STABILIZATION OF REMISSION FROM OPIOID DEPENDENCE WITH LONG-ACTING NALTREXONE IMPLANT: PHARMACOGENETIC APROACH

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Introduction

- Different drug formulations of opiate antagonist naltrexone (oral, implantable and injectable) are widely used for treatment of opiate dependence in Russian Federation.
- The main problem of naltrexone therapy is low level of compliance.
- Pharmacogenetic approach to the naltrexone treatment has great potential for improving treatment outcomes by determination of responders and non-responders to pharmacotherapy.

Study was aimed to assess the effectiveness of oral and implantable naltrexone on the treatment outcomes of opioid dependence versus placebo with inclusion of genetic covariates (genes of mu- and kappa-opioid receptors, dopamine-receptors D2, protein-transmembrane dopamine transporter and catechol-ortho-methyltransferase).

Materials and Methods

•It was the double blind double dummy study.
•306 opioid addicts after detoxification have been randomly assigned to one of the 3 groups (102 patients in each group).

NI+OP	**naltrexone implant** (3 times during 6 months (1000 mg) + **oral placebo**
PI+ON	**oral naltrexone** (50 mg/day) + **placebo implant**
PI+OP	**placebo implant** + **oral placebo**

•All patients received the individual drug counseling every two weeks.
•All patients had at least one family member who was able to control medication compliance.
•Monitoring of remissions has been doing by the urine tests for drugs.
•Every patient received the naloxone challenge test, after which they received the surgical naltrexone implantation.

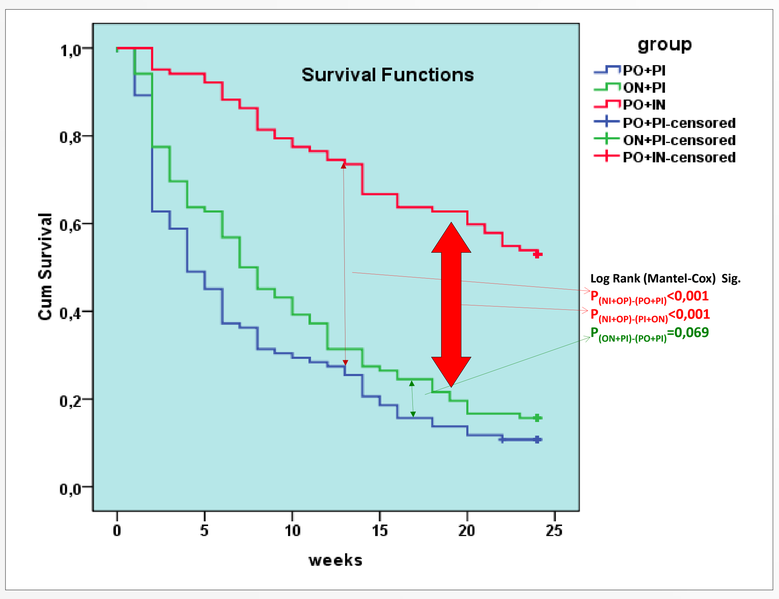
Genetic analysis:
1) Opiate receptor genes:
OPRM11, OPRM12, OPRM13, and OPRK1
2) Genes of enzymes:
Catechol-ortho-methyl-transferase (COMT) and
Dopamine-beta-hydroxilase (DBH)
3) Dopamine receptor genes:
Dopamine receptors (D2 и D4) and
Dopamine transporter (DAT)

Statistical analysis: Data were analyzed using SPSS statistical software package. Results were considered significant at P<0.05. Categorical variables were analyzed with the Kaplan-Meier estimator and Fisher exact test.

Results

Kaplan-Meier Survival Functions: Drop out

The retention in treatment program according the Kaplan-Meier survival analysis was significantly higher in naltrexone implant *group (p<0.01).*

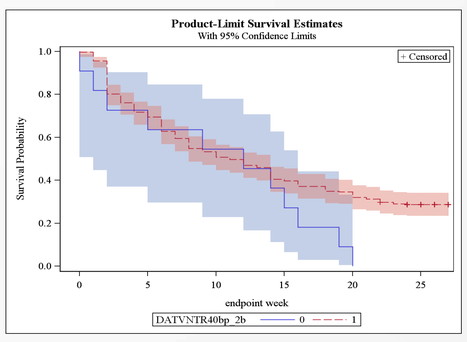


DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Medication group	NI+OP	PI+ON	PI+OP
Age (years) (M±SE)	28,0±0,40	27,9±0,39	28,7±0,45
Male (%)	72,50%	72,50%	72,50%
Duration of heroin abuse (years) (M±SE)	7,8±0,38	7,9±0,41	8,3±0,39
Average daily dose of heroin (mg) (M±SE)	1,1±0,07	0,9±0,08	0,9±0,07
Use of amphetamines	11,8%	5,9%	17,6%
Use marijuana	34,3%	21,6%	24,5%
Use of sedatives (benzos)	14,7%	9,8%	8,8%
Use of alcohol (grams of ethanol per day)	10,2±1,69	9,0±1,72	9,6±1,58
Number of previous treatments (M±SE)	4,9±0,41	4,3±0,37	3,8±0,31
Employment (%)	46,1%	41,2%	50,0%
HIV positive	43,0%	52,0%	46,5%
Hepatitis B	17,8%	16,0%	13,0%
Hepatitis C	96,1%	96,0%	95,1%

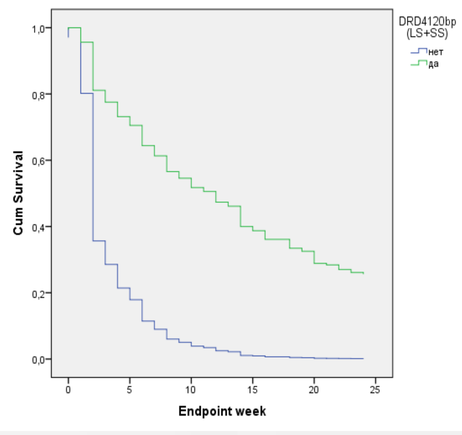
EFFECTIVNESS OF THE TREATMENT REGARDLESS ANY THERAPY

DAT: locus VNTR40bp



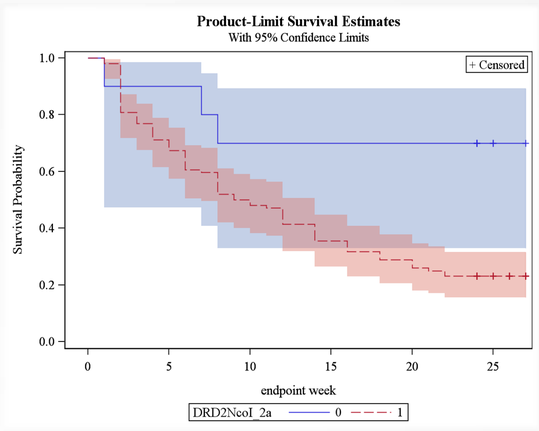
Kaplan-Meier survival functions (retention in treatment).
Homozygote 9\9 (blue line), heterozygote 9\10 and homozygote 10\10 – red line (p=0,09; Log-rang criterion).

D-4: locus DRD4120bp



•Homozygote LL and heterozygote LS had a higher chance to relapse compared to homozygote SS (p=0,05; Fisher Exact Test - FET)
•Cox regression analysis: Homozygote SS and heterozygote LS (green line) had a lower chance to relapse (OR = 0,2; 95% CI: 0,05 – 0,84; p=0,03).

Combination of OPRK1 & DRD2Ncol



Kaplan-Meier survival functions
•Among homozygote CC and heterozygote CT of OPRK1: homozygote TT of DRD2Ncol (blue line) had a high chance to complete treatment program compared to homozygote CC and heterozygote CT of DRD2Ncol (p=0,016; Log-rang criterion).

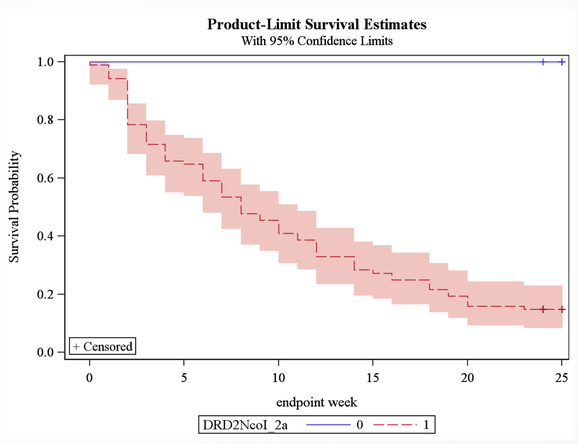
Effect of combination of alleles of the other two genes on the treatment program completion

Alleles of the first gene	*Second gene*	*Alleles of the second gene*	*Chance to complete treatment program*	*p (FET)*
OPRK1 (CC & CT)	DRD2C957T	CC	Higher	0,021
		TT & TC	Lower	
OPRM11 (CC)	DRD2C957T	CC	Higher	0,048
		TT & TC	Lower	
OPRM13 (AA)	DRD2TaqI	TT	Higher	0,021
		CC & CT	Lower	
OPRM13 (AA)	DRD2C957T	CC	Higher	0,046
		TT & TC	Lower	
COMT1 (GG & GA)	DRD2NcoI	TT	Higher	0,041
		CC & CT	Lower	
COMT1 (GG & GA)	DRD2C957T	CC	Higher	0,048
		TT & TC	Lower	
DRD4120bp (SS)	DRD4521ct	CC & CT	Higher	0,021
		TT	Lower	
DRD4521ct (TT)	DRD2C957T	CC & CT	Higher	0,041
		TT	Lower	
DRD2TaqI (TT)	DBHFau	TT & TC	Higher	0,049
		CC	Lower	

•Among homozygote CC and heterozygote CT of OPRK1:homozygote TT of DRD2Ncolhad a high chance to complete treatment program compared to homozygote CC and heterozygote CT of DRD2Ncol(p=0,004; FET).

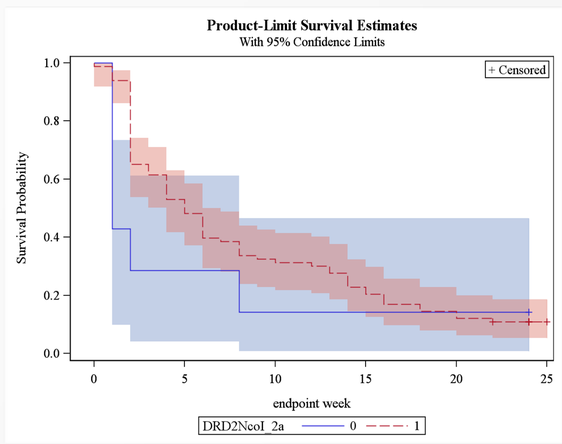
EFFECTIVNESS OF THE TREATMENT WHICH DEPENDS ON A TREATMENT GROUP

Effect of combination of the OPRK1 & DRD2Ncol in the ON+PI group



Kaplan-Meier survival functions ON+PI group:
Among homozygote CC and heterozygote CTof OPRK1, homozygote TT of DRD2Ncol (blue line) had a higher chance to complete treatment program compared to heterozygote CT and homozygote CC – red line) of DRD2Ncol (p=0,03; Wilcoxone test)

Combination of the OPRK1 & DRD2Ncol in the OP+PI group



OP+PI group: Among homozygote CC and heterozygote CT of OPRK1, homozygote TT of DRD2Ncol (blue line) had a lower chance to complete treatment program compared to c heterozygote CT and homozygote CC (red line) of DRD2Ncol (p=0,01; Wilcoxone test).

Conclusions

- ✓ Naltrexone implant is the effective for opiate dependence therapy, superior in effectiveness then oral naltrexone and placebo-implant.
- ✓ The genetic carrier of AAAGTT or AGAGTT alleles of OPRM13 genes, OPRK1 and COMT, and also CCAGTT or CTAGTT alleles OPRM11 genes, OPRK1 and COMT have better effectiveness of any therapy.
- ✓ Combination of genetic analysis of dopamine and opiate receptors system may be useful to define responders to opiate dependence of any therapy and therapy by naltrexone.