Dr. Adil Virani
Director, Lower Mainland Pharmacy Services
Associate Professor
Faculty of Pharmaceutical Sciences

Overview

- Case
- Treatment Options
- Treatment Guidelines
- Adverse effects
- Monitoring Parameters

Case: Oliver DePlace

- ID: 7 year old boy with combined type of ADHD
- HPI: Oliver is easily distracted, constantly interrupts others and talks excessively. He consistently fidgets with his hands and runs around the house often yelling at the top of his lungs. He currently has difficulty concentrating and following instructions.

Please write down what first comes to mind as your best treatment option. How well does that option work and what are 2 pros and cons?

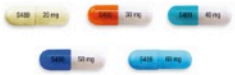
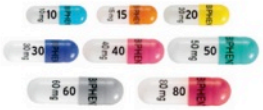
Treatment Options in ADHD

- Behaviour Management
- Stimulants
  - Methylphenidate (MPH, Concerta® ®)
  - Amphetamines (Dexadrine, Vyvanse®, Adderall XR®)
  - Dexmethylphenidate** (Focalin®)
- Nonstimulants
  - Atomoxetine
- Antidepressants
  - TCA's, Bupropion, Venlafaxine
- Alpha-2 Agonists
  - Clonidine, Guanfacine (Intuitiv)**
- Other agents
  - Atypical antipsychotics, modafinil, herbals, mood stabilizers

Probability that there will be a 50% reduction in CORE symptoms

- Behaviour Management **40-60%**
- Stimulants
  - Methylphenidate (MPH, Concerta®,) **65-80%**
  - Amphetamines (Dexadrine, Vyvanse®, Adderall XR®)
  - Dexmethylphenidate** (Focalin®)
- Nonstimulants **50-60%**
  - Atomoxetine
- Antidepressants **~50%**
  - TCA's, Bupropion, Venlafaxine
- Alpha-2 Agonists **~40%**
  - Clonidine, Guanfacine**
- Other agents
  - Atypical antipsychotics, modafinil, herbals, mood stabilizers

Pharmacological Treatments for ADHD March 2012 - CANADA

Medications available and illustrations of tablets/capsules	Duration of action	Starting dose	Dose titration as per product monograph	Dose titration as per CADDRA www.caddra.ca
AMPHETAMINE-BASED PSYCHOSTIMULANTS				
Dexedrine® tablets 5 mg  Dexedrine® spansules 10, 15 mg 	~ 4 h ~ 6 - 8 h	tablets = 2.5 to 5 mg BID spansules = 10 mg q.d. a.m.	↑ 2.5 - 5 mg at weekly intervals; max. dose/day: (q.d. or b.i.d.) All ages = 40 mg	↑ 2.5 - 5 mg/day at weekly intervals max. dose/day: (q.d. or b.i.d.) Children and Adolescents = 20 - 30 mg Adults = 50 mg
AdderallXR® Capsules 5, 10, 15, 20, 25, 30 mg 	~ 12 h	5 - 10 mg q.d. a.m.	↑ 5 - 10 mg at weekly intervals max. dose/day: Children = 30 mg Adolescents and Adults = 20-30 mg	Children: ↑ 5 mg at weekly intervals max. dose/day = 30 mg Adolescents and Adults: ↑ 5 - 10 mg at weekly intervals max. dose/day = 50 mg
Vyvanse® Capsules 20, 30, 40 50, 60 mg 	~ 13 - 14 h	20 - 30 mg q.d. a.m.	↑ by clinical discretion at weekly intervals max. dose/day: All ages = 60 mg	↑ 10 mg at weekly intervals max. dose/day: Children = 60mg Adolescents and Adults = 70 mg
METHYLPHENIDATE-BASED PSYCHOSTIMULANTS				
Methylphenidate short acting, tablet 5mg (generic) 10, 20 mg (Ritalin®) 	~ 3 - 4 h	5 mg b.i.d. to t.i.d. Adult = consider q.i.d.	↑ 5 - 10 mg at weekly intervals max. dose/day: All ages = 60 mg	↑ 5 - 10 mg at weekly intervals max. dose/day: Children and Adolescents = 60 mg Adults = 100 mg
Biphentin® Capsules 10, 15, 20, 30, 40, 50, 60, 80 mg 	~ 10 - 12 h	10 - 20 mg q.d. a.m.	↑ 10 mg at weekly intervals max. dose/day: Children and Adolescents = 60 mg Adults = 80 mg	↑ 10 mg at weekly intervals max. dose/day: Children = 60 mg Adolescents and Adults = 80 mg
Concerta® Extended Release Capsules 18, 27, 36, 54 mg 	~ 10 - 12 h	18 mg q.d. a.m.	↑ 18 mg at weekly intervals max. dose/day: Children = 54 mg Adolescents = 54 mg / Adults = 72 mg	↑ 18 mg at weekly intervals max. dose/day: Children = 72 mg Adolescents = 90 mg / Adults = 108 mg
NON PSYCHOSTIMULANT				
Strattera® Capsules 10, 18, 25, 40, 60, 80, 100 mg 	Up to 24 h	Children and Adolescents : 0.5 mg/kg/day Adults = 40 mg q.d. for 7-14 days	Maintain dose for a minimum of 7 - 14 days before adjusting: Children = 0.8 then 1.2 mg/kg/day 70 kg or Adults = 60 then 80 mg/day max. dose/day : 1.4 mg/kg/day or 100 mg	Maintain dose for a minimum of 7 - 14 days before adjusting: Children = 0.8 then 1.2 mg/kg/day 70 kg or Adults = 60 then 80 mg/day max. dose/day: 1.4 mg/kg/day or 100 mg

Illustrations do not reflect real size of pills/capsules.

This table was developed jointly by développement professionnel continu, Laval University, Quebec (www.fmed.ulaval.ca/fmc) and CADDRA (www.caddra.ca)

Stimulants: What You Should Know…

- Overall ‘response’ rate of ~ 75%[1-4]
- No large clinical trials comparing stimulants
- Effective on day 1 and continue over the following months
- Side effects (sleep disruption, weight loss) are common
- Immediate release preparation should be dosed 2-3 times /day
- ‘Non-addictive’ in ADHD pts
- Cardiac concerns

1. Stein *Pediatr* 2003; 2. Pelham *Pediatr* 2001; 3. Greenhill *APA* 2004; 4. Kemner *APA* 2004

Psychostimulants

THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Benefits of stimulants include:

- Decreased aggression, improved social interaction & academic performance (parent & teacher rating)

Stimulants do not improve:

- Anxiety, academic performance (testing), delinquency/substance abuse at 3 years

Not studied:

- QOL, school completion, employment, future health

Stimulants associated with ↓ ht/wt at 3 yrs

Therapeutics Initiative Newsletter 69. March-May 2008.

Stimulant Adverse Effects

- adverse effects fairly well characterized
- CNS: insomnia, anxiety, activation, irritability (rebound), worsening tics, psychosis/mania
- HEENT: xerostomia, mydriasis
- CVS: ↑HR, ↑BP, palpitations, Sudden Cardiac Death
- RESP: URTI, sinusitis, cough
- GI: Anorexia, nausea, abdominal pain, wt loss
- GU: urinary retention, sexual dysfunction
- LAB/MSK/EXTR: growth delay (ht & wt), rash, leukopenia, anemia

2011 CADDRA GUIDELINES

Table 1. MEDICAL TREATMENT FOR ADHD UNCOMPLICATED – CHILDREN
Alphabetically Listed – Refer to product monographs for complete prescribing information.

Would you agree that these are the only first line agents or that all should be first line agents?

Bran… (act…					day[1] hild)	
						Per CADDRA Board*
FIR…						
Adderall XR® *(amphetamine mixed salts)*	5, 10, 15, 20, 25, 30 mg cap	5-10 mg q.d. a.m.	↑ 5-10 mg	↑ 5-10 mg	30 mg	30 mg
Biphentin® *(methylphenidate HCl)*	10, 15, 20, 30, 40 50, 60, 80 mg cap	10-20 mg q.d. a.m.	↑ 10 mg	↑ 10 mg	60 mg	60 mg
Concerta® *(methylphenidate HCl)*	18, 27, 36, 54 mg tab	18 mg q.d. a.m.	↑ 18 mg	↑ 18 mg	54 mg	72 mg
Strattera® *(atomoxetine)*	10, 18, 25, 40, 60, 80, 100 mg cap	0.5 mg/kg/day	Maintain Dose for a min. of 7-14 days before adjusting to 0.8 mg/kg/day then 1.2 mg/kg/day	Maintain Dose for a min. of 7-14 days before adjusting to 0.8 mg/kg/day then 1.2 mg/kg/day	lesser of 1.4 mg/kg/day or 60 mg/day	lesser of 1.4 mg/kg/day or 60 mg/day
Vyvanse® *(lisdexamfetamine dimesylate)*	20, 30, 40, 50, 60 mg cap	20-30 mg q.d. a.m.	By clinical discretion	↑ 10 mg	60 mg	60 mg

2011 CADDRA GUIDELINES

SECOND LINE/ADJUNCTIVE AGENTS – short-acting and intermediate-acting preparations

Indications for use: a) p.r.n. for particular activities; b) to augment long-acting formulations early or late in the day, or early in the eveni c) when LA agents are cost prohibitive. To augment Adderall XR® or Vyvanse®, short-acting and intermediate-acting dextro-amphetamine produc To augment Biphentin® or Concerta® short-acting MPH products can be used. b.i.d. refers to qam and qnoon and t.i.d. refers to qam, qnoon an

Dexedrine® *(dextro-amphetamine sulphate)*	5 mg tab	2.5-5 mg b.i.d.	↑ 2.5-5 mg	↑ 2.5-5 mg	40 mg
Dexedrine® Spansule[2] *(dextro-amphetamine sulphate)*	10, 15 mg cap	10 mg q.d. a.m.	↑ 5 mg	↑ 5 mg	40 mg
Ritalin® (methylphenidate)	10, 20 mg tab	5 mg b.i.d. to t.i.d.	↑ 5-10	↑ 5-10	60 mg
Ritalin® SR[3] *(methylphenidate HCl)*	20 mg tab	20 mg q.d. a.m.	↑ 20 mg	↑ 20 mg	60 mg

[1] *The maximum daily dose can be split into once daily (q.d.), twice daily (b.i.d.) or three times daily (t.i.d.) doses except for once a day formula*

[2] *Dexedrine® Spansule may last 6-8 hours*

[3] *Ritalin® SR may help cover the noon period but clinical experience suggests an effect similar to short-acting preparations. An increased dose co include q2pm dose with a daily maximum of 60 mg.*

2011 CADDRA GUIDELINES

SECOND LINE/ADJUNCTIVE AGENTS – short-acting and intermediate-acting preparations

Indications for use: a) p.r.n. for particular activities; b) to augment long-acting formulations early or late in the day, or early in the eveni c) when LA agents are cost prohibitive. To augment Adderall XR® or Vyvanse®, short-acting and intermediate-acting dextro-amphetamine produc To augment Biphentin® or Concerta® short-acting MPH products can be used. b.i.d. refers to qam and qnoon and t.i.d. refers to qam, qnoon an

Dexedrine® *(dextro-amphetamine sulphate)*	5 mg tab	2.5-5 mg b.i.d.	↑ 2.5-5 mg	↑ 2.5-5 mg	40 mg
Dexedrine® Spansule[2] *(dextro-amphetamine sulphate)*	10, 15 mg cap	10 mg q.d. a.m.	↑ 5 mg	↑ 5 mg	40 mg
Ritalin® (methylphenidate)	10, 20 mg tab	5 mg b.i.d. to t.i.d.	↑ 5-10	↑ 5-10	60 mg
Ritalin® SR[3] *(methylphenidate HCl)*	20 mg tab	20 mg q.d. a.m.	↑ 20 mg	↑ 20 mg	60 mg

[1] *The maximum daily dose can be split into once daily (q.d.), twice daily (b.i.d.) or three times daily (t.i.d.) doses except for once a day formula*

[2] *Dexedrine® Spansule may last 6-8 hours*

[3] *Ritalin® SR may help cover the noon period but clinical experience suggests an effect similar to short-acting preparations. An increased dose co include q2pm dose with a daily maximum of 60 mg.*

CADDRA 2011 2nd and 3rd line options?

Table 1. MEDICAL TREATMENT FOR ADHD UNCOMPLICATED – CHILDREN (continue
Alphabetically Listed – Refer to product monographs for complete prescribing informa

Brand Name *(active chemical)*	Dosage Form	Starting Dose	Titration Schedule Every 7 days		Maximu (up to 4
			Per product Monograph	Per CADDRA Board	Per Product Monograph
GENERIC MEDICATIONS					
PMS® or Ratio®-methylphenidate	5, 10, 20, mg tab	5 mg q.d. a.m. and noon	↑ 5 mg (add q4pm dose)	↑ 5 mg	60 mg
Novo-MPH ER-C® *(methylphenidate)*	18, 27, 36, 54 mg tab	18 mg q.d. a.m.	↑18 mg	↑18 mg	54 mg

THIRD LINE AGENTS

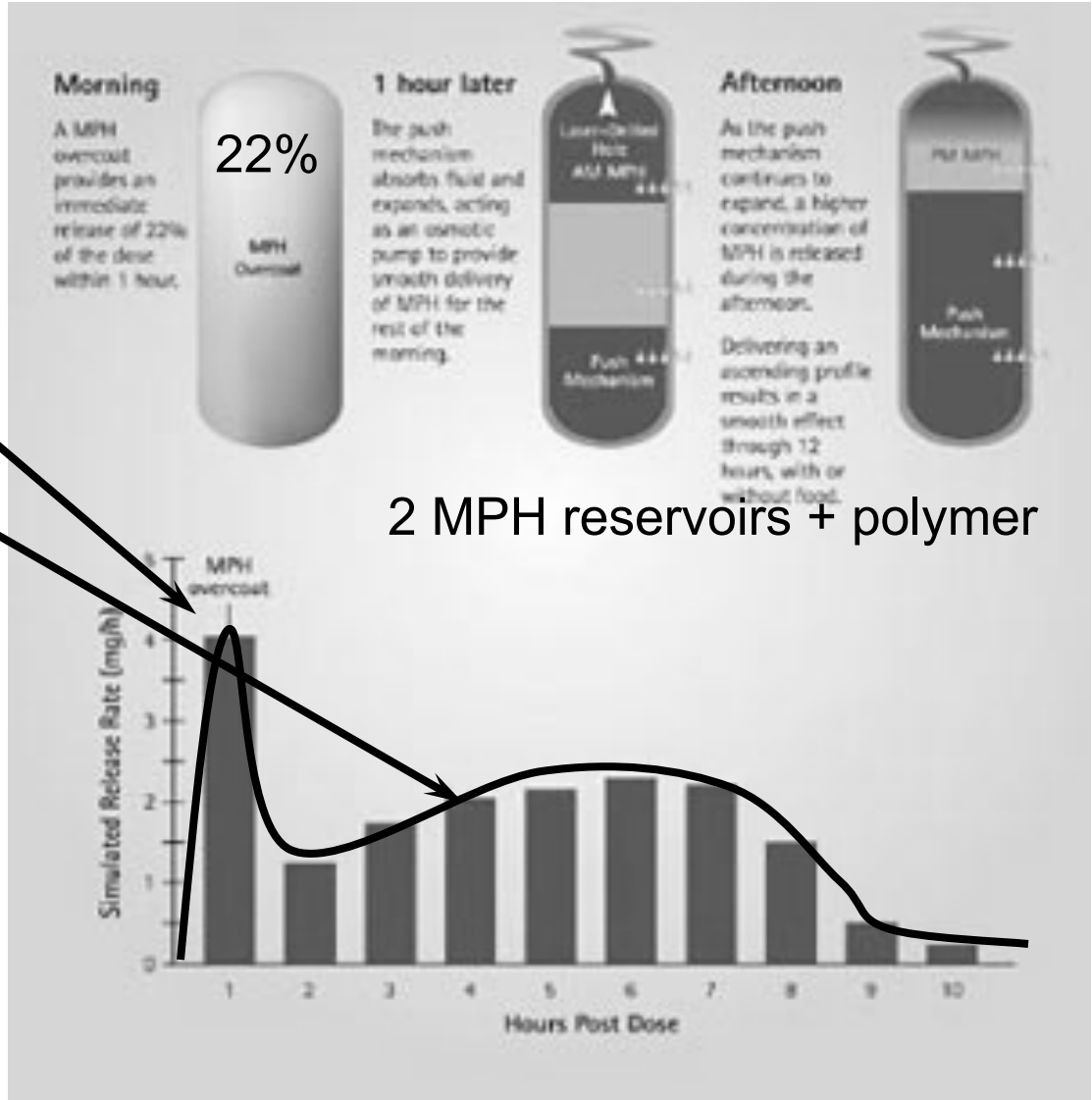
These medications (impramine, buproprion, modafinal, etc.) should only be initially or first prescribed by a spec

Benefits of Once Daily Agents

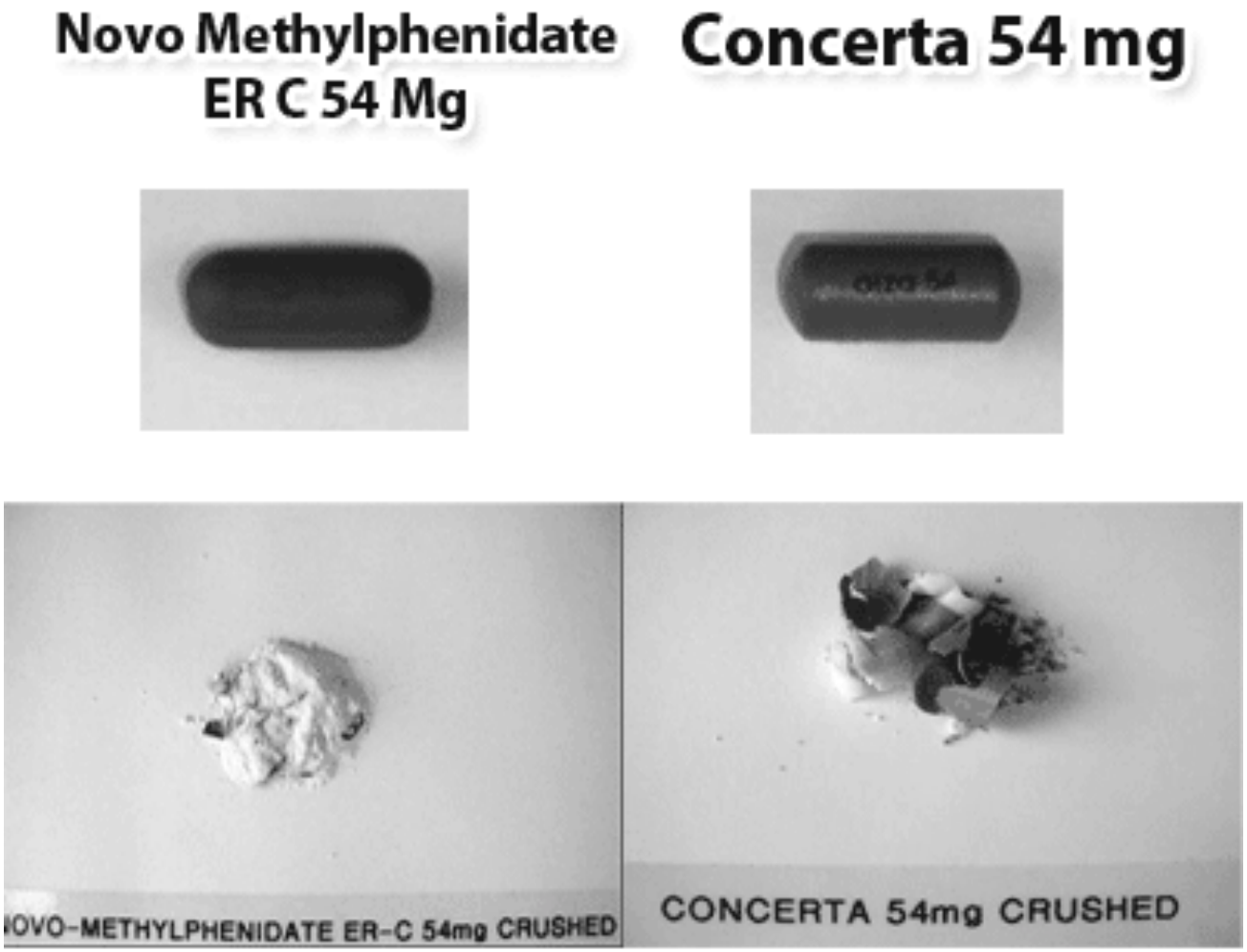
- Adherence
- Coverage during evening and early morning
  - Homework, extracurricular activities, social interactions
- Decreased abuse potential
- Problems with in-school dosing
  - Privacy issues
    - Decreased embarrassment
  - Storage of controlled medications
    - Less drug diversion (“sharing”)
- Ascending schedule decreases acute tolerance

OROS-Methylphenidate (Concerta®)

- Controlled release
  - Initial bolus
  - ↑ conc'n during the day
- Non-absorbable tablet shell is eliminated in stool
- Crush-resistant
  - Deters abuse
- 18 mg, 27 mg, 36 mg, 54 mg 'tablets'

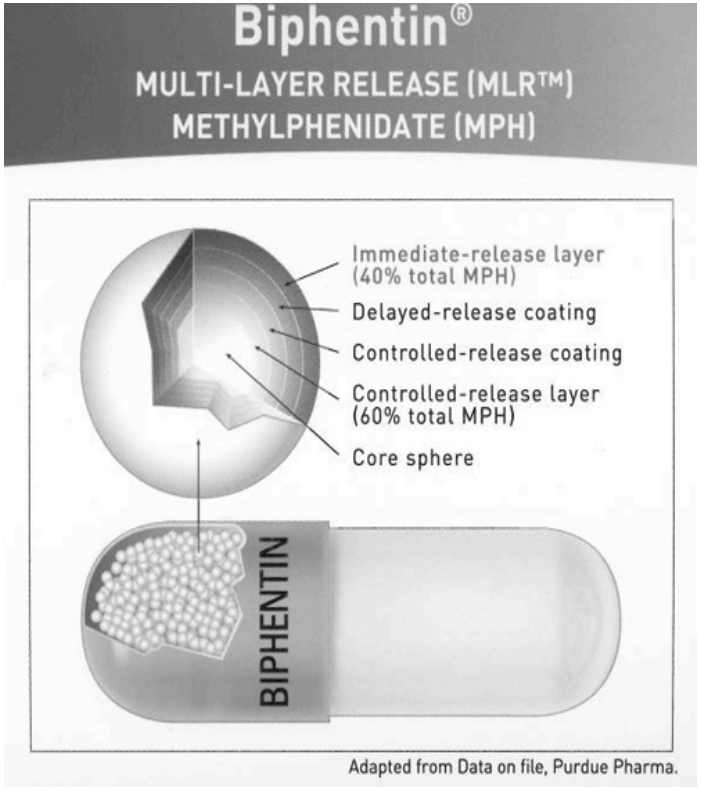


Generic Concerta – but is it really?



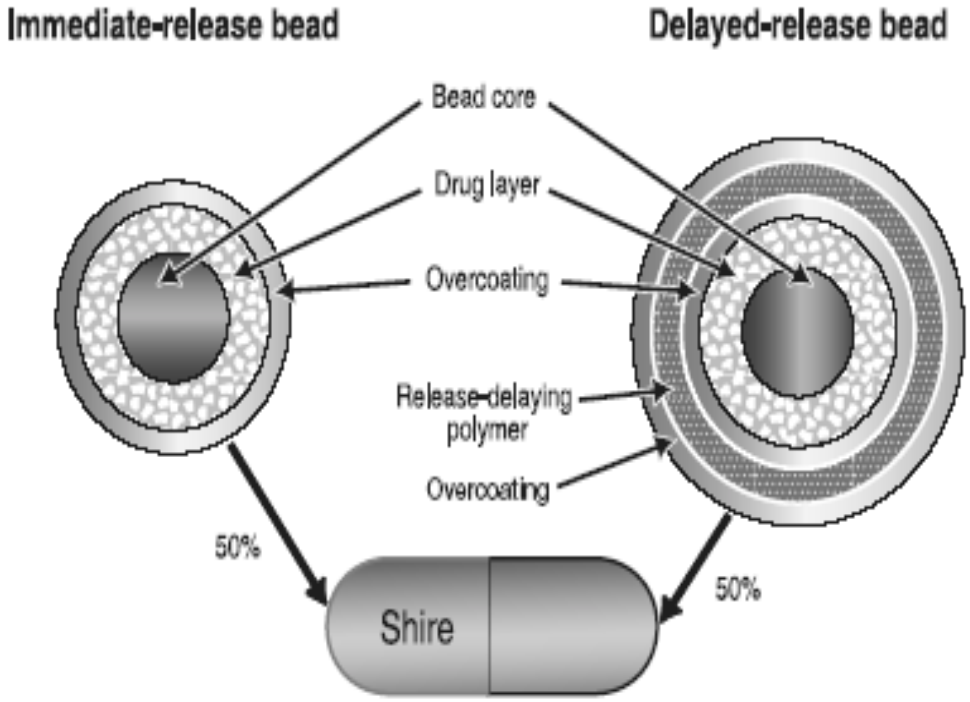
Methylphenidate (Biphentin®)

- Canadian 40% IR / 60% CR release formulation
- Multilayer beads inside gelatin capsule (can sprinkle)
- First peak: ~2 hrs
- Second peak: ~6-7 hrs
- Duration: Up to 12 hrs
- Available: 10, 15, 20, 30, 40, 50, 60, 80 mg capsules



Mixed Amphetamine Salts (Adderall XR®)

- 50:50 ratio of immediate to delayed release beads
- 4 salts: 75% d-amphet. & 25% l-amphet.
- Don't chew
- OK to sprinkle
- 10-12 hr DoA
- Well tolerated
- Controlled trials support the efficacy of MAS over placebo in >3000 pts
  - None looking at remission



ADDERALL XR Capsule
Available in 5-, 10-, 15-, 20-, 25-mg, and 30-mg capsules

Greenhill LL, et al. *J Am Acad Child Adolesc Psychiatry* 2003;42:1234

McCracken, et al. JAACAP 2003;42(6):673-683; Biederman et al. *Pediatrics* 2002;110(2):258

Lisdexamfetamine (Vyvanse)

- Prodrug converted to dextroamphetamine by erythrocytes
- Can dissolve in water or sprinkle on food
- 20-30 mg once daily; increase by 10 mg at weekly intervals (70 mg max)
- Capsules: 20mg, 30mg, 40mg, 50mg, 60mg

Atomoxetine

- "Selective" presynaptic NE reuptake inhibitor
- Nonstimulant agent indicated for ADHD in children (≥6 years old), adolescents & adults
- Marketed in Canada Dec 2004
- Non-controlled substance
- Leads to increases in PFC NE/DA
- Metabolized by CYP2D6 (90% Extensive/10% Poor)
- Half-life of 5 hrs, however duration of action is significantly longer (18-21 hrs)
- 10mg, 18 mg, 25 mg, 40 mg, 60 mg capsules

Atomoxetine Side Effects

- Decreased Appetite
- Nausea
- Dyspepsia (7%)
- Vomiting*
- Somnolence(15%)*
- Fatigue
- Dizziness
- Hepatic (2/3,400,000)
- Mood Swings
- Transient Weight Loss (0.5 kg)
- Increased:
  - HR (8 bpm)
  - SBP (3 mmHg)
  - DBP (2 mmHg)
- Sexual Dysfunction
- Suicidal ideation?

*Occurred significantly more frequently in atomox. vs MPH patients

Wernicke JF, et al. *J Clin Psychiatry.* 2002;63 (suppl 12):50-5.; Kratochvil CJ, et al. *JAACAP* 2002;41:776-84.
Kelsey DK et al. Pediatrics. 2004 Jul;114(1):e1-8.

Atomoxetine Safety data

- Meta-analysis of PC trials in children (ages 7-12)
  - 5/1357 (0.37%) atom vs. (0/851) PLB grp
- "No events" in those >12 yrs old (25% of study pop, in meta-analysis)
- Analysis of adult data did not indicate an increased risk of "suicide related events"
- Slight "increase in risk of side-effects such as suicidal thoughts, hostility, and mood swings"
- Need to inform patient/caregiver & document
- Need for monitoring

http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/strattera_hpc-cps_e.pdf

Atomoxetine's Role

- Stimulant non-responder
- Stimulants not tolerated
- Concern over using stimulants (e.g., abuse)
- Inattentive type of ADHD?
- Comorbid anxiety/depression?

Kratochvil CJ et al. Atomox mono vs. Atomox/Fluox. JAACAP. 2005 Sep;44(9):915-24.