

Toward optimal use of buprenorphine and methadone in treatment of heroin dependence

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What is the optimal use of methadone and buprenorphine in unselected heroin addicts?

- Buprenorphine – partial agonist

- Pros

- lower abuse liability
- better safety
- deaths / 1000 users

- methadone: 0.7
- buprenorphine: 0.2

- Cons

- lower efficacy (?)

- Methadone – full agonist

- Pros

- higher potency
- more effective anti-craving action
- best documented clinical efficacy

- Cons

- respiratory suppression
- risk for overdose death
- requires higher degree of control

Buprenorphine vs methadone maintenance?

(Mattick et al, Addiction 2003)

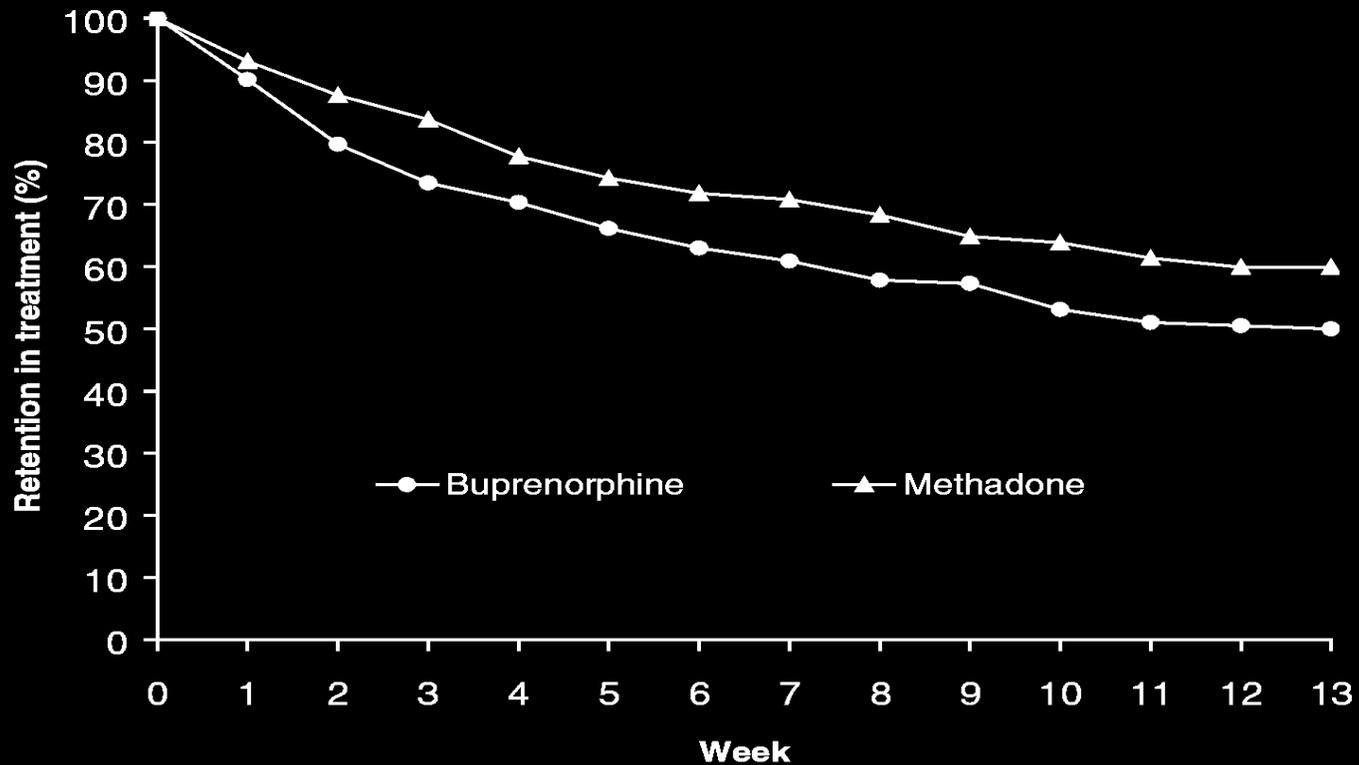
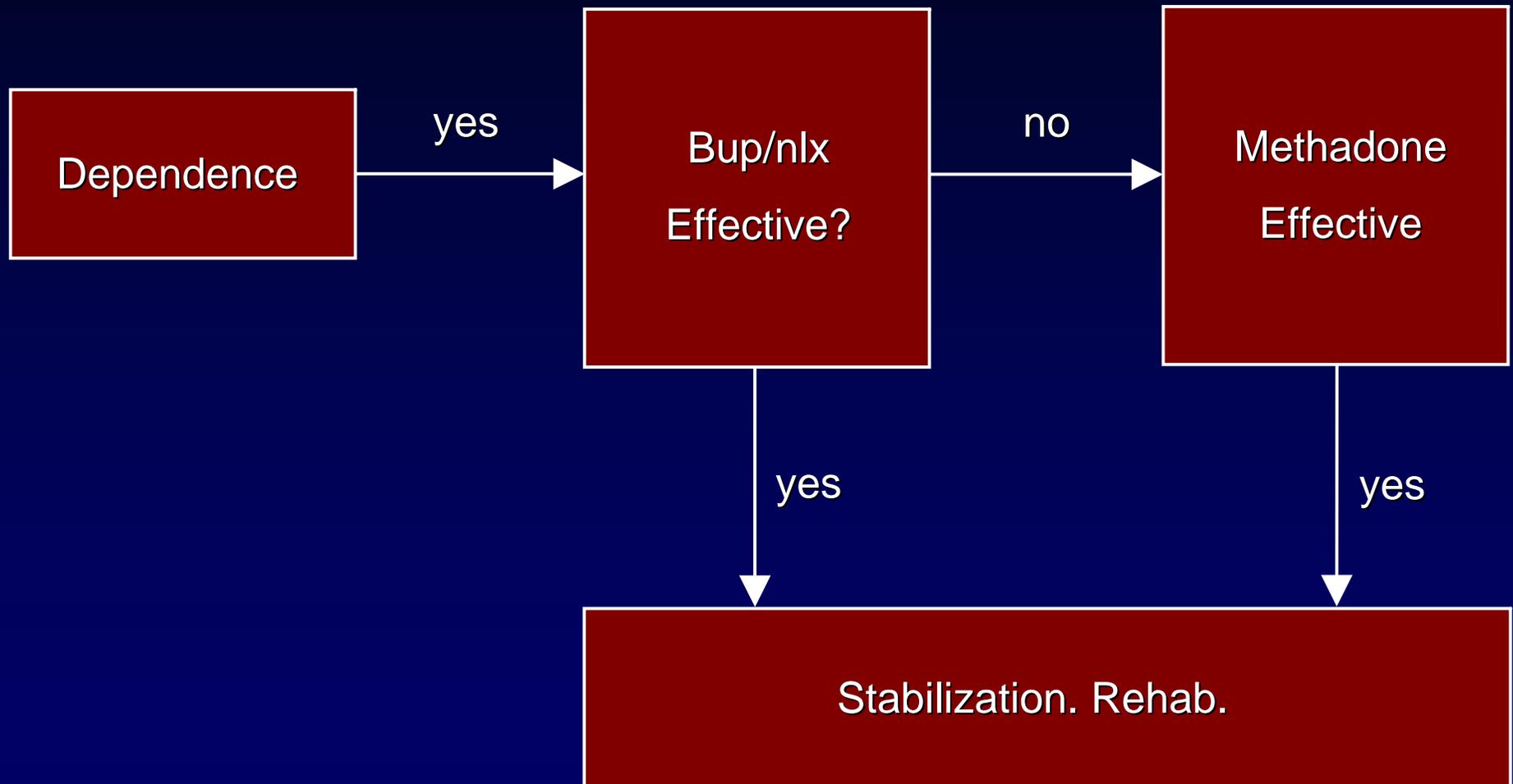


Figure 2 Retention in treatment

Or:
Toward optimal use of both



The Swedish 3G study: objectives and research questions

- Can a stepped strategy be developed that
 - capitalizes on the safety advantages of buprenorphine
 - adaptively shifts to methadone only if needed
 - overall does as well as optimal methadone maintenance
- Can we identify predictors of the need for methadone?

An unselected group of heroin addicts

- Broad inclusion criteria
 - 1 year DSM IV heroin dependence (self-reported)
 - minimum 20 years of age
 - acceptance of treatment principles
- Minimalistic exclusion criteria
 - Dementia or psychosis (unable to provide consent)
 - Unstable psychiatric or medical condition
 - Anti-epileptics, disulfiram or antiretroviral treatment
 - Pregnancy / nursing
- 86% of screened subjects were included!

Design

- Randomized controlled trial
- Stockholm (2/3) and Uppsala (1/3)
- 96 heroin-dependent patients
- Double-blind first month, single-blind thereafter
- Randomised to
 - MMT: best practice methadone maintenance, or
 - STEP: bup/nlx; switch to methadone only if needed

One month uniform induction, followed by five months of flexible dosing based on clinical criteria

- Dose increase if

- patient reported craving or withdrawal at nadir, or
- urine positive for illicit drugs

and patient

- had not missed more than 2 doses during the interval, and
- did not show signs of sedation etc

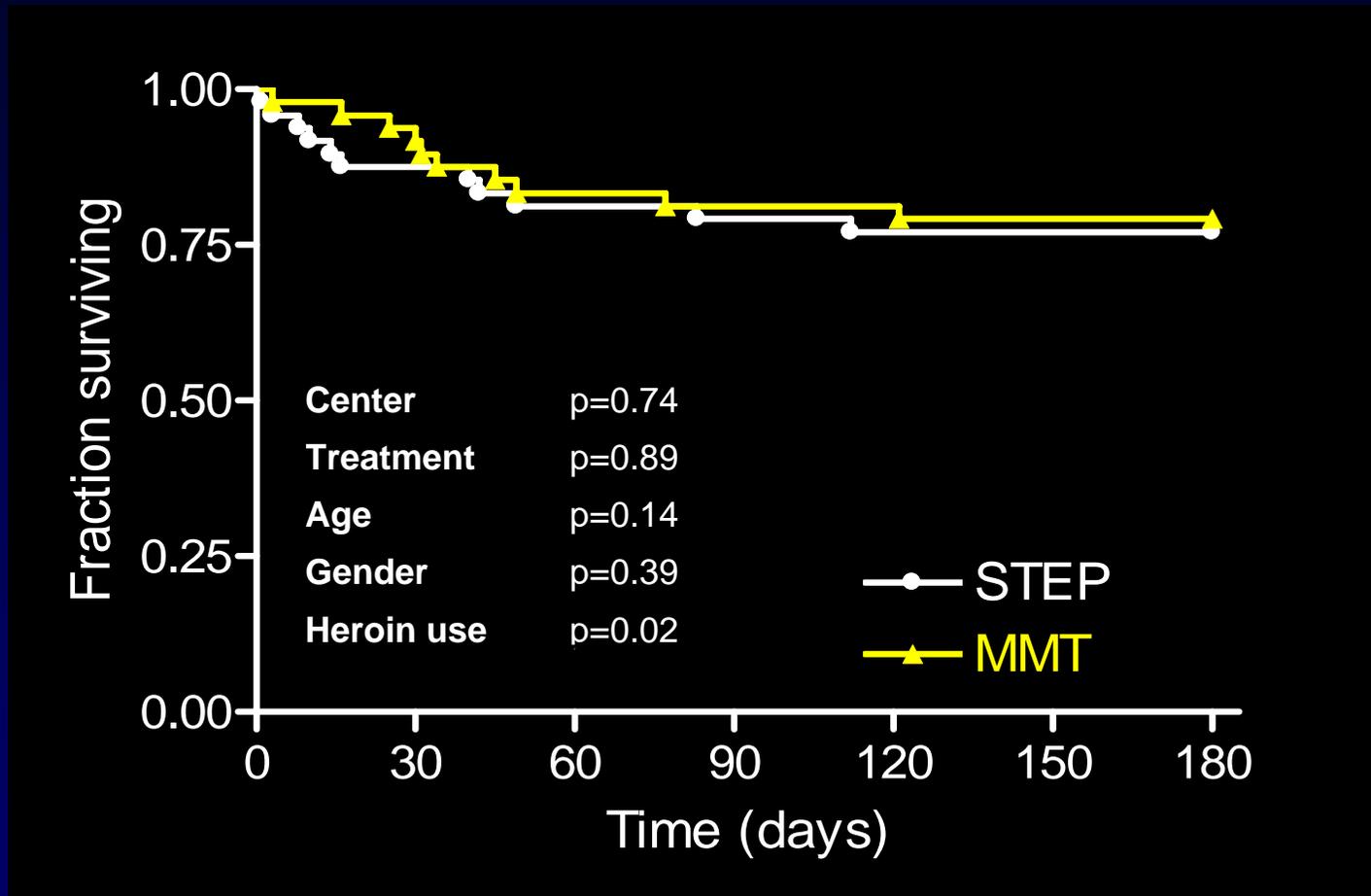
Baseline participant characteristics

(Kakko et al., Am J Psychiat 2007)

| | eMMT | STEP |
|-------------------------------|-------------|-------------|
| Age (years±SD) | 36.5 ± 8.9 | 34.8 ± 8.9 |
| Heroin use (years±SD) | 9.4 ± 6.0 | 10.2 ± 7.0 |
| Gender (male / female) | 43 / 5 | 33 / 15 |
| I.v. use | 46 / 48 | 46 / 48 |
| Hepatitis B | 4 / 48 | 7 / 48 |
| Hepatitis C | 42 / 48 | 39 / 48 |
| HIV | 1 / 48 | 1 / 48 |

Virtually identical results on the primary outcome: retention in treatment in STEP and MMT

(Kakko et al., Am J Psychiat 2007)

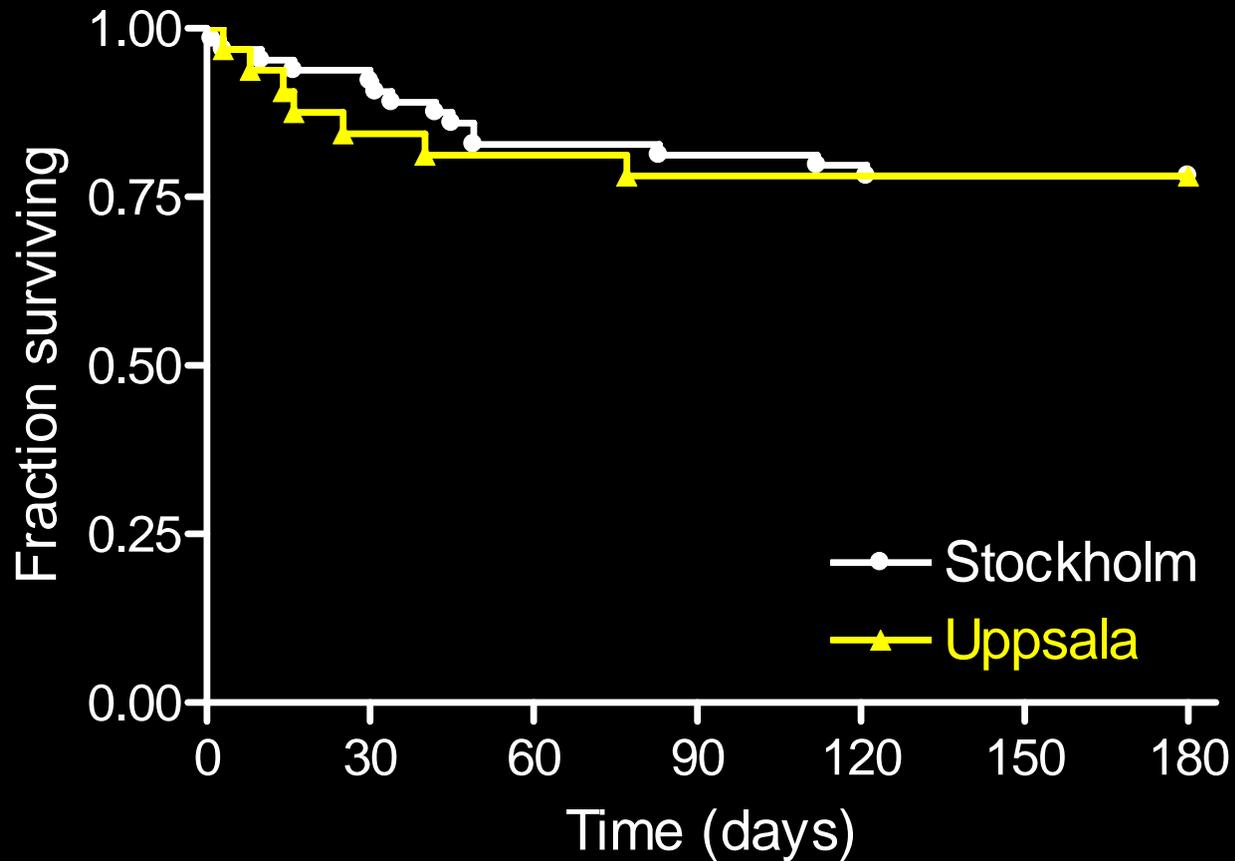


Formal equivalence analysis

- Objective:
 - to estimate the (im)probability that STEP is inferior to MMT
 - different from testing for a difference!
- Power:
 - Study had 80% power to demonstrate equivalence within a "triviality interval" of retention of 15%
- Result:
 - Inferiority of STEP could be rejected at $p < 0.05$

Identical results on primary outcome by study site

(Kakko et al., Am J Psychiat 2007)

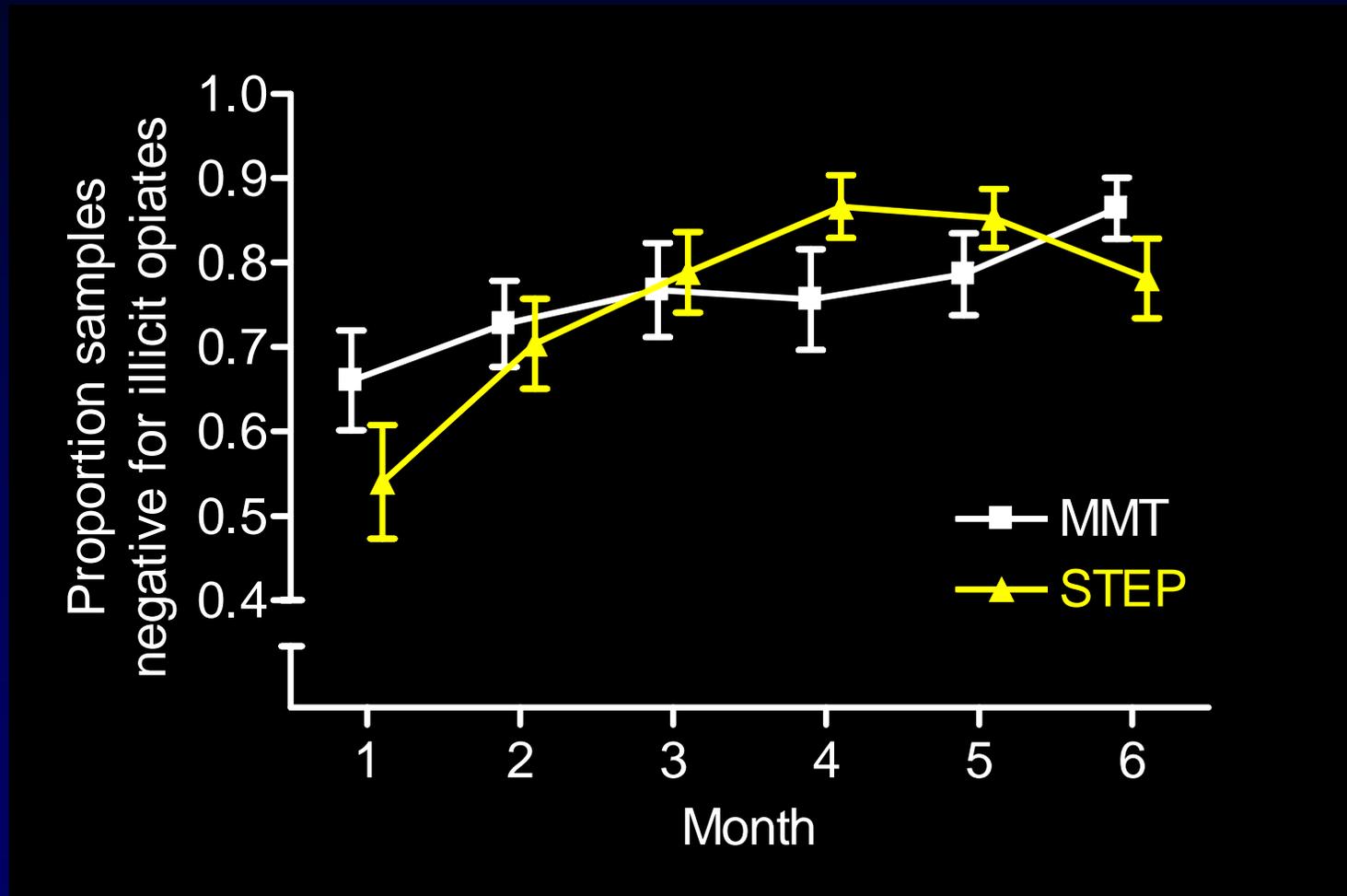


Doses and switches:
close to half of patients do well on bup/nlx
(Kakko et al., Am J Psychiat 2007)

| Group | N | Final daily dose (mg±SD) |
|---------------------|----------|---------------------------------|
| MMT | 38 | 110.0 ±13.2 mg methadone |
| STEP, non-switchers | 17 | 29.6 ± 4.7 mg buprenorphine |
| STEP, switchers | 20 | 111.0 ±11.7 mg methadone |

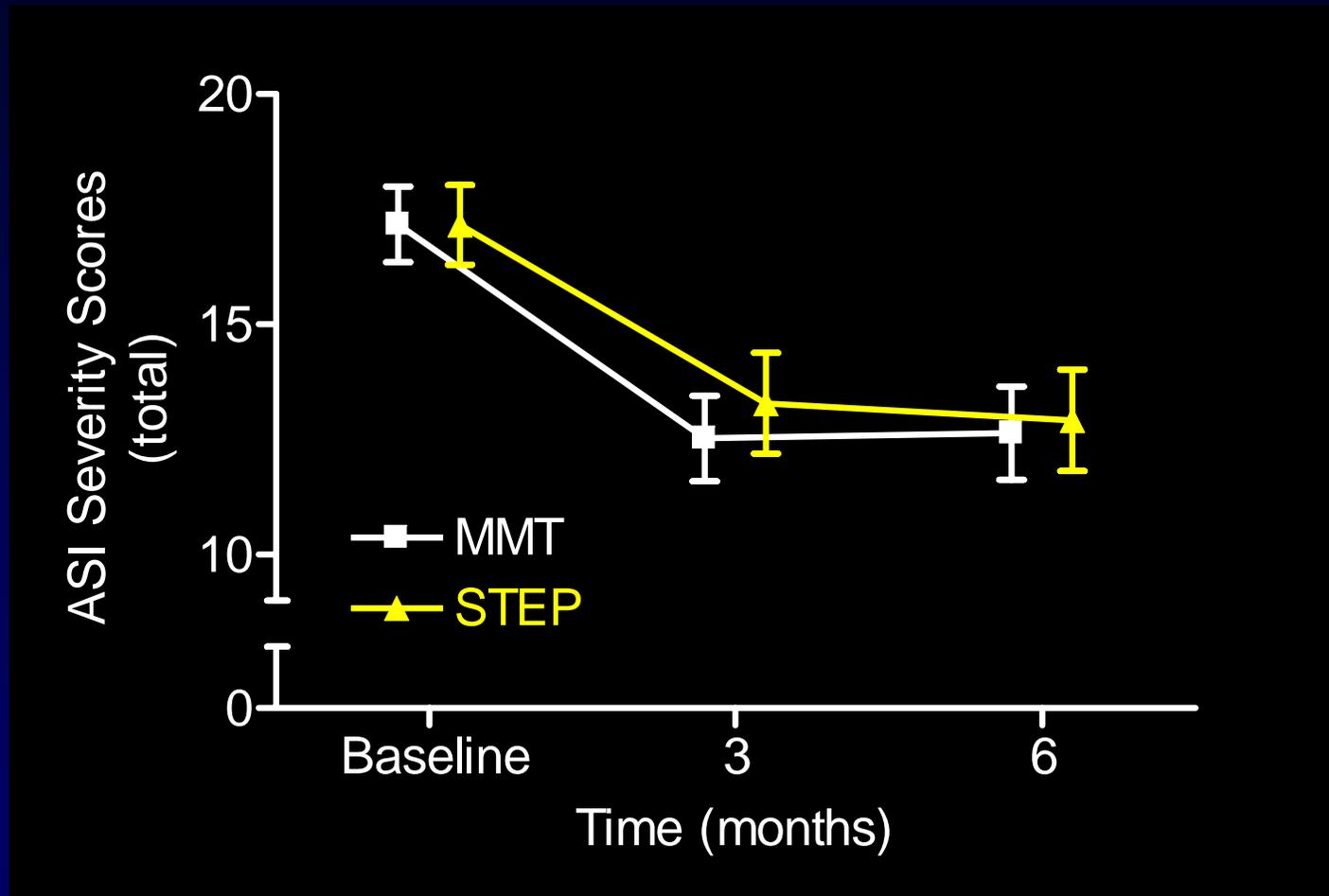
Marked improvement over time indicated by urine toxicology and uniform between treatment arms

(Kakko et al., Am J Psychiat 2007)



Highly significant reduction of problem severity over time, no difference between treatments

(Kakko et al., Am J Psychiat 2007)



3G conclusions

- A stepped strategy, overall
 - as effective as best-practice methadone
 - safer
- Patient variables typically assumed as predictors
 - we looked, and had enough variance
 - they didn't predict!
- Unless compelling reasons, buprenorphine should be first line

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