ISCTM
International Society for CNS Clinical Trials and Methodology

Craving: Endpoint, Measurement, Indication
(Craving as a Treatment Endpoint: Rationale and Evidence)

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Disclosures

- No COI related to this presentation.

- Grants from Industry
    - Indivior, Camurus, Recordati

Outline

- Current endpoints
- What rationale for craving as an endpoint?
- What evidence?
- Next steps

Endpoints in Clinical Trials for SUD

What's the goal?

- Measure something related to treatment outcome
- Measure something that is beneficial for the patient
- Measure something that is reliable
- Measure something that is meaningful about SUD
  - Predictive/etiological vs. consequential

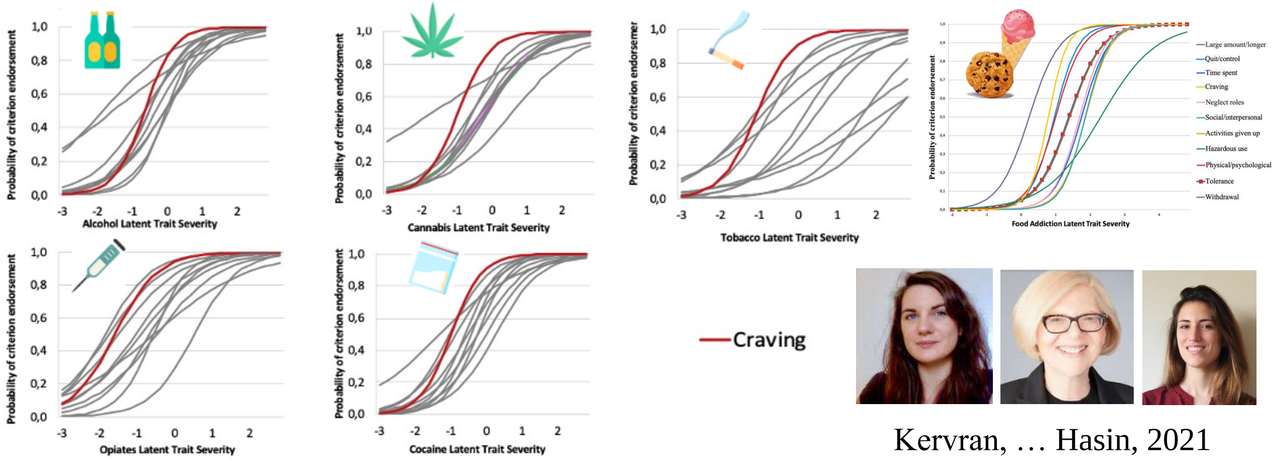
What do we do: Urine tox

- Yes
- Maybe, but …
- Yes, but …
- No

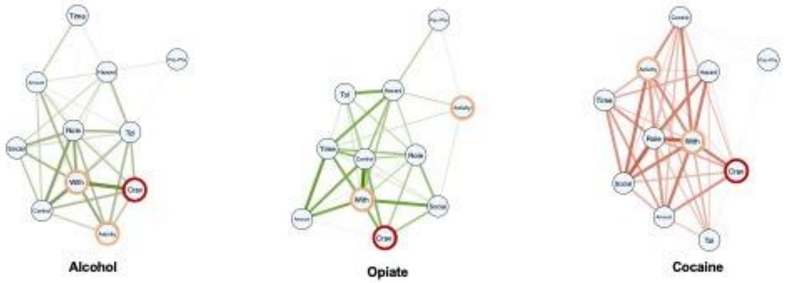
A need for alternative endpoints: Rationale for craving as an endpoint

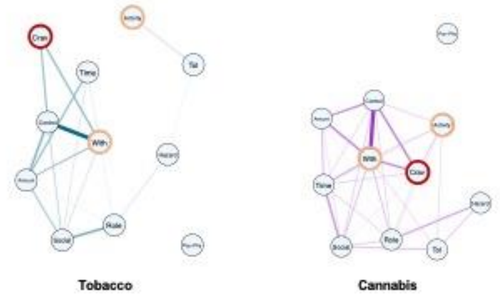
Addiction / Substance Use Disorder
Individual Diagnostic Criteria: how much is craving special?

Item Response Theory Analysis



Kervran, 1997, 2020, 2021





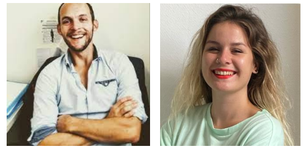
Symptom network of the 11 SUD criteria

Craving most consistently central across substances
Linked to Withdrawal that is sometimes central or peripheral

Amount: Large amount/longer
Control: Quit/control
Time: Time spent
Crav: Craving
Social: Social/interpersonal problem
Role: Neglect role
Activity: Activities given up
Hazard: Hazardous use
Psy–Phy: Psychological/physical problem
Tol: Tolerance
With: Withdrawal

Gauld, Baillet, 2022

Kervran, … Hasin, 2021
Chapron, Kervran, 2023



- DSM 5 Substance Use Disorder

  Significant impairment and …

  - At least 2 over 12 months

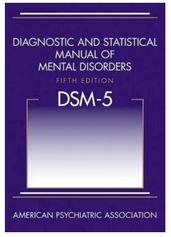
    1) Large amount/longer
    2) Quit/Control
    3) Time spent
    4) Craving
    5) Neglect role
    6) Social/Interpersonal problems
    7) Activities given up
    8) Hazardous use
    9) Psychological/Physical problems
    10) Tolerance*
    11) Withdrawal*

    *does not apply to prescriptions

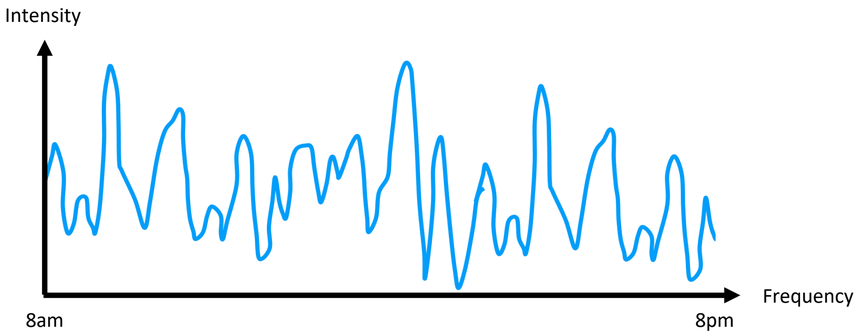
Central

Consequential

APA 2013



Is craving more then a diagnostic criterion?



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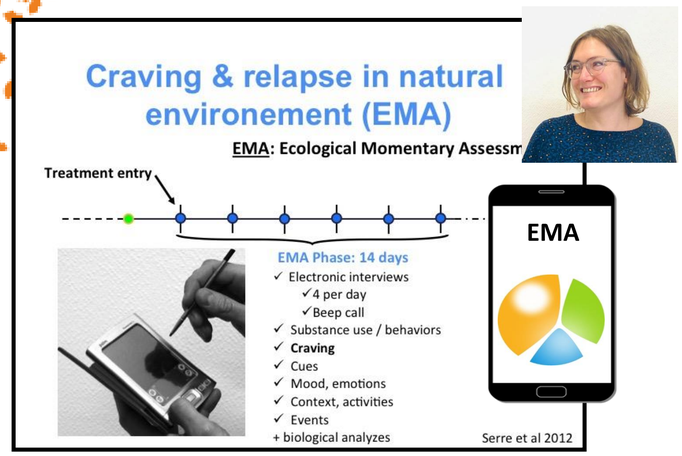
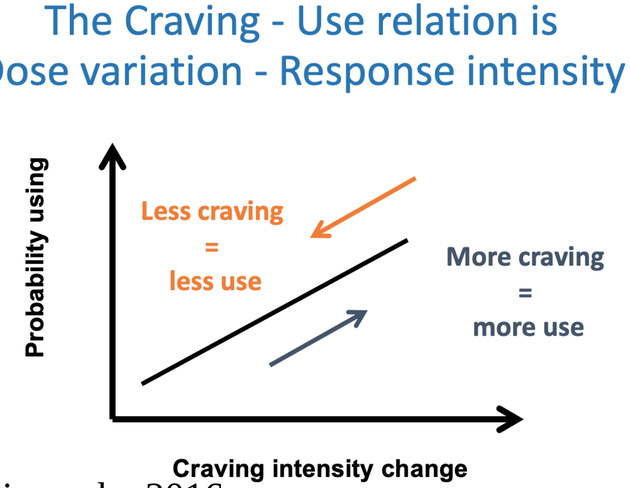
Subjective

Fluctuating

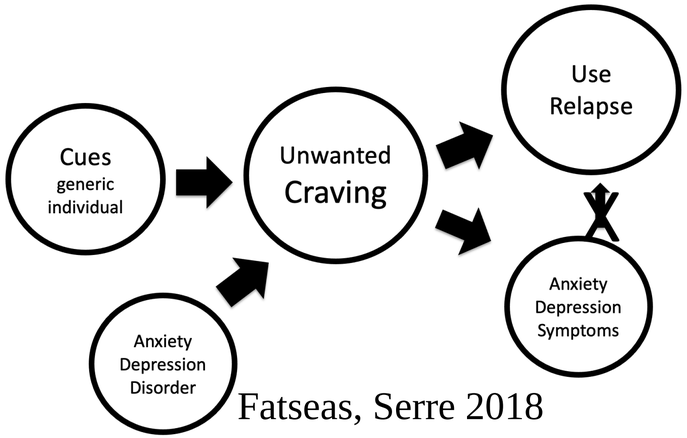
How to access craving? Cues - Craving - Use



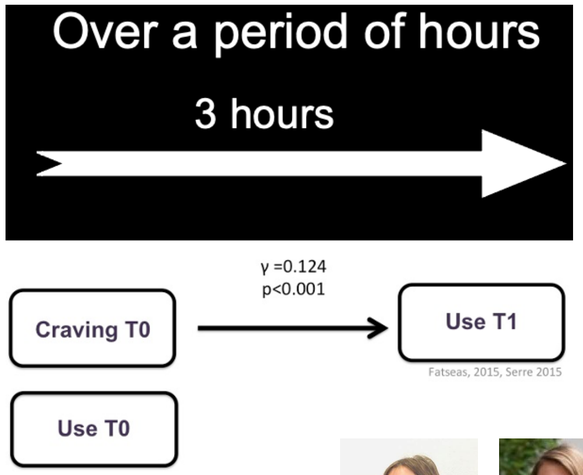
Serre 2012, 2015, 2018



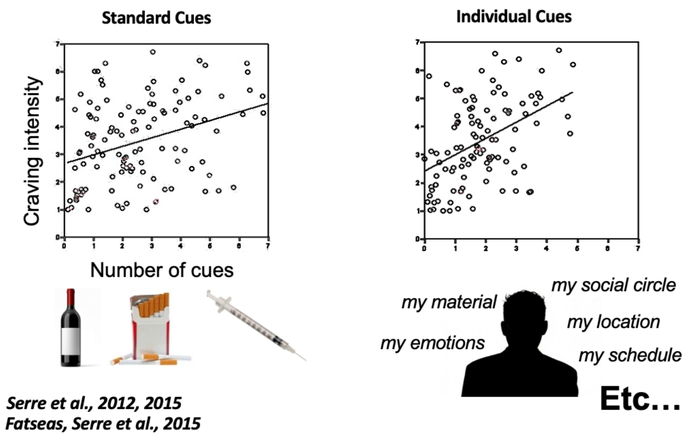
Auriacombe 2016



Fatseas, Serre 2018



Fatseas, Serre 2015



Serre et al., 2012, 2015
Fatseas, Serre et al., 2015

Auriacombe 2018

Craving a prognostic and etiological marker of addiction!

A target for treatment!

JAMA Psychiatry | Original Investigation 2022

Association of Drug Cues and Craving With Drug Use and Relapse
A Systematic Review and Meta-analysis

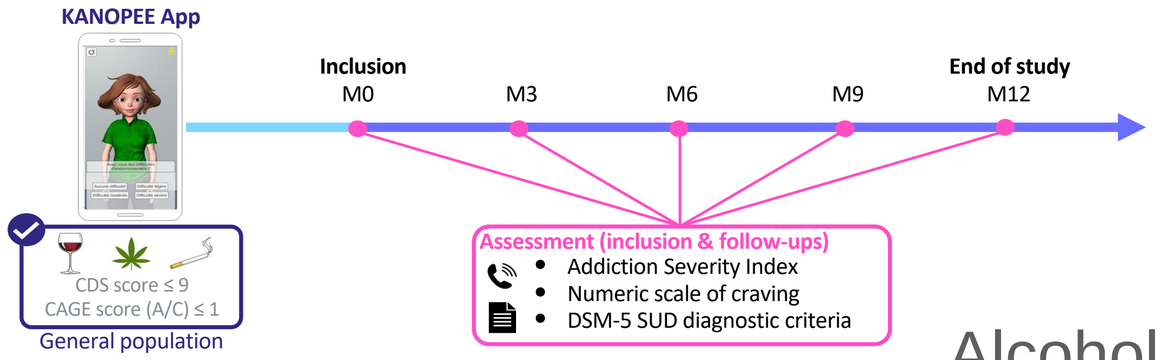
Nilofar Vafaie, MS; Hedy Kober, PhD

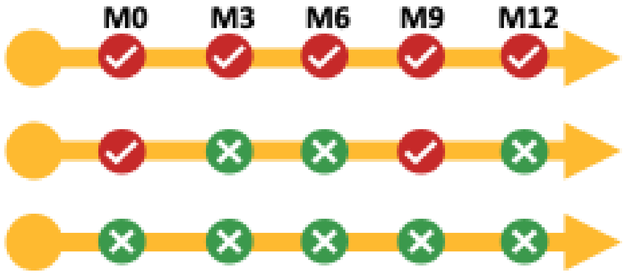
- 237 studies; 656 stat analysis; 51788 participants (21216 confirmed SUD)
- Measures
  - craving: spontaneous, cue reactivity, Human lab, EMA
  - prospective association (hours/days/months/years) with use/relapse
- All craving modalities associated to use/relapse
  - +1 craving predicts use x 2 (OR, 2.05; 95% CI, 1.94-2.15)
  - Most significant results (x3) : craving unidimensional (VAS), EMA, hours, SUD
- Potential causal inference for the role of craving with drug use and relapse
  - Main outcome measure for treatment trials
  - Main outcome measure for individual treatment follow-up

Further rationale for craving as a treatment endpoint

Craving is an early marker of SUD

Craving predicts more diagnostic criteria and more use over 12 Months





C_{always}

$C_{sometimes}$

C_{never}

eceda

Explore Craving for Early Detection of Addiction

Emmanuelle Baillet

2023

Alcohol

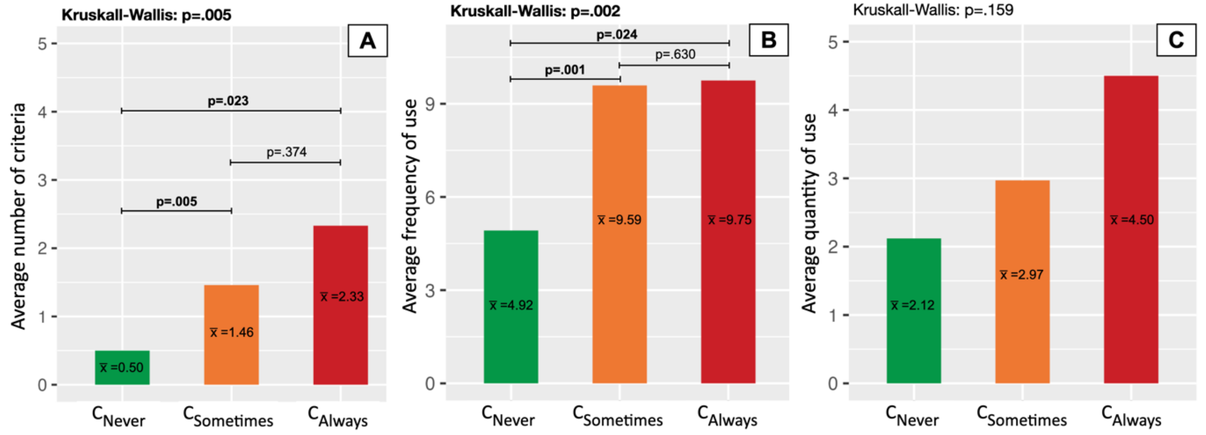
N= 78

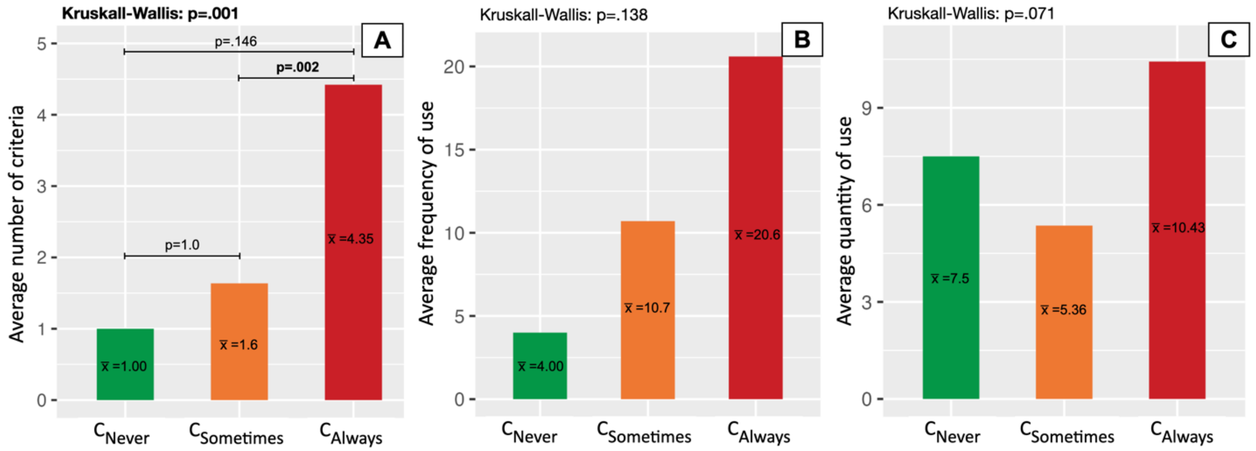
Tobacco

N= 39

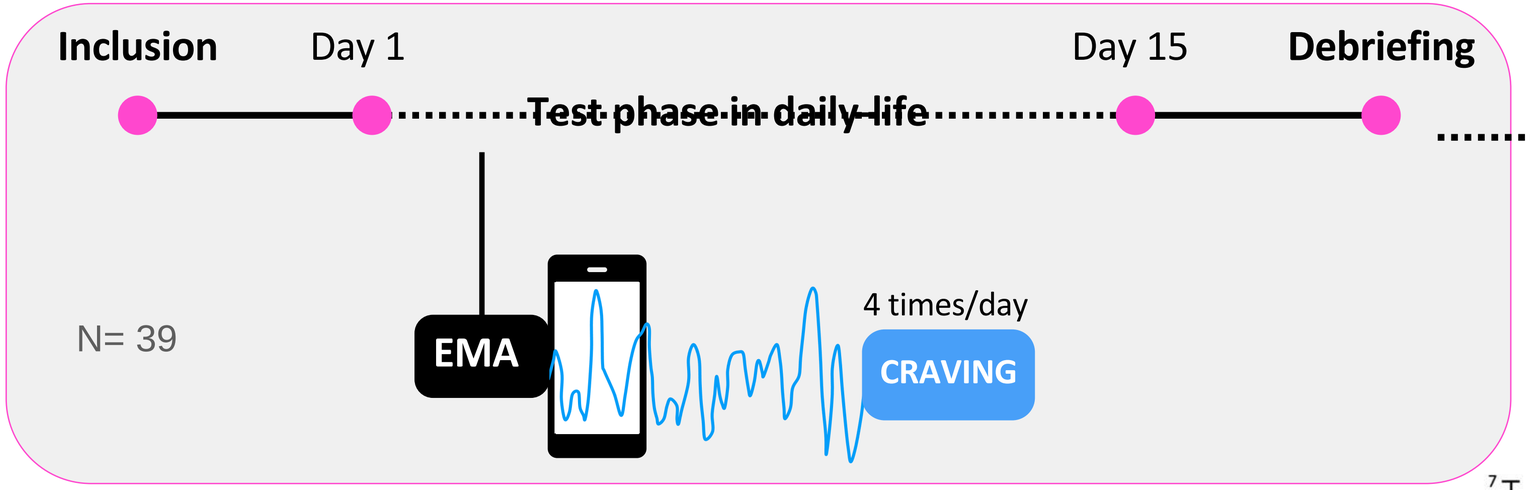
(A) Nb of DSM5 criteria at 12M (except craving)

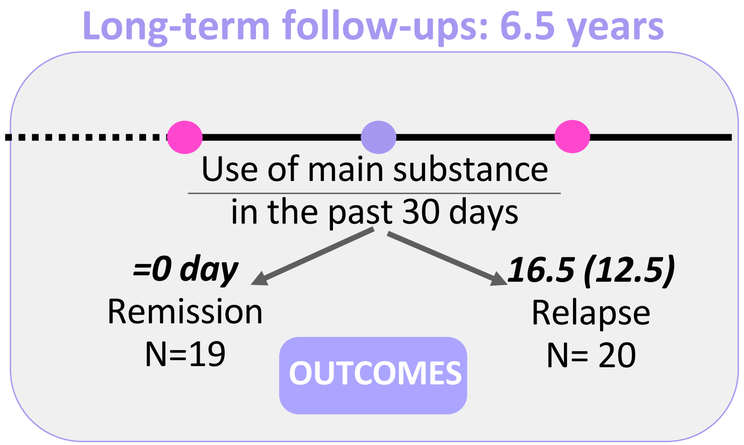
(B) Nb of days use/30 days at 12M



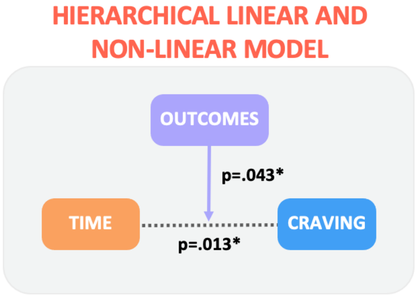


Craving is an early predictor of SUD abstinence/use Outcome

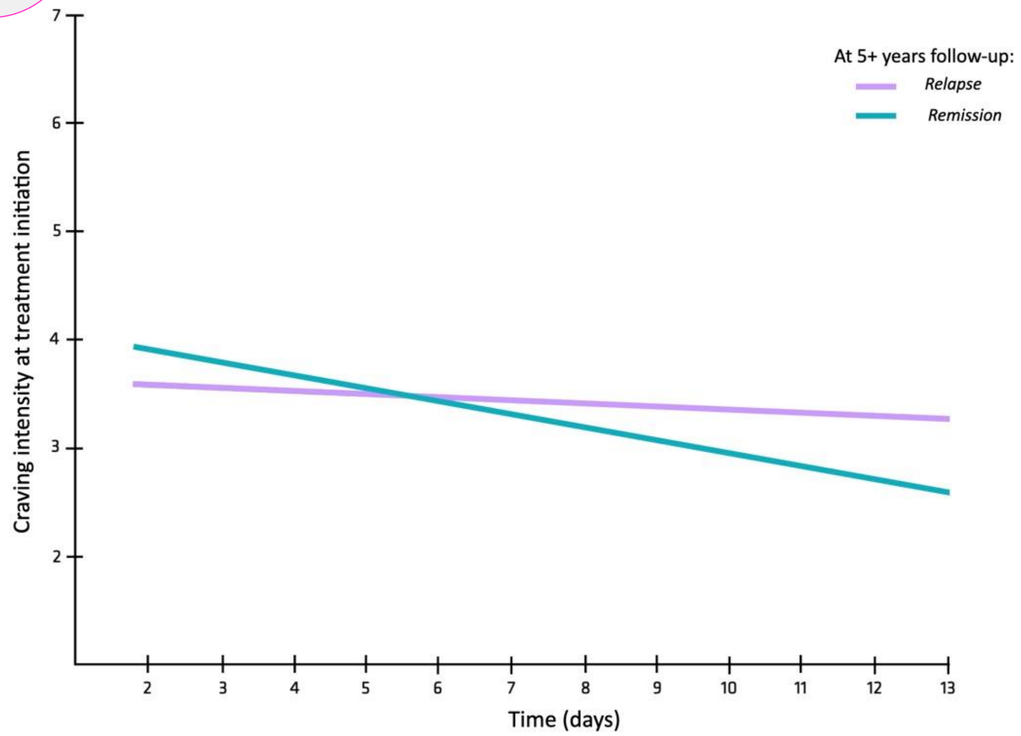




Craving reduction at intake predicts abstinence/use outcome at 5+ years



slower decrease for participants in the Relapse group



Bailet, Serre 2020
Baillet, Auriacombe, … Serre 2024

To sum-up rationale for Craving as a treatment endpoint

- Craving changes overtime predict
  - Use
  - SUD severity
  - Abstinence/use long term
- Should we turn away from searching/waiting for consequences to disappear/show-up?

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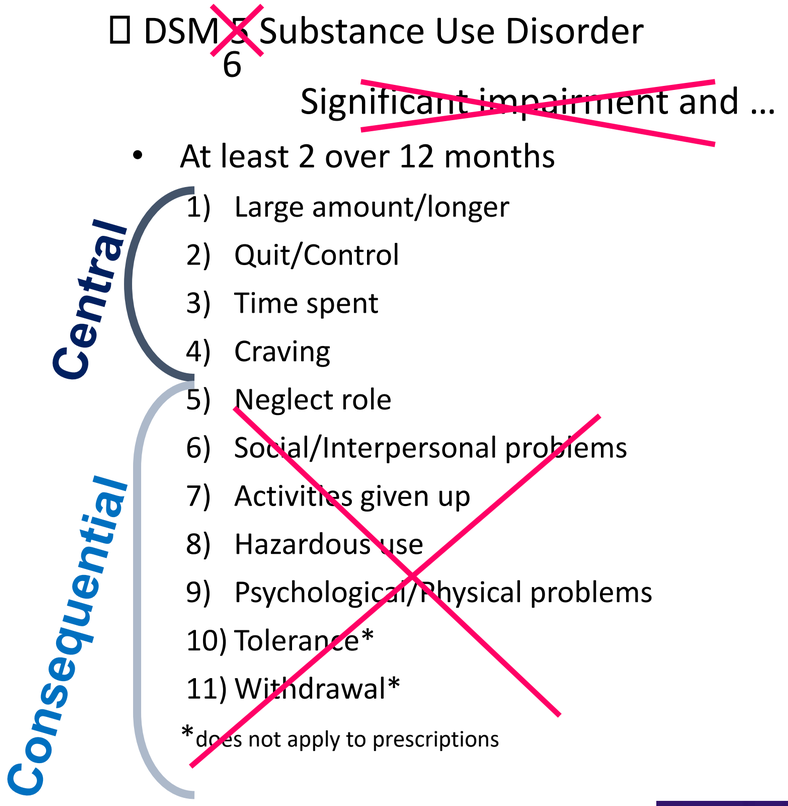
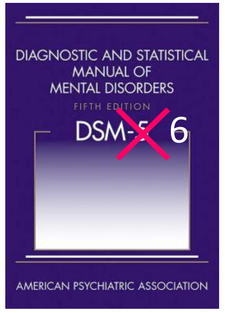


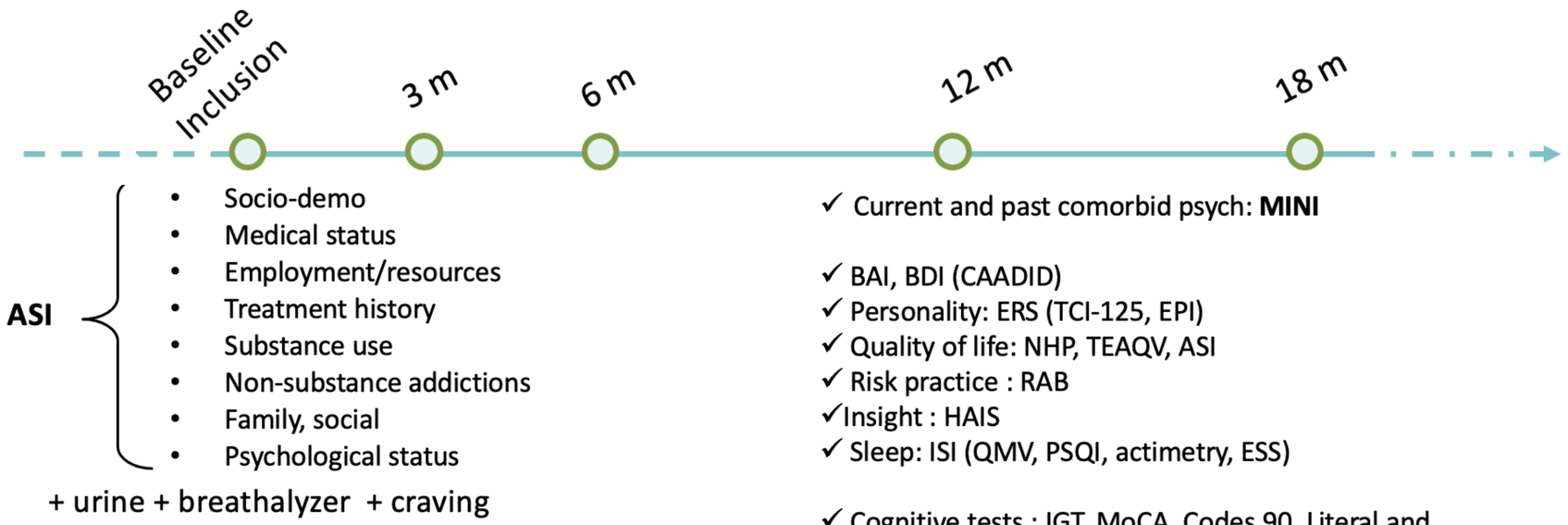
What next?

We have a rationale, what's the evidence?



ADDICTAQUI Addiction Aquitaine Cohort

Prospective multicenter open cohort



How to validate craving as a treatment endpoint?

At one-year+ follow-up

N= 205

43 y.o. (SD=11.3)

33 % women

Craving and Use as Dimensional Outcomes

Craving frequency /30days
(Mean 15/30 days; SD: 13)

Craving frequency /30days
(Mean 12/30 days; SD: 13)

β=0.096, P < .001

Nb of SUD criteria

β=0.041, P < .001

Intensity preocupation about use

β=0.031, P .002

Perceived need for treatment

β=0.463, P < .001

Nb of days of preoccupation

β=0.367, P < .001

Frequency of use /30 days
(Mean 15/30 days; SD: 13)

NS

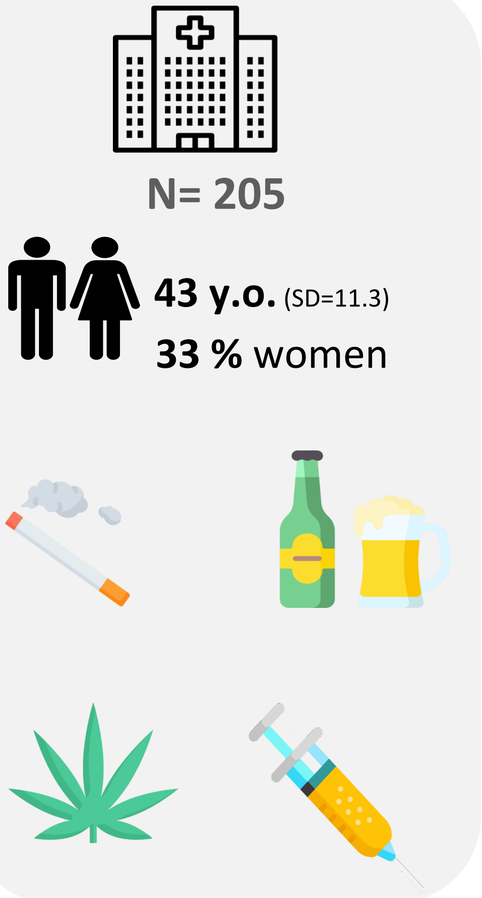
NS

NS

Linear regression

Frequency of use /30 days
(Mean 21/30 days; SD: 11)

At one-year+ follow-up



N= 205

43 y.o. (SD=11.3)

33 % women

No-Use

24% (n=49) success

No-Craving

32% (n=65) success

75% consistent

25% change status

P < .001

Craving and Use as Categorical Outcomes

To conclude and next steps

- Use is easy to measure
  - Associated to some positive outcomes
  - But it is an indirect measure of SUD
- Craving is considered less easy to measure
  - But is better associated to more positive outcomes
  - Is a more direct/proximal measure of SUD
  - Craving should be further explored as a treatment endpoint

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