Доказательная фармакотерапия наркологических заболеваний

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Доказательная фармакотерапия наркологических заболеваний

- Зависимость от алкоголя
- Зависимость от опиатов
- Зависимость от никотина

Доказательная фармакотерапия наркологических заболеваний

- Зависимость от алкоголя
- Зависимость от опиатов
- Зависимость от никотина

Препараты, официально зарегистрированные как средства лечения алкоголизма в большинстве стран Европы и США

- **Дисульфирам**
- **Акампросат**
- **Налтрексон:**
  -Пероральный
  -Инъекционный пролонг (ВИВИТРОЛ)

Препараты, продемонстрировавшие эффективность в отношении лечения алкоголизма в отдельных научных (доказательных) исследованиях

- **Топирамат**
- **Ондансетрон**
- **Налмефен**

Фармакотерапия алкоголизма

Registered for Alcohol Dependence

- Disulfiram
- Naltrexone
- Acamprosate

Off Label Use for Alcohol Dependence

- Topiramate
- Ondansetron

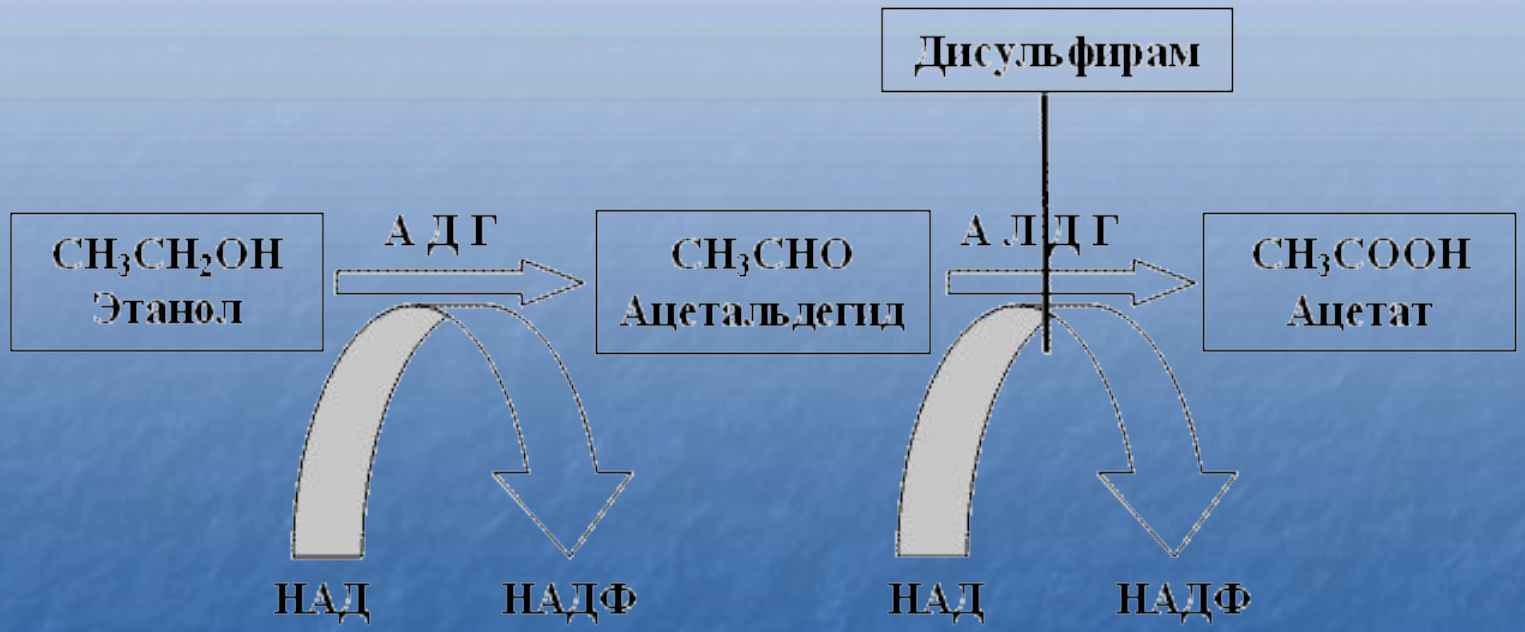
New Medications

- Nalmefene

ЗАРЕГИСТРИРОВАННЫЕ ПРЕПАРАТЫ

1. Дисульфирам
2. Акампросат
3. Налтрексон

Схема ферментной биотрансформации алкоголя и действие на неё дисульфирама



Эспераль

REVIEW

Pharmacological Treatment of Alcohol Dependence

A Review of the Evidence

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Kathleen N. Lohr, PhD
Fulton T. Crews, PhD

JAMA®
The Journal of the American Medical Association

Context Alcoholism affects approximately 10% of Americans at some time in their lives. Treatment consists of psychosocial interventions, pharmacological interventions, or both, but which drugs are most effective at enhancing abstinence and preventing relapse has not been systematically reviewed.

Objective To evaluate the efficacy of 5 categories of drugs used to treat alcohol dependence—disulfiram, the opioid antagonists naltrexone and nalmefene, acamprosate, various serotonergic agents (including selective serotonergic reuptake inhibitors), and lithium.

Table 4. Randomized Controlled Trials to Evaluate the Efficacy of Pharmacotherapies Used for Maintaining Abstinence in Alcohol-Dependent Patients*

Source, y	Initial/ Final Sample Size	Trial Length, wk	Efficacy: Drinking/ Nondrinking Days	Efficacy: Return to Drinking	Efficacy: Time to First Drink	Efficacy: Alcohol Consumed Per Unit of Time	Efficacy: Craving	Efficacy: Relapse	Quality Rating
Disulfiram (Grade, B) Oral Disulfiram									
Fuller and Roth,[9] 1979	128/NA	52	–	–	NM/R	NM/R	NM/R	NM/R	62
Fuller et al,[10] 1986	605/577	52	+	–	–	NM/R	NM/R	NM/R	88
Schuckit,[11] 1985†	348/348	52	–	NM/R	NM/R	–	NM/R	NM/R	69
Chick et al,[14] 1992	126/69	24	+	NM/R	NM/R	+	NM/R	NM/R	72
Disulfiram Implants									
Whyte and O'Brien,[15] 1074†	45/NA	NA	NM/R	NM/R	+	NM/R	NM/R	NM/R	34
Wilson et al,[17] 1975	20/NA	NA	NM/R	–	–	NM/R	NM/R	NM/R	26
Wilson et al,[18] 1980	100/78	48	+	–	NM/R	NM/R	NM/R	NM/R	41
Johnsen et al,[20] 1987	21/21	20	–	NM/R	–	–	NM/R	NM/R	60
Johnsen and Morland,[21] 1001	76/63	40	–	–	–	–	NM/R	NM/R	71
Naltrexone (Grade, A)									
O'Malley et al,[22] 1002	104/68	12	+	+	NM/R	–/+‡	–/+‡	+	88
Volpicelli et al,[23] 1002	70/44	12	+	–	NM/R	NM/R	+	+	90
Volpicelli et al,[24] 1997	97/71	12	–/+§	–/+§	NM/R	NM/R	–	–/+§	95
Acamprosate (Grade, A)									
Gerra et al,[31] 1992‖	28/NA	4	NM/R	NM/R	NM/R	–/+¶	NM/R	NM/R	72
Ladewig et al,[32] 1993	61/NA	24	+	–	NM/R	NM/R	NM/R	NM/R	75
Paille et al,[33] 1995	598/NA	52	+	–	+	NM/R	–	NM/R	69
Rousseaux et al,[34] 1996	127/90	12	NM/R	–	NM/R	NM/R	–	NM/R	65
Sass et al,[35] 1996	272/134	48	+	+	+	NM/R	–	NM/R	91
Whitworth et al,[36] 1996	448/180	52	+	+	NM/R	NM/R	NM/R	NM/R	52
Geerlings et al,[37] 1997	262/94	24	+	–	–	NM/R	NM/R	NM/R	60
Pelc et al,[38] 1997	188/110	12	+	+	+	NM/R	+	NM/R	66
Poldrugo,[39] 1997	246/112	26	+	+	+	NM/R	–	NM/R	83
Serotonergic Agents (Grade, I) Patients With Varying Comorbidity									
Gerra et al,[31] 1992 (fluoxetine)‖	28/NA	4	NM/R	NM/R	NM/R	–/+#	NM/R	NM/R	72
Gorelick and Paredes,[40] 1992 (fluoxetine)	20/17	4	NM/R	NM/R	NM/R	–	–	NM/R	72
Kranzler et al,[41] 1995 (fluoxetine)	101/95	12	–	NM/R	NM/R	–	NM/R	NM/R	73
Janiri et al,[42] 1996 (fluoxetine)	50/33	8	NM/R	+	NM/R	NM/R	–	+	60
Kabel and Petty,[43] 1996 (fluoxetine)	28/19	12	NM/R	NM/R	NM/R	NM/R	+	–	87
Malec et al,[47] 1996 (buspirone hydrochloride)	57/36	12	+	–	NM/R	–	–	NM/R	68
Sellers et al,[48] 1994 (ondansetron hydrochloride)	71/56	8	NM/R	NM/R	NM/R	–/+**	NM/R	NM/R	82
Tiihonen et al,[49] 1996 (citalopram)	62/34	12	NM/R	NM/R	NM/R	NM/R	NM/R	NM/R	66
Patients With Anxiety or Mood Disorders									
Malcolm et al,[46] 1992 (buspirone hydrochloride)	67/20	26	NM/R	–	–	–	–	NM/R	90
Kranzler et al,[45] 1994 (buspirone hydrochloride)	61/42	12	–	NM/R	+	–	NM/R	NM/R	95
Cornelius et al,[50] 1997 (fluoxetine)	51/46	12	+	–	–	+	NM/R	NM/R	93
Lithium (Grade, C)									
Merry et al,[52] 1976	71/38	52	+††	NM/R	NM/R	NM/R	NM/R	NM/R	59
de la Fuente et al,[54] 1989	53/27	26	+	+	NM/R	NM/R	NM/R	NM/R	71
Clark and Faweett,[53] 1060	122/NA	72	NM/R	+‡‡	NM/R	NM/R	NM/R	NM/R	77
Dorus et al,[55] 1080	457/280	52	–	–	NM/R	NM/R	NM/R	NM/R	94

*NA indicates information not available; NM/R, outcome was not measured or data not reported; plus sign, intervention showed efficacy compared with placebo ($P<.05$); and minus sign, intervention did not show efficacy compared with placebo. Grades are explained in Table 3. Quality rating is based on a scale of 1 to 100.
†Nonrandomized study.
‡Interaction between medication and psychotherapy was significant ($P<.05$ for amount consumed per unit of time and $P<.01$ for craving).
§Compliant subjects showed positive drug effect.
‖Fluoxetine and acamprosate (crossover study design).
¶In nonfamilial alcohol-dependent subjects only.
#In familial alcohol-dependent subjects only.
**Low dosages in light drinkers only.
††Patients with depression only.
‡‡High-blood-level lithium subjects only.

Conclusions Recent reports documenting that naltrexone and acamprosate are more effective than placebo in the treatment of alcoholism justify clinical interest in use of these medications for alcohol-dependent patients. Use of disulfiram is widespread but less clearly supported by the clinical trial evidence; however, targeted studies on supervised administration of disulfiram may be warranted. Use of existing serotonergic agents or lithium for patients with primary alcohol dependence does not appear to be supported by the efficacy data available at this time; these medications may still have a positive effect in patients with coexisting psychiatric disorders.

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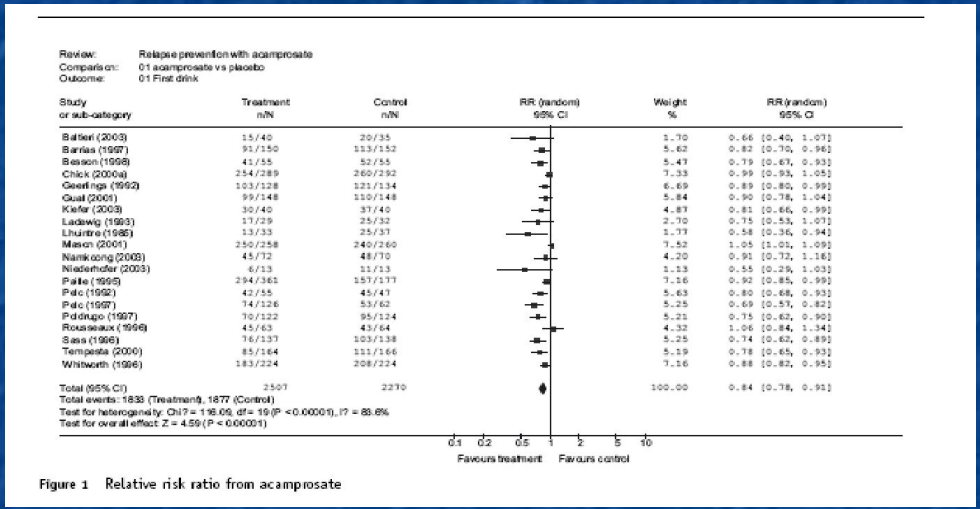
ЗАРЕГИСТРИРОВАННЫЕ ПРЕПАРАТЫ

1. Дисульфирам
2. Акампросат
3. Налтрексон

Acamprosate and Naltrexone
Abstinence/First Drink



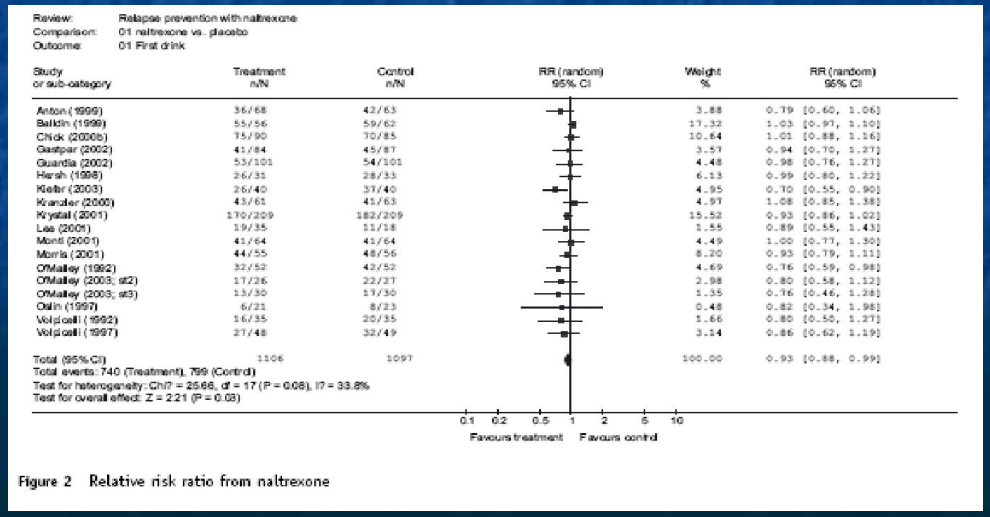
Review: Relapse prevention with acamprosate
Comparison: 01 acamprosate vs placebo
Outcome: 01 First drink

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Ballieri (2003)	15/40	20/35		1.70	0.66 [0.40, 1.07]
Barrias (1997)	91/150	113/152		5.62	0.82 [0.70, 0.96]
Besson (1998)	41/55	52/55		5.47	0.79 [0.67, 0.93]
Chick (2000a)	254/289	260/292		7.33	0.99 [0.93, 1.05]
Geerlings (1992)	103/128	121/134		6.69	0.89 [0.80, 0.99]
Gual (2001)	99/148	110/148		5.84	0.90 [0.78, 1.04]
Kiefer (2003)	30/40	37/40		4.87	0.81 [0.66, 0.99]
Ladewig (1993)	17/29	25/32		2.70	0.75 [0.53, 1.07]
Lhuintre (1985)	13/33	25/37		1.77	0.58 [0.36, 0.94]
Mason (2001)	250/258	240/260		7.52	1.05 [1.01, 1.09]
Namkoong (2003)	45/72	48/70		4.20	0.91 [0.72, 1.16]
Niederhofer (2003)	6/13	11/13		1.13	0.55 [0.29, 1.03]
Paille (1995)	294/361	157/177		7.16	0.92 [0.85, 0.99]
Pelc (1992)	42/55	45/47		5.63	0.80 [0.68, 0.93]
Pelc (1997)	74/126	53/62		5.25	0.69 [0.57, 0.82]
Pelciugo (1997)	70/122	95/124		5.21	0.75 [0.62, 0.90]
Rousseaux (1996)	45/63	43/64		4.32	1.06 [0.84, 1.34]
Sass (1996)	76/137	103/138		5.25	0.74 [0.62, 0.89]
Tempesta (2000)	85/164	111/166		5.19	0.78 [0.65, 0.93]
Whitworth (1996)	183/224	208/224		7.16	0.88 [0.82, 0.95]
Total (95% CI)	2507	2270		100.00	0.84 [0.78, 0.91]

Total events: 1833 (Treatment), 1877 (Control)
Test for heterogeneity: Chi? = 116.09, df = 19 (P <0.00001), I? = 88.6%
Test for overall effect: Z = 4.59 (P < 0.00001)

0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

Figure 1 Relative risk ratio from acamprosate



Review: Relapse prevention with naltrexone
Comparison: 01 naltrexone vs. placebo
Outcome: 01 First drink

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Anton (1999)	36/68	42/63		3.88	0.79 [0.60, 1.06]
Balldin (1999)	55/56	59/62		17.32	1.03 [0.97, 1.10]
Chick (2000b)	75/90	70/85		10.64	1.01 [0.88, 1.16]
Gastpar (2002)	41/84	45/87		3.57	0.94 [0.70, 1.27]
Guardia (2002)	53/101	54/101		4.48	0.98 [0.76, 1.27]
Hersh (1998)	26/31	28/33		6.13	0.99 [0.80, 1.22]
Kiefer (2003)	26/40	37/40		4.95	0.70 [0.55, 0.90]
Kranzler (2000)	43/61	41/63		4.97	1.08 [0.85, 1.38]
Krystal (2001)	170/209	182/209		15.52	0.93 [0.86, 1.02]
Lee (2001)	19/35	11/18		1.55	0.89 [0.55, 1.43]
Monti (2001)	41/64	41/64		4.49	1.00 [0.77, 1.30]
Morris (2001)	44/55	48/56		8.20	0.93 [0.79, 1.11]
OMalley (1992)	32/52	42/52		4.69	0.76 [0.59, 0.98]
OMalley (2003; st2)	17/26	22/27		2.98	0.80 [0.58, 1.12]
OMalley (2003; st3)	13/30	17/30		1.35	0.76 [0.46, 1.28]
Oslin (1997)	6/21	8/23		0.48	0.82 [0.34, 1.98]
Volpicelli (1992)	16/35	20/35		1.66	0.80 [0.50, 1.27]
Volpicelli (1997)	27/48	32/49		3.14	0.86 [0.62, 1.19]
Total (95% CI)	1106	1097		100.00	0.93 [0.88, 0.99]

Total events: 740 (Treatment), 799 (Control)
Test for heterogeneity: Chi? = 25.66, df = 17 (P = 0.08), I? = 33.8%
Test for overall effect: Z = 2.21 (P = 0.03)

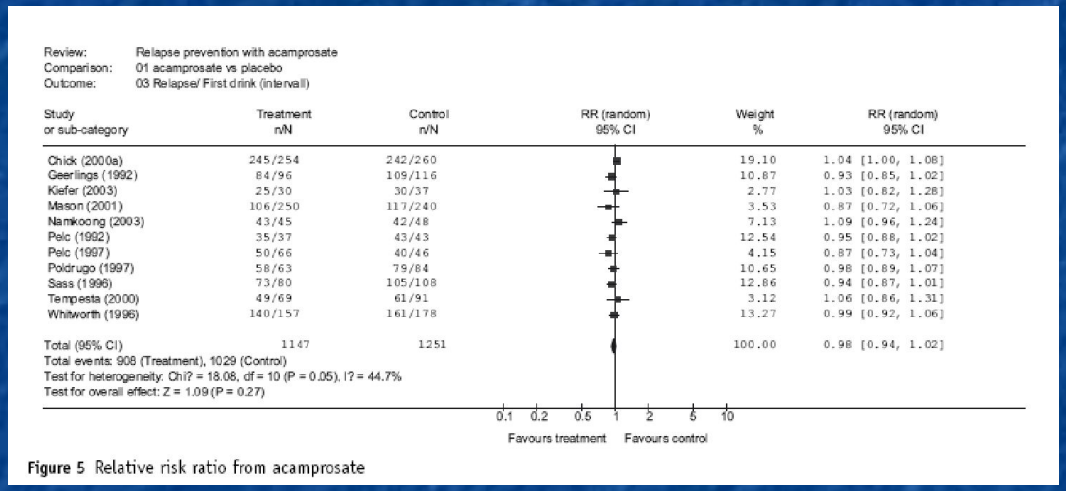
0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

Figure 2 Relative risk ratio from naltrexone

Acamprosate
RR = 0.84
NNT = 7.7

Naltrexone
RR = 0.93
(ns)
NNT = 17.4
(ns)

Acamprosate and Naltrexone Heavy Drinking in Non-Abstinent Patients



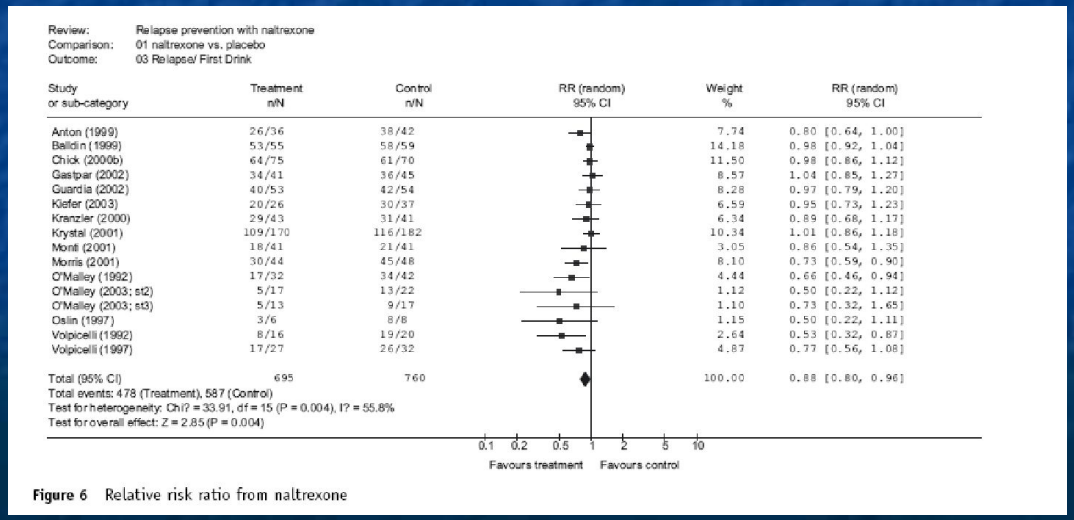
Review: Relapse prevention with acamprosate
Comparison: 01 acamprosate vs placebo
Outcome: 03 Relapse/ First drink (interval)

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Chick (2000a)	245/254	242/260		19.10	1.04 [1.00, 1.08]
Geerlings (1992)	84/96	109/116		10.87	0.93 [0.85, 1.02]
Kiefer (2003)	25/30	30/37		2.77	1.03 [0.82, 1.28]
Mason (2001)	106/250	117/240		3.53	0.87 [0.72, 1.06]
Namkoong (2003)	43/45	42/48		7.13	1.09 [0.96, 1.24]
Pelc (1992)	35/37	43/43		12.54	0.95 [0.88, 1.02]
Pelc (1997)	50/66	40/46		4.15	0.87 [0.73, 1.04]
Poldrugo (1997)	58/63	79/84		10.65	0.98 [0.89, 1.07]
Sass (1996)	73/80	105/108		12.86	0.94 [0.87, 1.01]
Tempesta (2000)	49/69	61/91		3.12	1.06 [0.86, 1.31]
Whitworth (1996)	140/157	161/178		13.27	0.99 [0.92, 1.06]
Total (95% CI)	1147	1251		100.00	0.98 [0.94, 1.02]

Total events: 908 (Treatment), 1029 (Control)
Test for heterogeneity: Chi? = 18.08, df = 10 (P = 0.05), I? = 44.7%
Test for overall effect: Z = 1.09 (P = 0.27)

0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

Figure 5 Relative risk ratio from acamprosate



Review: Relapse prevention with naltrexone
Comparison: 01 naltrexone vs. placebo
Outcome: 03 Relapse/ First Drink

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Anton (1999)	26/36	38/42		7.74	0.80 [0.64, 1.00]
Baldin (1999)	53/55	58/59		14.18	0.98 [0.92, 1.04]
Chick (2000b)	64/75	61/70		11.50	0.98 [0.86, 1.12]
Gastpar (2002)	34/41	36/45		8.57	1.04 [0.85, 1.27]
Guardia (2002)	40/53	42/54		8.28	0.97 [0.79, 1.20]
Kiefer (2003)	20/26	30/37		6.59	0.95 [0.73, 1.23]
Kranzler (2000)	29/43	31/41		6.34	0.89 [0.68, 1.17]
Krystal (2001)	109/170	116/182		10.34	1.01 [0.86, 1.18]
Monti (2001)	18/41	21/41		3.05	0.86 [0.54, 1.35]
Morris (2001)	30/44	45/48		8.10	0.73 [0.59, 0.90]
O'Malley (1992)	17/32	34/42		4.44	0.66 [0.46, 0.94]
O'Malley (2003; st2)	5/17	13/22		1.12	0.50 [0.22, 1.12]
O'Malley (2003; st3)	5/13	9/17		1.10	0.73 [0.32, 1.65]
Oslin (1997)	3/6	8/8		1.15	0.50 [0.22, 1.11]
Volpicelli (1992)	8/16	19/20		2.64	0.53 [0.32, 0.87]
Volpicelli (1997)	17/27	26/32		4.87	0.77 [0.56, 1.08]
Total (95% CI)	695	760		100.00	0.88 [0.80, 0.96]

Total events: 478 (Treatment), 587 (Control)
Test for heterogeneity: Chi? = 33.91, df = 15 (P = 0.004), I? = 55.8%
Test for overall effect: Z = 2.85 (P = 0.004)

0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

Figure 6 Relative risk ratio from naltrexone

Acamprosate
RR = 0.98
(ns)
NNT = 33.3
(ns)

Naltrexone
RR = 0.88
NNT = 12.5

АКАМПРОСАТ:

- Оптимизм в отношении этого препарата, обусловленный первоначальными исследованиями в Европе, значительно уменьшился после результатов исследований, выполненных в США, а также недавних европейских исследований

ЗАРЕГИСТРИРОВАННЫЕ

препараты

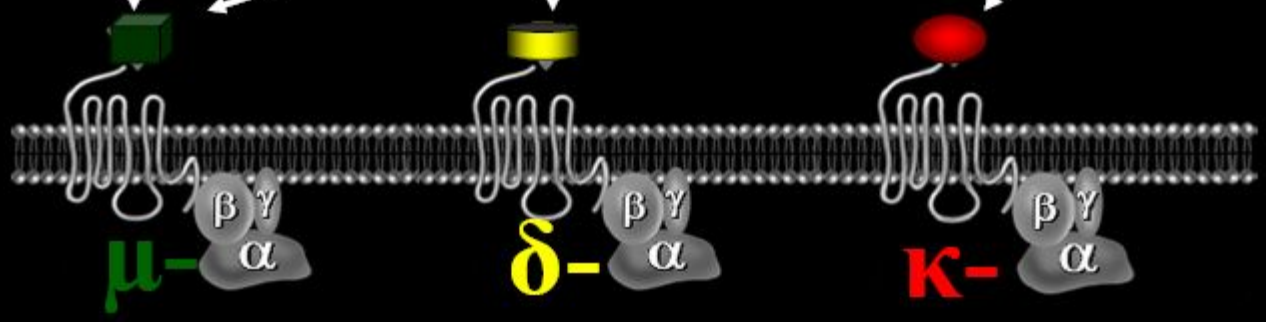
1. Дисульфирам
2. Акампросат
3. Налтрексон

The opioid ”mafia”

POMC → β-Endorphin

Proenkephalin → Enkephalins

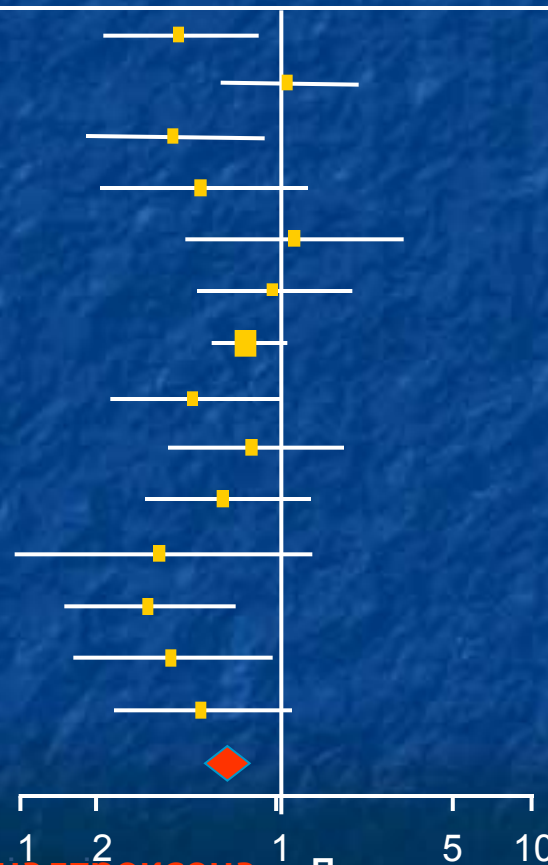
Prodynorphin → Dynorphins



Opioid receptors

Налтрексон уменьшает тяжелое пьянство

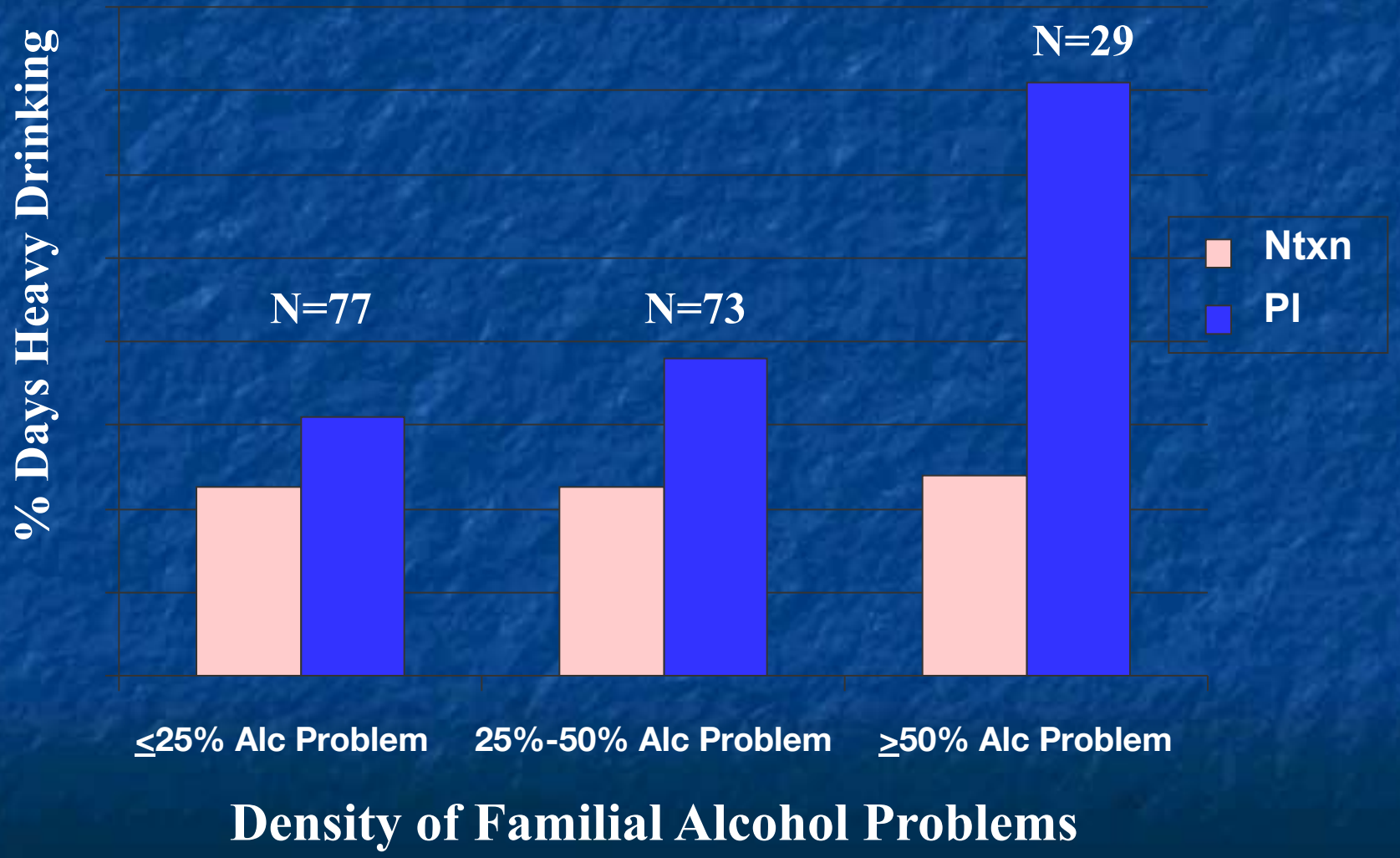
Study	Treatment n/N	Control n/N	Peto OR (95% CI fixed)	Weight %	Peto OR (95% CI fixed)
Anton 1999	26/68	38/63		7.	0.42 (0.21, 0.82)
Chick 2000	59/90	54/85		9.	1.09 (0.59, 2.03)
Guardia 2002	8/101	19/101		5.	0.39 (0.17, 0.88)
Heinala 2001	49/63	51/58		4.	0.50 (0.19, 1.27)
Hersch 1998	15/31	15/33		3.	1.12 (0.42, 2.98)
Kranzler 2000	29/61	31/63		7.	0.94 (0.46, 1.89)
Krystal 2001	142/378	83/187		27	0.75 (0.53, 1.08)
Latt 2002	19/56	27/51		6.	0.46 (0.22, 0.99)
Monti 2001	16/64	19/64		5.	0.79 (0.36, 1.72)
Morris 2001	19/55	26/56		6.	0.61 (0.29, 1.30)
Oslin 1997	3/21	8/23		1.	0.34 (0.09, 1.33)
O'Malley 1992	16/52	31/52		5.	0.32 (0.15, 0.68)
Volpicelli 1995	10/54	17/45		4.	0.38 (0.16, 0.93)
Volpicelli 1997	17/48	26/49		5.	0.49 (0.22, 1.09)



Общий эффект: Z=4.97; *P*<.00001.

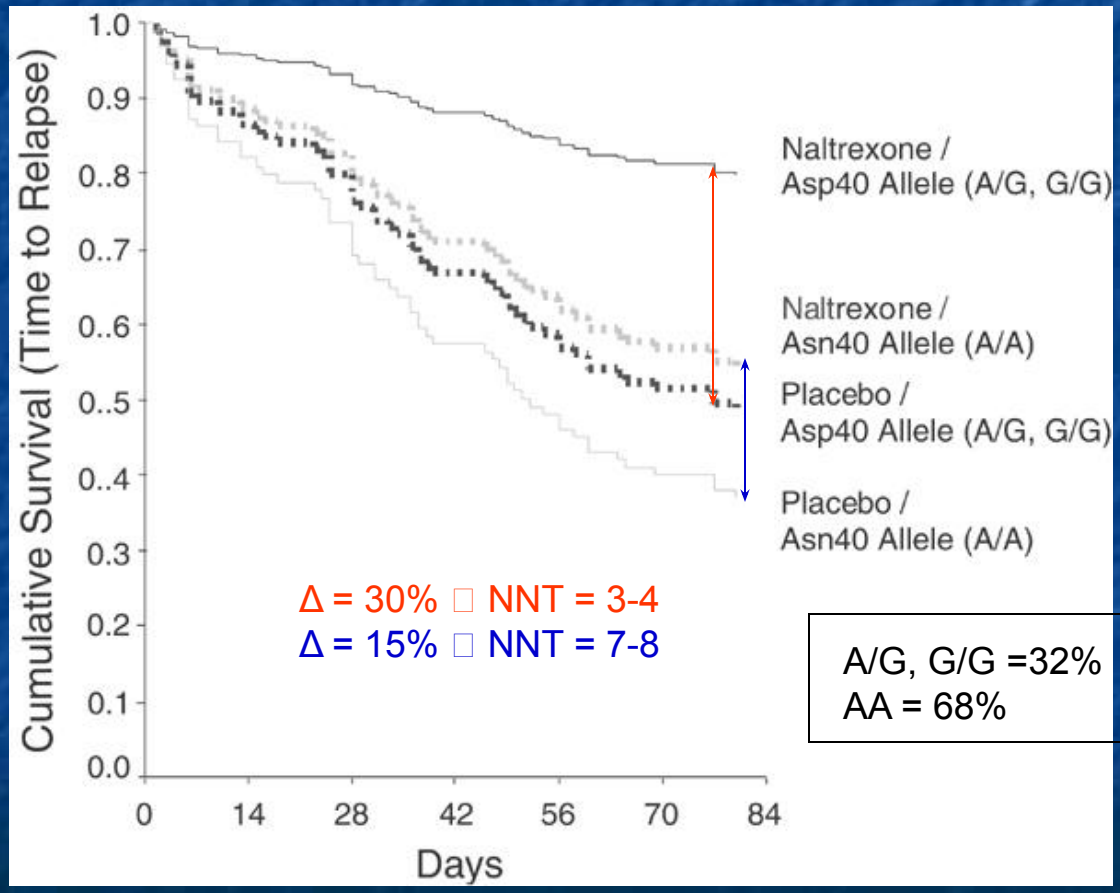
Bouza C et al. *Addiction.* 2004;99:811-828.

Family History and Naltrexone Efficacy



Naltrexone Pharmacogenomics

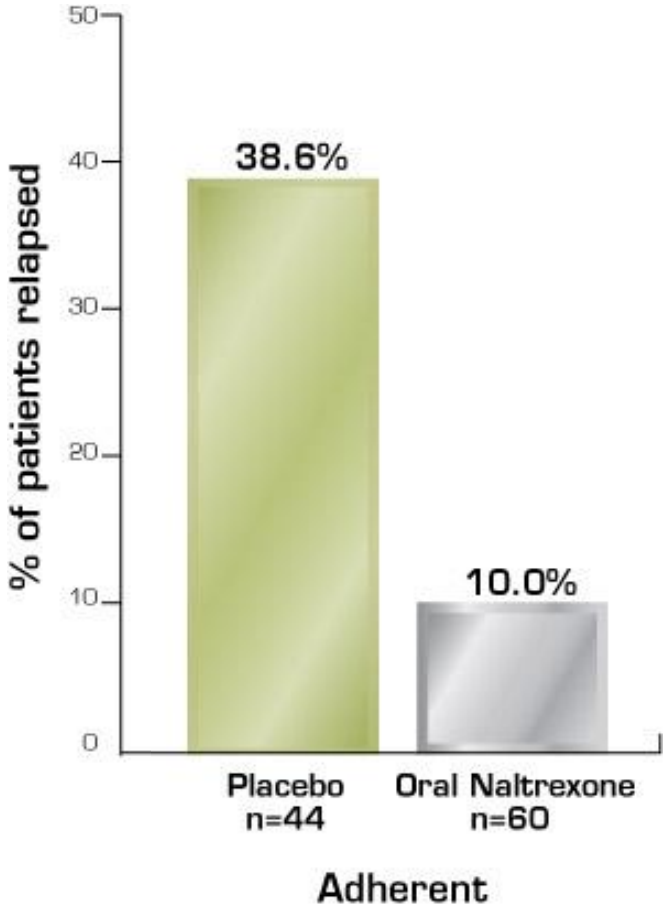
Oslin et al (2003) Neuropsychopharmacology



A/G, G/G =32%
AA = 68%

McGeary et al. 2006	+
Gerlernter et al. 2007	-
Anton et al. 2008	+
Kim et al. 2008	+
Ooteman, submitted	+

Налтрексон: Комплайенс vs Нон-Комплайенс



Pettinati HM, et al. *J Addict Dis.* 2000;19:71-83.

Addiction

RESEARCH REPORT

doi:10.1111/j.1360-0443.2008.02345.x

Persistence with oral naltrexone for alcohol treatment: implications for health-care utilization

Henry R. Kranzler[1], Judith J. Stephenson[2], Leslie Montejano[3], Shaohung Wang[3] & David R. Gastfriend[4]

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ABSTRACT

Aims Concerns have been raised about patients' failure to persist in alcohol treatment. We examined prescriptions for oral naltrexone in a large, nationally distributed treatment population to identify characteristics and health-care utilization patterns associated with persistence. **Design** Data from the 2000–2004 MarketScan® Commercial Claims and Encounters Database were used to identify patients with alcohol-related claims who were prescribed naltrexone. **Measurements** Analysis identified patient characteristics that predicted persistence with naltrexone (defined as having filled prescriptions for ≥80% of the 6-month treatment period) and its association to health-care utilization. **Findings** Of 1138 patients, 162 (14.2%) were persistent in obtaining naltrexone. Non-persistent patients were significantly younger, more likely to be hourly employees and to live in an area with a lower median income, and less likely to be newly diagnosed with an alcohol-related disorder. Non-persistence in obtaining naltrexone was associated with significantly more intensive treatments, including inpatient detoxification, emergency room visits and hospitalizations. **Conclusions** Over a 6-month period, 85.8% of patients who filled an initial prescription for naltrexone did not persist in obtaining the medication. Non-persistence was associated with significantly greater use of costly health-care services. Because the study was correlational, it is not possible to conclude that persistence reduced health-care costs, as patients with a better prognosis may have been more persistent. Research is needed to determine whether interventions that enhance persistence with naltrexone therapy improve treatment outcomes and reduce health-care costs.

Keywords Adherence, alcohol-related, alcohol treatment, health-care costs, health-care utilization, naltrexone, persistence, pharmacotherapy.

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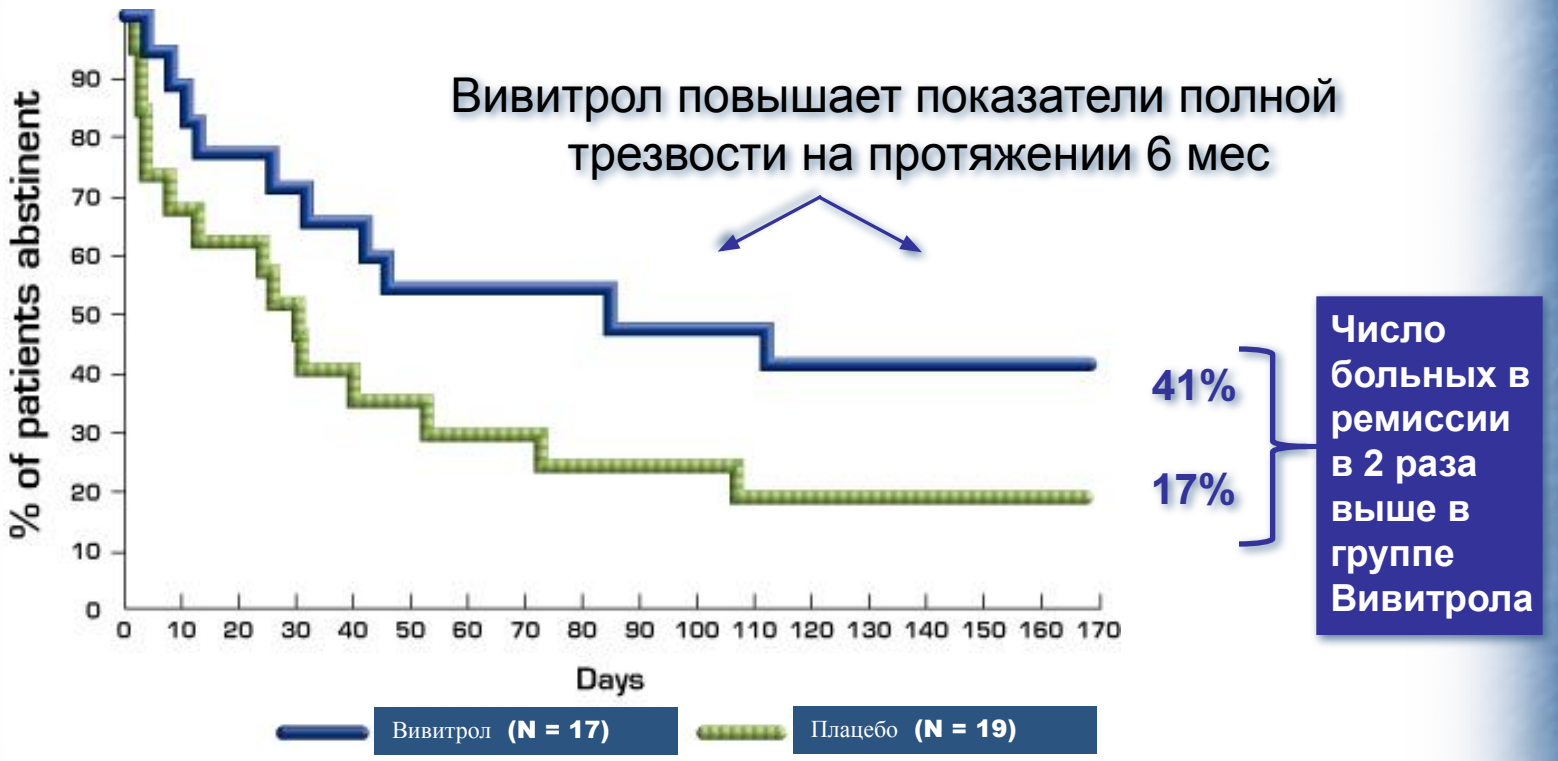
Долго действующая депо-форма налтрексона (Вивитрол)

Вивитрол (380mg налтрексона):

- **Зарегистрирован в США в 2006 г. как средство для лечения алкоголизма**
- **Зарегистрирован в России в 2008 г. как средство для лечения алкоголизма**

Вивитрол улучшает показатели ремиссии (полной трезвости)[1]

Среди больных, которые не употребляли алкоголь 7 дней и более до рандомизации

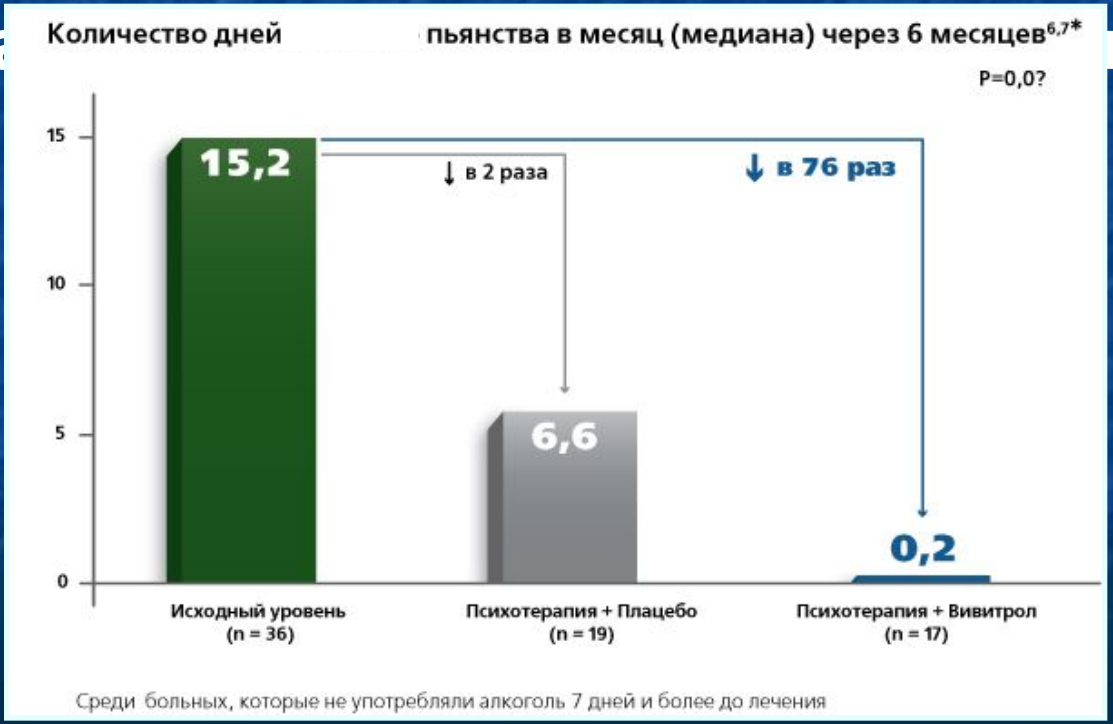


Garbutt JC, et al. *JAMA.* 2005;293:1617-1625.

Вивитрол

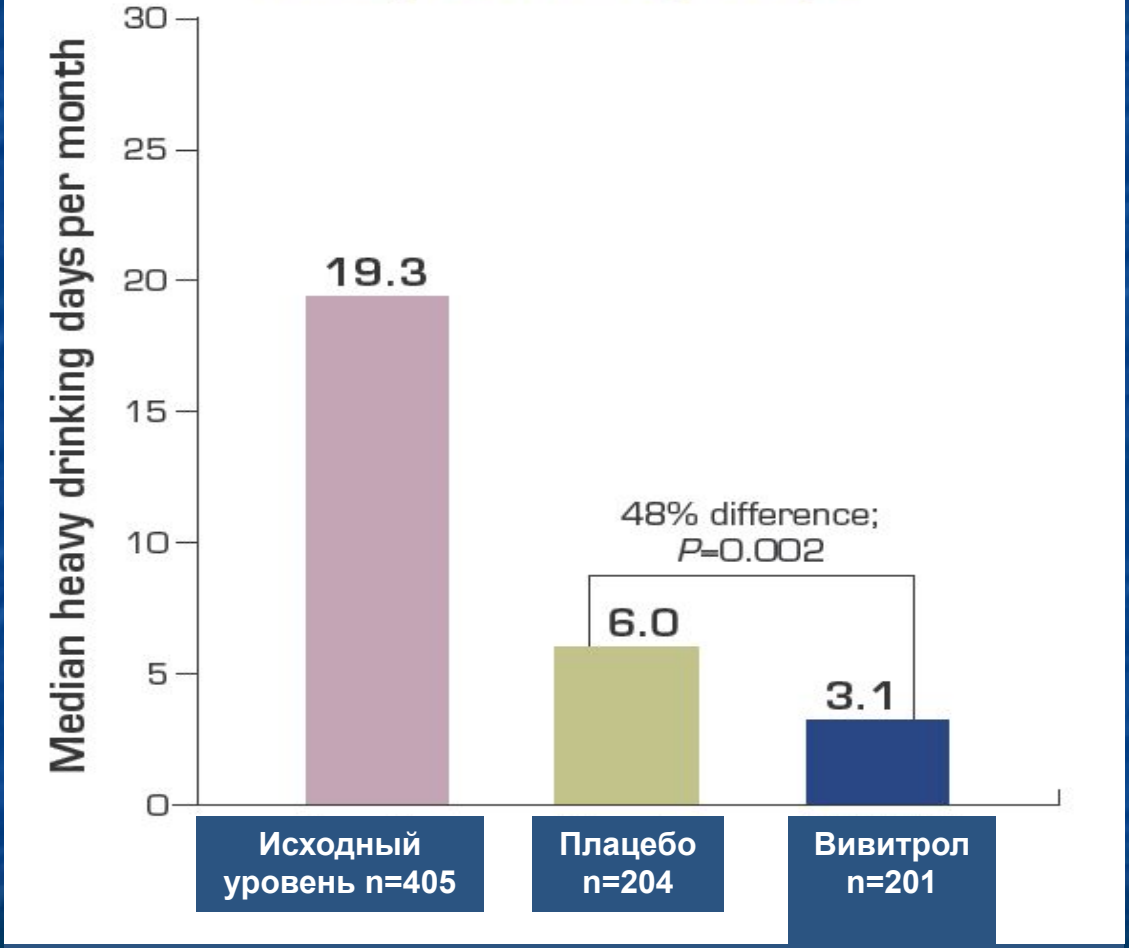
Обеспечивает достижение и стабилизацию ремиссии при алкогольной зависимости

- **Вивитрол обеспечивает частичную ремиссию, значительно снижая количество дней пьянства**
- **Вивитрол уменьшает количество дней пьянства**



1. Garbutt JC, et al. *JAMA*. 2005;293:1617-1625.
2. Volpicelli JR, et al. *Combining Medication and Psychosocial Treatments for Addictions: The BRENDA Approach*. 2001.

Вивитрол уменьшает количество дней тяжелого пьянства



Adapted from Garbutt et al. *JAMA.* 2005;293:1617-1625.

налмефен

- новый опиоидныЙ антагонист
- отсутствует токсическое действие на печень в зависимости от дозы
- большая биодоступность при пероральном употреблении
- более продолжительное антагонистическое действие
- большая афинность к опиатным рецепторам
- **Targeted use**

Nalmefene Working Mechanism

0145-6008/04/2809-1362$03.00/0
ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH
Vol. 28, No. 9
September 2004

Effects of Naltrexone and Nalmefene on Subjective Response to Alcohol Among Non-Treatment-Seeking Alcoholics and Social Drinkers

David J. Drobes, Raymond F. Anton, Suzanne E. Thomas, and Konstantin Voronin

Background: Despite the relative success of opiate antagonist medication within controlled clinical trials for alcoholism, laboratory studies have not fully examined potential mechanisms for their efficacy in alcohol-dependent persons. The present study evaluated the impact of naltrexone and nalmefene on craving and subjective effects after a moderate alcohol dose among non-treatment-seeking alcoholics (n = 125) and social drinkers (n = 90).

Methods: Participants were randomly assigned to receive placebo, naltrexone (titrated to 50 mg/day), or nalmefene (titrated to 40 mg/day) for seven days before an alcohol challenge clinical laboratory session. During the clinical laboratory session, a drink of alcohol (0.4 mg/kg for men, 0.34 mg/kg for women) was provided in a bar-like setting. The effects of the alcohol dose on subjective craving, stimulation, and sedation were measured before having free access to alcohol.

Results: Alcoholics reported higher levels of craving than social drinkers before and after the drink as well as higher levels of alcohol-induced stimulation. Both opiate antagonist medications suppressed initial increases in craving and stimulation.

Conclusions: These findings demonstrate that both naltrexone and nalmefene are associated with reduced alcohol-induced craving and stimulation among alcoholics who are not actively attempting to reduce drinking. These data provide insights into potential mechanisms that may underlie opiate antagonists' effects in the context of treatment.

Key Words: Naltrexone, Nalmefene, Alcohol, Craving, Stimulation.

Naltrexone and Nalmefene are associated with reduced craving and reduced stimulation

«TARGETED» использование антагонистов опиатов при алкоголизме

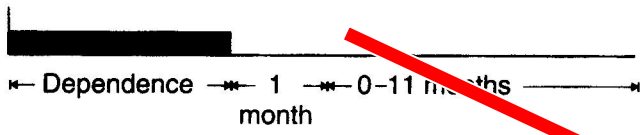
Может ли больной алкоголизмом пить «в меру» (контролировано) ???

Традиционная парадигма в российской наркологии:

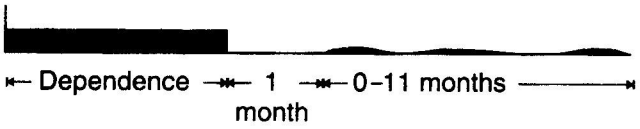
- **НЕ ДЕЛАЙ ПЕРВОГО ГЛОТКА!!!!!!**
- **ИНАЧЕ ЗАПЪЕШЬ !!!**

DSM-IV, page 180

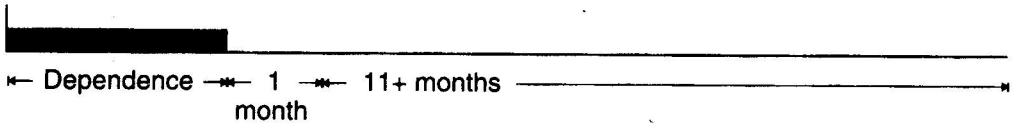
Early Full Remission. This specifier is used if, for at least 1 month, but for less than 12 months, no criteria for Dependence or Abuse have been met.



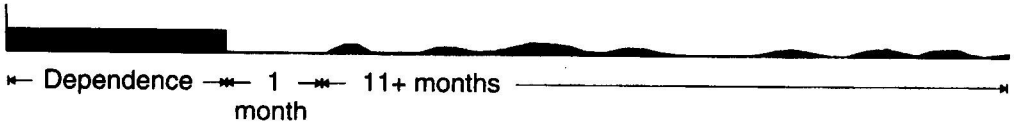
Early Partial Remission. This specifier is used if, for at least 1 month, but less than 12 months, one or more criteria for Dependence or Abuse have been met (but the full criteria for Dependence have not been met).



Sustained Full Remission. This specifier is used if none of the criteria for Dependence or Abuse have been met at any time during a period of 12 months or longer.



Sustained Partial Remission. This specifier is used if full criteria for Dependence have not been met for a period of 12 months or longer; however, one or more criteria for Dependence or Abuse have been met.



Recovery from DSM-IV alcohol dependence: United States, 2001–2002

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Submitted 23 April 2004;
initial review completed 3 August 2004;
final version accepted 28 September 2004

ABSTRACT

Aims To investigate the prevalence and correlates of recovery from *Diagnostic and Statistical Manual* version IV (DSM-IV) alcohol dependence by examining the past-year status of individuals who met the criteria for prior-to-past-year (PPY) dependence.

Design Cross-sectional, retrospective survey of a nationally representative sample of US adults 18 years of age and over (first wave of a planned longitudinal survey).

Methods This analysis is based on data from the 2001–02 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), in which data were collected in personal interviews conducted with one randomly selected adult in each sample household. A subset of the NESARC sample (total $n = 43\,093$), consisting of 4422 US adults 18 years of age and over classified with PPY DSM-IV alcohol dependence, were evaluated with respect to their past-year recovery status: past-year dependence, partial remission, full remission, asymptomatic risk drinking, abstinent recovery (AR) and non-abstinent recovery (NR). Correlates of past-year status were examined in bivariate analyses and using multivariate logistic regression models.

Findings Of people classified with PPY alcohol dependence, 25.6% were still classified as dependent in the past year; 27.3% were classified as being in partial remission; 11.8% were asymptomatic risk drinkers who demonstrated a pattern of drinking that put them at risk of relapse; 17.7% were low-risk drinkers; and 18.2% were abstainers. Only 25.5% of people with PPY dependence ever received treatment. Being married was associated positively with the odds of both AR and NR, and ethanol intake was negatively associated with both. Severity of dependence increased the odds of AR but decreased the odds of NR. The odds of AR (but not NR) increased with age and female gender but were decreased by the presence of a personality disorder. Treatment history modified the effects of college attendance/graduation, age at onset and interval since onset on the odds of recovery.

Conclusions There is a substantial level of recovery from alcohol dependence. Information on factors associated with recovery may be useful in targeting appropriate treatment modalities.

KEYWORDS Dependence, natural recovery, remission, recovery, risk drinking.

ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Vol. 31, No. 7
July 2007

Targeted Nalmefene With Simple Medical Management in the Treatment of Heavy Drinkers: A Randomized Double-Blind Placebo-Controlled Multicenter Study

Sakari Karhuvaara, Kaarlo Simojoki, Antti Virta, Markus Rosberg, Eliisa Löyttyniemi, Tommi Nurminen, Antero Kallio, and Rauno Mäkelä

Table 3. Drinking Outcomes by Study Month, Means, and Standard Deviations (Medians and Quartile Ranges for VHDD)

Study month	*N*	HDD	Abstinence days	VHDD	Drinks/DD	Drinks/wk
Nalmefene						
Prestudy	236	15.5 (6.9)	8.8 (6.6)	7.0 (3.0–10.5)	9.6 (4.8)	43.2 (22.4)
1	217	8.9 (6.8)	13.7 (8.2)	2.0 (0.0–5.0)	6.5 (3.3)	23.1 (16.9)
2	195	8.8 (6.9)	14.0 (8.3)	1.0 (0.0–5.0)	6.5 (4.1)	22.8 (17.4)
3	176	8.6 (7.1)	14.1 (8.7)	1.0 (0.0–4.0)	6.5 (4.1)	22.7 (18.2)
4	161	9.2 (7.4)	13.2 (8.5)	2.0 (0.0–4.0)	6.7 (4.1)	25.0 (22.6)
5	149	8.9 (7.3)	13.4 (8.8)	1.0 (0.0–5.0)	6.8 (4.4)	24.4 (20.4)
6	149	9.3 (7.6)	13.2 (8.9)	1.0 (0.0–5.0)	6.8 (4.2)	25.5 (23.7)
7	131	8.8 (7.3) -6.7	13.8 (8.9) +5.0	1.0 (0.0–5.0) -6.0	6.3 (3.9) -3.3	23.2 (20.8) -20.0
Placebo						
Prestudy	159	16.2 (6.9)	8.5 (6.6)	8.0 (3.0–12.0)	9.5 (4.0)	45.0 (23.3)
1	143	11.8 (7.5)	12.2 (8.4)	5.0 (2.0–9.0)	8.1 (3.4)	32.2 (21.0)
2	133	11.4 (7.4)	12.6 (8.1)	5.0 (1.0–8.0)	7.8 (3.6)	30.8 (21.0)
3	128	12.0 (7.6)	12.8 (8.0)	5.0 (2.0–10.0)	8.4 (3.6)	32.6 (22.1)
4	123	11.2 (7.6)	13.3 (8.0)	4.0 (1.0–8.0)	8.1 (3.6)	30.3 (21.5)
5	118	11.5 (7.9)	12.4 (8.4)	4.5 (1.0–8.0)	7.9 (3.8)	31.6 (22.3)
6	114	11.7 (8.2)	12.6 (8.2)	4.0 (1.0–9.0)	7.9 (4.0)	32.0 (23.9)
7	102	10.6 (8.3) -5.6	13.7 (8.2) +5.2	4.0 (0.0–7.0) -4.0	7.3 (3.7) -2.2	28.5 (23.7) -16.5
p-values		0.0065[a]	0.0499[a]	<0.0001[b]	0.0134[a]	0.0018[a]

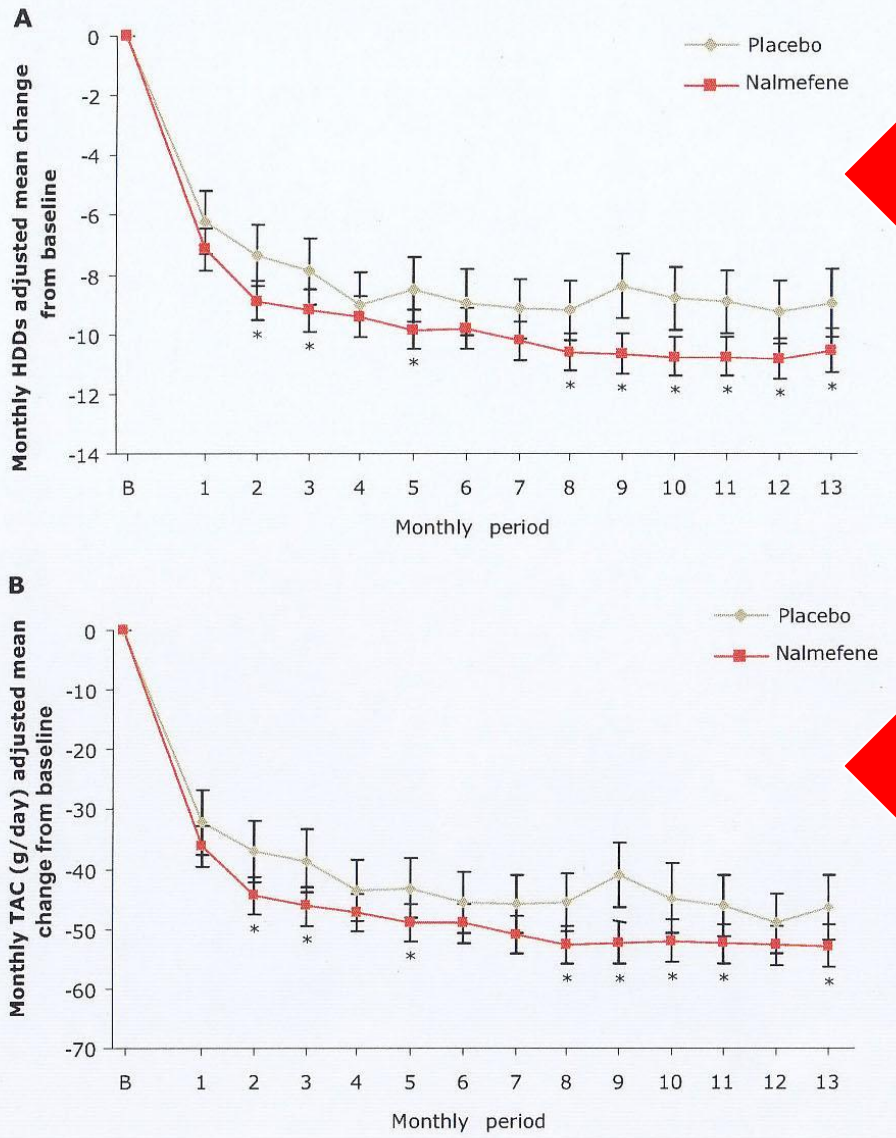
[a]Treatment–time interaction, repeated measures analysis of variance (ANOVA).
[b]Treatment, Poisson's regression for repeated measures.
HDD, heavy drinking days; VHDD, very heavy drinking days; Drinks/DD, number of standard drinks per drinking day.

Phase III Program - Lundbeck

Study Name	Dose regimen & duration	Patients (alcohol dependence by DSM-IV)	Countries
ESENSE 1 (12014A)	**20 mg, as needed, placebo controlled, 6-month**	**604**	**Germany, Finland, Sweden, Austria**
ESENSE 2 (12023A)	**20 mg as needed, placebo controlled, 6-month**	**718**	**Spain, Italy, Portugal, France, Belgium, Poland, Czech Rep**
SENSE (12013A)	**20 mg as needed, placebo controlled, 12-month**	**675**	**Czech Rep, Estonia, Hungary, Latvia, Lithuania, Poland, Russia, Slovakia, Ukraine, United Kingdom**

* Adapted from www.clinicaltrials.gov

Figure 2: Change in alcohol consumption



(A) Adjusted mean change from baseline in monthly heavy drinking days (HDDs); (B) Adjusted mean change from baseline in monthly total alcohol consumption (TAC; g/day) *=p<0.05. B=baseline.

Ежемесячное количество дней тяжелого пьянства

Среднее количество алкоголя в день (г/день)

Препараты, продемонстрировавшие эффективность в отношении лечения алкоголизма в отдельных научных (доказательных) исследованиях

- **Топирамат**
- **Ондансетрон**
- **Антидепрессанты**

Efficacy of Topiramate

Oral topiramate for treatment of alcohol dependence: a randomised controlled trial

Bankole A Johnson, Nassima Ait-Daoud, Charles L Bowden, Carlo C DiClemente, John D Roache, Kevin Lawson, Martin A Javors, Jennie Z Ma

Topiramate for Treating Alcohol Dependence
A Randomized Controlled Trial

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Norman Rosenthal, MD
Julie A. Capece, BA
Frank Wiegand, MD
Lian Mao, PhD
Karen Beyers, MS
Amy McKay, PharmD
Nassima Ait-Daoud, MD
Raymond F. Anton, MD
Domenic A. Ciraulo, MD
Henry R. Kranzler, MD
Karl Mann, MD
Stephanie S. O'Malley, PhD
Robert M. Swift, MD, PhD
for the Topiramate for Alcoholism Advisory Board and the Topiramate for Alcoholism Study Group

Context Hypothetically, topiramate can improve drinking outcomes among alcohol-dependent individuals by reducing alcohol's reinforcing effects through facilitation of γ-aminobutyric acid function and inhibition of glutaminergic pathways in the corticomesolimbic system.

Objective To determine if topiramate is a safe and efficacious treatment for alcohol dependence.

Design, Setting, and Participants Double-blind, randomized, placebo-controlled, 14-week trial of 371 men and women aged 18 to 65 years diagnosed with alcohol dependence, conducted between January 27, 2004, and August 4, 2006, at 17 US sites.

Interventions Up to 300 mg/d of topiramate (n=183) or placebo (n=188), along with a weekly compliance enhancement intervention.

Main Outcome Measures Primary efficacy variable was self-reported percentage of heavy drinking days. Secondary outcomes included other self-reported drinking measures (percentage of days abstinent and drinks per drinking day) along with the laboratory measure of alcohol consumption (plasma γ-glutamyltransferase).

Results Treating all dropouts as relapse to baseline, topiramate was more efficacious than placebo at reducing the percentage of heavy drinking days from baseline to week 14 (mean difference, 8.44%; 95% confidence interval, 3.07%-13.80%; P=.002). Prespecified mixed-model analysis also showed that topiramate compared with placebo decreased the percentage of heavy drinking days (mean difference, 16.19%; 95% confidence interval, 10.79%-21.60%; P<.001) and all other drinking out-

Johnson et al
Lancet, 2003
(n=150; 1 site)

Johnson et al
JAMA, 2007
(n=371; multi-site)

Топирамат

- **Механизмы действия:**
  - Блокирует постсинаптические AMPA-рецепторы (подтип рецепторов глютамата)
  - Активирует ГАМК-эргическую систему мозга
  - Блоктрует дигидропиридин-чувствительные потенциал-зависимые кальциевые каналы (L-типа)
- **При ААС:**
  - Активирована глютаматергическая нейротрансмиссия
  - Снижена ГАМК-эргическая нейротрансмиссия
  - Гиперактивность дигидропиридин-чувствительных потенциал-зависимых кальциевых каналов

Alcoholism: Clinical and Experimental Research

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April 2007

Antiglutamatergic Strategies for Ethanol Detoxification: Comparison With Placebo and Diazepam

Evgeny M. Krupitsky, Anatoly A. Rudenko, Andrey M. Burakov, Tatyana Y. Slavina, Alexander A. Grinenko, Brian Pittman, Ralitza Gueorguieva, Ismene L. Petrakis, Edwin E. Zvartau, and John H. Krystal

Background: Benzodiazepines are the standard pharmacotherapies for ethanol detoxification, but concerns about their abuse potential and negative effects upon the transition to alcohol abstinence drive the search for new treatments. Glutamatergic activation and glutamate receptor up-regulation contribute to ethanol dependence and withdrawal. This study compared 3 antiglutamatergic strategies for ethanol detoxification with placebo and to the benzodiazepine, diazepam: the glutamate release inhibitor, lamotrigine; the *N*-methyl-D-aspartate glutamate receptor antagonist, memantine; and the AMPA/kainite receptor inhibitor, topiramate.

Methods: This placebo-controlled randomized single-blinded psychopharmacology trial studied male alcohol-dependent inpatients ($n = 127$) with clinically significant alcohol withdrawal symptoms. Subjects were assigned to 1 of 5 treatments for 7 days: placebo, diazepam 10 mg TID, lamotrigine 25 mg QID, memantine 10 mg TID, or topiramate 25 mg QID. Additional diazepam was administered when the assigned medication failed to suppress withdrawal symptoms adequately.

Results: All active medications significantly reduced observer-rated and self-rated withdrawal severity, dysphoric mood, and supplementary diazepam administration compared with placebo. The active medications did not differ from diazepam.

Conclusions: This study provides the first systematic clinical evidence supporting the efficacy of a number of antiglutamatergic approaches for treating alcohol withdrawal symptoms. These data support the hypothesis that glutamatergic activation contributes to human alcohol withdrawal. Definitive studies of each of these medications are now needed to further evaluate their effectiveness in treating alcohol withdrawal.

Key Words: Ethanol, Alcoholism, Dependence, Withdrawal, Glutamate, Glutamate Receptors (NMDA, AMPA, Kainate), Anticonvulsant, Lamotrigine, Memantine, Topiramate.

Effect of Memantine on Cue-Induced Alcohol Craving in Recovering Alcohol-Dependent Patients

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Dimitry Masalov, M.D.
Andrey M. Burakov, M.D., Ph.D.
Tatyana Didenko, M.D.
Tatyana Romanova, Ph.D.
Marina Tsoy, M.D.
Anton Bespalov, M.D., Ph.D.
Tatyana Y. Slavina, M.D., Ph.D.
Alexander A. Grinenko, M.D., Ph.D.
Ismene L. Petrakis, M.D.
Brian Pittman, M.S.
Ralitza Gueorguieva, Ph.D.
Edwin E. Zvartau, M.D., D.M.Sci.
John H. Krystal, M.D.

Objective: Ethanol blocks *N*-methyl-D-aspartic acid (NMDA) glutamate receptors. Increased NMDA receptor function may contribute to motivational disturbances that contribute to alcoholism. The authors assessed whether the NMDA receptor antagonist memantine reduces cue-induced alcohol craving and produces ethanol-like subjective effects.

Method: Thirty-eight alcohol-dependent inpatients participated in three daylong testing sessions in a randomized order under double-blind conditions. On each test day, subjects received 20 mg of memantine, 40 mg of memantine, or placebo, and subjective responses to treatment were assessed. The level of alcohol craving was assessed before and after exposure to an alcohol cue.

Results: Memantine did not stimulate alcohol craving before exposure to an alcohol cue, and it attenuated alcohol cue-induced craving in a dose-related fashion. It produced dose-related ethanol-like effects without adverse cognitive or behavioral effects.

Conclusions: These data support further exploration of whether well-tolerated NMDA receptor antagonists might have a role in the treatment of alcoholism.

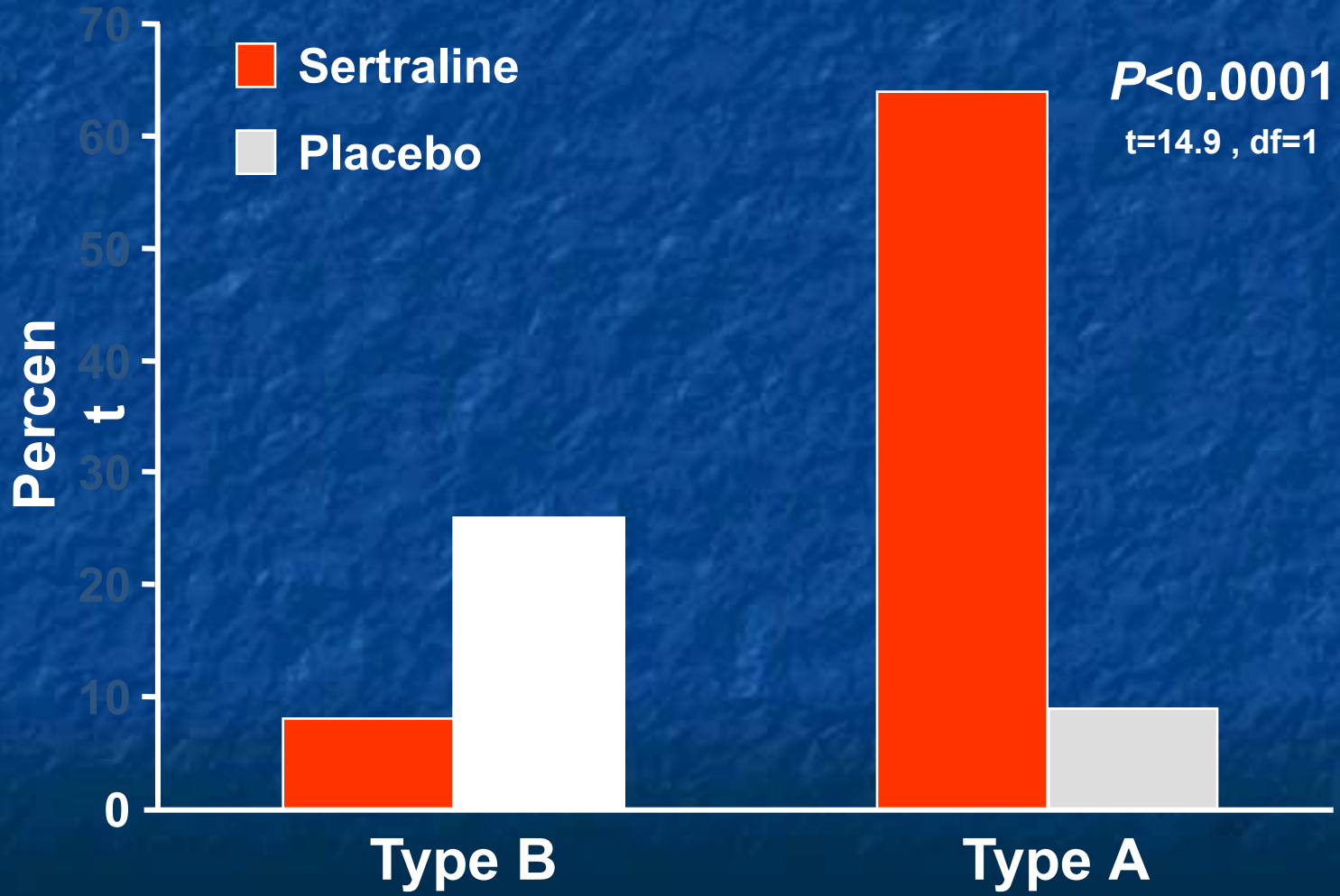
(Am J Psychiatry 2007; 164:519–523)

Antagonists of *N*-methyl-D-aspartate (NMDA) glutamate receptors may have a role in the pharmacotherapy of alcoholism (1–3). Blockade of NMDA receptors by ethanol contributes to ethanol's effects in animal and human subjects (1). Groups at risk of heavy drinking exhibit decreased dysphoric mood responses to NMDA receptor antagonists (1, 4). Enhanced NMDA receptor function in alcohol dependence also may contribute to disturbances

Препараты, продемонстрировавшие эффективность в отношении лечения алкоголизма в отдельных научных (доказательных) исследованиях

- **Топирамат**
- **Ондансетрон**
- **Антидепрессанты**

Percent Completely Abstinent



Pettinati HM, Volpicelli JR, Kranzler HR et al. *Alcohol Clin Exp Res.* 2000;24:1041-1049.

RCT of Sertraline for Alcohol Dependence: Moderation by Age of Onset and Genotype

H.R. Kranzler, S. Armeli, H. Tennen, J. Covault, R. Feinn, A.J. Arias, H. Pettinati, & C. Oncken
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Background

Late-onset/low vulnerability alcoholics (LOAs) appear to drink less when treated with a selective serotonin reuptake inhibitor (SSRI) than placebo, whereas early-onset/high vulnerability alcoholics (EOAs) show the opposite effect (Kranzler et al. 1996, Pettinati et al. 2000, Chick et al. 2004). We conducted a 12-week, parallel-groups, placebo-controlled trial of the efficacy of sertraline in alcohol dependence (AD) in LOAs compared with EOAs. We also examined a functional polymorphism in the serotonin transporter gene (5-HTTLPR) as a moderator of the medication effects.

Methods

134 patients (80.6% male; 34.3% EOAs) with DSM-IV AD received up to 200 mg of sertraline (N=63) or placebo (N=71) daily. Assignment was by urn randomization, which included Age of Onset of AD as a factor. There were no pretreatment factors that differed significantly by Medication Group X Age of Onset. Patients were genotyped for the tri-allelic 5-HTTLPR polymorphism. Planned analyses included main and interaction effects of Medication Group, Age of Onset (≤ 25 years vs. > 25 years), and Genotype (L'/L' vs. S'carriers) on drinking days and heavy drinking days.

Figure 1: Drinking Days

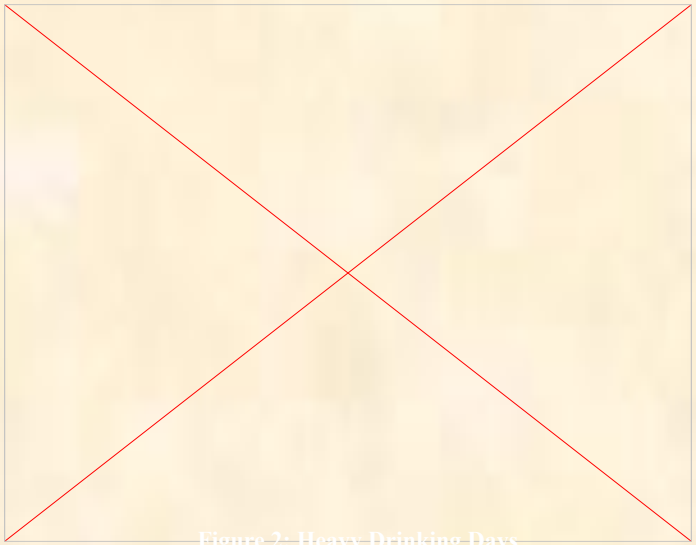
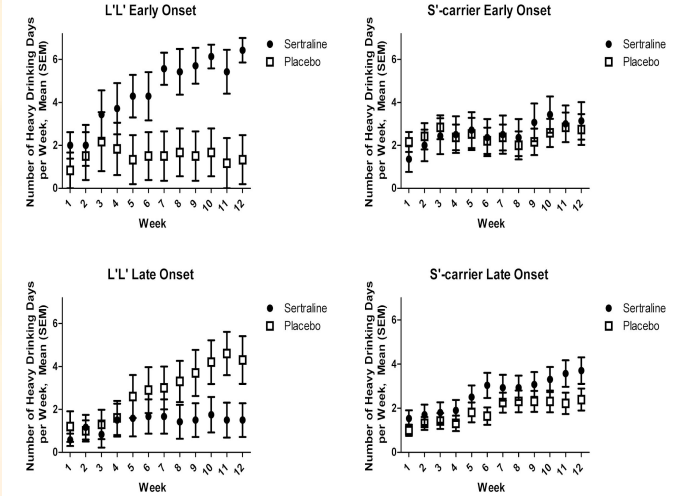


Figure 2: Heavy Drinking Days



Results

As shown in the figures, the moderating effect of Age of Onset on the response to sertraline was conditional on 5-HTTLPR Genotype. Although there were no main or interaction effects among S' allele carriers, among L' homozygotes the effects of Medication Group varied by Age of Onset ($P = 0.002$). Whereas, at the end of treatment, LOAs reported fewer drinking days (Fig. 1) and heavy drinking days (Fig. 2) when treated with sertraline ($P = 0.011$), EOAs had fewer drinking and heavy drinking days when treated with placebo ($P < 0.001$).

Conclusions

Effects of sertraline on drinking behavior in L' homozygotes were moderated by Age of Onset. This partially replicates prior findings with SSRIs for treatment of AD. Variation among samples in the prevalence of the L' allele could help to explain differences in the form of the interaction effect observed in previous reports. Because AD is common and SSRIs are widely prescribed, these findings have potential public health significance and warrant further study.

Supported by NIAAA grants R01 AA13631 and K24 AA13736 and NCRR grant M01 RR06192
Registration # NCT00368550 on www.clinicaltrials.gov

ОБОЗРЕНИЕ ПСИХИАТРИИ И МЕДИЦИНСКОЙ ПСИХОЛОГИИ № 1, 2012

Исследования

Простое слепое рандомизированное плацебо-контролируемое исследование эффективности применения тразодона для коррекции аффективных расстройств у больных с алкогольной зависимостью в ремиссии

Е.М. Крупицкий, С.М. Ериш, К.В. Рыбакова, А.С. Киселев, В.А. Бернцев, М.Н. Торбан, С.П. Ерошин, О.Ф. Ерышев
Санкт-Петербургский научно-исследовательский психоневрологический институт им. В.М. Бехтерева

ДВОЙНОЕ СЛЕПОЕ РАНДОМИЗИРОВАННОЕ ПЛАЦЕБО-КОНТРОЛИРУЕМОЕ ИССЛЕДОВАНИЕ ЭФФЕКТИВНОСТИ ПРИМЕНЕНИЯ ЭСЦИТАЛОПРАМА ДЛЯ КОРРЕКЦИИ АФФЕКТИВНЫХ РАССТРОЙСТВ У БОЛЬНЫХ АЛКОГОЛЬНОЙ ЗАВИСИМОСТЬЮ В РЕМИССИИ

Крупицкий Е.М., Ериш С.М., Бернцев В.А., Киселев А.С., Александровский Н.А., Торбан М.Н., Ерошин С.П., Ерышев О.Ф.

Санкт-Петербургский научно-исследовательский психоневрологический институт им. В.М. Бехтерева
192019, Санкт-Петербург, ул. Бехтерева, 3

Доказательная фармакотерапия наркологических заболеваний

- Зависимость от алкоголя
- Зависимость от опиатов
- Зависимость от никотина

ДОКАЗАТЕЛЬНАЯ ФАРМАКОТЕРАПИЯ ОПИЙНОЙ НАРКОМАНИИ

- Полные агонисты опиатных рецепторов
- Парциальные агонисты-антагонисты
- Полные антагонисты (натрексон)

NALTREXONE

Разные лекарственные формы:

1. Пероральная
2. Имплантируемая
3. Иньекционная

ELSEVIER

Journal of Substance Abuse Treatment 26 (2004) 285–294

Journal of Substance Abuse Treatment

Regular article

Naltrexone for heroin dependence treatment in St. Petersburg, Russia

Evgeny M. Krupitsky, M.D., Ph.D.[a], Edwin E. Zvartau, M.D., Ph.D.[a], Dimitry V. Masalov, M.D.[a], Marina V. Tsoi, M.D.[a], Andrey M. Burakov, M.D.[a], Valentina Y. Egorova, M.D.[a], Tatyana Y. Didenko, M.D.[a], Tatyana N. Romanova, M.S[a], Eva B. Ivanova, M.D., Ph.D.[a], Anton Y. Bespalov, M.D., Ph.D.[a], Elena V. Verbitskaya, Ph.D.[a], Nikolai G. Neznanov, M.D., Ph.D.[a], Alexandr Y. Grinenko, M.D., Ph.D.[a], Charles P. O'Brien, M.D.[b], George E. Woody, M.D.[b,*]

[a] *St. Petersburg Scientific Research Center of Addictions and Psychopharmacology, affiliated with St. Petersburg State Pavlov Medical University, Russia*

[b] *University of Pennsylvania, Department of Psychiatry and Veterans Affairs Medical Center, Philadelphia, Pennsylvania, USA*

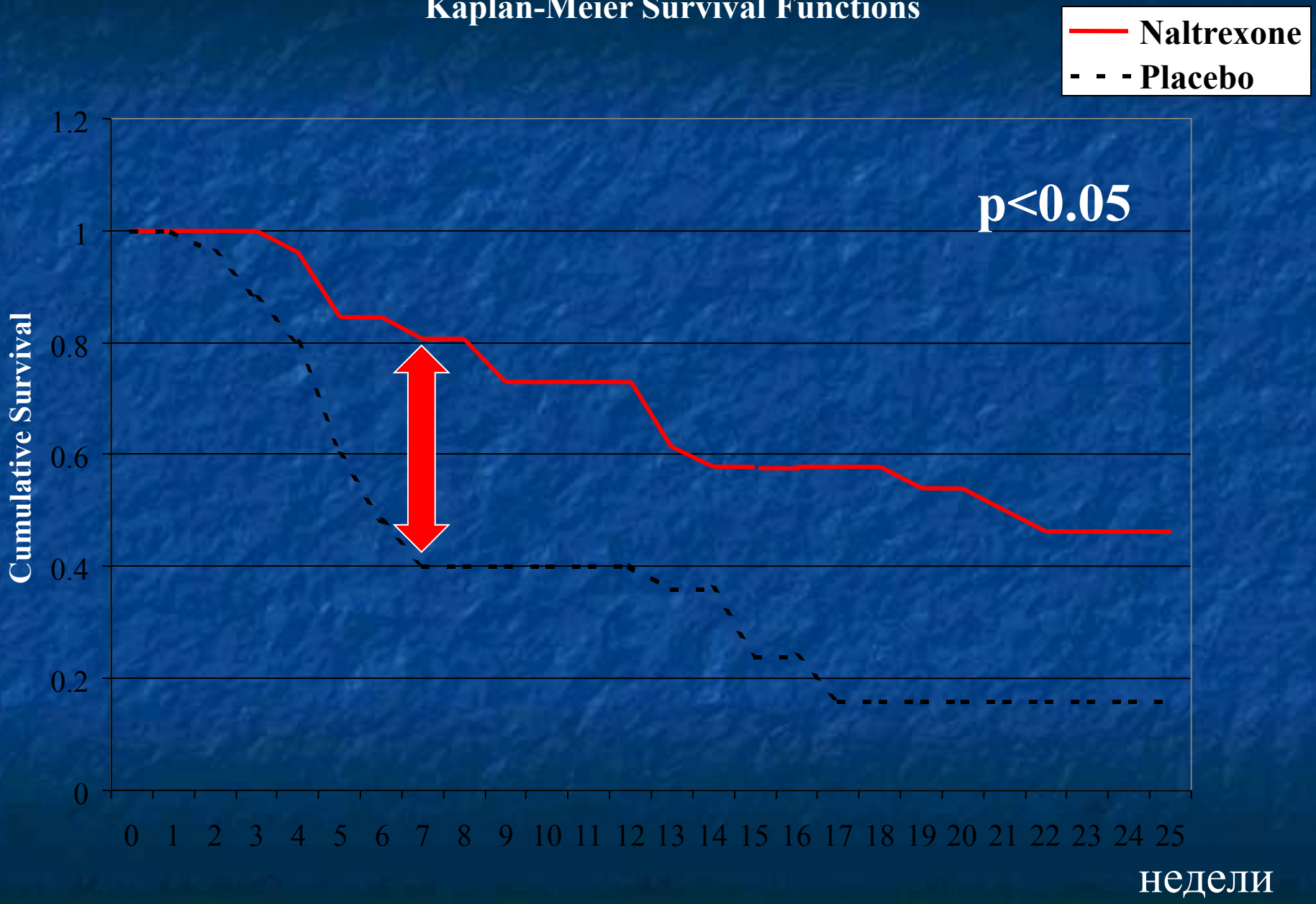
Received 13 July 2003; received in revised form 4 December 2003; accepted 5 February 2004

Abstract

Naltrexone may be more effective for treating opioid (heroin) dependence in Russia than in the U.S. because patients are mostly young and living with their parents, who can control medication compliance. In this pilot study we randomized 52 consenting patients who completed detoxification in St. Petersburg to a double blind, 6-month course of biweekly drug counseling and naltrexone, or counseling and placebo naltrexone. Significant differences in retention and relapse favoring naltrexone were seen beginning at 1 month and continuing throughout the study. At the end of 6 months, 12 of the 27 naltrexone patients (44.4%) remained in treatment and had not relapsed as compared to 4 of 25 placebo patients (16%; $p < 0.05$). Since heroin dependence is the main way HIV is being spread in Russia, naltrexone is likely to improve treatment outcome and help reduce the spread of HIV if it can be made more widely available.

Keywords: Naltrexone; Heroin addiction; Treatment

Ремисси (по группам лечения)



Пероральный налтрексон

- Налтрексон является эффективным методом лечения опийной наркомании (Krupitsky et al, Journal Substance Abuse Treatment, 2004)
- Однако налтрексон не влиял на симптомы постабстиентного синдрома: депрессию, тревогу, влечение к героину

ГИПОТЕЗА

- Антидепрессанты (СИОЗ) могут уменьшить проявления постабстинентных расстройств у больных опийной наркоманией, и, при их комбинации с налтрексоном, улучшить комплайенс с приёмом налтрексона, и, тем самым, его эффективность в отношении стабилизации ремиссии.

ELSEVIER

Journal of Substance Abuse Treatment xxx (2006) xxx–xxx

Journal of Substance Abuse Treatment

Regular article

Naltrexone with or without fluoxetine for preventing relapse to heroin addiction in St. Petersburg, Russia

Evgeny M. Krupitsky, (M.D., Ph.D.)[a], Edwin E. Zvartau, (M.D., Ph.D.)[a], Dimitry V. Masalov, (M.D.)[a], Marina V. Tsoy, (M.D.)[a], Andrey M. Burakov, (M.D.)[a], Valentina Y. Egorova, (M.D.)[a], Tatyana Y. Didenko, (M.D.)[a], Tatyana N. Romanova, (M.S.)[a], Eva B. Ivanova, (M.D., Ph.D.)[a], Anton Y. Bespalov, (M.D., Ph.D.)[a], Elena V. Verbitskaya, (Ph.D.)[a], Nikolai G. Neznanov, (M.D., Ph.D.)[a], Alexandr Y. Grinenko, (M.D., Ph.D.)[a], Charles P. O'Brien, (M.D., Ph.D.)[b], George E. Woody, (M.D.)[b,*]

[a]*St. Petersburg Scientific-Research Center of Addictions and Psychopharmacology (affiliated with St. Petersburg State Pavlov Medical University and Bekhterev Research Psychoneurological Institute), St. Petersburg, Russia*

[b]*Department of Psychiatry and Veterans Affairs Medical Center, University of Pennsylvania, Philadelphia, PA, USA*

Received 1 March 2006; received in revised form 12 May 2006; accepted 12 May 2006

Abstract

This randomized placebo-controlled trial tested the efficacy of oral naltrexone with or without fluoxetine for preventing relapse to heroin addiction and for reducing HIV risk, psychiatric symptoms, and outcome. All patients received drug counseling with parental or significant-other involvement to encourage adherence. Patients totaling 414 were approached, 343 gave informed consent, and 280 were randomized (mean age, 23.6 ± 0.4 years). At 6 months, two to three times as many naltrexone patients as naltrexone placebo patients remained in treatment and had not relapsed, odds ratio (OR) = 3.5 (1.96–6.12), $p < .0001$. Overall, adding fluoxetine did not improve outcomes, OR = 1.35 (0.68–2.66), $p = .49$; however, women receiving naltrexone and fluoxetine showed a trend toward a statistically significant advantage when compared to women receiving naltrexone and fluoxetine placebo, OR = 2.4 (0.88–6.59), $p = .08$. HIV risk, psychiatric symptoms, and overall adjustment were markedly improved among all patients who remained on treatment and did not relapse, regardless of group assignment. More widespread use of naltrexone could be an important addition to addiction treatment and HIV prevention in Russia.

Keywords: Naltrexone; Heroin addiction; HIV

МЕТОДЫ

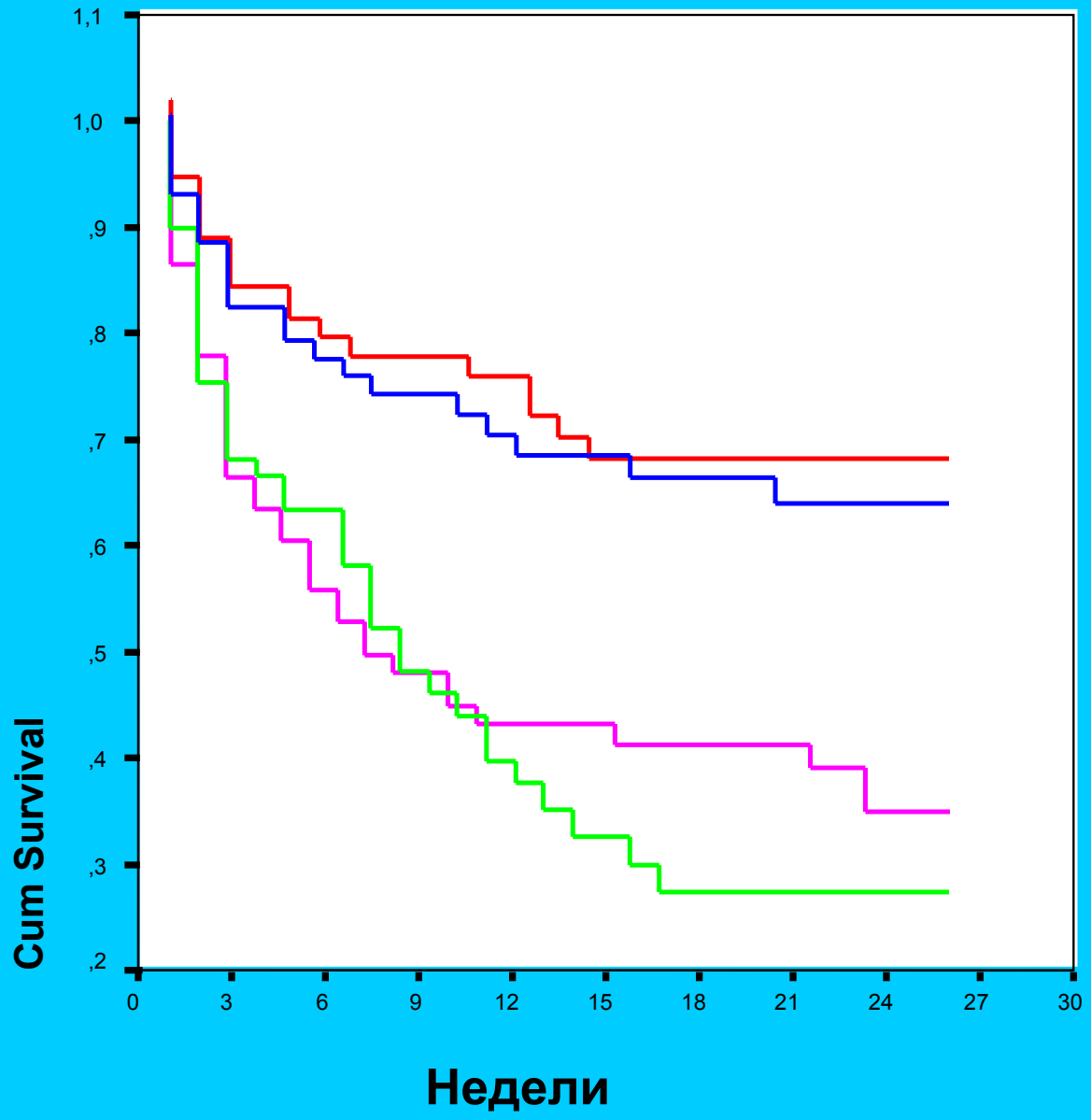
- 280 больных героиновой наркоманией после детоксикации, подписания информированного согласия и прохождения налоксонового теста, были рандомизированны в одну из 4 групп (70 человек в каждой группе).

«Четырёхклеточный дизайн»:

1. Налтрексон (50 мг/сутки) + Флуоксетин (20мг/сутки) (N+F)
2. Налтрексон (50 мг/сутки) + Плацебо-флуоксетин (N+FP)
3. Налтрексон-плацебо + Флуоксетин (20 мг/сутки) (NP+F)
4. Налтрексон-плацебо + Флуоксетин-плацебо (NP+FP)

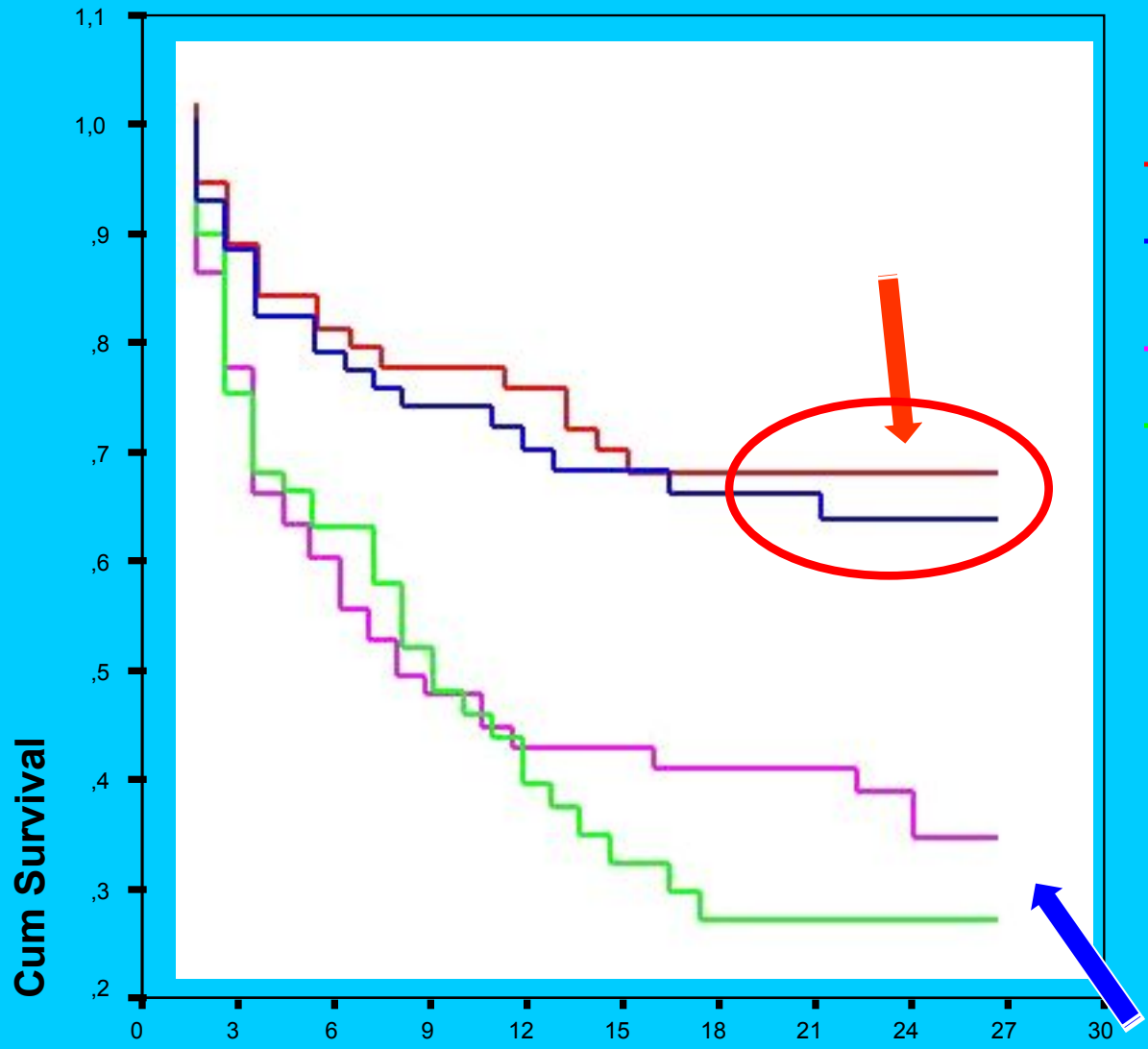
- Лечение продолжалось 6 месяцев
- Всем пациентам раз в две недели проводилась психотерапия в соответствии с руководством, разработанном в Пенсильванском университете.
- Все пациенты имели хотя бы одного члена семьи, который контролировал приём препаратов.
- Дизайн исследования: Двойное слепое рандомизированное плацебо контролируемое

Кривые выживаемости Каплана-Мейера



N+F>NP+FP
N+F>F+NP
N+FP>NP+FP
N+FP>F+NP
F+NP=NP+FP
N+F=N+FP

Кривые выживаемости Каплана-Мейера



N+F>NP+FP

N+F>F+NP

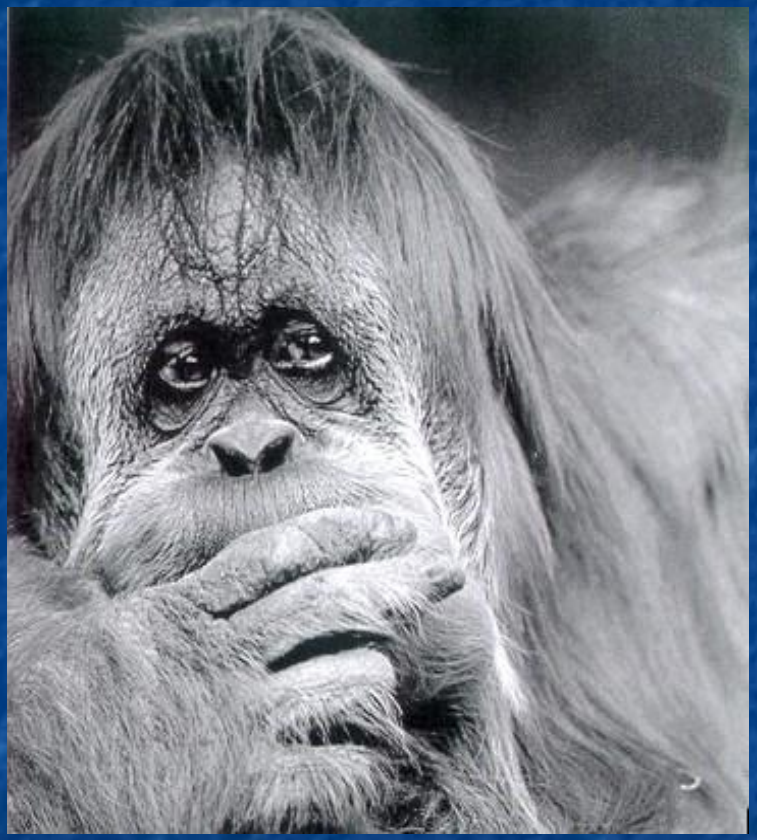
N+FP>NP+FP

N+FP>F+NP

F+NP=NP+FP

N+F=N+FP

Есть ли дугой подход к повышению эффективности ?



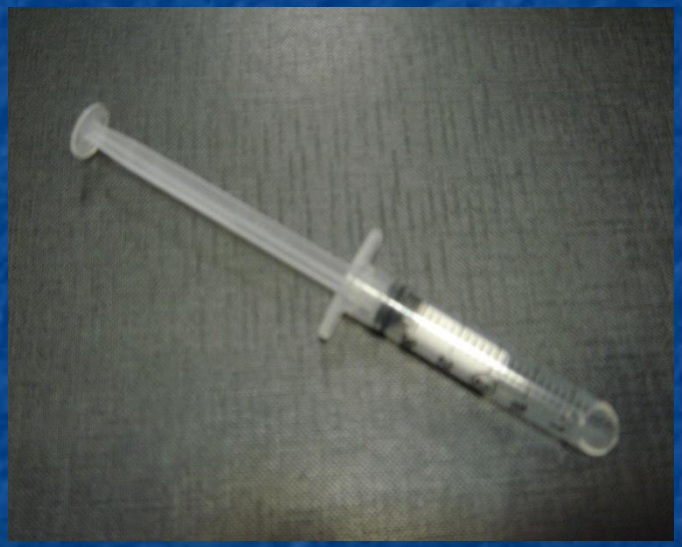
НАЛТРЕКСОН

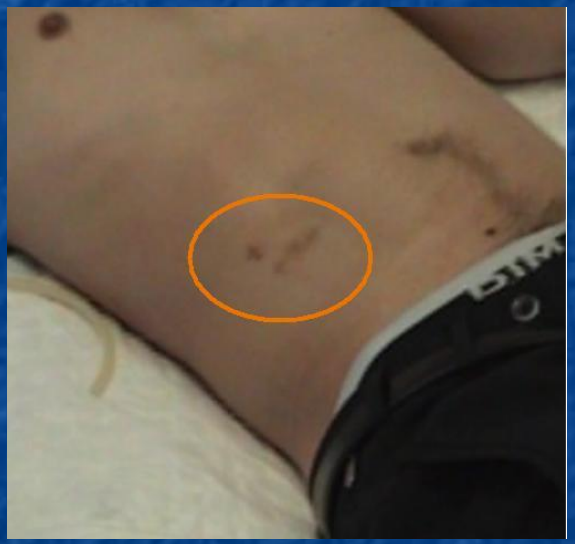
Лекарственные формы:

1. Пероральная
2. Имплантируемая
3. Инъекционаная

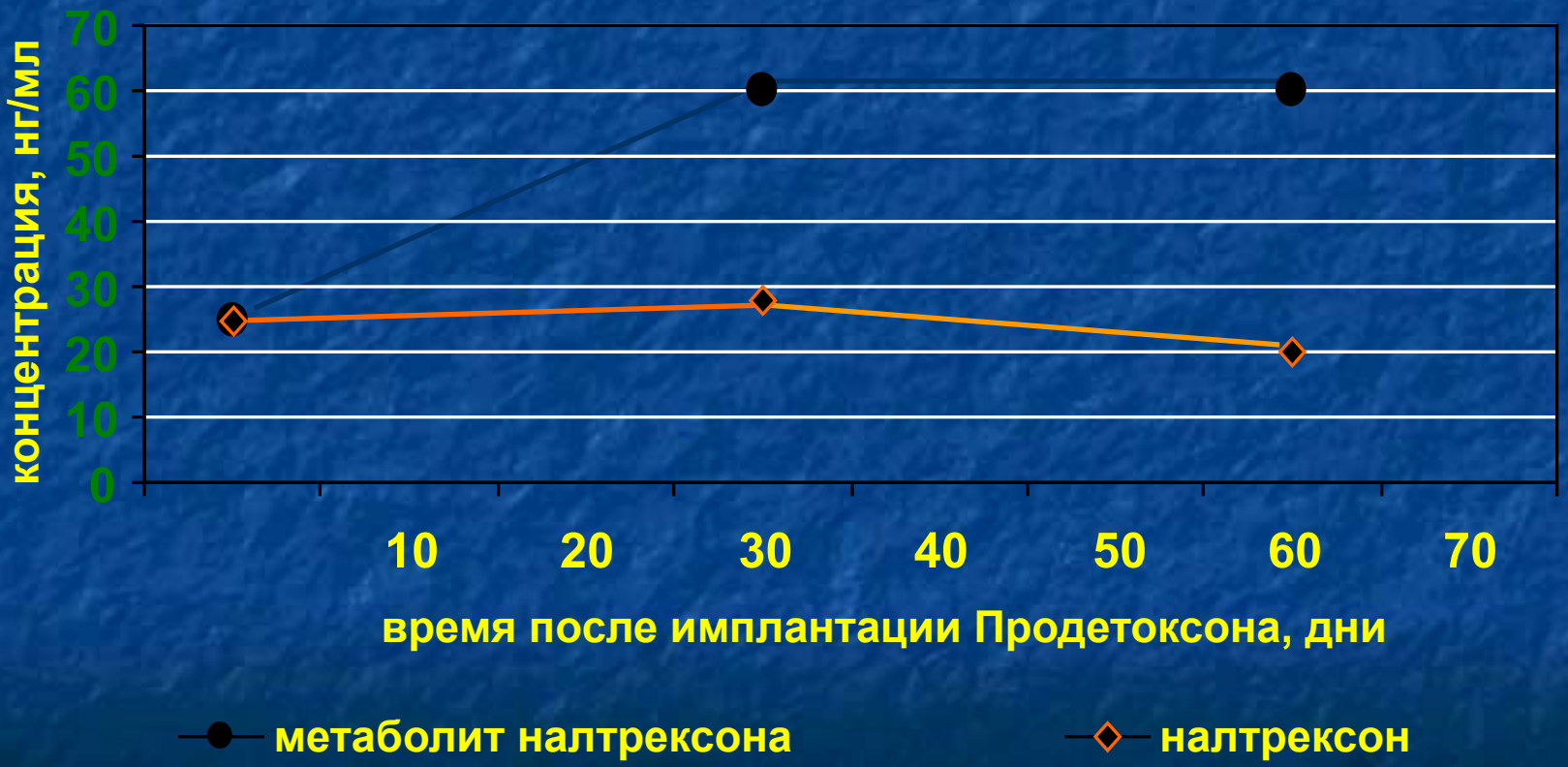
Способ применения и дозы

ПРОДЕТОКСОН®, таблетки для имплантации, налтрексон 1000 мг





ЛАБОРАТОРНЫЕ ДАННЫЕ ПО ФАРМАКОКИНЕТИКЕ ПРОДЕТОКСОНА



Отбор проб плазмы крови производился
через 1 неделю, 1 и 2 месяца после имплантации препарата

ORIGINAL ARTICLE

Randomized Trial of Long-Acting Sustained-Release Naltrexone Implant vs Oral Naltrexone or Placebo for Preventing Relapse to Opioid Dependence

Evgeny Krupitsky, MD, PhD, DMedSci; Edwin Zvartau, MD, PhD, DMedSci; Elena Blokhina, MD, PhD; Elena Verbitskaya, PhD; Valentina Wahlgren, MD; Marina Tsoy-Podosenin, MD, PhD; Natalia Bushara, MD; Andrey Burakov, MD, PhD; Dmitry Masalov, MD; Tatyana Romanova, PsyD; Arina Tyurina, MD; Vladimir Palatkin, MD; Tatyana Slavina, MD, PhD; Anna Pecoraro, PsyD; George E. Woody, MD

Context: Sustained-release naltrexone implants may improve outcomes of nonagonist treatment of opioid addiction.

Objective: To compare outcomes of naltrexone implants, oral naltrexone hydrochloride, and nonmedication treatment.

Design: Six-month double-blind, double-dummy, randomized trial.

Setting: Addiction treatment programs in St Petersburg, Russia.

Participants: Three hundred six opioid-addicted patients recently undergoing detoxification.

Interventions: Biweekly counseling and 1 of the following 3 treatments for 24 weeks: (1) 1000-mg naltrexone implant and oral placebo (NI+OP group; 102 patients); (2) placebo implant and 50-mg oral naltrexone hydrochloride (PI+ON group; 102 patients); or (3) placebo implant and oral placebo (PI+OP group; 102 patients).

Main Outcome Measure: Percentage of patients retained in treatment without relapse.

Results: By month 6, 54 of 102 patients in the NI+OP group (52.9%) remained in treatment without relapse compared with 16 of 102 patients in the PI+ON group (15.7%) (survival analysis, log-rank test, $P<.001$) and 11 of 102 patients in the PI+OP group (10.8%) ($P<.001$). The PI+ON vs PI+OP comparison showed a nonsignificant trend favoring the PI+ON group ($P=.07$). Counting missing test results as positive, the proportion of urine screening tests yielding negative results for opiates was 63.6% (95% CI, 60%-66%) for the NI+OP group; 42.7% (40%-45%) for the PI+ON group; and 34.1% (32%-37%) for the PI+OP group ($P<.001$, Fisher exact test, compared with the NI+OP group). Twelve wound infections occurred among 244 implantations (4.9%) in the NI+OP group, 2 among 181 (1.1%) in the PI+ON group, and 1 among 148 (0.7%) in the PI+OP group ($P=.02$). All events were in the first 2 weeks after implantation and resolved with antibiotic therapy. Four local-site reactions (redness and swelling) occurred in the second month after implantation in the NI+OP group ($P=.12$), and all resolved with antiallergy medication treatment. Other nonlocal-site adverse effects were reported in 8 of 886 visits (0.9%) in the NI+OP group, 4 of 522 visits (0.8%) in the PI+ON group, and 3 of 394 visits (0.8%) in the PI+ON group; all resolved and none were serious. No evidence of increased deaths from overdose after naltrexone treatment ended was found.

Conclusions: The implant is more effective than oral naltrexone or placebo. More patients in the NI+OP than in the other groups develop wound infections or local irritation, but none are serious and all resolve with treatment.

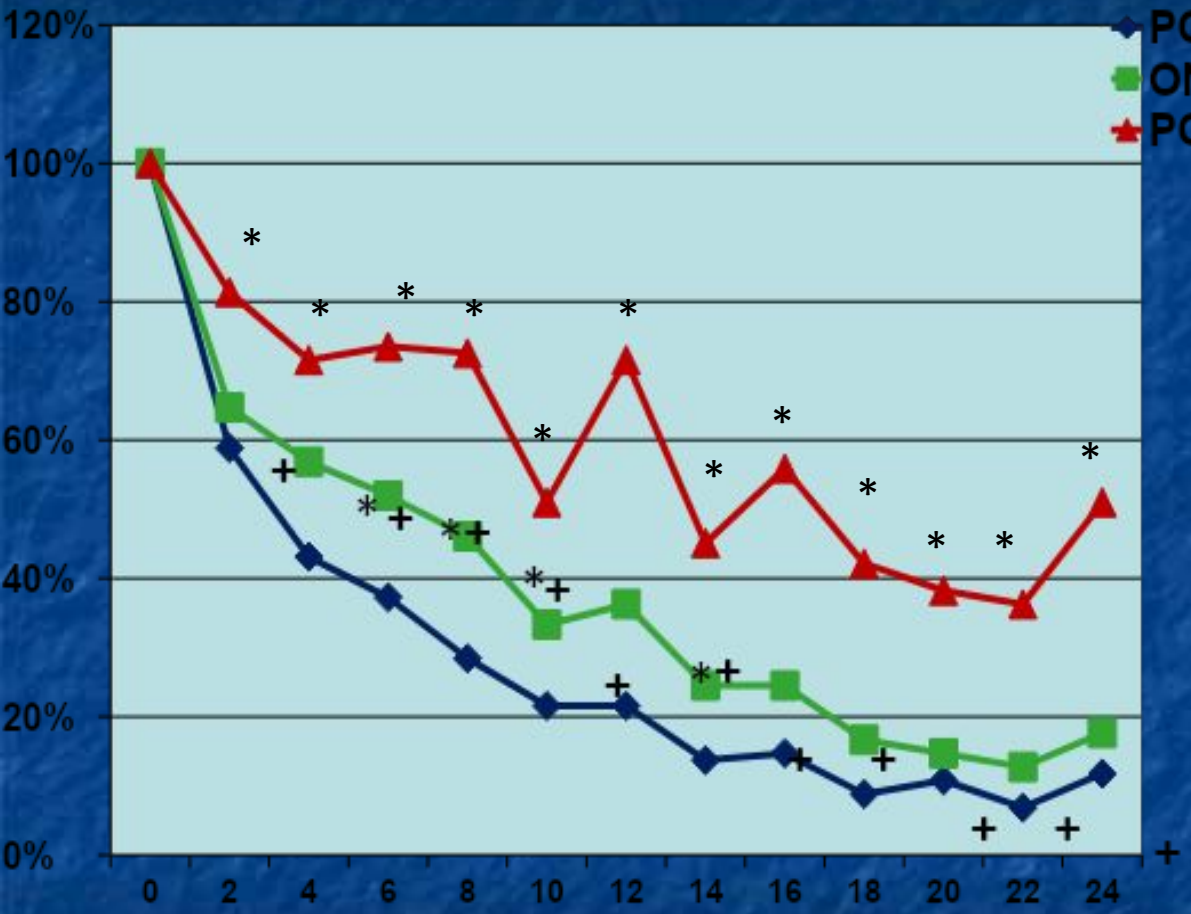
Trial Registration: clinicaltrials.gov Identifier: NCT00678418

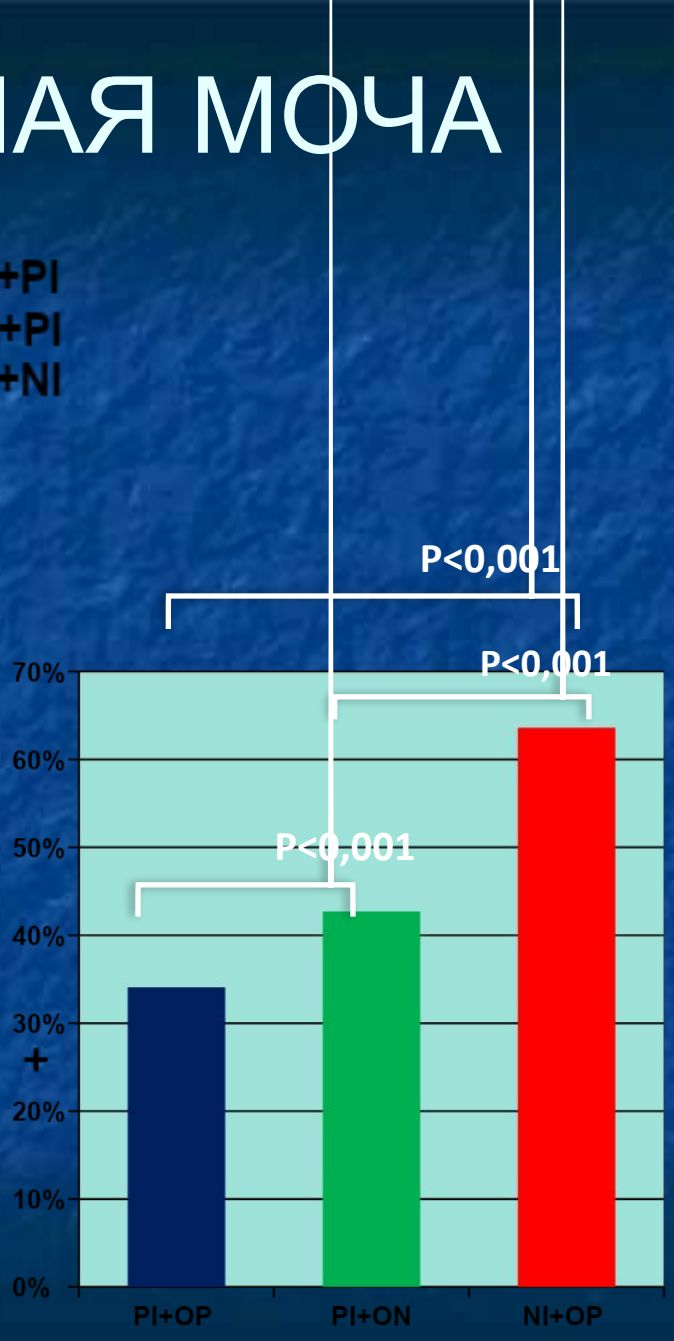
Arch Gen Psychiatry. 2012;69(9):973-981

МЕТОДЫ: ОБЩИЙ ДИЗАЙН

- 306 мужчин и женщин с героиновой наркоманией после дезинтоксикации, подписания информированного согласия и пробы с налоксоном, были в случайном порядке распределены в (РАНДОМИЗИРОВАНЫ) одну из трех групп (со стратификацией по гендерному признаку).
- **Трехклеточный дизайн:**
  - 1. **Налтрексон-имплантат (1000 мг, 3 раза с интервалом 2 месяца) (OP+NI) + Плацебо перорально. 102 пациента.**
  - **2. Пероральный налтрексон + Плацебо имплантат (3 раза с интервалом 2 месяца) (ON+PI). 102 пациента.**
  - **3. Плацебо перорально + Плацебо имплантат (OP+PI). 102 пациента.**
- Всем пациентам раз в две недели проводилась психотерапия в соответствии с руководством, разработанном в Пенсильванском университете.
- Котроль мочи на наркотики, комплайенса по рибофлавину в моче, побочных эффектов и клинико-психологическое обследование проводилось раз в две недели.
- Продолжительность программы лечения – 6 мес.
- Дизайн исследования: двойное слепое рандомизированное плацебо контролируемое клиническое исследование с двойной маскировкой.

ГЕРОИН-НЕГАТИВНАЯ МОЧА

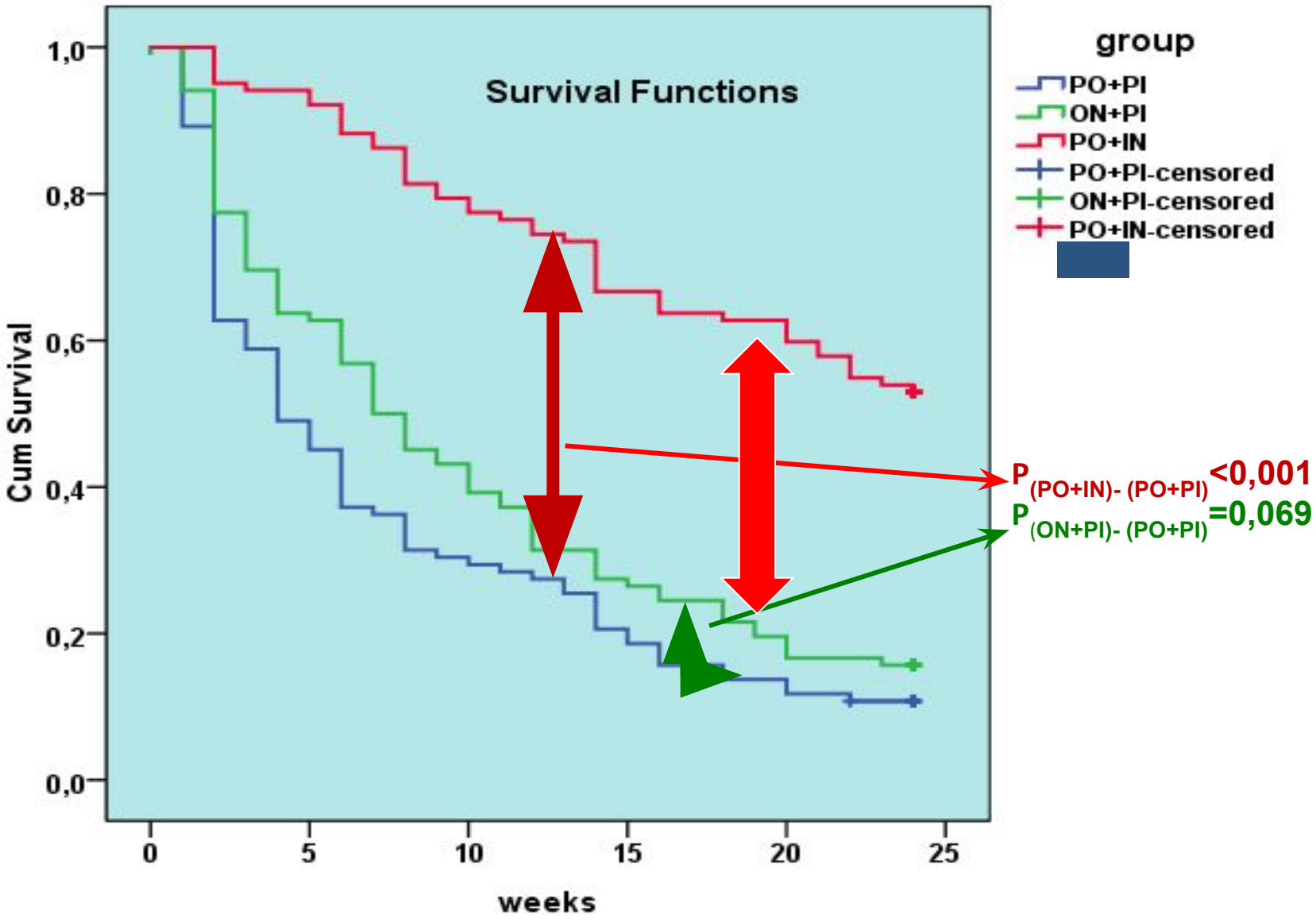




*- P<0,01 Fisher's Exact Test to placebo

+ - P<0,01 Fisher's Exact Test to Ntxn implant group

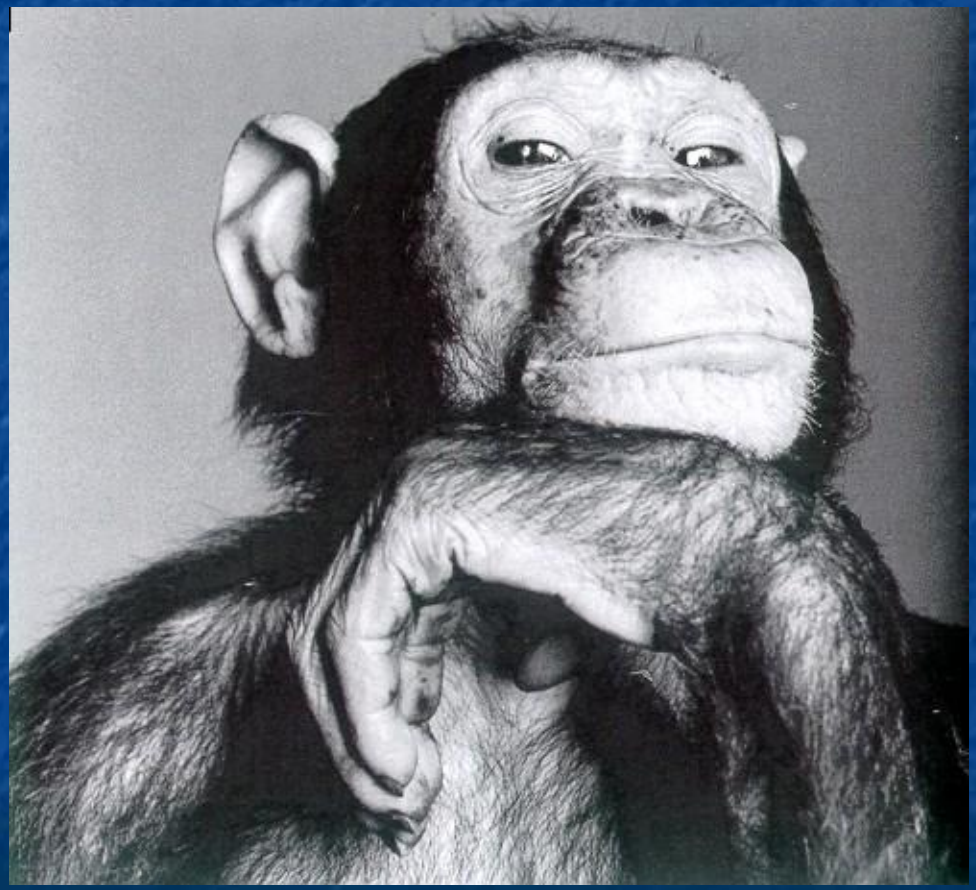
Kaplan-Meier Survival Functions: Drop out



ОГРАНИЧЕНИЯ ИМПЛАНТАТОВ НАЛТРЕКСОНА

1. Хирургическая процедура введения
2. Хирургические осложнения (в особенности опасны у ВИЧ+)
3. Косметические дефекты (в особенности беспокоят женщин)
4. Относительно несложно удалить (в первые недели после имплантации)
5. Не всегда обеспечивает достаточно длительную блокаду (у сравнительно небольшого числа больных)

Что еще может повысить эффективность лечения зависимости от опиатов?

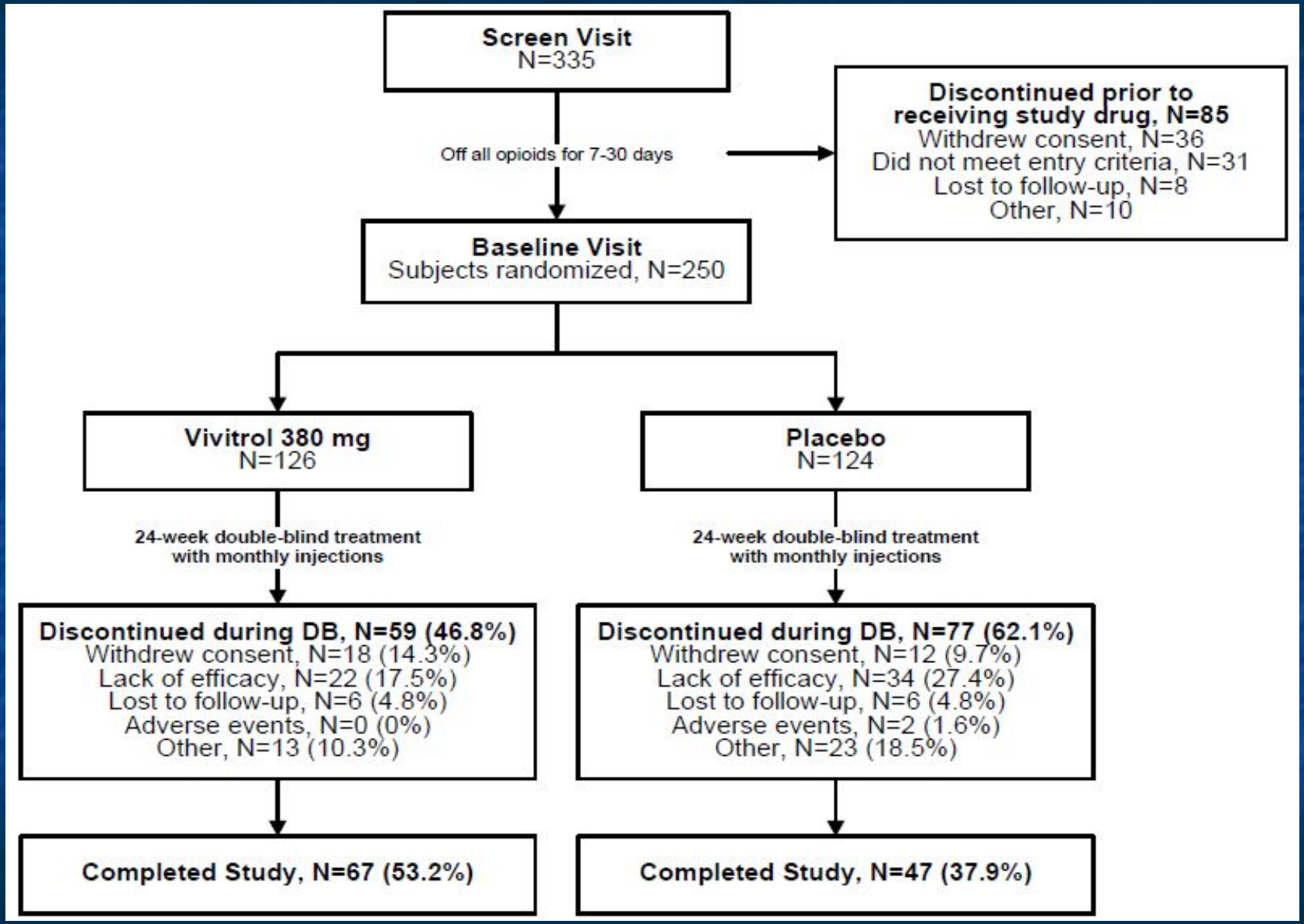


НАЛТРЕКСОН

Лекарственные формы:

1. Пероральная
2. Имплантируемая
3. Инъекционаная

Схема исследования



*Two discontinuations (1.6%) were subsequently ruled to be due to adverse events by the U.S. FDA

THE LANCET

Volume 377 · Number 9776 · Pages 1465–1542 · April 30–May 6, 2011 www.thelancet.com

Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial

Evgeny Krupitsky, Edward V Nunes, Walter Ling, Ari Illeperuma, David R Gastfriend, Bernard L Silverman

Lancet 2011; 377: 1506–13

Published Online April 28, 2011

DOI:10.1016/S0140-6736(11)60358-9

See **Comment** page 1468

Bekhterev Research Psychoneurological Institute, St Petersburg State Pavlov Medical University, St Petersburg, Russia (Prof E Krupitsky MD); **New York State Psychiatric Institute and Department of Psychiatry, Columbia University, New York, NY, USA** (Prof E V Nunes MD); **Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles, Los Angeles, CA, USA** (Prof W Ling MD); **and Alkermes, Waltham, MA, USA** (A Illeperuma MA, D R Gastfriend MD, B L Silverman MD)

Correspondence to: Prof Evgeny Krupitsky, Department of Addictions, St Petersburg Bekhterev Psychoneurological Research Institute, Bekhtereva Street 3, St Petersburg 192019, Russia **kruenator@gmail.com**

Summary

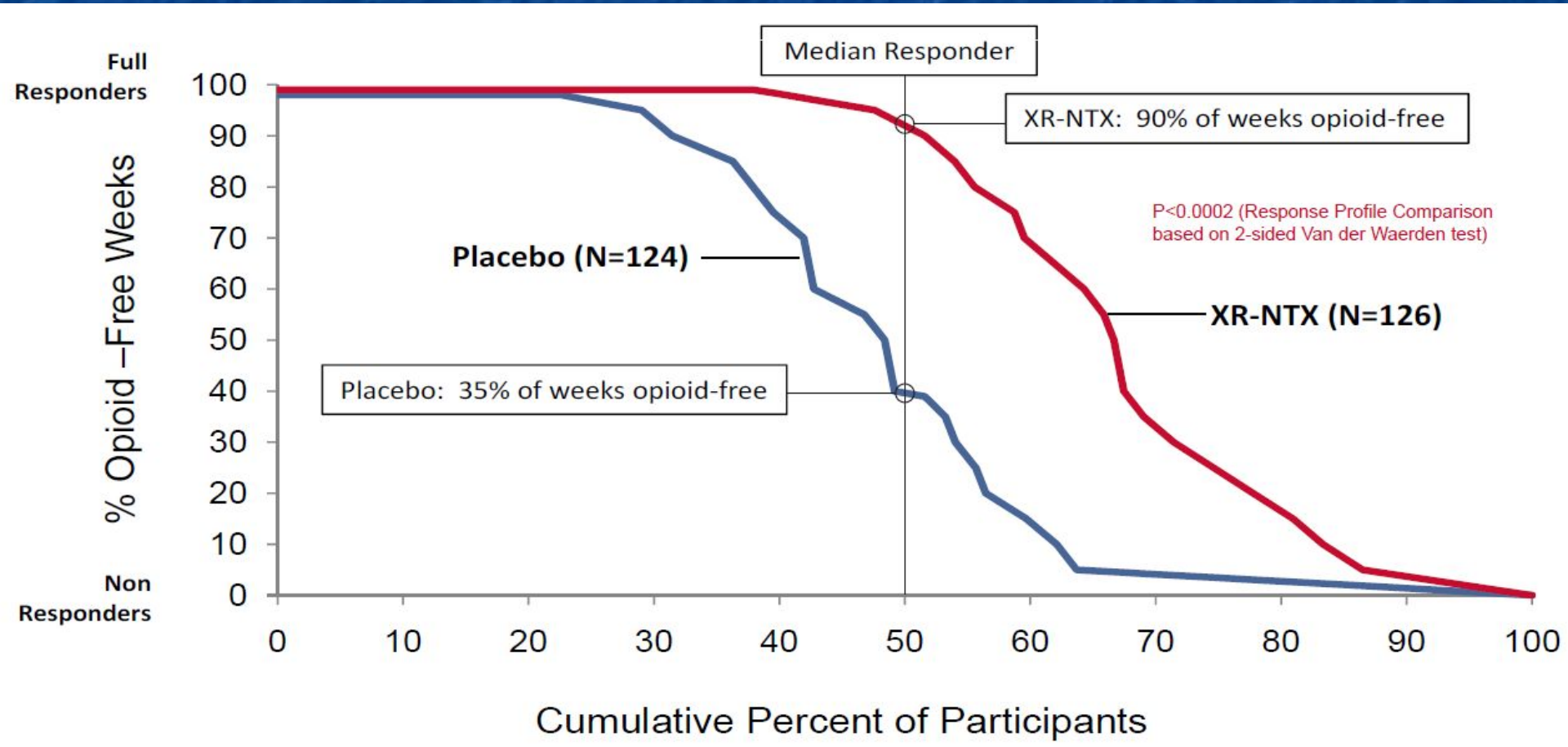
Background Opioid dependence is associated with low rates of treatment-seeking, poor adherence to treatment, frequent relapse, and major societal consequences. We aimed to assess the efficacy, safety, and patient-reported outcomes of an injectable, once monthly extended-release formulation of the opioid antagonist naltrexone (XR-NTX) for treatment of patients with opioid dependence after detoxification.

Methods We did a double-blind, placebo-controlled, randomised, 24-week trial of patients with opioid dependence disorder. Patients aged 18 years or over who had 30 days or less of inpatient detoxification and 7 days or more off all opioids were enrolled at 13 clinical sites in Russia. We randomly assigned patients (1:1) to either 380 mg XR-NTX or placebo by an interactive voice response system, stratified by site and gender in a centralised, permuted-block method. Participants also received 12 biweekly counselling sessions. Participants, investigators, staff, and the sponsor were masked to treatment allocation. The primary endpoint was the response profile for confirmed abstinence during weeks 5–24, assessed by urine drug tests and self report of non-use. Secondary endpoints were self-reported opioid-free days, opioid craving scores, number of days of retention, and relapse to physiological opioid dependence. Analyses were by intention to treat. This trial is registered at ClinicalTrials.gov, NCT00678418.

Findings Between July 3, 2008, and Oct 5, 2009, 250 patients were randomly assigned to XR-NTX (n=126) or placebo (n=124). The median proportion of weeks of confirmed abstinence was 90·0% (95% CI 69·9–92·4) in the XR-NTX group compared with 35·0% (11·4–63·8) in the placebo group (p=0·0002). Patients in the XR-NTX group self-reported a median of 99·2% (range 89·1–99·4) opioid-free days compared with 60·4% (46·2–94·0) for the placebo group (p=0·0004). The mean change in craving was –10·1 (95% CI –12·3 to –7·8) in the XR-NTX group compared with 0·7 (–3·1 to 4·4) in the placebo group (p<0·0001). Median retention was over 168 days in the XR-NTX group compared with 96 days (95% CI 63–165) in the placebo group (p=0·0042). Naloxone challenge confirmed relapse to physiological opioid dependence in 17 patients in the placebo group compared with one in the XR-NTX group (p<0·0001). XR-NTX was well tolerated. Two patients in each group discontinued owing to adverse events. No XR-NTX-treated patients died, overdosed, or discontinued owing to severe adverse events.

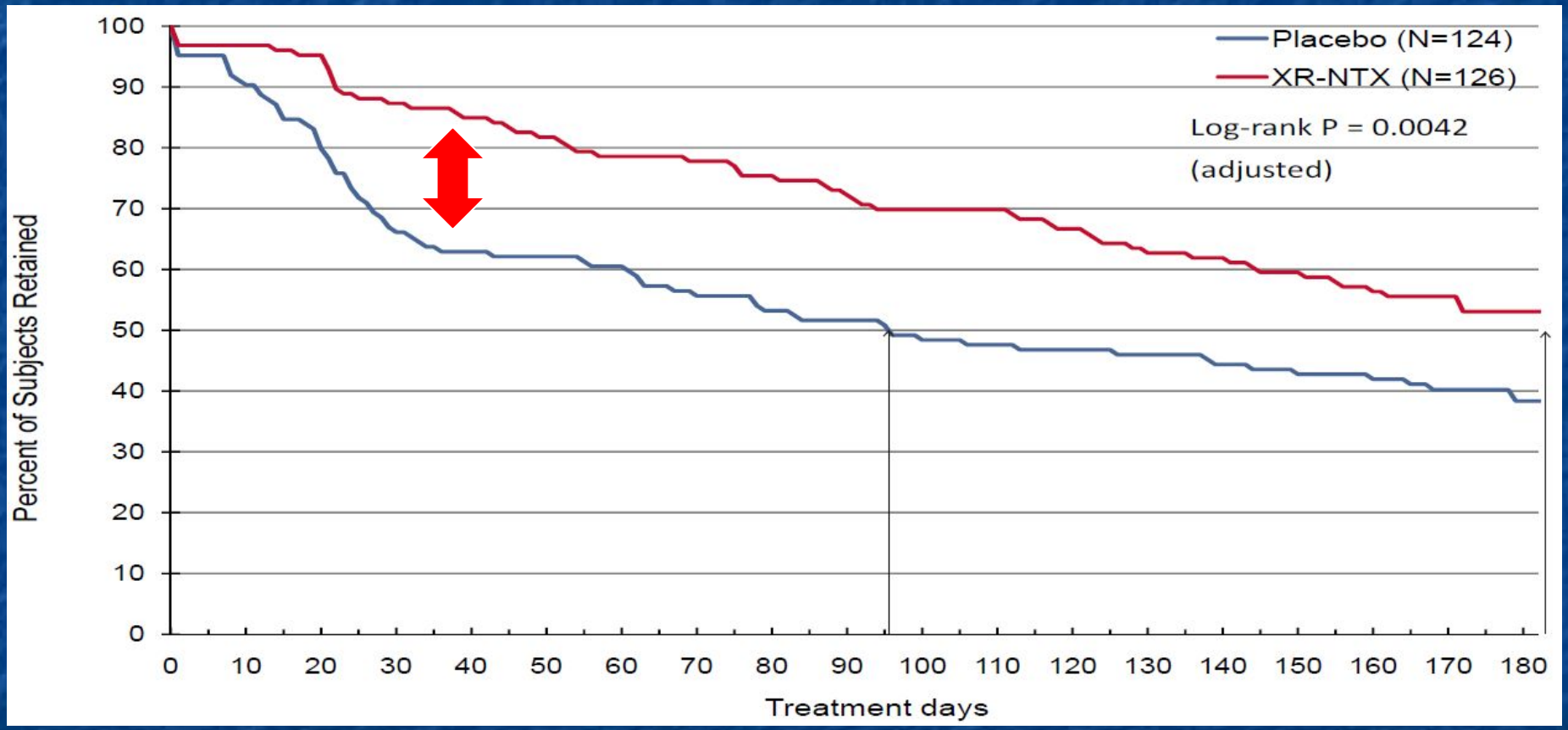
Interpretation XR-NTX represents a new treatment option that is distinct from opioid agonist maintenance treatment. XR-NTX in conjunction with psychosocial treatment might improve acceptance of opioid dependence pharmacotherapy and provide a useful treatment option for many patients.

Отрицательные анализы мочи на опиаты



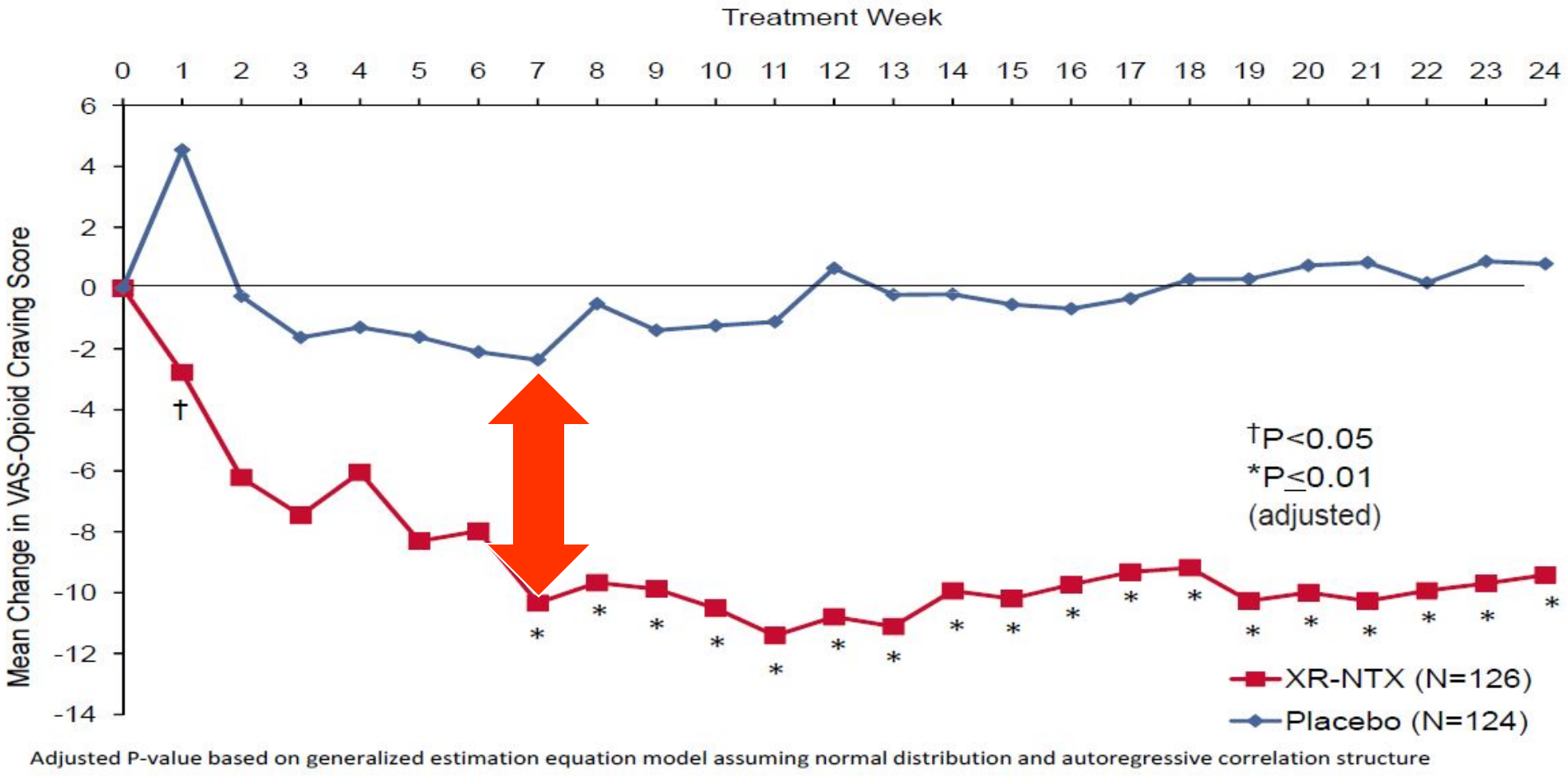
- Total abstinence (100% opioid-free weeks) during Weeks 5-24 was reported in 45 (35.7%) of subjects in the XR-NTX group versus 28 (22.6%) subjects in placebo group (P=0.0224).

Kaplan-Meier Analysis: Выбывание из исследования



- Median days on treatment was significantly longer for patients in the XR-NTX *vs.* placebo group: >168 days *vs.* 96 days in the placebo group (P=0.0042, log-rank test, adjusted for multiplicity)

Результаты оценки влечения к опиатам: *изменение по сравнению с исходными данными*



Adjusted P-value based on generalized estimation equation model assuming normal distribution and autoregressive correlation structure

Вивитрол обусловил 50% снижение крэйвинга *при отсутствии изменений в группе плацебо*

FDA NEWS RELEASE

For Immediate Release: Oct. 12, 2010
Media Inquiries: Shelly Burgess, 301-796-4651 , shelly.burgess@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves injectable drug to treat opioid-dependent patients

The U.S. Food and Drug Administration today approved Vivitrol to treat and prevent relapse after patients with opioid dependence have undergone detoxification treatment.

Vivitrol is an extended-release formulation of naltrexone administered by intramuscular injection once a month. Naltrexone works to block opioid receptors in the brain. It blocks the effects of drugs like morphine, heroin, and other opioids. It was approved to treat alcohol dependence in 2006.

"Addiction is a serious problem in this country, and can have devastating effects on individuals who are drug-dependent, and on their family members and society," said Janet Woodcock, M.D., director of FDA's Center for Drug Evaluation and Research. "This drug approval represents a significant advancement in addiction treatment."

The safety and efficacy of Vivitrol were studied for six months, comparing Vivitrol treatment to placebo treatment in patients who had completed detoxification and who were no longer physically dependent on opioids. Patients treated with Vivitrol were more likely to stay in treatment and to refrain from using illicit drugs. Thirty-six percent of the Vivitrol-treated patients were able to stay in treatment for the full six months without using drugs, compared with 23 percent in the placebo group.

Patients must not have any opioids in their system when they start taking Vivitrol; otherwise, they may experience withdrawal symptoms from the opioids. Also, patients may be more sensitive to opioids while taking Vivitrol at the time their next scheduled dose is due. If they miss a dose or after treatment with Vivitrol has ended, patients can accidentally overdose if they restart opioid use.

Side effects experienced by those using Vivitrol included nausea, tiredness, headache, dizziness, vomiting, decreased appetite, painful joints, and muscle cramps. Other serious side effects included reactions at the site of the injection, which can be severe and may require surgical intervention, liver damage, allergic reactions such as hives, rashes, swelling of the face, pneumonia, depressed mood, suicide, suicidal thoughts, and suicidal behavior.

Vivitrol should be administered only by a health care provider as an intramuscular injection, using special administration needles that are provided with the product. Vivitrol should not be injected using any other needle. The recommended dosing regimen is once a month.

Consumers and health care professionals are encouraged to report adverse events to the FDA's MedWatch program at 800-FDA-1088 or online at www.fda.gov/medwatch/how.htm.

Vivitrol is manufactured by Alkermes, Inc.

For more information:

- Drugs@FDA

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Message from the Director on Important Treatment Advances for Addiction to Heroin and other Opiates

Heroin addiction afflicts an estimated 810,000 people in this country, the great majority of who do not either seek or receive treatment. Further, in 2008 1.85 million people in the U.S. met the diagnostic criteria for abuse or dependence on opioid pain relievers, such as Oxycontin and Vicodin (NSDUH, 2009). In fact, opioid abuse (including heroin) is a worldwide problem, with between 12.8 and 21.9 million people abusing opiates in the past year (UNODC, 2010). Two recent developments in the treatment of opioid addiction herald important advances for addressing this worldwide epidemic.

First, the U.S. Food and Drug Administration (FDA) today announced its approval of Vivitrol®

Nora D. Volkow, M.D., Director, NIDA

(http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm229109.htm) for the treatment of opioid addiction. Vivitrol is an extended release formulation of naltrexone, an opioid receptor antagonist. Double-blind, placebo controlled clinical trials have shown Vivitrol to be effective in preventing not only relapse to drug use

How to Order Free Publications

- NIDA DrugPubs - Online Ordering

Additional Resources:

- NIDA Addiction Science and Clinical Practice - a peer-reviewed journal
- NIDA Notes

ВЫВОДЫ

13-ЛЕТНИХ ИССЛЕДОВАНИЙ ПРИМЕНЕНИЯ РАЗЛИЧНЫХ ЛЕКАРСТВЕННЫХ ФОРМ НАЛТРЕКСОНА ДЛЯ ЛЕЧЕНИЯ 1132 БОЛЬНЫХ ОПИЙНОЙ НАРКОМАНИЕЙ

Пероральный налтрексон :

- Эффективен при условии обеспечения комплайенса родственниками больных
- По мере «старения» популяции наркозависимых эффективность терапии уменьшается
- Комбинация налтрексона с антидепрессантами или гуанфацином незначительно повышает эффективность терапии

Пролонги налтрексона:

Имплантат налтрексона:

- Эффективнее пероального налтрексона
- Более длительная блокада (2-3 мес)
- «Хирургические» побочные эффекты

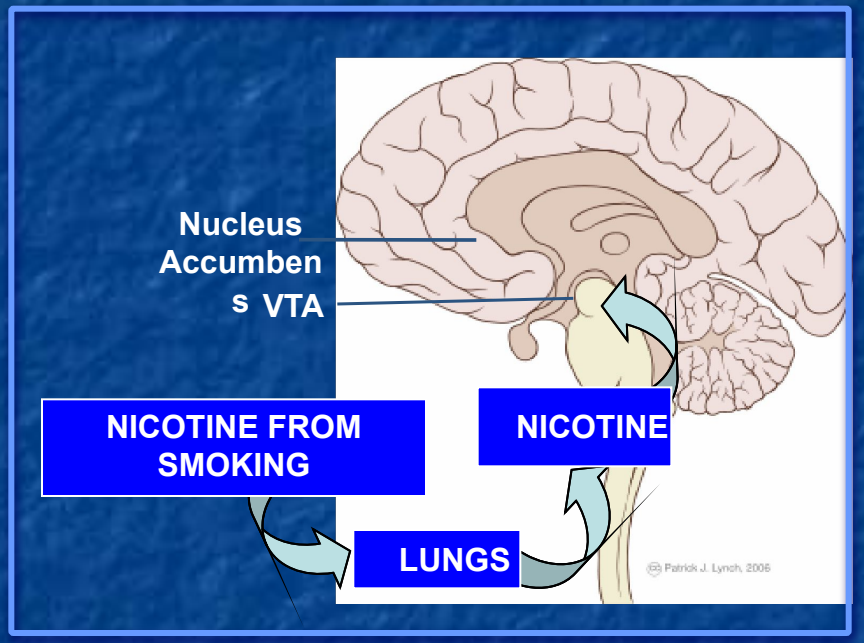
Инъекционный налтрексон:

- Проще в использовании
- Хорошая переносимость
- Более короткая блокада (1 мес)

Доказательная фармакотерапия наркологических заболеваний

- Зависимость от алкоголя
- Зависимость от опиатов
- Зависимость от никотина

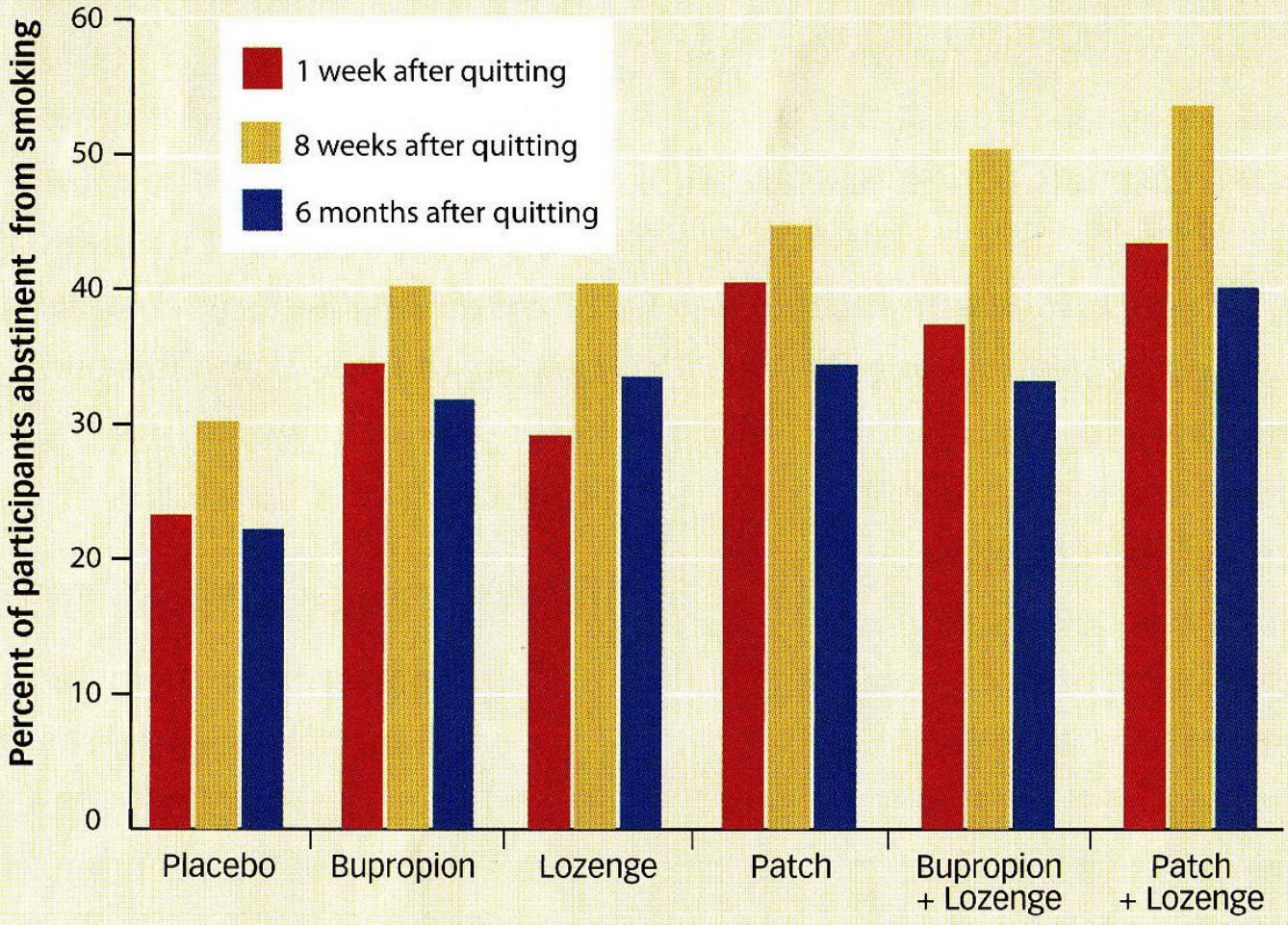
Доказательная фармакотерапия зависимости от никотина



Лечение никотиновой зависимости:

- Заместительные препараты (никотиновый пластырь и жевательная резинка)
- Бупропион (антидепрессант). Особенно эффективен у женщин с низкой активностью CYP2B6)
- Варениклин

MANY THERAPIES REDUCE SMOKING Abstinence rates for all treatments peaked at the 8-week assessment. Abstinence was confirmed by breath carbon monoxide levels measured during visits to the clinic.



J. Med. Chem. **2005,** *48,* 3474−3477

Varenicline: An α4β2 Nicotinic Receptor Partial Agonist for Smoking Cessation

Jotham W. Coe,* Paige R. Brooks,
Michael G. Vetelino, Michael C. Wirtz,
Eric P. Arnold, Jianhua Huang, Steven B. Sands,
Thomas I. Davis, Lorraine A. Lebel, Carol B. Fox,
Alka Shrikhande, James H. Heym, Eric Schaeffer,
Hans Rollema, Yi Lu, Robert S. Mansbach,
Leslie K. Chambers, Charles C. Rovetti,
David W. Schulz, F. David Tingley, III, and
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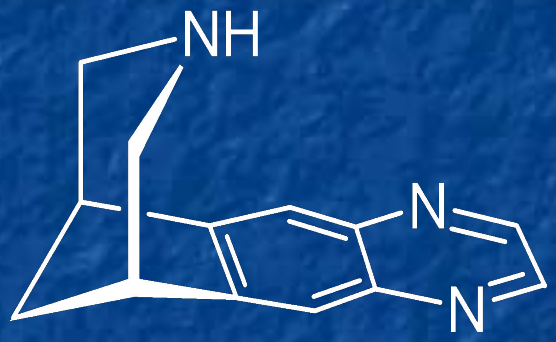
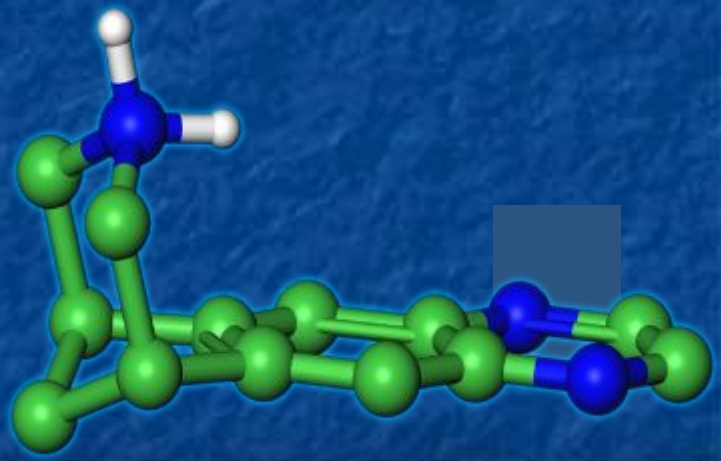
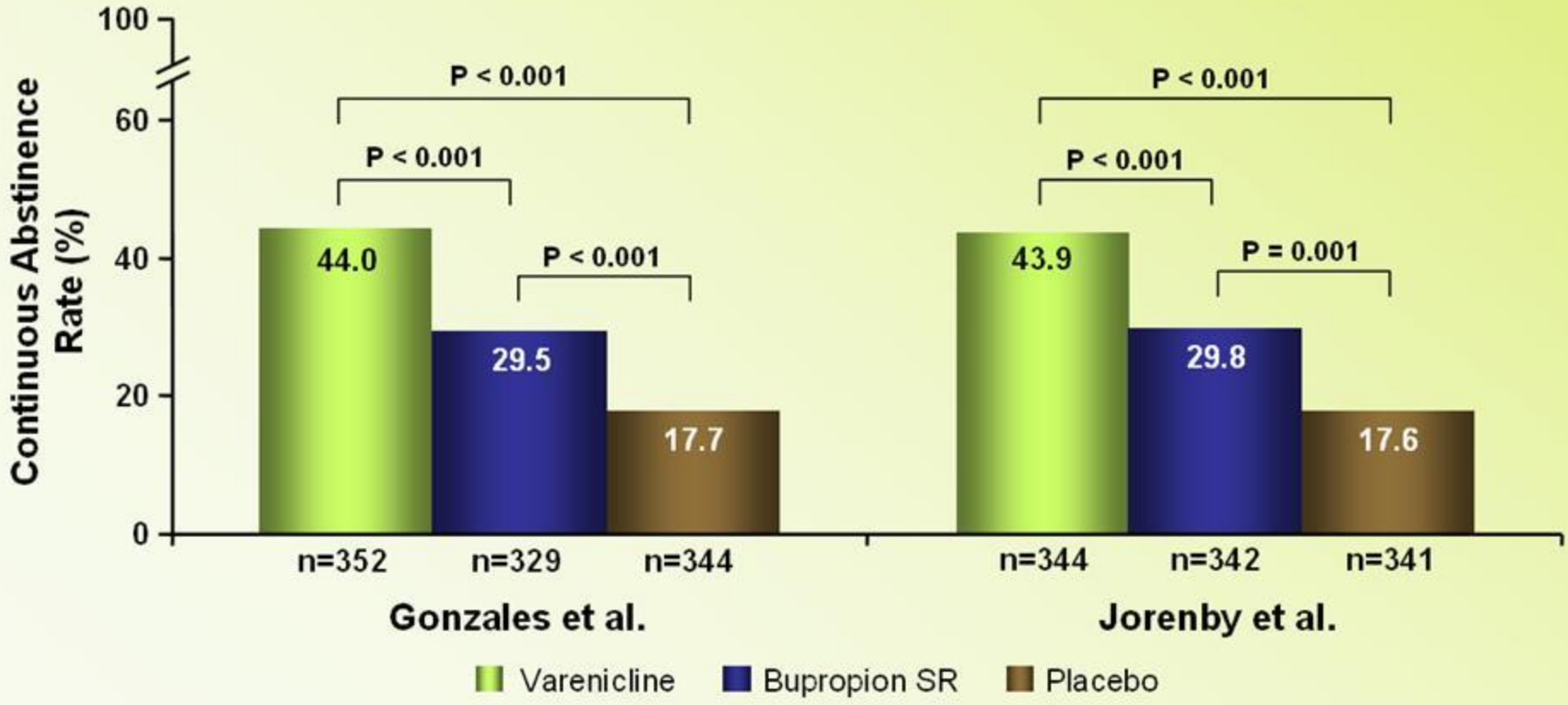
Received January 25, 2005





Varenicline

Chantix™ (varenicline) Phase 3 Studies: Efficacy Measurements: CO-Confirmed 4-Wk Continuous Abstinence Rates Wks 9–12

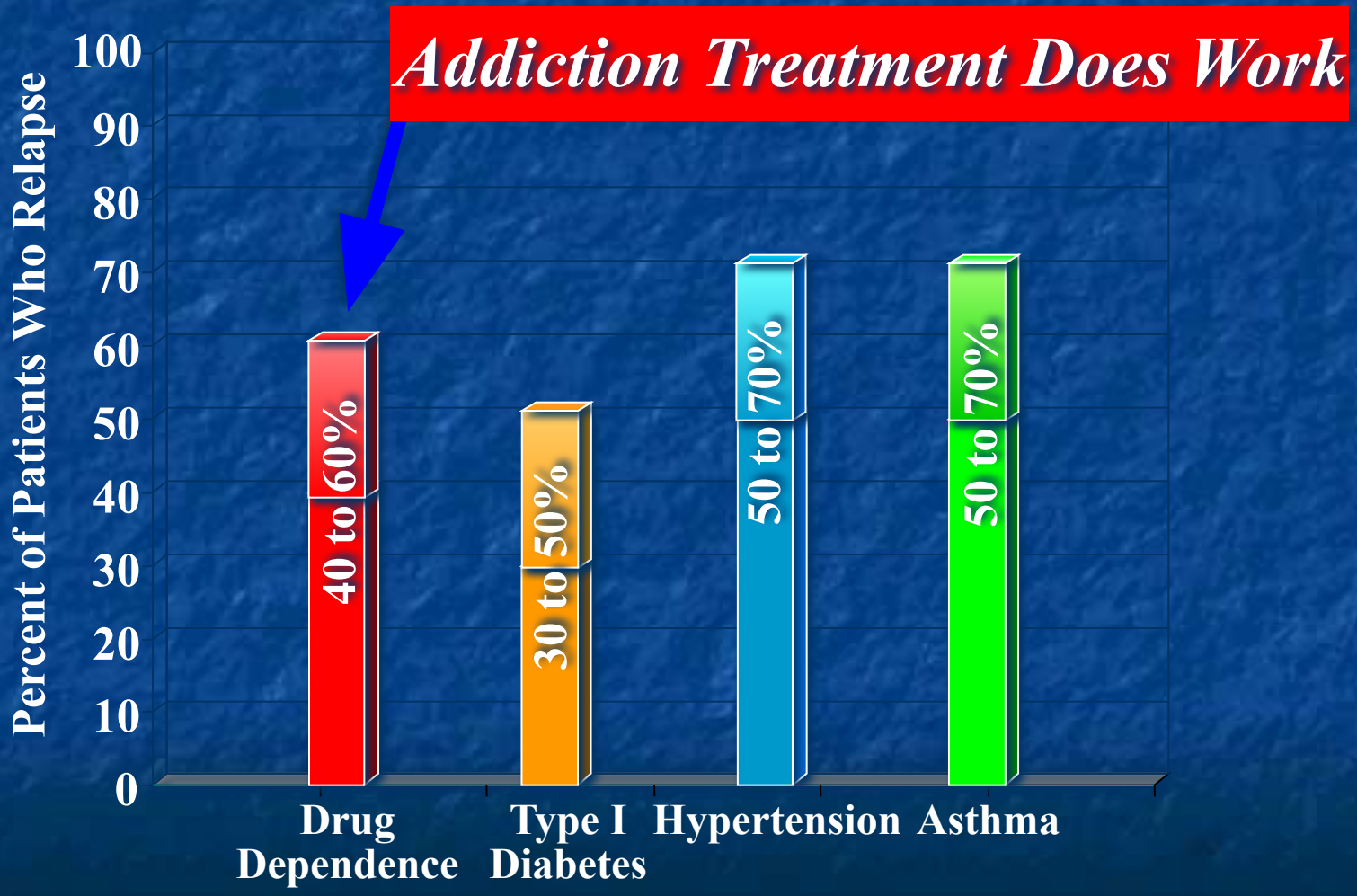


The 9-12 week Continuous Abstinence Rate is defined as the percentage of subjects who abstained from smoking (not even a puff) from Week 9 through 12 of the study as confirmed by both subject self-report and by end-expiratory carbon monoxide (CO) measurement

The most frequently reported adverse events (>10%) with Chantix were nausea, headache, insomnia, and abnormal dreams

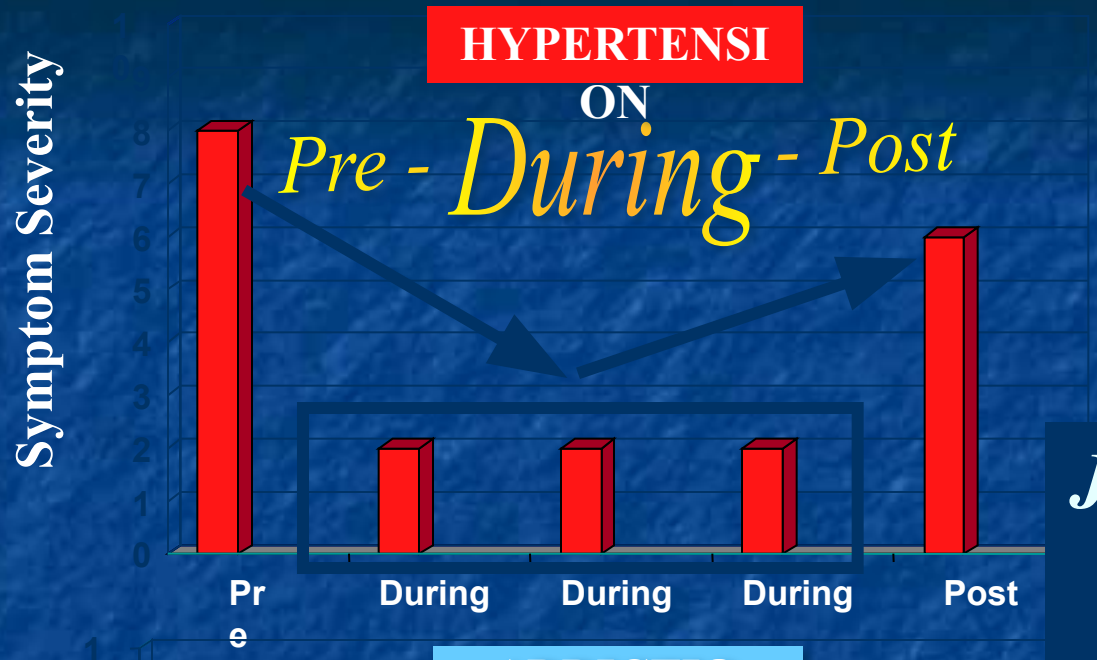
1. Gonzalez D et al. *JAMA*. 2006;296:47-55. 2. Jorenby DE et al. *JAMA*. 2006;296:56-63.

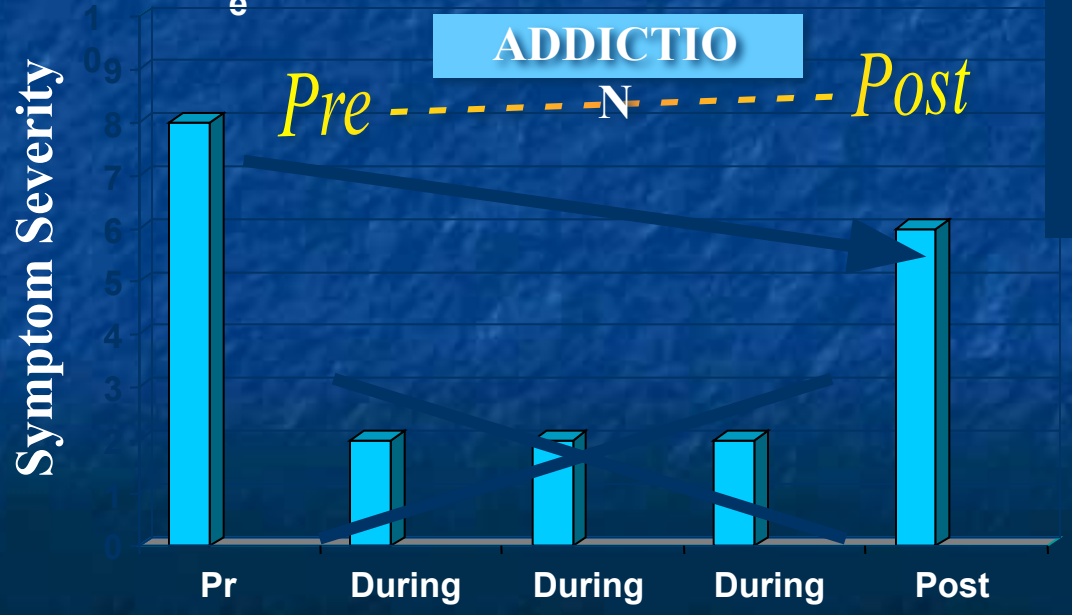
Relapse Rates Are Similar for Drug Dependence And Other Chronic Illnesses



Source: McLellan, A.T. et al., JAMA, Vol 284(13), October 4, 2000.

Evaluation of A Hypothetical Treatment





Just Like Hypertension, Addiction Is A Chronic Disease That Requires Continued Care

Source: McLellan, AT, Addiction 97, 249-252, 2002

Доказательная наркология: найти сокровища знания

ПОВЫСИТЬ ЭФФЕКТИВНОСТЬ ЛЕЧЕНИЯ НАРКОЛОГИЧЕСКИХ БОЛЬНЫХ

- **Благодарю за внимание**