Шагиахметов Фарид

ОПИОИДНЫЕ АНТАГОНИСТЫ В ПСИХИАТРИИ

ДЕПРЕССИЯ, АНГЕДОНИЯ И ТЕРАПЕВТИЧЕСКАЯ РЕЗИСТЕНТНОСТЬ

Москва 2020

ДЕПРЕССИЯ:
НЕПОЛНЫЙ ОТВЕТ и ТЕРАПЕВТИЧЕСКАЯ РЕЗИСТЕНТНОСТЬ

- Более **300 млн.** человек на планете **страдает** депрессией [ВОЗ]
- Около **1 млн. ежегодно погибает** в результате **суицида** [ВОЗ]
- Экономический **ущерб** от депрессии в одних только **США** составляет **$210.5 млр. в год** [PMC5540329]
- Лишь у **40%** больных удается достичь **ремиссии** после **первого антидепрессанта** [PMID:17074942]
- **Треть** всех больных депрессией отвечает критериям **терапевтической резистентности** [PMC4919246, PMC5540329, PMC4518696]
- **30%** больных **ТРД не отвечает** ни на какую **дальнейшую терапию** [PMC3363299]

АНГЕДОНИЯ = УТРАТА ПОЛОЖИТЕЛЬНЫХ ЭМОЦИЙ

fMRI suggest **distinct components** of anhedonia [PMID: 31270605]:

- MOTIVATIONAL anhedonia = decreased WANTING – loss of **interest** (*positive emotions* associated with reward *anticipation*)
- CONSUMMATORY anhedonia = decreased LIKING – loss of **pleasure** (*positive emotions* associated with reward *consumption*)

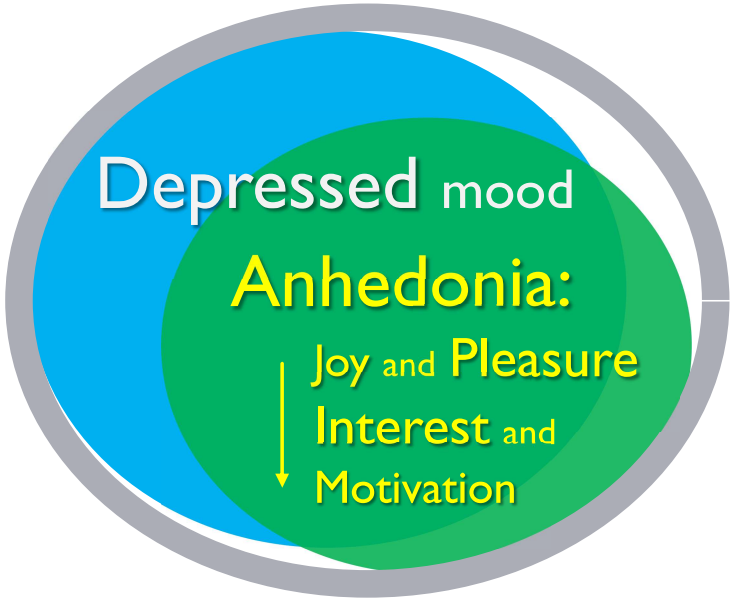
Anhedonia is **associated** with **suicidal** ideation **independently** of **depression** [PMID: 29232491]:

- Meta-analysis finds the robust association between anhedonia and current suicidal ideation, independently of depression
- This may help the development of therapeutics for suicide prevention

Core symptoms of depression [DSM-5]:

- Depressed mood most of the day
- Anhedonia (decreased interest or pleasure)

ДЕФИЦИТ **ПОЛОЖИТЕЛЬНЫХ** ЭМОЦИЙ — **РЕЗИСТЕНТНОЕ ЯДРО** ДЕПРЕССИИ



CORE SYMPTOMS

- **Low hedonic tone** strongly predicts **poor** treatment **outcome**, irrespective of depression **severity** and **antidepressant type** used [PMC3536476, PMC3787526, PMC5003599]
- **Early** (Week 2) **improvement** on the **core** symptoms is a good **predictor** of future **response** and **remission** with antidepressants, ECT, TMS and CBT [PMC4646593, PMC6771780, PMC5912302, PMC6149933, PMID: 29656263, 26160153, 23416024, 24571916, 24583567, 26250147]
- **Lack** of 20% improvement by Week 2 is **highly predictive** of **unsuccessful** treatment **outcome** [PMID: 19204654, 19254516, 29107623]

Higher level of anhedonia is linked to **decreased** extrastriatal **dopaminergic functioning**. Greater D2/D3 binding in the DLPFC in high anhedonia patients suggests the DLPFC may be particularly involved in the subjective experience of anhedonia [https://www.ecnp.eu/presentationpdfs/70/P.2.b.003.pdf]

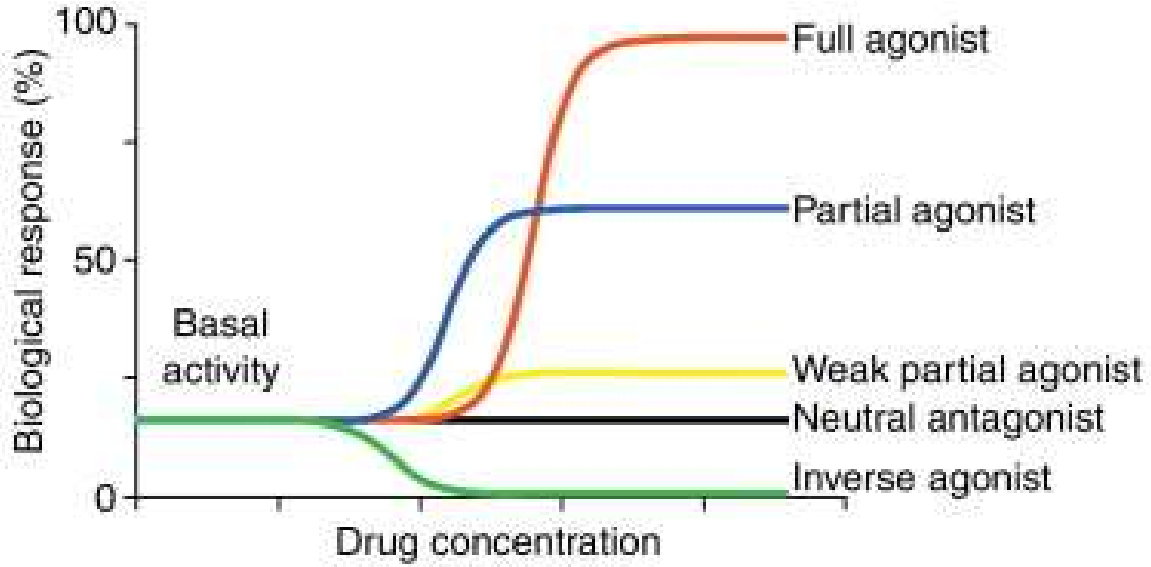
EARLY BUPRENORPHINE STUDIES DEMONSTRATED a RAPID and SUSTAINED ALLEVIATION of SEVERE TRD

Opioid-Based Compounds Reporting Positive Effects in Clinical Studies

Compound	Clinical trial	Reference	Inclusion criteria	Dosing regimen	Outcomes
Buprenorphine		Emrich et al. (1982)[81]	TRD	0.2 mg twice daily for 8 days	5/10 patients in remission (= 50% reduction in HAM-D scores)
		Kosten et al. (1990)[82]	Opioid-dependent outpatients with depression	Buprenorphine maintenance: 2–8 mg daily for 4 weeks	Reduction in depressive symptoms by 1 week
		Bodkin et al. (1995)[83]	TRD to ECT	0.5–1.8 mg daily for 4–6 weeks	4/5 patients in remission (= 50% reduction in HAM-D scores)
		Nyhuis et al. (2008)[84]	TRD	0.8–2 mg daily for 1 week	6/6 patients improved over 1 week; 5/6 patients in remission (= 50% reduction in HAM-D scores)
		Norelli et al. (2013)[85]	NSSI	Personalized doses, augmentation	5/6 patients had significant improvement in mood Reduction in NSSI episodes
		Gerra et al. (2014)[86]	Heroin dependence	Buprenorphine 2 mg daily or methadone 20 mg daily for 12 weeks	Decreased SCL-90 depression scores in both groups upon study completion Better scores & fewer opioid-positive urines for buprenorphine-maintained subjects

Opioid-Based Therapeutics for Depression [Browne et al., 2020: PMID:31913981]

E_{MAX} (IA) [%]
МАКСИМАЛЬНАЯ ЭФФЕКТИВНОСТЬ АГОНИЗМА [от +100% до –100%]



E_{max} = 100% (эндогенный лиганд)

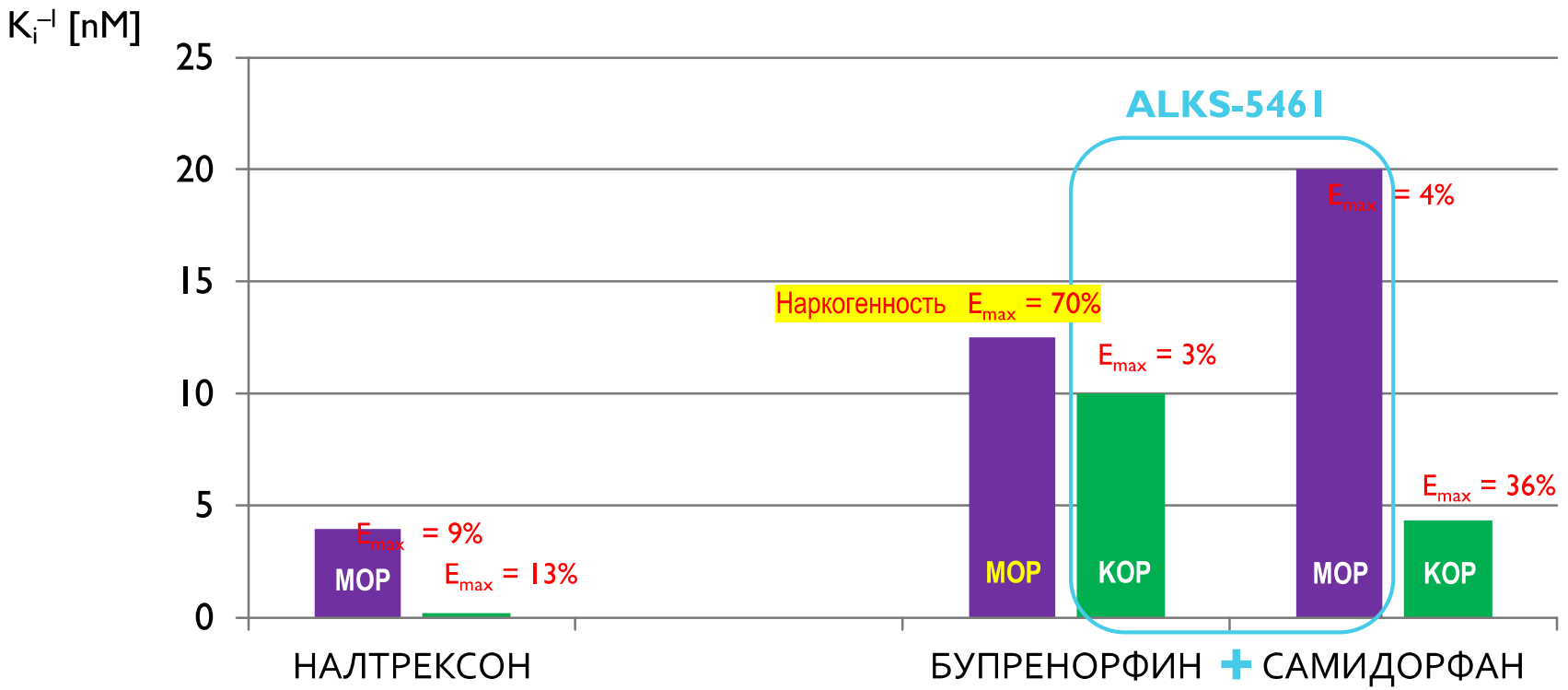
E_{max} < 100%

E_{max} < 10%

E_{max} = 0

E_{max} < 0

ALKS-5461 [buprenorphine + samidorphan]



Samidorphan mitigates abuse potential of buprenorphine in 1:1 ratio

ALKS-5461 [buprenorphine + samidorphan]

Compound	Clinical trial	Reference	Inclusion criteria	Dosing regimen	Outcomes
ALKS-5461	NCT01381107	Ehrich et al. (2015)[91]	TRD: current MDD episode resistant to 8 weeks of treatment with SSRI or SNRI HAM-D-17 = 19.4 ±2.7 MADRS = 26.4 ± 4.4	1:1 & 8:1 ratio buprenorphine/ samidorphan for 7 days; augmentation to current therapeutic	1:1 ratio produced a robust change from baseline: HAM-D-17 = −6.7 ± 3.4; MADRS = −11.5 ± 6.5
	NCT01500200	Fava et al. (2016)[92]	TRD HAM-D for stage 1 subjects: placebo = 23.2; 2 mg/2 mg = 22.7; 8 mg/8 mg = 21.9 HAM-D for stage 2 subjects: placebo = 22.3; 2 mg/2 mg = 22.1; 8 mg/8 mg = 23.3	Stage 1: 2 mg/2 mg or 8 mg/8 mg for 4 weeks Stage 2: placebo nonresponders randomized to 2 mg/2 mg or 8 mg/8 mg for 4 weeks	2 mg/2 mg group exhibited the best outcomes Stage 1: change from baseline on HAM-D = −9.2 ± 8.2 Stage 2: change from baseline on HAM-D = −5.1 ± 6

- In trials conducted **in opioid-experienced** individuals and in those experiencing a current treatment-refractory depressive episode, the **1:1 ratio** combination produced no sedation and **no subjective high**
- ALKS-5461 **add-on** to **current SSRI / SNRI treatment** in patients with **inadequate response** after 1 WEEK yielded a robust reduction in depression severity as per **HAM-D, MADRS** and **CGI** scales
- ALKS-5461 was granted a Fast Track Designated by the FDA in October 2017

Opioid-Based Therapeutics for Depression [Browne et al., 2020: PMID:31913981]

ALKS-5461 [buprenorphine + samidorphan]

Compound	Clinical trial	Reference	Inclusion criteria	Dosing regimen	Outcomes
ALKS-5461					
	FORWARD-4, NCT02158533	Fava et al. (2018)[93]	MDD MADRS: placebo = 31.9; 0.5 mg/0.5 mg = 32.7; 2 mg/2 mg = 32	0.5 mg/0.5 mg or 2 mg/2 mg daily for 11 weeks Augmentation	Best outcome with 2 mg/2 mg regimen: at trial completion, MADRS = 26.2 ± 7.47
	FORWARD-5, NCT02218008	Fava et al. (2018)[93]	MDD MADRS: placebo = 31.7; 1 mg/1 mg = 31.8; 2 mg/2 mg = 31.8	1 mg/1 mg or 2 mg/2 mg daily for 11 weeks Augmentation	Best outcome with 2 mg/2 mg regimen: at trial completion, MADRS = 26.0 ± 6.45
	FORWARD-3, NCT02158546	Zajecka et al. (2019)[94]	TRD	10 weeks Augmentation	Did not meet primary outcome at 3 weeks, but reduced MADRS scores at later time points

- Subsequent **Fo**cused on **R**esults **W**ith **A R**ethinking of **D**epression (**FORWARD**) trials did not yield the evidence **required** to gain FDA approval
- The **FORWARD-3** study failed to meet the primary efficacy endpoint
- **Despite positive results** of **FORWARD-4** and **-5** trials in February 2019, the FDA ruled that additional studies are needed to confirm the usual efficacy
- **NCT03188185** and **NCT03610048** studies have been initiated to provide additional support for the drug efficacy

Opioid-Based Therapeutics for Depression [Browne et al., 2020: PMID:31913981]

MORPHINAN CLASS **ANTAGONISTs INDUCE** RECEPTOR **UP-REGULATION** and PHARMACODYNAMIC **TOLERANCE** upon **SUSTAINED** ADMINISTRATION

NTX and NMF are known to produce treatment time-dependent up-regulation and functional supersensitivity of all opioid receptor subtypes and behavioral supersensitivity in rodents and monkeys (Zukin *et al.*, 1982; Bardo *et al.*, 1983; Yoburn *et al.*, 1986, 1989; France & Morse, 1989). While there might be a number of molecular mechanisms for the up-regulation, many opioid receptor ligands, especially hydrophobic membrane-permeable antagonist ligands (like the ones studied here), act efficiently as pharmacological chaperones for various opioid receptor subtypes (for review, see Petaja-Repo & Lackman, 2014). These ligands bind to early, non-mature opioid receptors in the endoplasmic reticulum (ER), alter their conformation so that bound receptors pass the ER quality control machinery, traffic to the cell membrane and form functional G protein-coupled receptors. At least the up-regulation of μ-opioid receptors by chronic antagonists does not need any new mRNA or protein synthesis (Unterwald *et al.*, 1995; Castelli *et al.*, 1997; Wannemacher *et al.*, 2007). To our knowledge, the process of opioid receptor up-regulation and supersensitivity induced by opioid antagonists has not been studied in humans, but it is likely that a similar chaperoning effect as seen in rodents also works in a clinical setting, based on the prolonged occupancy of μ-opioid receptors in the human brain after a single dose of NTX or NMF.

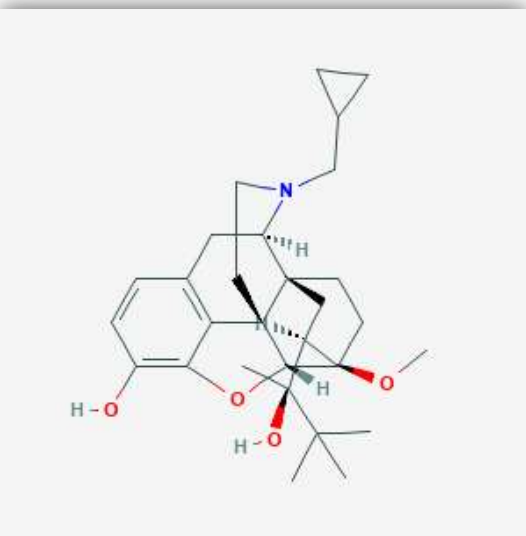
[Korpi et al., 2017: PMID:26990998]

NEUTRAL ANTAGONISTS are NOT IDEAL CANDIDATES

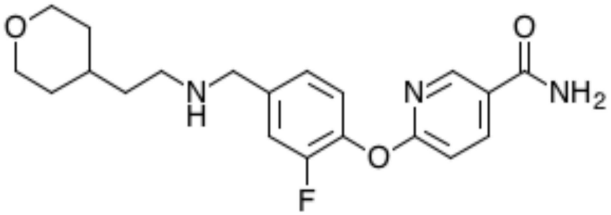
Polter et al., 2017 demonstrated [PMC5389861] that:

- Administration of neutral KOP antagonist does not prevent stress-induced reinstatement of cocaine seeking behavior, while inverse agonist – does prevent
- This work suggests that novel KOP receptor antagonists which LACK inverse agonist activity are not ideal candidates for the treatment of cocaine dependence
- Inverse agonists are known to exert more powerful clinical effect then neutral antagonists

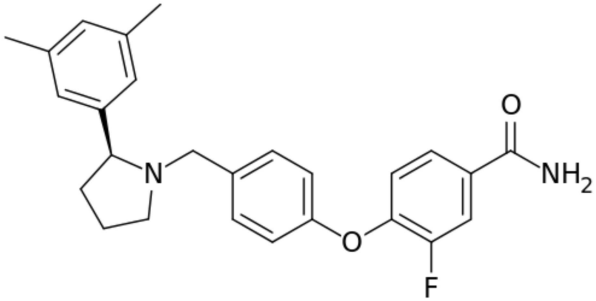
ATICAPRANT and **ONDELOPRAN** are STRUCTURALLY SIMILAR and NOT RESEMBLE MORPHINANS



BUPRENORPHINE
neutral antagonist



Ondelopran
(LY2196044)
KOP + MOP + DOP
inverse agonist



Aticaprant
(LY2456302)
Selective KOP
undisclosed E_{max} antagonist

Ondelopran (LY2196044) is a novel potent **non-selective opioid** receptor **antagonist**. In contrast to morphinan antagonists, ondelopran exhibits **enhanced binding** to opioid receptors in the **presence of Na^+** ions. Unlike neutral antagonists inverse agonists of opioid receptors have been shown to demonstrate similar enhancement of binding affinity in the presence of sodium ions. Ondelopran exhibits no detectable agonistic activity at MOP, KOP and DOP receptors. Ondelopran shows antagonist potency (K_b) of 0.4, **0.6** and 1.9 **nM** at human MOP, **KOP** and DOP receptors, respectively

ATICAPRANT (JNJ-67953964; CERC-501; LY2456302) SELECTIVE **KOP** ANTAGONIST

- **Cerecor** acquired the rights to CERC-501 (LY2456302), through an exclusive, worldwide license from **Eli Lilly** in **February 2015**
- Preclinical studies showed that CERC-501 dose-dependently produced an antidepressant-like response in and significantly attenuated continuous ethanol self-administration in female alcohol-preferring rats
- In **May 2017**, Cereceor announced **encouraging results** from a small proof-of-concept study of CERC-501 **in treatment-resistant depression**
- In **August 2017**, Janssen Pharmaceuticals had acquired **CERC-501** from Cerecor for **$25 million** plus a possible $20 million milestone payment

ATICAPRANT (JNJ-67953964) PROOF-OF-CONCEPT TRIAL of CERC-501 AUGMENTATION of ANTIDEPRESSANT THERAPY in TRD [RAPID KOR]

- **Phase 2** RCT with sequential parallel comparison designed
- **8 subjects enrolled** with TRDcurrently on stable antidepressant therapy
- Subjects participated in **two sequential 72 hour periods**
- Placebo non-responders in Period 1 were re-randomized to either CERC-501 or placebo for Period 2

Recruitment Status : Terminated (slow enrollment)
First Posted : August 1, 2013
Results First Posted : July 2, 2017
Last Update Posted : July 2, 2017

The **trial** was **terminated** early **due to recruitment** issues, and **no statistical analysis was performed** due to the small sample size

Clinically Meaningful Improvements Observed at Day 3:

- Clinically meaningful **2.0-point difference** from placebo on the **HAMD-6**, change from baseline **to 72 hours** (primary efficacy measure) was observed in patients treated with CERC-501
- The results on the **Perceived Stress Scale** (**3.5 point decrease** for CERC-501 treated patients and 0.5 point increase in placebo treated patients) **have not been seen before in only three days of treatment** with standard antidepressants
- **Clinically meaningful differences** were also observed across **multiple secondary efficacy measures**

[NCT01913535]

ATICAPRANT (JNJ-67953964)
FIRST IMPLEMENTATION OF THE NIMH **FAST-FAIL APPROACH** TO PSYCHIATRIC DRUG DEVELOPMENT

Table 1 | **Summary of the 'fast-fail' approach to early-phase psychiatric drug development**

Key step in fast-fail approach	Comments
Develop/select a biomarker that reflects activity of the experimental compound at the neurobiological target	Ideally, this would be PET receptor occupancy or other imaging-based probes of target engagement (for example, functional magnetic resonance imaging, magnetic resonance spectroscopy)
Use this target engagement biomarker to determine doses of a selective drug that robustly engages the target for use in subsequent studies	Where the measure is PET receptor occupancy, robust engagement would be indicated by near-complete receptor occupancy (occupancy levels that are in the asymptotic portion of the dose–occupancy curve)
Conduct phase IIa studies testing the specific proof of mechanism hypothesis that engaging the target achieves an effect on the brain thought to mediate the anticipated clinical effect	The rationale is that effects on the brain are closer to the direct neurobiological effects of the drug than to the clinical effects, and, as a result are likely to be detectable more reliably and with a smaller number of subjects than the clinical effects. This addresses the problem that phase II studies with clinical end points have produced misleading results because they are nearly always underpowered
Proceed to studies with clinical end points only if proof of mechanism is established; otherwise, 'fail' the drug	Demonstrating that engaging the target activates the mechanisms thought to mediate clinical effects de-risks proceeding to larger clinical studies. It provides reassurance that effects on clinical end points found in phase IIb studies are likely to be mediated by those hypothesized neural mechanisms rather than the result of bias and other non-specific effects that do not reflect an actual therapeutic effect of engaging the target , which have been the bane of psychiatric drug development

PET, positron emission tomography.

NATURE REVIEWS | DRUG DISCOVERY www.nature.com/nrd

[Krystal et al., 2018: PMC6816017]

ATICAPRANT (JNJ-67953964)
FAST-FAIL TRIALS IN MOOD AND ANXIETY SPECTRUM DISORDERS; KAPPA OPIOID RECEPTOR PHASE 2A (FASTMAS_KOR2)

Compound	Clinical trial	Reference	Inclusion criteria	Dosing regimen	Outcomes
JNJ-67953964	NCT02218736	Krystal et al. (2019)[78]	DSM-5 mood/anxiety disorder with anhedonia SHAPS ≥20	Placebo or 10 mg orally once daily for 8 weeks	Enhanced ventral striatal activation during monetary incentive delay task SHAPS score reduction (JNJ-67953964 = 30.777; placebo = 32.363)

- As part of the **National Institutes of Mental Health** FAST-FAIL initiative a **phase 2a proof-of-mechanism** study of JNJ-67953964 (at a fixed oral dose of **10mg per day**) versus placebo, conducted at six US academic medical centers in patients meeting DSM-5 mood or anxiety disorder diagnostic criteria who also had anhedonia (**Snaith Hamilton Pleasure Scale Score ≥20**)
- Study demonstrated greater **ventral striatal activation**, measured by **fMRI**, during the **monetary incentive delay task**. These data **confirmed** the ability of **JNJ-67953964** to **modulate** this **critical hub of reward processing**.
- **Secondary measure** included **improved clinical anhedonia** on the Snaith-Hamilton Pleasure Scale (**SHAPS**) following JNJ-67953964 treatment
- Based on these data, the **Fast-Fail Trials** Program has **approved** the **continued** clinical **evaluation** of **JNJ-67953964** for treating **MDD**

[NCT02218736] [Krystal et al., 2018: PMC6816017]

http://s1.q4cdn.com/460208960/files/News/2016/CERC_INITIATION.pdf

ATICAPRANT (JNJ-67953964)
EFFICACY OF JNJ-67953964 IN THE TREATMENT OF DEPRESSION (PHASE 2A)

Study is to **evaluate the efficacy of JNJ-67953964** when administered as **adjunctive treatment** in participants with **MDD partially responsive to SSRI/SNRI** as assessed by Montgomery Asberg Depression Rating Scale (**MADRS**)

Recruitment Status : Recruiting
First Posted : June 18, 2018
Last Update Posted : February 10, 2020
See Contacts and Locations

Estimated Primary Completion Date :	May 13, 2020
Estimated Study Completion Date :	May 13, 2020

INCLUSION CRITERIA

- Participants must have a primary **DSM-5 diagnosis of MDD**
- Have a Snaith-Hamilton Pleasure Scale (**SHAPS**) total score **>20** at screening and baseline (Visit 2)

PRIMARY EFFICACY MEASURE

- **Change from baseline** in Montgomery Asberg Depression Rating Scale (**MADRS**) Score up to Treatment **Week 6**

PURSUED INDICATIONS

- JNJ-67953964 as **first-line monotherapy** for Major depressive disorder with marked anhedonia
- or **adjuvant therapy** with other first-line antidepressants for Treatment resistant depression

[NCT03559192]

Компания Ely Lilly
РАЗРАБОТАЛА 3 ОПИОИДНЫХ АНТАГОНИСТА

- **LY 2196044** = **ondelopran** (ondelopran) [**triple** opioid receptor antagonist: **MOP** + **KOP** + **DOP**]
- **LY 2456302** = CERC-501 = **JNJ-67953964** = aticaprant [**selective KOP** receptor antagonist]
- **LY 2940094** = **BTRX-246040** [**selective NOP** receptor antagonist]

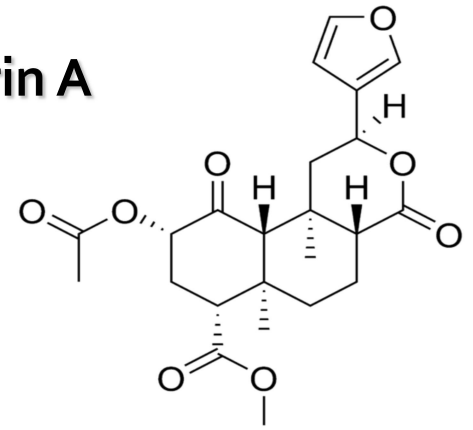
BTRX-246040 (LY2940094)

BTRX-246040	NCT01724112	Post et al. (2016)[79]	MDD HAM-D-17 ≥20	Placebo or 40 mg orally once daily for 8 weeks	Did not meet primary outcome Reduced depressed mood relative to placebo-treated subjects (item 1 of HAM-D-17) Greater emotional processing of positive stimuli after 1 week of treatment

- In both human and rodent brains two hours following BRTX-246040 administration approximately 80% of NOP receptors were occupied across the prefrontal cortex (PFC), occipital cortex, putamen, and thalamus
- Given the preclinical evidence demonstrating robust effects of BTRX-246040 in rodent tests that predict antidepressant potential and the demonstration of anti-stress effects in rodent models of stress, a proof of concept study for BTRX-246040 in depressed human patients reported a nonsignificant reduction in Hamilton Depression Scale (HAM-D)–17 scores following eight weeks of oral treatment
- Although the primary endpoint (reduced HAM-D-17 scores) was not achieved in that study, patients treated with BTRX-246040, relative to those treated with placebo, did exhibit greater emotional processing of positive stimuli and large reductions in depressed mood. These data support the further investigation of BTRX-246040 to treat MDD
- As such, several clinical trials evaluating BTRX-246040 in MDD subjects are ongoing: NCT01724112, NCT01404091, and NCT01263236

Salvia divinorum
(DISSOCIATIVE HALLUCINOGEN)

Salvinorin A



Most potent KOP receptor **super**agonist

- **S. divinorum** is a psychoactive plant which can induce **dissociative effects** and is a potent producer of "visions" and other **hallucinatory experiences**
- **Salvinorin A** is considered a **dissociative** exhibiting **atypical psychedelic effects**

ЭФФЕКТЫ КАППА-ОПИОИДНЫХ АГОНИСТОВ У ЧЕЛОВЕКА
[pentazocine, nalbufine, spiradoline, U62066E, S. divinorum и др.]

- **У здоровых добровольцев** введение агонистов KOP рецепторов оказывает **аверсивное**, седативное, **продисфорическое**, депрессогенное, **диссоциативно-галлюциногенное** (психотомиметическое) действие. Все эти эффекты снимаются налоксоном [Pfeiffer et al., 1986; Chappell et al., 1993; Rimoy et al., 1994; Ur et al., 1997; Walsh et al., 2001; Shippenberg et al., 2007; Lange et al., 2010]

- Показано, что **у больных депрессией**, **совершивших суицид**, наблюдается значительное **увеличение уровня мРНК продинорфина** и самого **динорфина** в **стриатуме и гиппокампе** [Shirayama et al., 2004; Hurd et al., 1997; Bruchas et al., 2010]

ДИССОЦИАТИВНЫЕ ГАЛЛЮЦИНОГЕНЫ

[ВКЛЮЧАЯ ДИССОЦИАТИВНЫЕ АНЕСТЕТИКИ: КЕТАМИН, ДЕКСТРОМЕТОРФАН, ФЕНЦИКЛИДИН]

- **Диссоциативы** – это **КЛАСС ГАЛЛЮЦИНОГЕНОВ** которые разобщают связь бодрствующего сознания с другими областями мозга, вызывая **ощущение отчужденности — диссоциированности от реальной действительности и от собственной личности**
- Диссоциативные феномены включают **деперсонализацию** – отчуждение от собственного мышления, личности и физического тела, и выраженную **дереализацию** – потерю чувства реальности происходящего, «осознание» того, что «мира и времени в не существует», переживания «небытия» [**near-death experience**]
- Вообще, **диссоциация —** психический процесс, относимый к **механизмам психологической защиты.** В результате которого окружающее воспринимается словно происходит с кем-то посторонним – как бы **со стороны**. Считается, что **диссоциированная позиция защищает от невыносимых моральных страданий.**
- Диссоциация, зачастую, **блокирует возможность адекватно оценивать эмоциональную составляющую ситуации.** Особенно **склонны диссоциировать** лица, **перенесшие** (особенно в детстве) **тяжелую психологическую травму**: подвергавшиеся **насилию**, пережившие **катастрофу** и др.
- Вероятно, эволюционное назначение **эндогенной опиоидной** системы заключается в **контроле запредельной болевой импульсации,** а точнее вообще **любого страдания**, в т.ч. и **морального**
- Таким образом, функции **динорфина** и **ноцицептина не сводятся** к **отрицательной регуляции эндогенной системы награды**, и включает также диссоциацию (разобщение сознания) от психотравмирующего опыта [**ПСИХИЧЕСКАЯ АНЕСТЕЗИЯ**] и **ВЫТЕСНЕНИЕ**, как механизмы психологической защиты

[Tamminga et Tanimoto, 1987; Vollenweider et Geyer, 2001; Kritchevsky et al., 2004; Stern, 2012]

DEPERSONALIZATION / DEREALIZATION DISORDER
DSM-5 [300.6]; ICD-11 [7B36]

A. THE PRESENCE OF **PERSISTENT** OR RECURRENT EXPERIENCES OF **DEPERSONALIZATION, DEREALIZATION** OR BOTH:

- **DEPERSONALIZATION**: Experiences of unreality, **detachment**, being an outside observer **with respect to** one's **thoughts**, **feelings**, sensations, body, or actions (e.g., perceptual alterations, distorted **sense of time**, unreal or **absent self**, **EMOTIONAL NUMBING**)

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ДЕВИТАЛИЗАЦИЯ

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- **DEREALIZATION**: Experiences of unreality, **detachment with respect to surroundings** (e.g., individuals or objects are experienced as unreal, dreamlike, foggy, **LIFELESS**, or visually distorted

DISSOCIATION and TREATMENT RESISTANCE

- **Dissociation** is an **IMPORTANT FACTOR THAT INFLUENCES THE TREATMENT EFFECTIVENESS** in anxiety/depression patients with or without personality disorders **resistant to treatment**

- **HIGHER** degree of dissociation at the beginning of the treatment predicted **MINOR** improvement, and also, **HIGHER** therapeutic change was connected to **GREATER** reduction of dissociation

[PMC5074730, PMC4928674, PMC4798215]

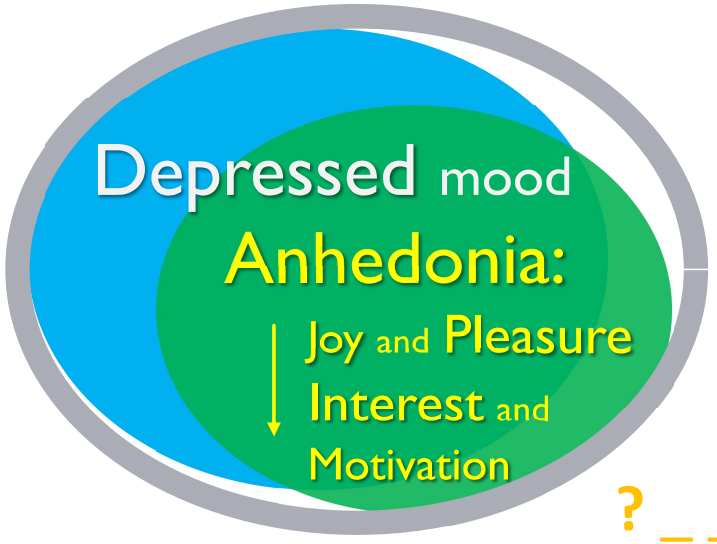
ЮРИЙ ЛЬВОВИЧ НУЛЛЕР [1929 – 2003]
«НАЛОКСОН В ТЕРАПИИ ДЕПЕРСОНАЛИЗАЦИОННОГО РАССТРОЙСТВА»

- «…еще один **тип реакции** в клинике обозначается как **деперсонализация** или **ПСИХИЧЕСКАЯ АНЕСТЕЗИЯ**. Защитная функция деперсонализации более очевидна, чем у остальных «регистров». Она возникает не только у больных, но и у здоровых людей **после крайне сильной тревоги**, **вызванной острой стрессорной ситуацией**: например, угрозой жизни, пытками, стихийными бедствиями, гибелью собственного ребенка и т.п.
- **Биологические механизмы** этой реакции связаны с **эндорфинами и опиоидными рецепторами**
- Исходя из этого предположения, мы использовали **для лечения** больных **деперсонализацией** антагонист морфина — **налоксон**, блокирующий опиоидные рецепторы
- Полученные положительные результаты, по-видимому, подтверждают правильность исходной гипотезы»
- «…**перспективы терапии деперсонализации** зависят от выявления ее патогенетических механизмов. **Обнадеживающими являются положительные результаты использования блокатора опиатных рецепторов налоксона**
- По-видимому, препараты этой группы **в скором времени** окажутся **эффективным методом лечения деперсонализации**

- …**ДЕПЕРСОНАЛИЗАЦИЯ** является **мучительным** состоянием, **часто приводящим к СУИЦИДАМ**… **деперсонализация РЕЗКО ПОВЫШАЕТ ТЕРАПЕВТИЧЕСКУЮ РЕЗИСТЕНТНОСТЬ** тех психических **расстройств, в рамках которых она возникает**

[Ю.Л.Нуллер, «Парадигмы в психиатрии», 1993]

KAPPA-ANTAGONISTs MAY SOON GIVE RISE to a NEW ERA in PSYCHIATRY



- **ANHEDONIA + DISSOCIATION** is a **TRANS-DIAGNOSTIC CORE** of many psychiatric disorders
- To date, ***effective*** *treatment* for **anhedonia + dissociation** is a HIGHLY **UNMET** CLINICAL NEED
- Given the broad range of potential indications it is possible that kappa-opioid receptor antagonists might segregate into a **NOVEL** PSYCHOPHARMACOLOGICAL CLASS for the treatment of *reward deficiency symptoms* [e.g."HEDOLIBERANTs" – from "liberate"]

Further indications expansion may be reasonably expected to include: (**1**) First-line monotherapy for Major depressive episode (including with marked anhedonia), (**2**) Adjuvant therapy in generalized anxiety disorder, (**3**) Posttraumatic stress disorder, (**4**) Social phobia, (**5**) Treatment resistant obsessive-compulsive disorder, (**6**) Dissociative disorders [*orphan or fast track designation*] and (**7**) Attention deficit hyperactivity disorder in adults

ПОЖАЛУЙСТА!

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