A HISTORICAL PERSPECTIVE ON HUMAN ABUSE LIABILITY STUDIES

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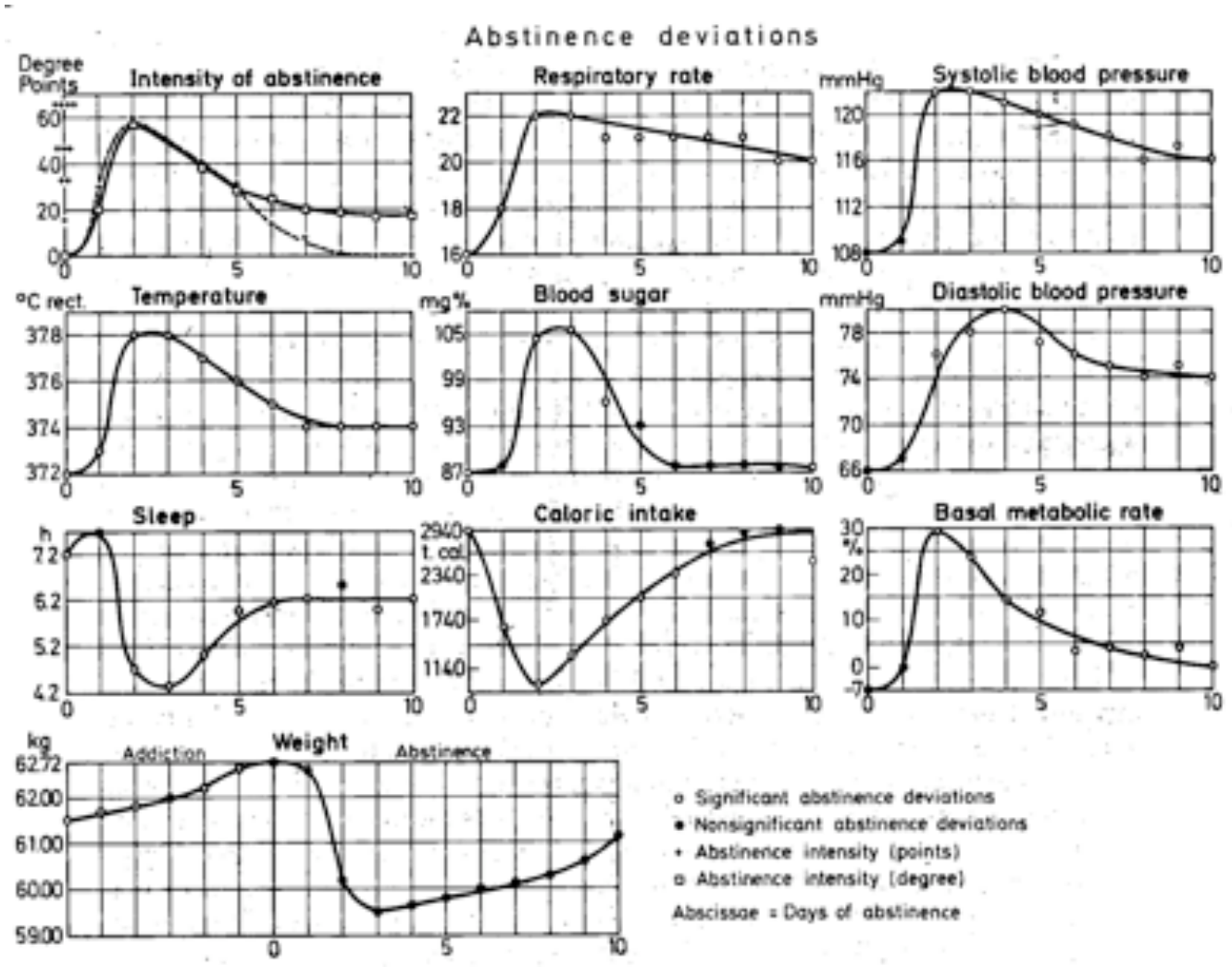
Origin of methods

- Modify morphine molecule
- Develop a selective analgesic lacking abuse potential
- Reduce public health and social problems associated with diversion of opiates

Clifton Himmelsbach

- Described and quantified the withdrawal syndrome
- Cross substitution of opiates
- Suppression and substitution studies
- Addiction potential described in terms of substitution studies

Untreated Opiate Withdrawal



Himmelsbach Score

- Behavior and physiological changes
- Ignored subjective responses

Changes

- Meperidine and methadone
- Non-opiate structure
- Control based on pharmacology
  - Addiction sustaining or addiction forming
- Principle of pharmacologic equivalence

Subjective effects

- Henry Beecher and subjective response to measure relief of pathologic pain
- Method
  - Placebo control
  - Cross-over
  - Quantitative measures
  - Dose response
  - Relative potency to morphine
- Study of subjective effects
  - Alterations in mood, thinking, feeling and perception

Subjective effects and abuse potential

- Harris Isbell
  - Single doses of morphine and placebo given double blind to volunteers with history of opiate dependence
    - Discriminate morphine from placebo
    - Discriminate among doses
    - Discriminate morphine from other drugs
    - Similar symptoms and signs
  - Introduced model from Beecher
    - Cross-over, double-blind, single dose, placebo
    - Pupillary constriction as measure of physiological response

Single Dose Questionnaires

- Subjects
  - Feel drug?
  - Identify drug
  - Symptoms
  - Liking Scale
- Observers
  - Drug effect
  - Identify drug
  - Signs
  - Liking Scale

Addiction Research Center Inventory ARCI

- Transitory changes in mood, thinking, feeling and perception
  - Drug induced
  - Withdrawal syndrome
  - Psychiatric syndromes
- 550 items
  - Measure state rather than trait
  - Yes or no response
  - Factorial analysis of patterns of responses under various conditions to derive scales

Usefulness of ARCI –MBG Scale

- Measures euphoria associated with reinforcing properties
- Liking is not specific
- Example
  - The alertness produced by modafanil is liked
  - There is no significant response on ARCI scales

Introduction of pre-clinical models

- Monkey model of physical dependence (1950's)
- Self administration (1960's)
- Drug discrimination
- Do not replace human studies for final decisions of abuse potential

Agonist Antagonist Opioids Kappa agonists

- Behavior and physiologic al response resemble morphine
- Subjects discriminate from morphine
- Little or nor liking
- Withdrawal signs and symptoms without drug seeking
- Precipitate withdrawal in morphine dependent subjects
- ARCI scales distinguished morphine from nalorphine
  - MBG Elevated with morphine but not nalorphine (Euphoria)
  - PCAG elevated with nalorphine but not morphine (Apathetic Sedation)
  - LSD Specific elevated with nalorphine but not morphine (Somatic discomfort)

Examples of single dose studies for reinforcing effects (euphoria)

Comparison of heroin, morphine, methadone and placebo intravenoulsly

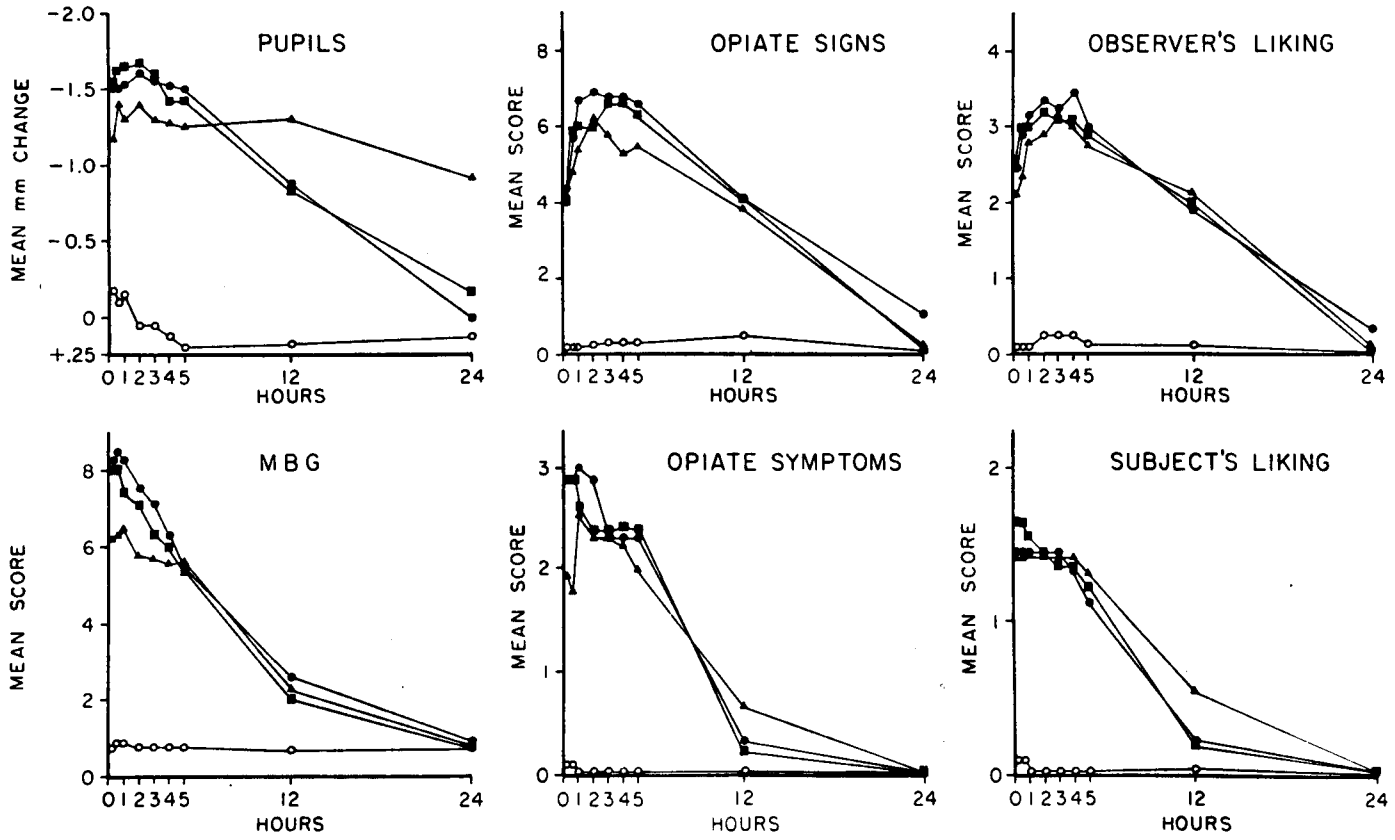


Fig. 1. Time action curves for changes in pupillary diameter, opiate signs and observers' liking scores, MBG, opiate symptom and subjects' liking scores for the comparison of intravenously administered heroin, 10 mg/70 kg (■——■); morphine, 20 mg/70 kg (●——●); methadone, 20 mg/70 kg (▲——▲); and placebo (○——○). For pupils, each point represents the mean change in pupil diameter from pre-drug controls. For signs and symptoms, liking and MBG scales, each point represents the mean response.

Comparison of heroin, morphine, methadone and placebo intravenously

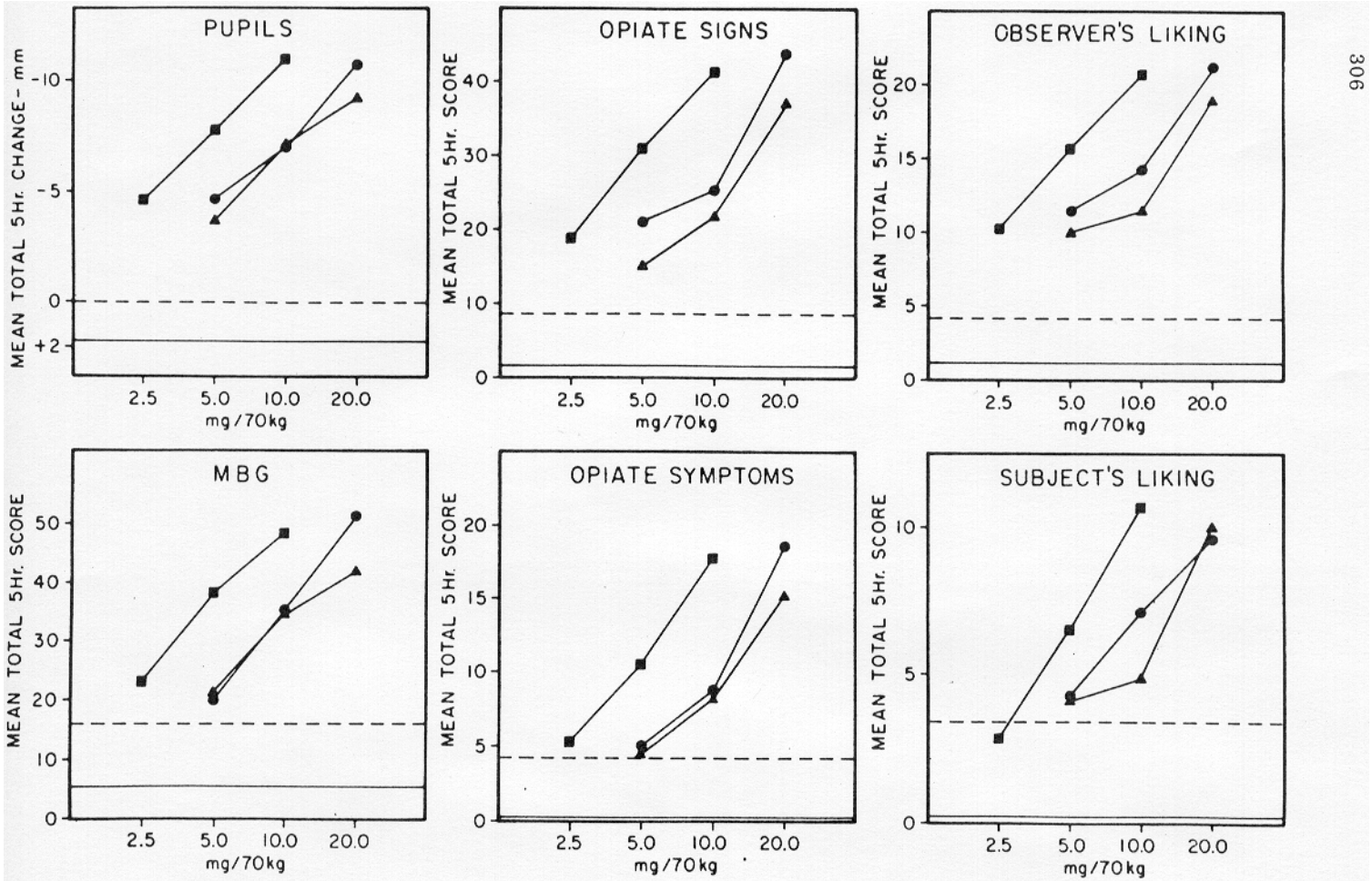


Fig. 2. Dose effect curves using 5-h total scores for pupillary change, opiate signs, observers' liking, MBG, opiate symptom and subjects' liking scores for the comparison of intravenously administered heroin, morphine and placebo. Morphine (M) (●——●); methadone (ME) (▲——▲); heroin (H) (■——■); placebo (——); 95% confidence limits/mean placebo response (— — —).

Relative potencies

- Heroin twice as potent as morphine
- Methadone equally potent to morphine
- No selectivity
- Similar potencies
  - Relief of pathologic pain
  - Effects in opiate abusers
    - Subjective scales and pupils
    - Withdrawal suppression
    - Direct addiction

relative potency differences but no selectivity and opiate like abuse potential

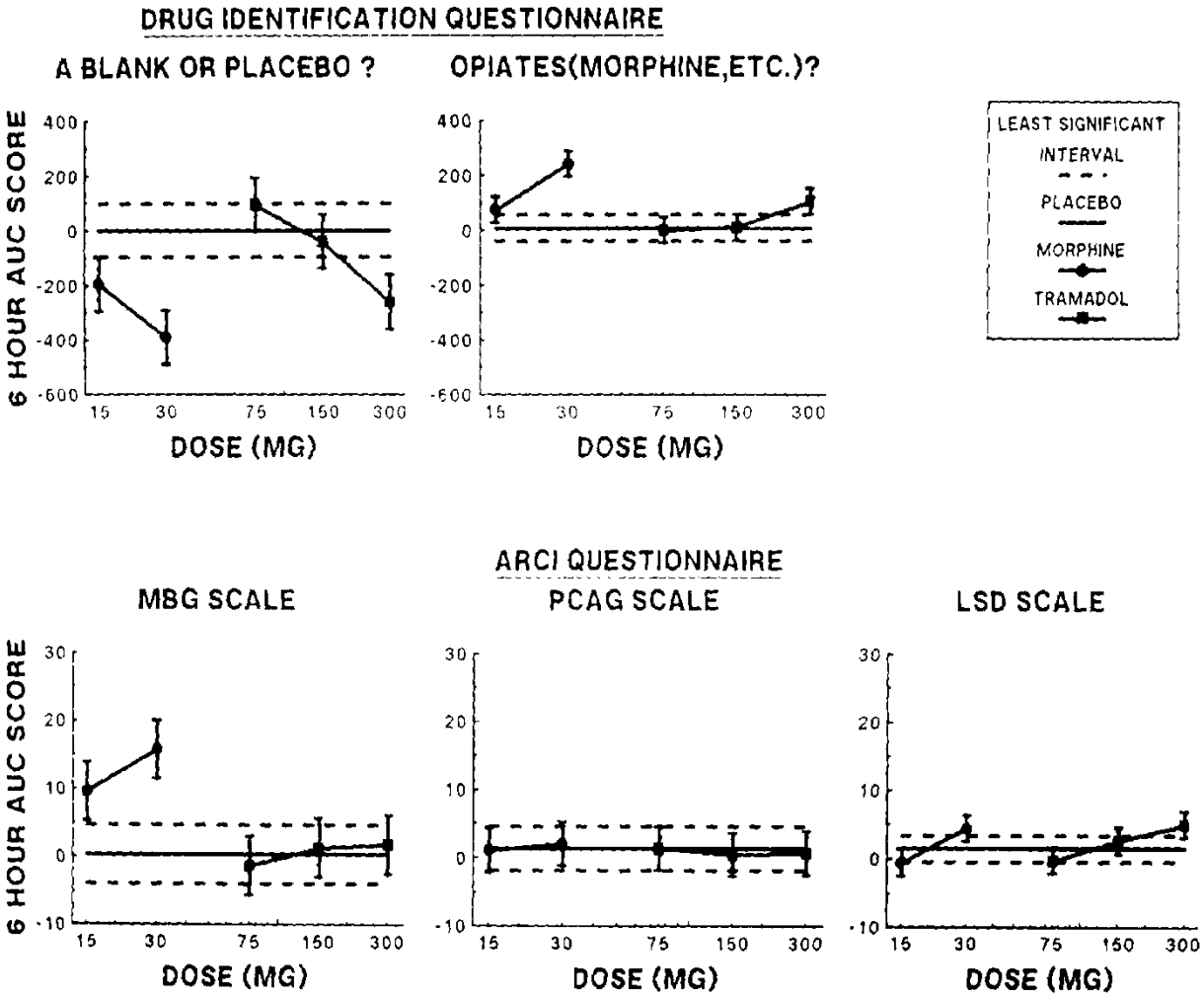
- MS injected 10 mg
- MS oral 60 mg
- codeine injected 100 mg
- codeine oral 210 mg
- hydromorphone injected 1.5 mg
- oxycodone injected 10 mg
- hydrocodone injected 10 mg
- hydromorphone oral 4.5 mg
- oxycodone oral 20 mg
- hydrocodone oral 20 mg(??)
- d-propoxyphene oral 350 mg

Abuse potential predictions of opioids validated from incidence of abuse

Predictions of low abuse potential

- Selectivity
  - dextromethorphan
  - tramadol
  - kappa agonists
  - partial agonists
- Solubility
  - diphenoxylate

Tramadol IM Study



Single Dose Procedures applied to other classes of drugs after Controlled Substances Act

- sedative hypnotics
- amphetamines
- hallucinogens
- cannabinoids
- nicotine

Preparations to lower relative abuse potential

- solubility
- add substance to produce disliking
- Prodrug
- Choice tests useful
  - First show dysphoria or lack of euphoria
  - Demonstrate through choice that behavior is altered

What is measured?

- Lawrence Kolb, Sr
- Positive versus negative euphoria
- Abuse potential studies in substance abusers measure positive euphoria
- zomepirac (NSAID)
  - Relieved cancer pain as effectively as morphine
  - Patients reported as euphoric with relief of pain
  - Dysphoric in opiate abusers

Abuse potential

- Ability to create public health and social problems
- More than reinforcing effects