Adolescents in HIV Biomedical Prevention Trials

Drug Development for Adolescents

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Drug Development for Adolescents

- Few therapeutics used in adolescents are approved for use in this age group (*off-label*)

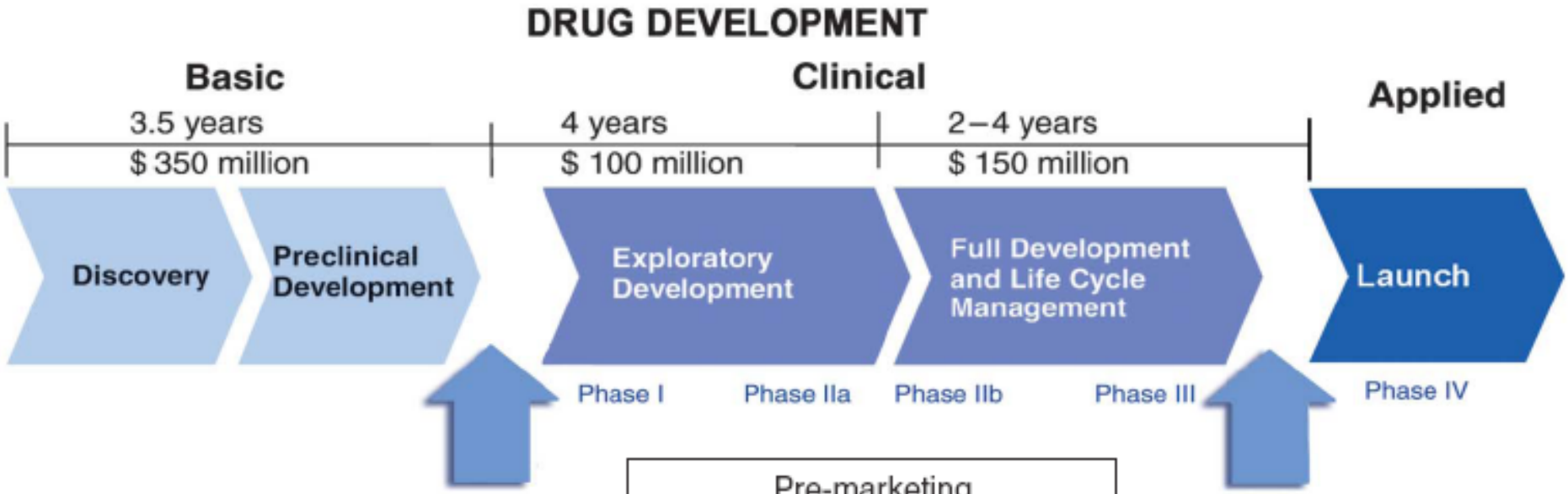
- Common examples of *off-label use* that every pediatrician and adolescent medicine provider contends with are antibiotics

- Pharmacokinetic (PK) data are very difficult to find for drugs used in adolescents

Drug Development for Adolescents

- Dosing regimens (*assumptions*) are typically based on PK studies in adults (men)

- Pharmacodynamic (PD) *assumptions* are based on studies in adults (men)
- Despite legal and regulatory adaptations to incentivize research on safety and efficacy of new agents in children, many such studies done with agents predominately marketed & used in adults



One area addressed late in drug development (***if at all***) is therapeutics during adolescence

According to the NIAID, 5.4% of the 9,500 participants in clinical trials supported in 2005 were adolescents

Pre-marketing clinical trials

- Restricted disease
- Restricted age
- Restricted sex
- No co-morbidities
- No concomitant medication

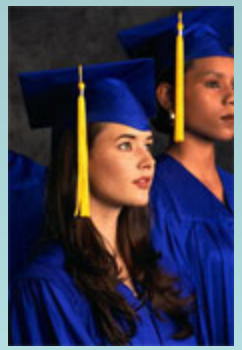
Dose range may apply only to a restricted target population

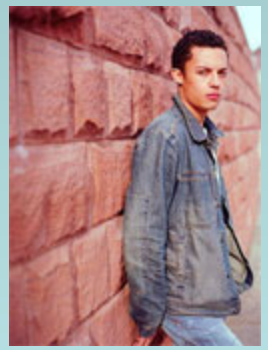
Do PK and PD change during adolescence?

How does health literacy impact participation in clinical studies and appropriate use of therapeutics?

Why do we need drug data on adolescents?

Biology

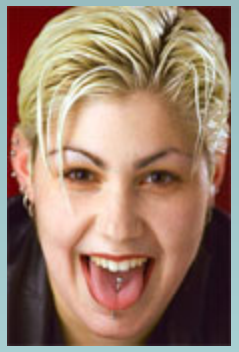




Why do we need drug data on adolescents?

- Physical changes in adolescence can result in unpredictable pharmacologic parameters that may not change in a consistent relationship with age, developmental stage or metabolic function, making it difficult to scale treatment based on studies in prepubescent children or adults.

Adolescent Life Contributor's Influence on Pharmacology



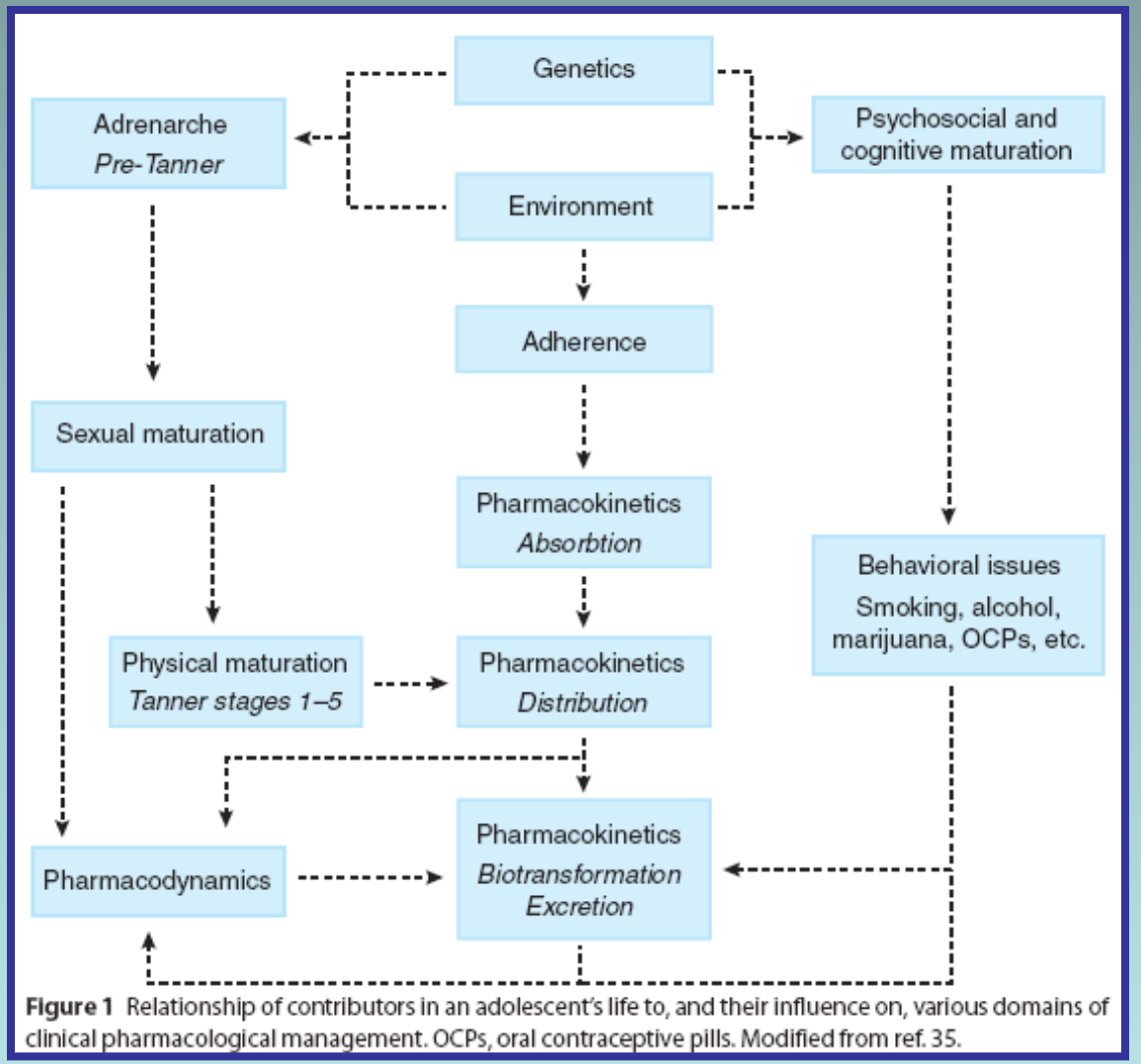


Figure 1 Relationship of contributors in an adolescent's life to, and their influence on, various domains of clinical pharmacological management. OCPs, oral contraceptive pills. Modified from ref. 35.

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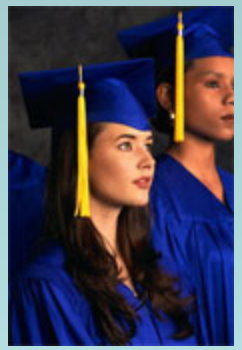
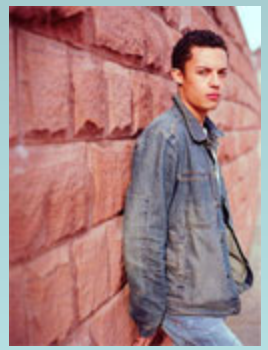
Why do we need drug data on adolescents?

Behavior





Why do we need drug data on adolescents?

- Risk behavior - an additional milestone entailing a complex process of interrelated conceptual domains
  - R Jessor. New Perspectives on Adolescent Risk Behavior. 1st ed. New York City: Cambridge University Press; 1998:1-10.

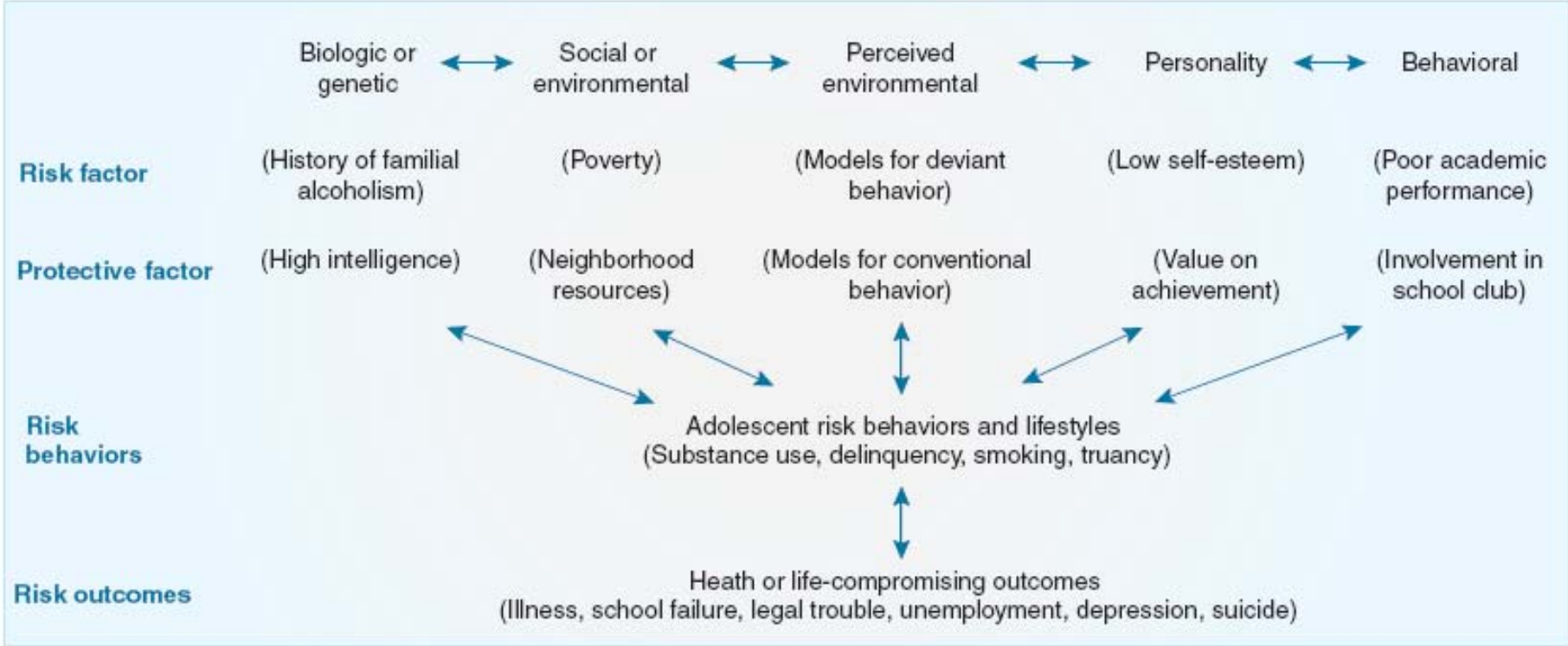
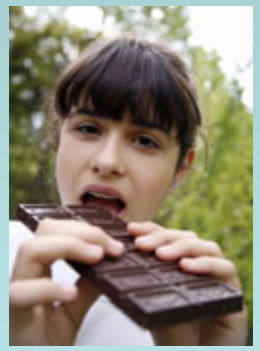
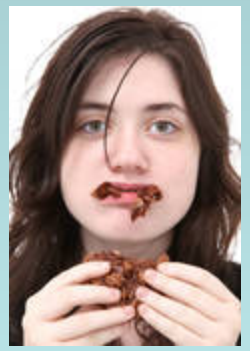


Figure 2 Interrelationships of various physical, social, behavioral, and environmental factors and the resulting risk behaviors, with their incumbent consequences. Modified from ref. 36.

Why do we need drug data on adolescents?

- Behavioral considerations during adolescence can compound this picture making selection of proper dosing of medications even more challenging.





Issues that Affect Adolescent Pharmacology

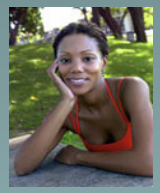


Table 1 Adolescent conditions and diseases affecting pharmacokinetics (PK)

PK parameter	Condition	Mechanism	Clinical outcome
Absorption	Eating disorders Bulemia Anorexia nervosa	Erratic intake, organ dysfunction, and electrolyte imbalance	Therapeutic failure, possible toxicity
Distribution	Obesity	Adipose tissue is a reservoir for lipophilic agents	Prolonged clearance
	Malnutrition	Decreased fat, muscle mass, and plasma protein	Increased clearance with/without enhanced drug effect or toxicity
	Renal dysfunction	Diseased protein binding	Increased unbound drug in face of low serum levels
	Burns	Massive fluid shifts; cell-membrane disruption; decreased serum albumin	Multifactorial
Biotransformation	Hepatic dysfunction Alcohol Drug-induced Infectious Steatosis	Impaired metabolism	Possible toxicity
Elimination	Renal dysfunction	Accumulation of endogenous acids that compete/displace plasma protein–bound drug, accumulation of drugs >40% renally excreted	Enhanced drug effect/toxicity for drugs >90% bound; toxicity profile depends on drug
	Burns	Renal blood flow and GFR decreased acutely	Possible toxicity

GFR, glomerular filtration rate. Modified from ref. 35, with data from Brater[37] and Bonate.[38]

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Adherence is a Major Player

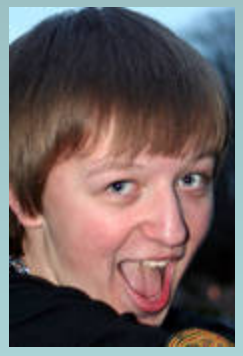

Table 2 Improving adolescent adherence
Communication, education, and comprehension
Provide respectful and age-appropriate communication *If youth is on medication, ask how he or she takes it*
Develop a satisfactory and collaborative relationship
Provide and encourage use of medication counseling, and encourage pharmacist involvement
Give clear instructions, with the most important information given first *Support verbal instructions with easy-to-read written information*
Assess patient's literacy and comprehension and modify educational counseling as needed *Don't rely exclusively on a patient's knowledge about his or her disease to improve compliance*
Regimen selection
Simplify regimen as often and whenever possible
Use the optimal dosage form and schedule for each youth
Compliance aids
Use behavioral techniques *Goal setting, self-monitoring, cognitive restructuring, skills training, contracts, and positive reinforcement*
Use mechanical compliance aids as needed *Sectioned pill boxes or trays, compliance packaging, color-coding*
Find solutions for youth with physical or sensory disabilities *Non–safety caps on bottles, large type for labels and written material, tape marks on syringes*
Judiciously enlist support and assistance from family or caregivers, as appropriate

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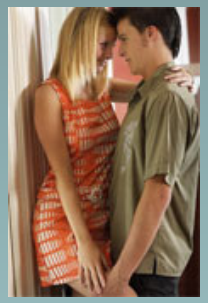
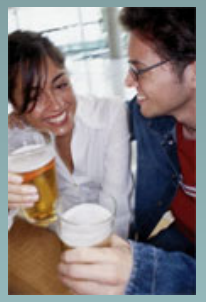
How Does the "Market" Influence Drug Development for Youth?

- Market is an important consideration for industry when embarking into drug development
  - HPV Vaccine
    - Extensive marketing campaign started in 2005
    - Could early uptake of the vaccine by the community have been better?

Why aren't more adolescents included in drug development efforts?

- Psychosocial issues
- Biological factors
- Physiologic events
- Pregnancy & reproductive health
- Ethical-legal considerations
  1. Age of consent
  2. Inadvertent disclosure of sensitive information to caregivers
  3. Access to care – i.e. insurance (see #2)

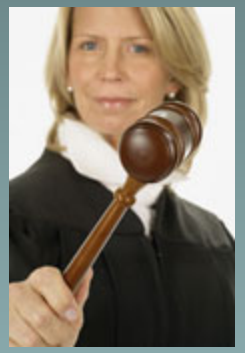

45 CFR §46.408
45 CFR §46.402

Summary

- There are substantial differences among pediatric, adolescent and adult populations in drug disposition and response

- Adolescent participation in clinical trials is essential so that research findings can be applicable to this group

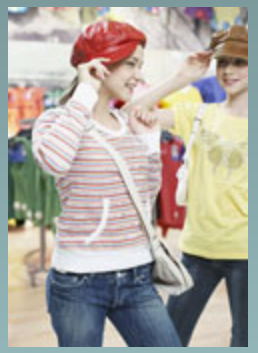
Goals

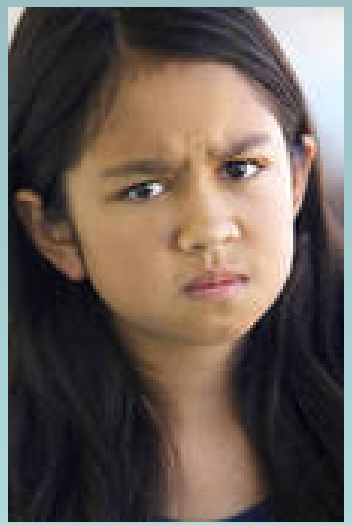


- To achieve improvement in the inclusion of adolescents in clinical trials, we must address the challenges specific to this population
  - Trial design
  - Safety
  - Legal, ethical, regulatory and operational factors
  - Community & key stakeholder buy-in

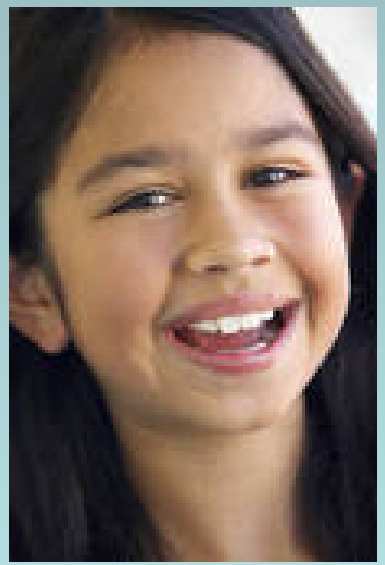
Goals

- Ethical biomedical research with adolescents should focus on two main goals:
  - Reasonable protection from research risks
  - Appropriate inclusion in clinical research that will improve our understanding of pharmacologic agents.





We don’t want them to be upset…



Say YES to adolescent participation!