

The Carter–Jenkins Center presents



Management of ADHD in Patients with Comorbidities, New Knowledge and Warnings

by

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A Picture is Worth a Thousand Words



ADHD MYTHS



- It only affects children not adults
- It disappears at puberty
- Children grow out of it
- Due to too much sugar or not enough
- Due to colorants or certain foods
- Due to fluorescent lighting, allergies etc, etc
- Psycho stimulants may lead to using drugs
- THE TRUTH:
- It is a genetic disorder, runs in families
- Present too during adolescence and adulthood

ADHD IS LIKE A TABLE, WITH THE TOP OF THE TABLE REPRESENTING THE TOTAL ILLNESS.:

- 1.- The first leg represents the attention problems**
- 2.- The second leg, the hyperactivity problems**
- 3.- The third leg represents the impulsivity problems**
- 4.- The fourth leg, the irritability problems**
- 5.- The combination of these ingredients is variable**
- 6.- One or two of the legs may be missing occasionally**



ADHD Medications and danger of Priapism

- FDA issued a warning for this rare but serious side effect.
 - The average age was 12.5 years (range 8 to 33 years).
 - It occurred with increases in methylphenidate dosis, or when medication was temporarily stopped for a short period of time, or when there was a longer period of time between dosis than typical, or after stopping the drug permanently.
- More common in patients on Strattera (Atomoxetine) than in those on methylphenidate.
- Erections lasting more than 4 hours require immediate attention to avoid damage to the penis.
- My experience with this problem in my patients.

What happens to their appetite?
What can you do?





What happens to their appetite?

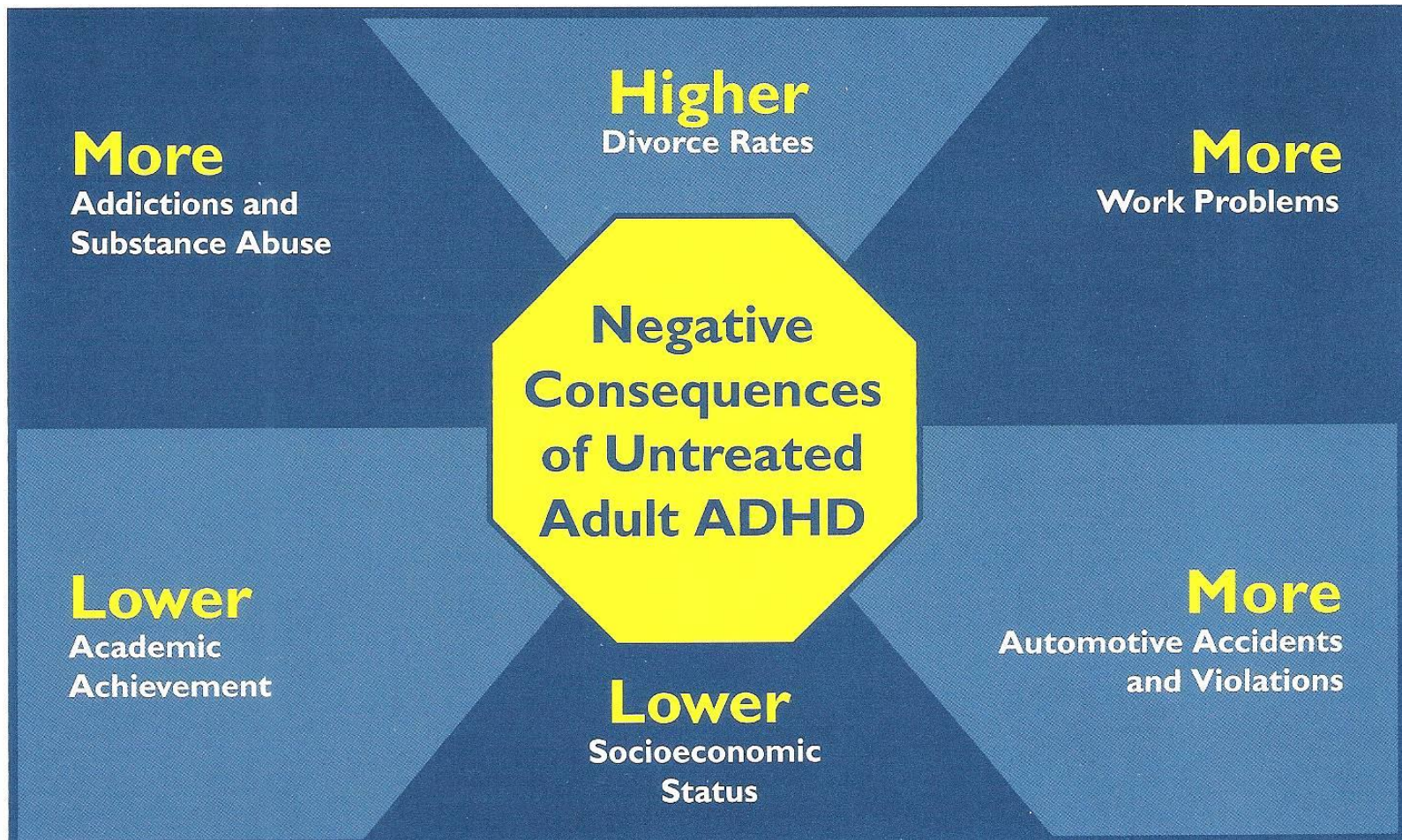
What can you do?

- 1) Appetite is decreased while meds are on board**
- 2) How long, depends on the half life of the meds being used, i.e. Concerta lasts 11 to 12 hours. Others last less**
- 3) Solution: Increase breakfast (add milk shakes, hamburgers, pizza etc) + late dinner + snack at bed time**
- 4) Allow supplements (protein shakes, nutrition bars)**

Where physicians fail and why?

- 1) Titrate higher as required but with care**
- 2) Do not do it by weight but by elimination of symptoms and/or appearance of side effects**
- 3) 35 to 40% of patients may need as much as 108 mg of Concerta in the A.M**
- 4) At least another 25 to 30% needs 72 mgs or more**
- 5) The above applies to both children and adults**
- 6) Doses can be increased every third day. Explain...**
- 7) Remember that MOST psycho-stimulans claiming to be full day medications last at most 5 1/2 – 6 hours**
- 8) Remember to talk to parents about the lost of appetite and what can be done about it**

ADULT ADHD: A GENETIC DISORDER WITH NEGATIVE CONSEQUENCES



What I Have Learned

- 1) ADHD is a misnomer. The word deficit seems to imply that they are lacking something
- 2) In fact what they are is hyper-attentive. In other words they pay attention to everything, to every stimuli that is produced around them, including smells. They can not ignore any stimuli.
- 3) The world is full of stimuli surrounding you everywhere. Think of a class room with 30 students. If they are hyper-attentive what is the real problem then?

What I Have Learned

4) People without ADHD can raise the threshold for stimuli so that they can ignore what they do not need. They hear it, or see it, or smell it, but they do not have to go there.

They do not have to follow every stimuli. Doing so is what takes ADHD patients away from staying where they need to be.

5) And that is why ADHD patients, can not stay focused, on what they are doing

Comorbidities Complicate ADHD Treatment

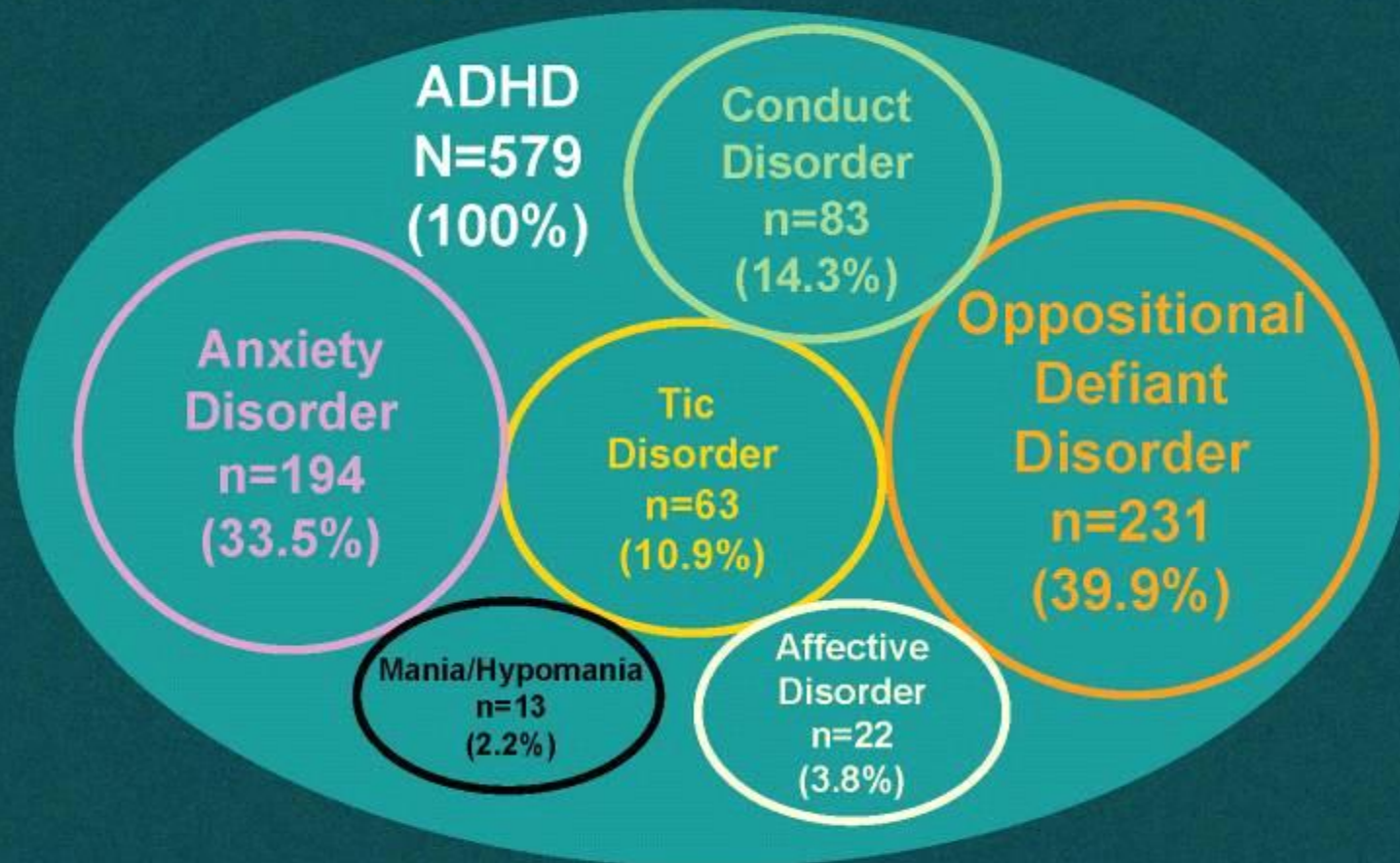
- The management of uncomplicated ADHD is usually straightforward
 - Stimulants among first-line treatments¹
- Persons with ADHD often experience comorbid psychiatric conditions^{1,2}
 - Comorbid symptoms may alter the response to stimulants²

1. American Academy of Pediatrics. *Pediatrics*. 2001;108:1033-1044.

2. Greenhill L, et al. *J Am Acad Child Adolesc Psychiatry*. 2002;41(2):26S-49S.



Comorbidities Reported in the MTA Study



MTA = Multisite Multimodal Treatment Study of Children With ADHD.

MTA Cooperative Group. *Arch Gen Psychiatry*. 1999;56:1073-1086.



Stimulant Treatment in ADHD

- Stimulant treatment in ADHD effectively improves core symptoms and associated impairments¹
 - Inattention^{1,2}
 - Hyperactivity^{1,2}
 - Impulsivity^{1,2}
 - Peer/family relations³
 - Academic outcomes³

1. Spencer T, et al. *J Am Acad Child Adolesc Psychiatry*. 1996;35:409-432.

2. Swanson JM, et al. *Lancet*. 1998;351:429-433.

3. Cunningham CE, et al. *J Child Psychol Psychiatry*. 1991;32:439-452.



AACAP Practice Parameters for Use of Stimulants: ADHD With Comorbidities

- According to the AACAP Practice Parameters, when a patient presents with ADHD comorbid with any of the following disorders, stimulants may be used for the treatment of ADHD symptoms
 - Oppositional defiant disorder
 - Conduct disorder
 - Learning disorders

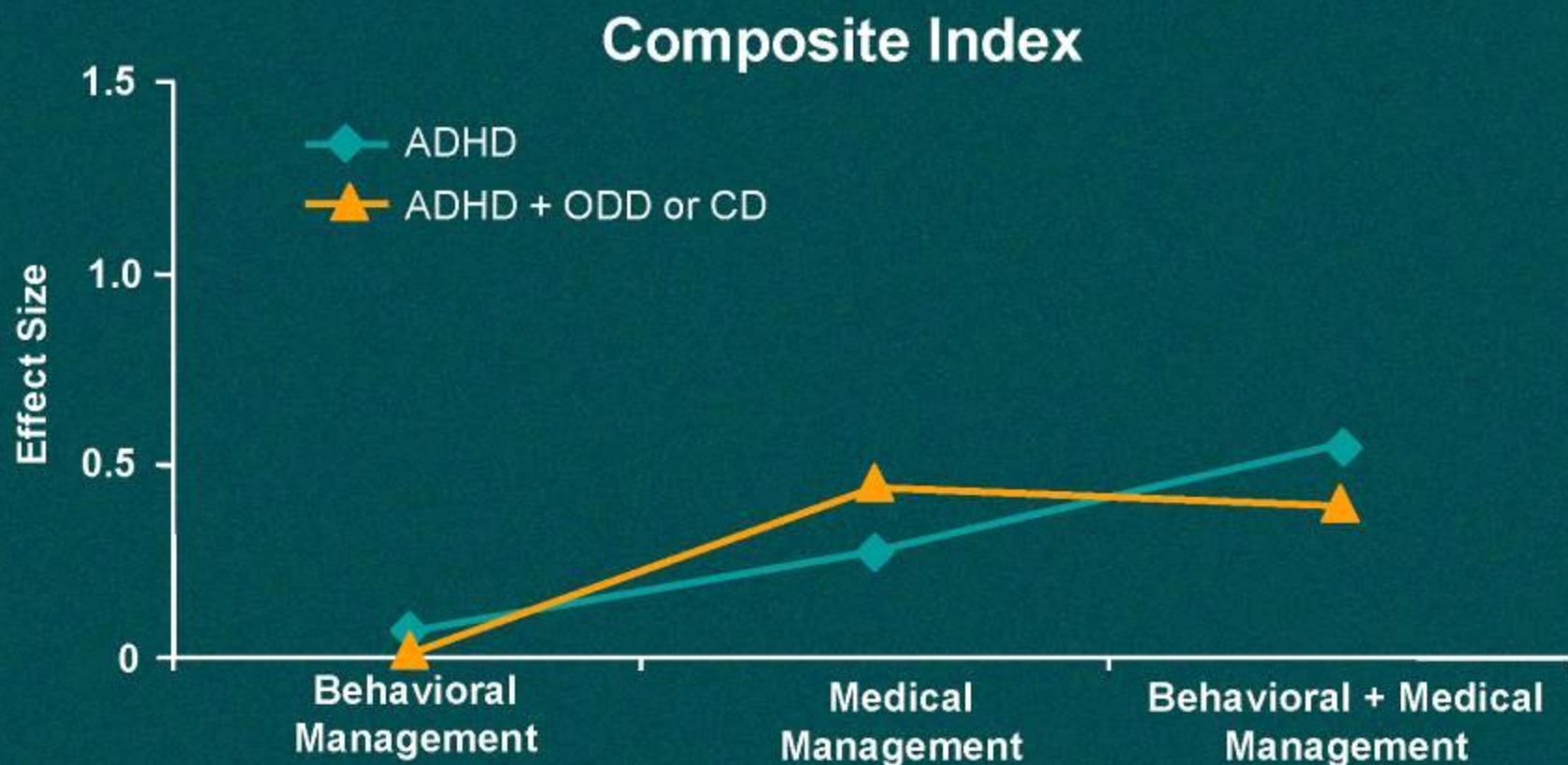


Oppositional Defiant Disorder and Conduct Disorder

- Children with ADHD with and without ODD or CD had an equal response to stimulant medication in the MTA study



Stimulant Treatment Response in Patients With ADHD and ODD or CD



CD = conduct disorder; ODD = oppositional defiant disorder.

Jensen PS, et al. *J Am Acad Child Adolesc Psychiatry*. 2001;40(2):147-158.



ADHD and Learning Disorders

- In subjects with ADHD and comorbid learning disorders, early intervention is important
 - ADHD often overlaps with various indices of academic underachievement during childhood
 - By adolescence, comorbid learning disorders are clearly associated with school failure
- Treatment improves ADHD symptoms and school performance but not the learning difficulty



Management of Comorbidities

- Comorbidities are frequent in patients with ADHD. Be sure to look for them.
- ADHD symptoms are the same if there are comorbid conditions
- Medications are effective in treating the ADHD patients with comorbid ODD / CD

Additional Safety Information

- Use ADHD medications with caution in patients with psychosis, bipolar disorder, history of seizure/EEG abnormalities, and hypertension
- ADHD medications should not be used in patients with pre-existing severe gastrointestinal narrowing, known structural cardiac abnormalities or other serious heart problems
- Stimulants may cause new psychotic or manic symptoms; discontinuation of treatment may be appropriate.
- Aggressive behavior or hostility should be monitored in patients beginning treatment.
- Methylphenidate may produce difficulties with accommodation and blurring of vision
- Hematologic monitoring is advised during prolonged therapy
- Methylphenidate should not be taken by children under 6 years of age
- Growth should be monitored. Patients who do not gain weight as expected should have their treatment interrupted

New knowledge, new warnings

- **Psychostimulants should not be used in patients with severe depression, schizophrenia or suicidal tendencies**
- **Psychostimulants are contraindicated in cases of angina pectoris, cardiac arrhythmias, heart failure, recent acute myocardial infarction or in cases of hyperthyroidism or thyrotoxicosis**
- **Psychostimulants should be used very cautiously in patients with high blood pressure. Blood pressure, should be monitored regularly in such cases**
- **Clear communications on side effects, potential dangers etc, must exist between parents, patients and doctors, so as to achieve a proper informed consent**
- **Mixing alcohol and MPH seems potentially dangerous****

WHY I PREFER MEDS LASTING 12 HOURS

If effective for 12 hours.:

- a) Children do not have to leave the class to take another dose at midday
- b) School does not need to be involved, it is a family business
- c) Schools do not always understand the need to overlap medication
- d) Occasional abuser of the dispenser of drugs at school (aspirin etc)
- e) Adolescents can not crush or pulverize capsules of Concerta (that last 12 h) to snort
- f) Children are covered to do homework with them
- g) Adults do not have to be carrying pills on them
- h) ADHD Adults are forgetful which can create problems at work, home etc if they have to remember taking the second or third doses...
- i) Many of the formulations do not last more than 5 1/2 hours though they are marketed as whole day medications. NOT TRUE, except for Strattera that is effective in my experience only about 30 or 40% of the time, decreases libido, and can cause priapism more frequently than MPHs, etc

New knowledge, new explanations

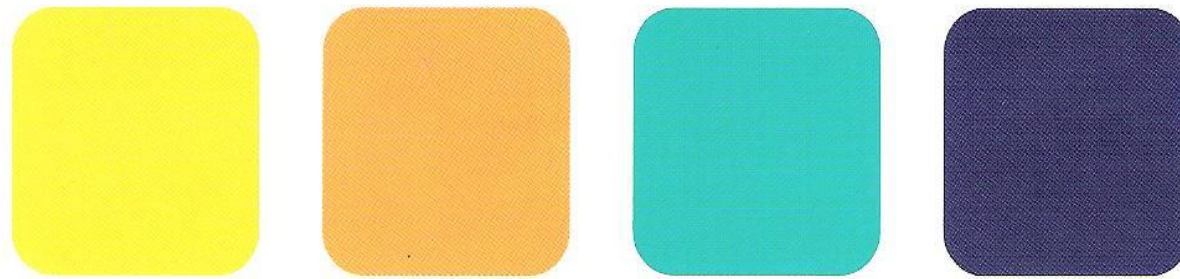
- **Studies continue to show that ADHD adults have an elevated prevalence of SUD (Substance Use Disorders)**
- **Alcohol abuse or dependence has been found in 17 to 45% of ADHD adults while 9 to 30% have histories of drug abuse or dependence**
- **A study by Biederman et al, showed that adults with ADHD, have a risk of a Substance Use Disorder twice as high, as non ADHD persons.**
- **The risks for ADHD patients treated with psychostimulants goes down to the norm for the United States that is, about 12% of SUDs**

New knowledge, new explanations





- The biggest jump in use of ADHD medications, --a 19% increase since 2004--, has taken place among adults in the age group of 20 to 44 years old**
- The increase in the group 10 to 19 years old was only 2%**
- The use of psychostimulants in children under 10 years of age fell during this period by 5 %**
- The total number of children 19 and younger in the United States taking ADHD medications is 3.3 millions**
- The total number of adults taking ADHD medication is between 1.5 and 1.7 millions**

The transdermal delivery system (MTS, Daytrana TM)

- 1) Patch was approved by the FDA on April 2006
- 2) The size of patch determines amount of drug delivered
- 3) The patch has a transparent backing and is known as a DOT matrix system. The MPH is loaded in dots in the silicone layer that leaves much of the silicone free to adhere to the skin
- 4) Apply only once daily. It delivers a constant amount of MPH while attached to the skin. Needs to be applied two hours before effects are desired. Remove in 9 hours for a 12 hours effect or remove earlier for shorter effect.
- 5) The drug is delivered transdermally thus passing through the skin directly into the blood stream which means that more drug may be available (particularly of the l-enantiomer removed by the liver) to reduce symptoms
- 6) Thus, more of the l-isomer circulates in the plasma than with oral medications. Less medication necessary? Not yet clear if this is the case



Daytrana™ Dosing

Dose Delivered Over 9 Hours ¹	Delivery Rate* ¹
 10 mg	1.1 mg/hr x 9 hrs
 15 mg	1.6 mg/hr x 9 hrs
 20 mg	2.2 mg/hr x 9 hrs
 30 mg	3.3 mg/hr x 9 hrs

- Daytrana is available in 4 dosage strengths: 10 mg, 15 mg, 20 mg, and 30 mg
- Daytrana is packaged in 10-count and 30-count trays
- Start all patients on the 10-mg patch; titrate dose to effect
- Daytrana should be worn for 9 hours to achieve a 12-hour duration of effect¹
 - Significance shown at 2 hours—the first time point measured¹⁻³
- Wear time can be individualized
 - Daytrana may be removed earlier than the recommended 9-hour wear time if a shorter duration of effect is desired or if late-day side effects appear¹

¹In pediatric subjects aged 6 to 12 when applied to the hip, based on a 9-hour wear period.¹

Table 2. MPH transdermal system sizes and delivery of MPH.

Patch surface area (cm ²)	Patch delivers* (mg/h)	MPH dose delivered over 9-h wear-time (mg)
12.5	1.1	10 (1.1 · 9 h)
18.75	1.78	15 (1.78 · 9 h)
25	2.21	20 (2.21 · 9 h)
37.5	2.97	30 (2.97 · 9 h)
*Nominal delivery rate/h in pediatric subjects aged 6–12 years based on 9-h wear-time [27]. MPH: methylphenidate.		

Taken from Wigal, Wigal and Kollins, “Advances in Methylphenidate Drug Delivery Systems for ADHD Therapy”, in *Advances in ADHD*, Vol. 1, No 1, 2006

The transdermal delivery system (MTS, Daytrana)

- 7) System is particularly useful for patients with swallowing problems and may allow in some patients for better control of the time of action of the medication**
- 8) Effects are independent of the gastrointestinal content**
- 9) Side effects are essentially the same of the oral products. Insomnia with the original 12 hour patch was a big problem. The FDA requested reduction to 9 hours for that reason. Sensitization to patch is possible (allergic reaction might then extend to oral forms of MPH?)**
- 10) Patch is applied to alternating areas of the child hips or thighs. In the provocation studies, applying patch in same place, led 13% of patients to develop sensitivity**
- 11) Redness is common but if edema, papules or vesicles appear a determination by a dermatologist is needed to ascertain whether sensitization has taken place**

The transdermal delivery system (MTS, Daytrana)

- 12) Patch has been studied only in children 6 to 12 years
- 13) Patch should be applied early in the morning. Effects take two hours to start. Should not be worn for more than 9 hours. Effects last for another 2 to 3 hours after patch is removed. DO NOT USE with MAOIs (14 days wash out)
- 14) The immediate release bolus of the patch is 6, 12 or 18 mg when doses used are 20, 40 or 60 mg (two patches of 20 or 30 mg must be used for the 40 and 60 mg doses)
- 15) The OROS system (Concerta) has an immediate release part of 4, 8, or 12 mg for the doses of 18, 36 and 54 mg capsules.
- 16) In my experience, the above amount seems enough for most patients in terms of immediate release needs. In the rare cases where that is not so, a small immediate release dosis may be added

The transdermal delivery system (MTS, Daytrana)

- The smaller patch should be used first (12.5 cm/10 mg) for a week and if the response is not satisfactory the patch size (and dosis) needs to be increased gradually every week until a good response is obtained**
- The erythema produced by the patch may not disappear until 8 hours after its removal**
- Remember too that there are formulations of methylphenidate in liquid form and as chewable tablets that may in many cases be an appropriate solution for children with difficulties swallowing**

Other drugs being considered

- 1) Modafinil (known as Provigil) proved effective for ADHD but was not approved by the FDA due to safety concerns. Was to be marketed as Sparlon. Provigil is used at present in narcolepsia, sleep apnea etc**
 - In the clinical trials Modafinil was associated with 31 cases of suicidal, aggressive or psychotic behavior as well as suspected cases of Steven- Johnson Syndrome that can be lethal**
- 2) A long acting version of guanfacine (alpha 2 adrenoceptor agonist) is being considered. A non-stimulant drug. Has being used as has clonidine, in the treatment of some aspects of ADHD for a long time**

For any further information about:

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(A Non-Profit Organization devoted to the education of professionals and communities all over the world), or to see the “Self Learning Programs on the Behavioral Sciences”, as well as the lectures on mental health available free

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The End

Questions?