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PSYCHIATRY ACADEMY

Progress in Novel Entactogens as Therapeutics

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Tactogen Inc

Disclosures

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I am employed by and hold equity in Tactogen Inc, a public benefit corporation developing MDMA-like medicines.

My work with Tactogen includes patents that have been assigned to Tactogen.

I have served as an advisor to Noetic Fund 2 and Journey Clinical.

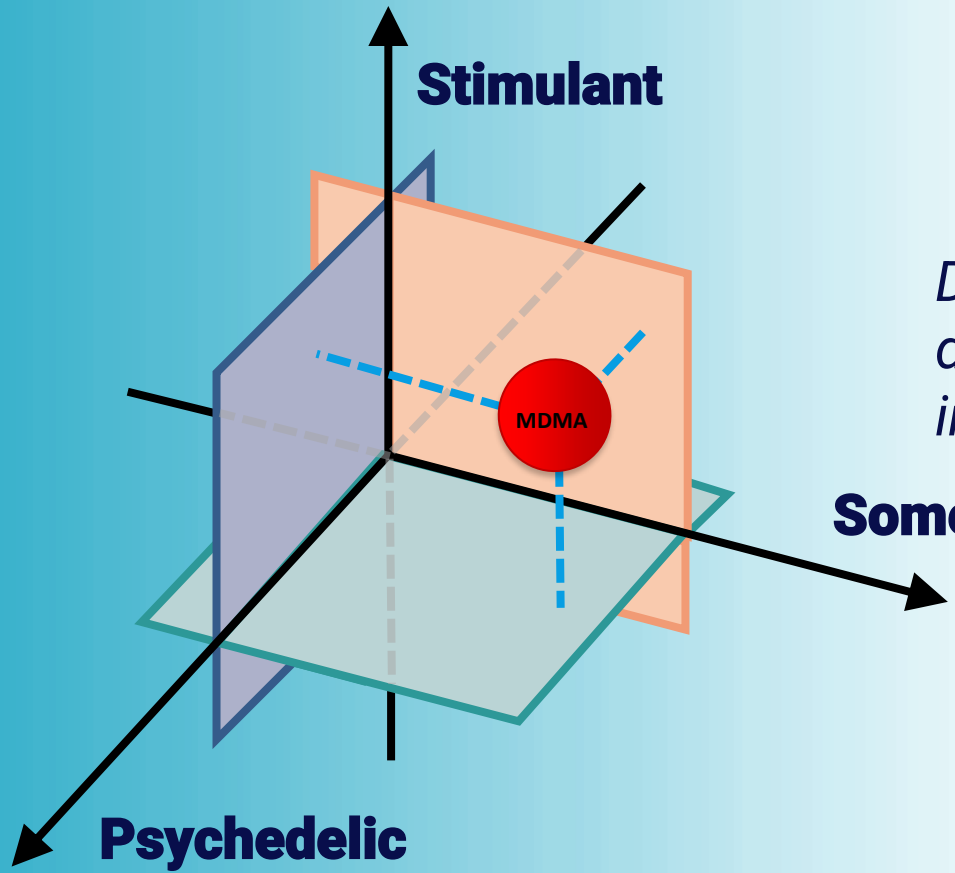
Three sections for this presentation

MDMA: its promise and limitations

5-MAPB: a gentler entactogen?

Novel compounds: TACT833

Midomafetamine (MDMA) resembles stimulants and psychedelics but also does something new



Decreased neuroticism, decreased avoidance, increased self-acceptance

Something new (Entactogen)

MDMA is a promising therapeutic

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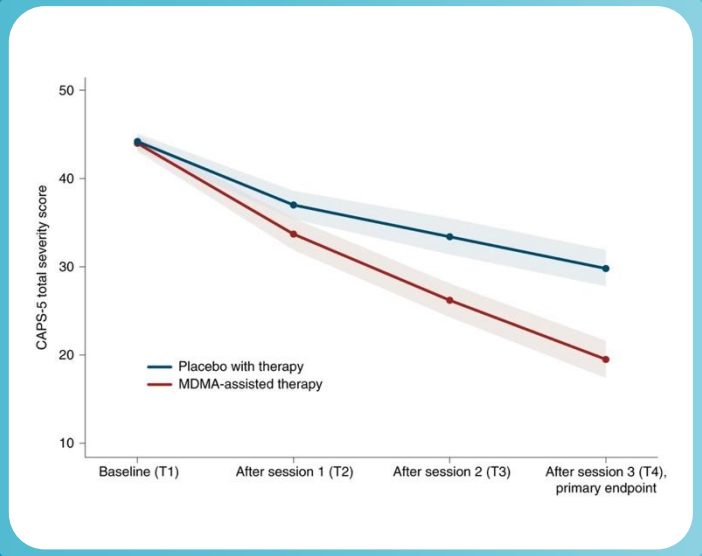
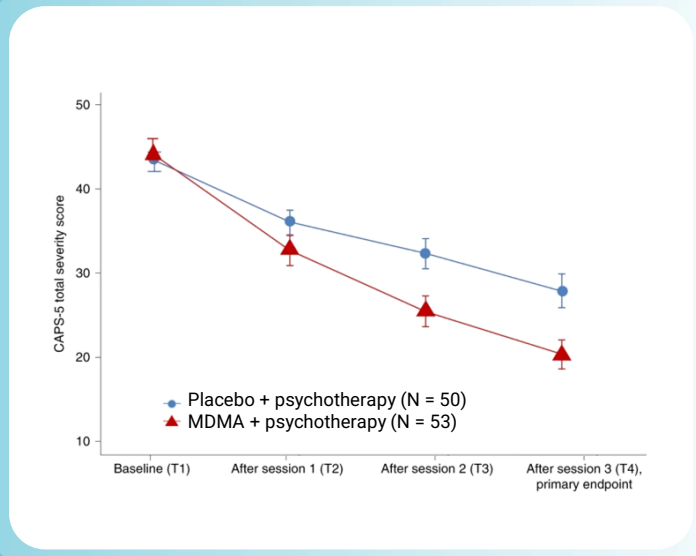
A New Drug Application from Lykos/Resilient is expected to gain eventual approval

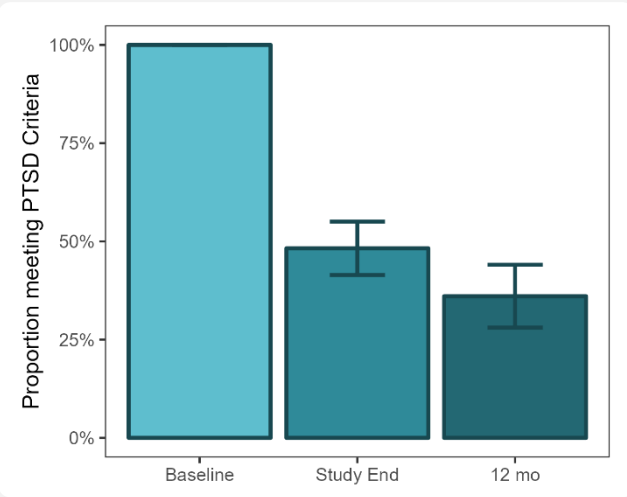
Initial Phase 3 Results › **Confirmatory Trial** › **Benefits in Phase 2 persisted at least 12 mos**



Mitchell et al. 2021



Mitchell et al. 2023



This is not specific to MDMA or Lykos/Resilient:
Transcend found the beta-keto analogue of MDMA improved PTSD in a Phase 2 trial

MDMA beat standard-of-care pharmaco-therapy for Alcohol Use Disorder (AUD)

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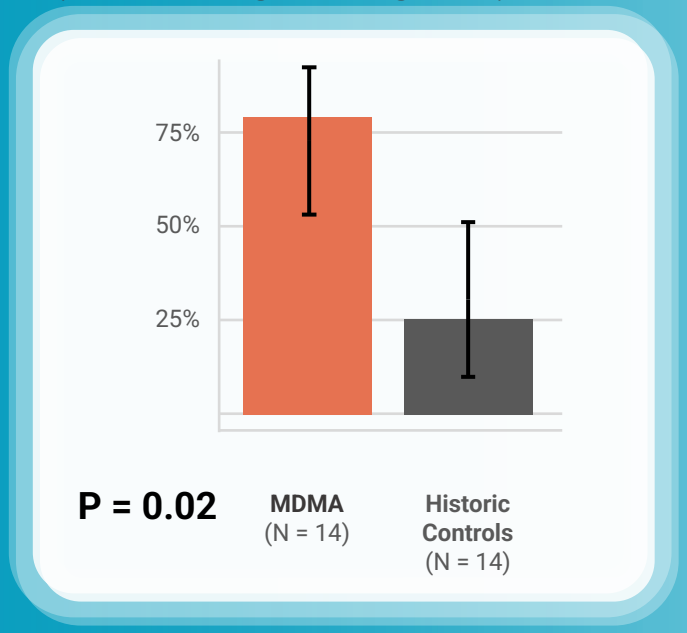
MDMA Improved Alcohol Use Disorder in an Open Label Trial

Proportion No Longer Drinking Heavily at 9 Months



Sessa et al. 2022

FDA Approved treatments are inadequate

Medicine	Mechanism	Adherence (6-mo)[1]	NNT to prevent drinking[2]
Naltrexone (ReVia, Vivitrol, Depade)	μ-opioid receptor antagonist	54.6%	20
Disulfiram (Antabuse)	ALDH2 and DβH inhibitor	41.3%	Not effective[3]
Acamprosate (Campral)	NMDA antagonist and GABA-A PAM	44.7%	9 to 12
MDMA	Psychedelic entactogenic amphetamine	98.1%	1.6

[1]Walker, et al. 2019. *Journal of Studies on Alcohol and Drugs*, *80*(5), pp.572-577. doi: 10.15288/jsad.2019.80.572; MDMA estimate is completion rate from Mitchell et al 2023 *Nature Medicine*, 29(10), pp.2473-2480. [2]NNT = Number Needed to Treat, non-MDMA data from Walker, et al. 2019. Journal of Studies on Alcohol and Drugs, 80(5), pp.572-577. 10.15288/jsad.2019.80.572. MDMA data from Sessa et al. 2022 *J. Psychopharmacology*, 35(4), pp.375-383. 10.1177/0269881121991792 [3]"little evidence supports its effectiveness outside of supervised settings" in Poorman et al. 2024. *American Family Physician*, *109*(1), pp.71-78.

MDMA has known issues that will limit its market

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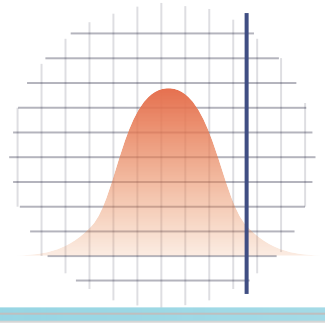
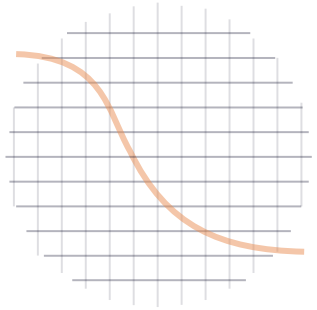


Cardiovascular	5% have systolic > 180 mmHg; 10% have heart rate > 120 bpm	Create a need for **clinical monitoring,** costing $15k
Emotional	5% report anxiety; Dose-dependent feelings of drunkenness, sedation; Overwhelming emotions	



After-effects	Mood decreased several days later in a subset of users	**Decrease acceptability** for patients
Loss of therapeutic effects	Therapeutic effects often diminish with repeated exposure	

A minimally impairing MDMA-like treatment, administrable outside clinical settings, would greatly help patient access.

Lowered mood can occur after controlled MDMA administration

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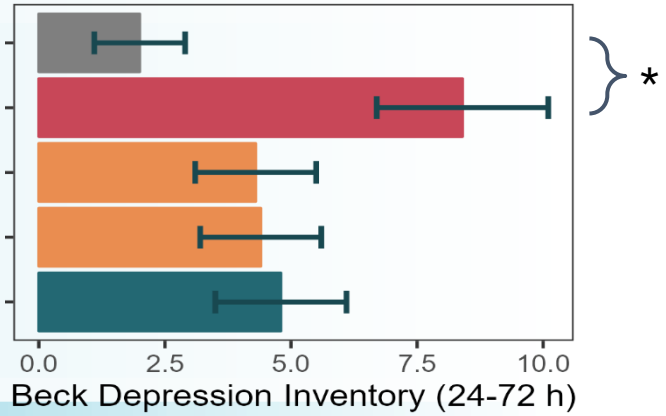
Straumann et al (2024) found that 125 mg S-MDMA (but not racemic or R MDMA) increased **Beck Depression Inventory** scores at 24–72 hr after dosing (N = 24):

Placebo:	2.0 ± 0.9
125 mg S-MDMA:	8.4 ± 1.7
125 mg R-MDMA:	4.3 ± 1.2
250 mg R-MDMA:	4.4 ± 1.2
125 mg MDMA:	4.8 ± 1.3



If we think of 125 mg S-MDMA as similar to 250 mg racemic MDMA, this after-effect may be associated with higher doses.

BDI Scores are mean + SEM; Data from Straumann I, Avedisian I, Klaiber A, Varghese N, Eckert A, Rudin D, Luethi D, Liechti ME. Acute effects of R-MDMA, S-MDMA, and racemic MDMA in a randomized double-blind cross-over trial in healthy participants. Neuropsychopharmacology. 2024 Aug 23:1-0.

Many users reported diminished effects with repeated use

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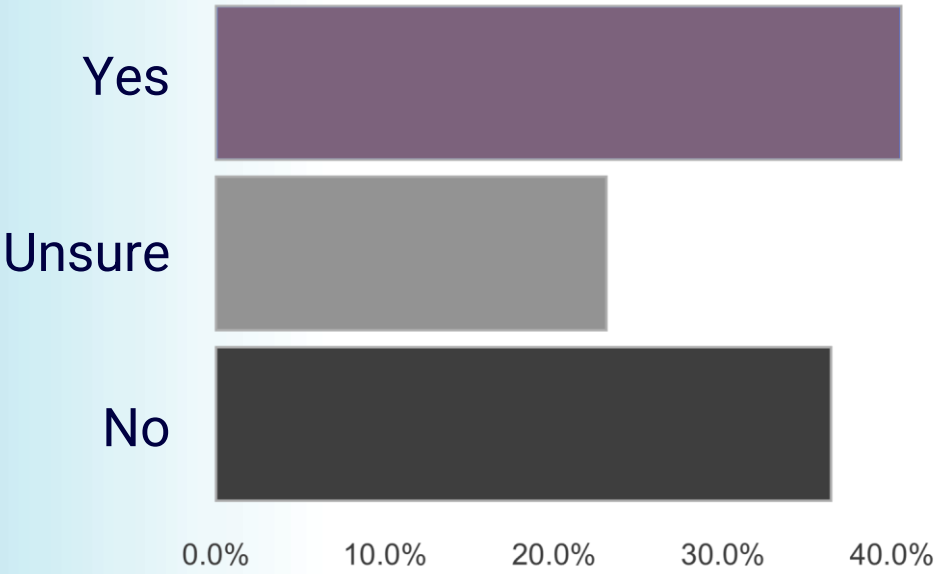
"My first experience with this drug was indeed magical. ... I was a person who had no secrets from himself and one who could trust others to be as honest with him as he was with himself. ... But that is usually lost after a few experiences and, I do believe, is never recovered. The stimulant properties are still there, and the eye-twitch and tooth-grinding are still there, and some of the warmth and comfortable interactions, but the magic is gone."

— Alexander Shulgin (2002)

40% of MDMA users (N = 600) reported changed effects

Have the effects of MDMA on you changed since you first started using it?



(Baggott, unpublished)

NIDA-funded MDMA research in the 80s and 90s focused on the risks of long-term serotonergic changes after nonmedical use

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Hallucinogenic Amphetamine Selectively ~~Destroys Brain Serotonin Nerve Terminals~~ down-regulates serotonin?

Abstract. *(±)-3,4-Methylenedioxyamphetamine (MDA), an amphetamine analog with hallucinogenic activity, produced selective long-lasting reductions in the level of serotonin, the number of serotonin uptake sites, and the concentration of 5-hydroxyindoleacetic acid in rat brain. Morphological studies suggested that these neurochemical deficits were due to serotonin nerve terminal degeneration. These results show that MDA has toxic activity for serotonin neurons in rats and raise the question of whether exposure to MDA and related hallucinogenic amphetamines can produce serotonin neurotoxicity in the human brain.*

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(±)-3,4-Methylenedioxyamphetamine (MDA) is a synthetic amphetamine derivative that produces a mixture of psychomotor stimulatory and hallucinogenic effects (*1*). This combination of psychotropic actions may stem from MDA's

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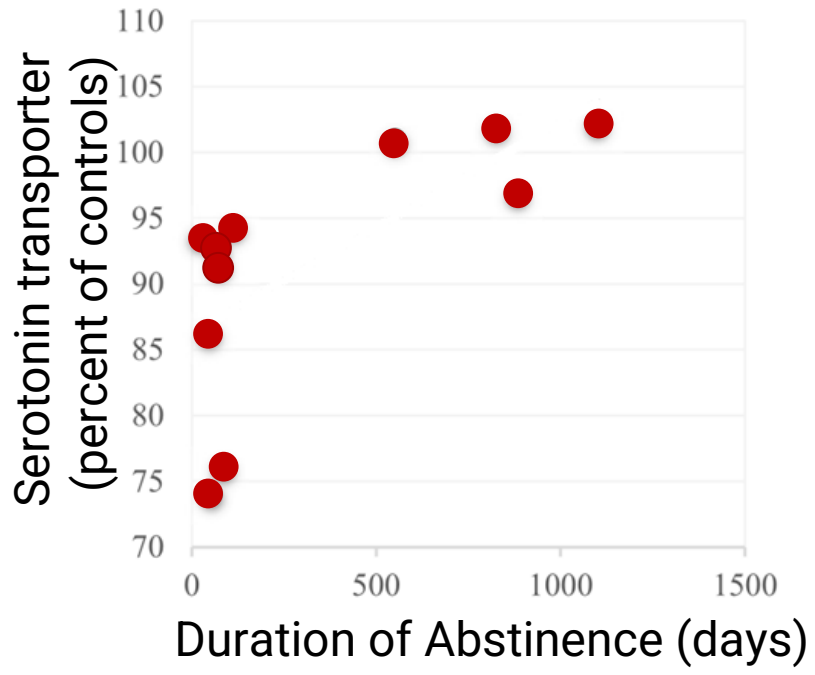
Changes may recover with abstinence

(van de Blaak & Dumont 2022)



MDMA has brief acute emotional effects and a longer plasma half-life

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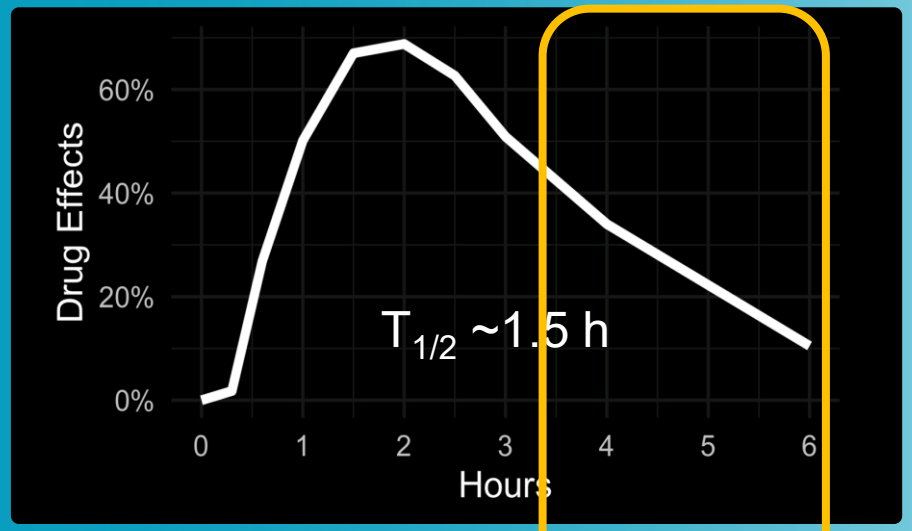

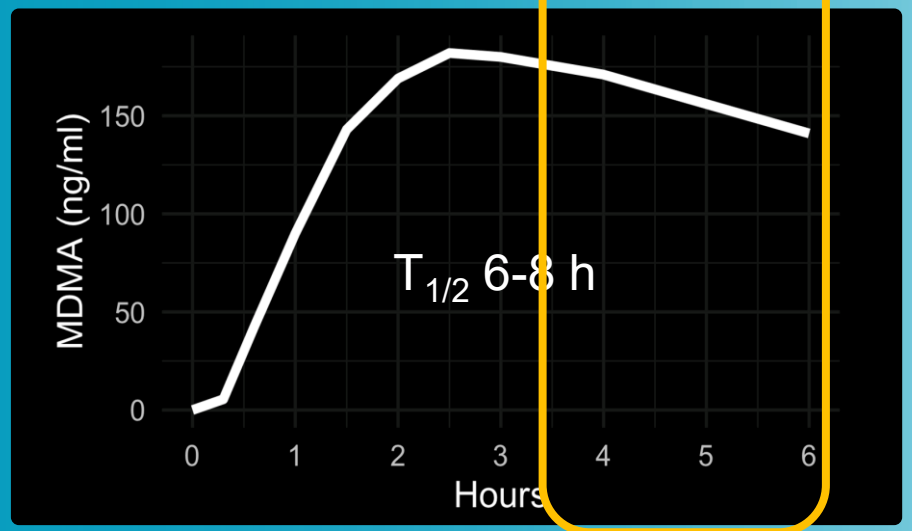

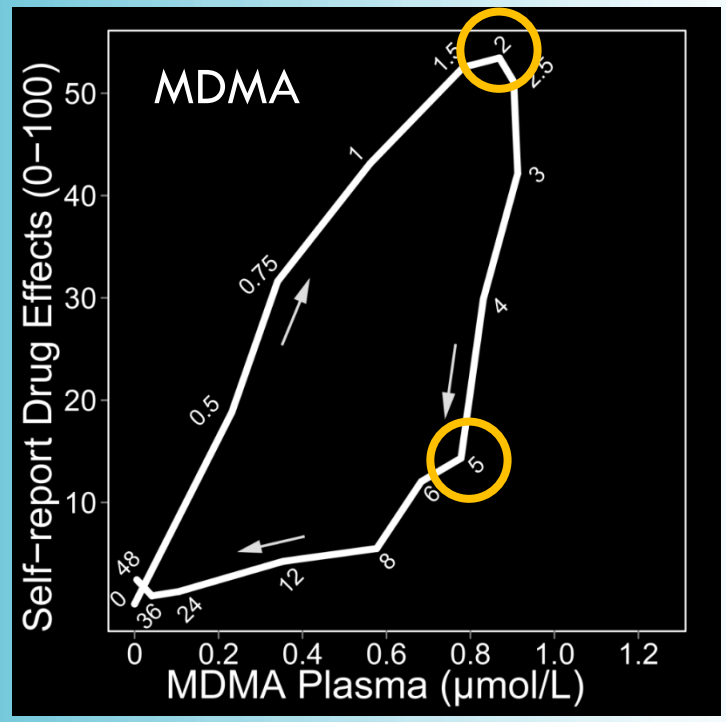

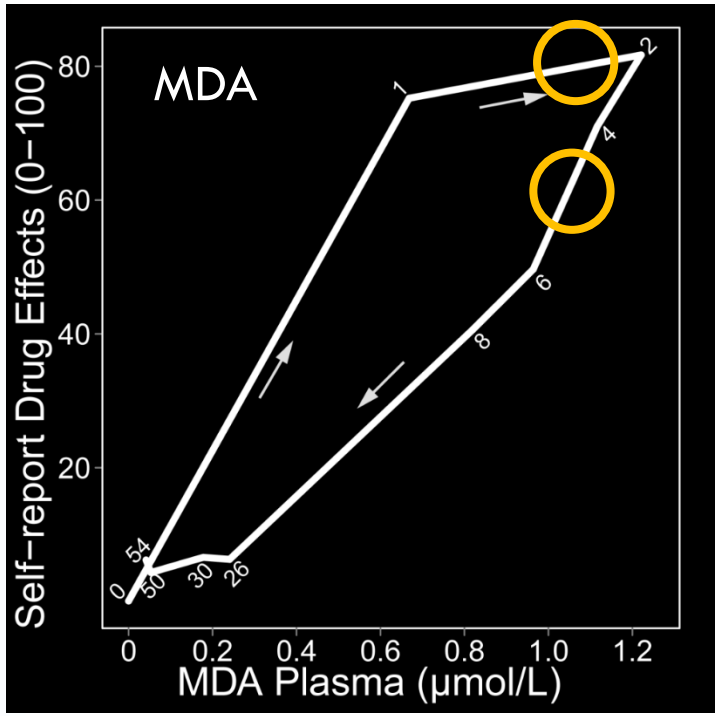

Does this later MDMA exposure have any therapeutic value?

Late blocking of SERT may improve MDMA's side effects profile

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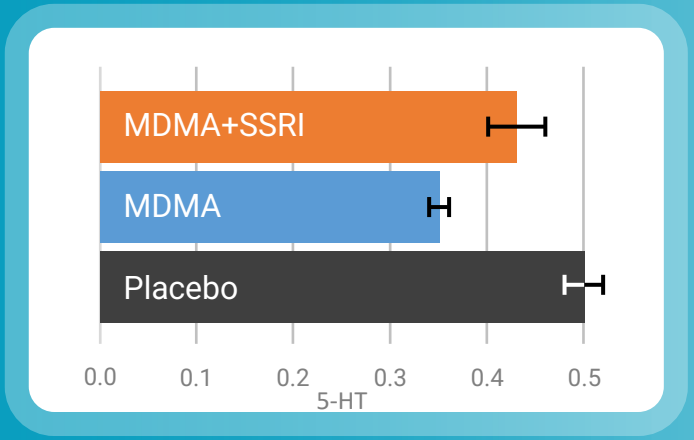
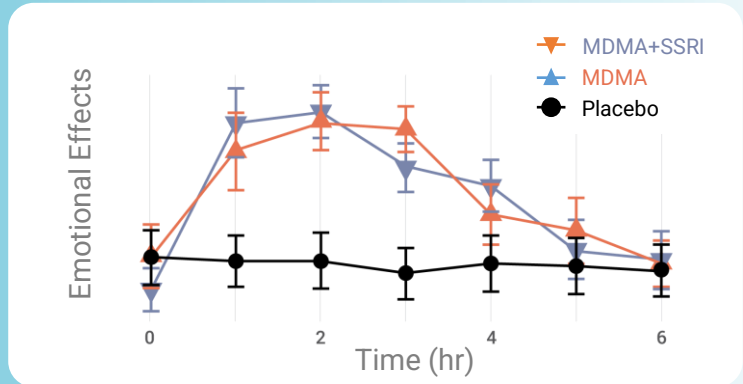
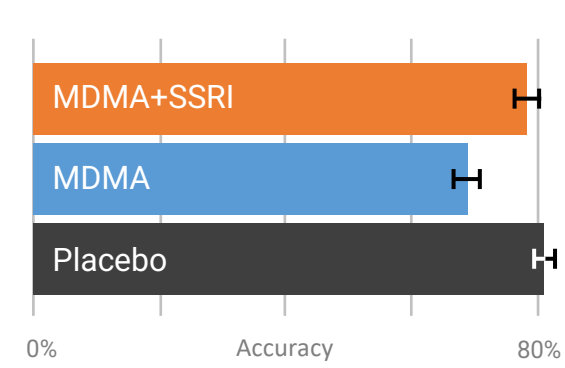
A combination of MDMA and a delayed SSRI could, perhaps should, become a standard way to administer MDMA.

Patients may prefer it: *"I had a smoothened comedown without the typical 'jagged' burned out feelings. More importantly, the 'standard' 3-day mild depression was completely absent."*







Baggott et al. in preparation

An SSRI partly protects against serotonin depletions when given 4 hours after MDMA in rat

An SSRI at 3 hours after MDMA preserves therapeutic response to MDMA in humans (N = 13)

The SSRI protects against next-day MDMA-induced cognitive impairment in humans

Three sections for this presentation

MDMA: its promise and limitations

5-MAPB: a gentler entactogen?

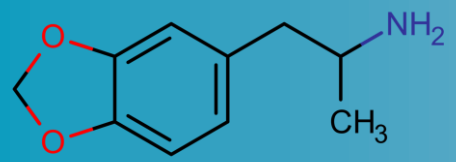
Novel compounds: TACT833

The (Disappointing) History of Trying to Improve on MDMA

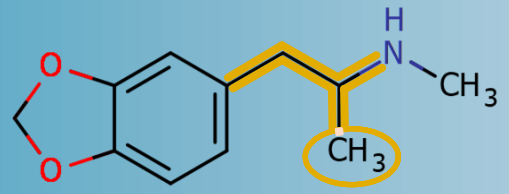
1970

2025

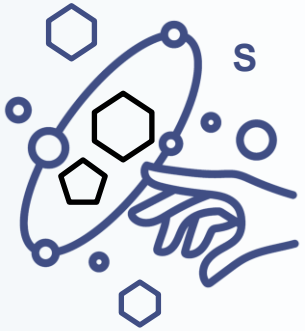
MDA
1970

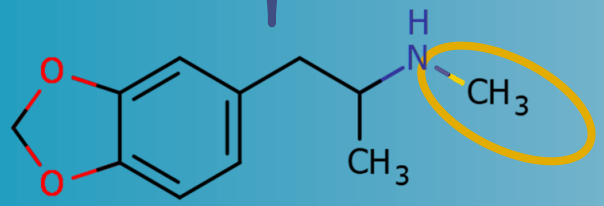


Side chain modifications
1982-1993

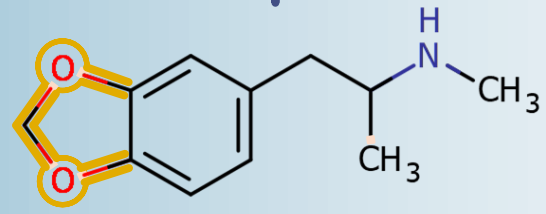


2020+
Many new ideas

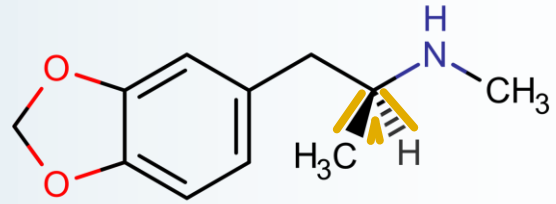




1970-1979
N-substitutions



1993+
Dioxole substitutions



2017
Reconsider enantiomers?

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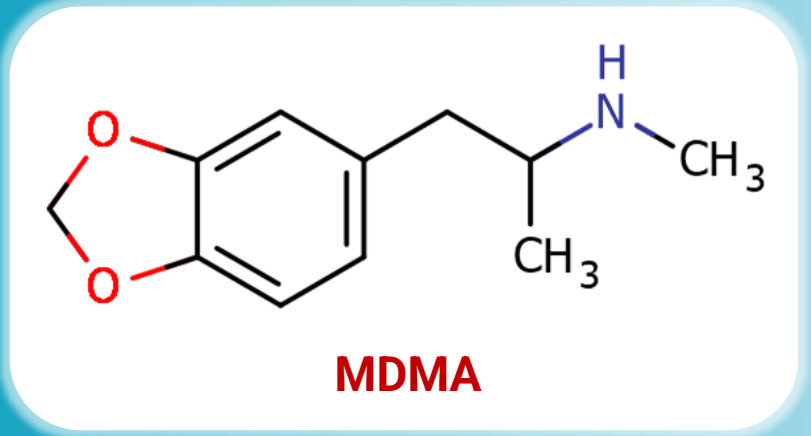
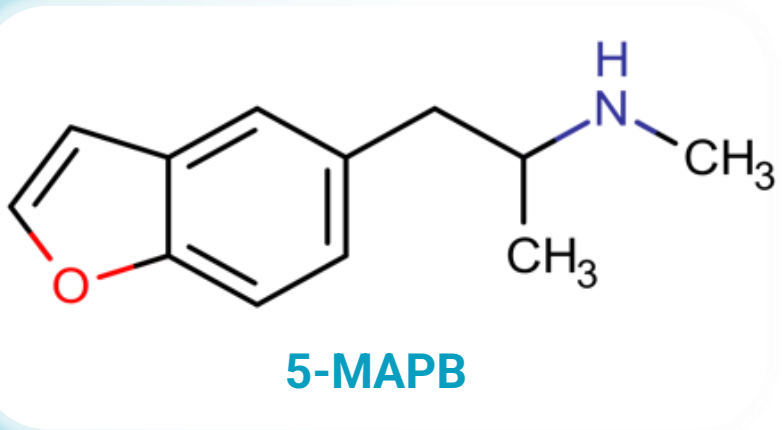
5-MAPB appeared on the grey market ca. 2010 as an MDMA substitute



MDMA

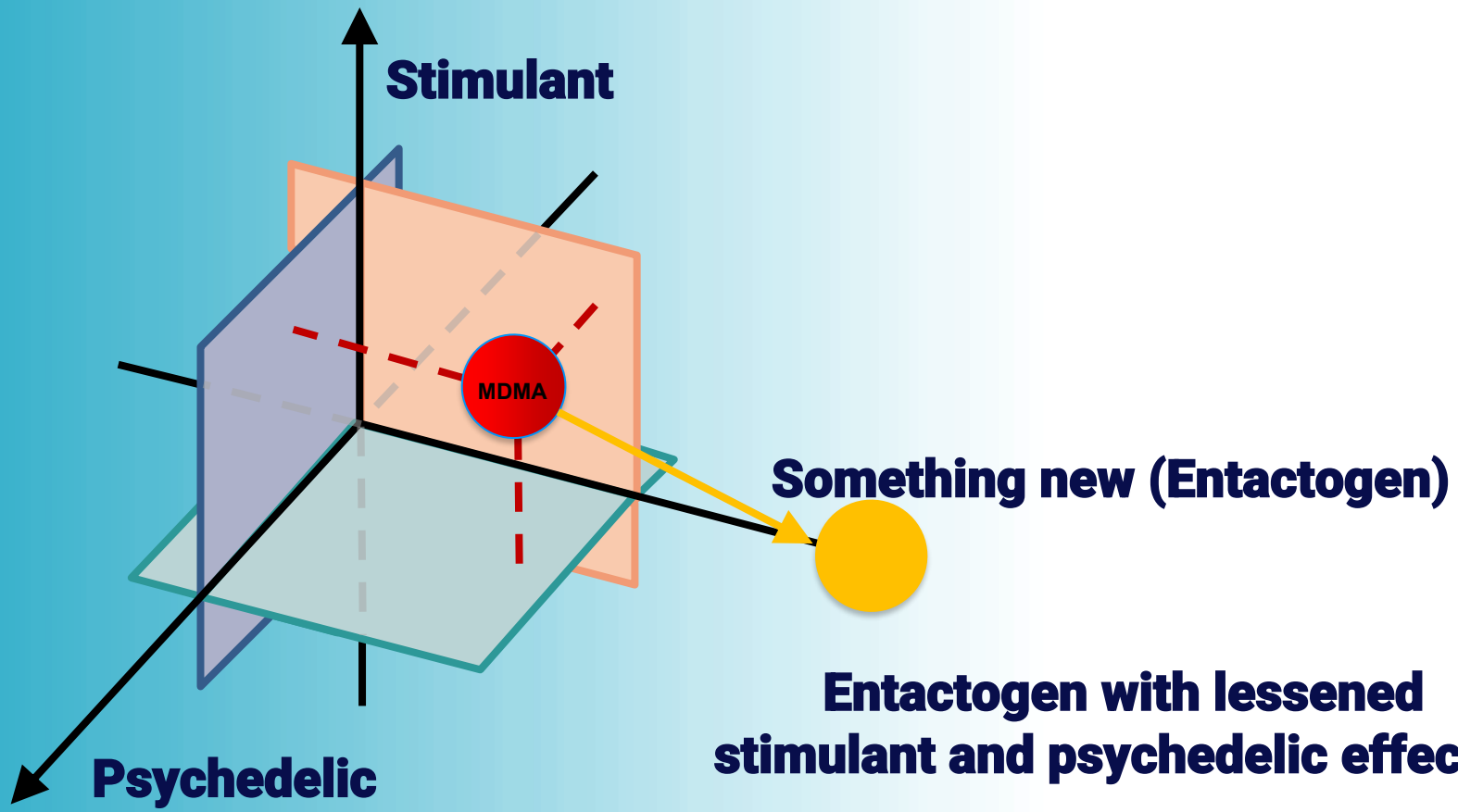


5-MAPB

5-MAPB developed a reputation as an entactogen that was longer-lasting and less stimulating than MDMA.

In 2014, Reddit user Borax began describing cocktails for creating MDMA experience, one of which was 5-MAPB plus a stimulant plus a small amount of a tryptamine psychedelic.

5-MAPB as a promising starting point



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Users report 5-MAPB is like MDMA but is less stimulating and has a better side effects profile

Representative comparisons from respondents

"They both have enabled me to face traumas in the past I hadn't previously admitted to myself had even happened. Likewise, both of them greatly facilitate opening up to others and them, being comfortable, opening up to you."

"MDMA is more energetic and gives a stronger body-high, but has a lot more issues with concentrating and you're more scatterbrained. 5-MAPB has a smoother comedown but a more abrupt come up, and the 'hangover' is much milder."

"5-MAPB is less energetic, and more long-lasting than MDMA. The comedown of 5-MAPB is also way lighter."

N = 38, Preliminary results of an ongoing anonymous web-based survey.

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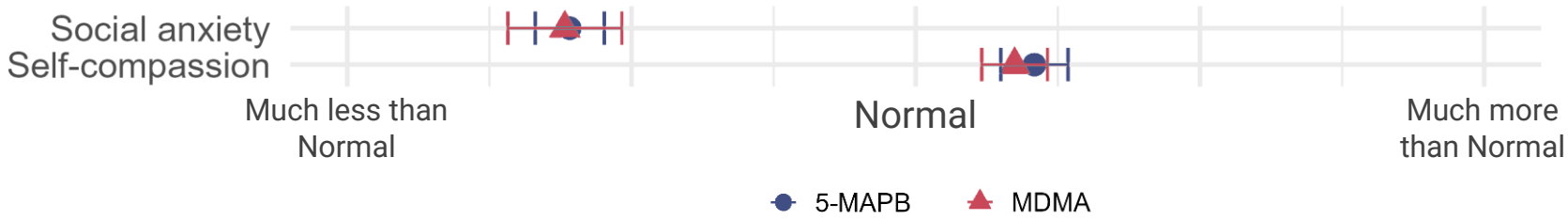
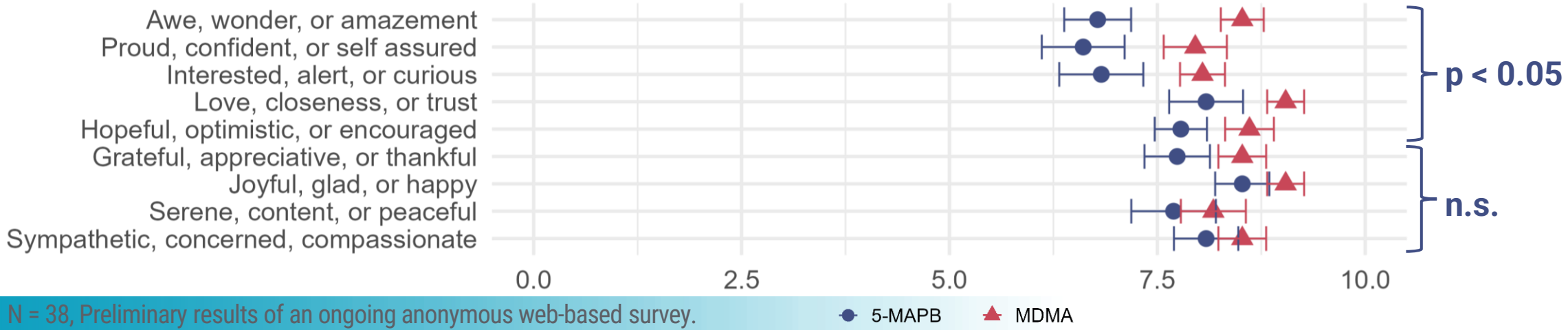
Users report 5-MAPB has similar emotional effects but is less stimulating than MDMA

Decreased social anxiety and increased self-compassion: 5-MAPB and MDMA do not differ



Positive emotions: 5-MAPB produces less positive activation than MDMA



N = 38, Preliminary results of an ongoing anonymous web-based survey.
Items are from b-FNE, Self-compassion scale, and mDES

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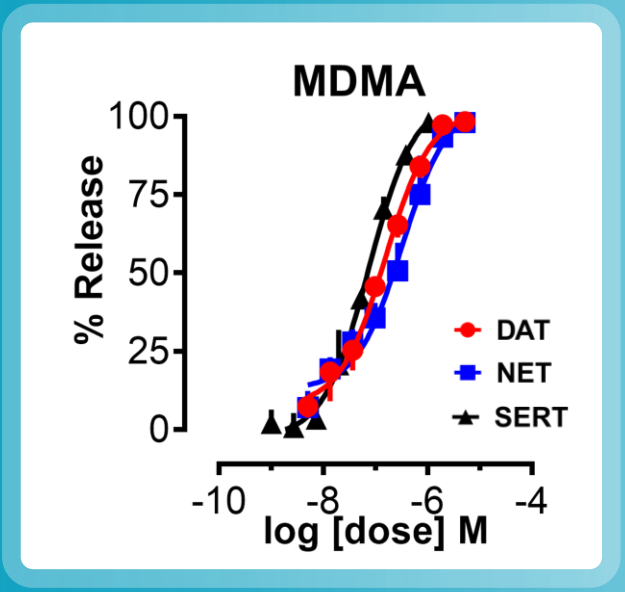
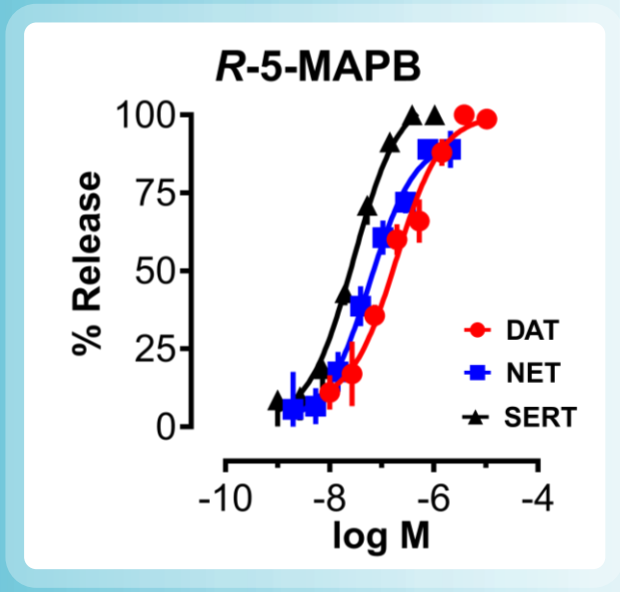
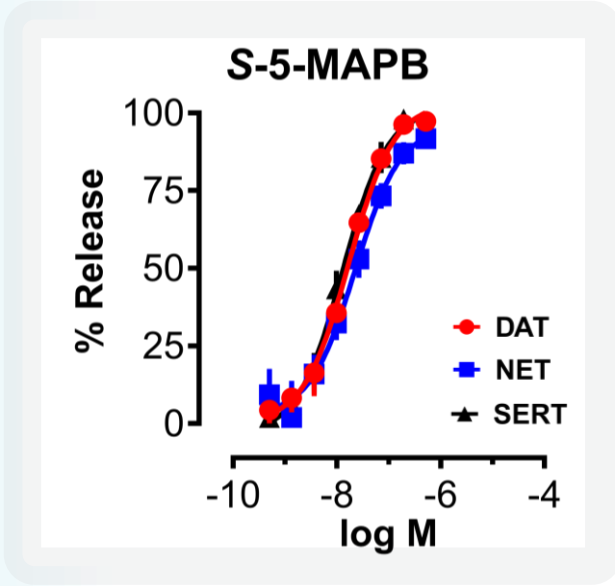
Both 5-MAPB enantiomers are potent MDMA-like monoamine releasers







EC50s for Release (nM)	DAT	NET	SERT	DAT vs. NET ratio	DAT vs. SERT ratio
MDMA	155.2 ± 22.7	116.5 ± 13.2	94.3 ± 13.6	0.75	0.61
***S*-MDMA**	142 ± 4	136 ± 9	74 ± 3	0.96	0.52
***R*-MDMA**	3700 ± 100	560 ± 40	340 ± 20	0.15	0.09
***S*-5-MAPB**	17.1 ± 1.5	22.4 ± 3.8	13.0 ± 1.2	1.3	0.76
***R*-5-MAPB**	191.6 ± 30.4	60.0 ± 9.0	29.3 ± 3.7	0.31	0.15

Non-*racemic* 5-MAPB appears more similar to MDMA than other historic entactogens

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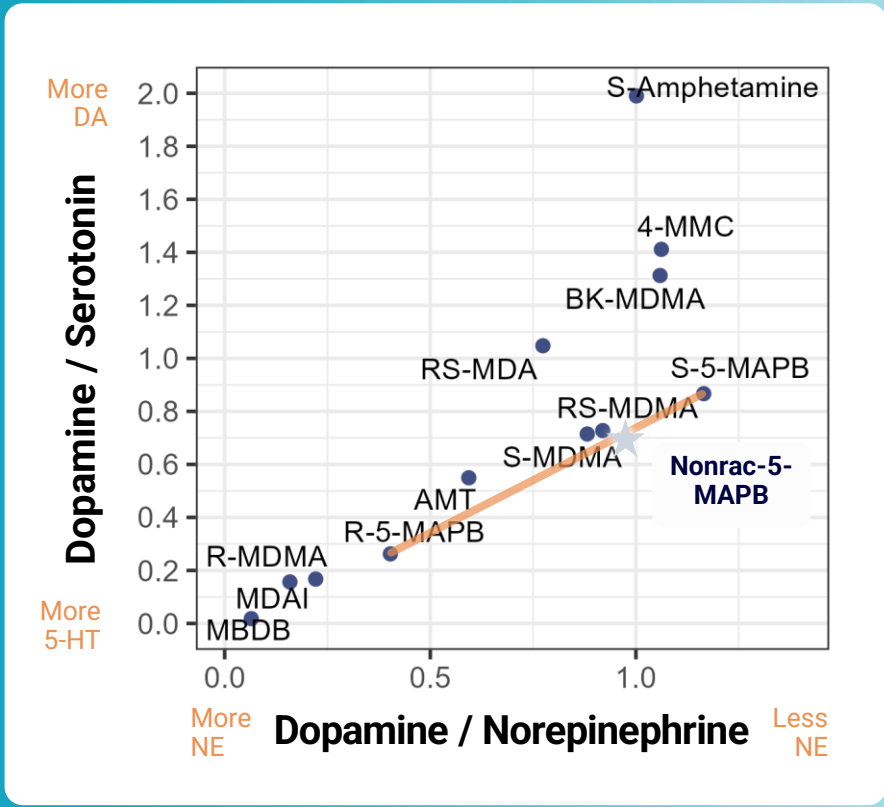
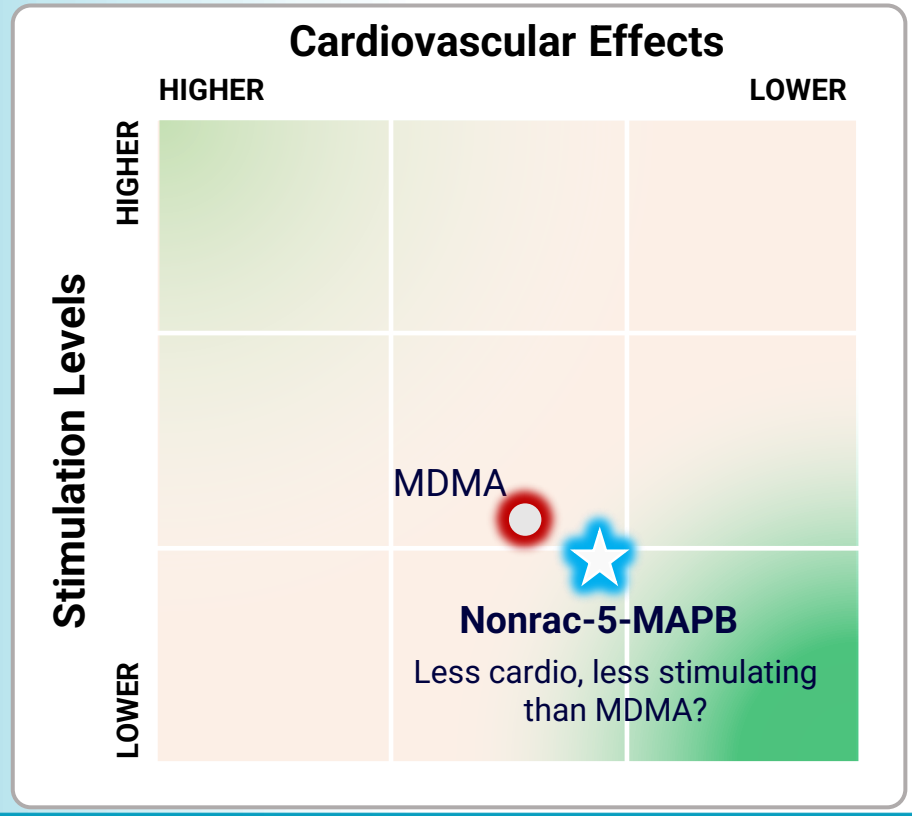
Non-racemic 5-MAPB may be the only known entactogen in a desirable monoaminergic green zone, retaining therapeutic emotional effects of MDMA while having lessened cardiovascular & stimulant effects.





Three sections for this presentation

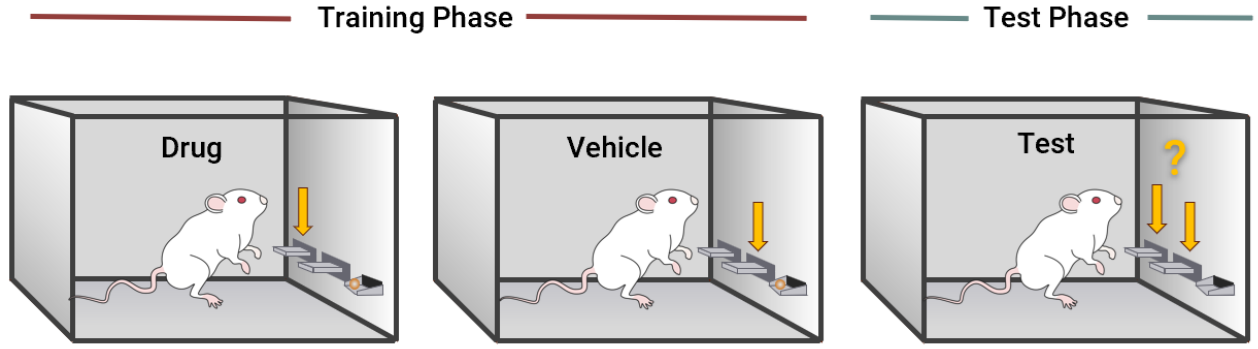
MDMA: its promise and limitations

5-MAPB: a gentler entactogen?

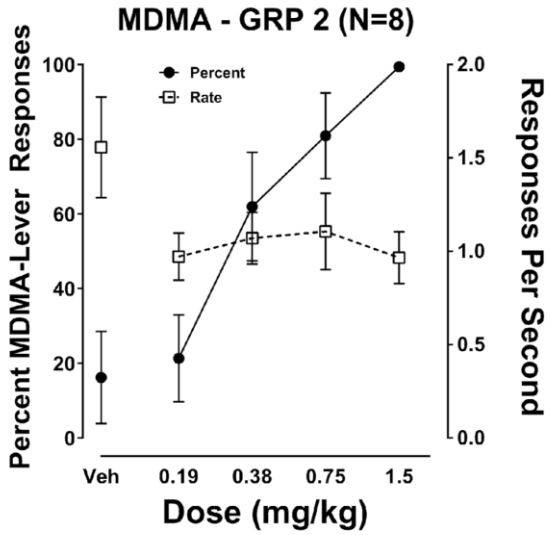
Novel compounds: TACT833

Screening for novel entactogens

The rodent drug discrimination paradigm enables efficient confirmation of MDMA-like psychoactivity



Sprague-Dawley rats are trained to discriminate 1.5 mg/kg IP MDMA from Vehicle under a fixed-ratio 20 schedule of food reinforcement. In each training session, either training drug or vehicle is given and only presses of the lever associated with the session's drug or vehicle are rewarded. During test sessions, a novel compound is administered, and both levers are rewarded. Percent responding on each lever and response rate are recorded and dose-response curves can be generated. By convention, 80% or greater drug appropriate responding is interpreted as 'generalization', indicating similarity between the training and test drug. Rodents can discriminate MDMA effects at doses/concentrations that are comparable to those producing therapeutic effects in humans (roughly 0.7 to 1.5 mg/kg). Further details can be found in Baker (2018).

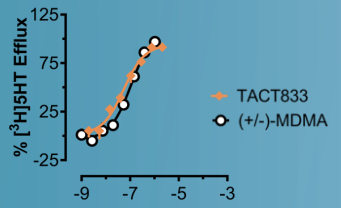


Note the high sensitivity: ED50s are typically very close to human ED50s with no need for interspecies dose conversion.

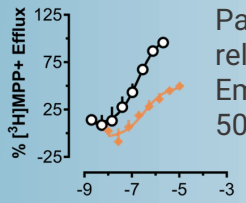
Drug discrimination data collected by Rachel Burroughs and Candace Johnson in Lisa Baker's lab at Western Michigan University

TACT833 has improved selectivity and profile over MDMA

Same 5-HT release

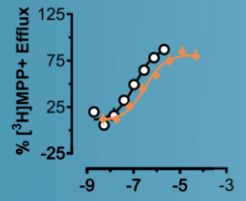


Much less DA release



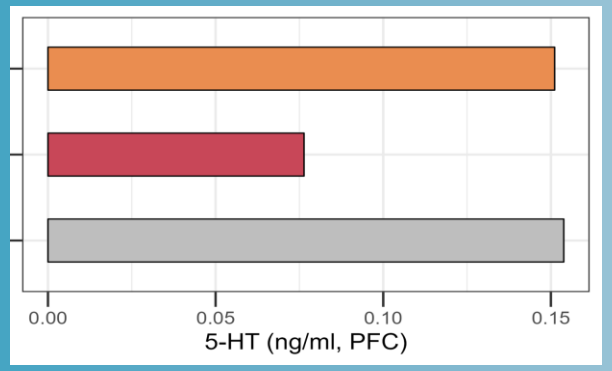
Partial releaser: Emax 50%

Less NE release



Limiting release of DA (dopamine) and NE (norepinephrine) minimizes stimulant-like abuse liability and cardiovascular effects, potentially avoiding the need for safety monitoring

Unlike MDMA, TACT833 does not cause long-term depletions of serotonin, linked to mood AEs



Measurement of Serotonin (5-HT) in the rat Prefrontal Cortex at two weeks after repeated high dose exposure

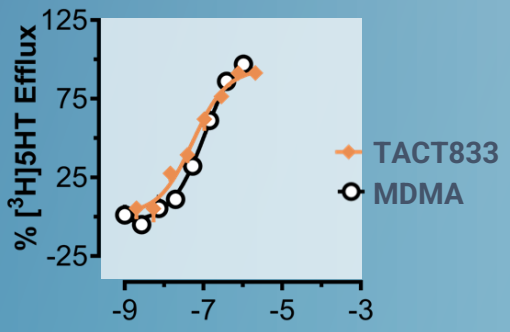
TACT833 has fewer off-target interactions than MDMA

	MDMA	TACT833
5-HT2A (EC50)	6,100	>30,000 nM
5-HT2B (EC50)	2,000	>30,000 nM
5-HT2C (EC50)	831	>30,000 nM
α2A (Ki)	2,532	>30,000 nM
α2B (Ki)	1,785	>30,000 nM
α2C (Ki)	1,123	>30,000 nM
D2 (Ki)	25,200	>30,000 nM
H1 (Ki)	2,138	>30,000 nM
M3 (Ki)	1,851	>30,000 nM
M4 (Ki)	8,245	>30,000 nM

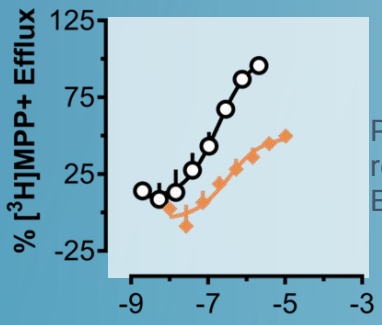
No hERG interactions seen with TACT833 in agonist/antagonist screening or in patch clamp studies

TACT833 limits dopamine release, minimizing the stimulant-like effects seen with MDMA

Same 5-HT release



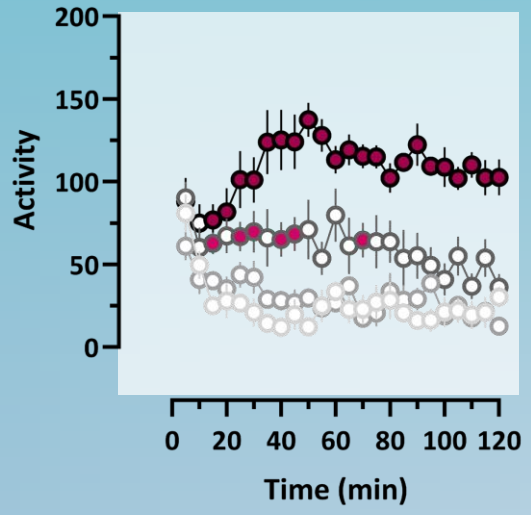
Much less DA release



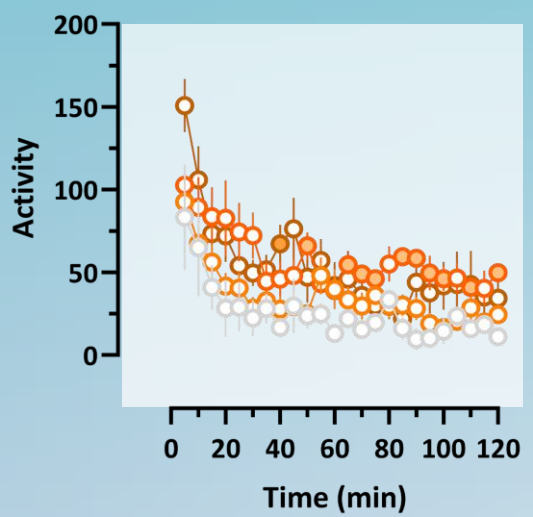
Partial releaser: Emax ~50%

MDMA increases locomotor activity, while TACT833 has more limited effects

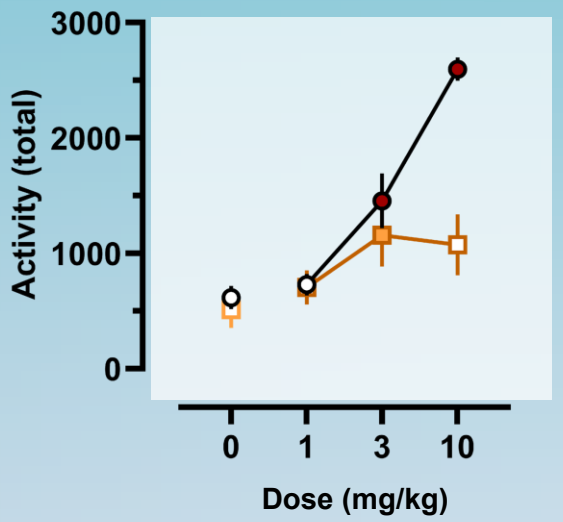
MDMA



TACT833



Comparison



We need reliable animal models of subacutely lowered mood and other unwanted MDMA effects

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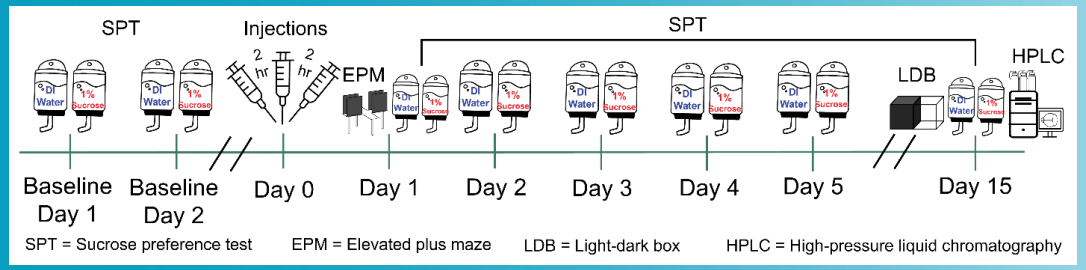
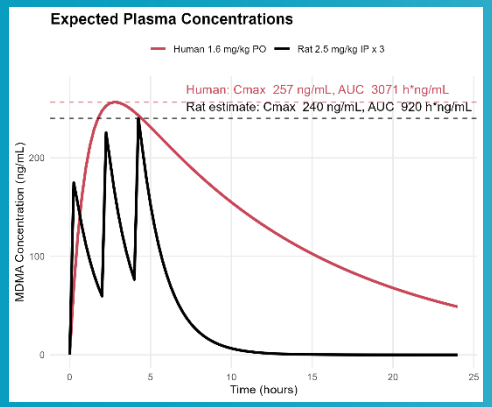
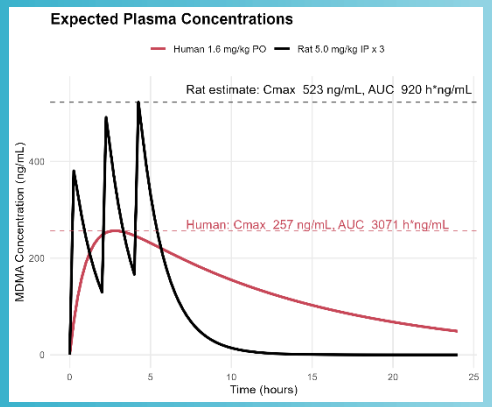
Study design



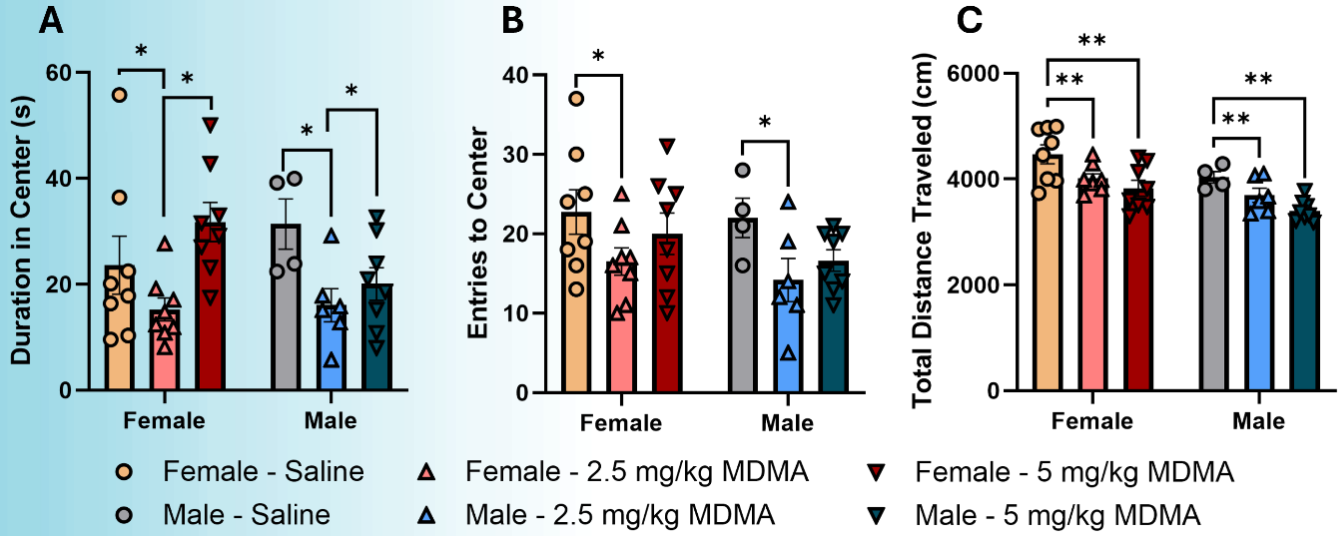
Predicted PK 2.5x3



Predicted PK 5.0x3



(Mac *et al.*, submitted.
Collaboration with Shane Perrine's lab at Wayne State)



One day after treatment, MDMA decreased locomotion and increases anxiety-like behavior in the open field test (OFT) compared to control. (A) Duration in center square of the arena. (B) Number of center square entries. (C) Distance traveled. * = $p < 0.05$. ** = $p < 0.01$. Error bars represent standard error of the mean (SEM).

Not shown: One day after exposure, MDMA decreased locomotion but did not affect anxiety-like behavior in the elevated plus maze (EPM) compared to control. MDMA also did not affect sucrose preference in the five days post-dose.

MDMA is often reported by users to cause both lowered mood (“comedown”) and improved mood (“afterglow”)

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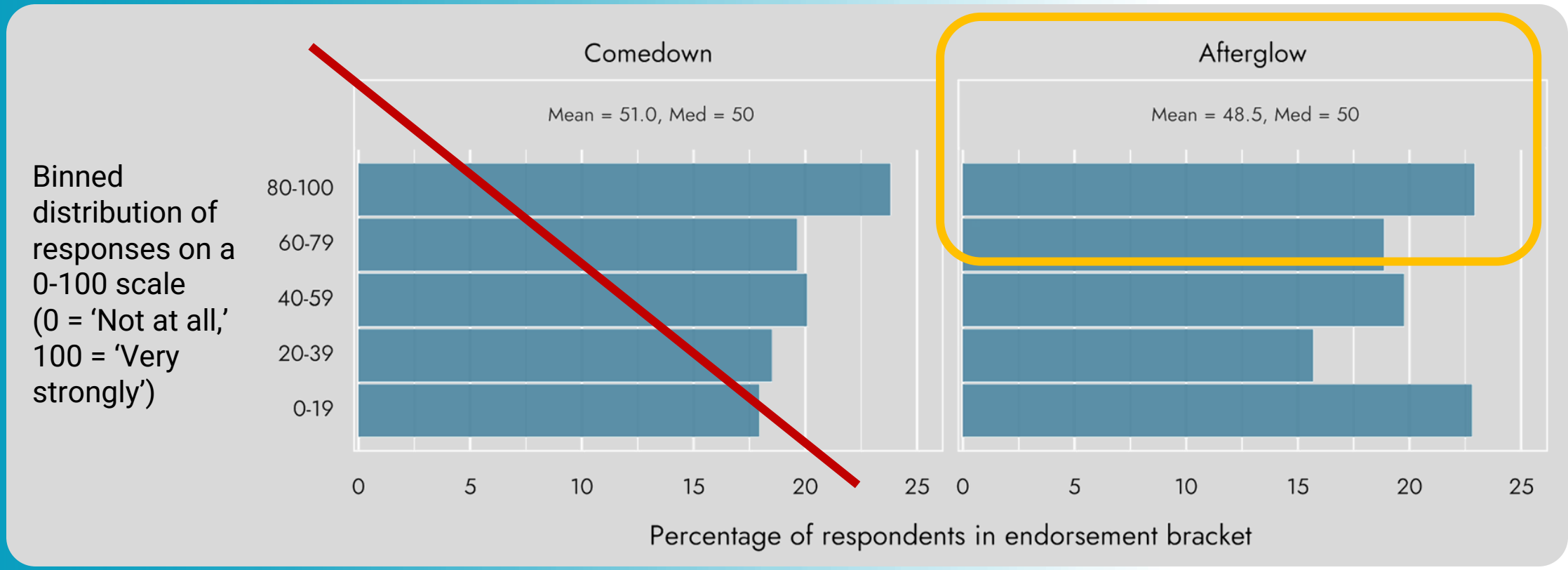

N = 886; “‘Comedown” effects - feeling depressed, irritable, low mood, or very tired/fatigued,’ and “‘Afterglow” effects - feeling peaceful, content, happy, or “cleansed”’. Figure modified from Elsey, J.W., Wuestman, V.A.F. and Fieten, A., 2023. User perceptions of long-term costs and benefits of MDMA use: Findings from a large online sample. Drugs: Education, Prevention and Policy, pp.1-13.

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Thank you

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