Cognitive effects of escalating doses of oral lisdexamfetamine in methamphetamine dependent adults

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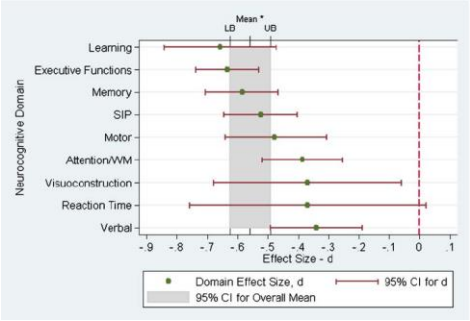
Why should we care about cognition in MA use disorder?

- Moderate magnitude impairment associated with MA-use disorder*
- Primary treatment for MA dependence: CBT based (d=0.53)
- CBT effectiveness varies with cognitive function
  - Esp. attention, memory, exec
- Cognition important relation to outcomes
  - Relapse (inhibitory control)
  - Functional outcome (memory/exec)



Scott et al, 2007: meta analysis of cognition in persons with methamphetamine use disorders

Cognition within the Lisdex Study

Dose-escalating, phase-2 study of oral lisdexamfetamine in adults with methamphetamine dependence

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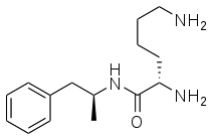


Trial registration:
ACTRN12615000391572
Funding: Hunter New England Local Health District; St Vincent's Health Network, Sydney; Curran Foundation, Sydney

Lisdexamfetamine:
- Dexamphetamine prodrug
- Kinetics superior:
  - slow onset, lower peak, longer duration

BMC Psychiatry 2016

Page 3

Effects of prescription stimulants in 'healthy adults': meta-analyses

Domain	ES (d/g)	95%CI
Processing speed accuracy	0.28*	(0.01-0.49)
Short term memory	0.20*	(0.01-0.38)
Delayed memory	0.45*	(0.27-0.63)
Working memory	0.13	(-0.02-0.27)
Executive functions:		
Inhibitory control	0.20*	(0.11-0.30)
Advantageous choices (GT)	-0.19	(-0.56-0.18)
Planning accuracy	0.05	(-0.19-0.29)
Planning time	-0.14	(-0.38-0.10)
Cognitive perseveration	0.01	(-0.14-0.25)

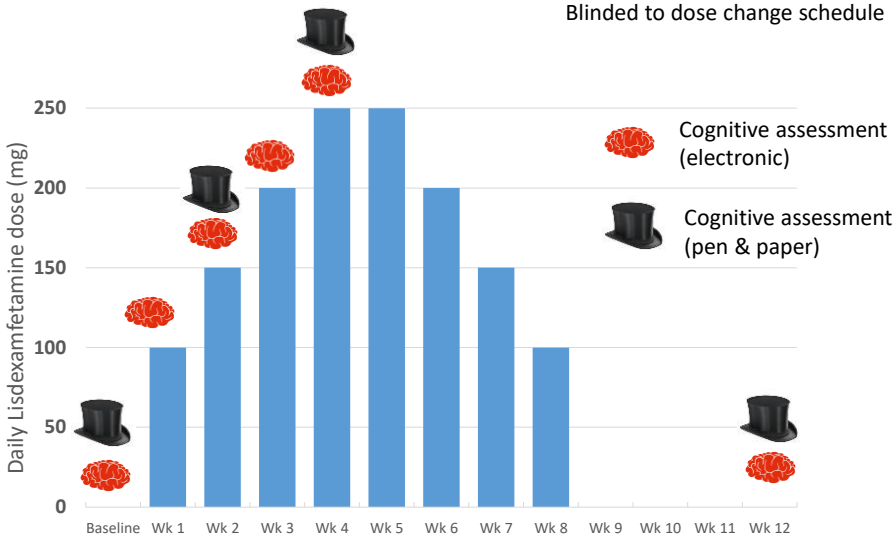
Ilieva et al, 2015; Marraccini et al, 2016

Stimulant medications in Adult ADHD: improve sustained attention but not executive: Advocat, 2010

Method Lisdex

Single group outpatient trial

Inclusion:
>2 year hx MA use disorder
MA use ≥14/28 days
Blinded to dose change schedule



Materials

Penscreen software (V6) for Android Tablets

Domain	Task	Format
General cognitive function	Wechsler Test of Adult Reading	P&P
Processing speed	Digit Symbol	Electronic
Sustained attention	Rapid Visual Information Processing	Electronic
Attention (focus)	Arrow Flankers	Electronic
Inhibition	Go- No-Go	Electronic
Switching	Trail Making Task	P&P
Working memory	Digit Sequencing	P&P
Verbal learning & memory	Ray Auditory Verbal Learning Task	P&P

All used random stimuli (penscreen) or alternate forms (P&P) to minimise learning

Participants (n=14)

Demographic	
Age	41 (SD=6, 33-51)
% Male	78% (n=11)
Years education	11 (SD=2; 8-12)
% Tertiary education	42% (n=6)
% Unemployed	86% (n=12)
Wender Utah >46 (ADHD screen)	42% (n=6)
Wechsler Test of Adult Reading	104 (SD=11, 81-120)
Montreal Cognitive Assessment	26 (SD=3, 21-30)
MoCA <23 (possible MCI)	14% (n=2)
Days methamphet use (/28)	21 (SD=5, 14-28)

Results I

All analyses (mixed models) control for sex, Wender-Utah ADHD score, WTAR performance and days MA use

Cognitive domain	Measure	F (time)#	P(time)#	n	Baseline vs 150mg Hedges' g	Baseline vs 250mg Hedges' g	Baseline vs follow-up Hedges' g	250mg vs follow-up Hedges' g
Processing Speed	Trail making test (A)	3.053	*0.081*	14	0.08	**0.62***	0.33	0.12
Switching	Trail making test (B)^	5.412^	**0.015**	14	0.20	0.32	**0.89***	-0.49
Working memory	Digit Sequencing Span	1.054	0.405	14	0.48	0.27	0.19	0.05
Immediate memory	RAVLT Trial 1	0.161	0.920	14	0.05	0.03	0.15	-0.16
Learning	RAVLT Trials 1-5	3.275	*0.060*	14	0.29	0.12	**0.62***	-0.49
Memory retention	RAVLT % Recalled (delay)	0.779	0.535	14	-0.02	0.02	0.31	-0.03
Recognition memory	RAVLT % recognised	0.238	0.867	14	0.21	0.15	0.12	-0.05

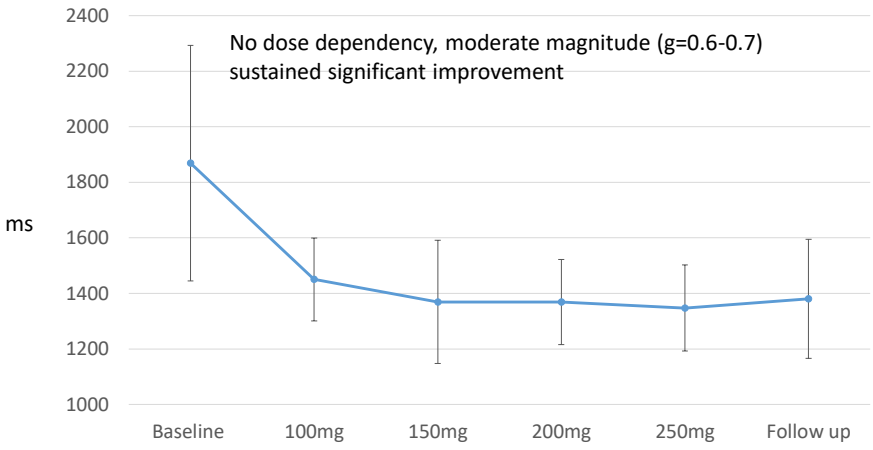
Note: *p<0.05 in adjusted paired comparison

Results II

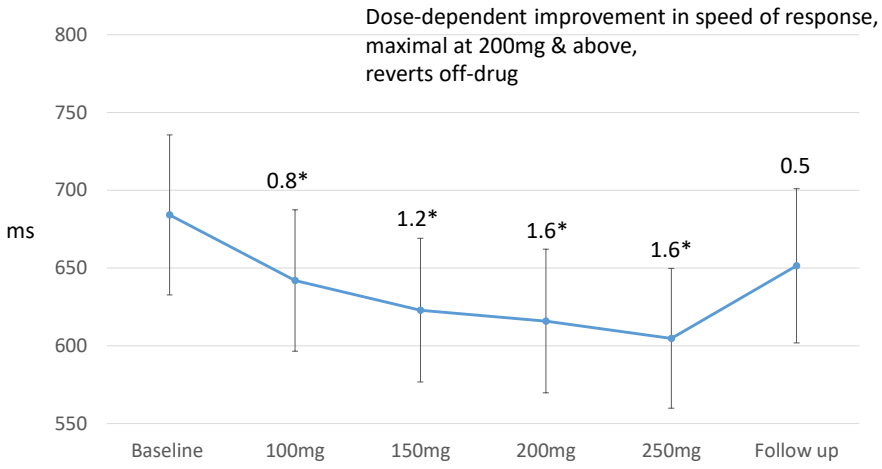
All analyses (mixed models) control for sex, Wender-Utah ADHD score, WTAR performance and days MA use

Cognitive domain	Measure	F (time)#	P(time)#	n	Baseline vs 100mg Hedges' g	Baseline vs 150mg Hedges' g	Baseline vs 200mg Hedges' g	Baseline vs 250mg Hedges' g	Baseline vs follow-up Hedges' g	250mg vs follow-up Hedges' g
Processing speed	Digit Symbol reaction time	2.684	0.071	13	**0.58***	**0.65***	**0.68***	**0.71***	**0.64***	0.11
Sustained attention	Rapid visual info processing RT	2.257	0.109	13	0.17	**0.75***	0.55	**0.67***	0.32	0.36
Sustained attention	Rapid visual info processing correct	2.457	0.111	13	0.08	0.56	**0.70***	**0.62***	0.48	0.08
Attention	**Arrow flankers RT**	9.336	**<0.001**	13	**0.81***	**1.19***	**1.59***	**1.59***	0.48	**1.10***
Attention	**Arrow flankers correct^**	3.056^	**0.024**	13	**0.75***	0.13	**0.97***	**0.65***	0.27	0.22
Inhibition	**No-go false positives**	6.979	**0.003**	13	**0.77***	**0.59***	**1.48***	**1.12***	**1.48***	-0.28

Basic processing speed (DSST)

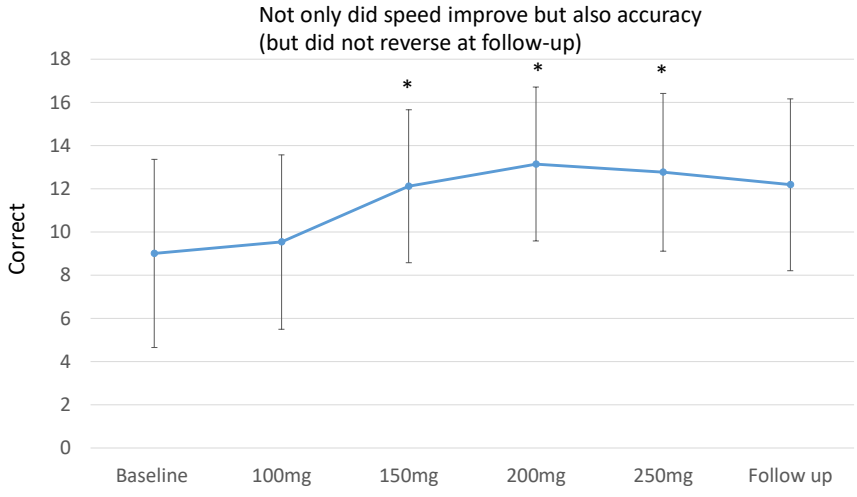


Attention (Arrow Flankers) (RT)



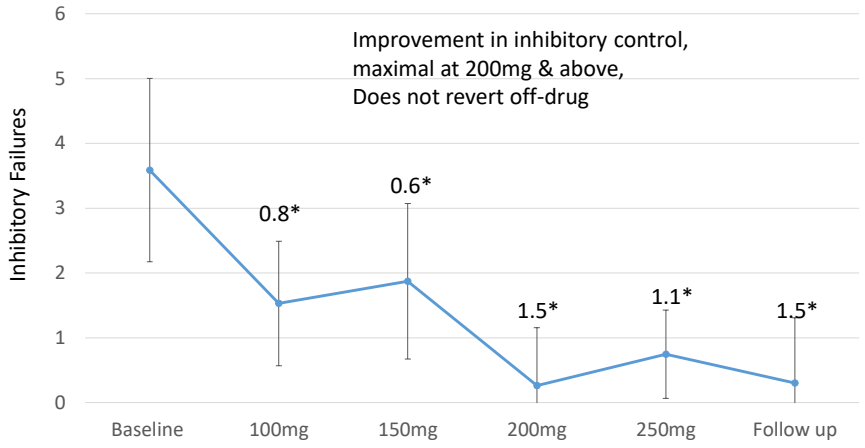
Numerical value is Hedges' g effect size, *p<0.05 in adjusted paired comparison

Attention (Arrow Flankers) - accuracy



Numerical value is Hedges' g effect size, *p<0.05 in adjusted paired comparison

Inhibitory control (no-go false positives)



Numerical value is Hedges' g effect size, *p<0.05 in adjusted paired comparison

Discussion

- Moderate-large magnitude improvements in processing speed, focussed attention, sustained attention and **inhibitory control** were seen over the course of the trial and were maximal at 200mg and above
- No meaningful changes in working memory, learning, retention and switching
- These performance improvements may reflect:
  - *Task learning*?
    - Some effects retained at FU, some not; learning *should* be minimal
  - *General improvements on speeded tasks due to the presence of stimulatory medication*?
    - Perhaps; accuracy also improved
  - *Stabilisation of cognitive performance with chronic/tonic stimulant use compared with phasic/intermittent illicit stimulant use*?*
    - Days used MA declined from 21/28 to 16/28 (week 4) and 14/28 FU*
    - If can stabilise cognition in unstable patients → beneficial*
- Positive, however:
  - Need to clarify in RCT (test learning/placebo & associations between cognition and functional outcomes)