PainWeek®

Doubling Down: Polysubstance Abuse and Associated Respiratory Depression

Joseph Pergolizzi , MD

Robert B Raffa, PhD

Disclosure

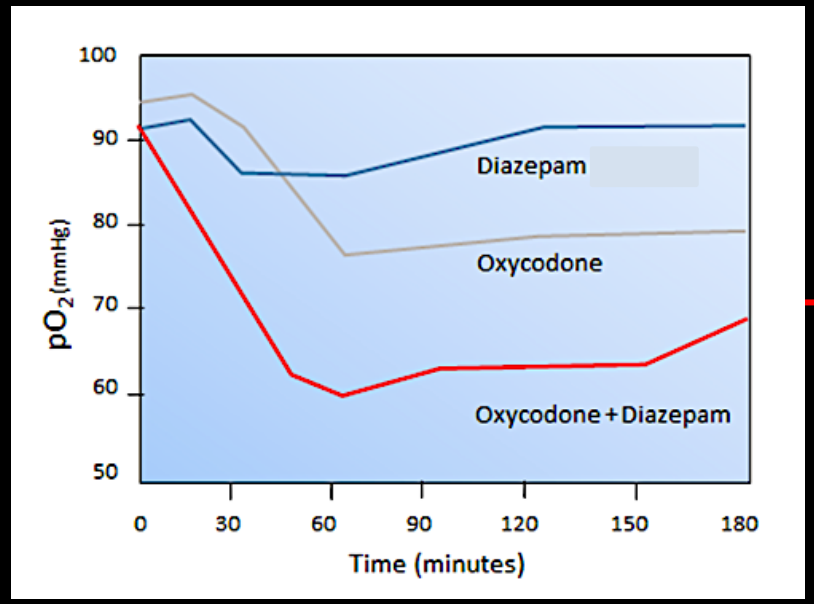
- Consultant/Independent Contractor: Neumentum
- Stock Shareholder: Neumentum

Learning Objectives

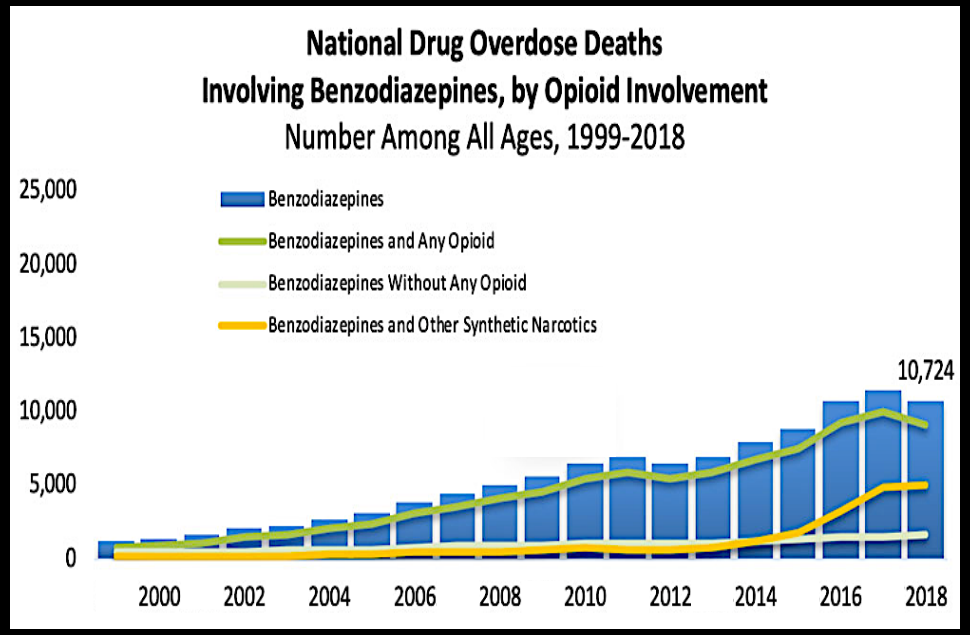
- List 3 or more respiratory-depression targets or agents
- Summarize their current status in the discovery/development process
- Compare the targets/agents for druggability

Polysubstance Abuse

The Problem



- BZD
  - –central &
  - –skeletal m

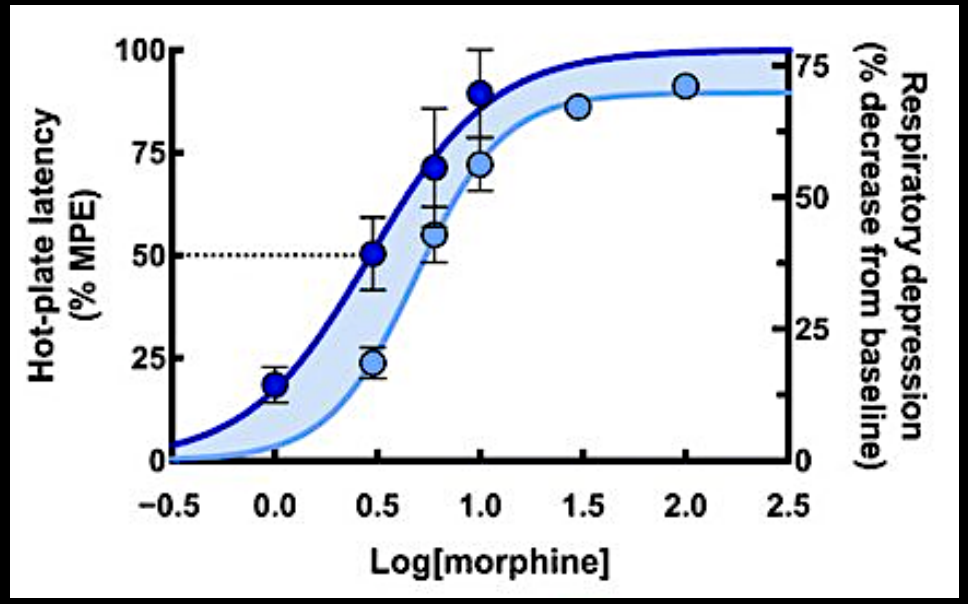


https://www.fda.gov/drugs/regulatory-science-action/impact-story-preclinical-research-achieve-safer-prescribing-psychoactive-therapeutics-patients-who

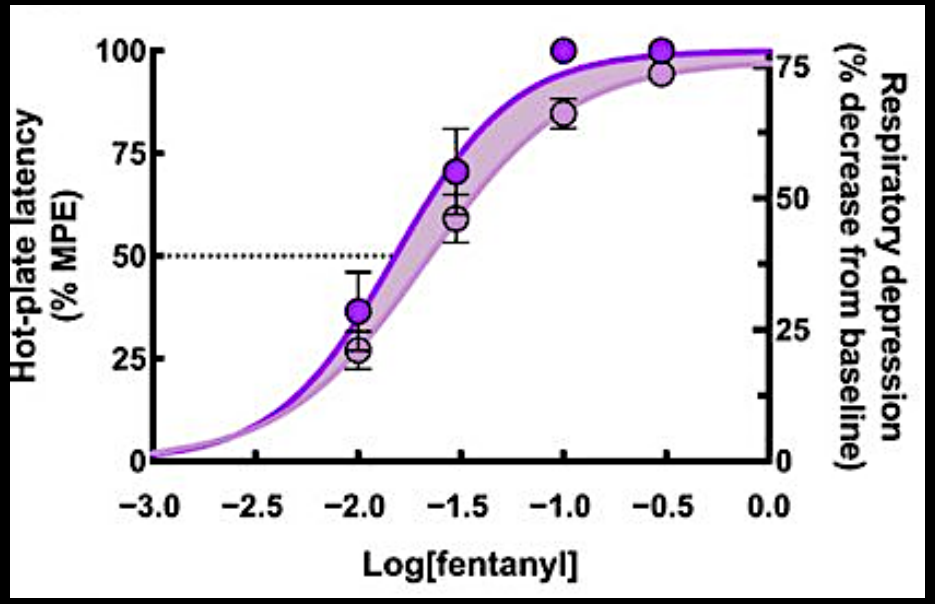
Opioid-induced Respiratory Depression

Opioid-induced Respiratory Depression

- Small separation from analgesia



morphine

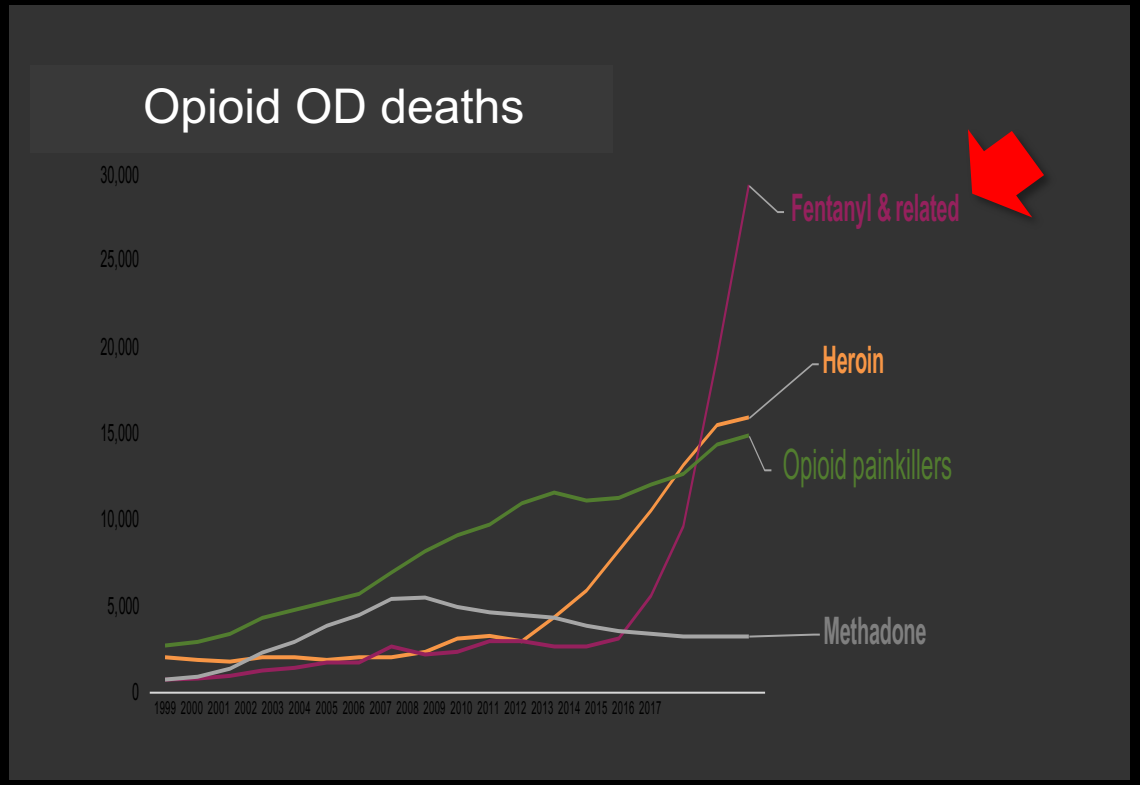


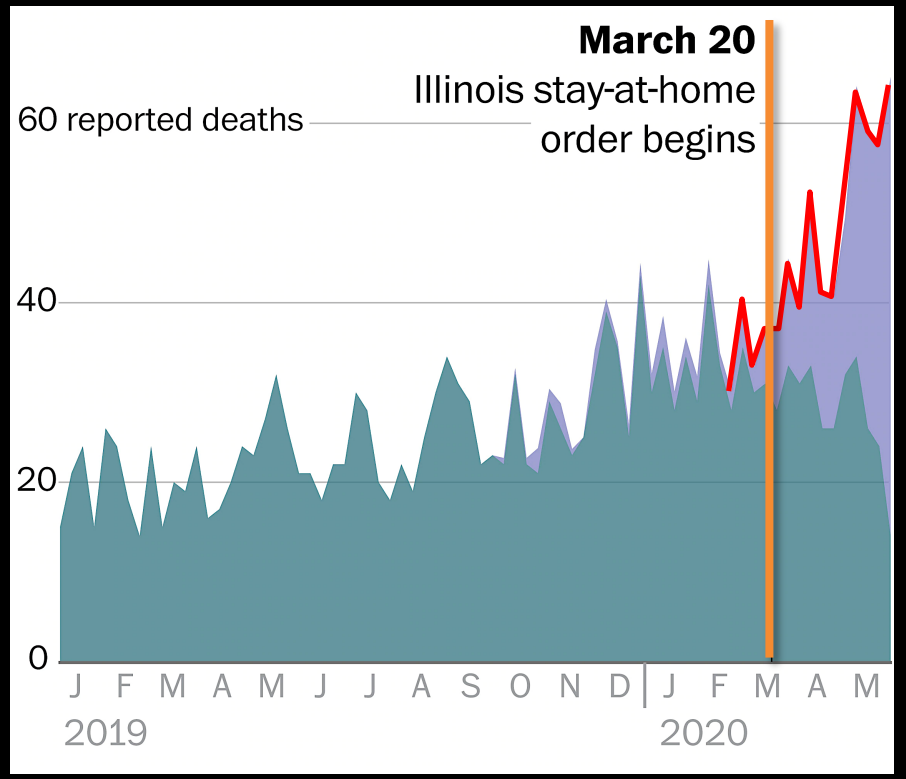
fentanyl

Gillis et al. (2020) Sci Signaling 13: eaaz3140 DOI: 10.1126/scisignal.aaz3140

Polysubstance Use in the Time of COVID

Polysubstance Use in the Time of COVID





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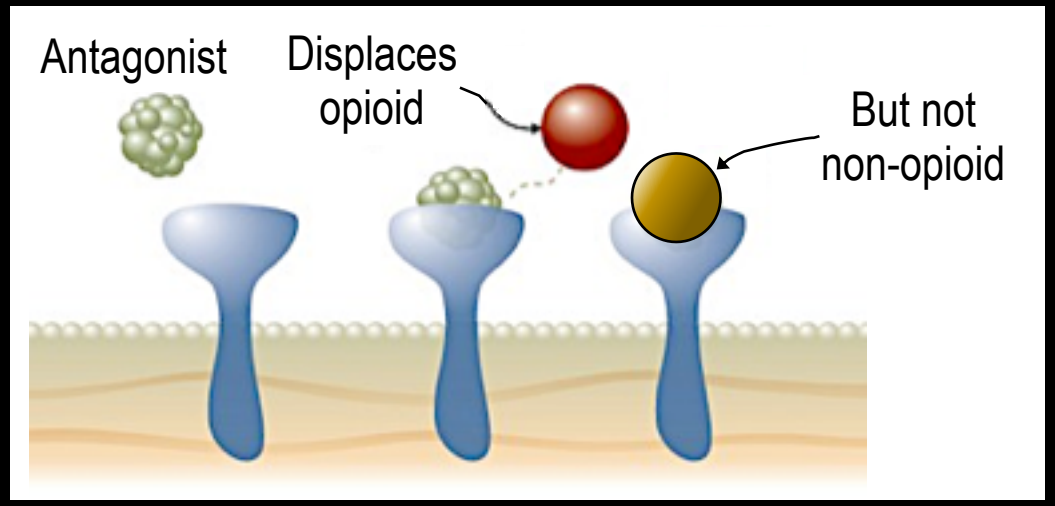
Data from Cook County Med Examiner – *The Washington Post*

How Do You Treat Polysubstance OD?

The Problem

- Opioid receptor antagonists can reverse opioids
- But not non-opioids
- They also block analgesia



A Possible Alternative

The Latest Pharmacologic Ventilator
Joseph F. Cotton (2014) Anesthesiology 121:442-444

- Ventilatory stimulant
  - –should be agnostic to cause
  - –should not block OR-mediated pain relief
  - –should not precipitate withdrawal (combativeness)

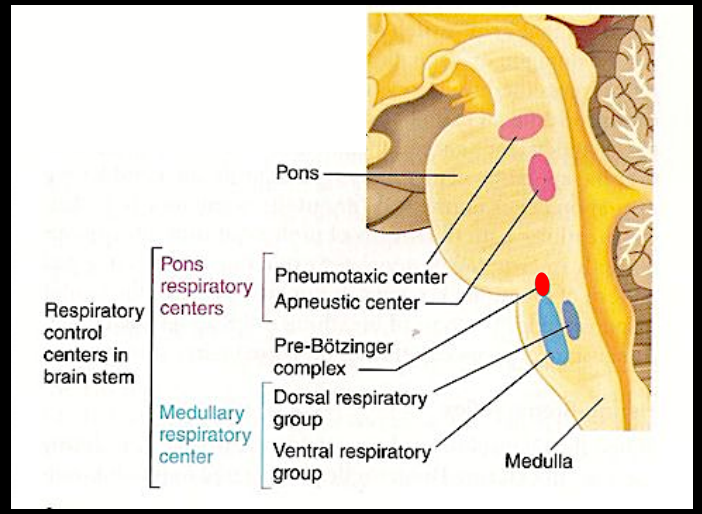
Breathing Stimulants (Support) – *caffeine*

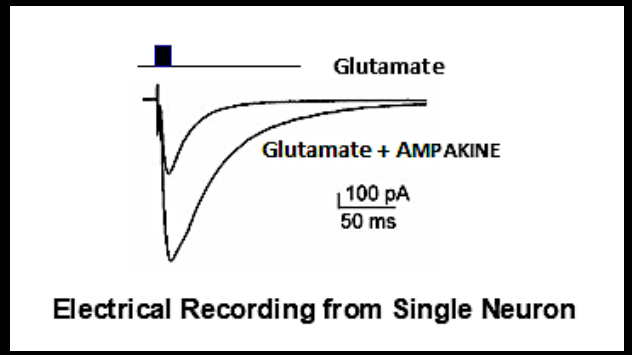
- Methylxanthines have been used in the neonatal ICU for more than 40 yr to treat and prevent apnea of prematurity.
- Among methylxanthines, caffeine is used most commonly because of its wide TI and longer $t_{½}$ that allows once-daily administration
- Multiple mechanisms of action beyond a reduction in apnea are likely to mediate the beneficial effects of caffeine.
- 'Support' more than 'rescue'.

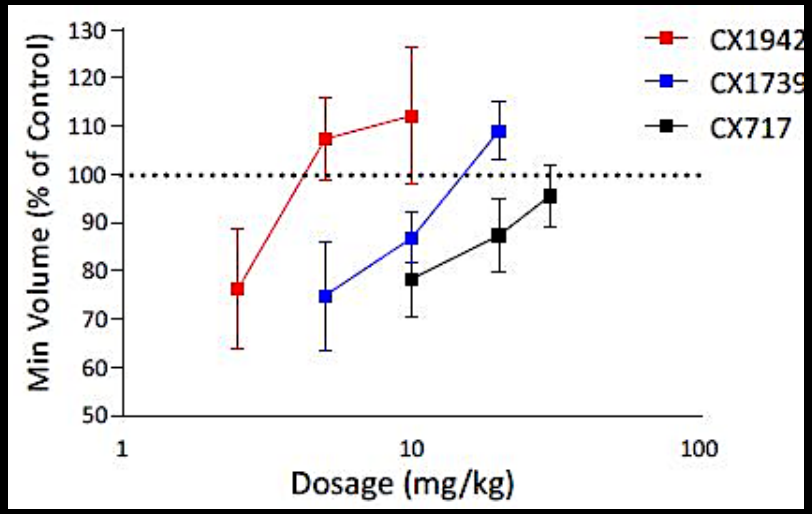
Dobson & Patel (2016) Clin Perinatol 43:773-782

Breathing Stimulants – *ampakines*

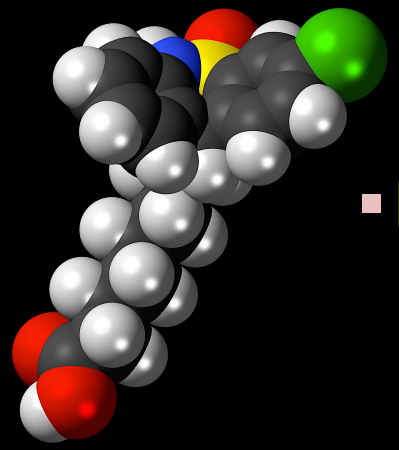
- Ampakines act centrally at AMPA-type glutamate receptors in the brainstem (pre-Botzinger complex)
  - CX1942
  - CX1739
  - CX717 (relatively poor oral bioavailability and BBB penetration)





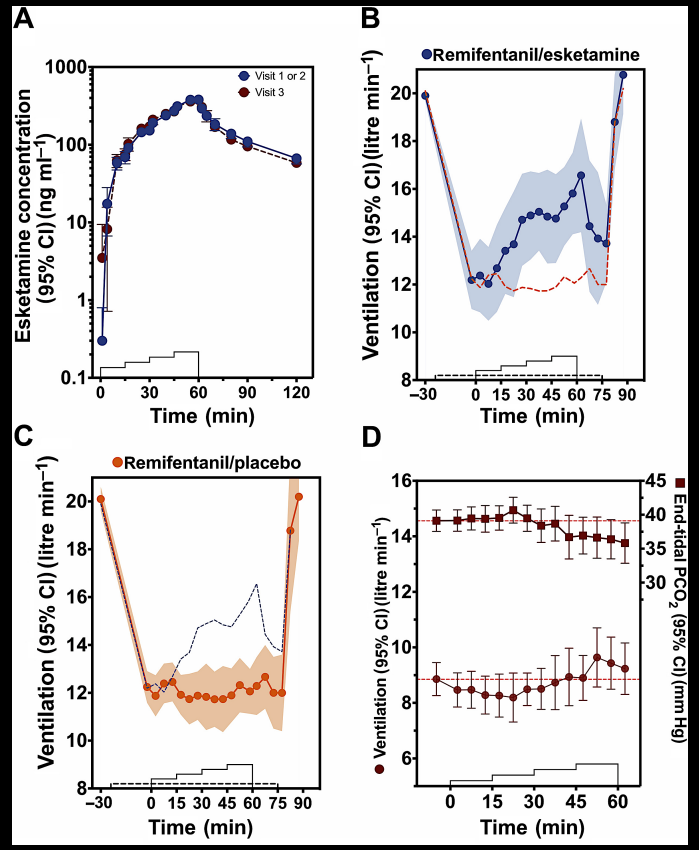


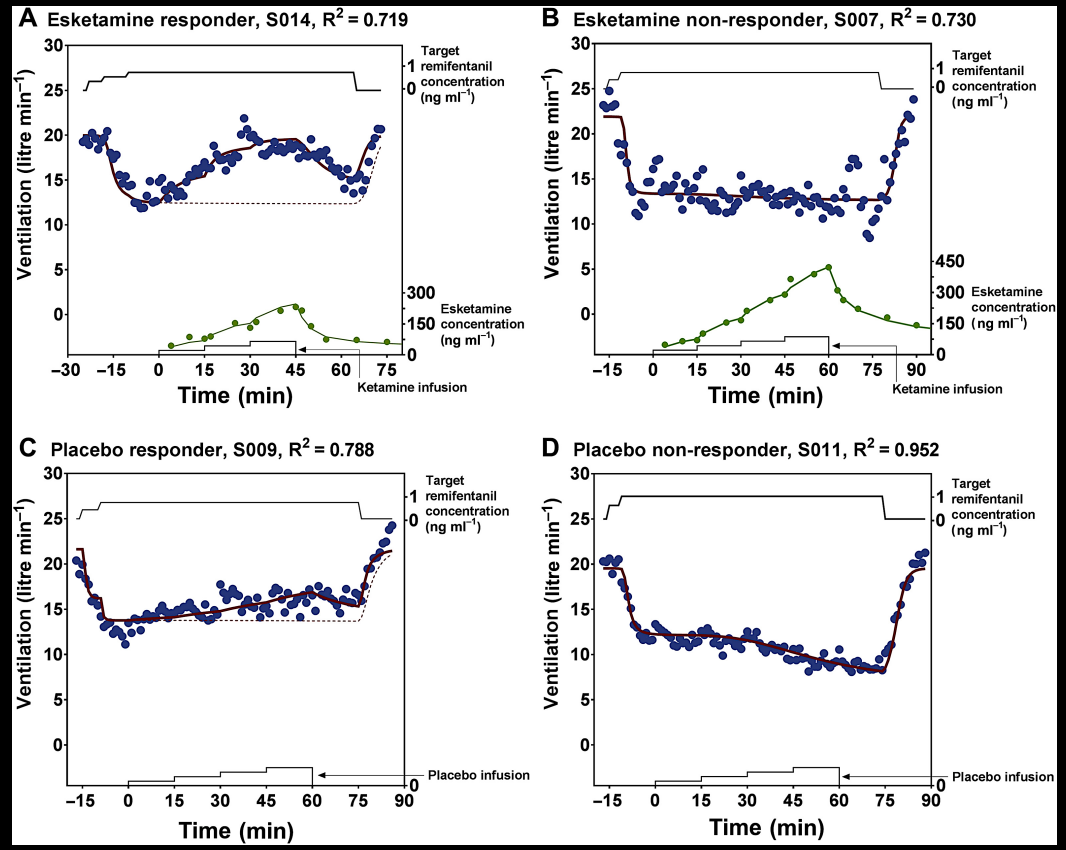
Breathing Stimulants – *repurposed*



- Rev-001 (tianeptine)
  - –antidepressant
  - –studied for prevention of OIRD
  - –complex pharmacology
  - –μ-OR affinity (biased ligand?)
  - –abuse potential at high doses

Esketamine – *S(+)-ketamine*

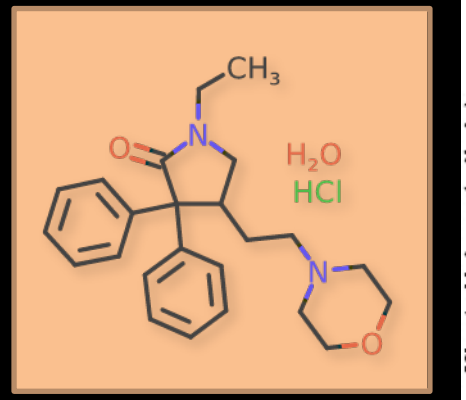


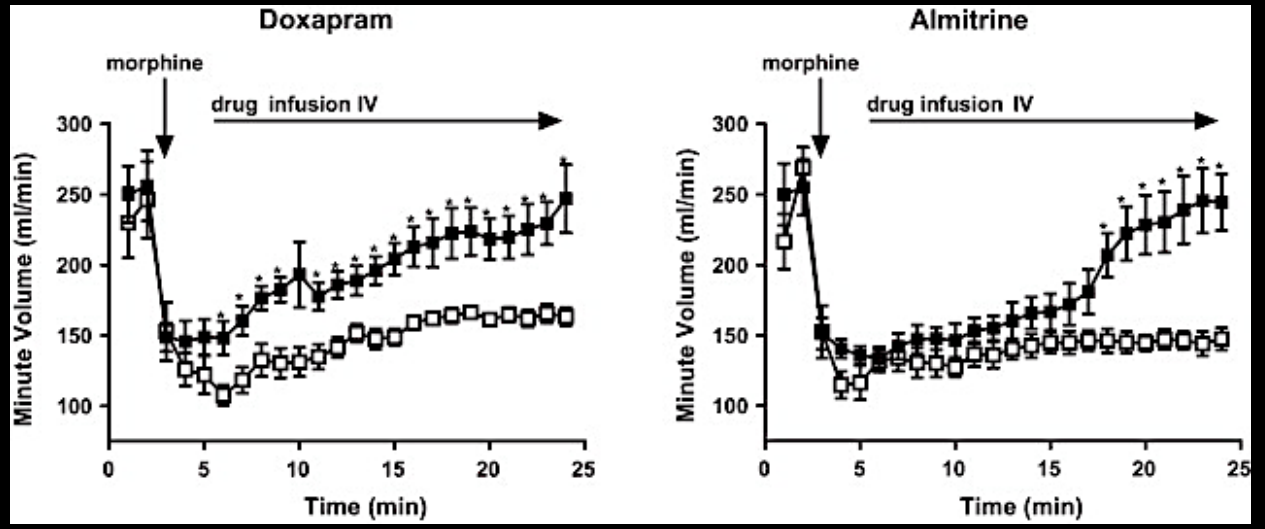


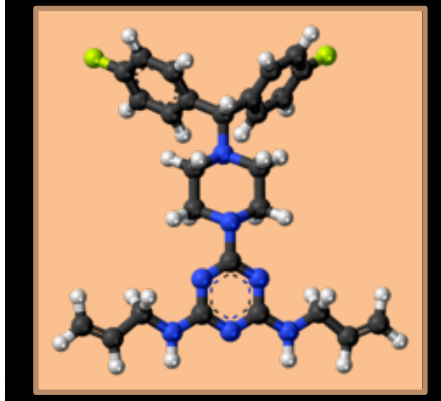
Jonkman et al. (2018) Brit J Anaesth 120:1117e1127

Respiratory Stimulants – *doxapram & almitrine*

- Doxapram and Almitrine



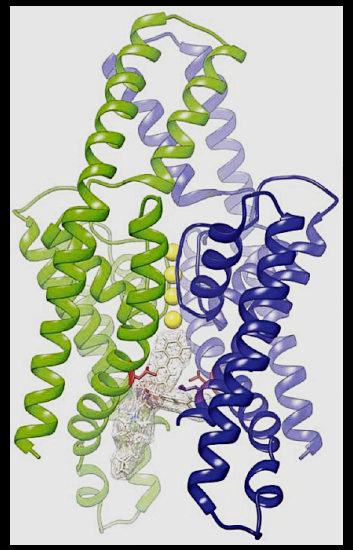


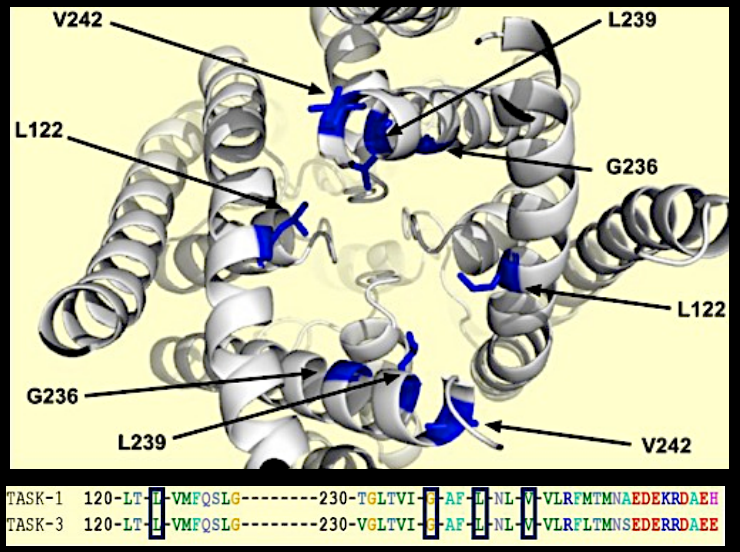


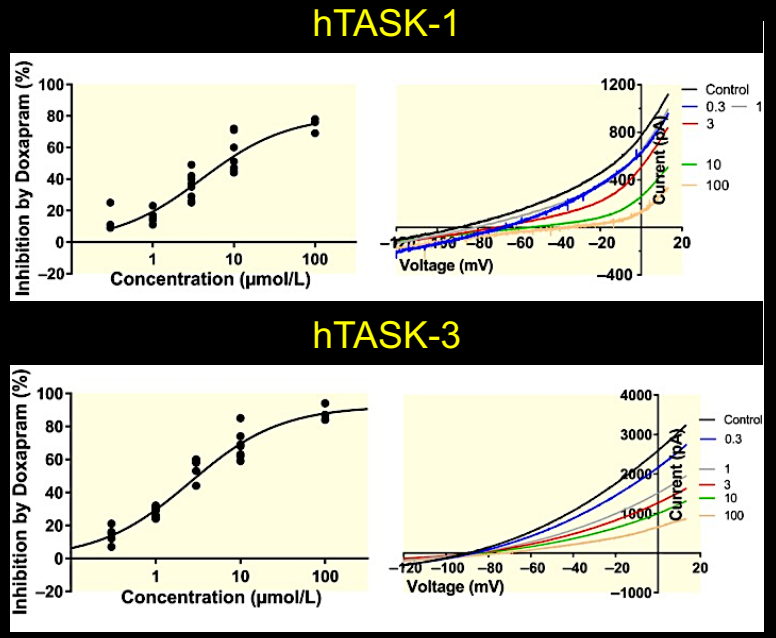
Golder *et al.* (2013) Resp Physiol Neurobiol 189:395 - 402

Doxapram

- Stimulates respiration by an action on peripheral carotid chemoreceptors
- Potent inhibitor of TASK-1 (KCNK3, K2P3.1) and TASK-3 (KCNK9, K2P9.1), but not TASK-2 (KCNK5, K2P5.1) K^+ channels in humans







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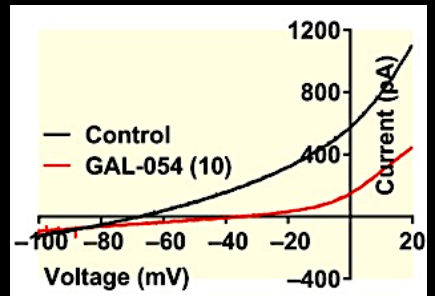
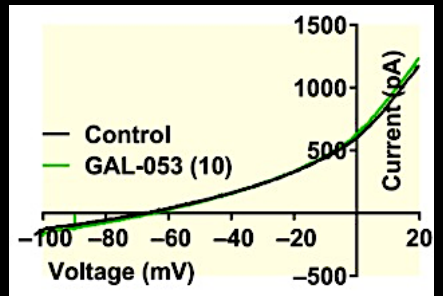
Chokshi *et al.* (2015) Molec Pharmacol 88:926-934
Cunningham *et al.* (2019) Acta Physiologica 228:e13361

Doxapram

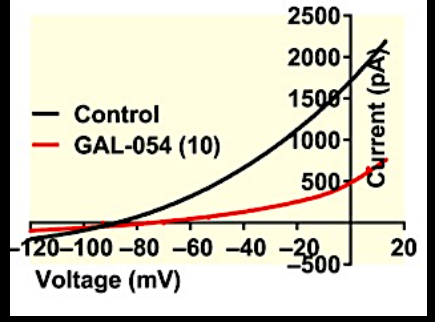
- The positive enantiomer of doxapram (GAL-054) is a more potent antagonist of TASK channels than is doxapram
- The negative enantiomer (GAL-053) has little inhibitory effect

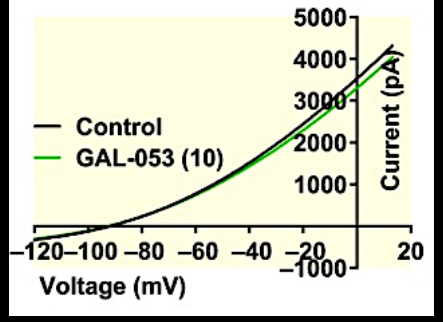
hTASK-1





hTASK-3

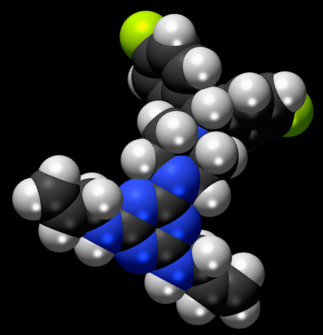


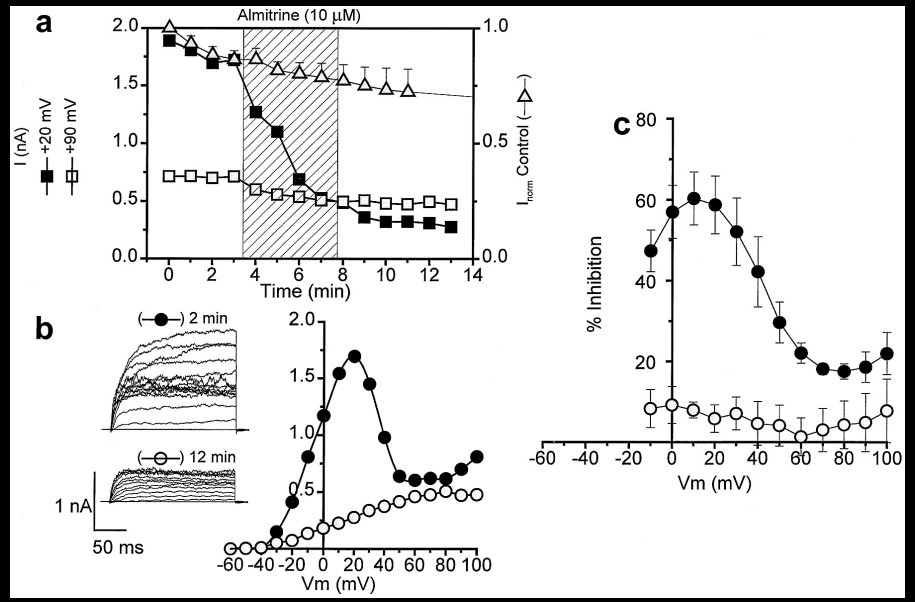


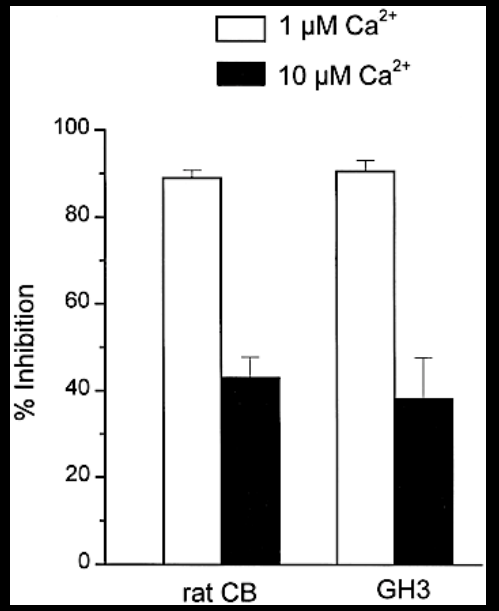
Chokshi *et al.* (2015) Molec Pharmacol 88:926-934; Cunningham *et al.* (2019) Acta Physiologica 228:e13361

Almitrine

- enhances respiration by acting as an agonist of chemoceptors located on the carotid bodies.







López-López et al. (1998) Molec Pharmacol 53:330-339

Doxapram *vs* Almitrine

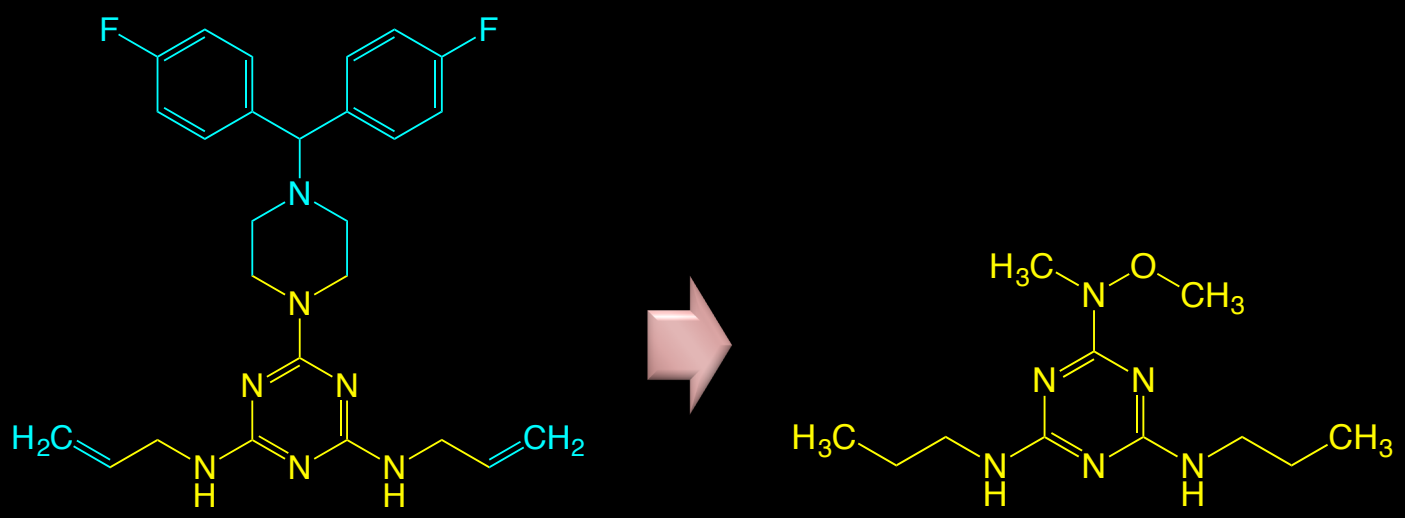
- Transecting the carotid sinus n. blocks the ventilatory effects of almitrine at all doses – and doxapram at normal clinical doses.
- Doxapram's action is manifested by increase in tidal volume associated with a slight increase in respiratory rate.
- At higher doses of doxapram, residual ventilatory stimulation persists in carotid and aortic denervated animals, indicating an additional site of action – presumably within the central nervous system (brain and sp. cord).

Uses and Concerns

- Exercising care to prevent vomiting and aspiration, doxapram may be used to stimulate respiration, hasten arousal and encourage the return of laryngo-pharyngeal reflexes in patients with mild to moderate respiratory and CNS depression due to drug overdose. AEs: panic, agitation, dyspnea, and hyper-tension.
- 2013: EU drug regulators recommended withdrawing oral almitrine-containing medicines from the market because their benefits no longer outweigh the risk for marked weight loss and long-lasting peripheral neuropathy.

Evolution to ENA-001 (formerly GAL-021)

- Remove difluorobenzhydrylpiperidine group
- Remove allyl groups



almitrine

GAL-021 (ENA-001)

ENA-001 (formerly GAL-021)

- MoA primarily thought to involve blocking BK_{Ca} K^+ channels
- BK_{Ca}-channels contain response elements for CO, O_2, and CO_2. Its block increases carotid body signaling, phrenic n. activity, and respiratory drive
- peripheral action
- secondary mechanisms may also be involved

McLeod *et al.* (2014) Brit J Anaesth 113:875-883

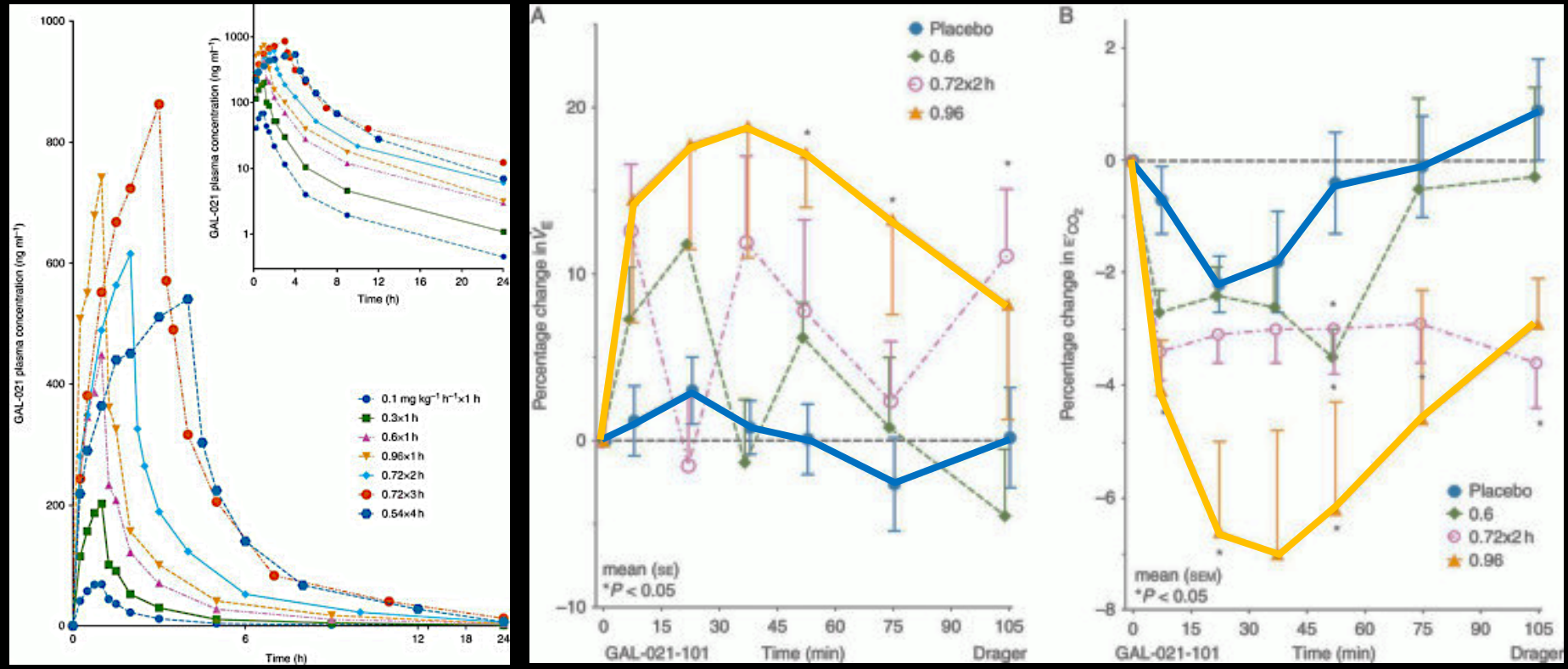
ENA-001 (formerly GAL-021)

- In human volunteers

Prof. Dr. Albert Dahan

ENA-001 (formerly GAL-021)

- In human volunteers



McLeod *et al.* (2014) Brit J Anaesth 113:875-883

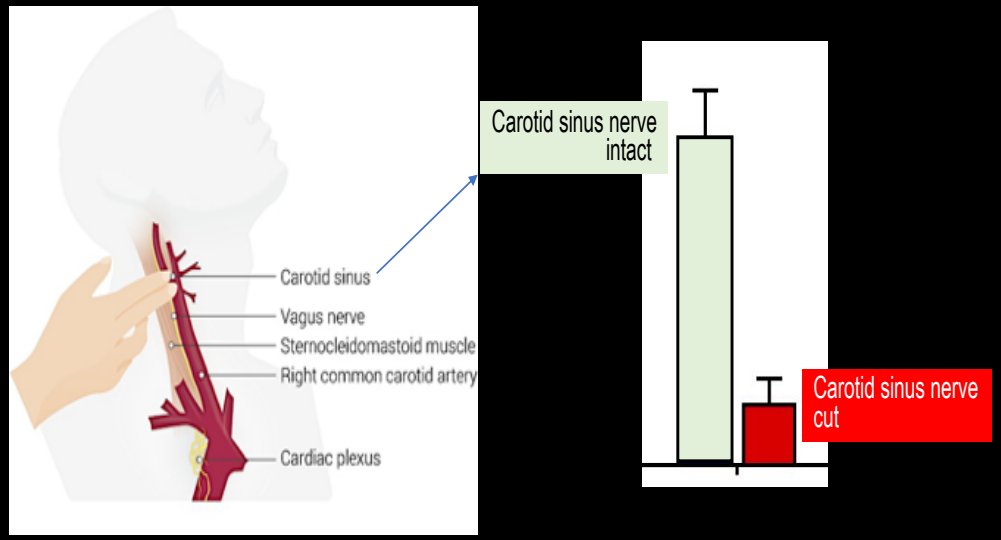
ENA-001 (formerly GAL-021)

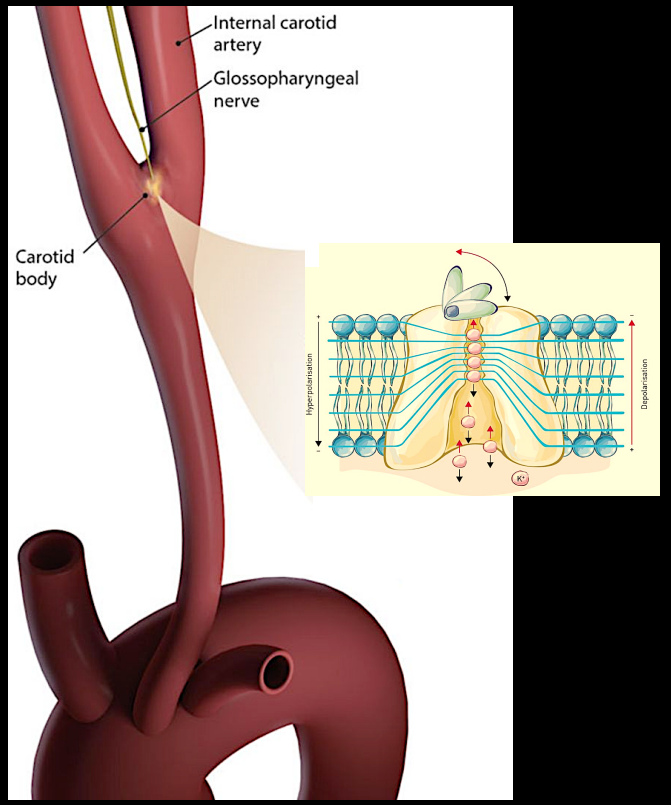
- Upon i.v. administration by bolus or infusion to rats[1] or cynomolgus monkeys[2] ENA-001 elicits dose-dependent increases in minute ventilation and shows a robust, dose-dependent, reversal of respiratory depression caused by opioids (morphine or fentanyl), benzodiazepines (midazolam), or by anesthetic agents (isoflurane or propofol).

[1] Baby *et al.* (2012) FASEB J 26:704.28
[2] Golder et al. (2012) FASEB J 26:704.27

ENA-001 (formerly GAL-021)

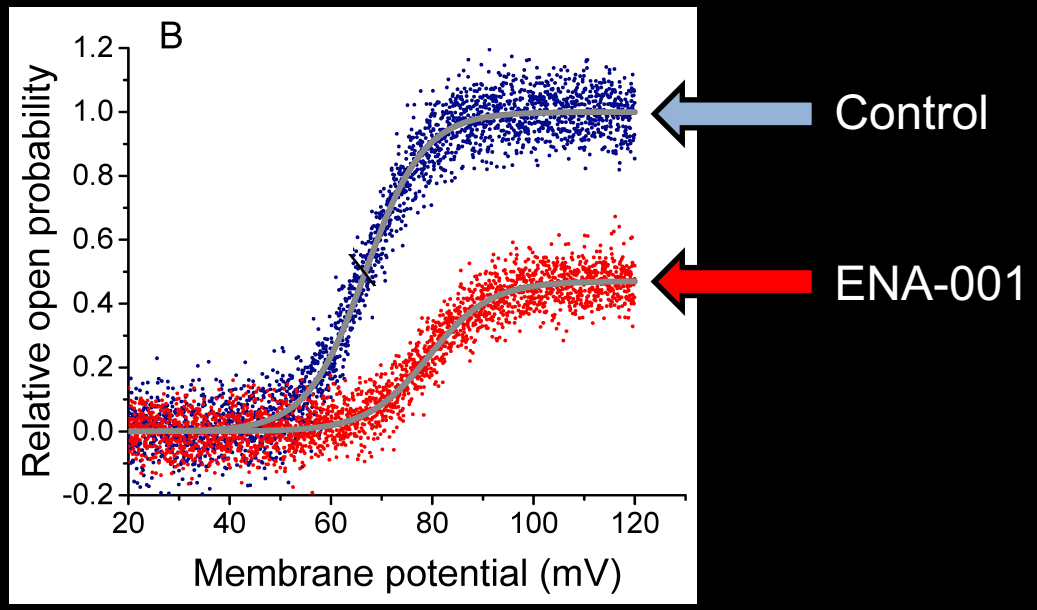
- Involvement of carotid body





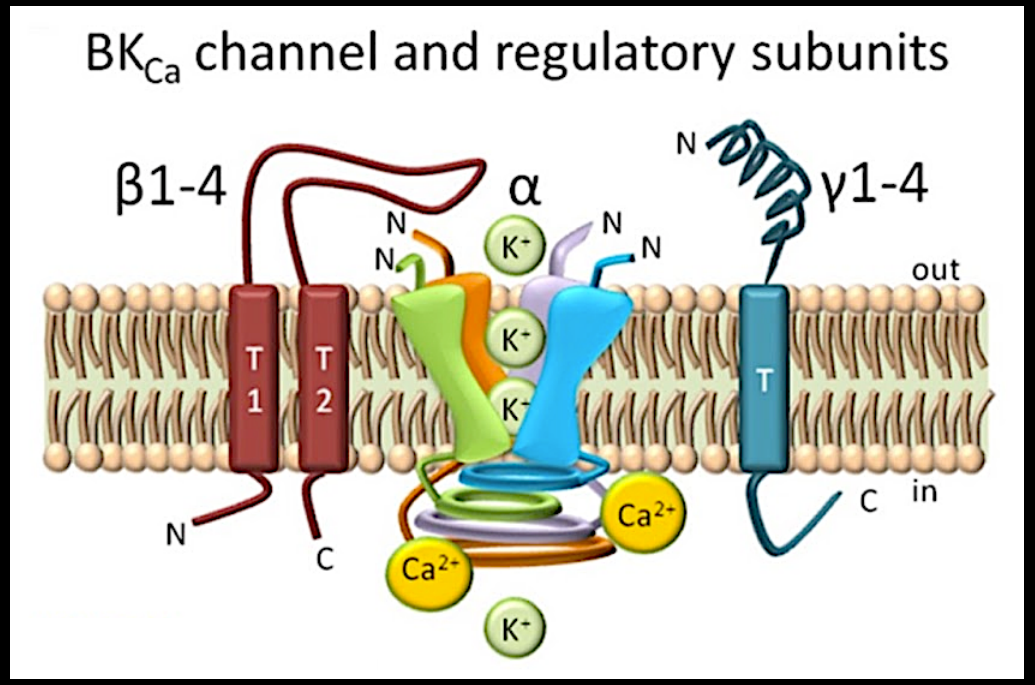
ENA-001 (formerly GAL-021)

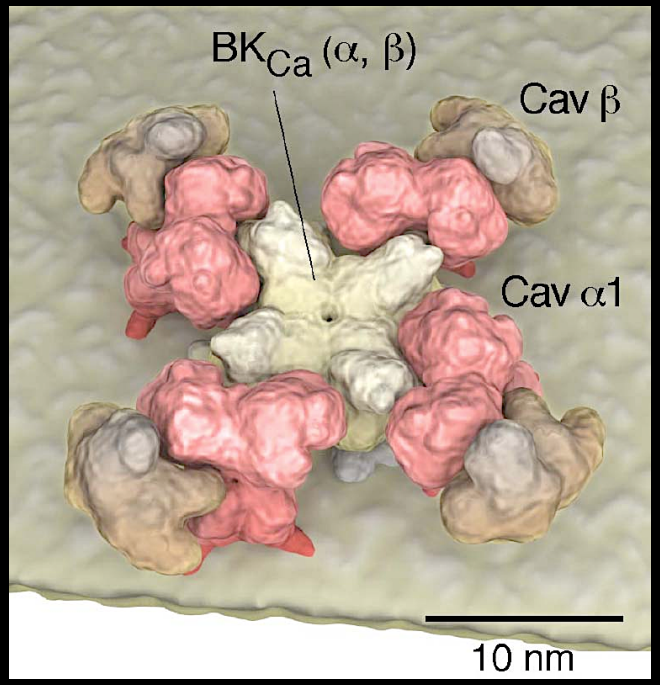
- decreases the amplitude of the macroscopic Ca^{2+}-activated K^+ current ($I_{K(Ca)}$) in a concentration-dependent manner
- lengthens mean closed time of BK_{Ca} channels, with no change in mean open time (in HEK293T cells expressing *α-hSlo*,).



Lu et al. (2020) Biomolecules 10:188 https://doi.org/10.3390/biom10020188

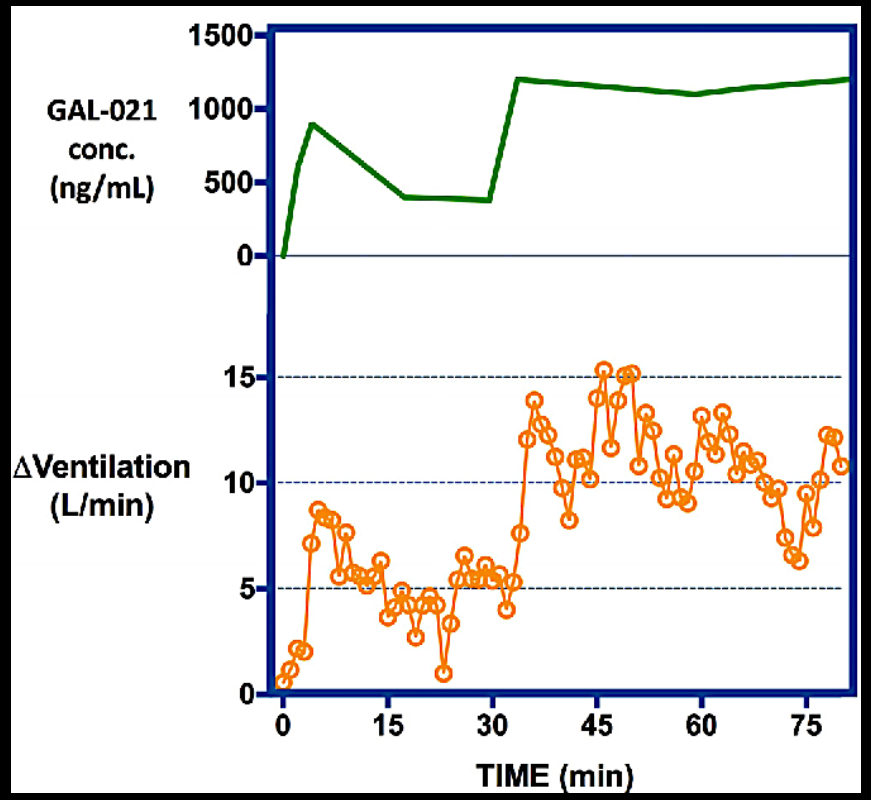
BK_{Ca} K^+ channels





https://multiple-sclerosis-research.org/2017/06/education-big-conductance-potassium-channels/
http://www.physiologie.uni-freiburg.de/molecular-physiology/news/neighborly-relationsbetween-ion-channels

ENA-001 (formerly GAL-021)



van der Schier et al. (2014) F1000Prime Reports 6:79 doi:10.12703/P6-79

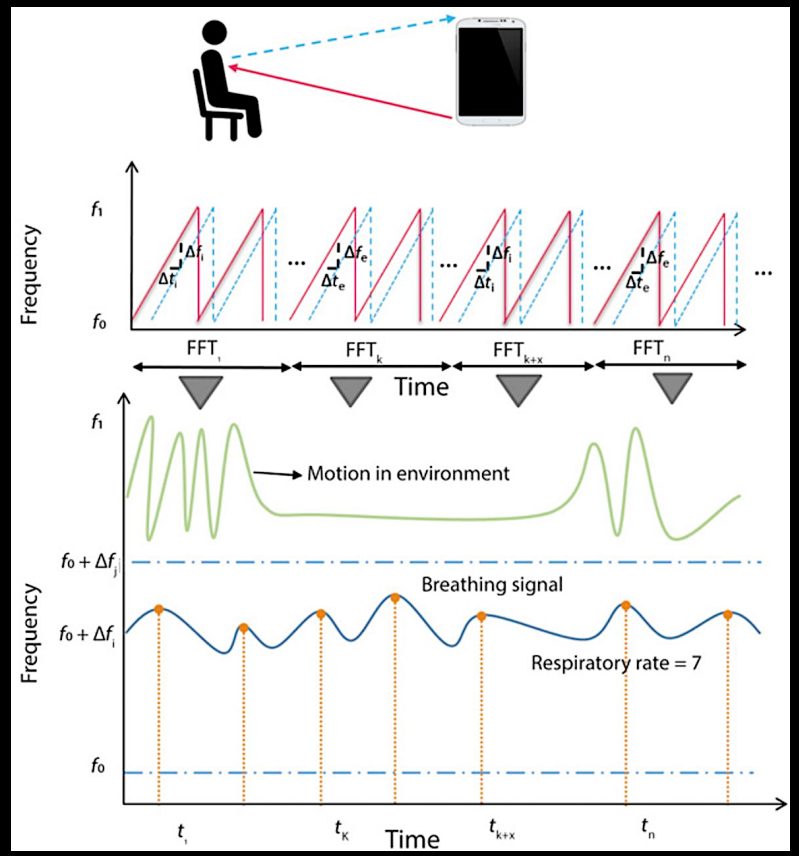
ENA-001 (formerly GAL-021)

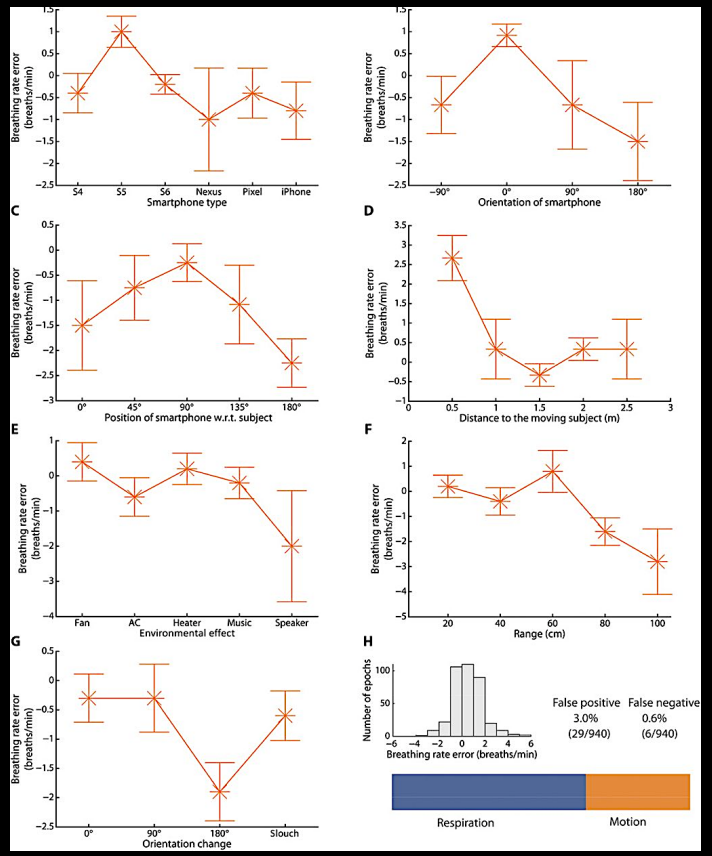
Summary

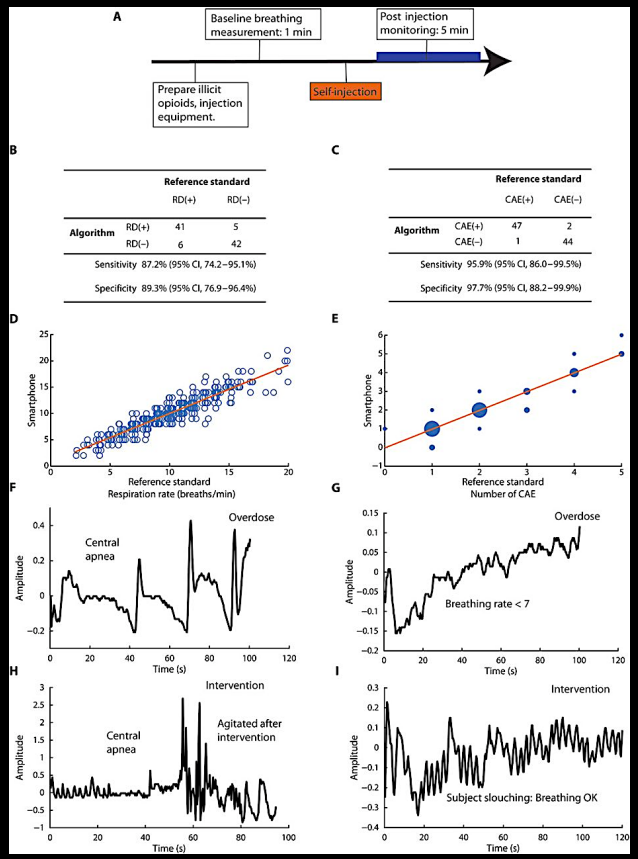
- MoA primarily thought to involve blocking BK_{Ca} K^+ channels
- peripheral action
- does not block opioid receptors (does not block opioid-induced analgesia)
- ‘agnostic’

Remote Sensing – *there's an App for that*

Telemedicine – *Smartphone*







Nandakumar R *et al*. (2019) Sci Transl Med 11: eaau8914

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Dr. Pergolizzi discloses the following relationships:

- Consultant/Independent Contractor: Lilly
- Grant/Research Support: Regeneron
- Honoraria: Salix
- Speaker's Bureau: BDSA
- Advisory Board: Enalare
- Stock/Shareholder: Enalare ,Neumentum

Learning Objectives

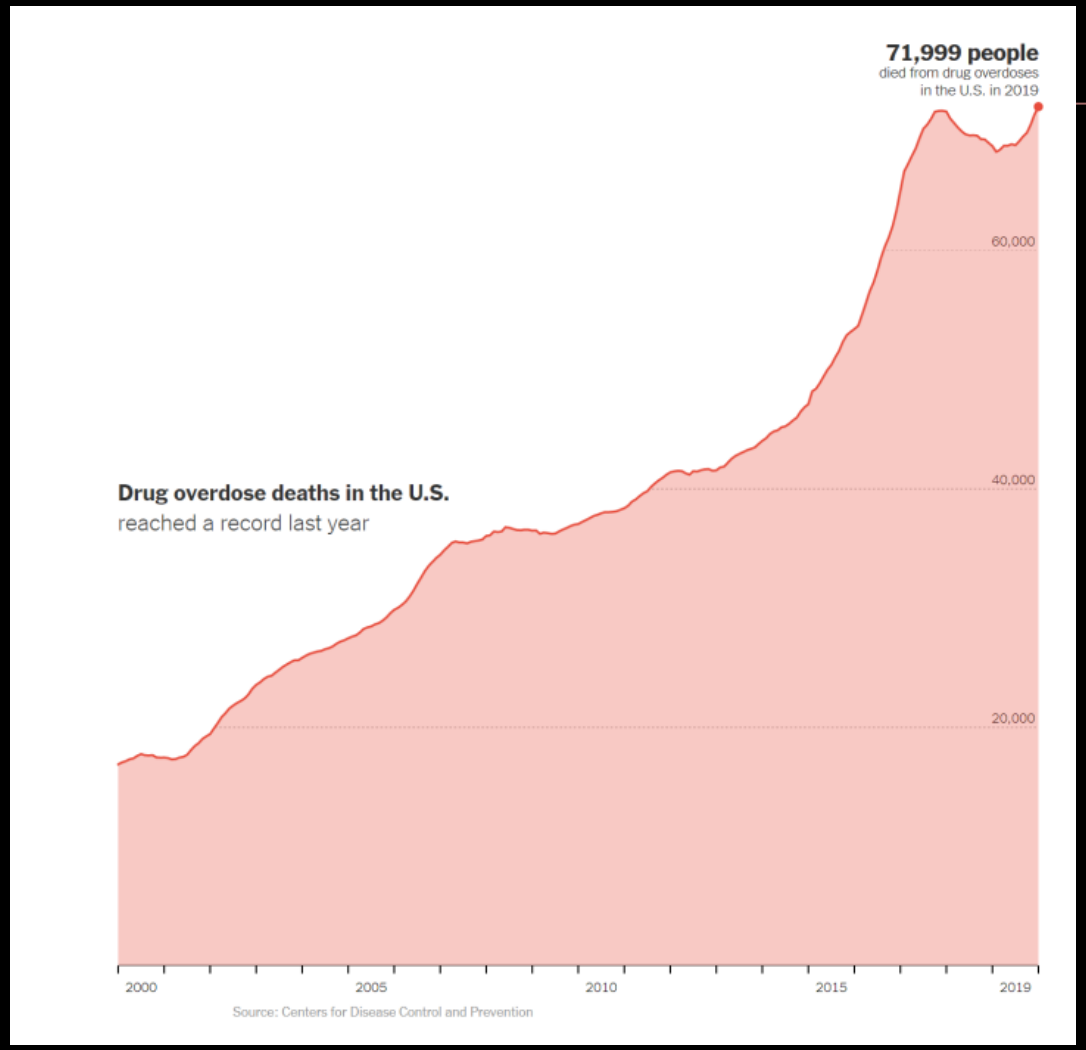
- Describe the impact of illicit manufactured fentanyl and polysubstance abuse contributes to overdose.
- Review the Impact of COIVD-19 on the Opioid Crises
- Summarize Polysubstance addiction and overdose
- Define the role of Naloxone in polysubstance overdose
- Discuss new agents in development that are addressing drug-induced respiratory depression

It does not just affect celebrities

COVID-19 and the Opioid Crises

https://www.ama-assn.org/system/files/2020-07/issue-brief-increases-in-opioid-related-overdose.pdf accessed AUG 2020

COVID-19 and the Drug Overdose Crisis



- Drug deaths in America, which fell for the first time in 25 years in 2018, rose to record numbers in 2019 and are continuing to climb, a resurgence that is being complicated and perhaps worsened by the coronavirus pandemic.
- Nearly 72,000 Americans died from drug overdoses last year, according to preliminary data released Wednesday by the Centers for Disease Control and Prevention — an increase of 5 percent from 2018.

https://www.nytimes.com/interactive/2020/07/15/upshot/drug-overdose-deaths.html accessed AUG 2020

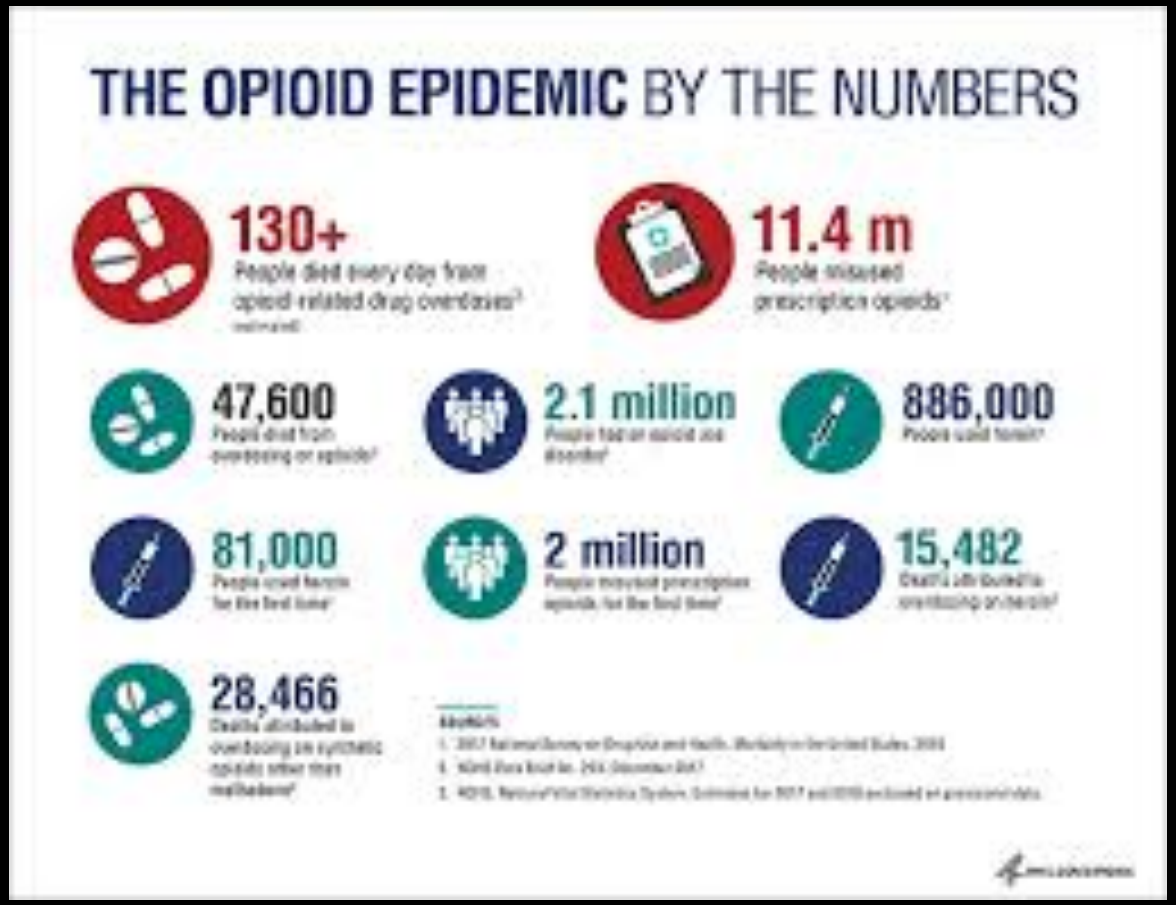
Drug abuse and overdose is no longer dominated by prescription drugs

PAINWeek AUG 2020 reports that a study on national UDT findings during the COVID -19 crises revealed:

- 31.96% increase for non-prescribed fentanyl
- 19.96% increase for methamphetamine
- 10.06% increase for cocaine
- 12.53% increase for heroin

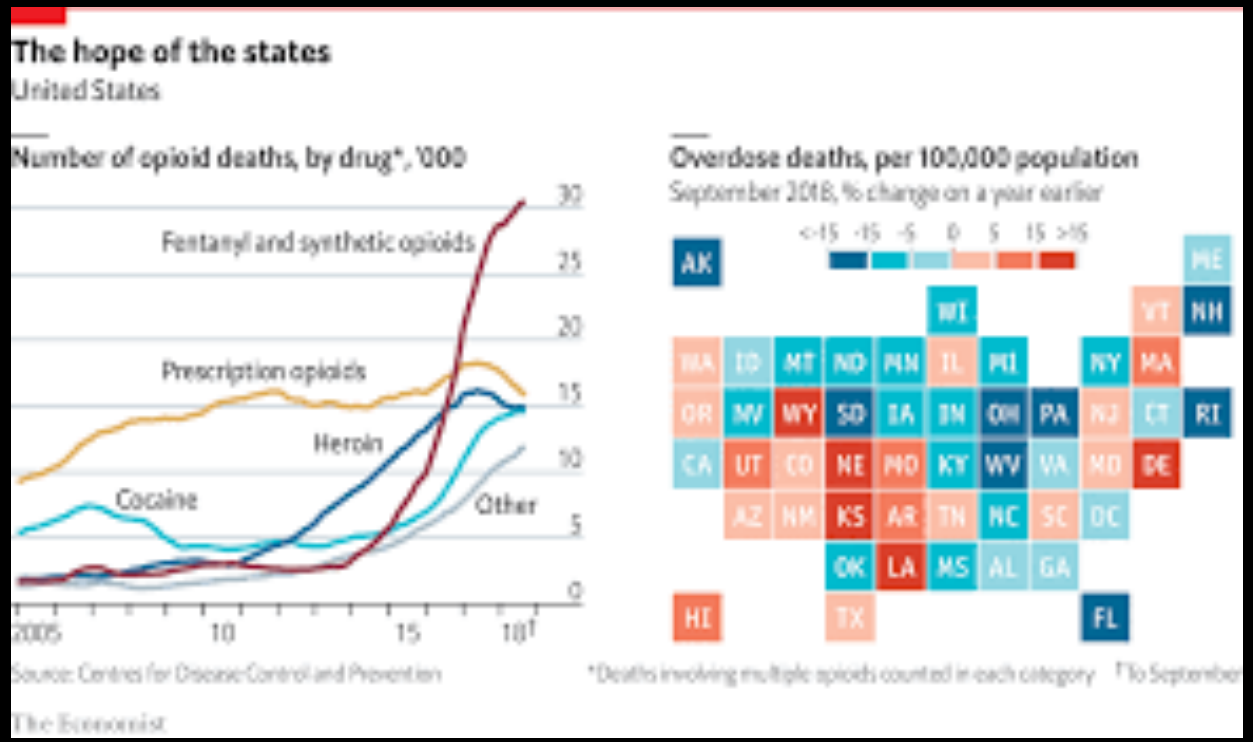
https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf

U.S. OPIOID CRISIS 2019



HHS.gov accessed AUG 2020

Impact of Illicitly Manufactured Fentanyl (IMF)



CDC Media Release 2020

- New Data Show Significant Changes in Drug Overdose Deaths
- *Overall decline in opioid-involved drug overdose deaths – but more deaths from synthetic opioids other than methadone*
  - –Synthetic opioids were involved in 31,335 overdose deaths — nearly half of all drug overdose deaths in 2018. Illicitly manufactured fentanyl (IMF) likely drove the increase in deaths involving synthetic opioids (excluding methadone) from 2017 to 2018.

PainWeek

Economist.com accessed AUG 2020
https://www.cdc.gov/media/releases/2020/p0318-data-show-changes-overdose-deaths.html accessed AUG 2020

Poly-what?

Silive.com accessed AUG 2020

Polyabuser (polyaddict)

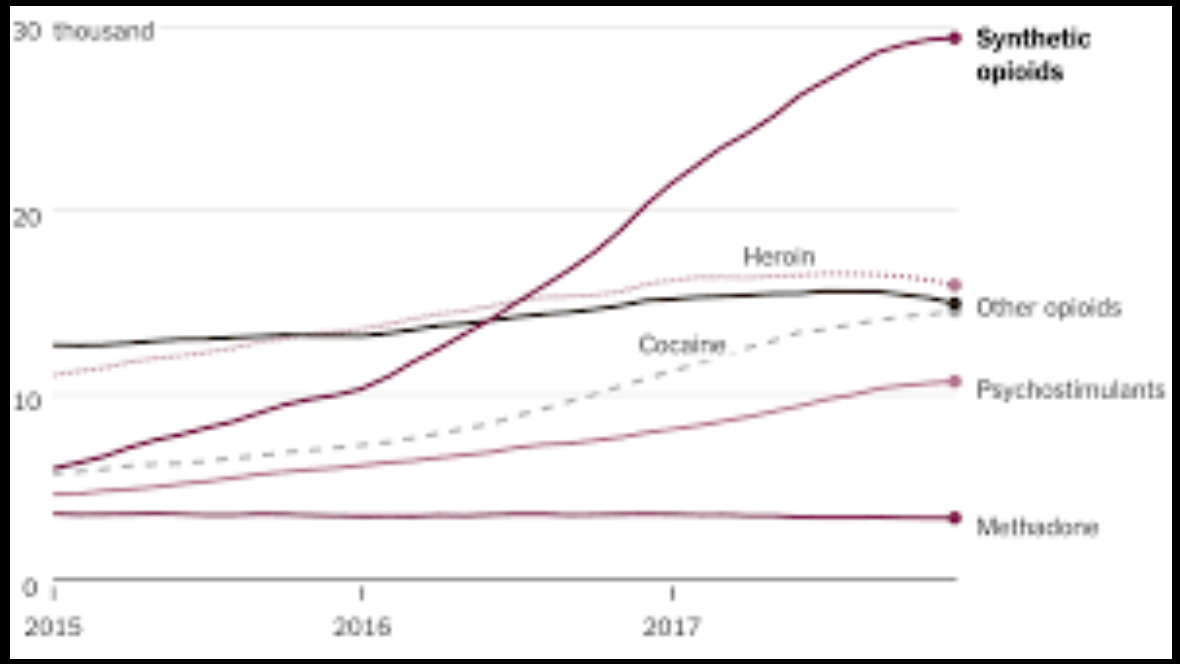
- Polyaddiction:
  - countable and uncountable, plural polyaddictions (medicine).
  - The condition of having more than one addiction.
- Polysubstance:
  - Polydrug use involves the consumption of more than one drug at once.
  - Although polysubstance abuse often refers to abuse of multiple illicit drugs, it's also inclusive of prescription medications used in nonmedical circumstances.
  - In some instances, those on prescription medication may unintentionally combine substances
- ICD-10-CM Code F19.
  - 10 - Other psychoactive substance abuse, uncomplicated.

Polysubstance Use and Abuse

- People intentionally engage in polysubstance abuse in an effort to experience greater effects from multiple substances.
- Oftentimes, users may have a preferred substance of abuse that they then combine with other substances at times to enhance the primary substance's effects.
  - For example, those who regularly abuse opioid drugs, like heroin or prescription painkillers, may sometimes take them with benzodiazepines to experience even greater relaxation or sedative effects.

https://americanaddictioncenters.org/polysubstance-abuse accessed AUG 2020

Synthetic Opioids together with Psychostimulants are a Leading Cause

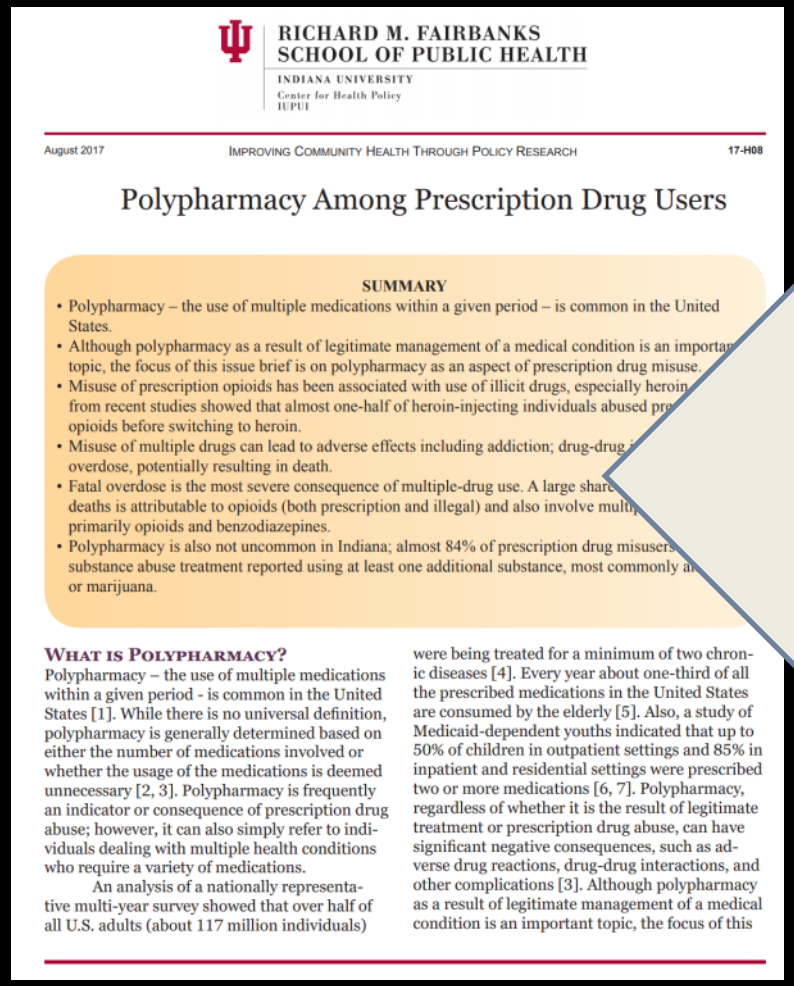


Data suggest that polysubstance use has become markedly more common than opioid use alone in the population of fatal opioid overdose victims, and a number of social factors appear to be linked to the adverse outcomes in this group.

Affirmhealth.com accessed AUG 2019

https://www.psychcongress.com/news-item/data-show-social-factors-linked-polysubstance-use-overdose accessed AUG 2019

Polypharmacy Drug Overdose



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INDIANA UNIVERSITY
Center for Health Policy
IUPUI

August 2017 — Improving Community Health Through Policy Research — 17-H08

Polypharmacy Among Prescription Drug Users

SUMMARY

- Polypharmacy – the use of multiple medications within a given period – is common in the United States.
- Although polypharmacy as a result of legitimate management of a medical condition is an importa topic, the focus of this issue brief is on polypharmacy as an aspect of prescription drug misuse.
- Misuse of prescription opioids has been associated with use of illicit drugs, especially heroin from recent studies showed that almost one-half of heroin-injecting individuals abused pre opioids before switching to heroin.
- Misuse of multiple drugs can lead to adverse effects including addiction; drug-drug i overdose, potentially resulting in death.
- Fatal overdose is the most severe consequence of multiple-drug use. A large share deaths is attributable to opioids (both prescription and illegal) and also involve multi primarily opioids and benzodiazepines.
- Polypharmacy is also not uncommon in Indiana; almost 84% of prescription drug misusers substance abuse treatment reported using at least one additional substance, most commonly a or marijuana.

WHAT IS POLYPHARMACY?

Polypharmacy – the use of multiple medications within a given period - is common in the United States [1]. While there is no universal definition, polypharmacy is generally determined based on either the number of medications involved or whether the usage of the medications is deemed unnecessary [2, 3]. Polypharmacy is frequently an indicator or consequence of prescription drug abuse; however, it can also simply refer to individuals dealing with multiple health conditions who require a variety of medications.

An analysis of a nationally representative multi-year survey showed that over half of all U.S. adults (about 117 million individuals) were being treated for a minimum of two chronic diseases [4]. Every year about one-third of all the prescribed medications in the United States are consumed by the elderly [5]. Also, a study of Medicaid-dependent youths indicated that up to 50% of children in outpatient settings and 85% in inpatient and residential settings were prescribed two or more medications [6, 7]. Polypharmacy, regardless of whether it is the result of legitimate treatment or prescription drug abuse, can have significant negative consequences, such as adverse drug reactions, drug-drug interactions, and other complications [3]. Although polypharmacy as a result of legitimate management of a medical condition is an important topic, the focus of this

Polypharmacy – the use of multiple medications within a given period – is common in the United States.

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Misuse of prescription opioids has been associated with use of illicit drugs, especially heroin. Results from recent studies showed that almost one-half of heroin-injecting individuals abused prescription opioids before switching to heroin.

Misuse of multiple drugs can lead to adverse effects including addiction; drug-drug interactions; and overdose, potentially resulting in death.

Fatal overdose is the most severe consequence of multiple-drug use. **A large share of drug-related deaths is attributable to opioids (both prescription and illegal) and also involve multiple substances, primarily opioids and benzodiazepines.**

Polypharmacy is also not uncommon in Indiana; almost 84% of prescription drug misusers receiving substance abuse treatment reported using at least one additional substance, most commonly alcohol or marijuana.

Goof Balling

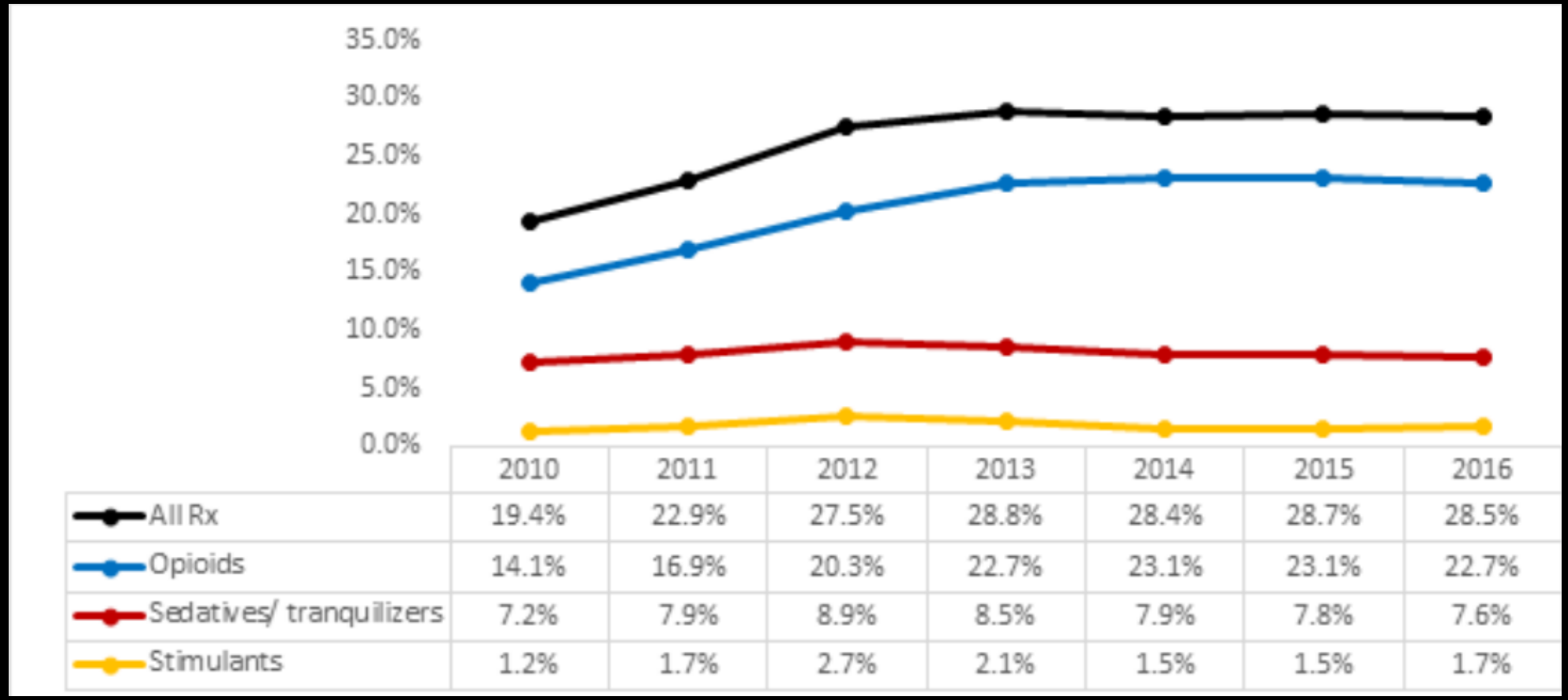
- Last year, a study of 2,244 opioid-related overdose deaths in Massachusetts from 2014 to 2015 found that 36% of patients also showed signs of stimulant use. "Persons older than 24 years, nonrural residents, those with comorbid mental illness, non-Hispanic black residents, and persons with recent homelessness were more likely than their counterparts to die with opioids and stimulants than opioids alone," the researchers reported (Drug Alcohol Depend. 2019 Jul 1;200:59-63).

- To the extent to which overdoses involving both an opioid and a stimulant are due to fentanyl contamination of the methamphetamine supply or intentional concurrent use – e.g., 'speedballing' or **'goof balling**' – or some other pattern of polysubstance use, such as using an opioid to come down off a methamphetamine high."

https://www.medscape.com/viewarticle/933527 accessed AUG 2020

Percentage of Indiana Treatment Admissions Reporting Nonmedical Use of Prescription Drugs, by Drug Category (TEDS 2010-2016)

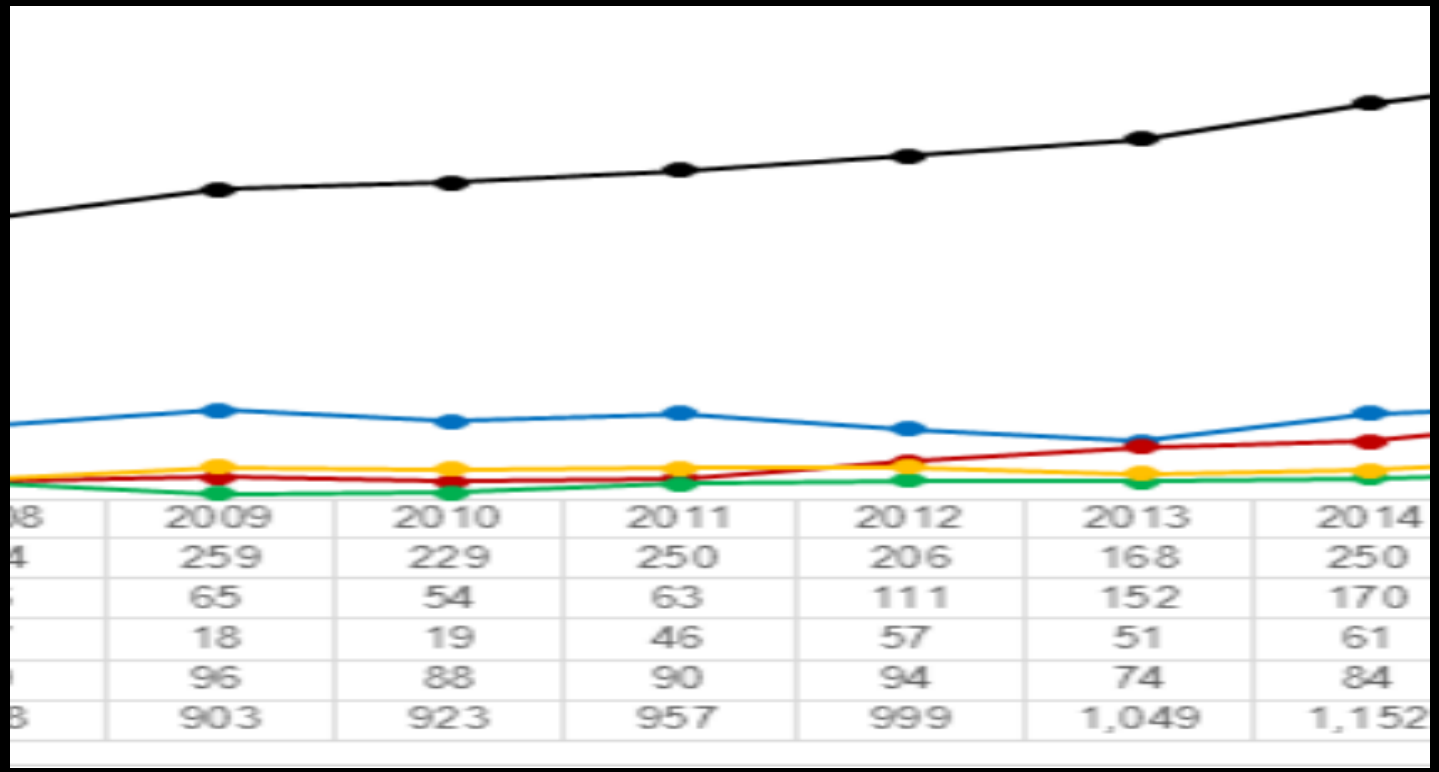
Indiana Division of Mental Health and Addiction, 2017



	2010	2011	2012	2013	2014	2015	2016
All Rx	19.4%	22.9%	27.5%	28.8%	28.4%	28.7%	28.5%
Opioids	14.1%	16.9%	20.3%	22.7%	23.1%	23.1%	22.7%
Sedatives/ tranquilizers	7.2%	7.9%	8.9%	8.5%	7.9%	7.8%	7.6%
Stimulants	1.2%	1.7%	2.7%	2.1%	1.5%	1.5%	1.7%

Drug Overdose Deaths Involving Opioid Pain Relievers and Other Drugs, Indiana, 2006-2015

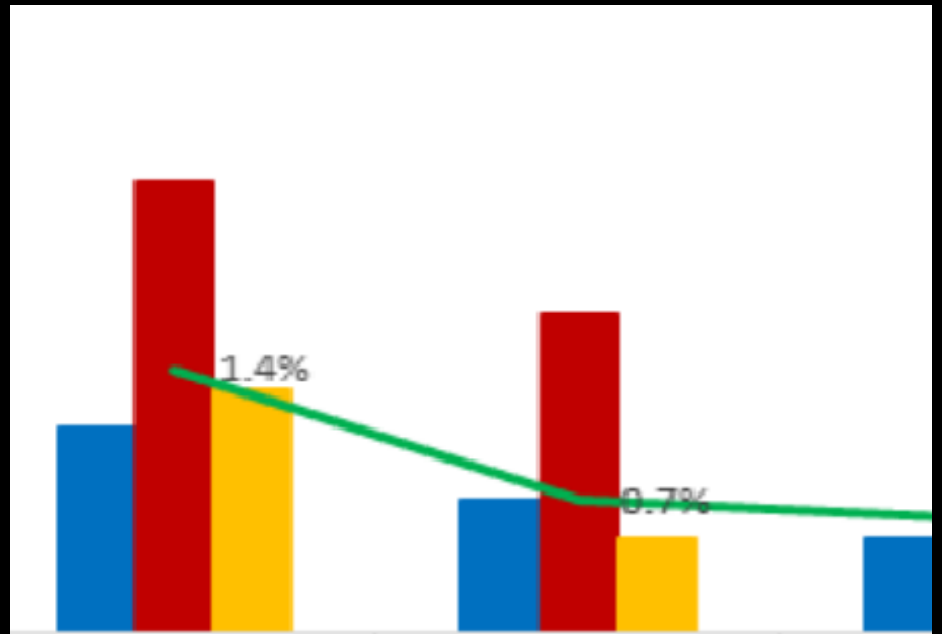
Indiana Division of Mental Health and Addiction, 2017



	2009	2010	2011	2012	2013	2014
4	259	229	250	206	168	250
	65	54	63	111	152	170
	18	19	46	57	51	61
	96	88	90	94	74	84
3	903	923	957	999	1,049	1,152

Note: Based on ICD-10 drug overdose/poisoning underlying causes of death X40-X44, X60-X64, X85, or Y10-Y14, as well as contributing causes of T40.2-T40.4 (prescription opioids), T40.1 (heroin), T40.6 (other and unspecified narcotics), and T42.4 (benzodiazepines

Center for Behavioral Health Statistics and Quality, 2016



Pain Relievers	Tranquilizers	Sti
1.1%	0.7%	
2.4%	1.7%	
1.3%	0.5%	
1.4%	0.7%	

Misuse of prescription pain relievers, tranquilizers, stimulants, and sedatives among the U.S. population ages 12 or older, by age group (National Survey on Drug Use and Health, 2015)

OPIOID TASK FORCE 2020 PROGRESS

- The American Medical Association just released a new OPIOID TASK FORCE 2020 PROGRESS REPORT in the hopes of reducing drug overdoses and deaths. Although prescription opioid overdose deaths have decreased, illicit drugs such as heroin, methamphetamine, and cocaine have risen. Last year, fentanyl deaths alone accounted for 36,000 deaths, up from 6,000.

- The AMA Opioid Task Force calls for substance use disorder (SUD) support, using treatments with evidence of efficacy, such as medication assisted treatment.

- Over 2,000,000 Americans have an untreated SUD, and one overdose is likely to lead to another. The report calls for removal of barriers to care to help end the overdose epidemic, and also calls for the help of health insurance companies, which currently may hamper pain care access.

- Arbitrary guidelines are used inappropriately as well, further contributing to restriction of nonopioid medication. The report hopes to prioritize preventing and treating SUD; employ surveillance strategies to identify at-risk patients; and implement proven evidence-based approaches

PAINWEEK

https://www.painweek.org/media/news/american-medical-association-combating-rising-numbers-overdoses?utm_campaign=Premiere%208%2F19&utm_medium=email&_hsmi=92674691&_hsenc=p2ANqtz-_o5iHYTNJvUFgaB5WSkxXFQxq9aZxaKegcwT0GnvFmpkg0_QqMMkJz-T0p7ixzg5oTUDFmxytNuqRrKHoWAytg5kMDzA&utm_content=92674691&utm_source=hs_email accessed AUG 2020

SOLUTIONS ARE URGENTLY NEEDED

Much More Than an Opioid Crisis

- Opioid+ Crisis

or

- OpiodPlus Crisis

or

- an OverDose Crisis

- What are the tools for an Opioid+ Crisis????
  - We have almost nothing today.
  - ENA001 can be the first adequate weapon for doctors and 1st responders

Limitations in Managing Polysubstance OD

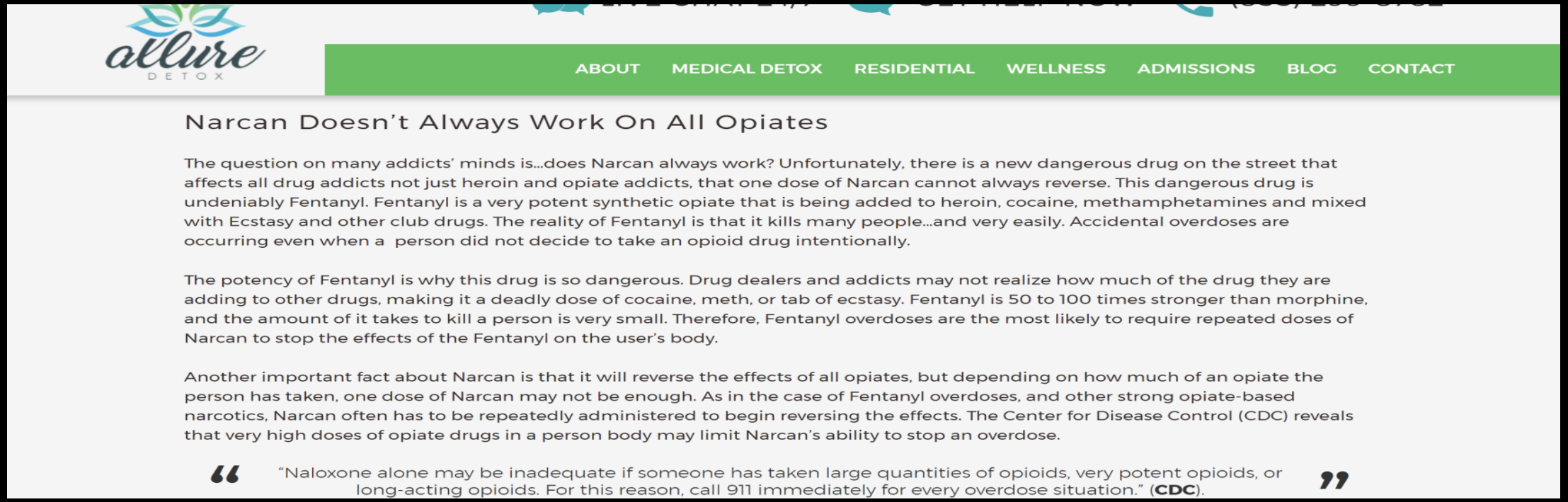
- **Naloxone** is an **opioid antagonist** indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression[1]

- Naloxone hydrochloride is an opioid antagonist that antagonizes opioid effects by competing for the same receptor sites[1]

- **Naloxone will** not reverse **overdose** resulting from non-opioid drugs, like cocaine, **benzodiazepines** (“**benzos**”), or alcohol. Given how safe **naloxone** is, a victim of a non-opioid **overdose**, or an **overdose** caused by a mixture of drugs **will** not be harmed by **naloxone**[2].

1. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208411lbl.pdf accessed AUG 2020
2. https://bjatta.bja.ojp.gov/naloxone/does-naloxone-reverse-any-overdose#:~:text=Naloxone%20will%20not%20reverse%20overdose,not%20be%20harmed%20by%20naloxone accessed AUG 2020

“Naloxone alone may be inadequate if someone has taken large quantities of opioids, very potent opioids, or long-acting opioids. immediately for every overdose situation.” (CDC)



allure DETOX

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Narcan Doesn’t Always Work On All Opiates

The question on many addicts’ minds is…does Narcan always work? Unfortunately, there is a new dangerous drug on the street that affects all drug addicts not just heroin and opiate addicts, that one dose of Narcan cannot always reverse. This dangerous drug is undeniably Fentanyl. Fentanyl is a very potent synthetic opiate that is being added to heroin, cocaine, methamphetamines and mixed with Ecstasy and other club drugs. The reality of Fentanyl is that it kills many people…and very easily. Accidental overdoses are occurring even when a person did not decide to take an opioid drug intentionally.

The potency of Fentanyl is why this drug is so dangerous. Drug dealers and addicts may not realize how much of the drug they are adding to other drugs, making it a deadly dose of cocaine, meth, or tab of ecstasy. Fentanyl is 50 to 100 times stronger than morphine, and the amount of it takes to kill a person is very small. Therefore, Fentanyl overdoses are the most likely to require repeated doses of Narcan to stop the effects of the Fentanyl on the user’s body.

Another important fact about Narcan is that it will reverse the effects of all opiates, but depending on how much of an opiate the person has taken, one dose of Narcan may not be enough. As in the case of Fentanyl overdoses, and other strong opiate-based narcotics, Narcan often has to be repeatedly administered to begin reversing the effects. The Center for Disease Control (CDC) reveals that very high doses of opiate drugs in a person body may limit Narcan’s ability to stop an overdose.

> “Naloxone alone may be inadequate if someone has taken large quantities of opioids, very potent opioids, or long-acting opioids. For this reason, call 911 immediately for every overdose situation.” (**CDC**).

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https://www.alluredetox.com/narcan-always-work accessed AUG 2020

An Indiana Police Department No Longer Reversing Overdoses During Pandemic: National Trend!

- Indiana law enforcement department has suspended police administration of naloxone, the opioid overdose reversal medication, until the end of the coronavirus pandemic due to concerns over possible transmission of the virus to responding officers. Overdose reversals will be left to emergency medical services.

- At least one person has reportedly been denied an overdose reversal since the directive took effect on March 19. Because of coronavirus, police in Lawrence are not allowed to administer naloxone anymore and what we had was what saved him.

https://filtermag.org/cops-naloxone-coronavirus/

When all you have is a hammer…

- Naloxone was approved ~50 years ago (1971).
- *"The ability to provide naloxone to people that have overdosed has saved so many lives — but that is for opioids."* Nora Volkow -NIH
- Other than a new delivery format in the nasal spray, there really hasn't been any innovation in this space for decades.
- It is much needed!

https://thehill.com/policy/healthcare/public-global-health/507598-fatal-drug-overdoses-rose-in-2019-reversing-previous accessed AUG 2020

We REALLY Need a Better Mousetrap

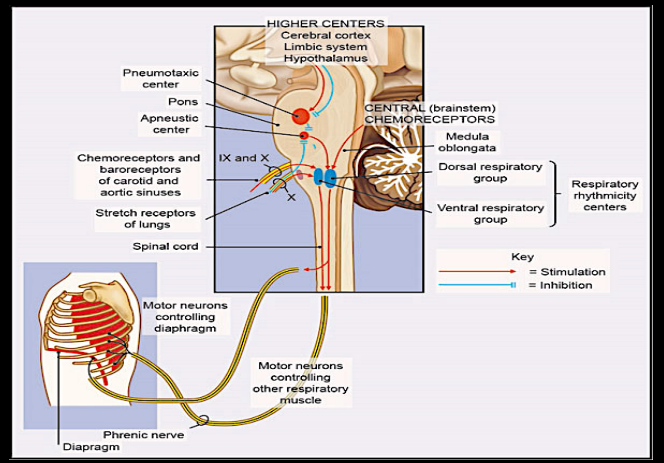
- Overdose reversal limited to opioids
  - does not address the growing issues of polypharmacy
- Inadequate against newer, more potent forms of drugs
  - may be ineffective or require multiple doses
- Patients often awaken in an agitated state
  - requiring additional hospital and first responder's resources and interfering with further treatment
- Reverses all the effects, which may not be desired for some patients or providers

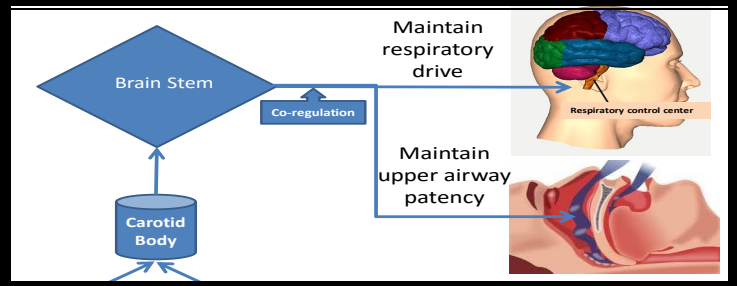
There is an urgent need for a new respiratory stimulant that is agnostic

ENA-001 a *"Pharmacologic ventilator"*

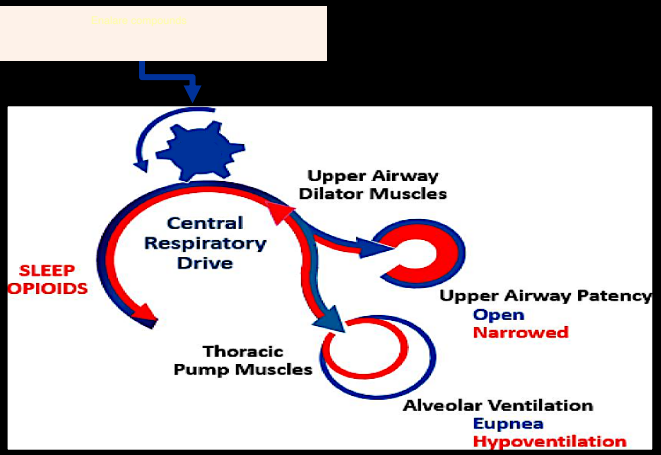
Therapeutic Effect:

Restore Breathing in Drug- and *Poly*-drug Induced Respiratory Depression – *opioids, propofol, BZD, etc.*





Enalare compounds



ENA-001 Preclinical Proof of Efficacy: Agonist Reversal

Upon i.v. administration by bolus or infusion to rats[1] or cynomolgus monkeys,[2]

ENA-001 elicits:

- dose-dependent increases in minute ventilation and
- shows a robust, dose-dependent, reversal of respiratory depression caused by:
  - opioids (morphine or fentanyl),
  - benzodiazepines (midazolam),
  - or by anesthetic agents (isoflurane or propofol).

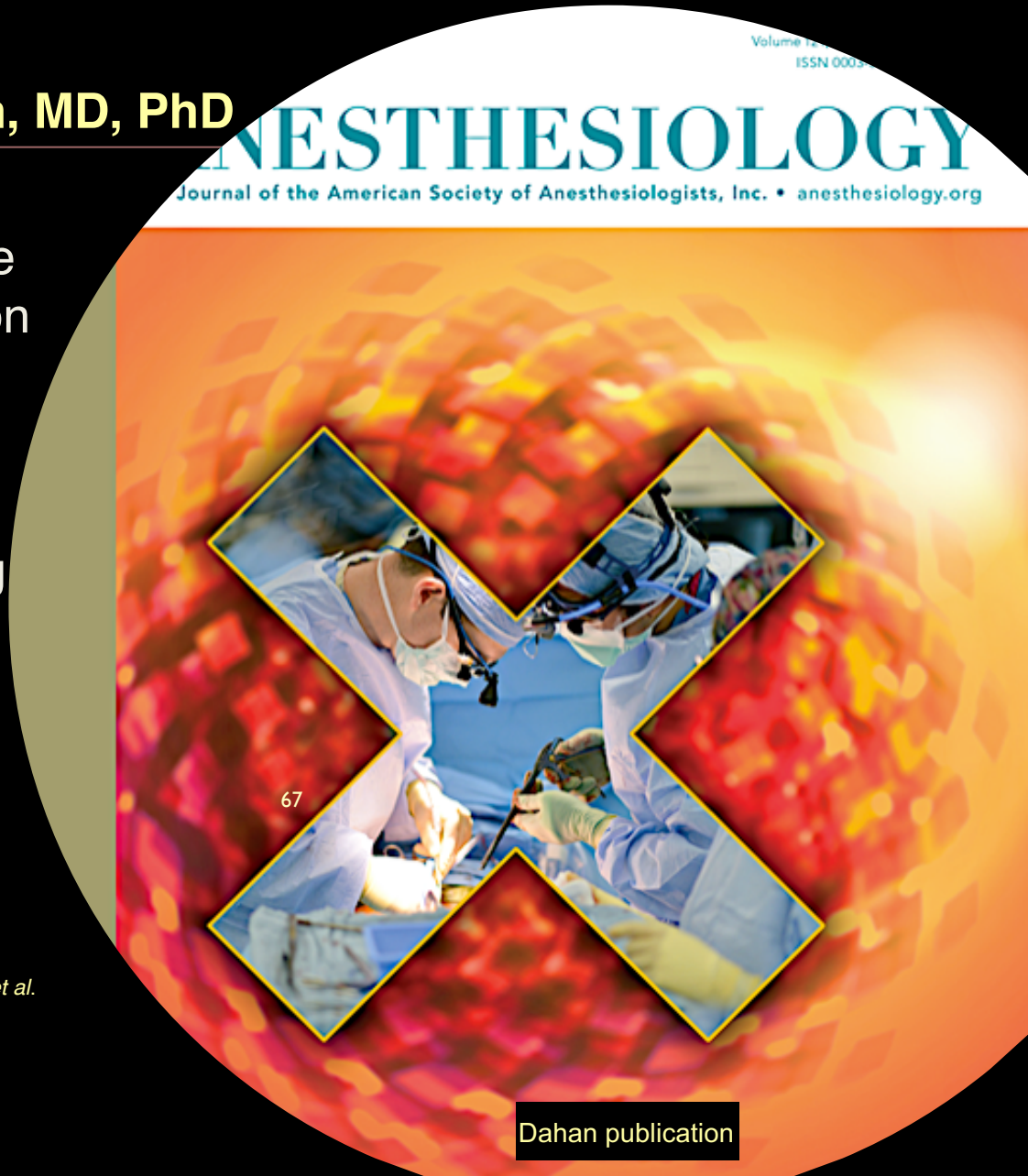
PAINWEEK®

[1] SM Baby, RB Gruber, V Puskovic, *et al.*GAL-021, a novel respiratory stimulant, attenuates opioid-induced respiratory depression without compromising analgesia. FASEB J, 26 (2012), pp. 704-728 [2] FJ Golder, RL Wardle, MR Van Scott, *et al.*GAL-021 acts as a novel respiratory stimulant in non-human primates. FASEB J, 26 (2012), pp. 704-727

Clinical Proof of Efficacy

"Pharmacologic ventilator" – Editorial, Joseph F. Cotten, MD, PhD

- In a double-blind, randomized, placebo-controlled crossover study, ENA-021 stimulated ventilation in male volunteers with alfentanil-induced respiratory depression at a clamped and elevated end-tidal carbon dioxide partial pressure, increasing both tidal volume and respiratory rate
- GAL021 also stimulated poikilocapnic ventilation during alfentanil administration, without affecting sedation, antinociception, hemodynamics, or safety parameters



Dahan publication

Margot Roozekrans, M.D.; Rutger van der Schrier, M.D.; Pieter Okkerse, M.D.; Justin Hay, Ph.D.; James F. McLeod, M.D.; *et al.*
Anesthesiology 09 2014, Vol.121, 459-468. doi:https://doi.org/10.1097/ALN.0000000000000367

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- https://www.painweek.org/media/news/american-medical-association-combating-rising-numbers-overdoses?utm_campaign=Premiere%208%2F19&utm_medium=email&_hsmi=92674691&_hsenc=p2ANqtz-_o5iHYTNJvUFgaB5WSkxXFQxq9aZxaKegcwT0GnvFmpkg0_QqMMkJz-T0p7ixzg5oTUDFmxytNuqRrKHoWAytg5kMDzA&utm_content=92674691&utm_source=hs_email accessed AUG 2020

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PainWeek®

Doubling Down: Polysubstance Abuse and Associated Respiratory Depression

Robert B Raffa, PhD

Disclosure

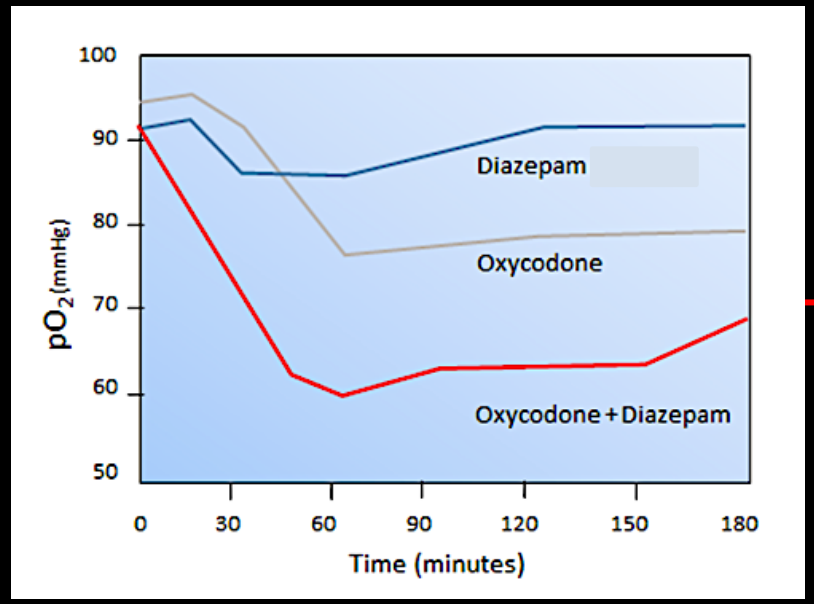
- Consultant/Independent Contractor: Neumentum
- Stock Shareholder: Neumentum

Learning Objectives

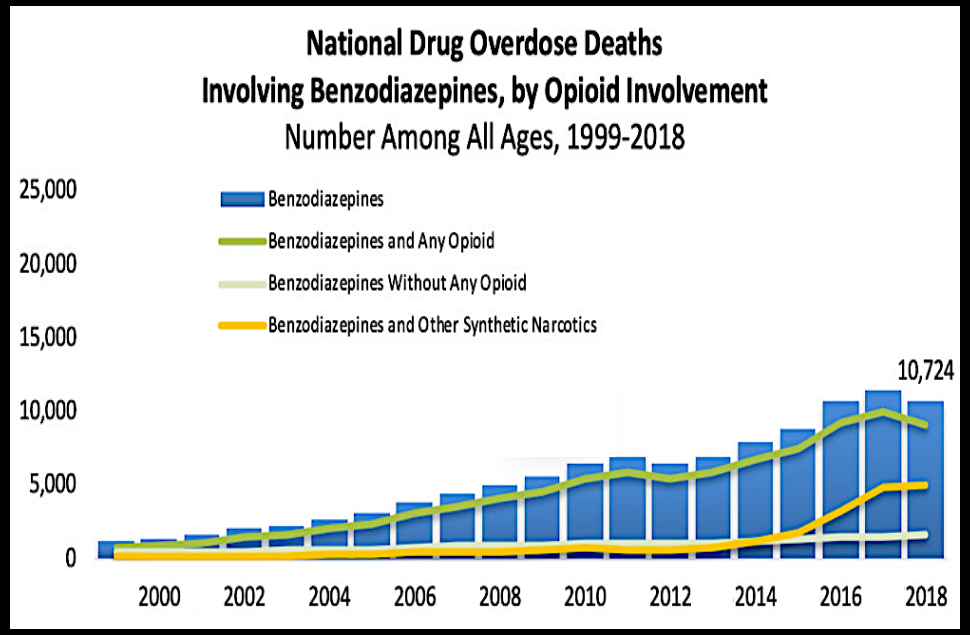
- List 3 or more respiratory-depression targets or agents
- Summarize their current status in the discovery/development process
- Compare the targets/agents for druggability

Polysubstance Abuse

The Problem



- BZD
  - –central &
  - –skeletal m

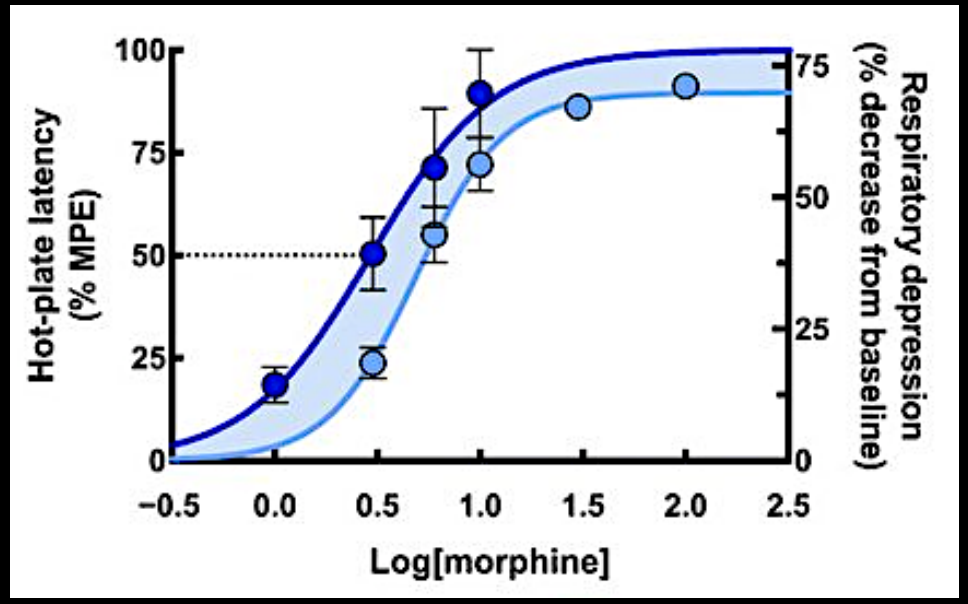


https://www.fda.gov/drugs/regulatory-science-action/impact-story-preclinical-research-achieve-safer-prescribing-psychoactive-therapeutics-patients-who

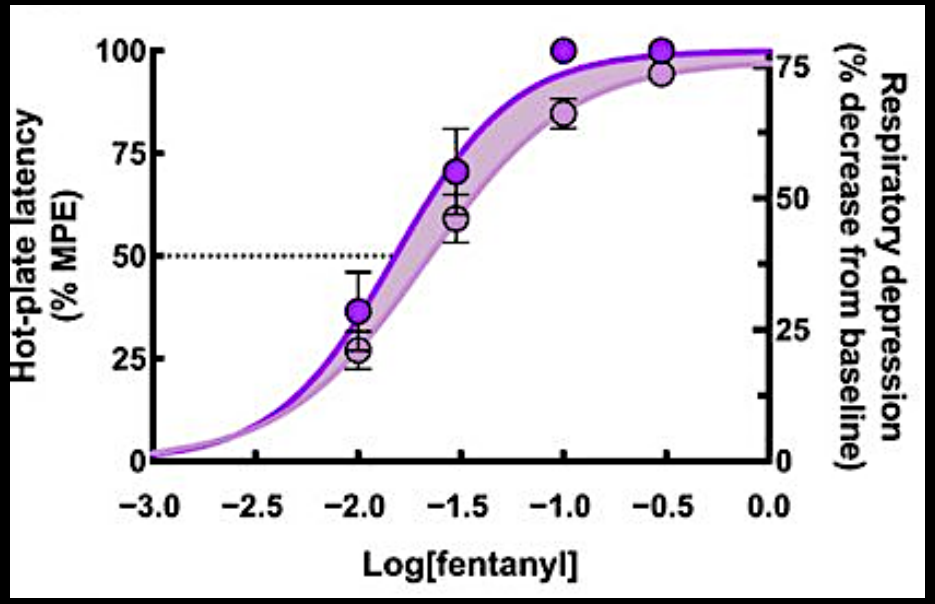
Opioid-induced Respiratory Depression

Opioid-induced Respiratory Depression

- Small separation from analgesia



morphine

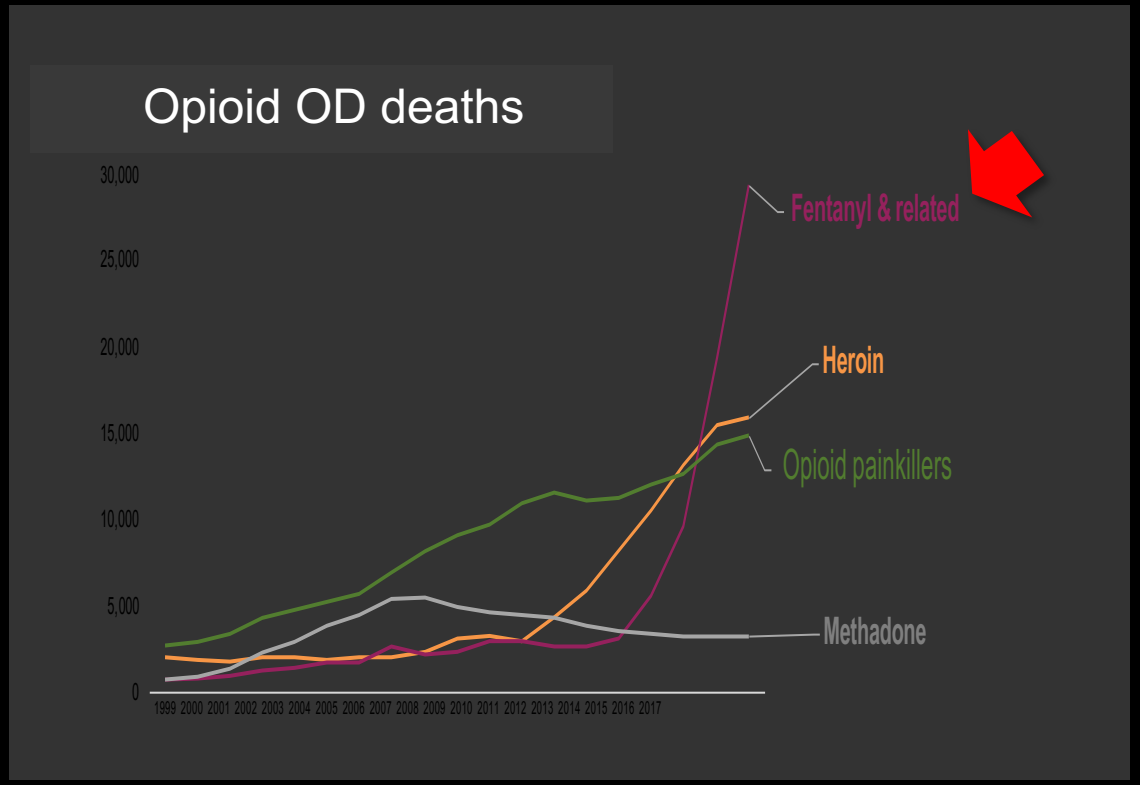


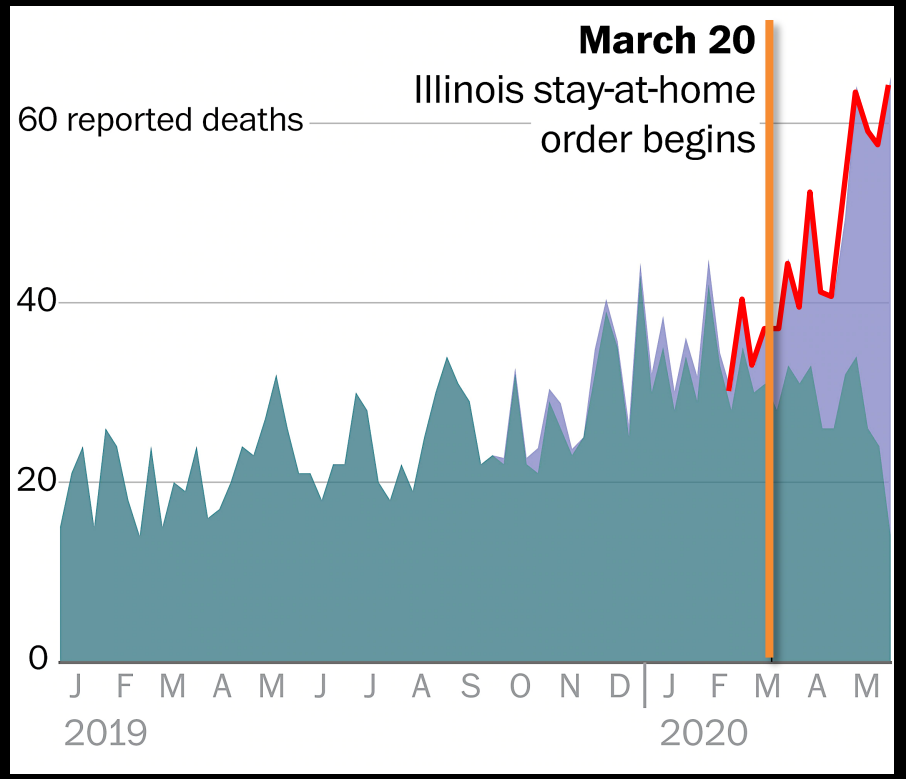
fentanyl

Gillis et al. (2020) Sci Signaling 13: eaaz3140 DOI: 10.1126/scisignal.aaz3140

Polysubstance Use in the Time of COVID

Polysubstance Use in the Time of COVID





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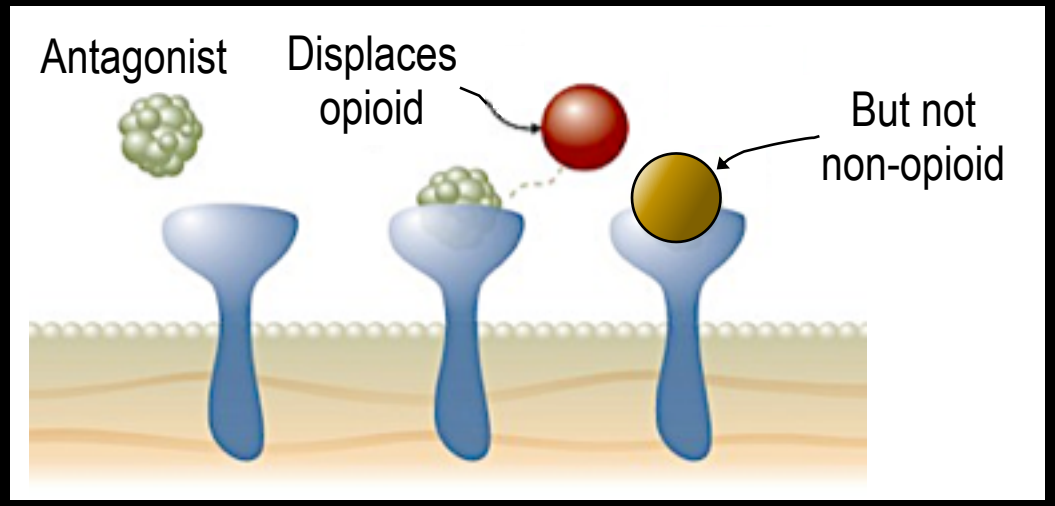
Data from Cook County Med Examiner – *The Washington Post*

How Do You Treat Polysubstance OD?

The Problem

- Opioid receptor antagonists can reverse opioids
- But not non-opioids
- They also block analgesia



A Possible Alternative

The Latest Pharmacologic Ventilator
Joseph F. Cotton (2014) Anesthesiology 121:442-444

- Ventilatory stimulant
  - –should be agnostic to cause
  - –should not block OR-mediated pain relief
  - –should not precipitate withdrawal (combativeness)

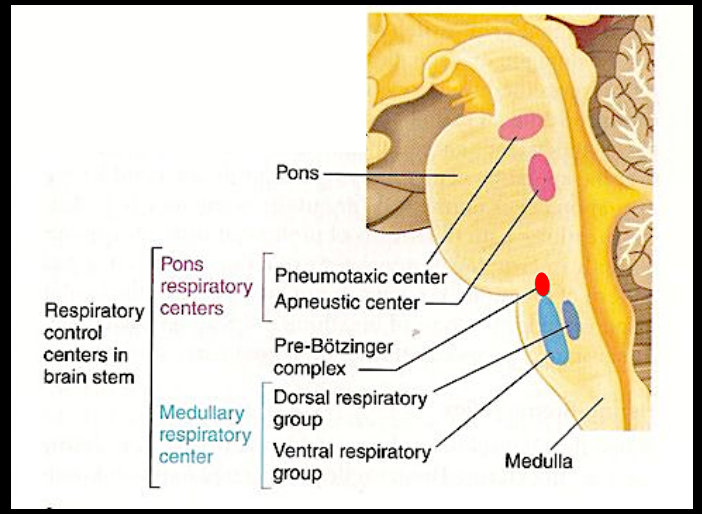
Breathing Stimulants (Support) – *caffeine*

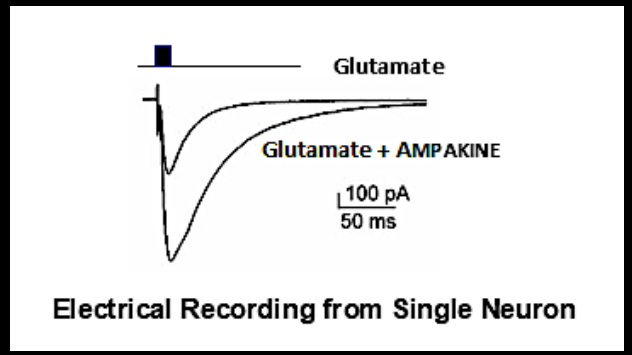
- Methylxanthines have been used in the neonatal ICU for more than 40 yr to treat and prevent apnea of prematurity.
- Among methylxanthines, caffeine is used most commonly because of its wide TI and longer $t_{½}$ that allows once-daily administration
- Multiple mechanisms of action beyond a reduction in apnea are likely to mediate the beneficial effects of caffeine.
- 'Support' more than 'rescue'.

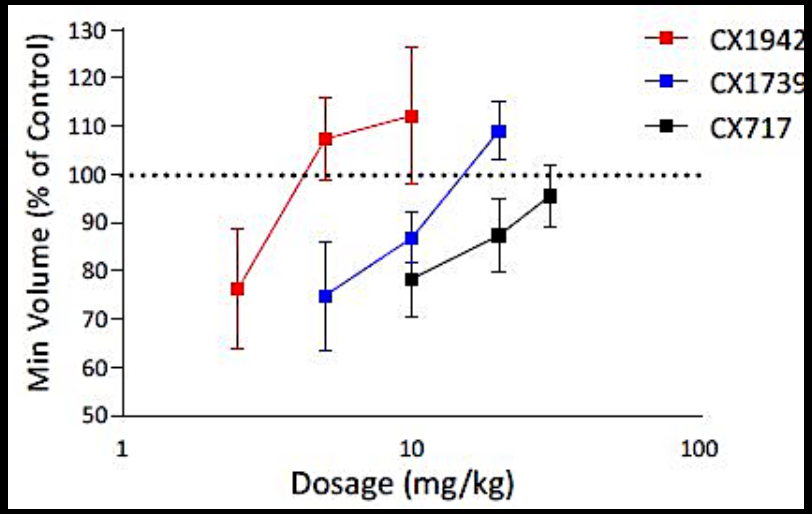
Dobson & Patel (2016) Clin Perinatol 43:773-782

Breathing Stimulants – *ampakines*

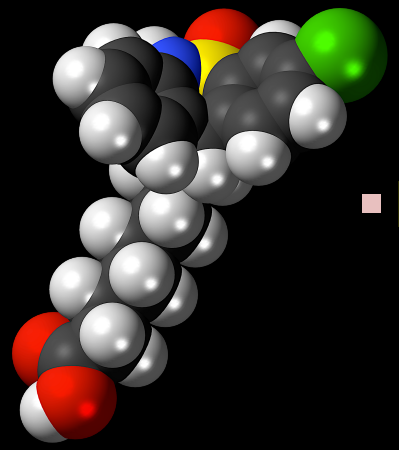
- Ampakines act centrally at AMPA-type glutamate receptors in the brainstem (pre-Botzinger complex)
  - CX1942
  - CX1739
  - CX717 (relatively poor oral bioavailability and BBB penetration)





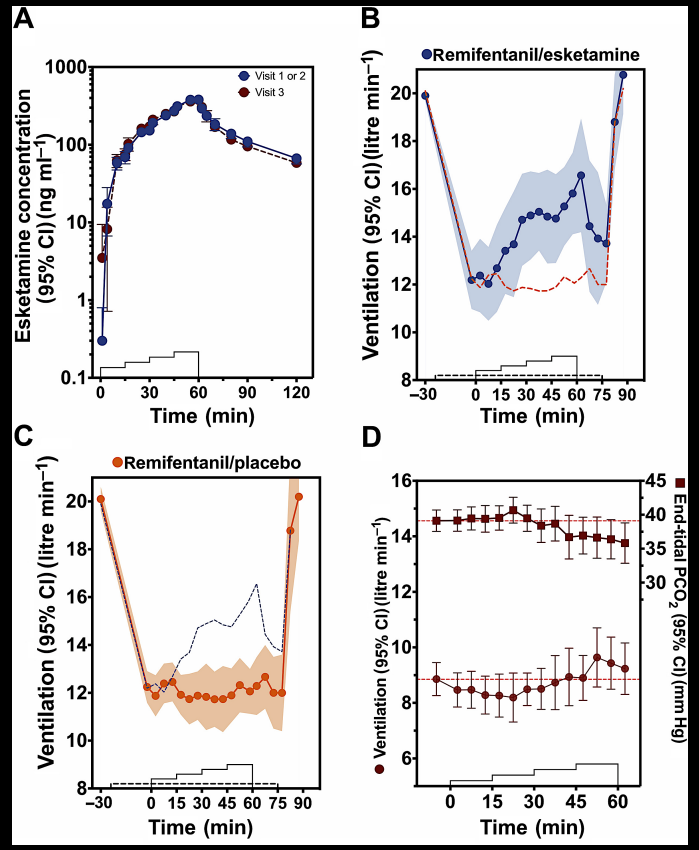


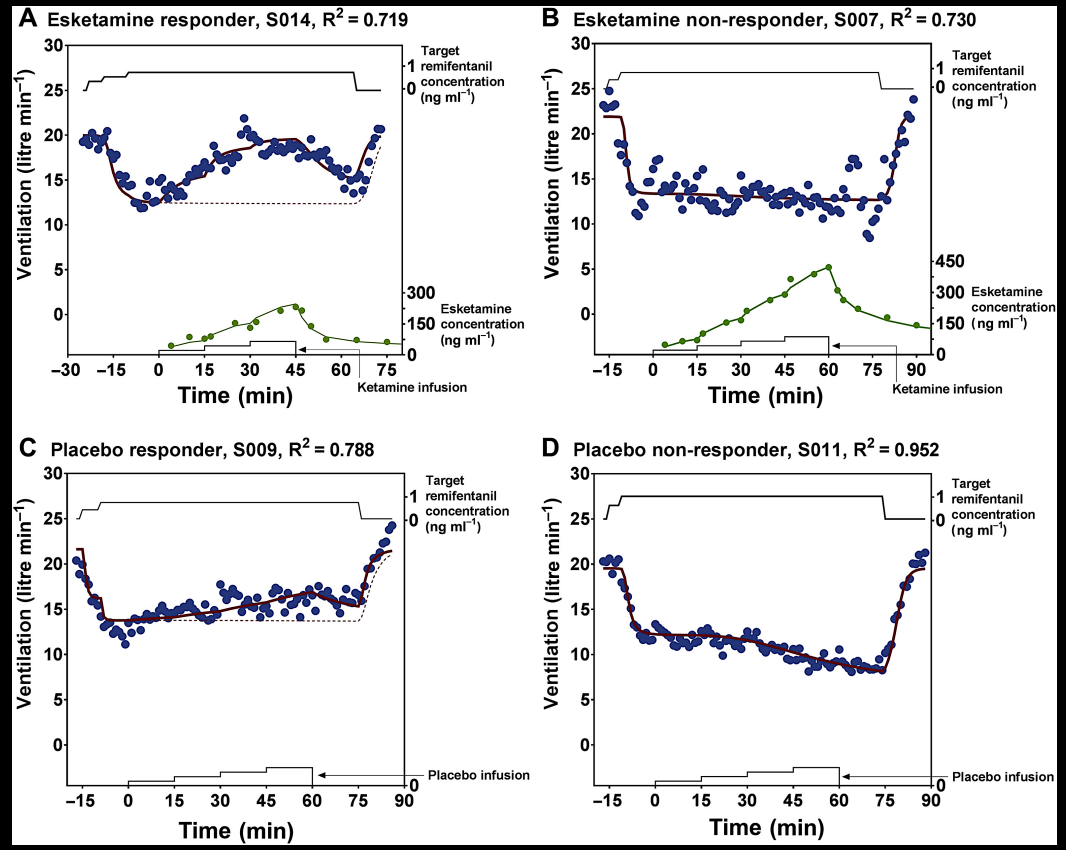
Breathing Stimulants – *repurposed*



- Rev-001 (tianeptine)
  - –antidepressant
  - –studied for prevention of OIRD
  - –complex pharmacology
  - –μ-OR affinity (biased ligand?)
  - –abuse potential at high doses

Esketamine – *S(+)-ketamine*

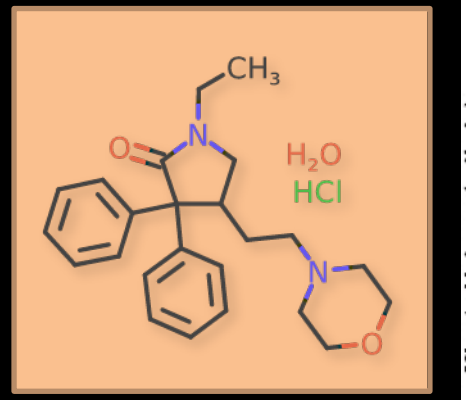


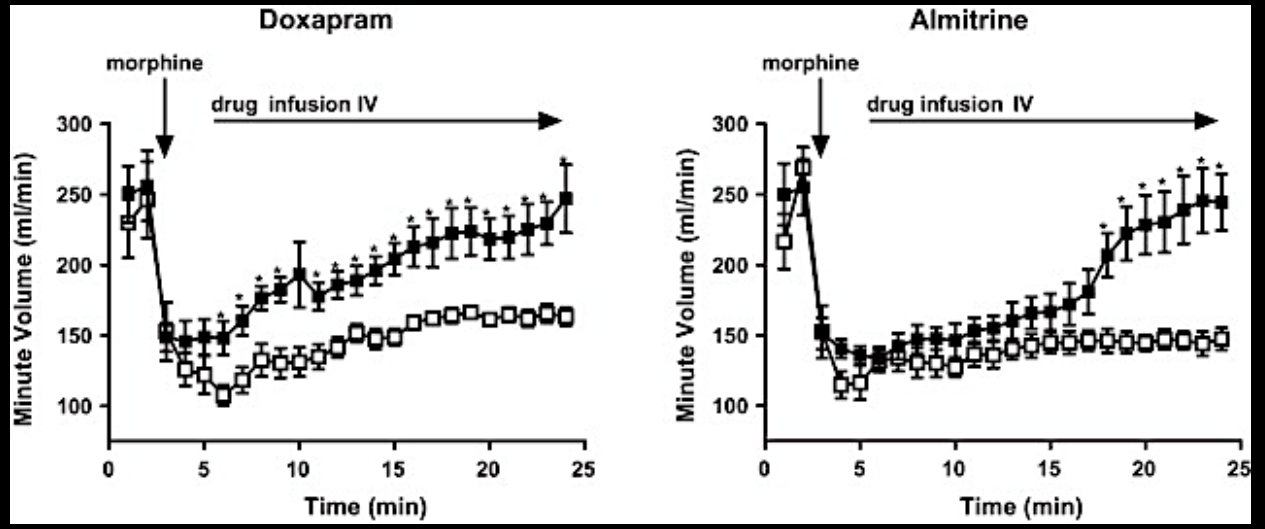


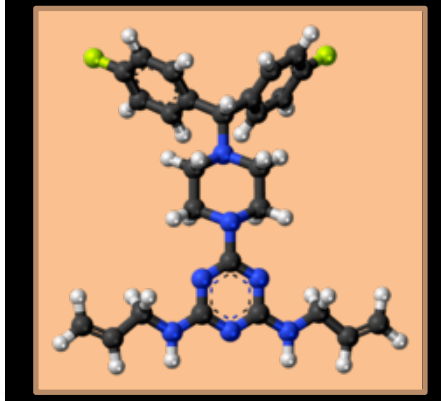
Jonkman et al. (2018) Brit J Anaesth 120:1117e1127

Respiratory Stimulants – *doxapram & almitrine*

- Doxapram and Almitrine



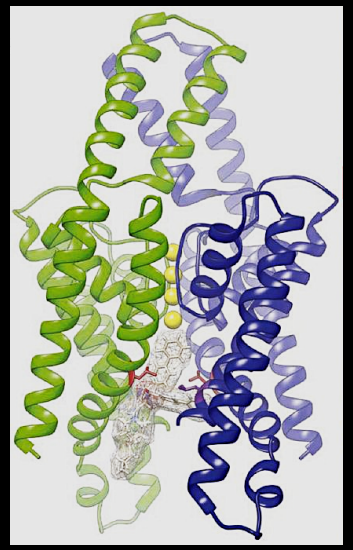


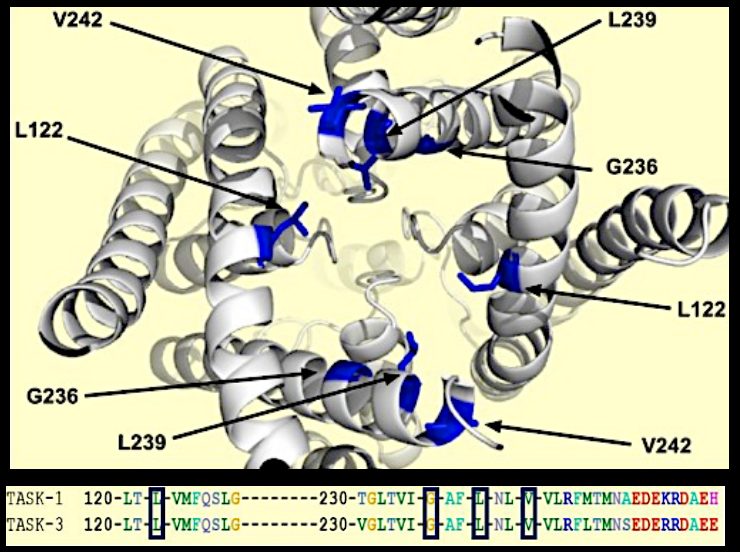


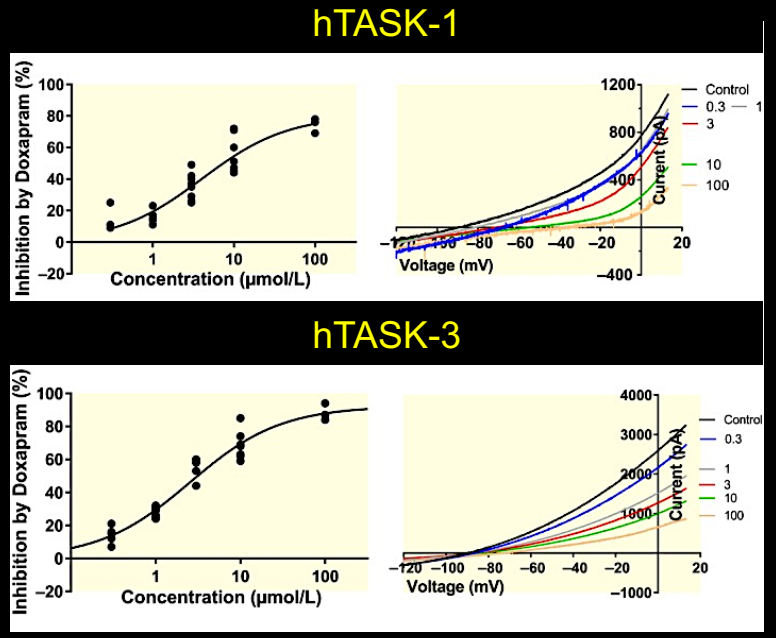
Golder *et al.* (2013) Resp Physiol Neurobiol 189:395 - 402

Doxapram

- Stimulates respiration by an action on peripheral carotid chemoreceptors
- Potent inhibitor of TASK-1 (KCNK3, K2P3.1) and TASK-3 (KCNK9, K2P9.1), but not TASK-2 (KCNK5, K2P5.1) K^+ channels in humans







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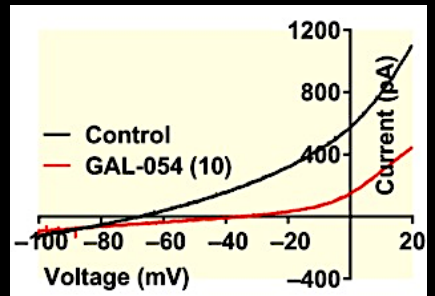
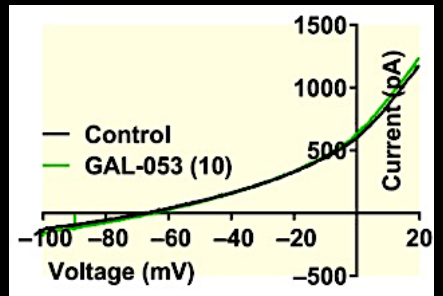
Chokshi *et al.* (2015) Molec Pharmacol 88:926-934
Cunningham *et al.* (2019) Acta Physiologica 228:e13361

Doxapram

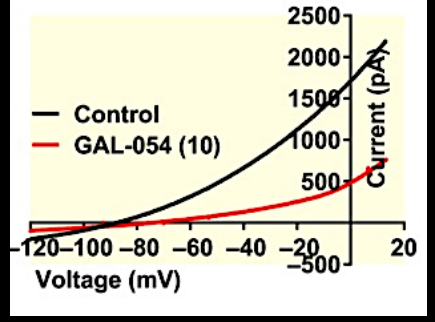
- The positive enantiomer of doxapram (GAL-054) is a more potent antagonist of TASK channels than is doxapram
- The negative enantiomer (GAL-053) has little inhibitory effect

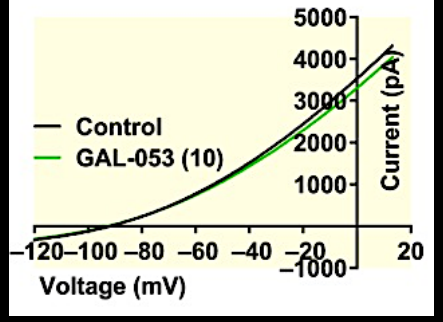
hTASK-1





hTASK-3

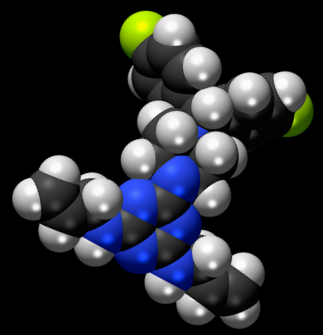


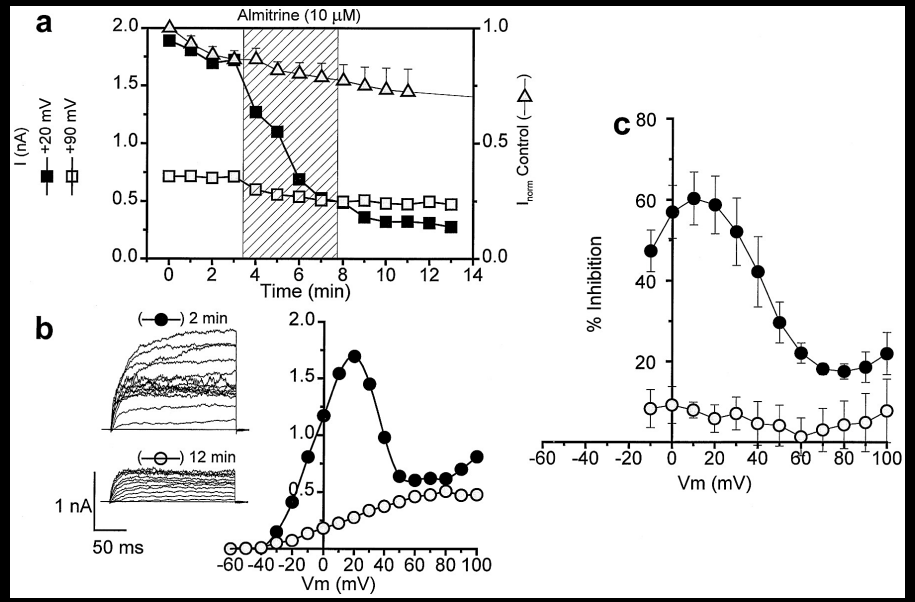


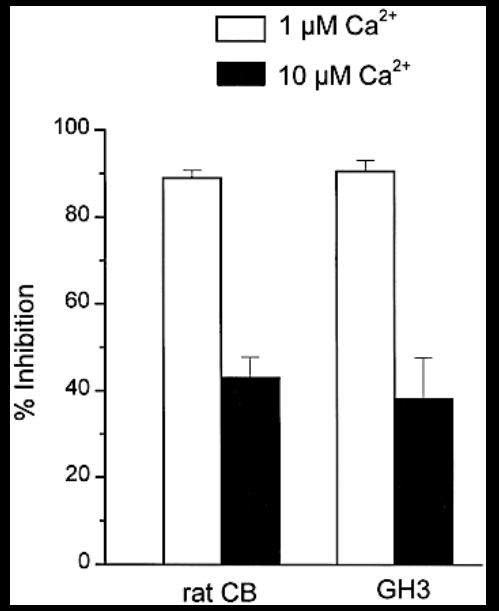
Chokshi *et al.* (2015) Molec Pharmacol 88:926-934; Cunningham *et al.* (2019) Acta Physiologica 228:e13361

Almitrine

- enhances respiration by acting as an agonist of chemoceptors located on the carotid bodies.







López-López et al. (1998) Molec Pharmacol 53:330-339

Doxapram *vs* Almitrine

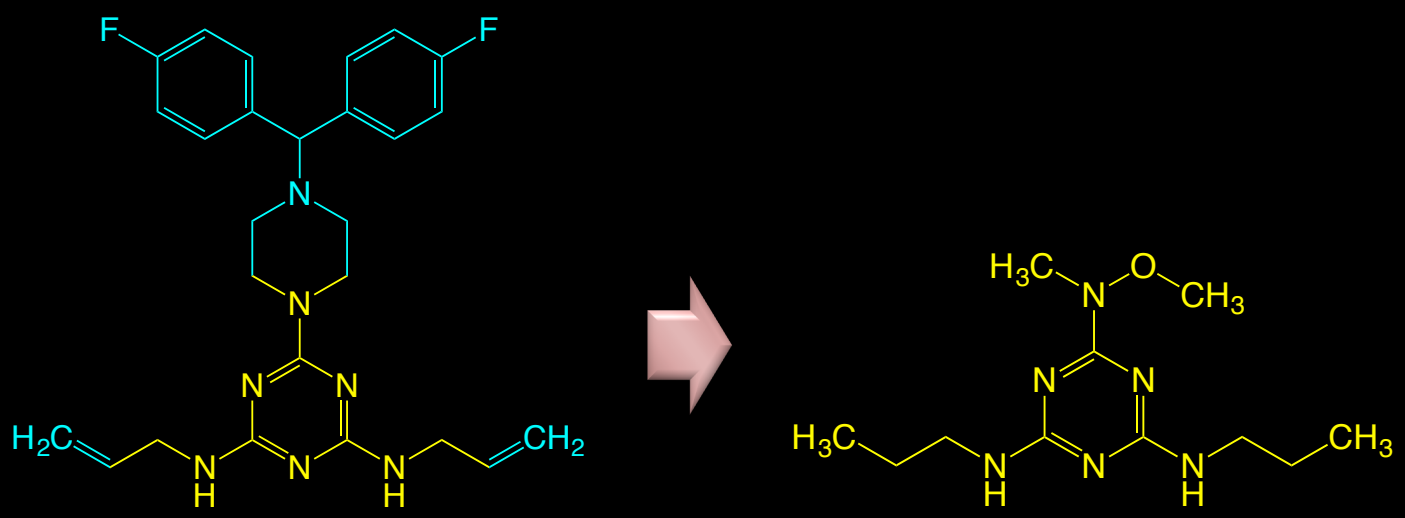
- Transecting the carotid sinus n. blocks the ventilatory effects of almitrine at all doses – and doxapram at normal clinical doses.
- Doxapram's action is manifested by increase in tidal volume associated with a slight increase in respiratory rate.
- At higher doses of doxapram, residual ventilatory stimulation persists in carotid and aortic denervated animals, indicating an additional site of action – presumably within the central nervous system (brain and sp. cord).

Uses and Concerns

- Exercising care to prevent vomiting and aspiration, doxapram may be used to stimulate respiration, hasten arousal and encourage the return of laryngo-pharyngeal reflexes in patients with mild to moderate respiratory and CNS depression due to drug overdose. AEs: panic, agitation, dyspnea, and hyper-tension.
- 2013: EU drug regulators recommended withdrawing oral almitrine-containing medicines from the market because their benefits no longer outweigh the risk for marked weight loss and long-lasting peripheral neuropathy.

Evolution to ENA-001 (formerly GAL-021)

- Remove difluorobenzhydrylpiperidine group
- Remove allyl groups



almitrine

GAL-021 (ENA-001)

ENA-001 (formerly GAL-021)

- MoA primarily thought to involve blocking BK_{Ca} K^+ channels
- BK_{Ca}-channels contain response elements for CO, O_2, and CO_2. Its block increases carotid body signaling, phrenic n. activity, and respiratory drive
- peripheral action
- secondary mechanisms may also be involved

McLeod *et al.* (2014) Brit J Anaesth 113:875-883

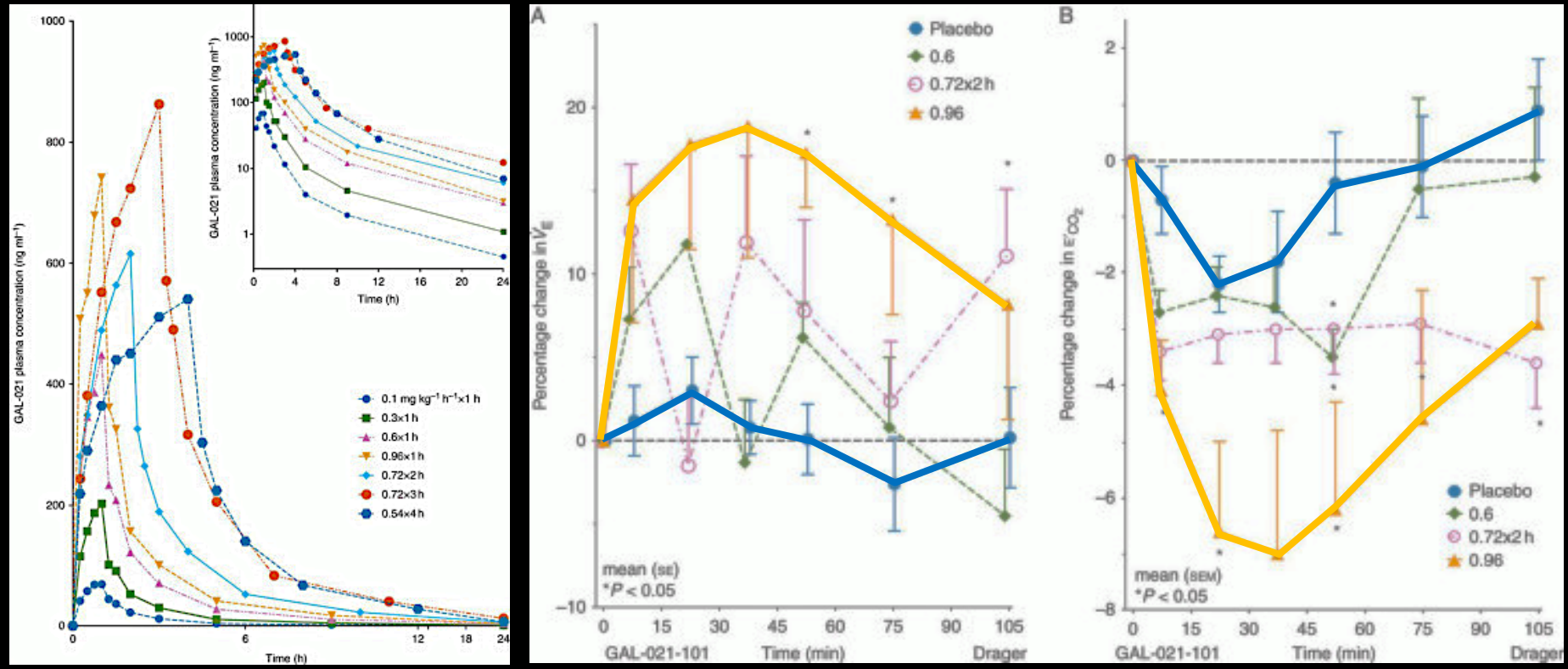
ENA-001 (formerly GAL-021)

- In human volunteers

Prof. Dr. Albert Dahan

ENA-001 (formerly GAL-021)

- In human volunteers



McLeod *et al.* (2014) Brit J Anaesth 113:875-883

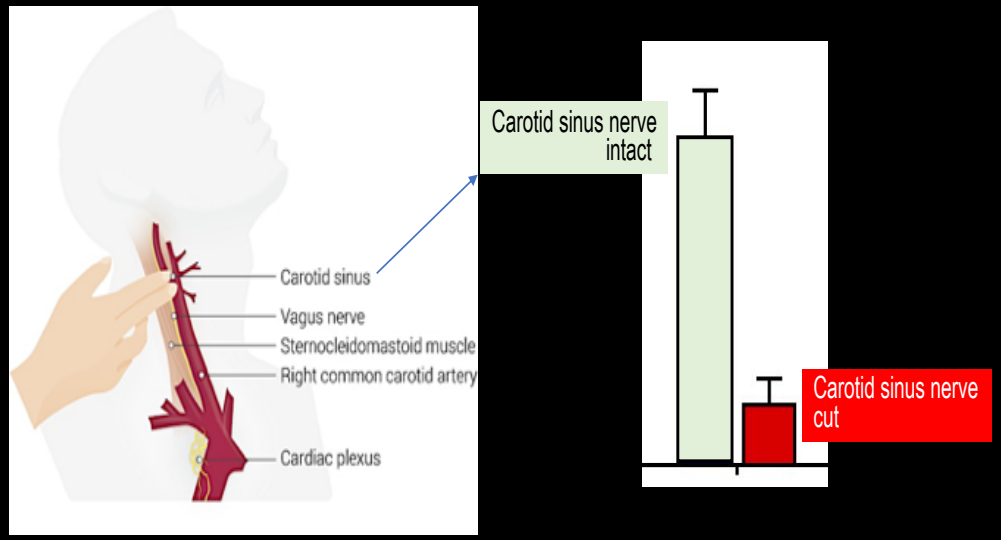
ENA-001 (formerly GAL-021)

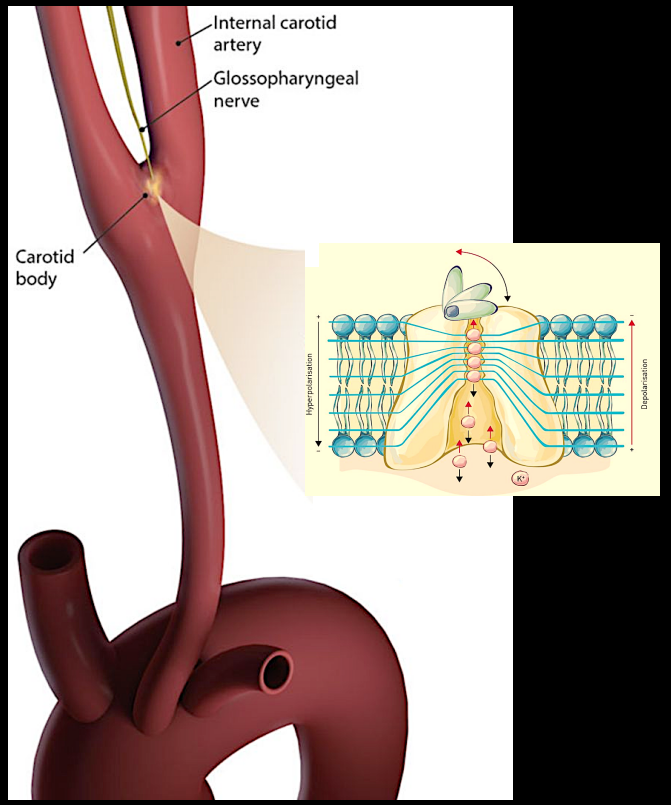
- Upon i.v. administration by bolus or infusion to rats[1] or cynomolgus monkeys[2] ENA-001 elicits dose-dependent increases in minute ventilation and shows a robust, dose-dependent, reversal of respiratory depression caused by opioids (morphine or fentanyl), benzodiazepines (midazolam), or by anesthetic agents (isoflurane or propofol).

[1] Baby *et al.* (2012) FASEB J 26:704.28
[2] Golder et al. (2012) FASEB J 26:704.27

ENA-001 (formerly GAL-021)

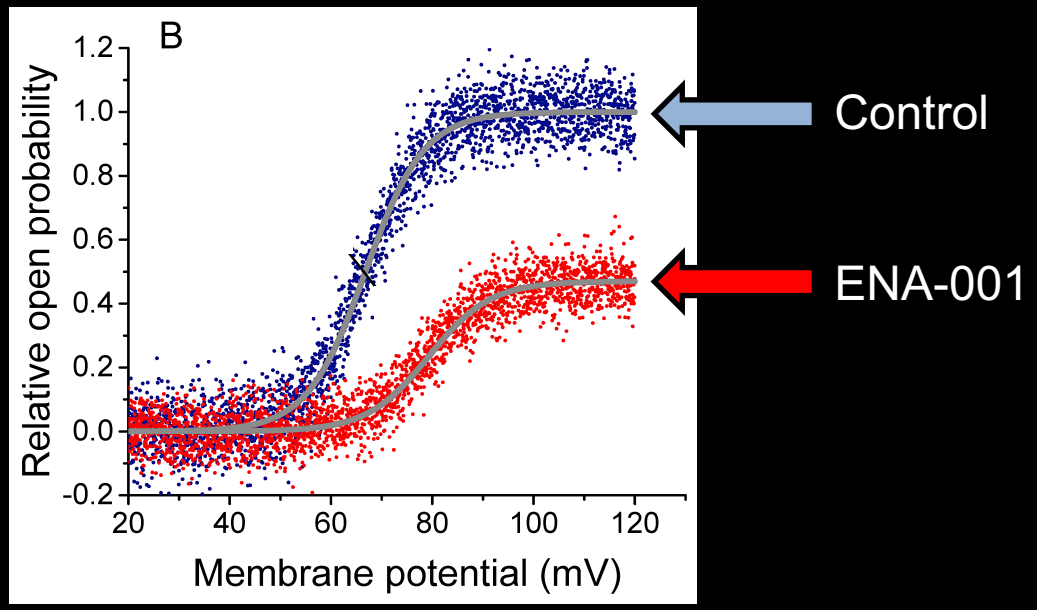
- Involvement of carotid body





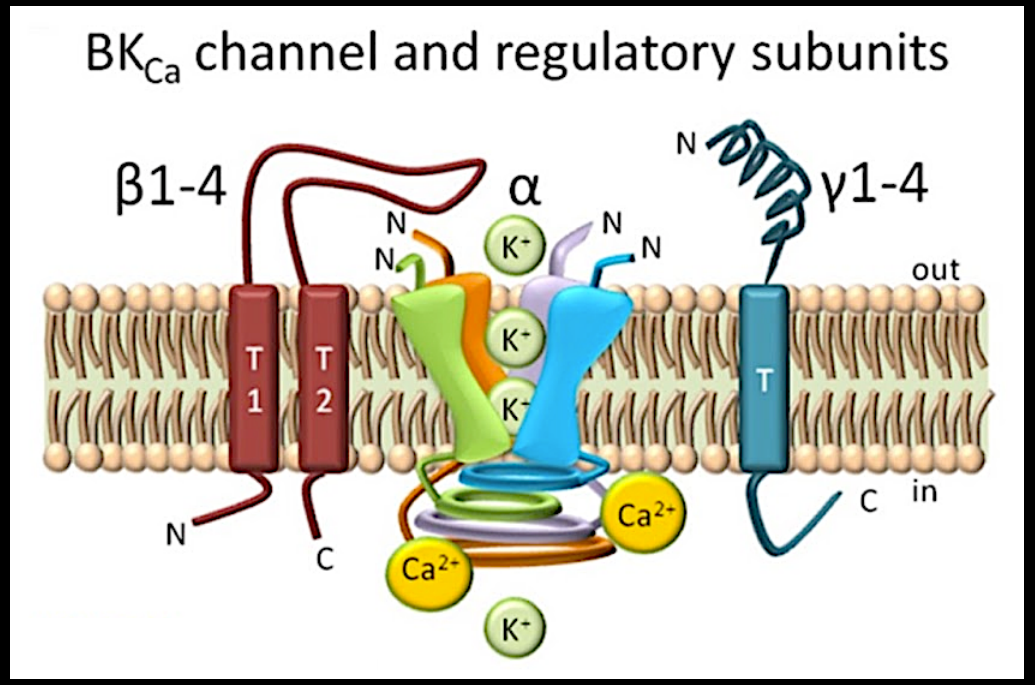
ENA-001 (formerly GAL-021)

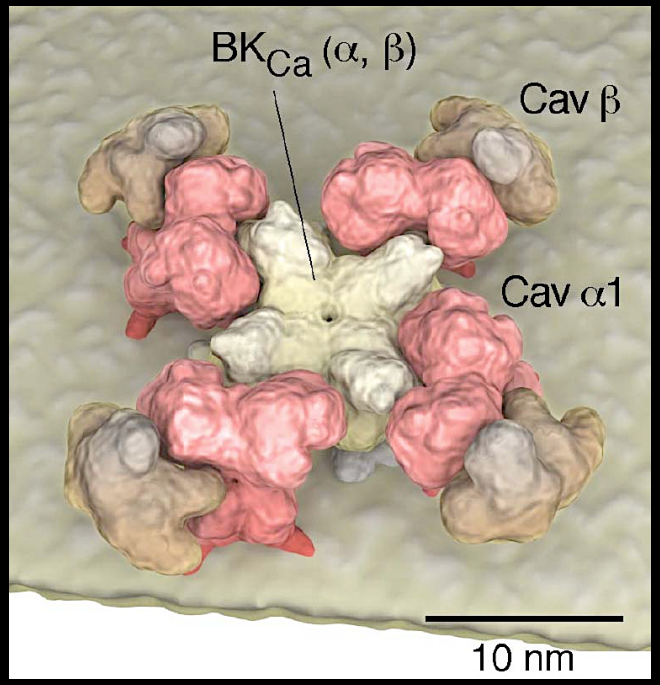
- decreases the amplitude of the macroscopic Ca^{2+}-activated K^+ current ($I_{K(Ca)}$) in a concentration-dependent manner
- lengthens mean closed time of BK_{Ca} channels, with no change in mean open time (in HEK293T cells expressing *α-hSlo*,).



Lu et al. (2020) Biomolecules 10:188 https://doi.org/10.3390/biom10020188

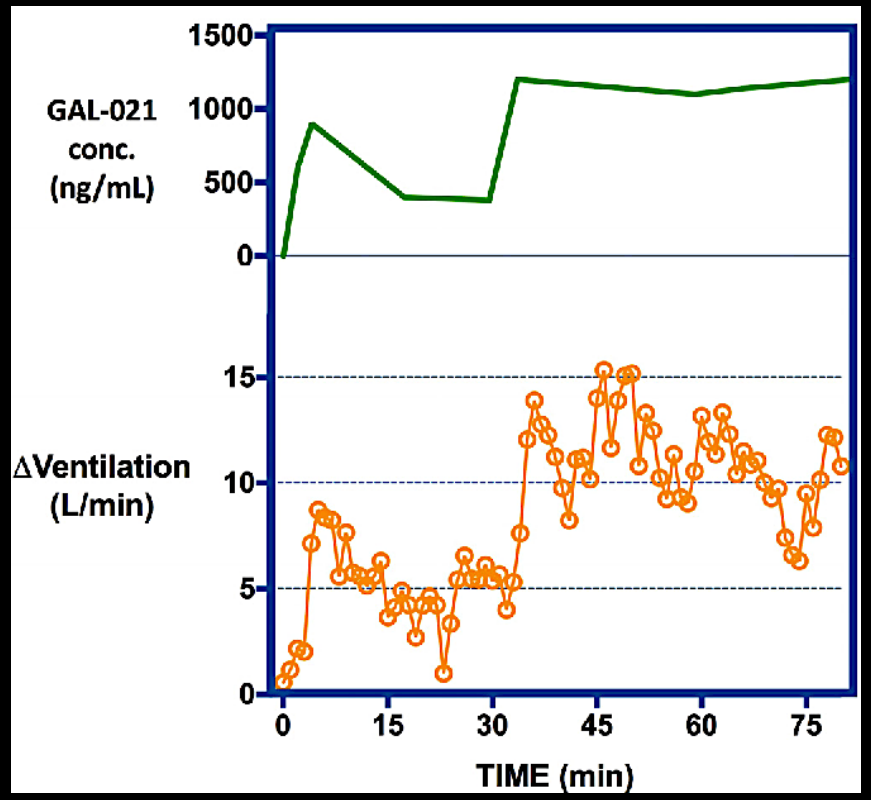
BK_{Ca} K^+ channels





https://multiple-sclerosis-research.org/2017/06/education-big-conductance-potassium-channels/
http://www.physiologie.uni-freiburg.de/molecular-physiology/news/neighborly-relationsbetween-ion-channels

ENA-001 (formerly GAL-021)



van der Schier et al. (2014) F1000Prime Reports 6:79 doi:10.12703/P6-79

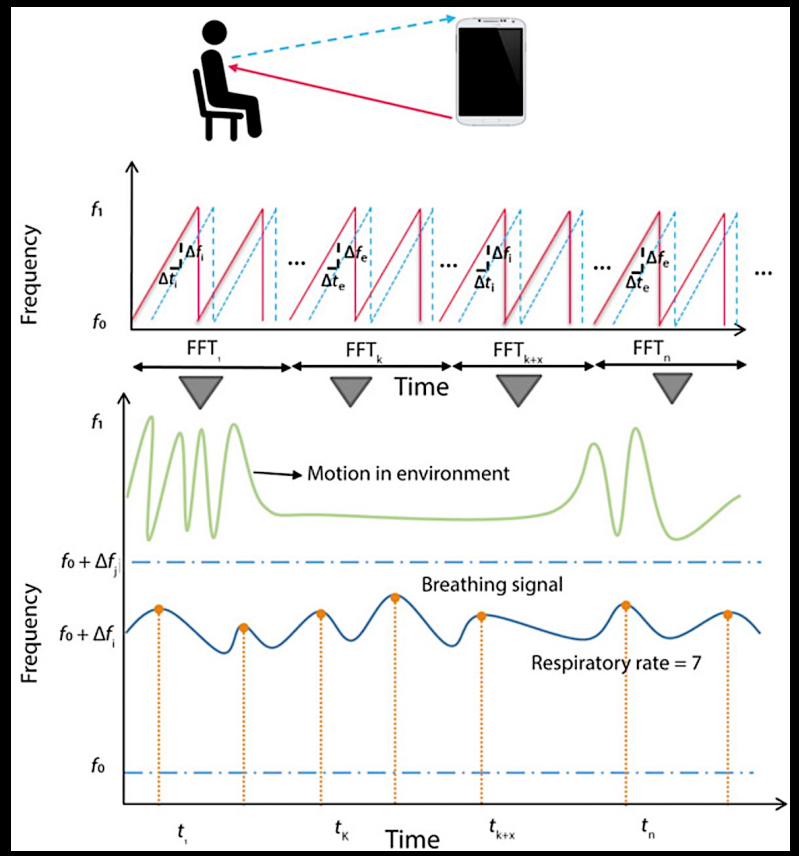
ENA-001 (formerly GAL-021)

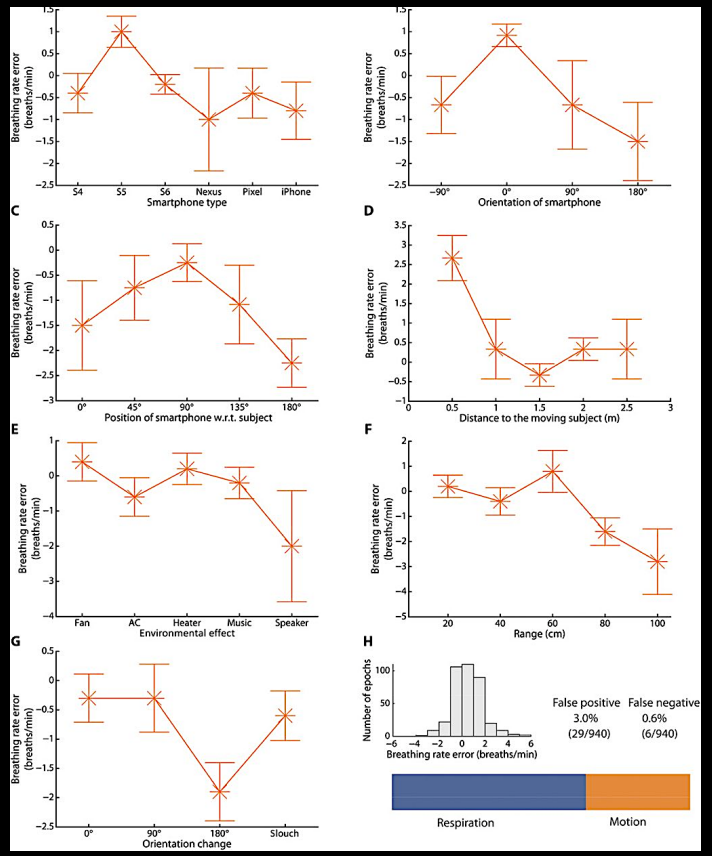
Summary

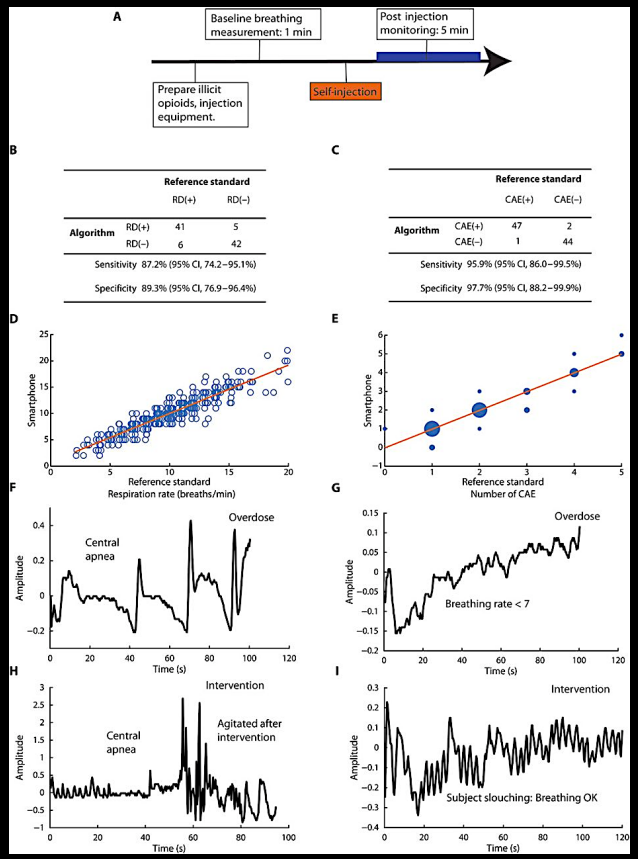
- MoA primarily thought to involve blocking BK_{Ca} K^+ channels
- peripheral action
- does not block opioid receptors (does not block opioid-induced analgesia)
- ‘agnostic’

Remote Sensing – *there's an App for that*

Telemedicine – *Smartphone*







Nandakumar R *et al*. (2019) Sci Transl Med 11: eaau8914

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