Centre for Community Child Health
Professional Development Program
October 17 2015

Executive function problems

The Royal Children's Hospital Melbourne

Executive function deficits

(Douglas 1970; Schachar 2012)

- Planning, preparing, initiating (Tower of Hanoi)
- Holding (WM – verbal, visuoaspatial)
- Switching (mental flexibility eg. Wisconsin card sorting test)
- Error processing – identification, adjustment
- Inhibitory control
  - withholding (Go-no go, CPT)
  - cancelling (braking eg. Stop signal task)

Cognitive deficits in ADHD

(*Faraone et al Nature Reviews 2015)*

- EF deficits:
  - visuospatial & verbal WM
  - allocation of attention *(Rappley NEJM 2005)*
  - planning
  - vigilance
  - inhibitory control

- “Reward dysregulation” (suboptimal decision-making)
  - prefer immediate over delayed rewards
  - overestimate magnitude of proximal relative to distal rewards

Cognitive deficits in ADHD (cont.)

(*Faraone et al Nature Reviews 2015*)

- Temporal information processing and timing
- Processing speed / response time variability
- Memory span
- Arousal / activation
- Motor control

Executive function deficits in ADHD

- Variable between subjects
  - Most have deficits in 1 or 2 domains
  - Some have no deficits
- Seen in all subtypes
- **Weak relationship with functional deficits**
- Insufficient sensitivity and specificity for diagnostic purposes
- Lacks utility to predict course / outcomes

Neurophysiology

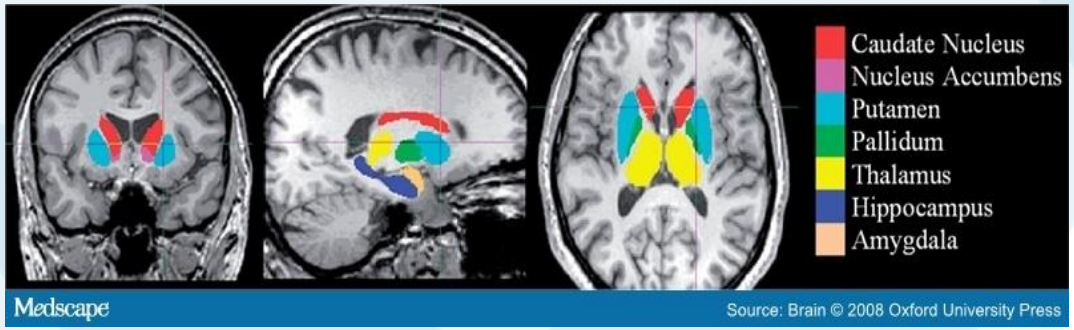
- Dopamine dysregulation (receptor / concentration) *(Sagvolden 2005)*
  - Mesolimbic – delay aversion, impulsivity, disinhibition
  - Mesocortical – inattention, poor planning
  - Nigrostriatal – neurological “soft signs”, clumsiness
- Disordered activation (fMRI)
  - under activation
  - activate more diffuse areas than controls during tasks
- Reduced “functional connectivity” (steady state) *(Sun 2012)*

Structural imaging

- MRI - total cerebral volume and cerebellar vol. 3% reduced cf controls *(Castellanos JAMA 2002)*
  - Reduced cortical thickness
  - Caudate vol smaller school-age, no diff older
  - Holds when control for med history
- Delayed cortical thickening, gyrification *(Shaw 2012)*
  - Normalization - remission / lack - persistence *(Halperin 2011)*
- Adults with ADHD – cortical thinning in DLPFC, R inf parietal lobe *(Makris 2007)*

Brain structures involved

(Castellanos & Tannock Nature 2002)



Pre frontal cortex

Parietal cortex

Limbic System (amygdala, hippocampus, anterior cingulate)

Deep grey matter

(caudate, putamen)

Cerebellum

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Polygenic disorders – pathway analysis *(Neale 2009)*

PHENOTYPE	behavioural traits
PHYSIOLOGY	functional connectivity, activation
STRUCTURE	
EPIGENETICS	Environmental influences
GENETICS	SNPs, microdeletions / microduplications,

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Polygenic disorders – pathway analysis *(Neale 2009)*

PHENOTYPE	behavioural traits
COGNITIVE ENDO-PHENOTYPE	**executive functions (developmental skills)**
PHYSIOLOGY	functional connectivity, activation
STRUCTURE	
EPIGENETICS	Environmental influences
GENETICS	SNPs, microdeletions / microduplications,

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Causal pathways

(*Nigg 2006, Sonuga-Barke 2010)*

VISION

Identify:

- Early developmental phenotypes
- Mediating processes (dynamic)

  - targets for early intervention

  Goals:

  - reduce likelihood emergence
  - limit persistence
  - increase likelihood remission
  - reduce long-term burdens

Early intervention

- Primary (prevention)
  - not feasible?; predictive power of risk markers not strong enough
- **Secondary**
  - risk factors (family Hx, prematurity) + early phenotypic indicators
    - behavioural eg. hyperactivity / dysregulation
    - cognitive endophenotype eg. delayed WM
- Tertiary (early tx of disorder)
  - pharmacol, non-pharmacol
  - no evidence of alteration to dev trajectories

Non-pharmacological interventions in ADHD

(Sonuga-Barke Am J Psychiatry 2013)

	Effect size (ADHD symptoms)
Elimination diet	0.5
Exclude artificial colourings	0.3
FFA supplements	0.2
Cognitive training	0
Behavioural interventions / parent training	0
Neurofeedback	0

Interventions which might alter developmental trajectories

- Operant conditioning
- Parent support & training *(Shaw 2008)*
  - Eg. Triple P *(Sanders)*, Incredible Years (*Webster-Stratton)*
    - Evidence red. levels oppositionality / conduct problems
- Neuropsychological (speed rate of dev)
  - Attention training *(Sohlberh & Mateer 2001)*
  - Working memory training *(Klingberg et al 2005)*
    - Improvements in lab performance demonstrated - ? transferrable to classroom / playground / home; sustained?
- Combination
  - homework exercises to improve self-regulation
    - Games: conc, turn-taking, delay gratification
    - “Teachable moments”
  - parents agents of change

Stimulant medication: behavioural effects

- Improved sustained attention / effortful behaviour
- Improved error detection (vigilance)
- Reduced emotional reactions to frustration (impulsiveness)
- Reduced extraneous motor activity

Stimulant medication: neuropsychological effects

- Improved sustained attention, attentional allocation
- Inconsistent findings on other measures:
  - WM (auditory, visuo-spatial)
  - processing speed / response variability
  - planning, cognitive flexibility / set-shifting
  - inhibitory control (errors of commission)
  - academic efficiency - verbal and non-verbal learning / retention
  - perceptual motor function
- No evidence of improved academic performance over time
  - Some evidence of assoc w worsening

April 18, 2014

The Royal Children's Hospital Melbourne

Writing With Adderall: A Personal Case Study

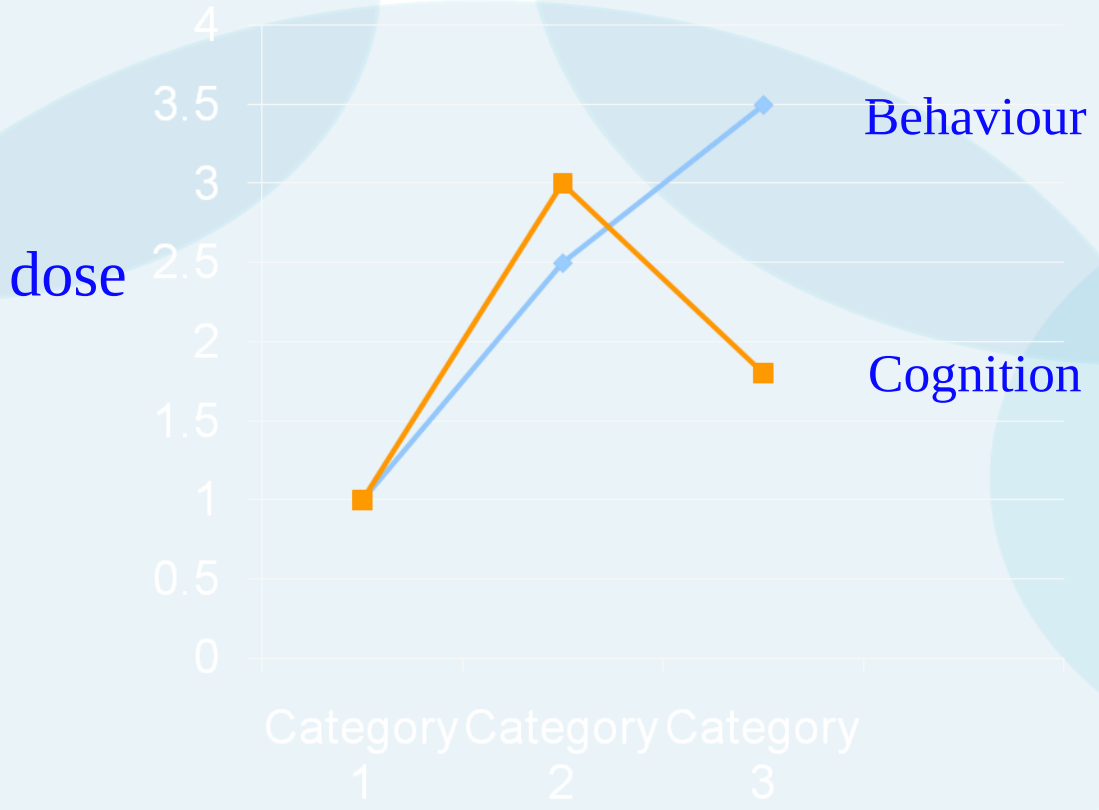
Are stimulants cognitive enhancers?

(Advocat 2010: review of studies in adults)

yes	no
increase arousal	reduce distractibility
reduce response latencies	improve planning
improve retention of previously acquired information?	adaptation / flexibility
facilitate memory consolidation?	promote acquisition of new information

- unclear if improvement only occurs when there is a baseline deficit
- Conclusion: Evidence suggests stimulant medications do not promote learning and academic achievement in adult college students with ADHD

Stimulants – dose-response curve



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What's the role for stimulant medications in LDs?

- Are all kids with LDs inattentive?
  - DDx or different / inter-related aspects of a cognitive weakness?
- The myth of cross-situational impairment: ADHD Inattentive type
- Would all kids with LDs benefit from stimulants?
  - Mental efficiency - using more brain-power / unit of time

What is APRN?

- A national research network for paediatricians
- Research in secondary care (outpatient, private rooms) settings
- Goals
  - improve quality and quantity of research into 'common' conditions
  - involve more paediatricians in research
  - ensure adequate sample sizes and follow up
- Initiated Melbourne 2007

Children Attending Paediatricians Study (CAPS)

- Aim
  - document caseload of secondary care paediatricians
  - inform sample size calculations for future research

- Methodology
  - audit of outpatient caseload over 2 weeks or 100 consecutive patients, whichever came first
  - 2009, 2013
  - diagnosis, management, referral, Medicare code, investigations, BMI etc

Hiscock et al MJA 2011

8277152967

1. PATIENT INFORMATION - PLEASE PRINT IN CAPITAL LETTERS

a. Date of visit: 26 / 11 / 2008

b. Gender: (●) M ( ) F

c. Start Time (pls circle): 16:05 AM / PM

d. FAMILY Postcode: 3140

e. PAED postcode THIS session: 3052

f. Where seen?
- ( ) Public Outpatients
- (●) Private Room
- ( ) Community Heath Centre

g. Is English main language spoken at home?
(●) Y ( ) N → which language? _____

Need interpreter? ( ) Y ( ) N

h. Mark those that apply
- ( ) HCC / Carer's Allowance
- ( ) ATSI

i. Child's Date of Birth: 17 / 01 / 2002

Paediatrician ID: 0172

j. Parent overall rating of child's health
poor fair good v.good (excellent)

k. Parent overall rating of own health
poor fair good v.good (excellent)

l. Pls mark if parent refused (j)+(k): ( )

m. Child's Ht if possible: 122 cm

n. Child's Wt if possible: 19.2 kg

2. PROVIDER'S DIAGNOSIS FOR THIS VISIT

Current diagnoses/problem list at this visit - please refer to code list on opposite page and mark whether new or continuing. If **no code**, please specify the diagnosis.

	CODE	OR PLEASE PRINT Dx	New	Cont
(1)	C7		( )	(●)
(2)			( )	( )
(3)			( )	( )
(4)			( )	( )

3. MEDICATIONS & IMMUNIZATIONS

(●) NONE

Include Rx & OTC drugs, immunizations, allergy shots, anaesthetics, chemotherapy & dietary supplements that were ordered, supplied, administered or continued during visit.

		New	Cont
(1)		( )	( )
(2)		( )	( )
(3)		( )	( )
(4)		( )	( )

4. MEDICARE ITEMS

Medicare Item Nos: (Pls mark if applicable)

( ) New	110
(●) R/V	116
( ) New long	132
( ) R/V long	133
( ) Other	
( ) Other:	

5. INVESTIGATIONS

Mark all tests ordered or provided at this visit:

- ( ) Blood
- ( ) Urine
- ( ) Stool
- ( ) Chest X-ray
- ( ) Other X-ray
- ( ) CT/MRI
- ( ) Ultrasound
- ( ) Diagnostic/Screening qstre
- ( ) Other, please specify _____

6. REFERRALS FOR THIS VISIT

Mark all referrals made at this visit:

- ( ) Psychology
- ( ) Speech Pathology
- ( ) Audiology
- ( ) Subspecialist
- ( ) Multidisciplinary Team
- ( ) Other Allied Health
- ( ) Other, please specify _____

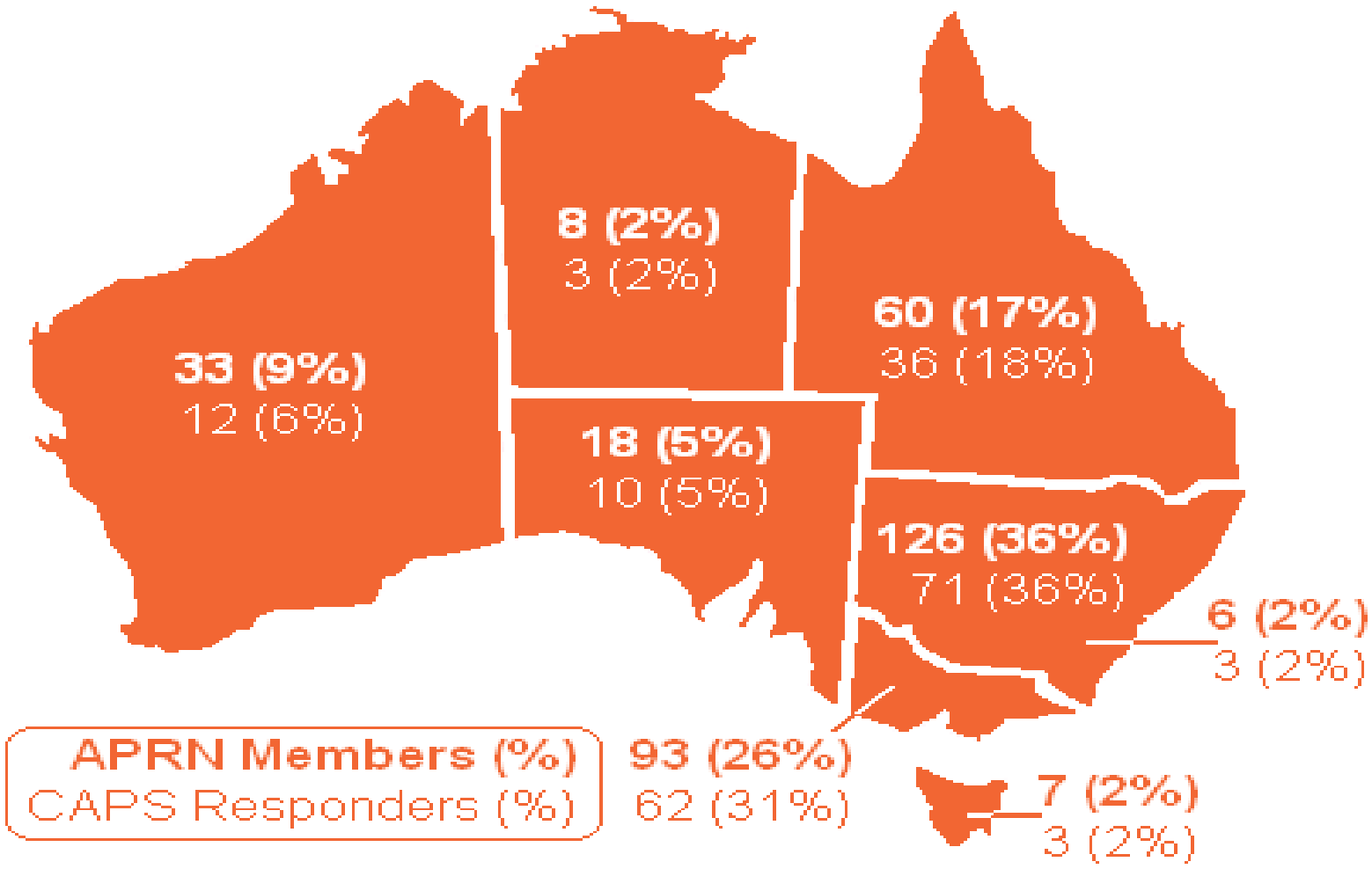
7. VISIT DISPOSITIONS

a. Please mark one:
- ( ) No further follow-up by me
- (●) Follow-up by me
- ( ) Admission

b. Finish time (pls circle): 16:44 AM / PM

c. Extra time required after visit (eg phone, letters): 3 mins

Responders by state/territory



CAPS: Psychotropic medication data

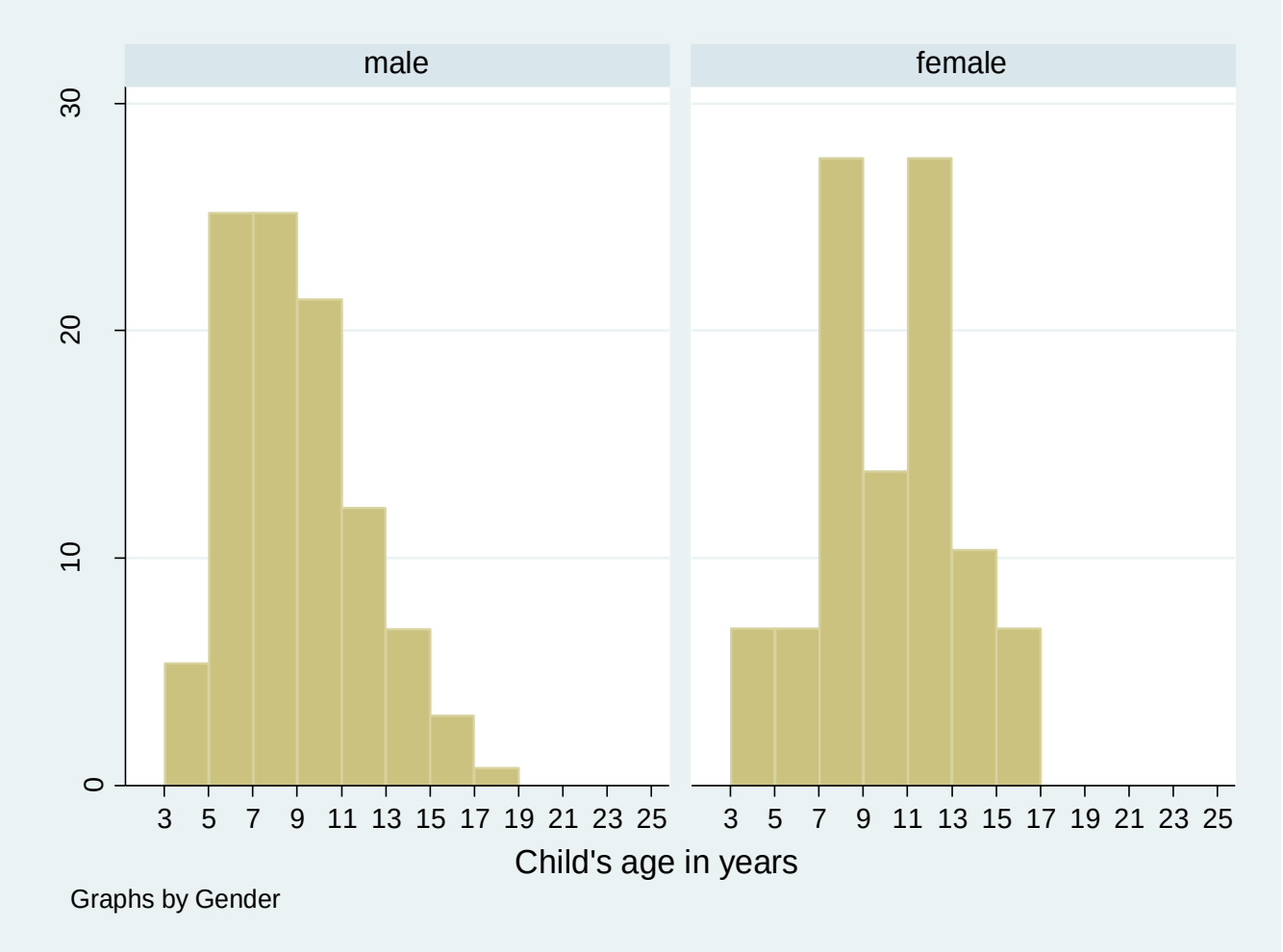
Medication group,	Proportion of consultations in which medication prescribed (%)	
	2008	**2013**
No. consultations	8345	7102
Psychostimulants	13.1	17.4
- Long-acting	5.2	9.6
- Other (short-acting, unspecified)	8.3	8.9
Atomoxetine	1.2	1.2
Clonidine	1.9	2.3
SSRIs /SNRIs	2.0	3.8
Tricyclics	0.4	0.5
Anti-psychotropic		
- First generation	0.02	0.04
- Second generation	2.0	2.9
AED	2.8	4.2
Melatonin	0.7	3.7

CAPS 2008: ADHD Patients

Variable	New diagnosis N = 179	Continuing diagnosis N = 1083	Overall N = 1528
Male (%)	82	81	**80**
Mean age (SD, range)	9.1 (3, 3-19)	11.4 (3.5 3-24)	11.1 (3.5 3-24)
English main language (%)	96	98	97
SEIFA code mean (range)	1001 (828 -1127)	992 (594 -1138)	994 (594-1144)
Setting (%) Private Public O/P Comm'ty HC			 **76** 18 6

CAPS 2008: ADHD Patients

Age at diagnosis



CAPS: ADHD Patients

Number of Comorbidities (%)	New diagnosis N = 179	Continuing diagnosis N = 1083	Overall N = 1528
0	30	40	**40**
1	46	42	42
2 or more	24	18	18

CAPS: ADHD Patients

Comorbidities %	New diagnosis N = 179	Continuing diagnosis N = 1083	Overall N = 1528
Learning disability	36	23	**24**
Oppositional Defiant Disorder	15	16	**15**
ASD	8	13	**13**
* Anxiety	11	7	8
Intellectual disability	5	7	7
Conduct disorder	5	5	5
Depression	3	3	3
Tics / Tourette	1	1	1

CAPS: ADHD Patients

Investigations & Referrals (%)	New diagnosis N = 179	Continuing diagnosis N = 1083
Medical investigations	16	5
Referrals **psychology**	**32**	**11**
speech pathology	9	3
MD team	3	1
audiology	6	0
psychiatry	1	1
other *	8	4

* Incl medical subspecialties, education services etc

CAPS: ADHD Patients

Medications (%)	New diagnosis N = 179	Continuing diagnosis N = 1083
- "core" (stim, ATX)	40	**82**
- other psychotropic	3	19
- other	6	6
Number of psychotropic medications		
0	59	15
1	39	65
2	2	16
3	0	4
4	0	1

CAPS: ADHD Patients

Core Medications (%)	New diagnosis N = 179	Continuing diagnosis N = 1083
- **methylphenidate**	31	**68**
- dexamphetamine	7	13
- atomoxetine	2	6
Other psychotropics		
- clonidine	1	9
- SSRI SNRI	1	5
- atypical antipsychotic	1	4
- anti-epileptic	0	2
- tricyclic antidepressant	0	2
- melatonin	0	1

CAPS: ADHD Patients

PREDICTORS OF MEDICATION PRESCRIPTION

- Core (stim, ATX)
  - age
  - not SEIFA code, gender or comorbidity

Stimulant use

- Deciding to prescribe
  - reasons / goals?
  - who's involved?
  - parental hesitancy
  - patient resistance
  - which visit?
  - information given
- Starting / titrating
  - dosage: starting, adjustments
  - frequency / modality of contact
  - evaluation of response: timing; method

Stimulant use

- Coverage
  - time of day, weekends
- Switch to long-acting?
- Monitoring
  - evaluating effectiveness
  - evaluating SEs
- Stopping
  - are they still working?
  - are they still needed?
- University / adults