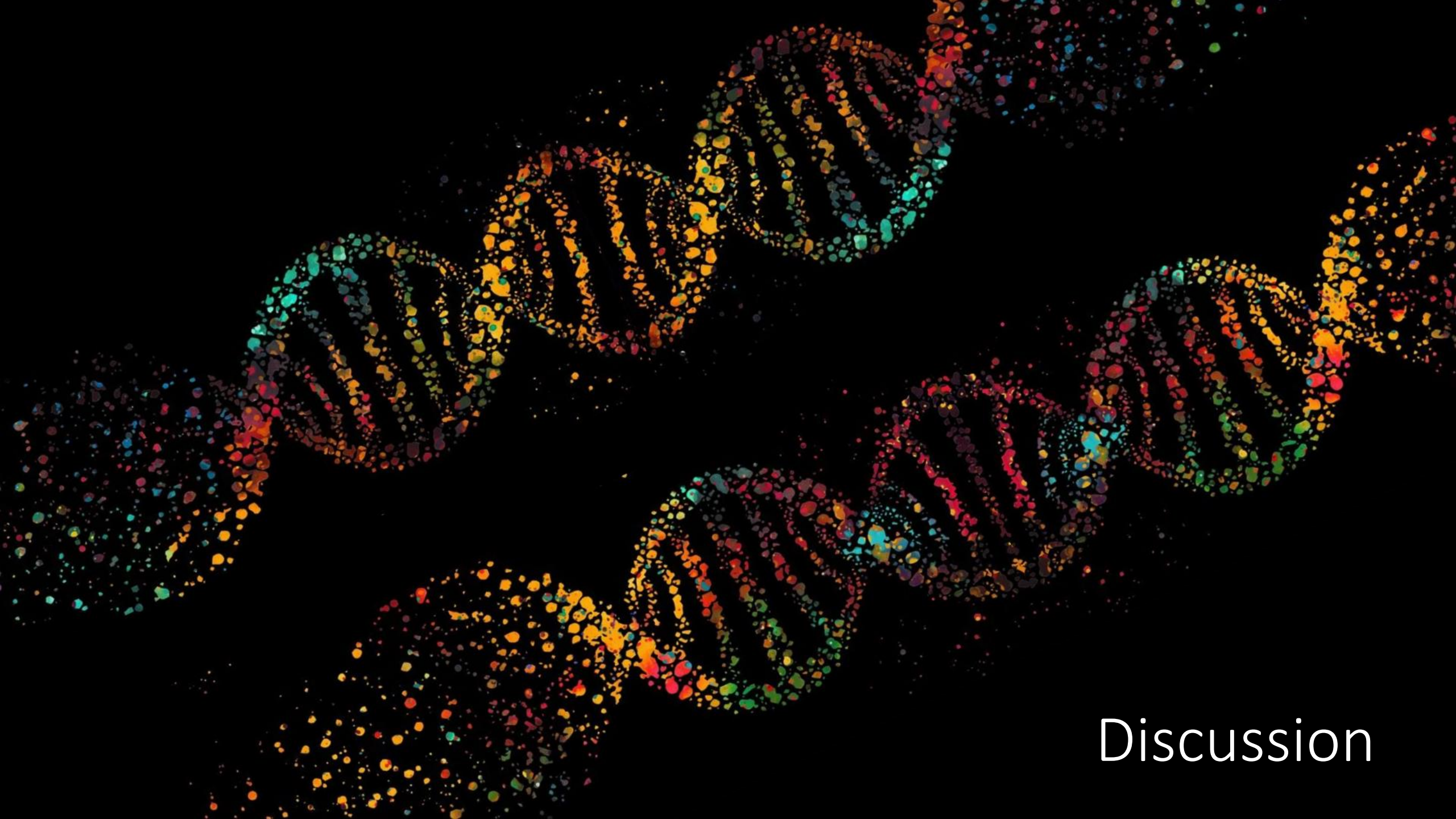
- The duration of the study was 16 days, whereas according to the majority of studies, antidepressants usually need 2–3 weeks to take effect.
- The absence of phenotyping of cytochrome P-450 isoenzymes.
- Due to the limited number of polymorphisms included in the genetic panel, the recommendations could be limited and biased.

Conclusion

The study demonstrated the **efficacy** of using a personalized pharmacogenetic **CDSS** to **improve psychopharmacotherapy dosing** (fluvoxamine, mirtazapine, carbamazepine) in patients with affective disorders and comorbid alcohol use disorder.

It was shown that pharmacogenetic-guided personalization of the drug dose can **reduce the risk** of undesirable side effects and pharmacoresistance.

It allows **recommending** the use of pharmacogenetic CDSSs for optimizing drug dosage.



Discussion

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- co-chair of European Federation of Psychiatric Trainees Research Working Group

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