Subjective Reports in Abuse Liability Assessment

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Domains of Subjective Reports

- Effects experienced
- Similarity to known drugs
- Liking
- Value
- Behavioral disposition

Prioritizing Data Sources

1. Epidemiological Experience
2. Human Laboratory/Behavioral Assessment
3. Animal Laboratory/Behavioral Assessment
4. Neurobiological Mechanisms
5. Chemical Structure

FDA Draft Guidelines, Balster & Bigelow, Drug & Alc Dep, 2003

Abuse Liability Assessment Methods

- Acute Profile and Time Course of Effects
- Drug Discrimination
- Drug Self-Administration
- Physical Dependence Assessment

Principles of Human Lab Assessment

- Test in experienced abusers
- Test a broad dose range
- Test high doses
- Include a negative comparator
- Include a positive comparator
- Assess time course

FDA Draft Guidelines, Balster & Bigelow, Drug & Alc Dep, 2003

Animal-Human Agreement

Human Abuse Risk	Animal Drug Self-administration: No	Animal Drug Self-administration: Yes
No	XXXXXXXX XXXXXXXX XXXX	XX
Yes	XX	XXXXXXXX XXXXXXXX XXXX

(Schematic Only; based on Griffiths and Balster, Clinical Pharmacology and Therapeutics, 1979)

Whose Subjective Reports?

- Experienced drug abusers are widely accepted as the appropriate and most sensitive clinical population for assessing abuse liability.

- "Many of these persons are pharmacological sophisticates, i. e., they can not only accurately distinguish between a potent drug and a placebo but can identify certain drugs with amazing accuracy…."
- "In the normal subjects…The drug most frequently associated with a dysphoric state was morphine."

(Lasagna, von Felsinger, Beecher, JAMA, 1955)

Domains of Subjective Reports

- Effects experienced
- Similarity to other/known drugs
- Liking
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Subjective Reports of Drug Effects

- Addiction Research Center Inventory (ARCI)
- Symptom reports
- Mood scales
- Adjective rating scales
- Visual analog scales

Addiction Research Center Inventory (ARCI)

- Historical prominence
- Empirically developed and validated in drug abusers
- Statements with True/False answer options
- Multiple scales
  - MBG -- “Euphoria” -- Morphine Benzedrine Group
  - PCAG -- “Sedative” -- Pentbarb Chlorpromazine Alc Group
  - LSD -- “Dysphoria” -- Lysergic Acid

ARCI MBG "Euphoria" Scale Example Items

- I feel so good that I know other people can tell it.
- Things around me seem more pleasing than usual.
- I feel a very pleasant emptiness.
- I feel as if something pleasant had just happened to me.
- I would be happy all the time if I felt as I do now.

Adjective Rating Scale Example Items

- Flushing
- Skin itchy
- Sweating
- Turning of stomach
- Nodding
- Relaxed
- Coasting or spaced out
- Talkative
- Heavy or sluggish feeling
- Dry mouth
- Sleepy
- Carefree
- Good mood
- Tingling

Common Visual Analog Scales

- Any Effects
- High
- Liking
- Good Effects
- Sick
- Bad Effects

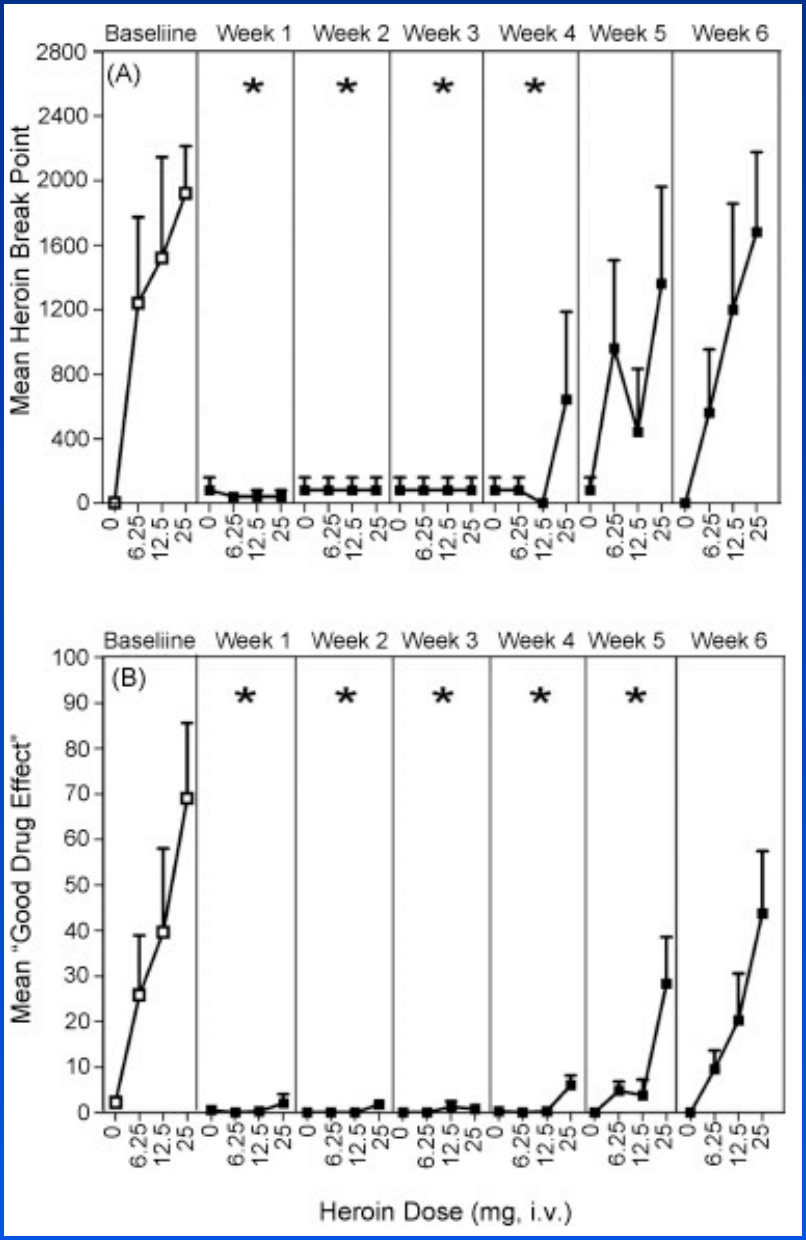
VAS & ARCI

Illustrative partial data and analyses

Outcome Measure	*p*	PCB 0	OXY 10	OXY 20	OXY 40
Visual analogs					
High	0.002	1.1	23.3	31.3	43.8
Drug effect	<0.0001	1.0	22.9	34.3	50.2
Good effect	<0.0001	1.0	27.8	37	59.4
Like	<0.0001	1.1	29.2	37.8	53
Desire op	0.025	50.3	34.4	37.7	48.8
ARCI					
PCAG	0.036	3.7	5.2	5.9	6.2
AMPH	0.024	2.1	2.4	3.7	4.6
MBG	0.041	3.0	3.6	4.9	7.6

Walsh, Nuzzo, Lofwall and Holtman
Drug and Alcohol Dependence (2008)

p-values are based on overall condition effect in analyses including hydrocodone & hydromorphone.



Heroin X Naltrexone Depot

Subjective reports of heroin's "Good Effects" and heroin self-administration are both similarly suppressed by long-acting naltrexone depot.

Sullivan, S.K. Vosburg and S.D. Comer
Psychopharmacology (2006).

Subjective Reports of Similarity

- Is it “dope?”
- Drug class identification
  - Placebo, opiate, sedative, stimulant, etc.
- Is it similar to [drug X -- heroin, oxycodone, etc.]?

Weaknesses of Effect and Similarity Assessments

- Based on similarity to known drugs
- May be insensitive to novel drugs
- Indices reflecting liking, value or behavioral disposition may be more sensitive and have broader applicability

Subjective Reports of Liking

- Do you like the drug effect?

Yes/ No

Not at all - A little -- Moderately - A good bit - A lot

Not at all Extremely

Subjective Reports of Value

- Street value in dollars
- How much would you pay?
- Drug versus money preference

Subjective Reports of Behavioral Disposition

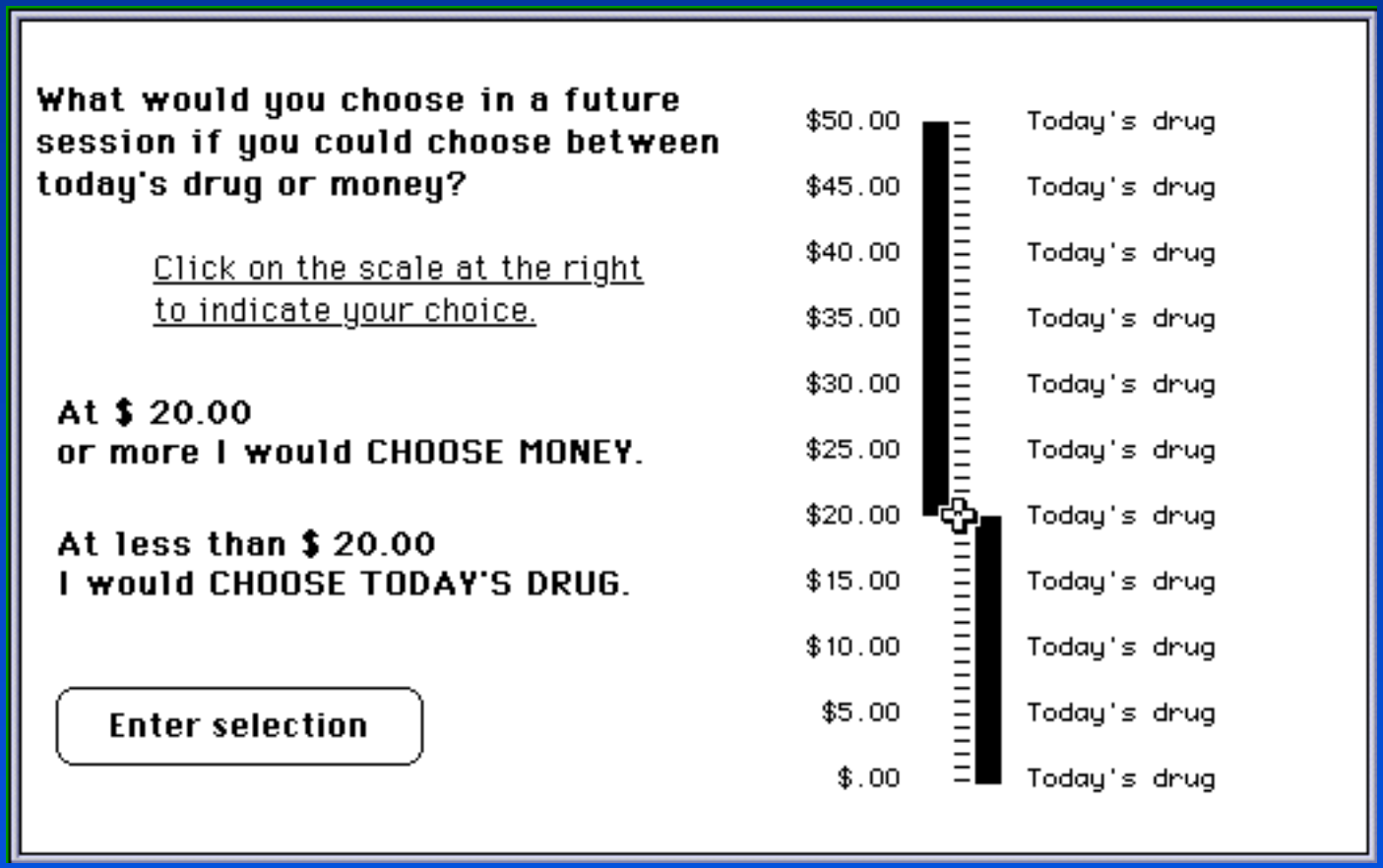
- Willingness to take again
- Desire to take again
- Drug versus money preference

Multiple Choice Procedure Questionnaire

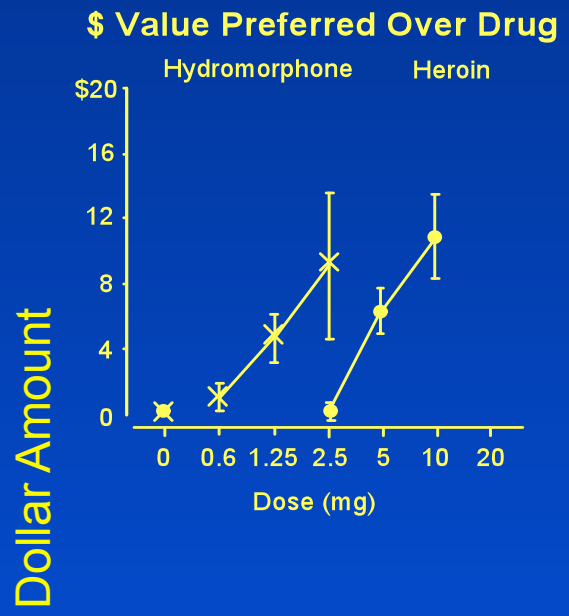
For each pair would you rather have that amount of money or receive today's drug again?

$20	Drug	….	….
$18	Drug	$1.50	Drug
$16	Drug	$1.00	Drug
$14	Drug	$0.50	Drug
$12	Drug	$0.00	Drug
$10	Drug	-$0.50	Drug
$8	Drug	-$1.00	Drug
$6	Drug	-$1.50	Drug
….	….	….	….

Drug versus Money Choice Question



Heroin versus Hydromorphone, i.v.



Applicability to Newer Formulations

- Uncertain and/or variable applicability
- Depends on mechanism of the new formulation
- Developed for assessing chemical entities
- New formulations may target a niche problem
- Method adaptations may be needed

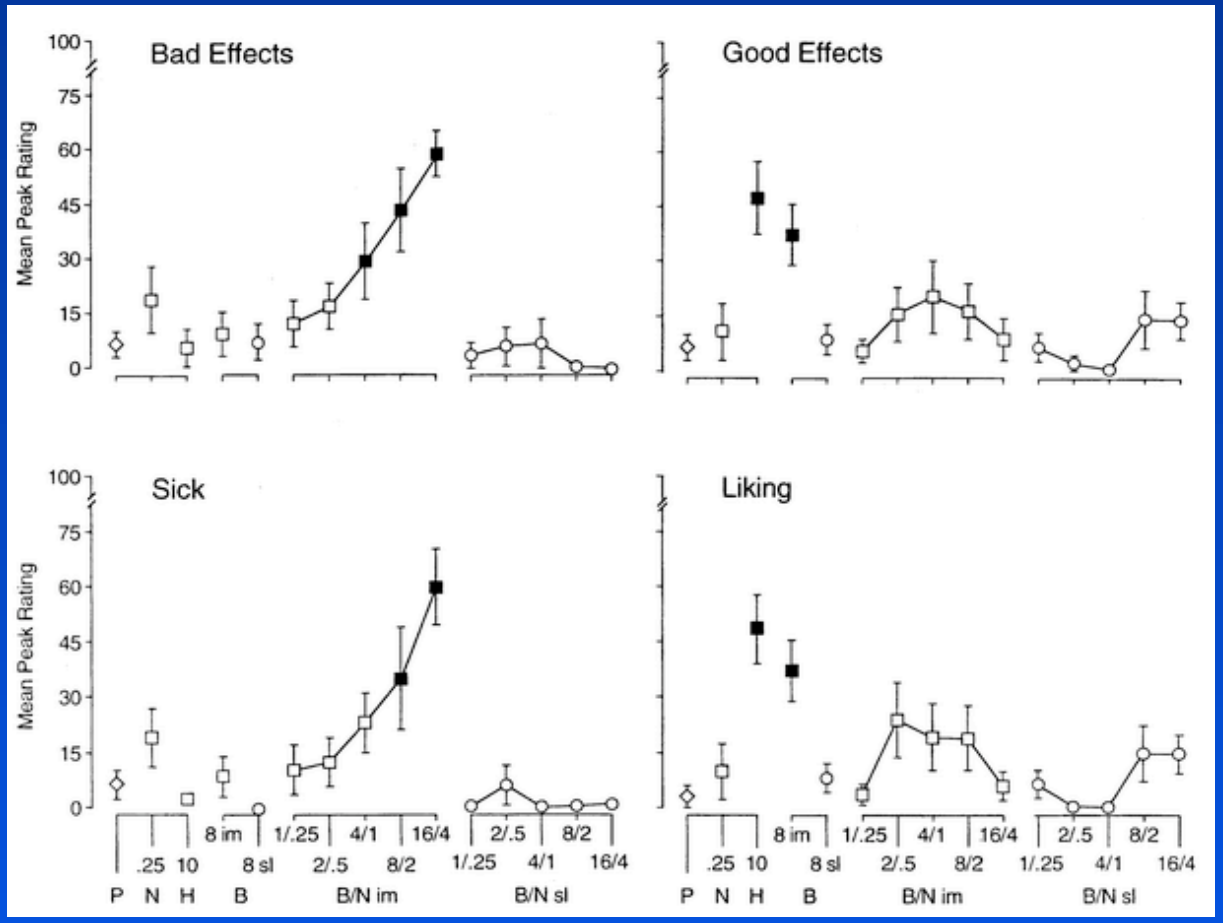
Examples of "Engineered" Newer Formulations

- OxyContin -- sustained release oxycodone
- Vyvanse -- enzymatically released amphetamine
- Suboxone -- buprenorphine plus naloxone
- Embeda -- sequestered naltrexone
- Remoxy -- non-crushable SR oxycodone

Suboxone Engineering

- Buprenorphine-Naloxone combination
- Sublingual administration
- Relies on poor sublingual delivery of naloxone
- Injection use (misuse) delivers full naloxone
- Precipitates withdrawal in dependent Ss

Buprenorphine/Naloxone (Suboxone) Route of Administration Effects in Opioid-Dependent Subjects



Stoller et al, Psychopharmacology, 2001

Strengths, Weaknesses and Applicability

- Excellent for addressing pharmacology
- Doesn’t address clinical or epidemiological context
- Abuse liability is a function of both
- Not all questions are best answered by drug users
- Not all questions require experiments to answer

Is There One Best Assessment?

In There One Best Assessment?

- Probably not
- Liking, Value, and Behavioral Disposition are leading candidates

Conclusions

- Many useful subjective report indices
- Convergence of multiple indices is most persuasive
- Indices of liking, value, and behavioral disposition appear most useful
- Applicability to abuse-deterrent technologies is a work in progress

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