Developmental Pharmacodynamics: An Overview

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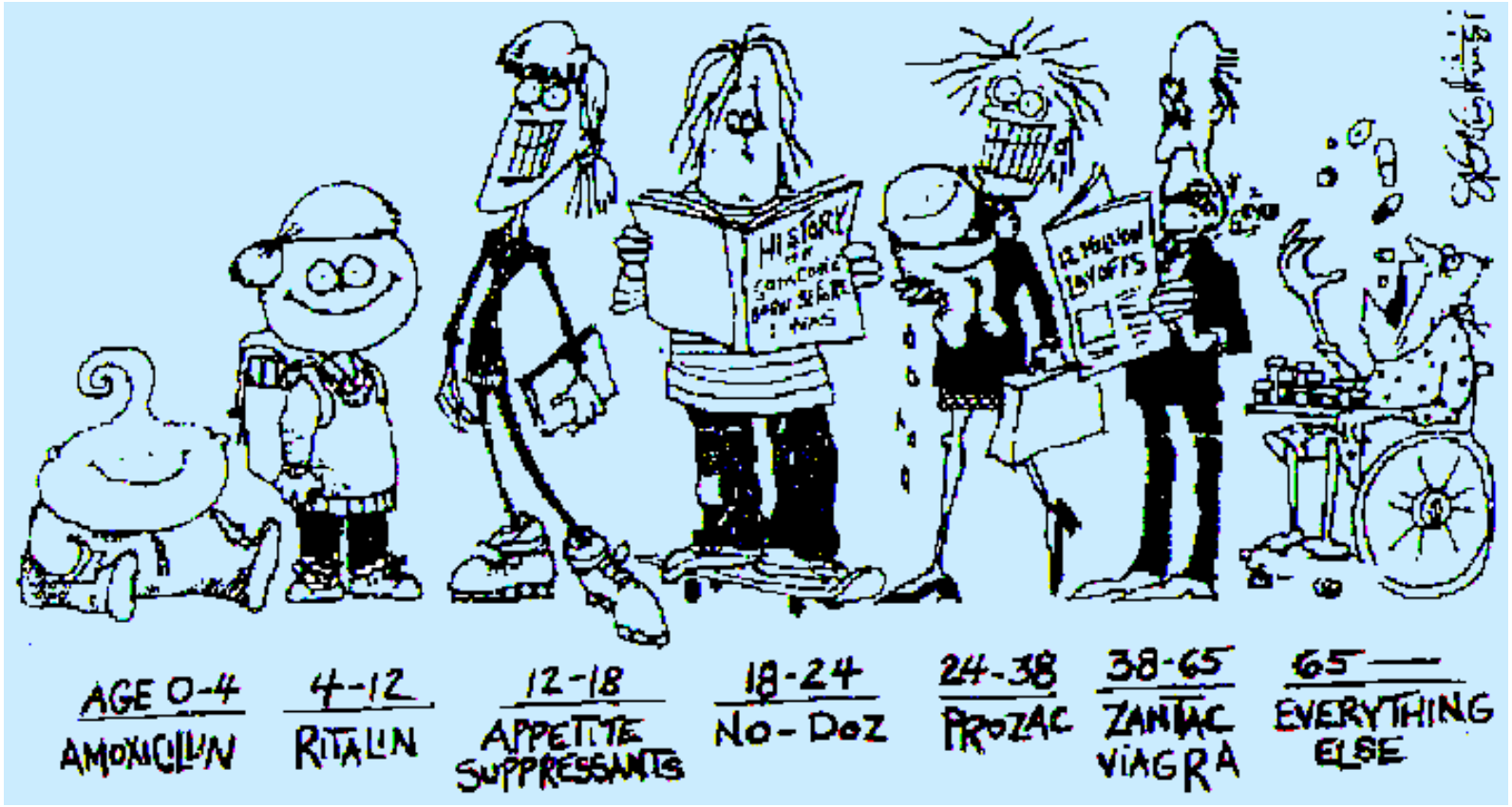
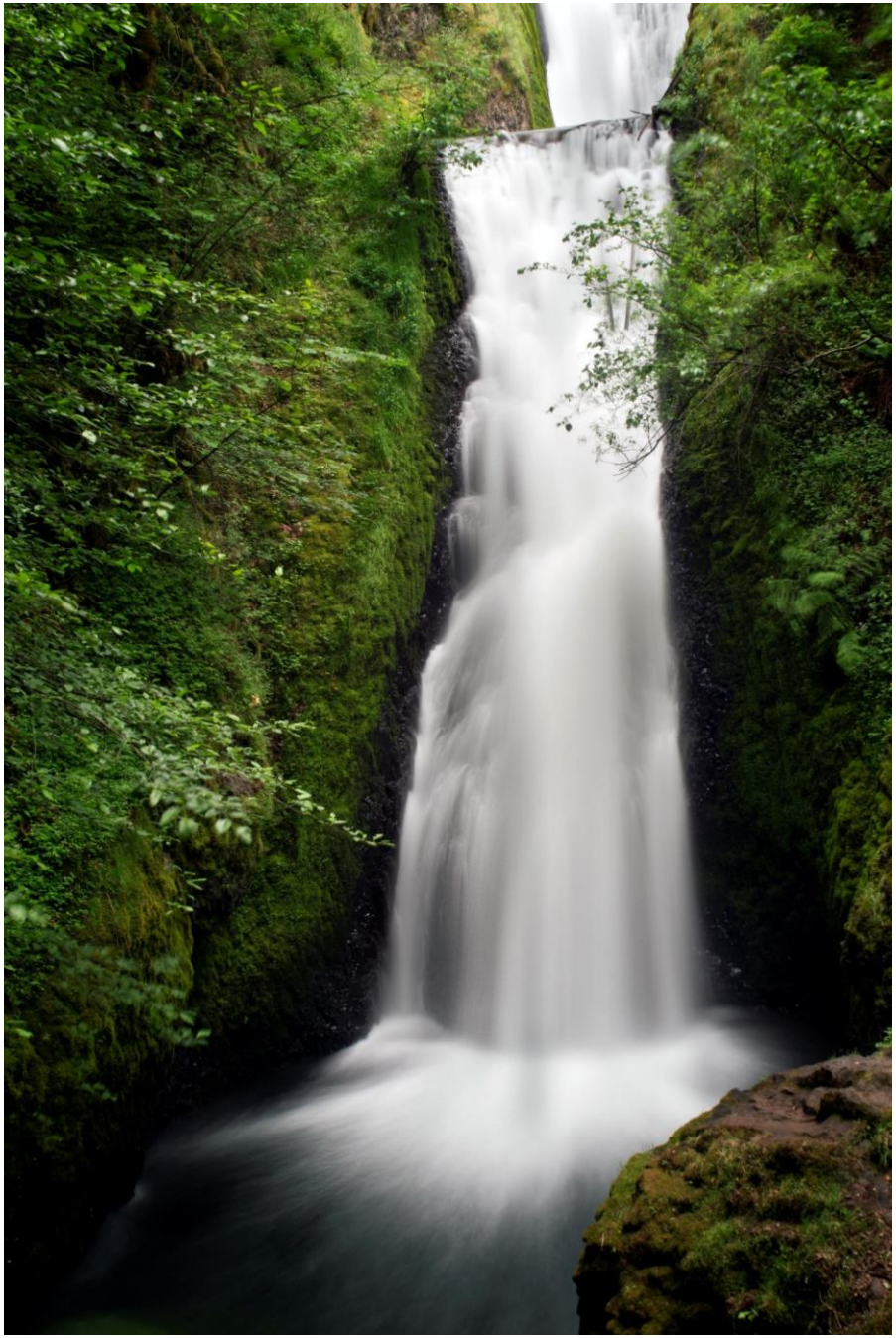
Introduction to Developmental Pharmacology…



Supplement Article
The Journal of Clinical Pharmacology 2018, 58(S10) S10–S25**DOI: 10.1002/jcph.1284**

Developmental Changes in Pharmacokinetics and Pharmacodynamics

John van den Anker, MD, PhD, FCP[1,2,3], Michael D. Reed, PharmD, FCCP, FCP[4], Karel Allegaert, MD, PhD[3,5,6], and Gregory L. Kearns, PharmD, PhD, FCP



DOSE

↓

CONCENTRATION

↓

EFFECT

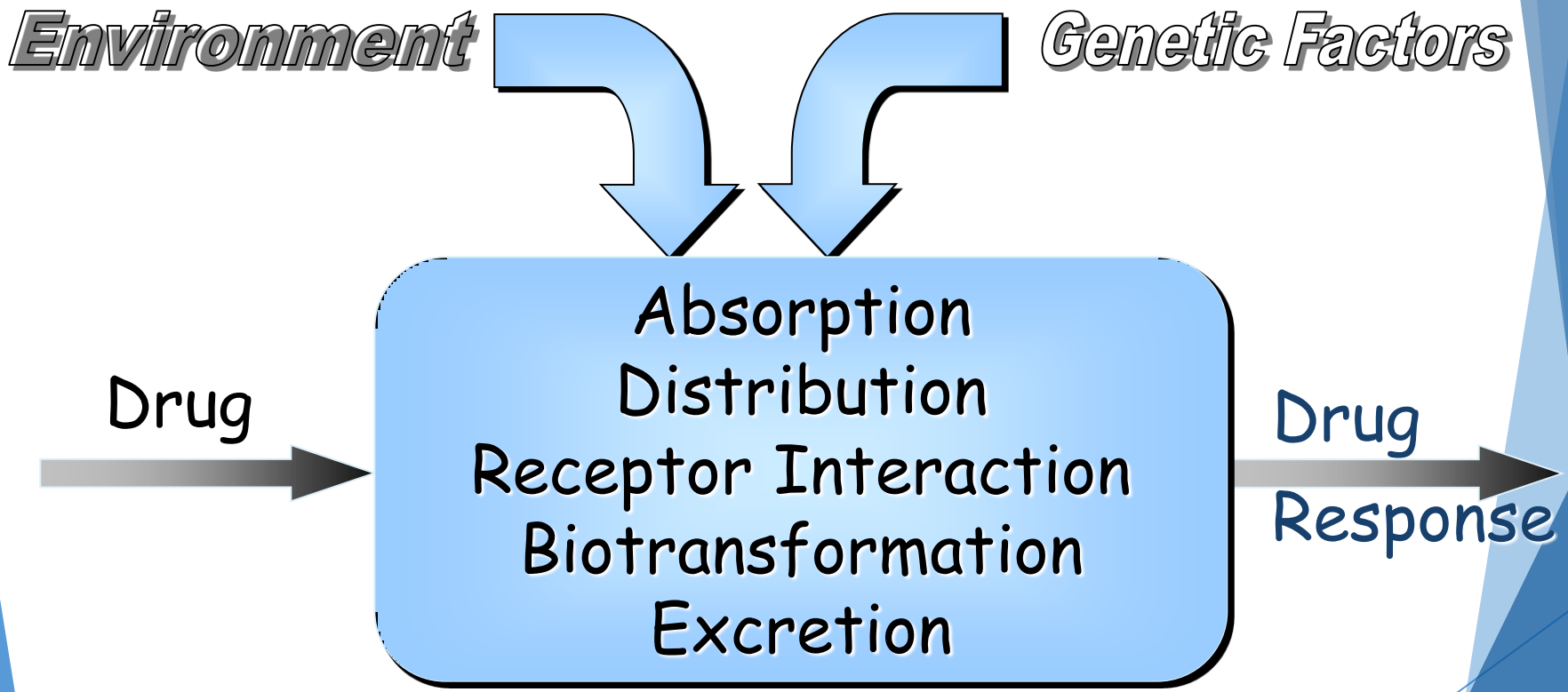
↓

EFFICACY

↓

TREATMENT OUTCOME

Variation in Drug Response



REVIEW ARTICLE

Pediatr Drugs 2010; 12 (4): 223-233
1174-5878/10/0004-0223/$49.95/0

Understanding Developmental Pharmacodynamics

Importance for Drug Development and Clinical Practice

Hussain Mulla

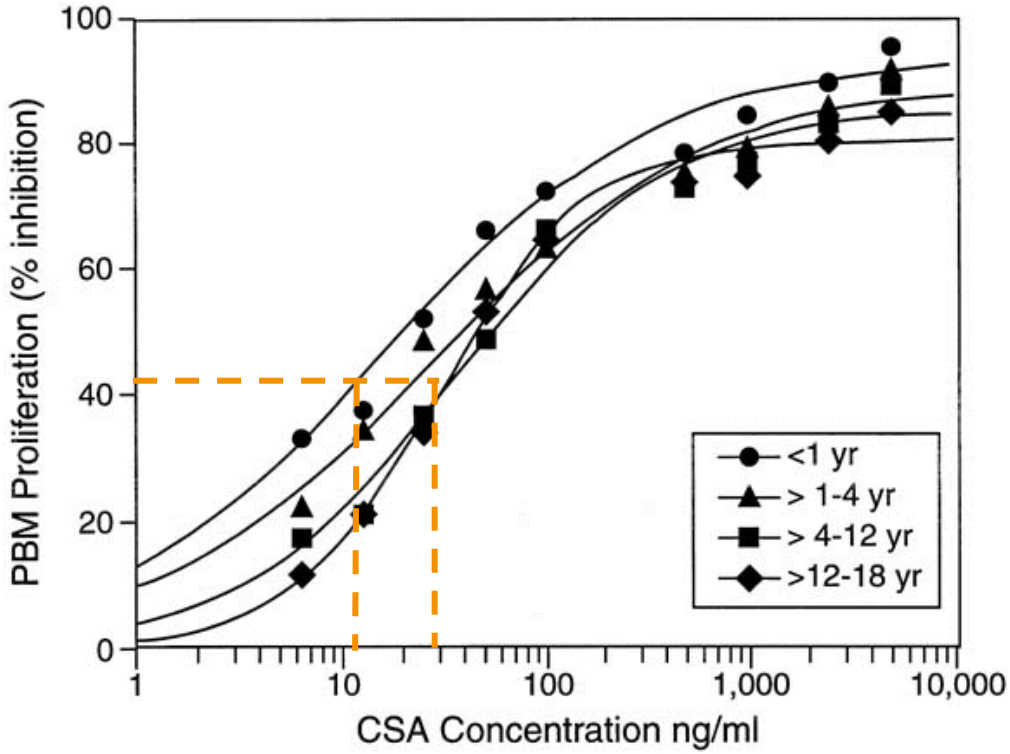
Centre for Therapeutic Evaluation of Drugs in Children, University Hospitals of Leicester, Leicester, UK

"the study of age-related maturation of the structure and activity of biologic systems and their effects on response of children to pharmacotherapy"

Mulla H. Understanding developmental pharmacodynamics. *Paediatr Drugs*. 2010 Aug 1;12(4):223-33.


TERRACOTTA
INDOOR BABIES
$7.95

Cyclosporine Effect Is Age-Related



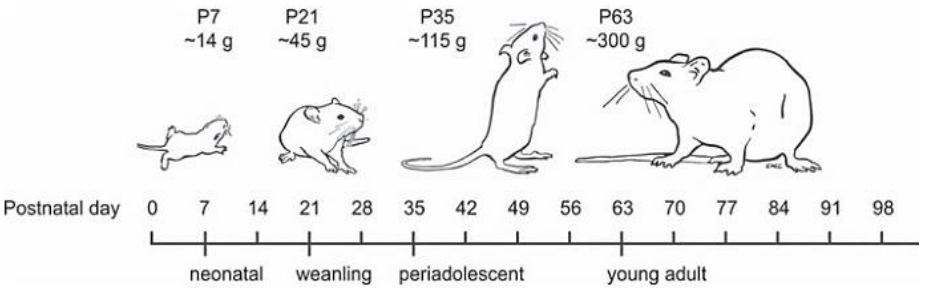
Infant lymphocyte proliferation response at EC_{50} was 2-fold less in infants as compared to older subjects

Marshall JD, Kearns GL. *Clin Pharmacol Ther* 1999;66:66-75

Animal Studies in Developmental PD

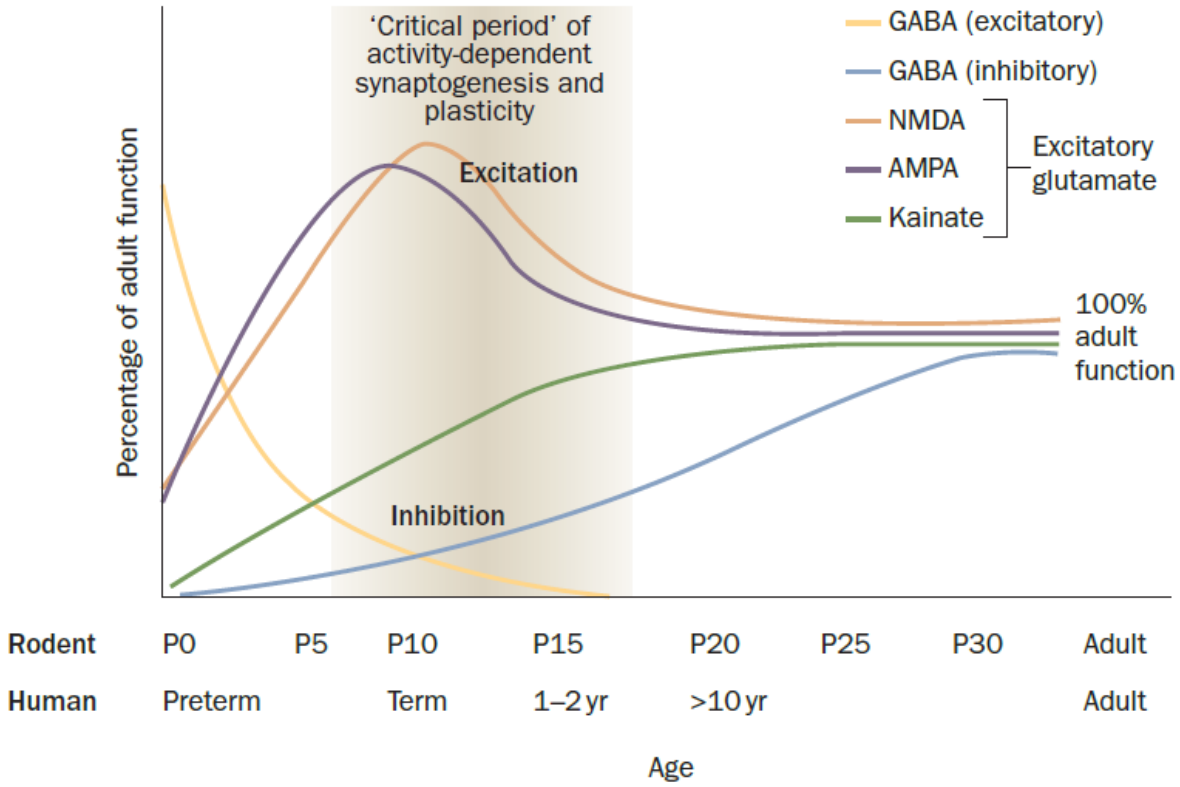
- Animals are commonly used as surrogates for developmental PD studies
- Caveats
  - Different ADME
  - Different body size
  - Different receptors?
    - (e.g., neurodevelopment)

Stage	Rat	Human
Life span	3 years	80 years
Neonate	7-14 days	1 month
Weaning	21 days	6 months
Sexual maturity	50 days	11.5 years
Mature	7-8 months	20 years
Senescence	15-24 months	51 years



Quinn 2005, *Nutrition*

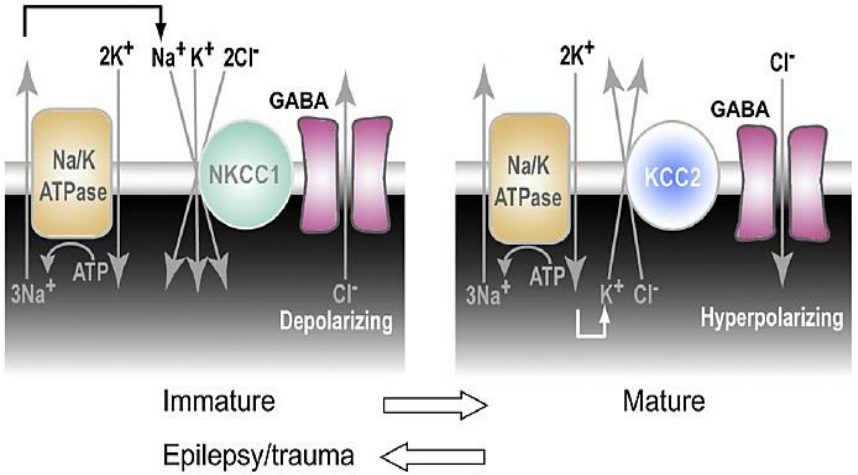
Ontogeny of GABA & Glutamate Receptors



Rakhade and Jensen 2009, *Nature*

Impact of Development on GABA Receptor Function

- High concentration of chloride present in nerve cells during early development, which causes excitation
- Intracellular chloride concentrations decrease during development resulting in inhibitory neurotransmitters



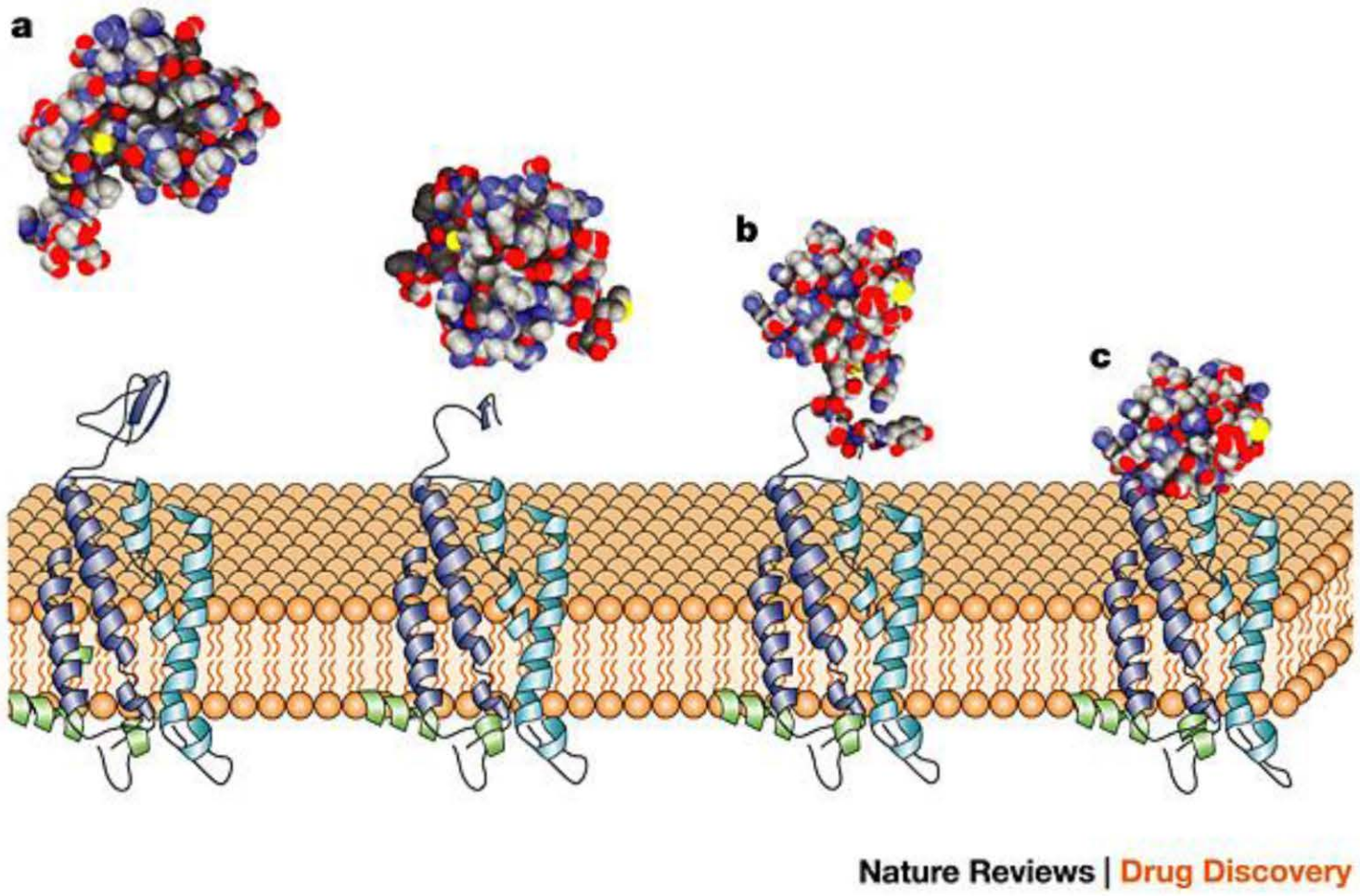
- GABA receptors functions differently in mature and immature subjects
  - Mature brain: inhibitory neurotransmitter
  - Immature brain: tropic factor influences proliferation, migration, differentiation, synapse maturation and cell death

Loscher et al 2012 *Neuropharmacology*

Examples of Age-Dependent Differences in Pharmacodynamics

- Higher incidence of VPA-associated hepatotoxicity in young infants
- Greater frequency of paradoxical CNS reactions to diphenhydramine in infants
- Greater weight gain associated with atypical antipsychotic agents in adolescents
- Altered warfarin dose – effect in children with congenital heart disease & prepubertal children
  - Developmental differences in Vitamin K-dependent clotting factors
  - Lower protein C concentration
  - Lower prothrombin fragments 1 and 2

Lowry JA, et al. Chapter 57: Principles of Drug Therapy in Nelson's Textbook of Pediatrics, 20th ed., 2014

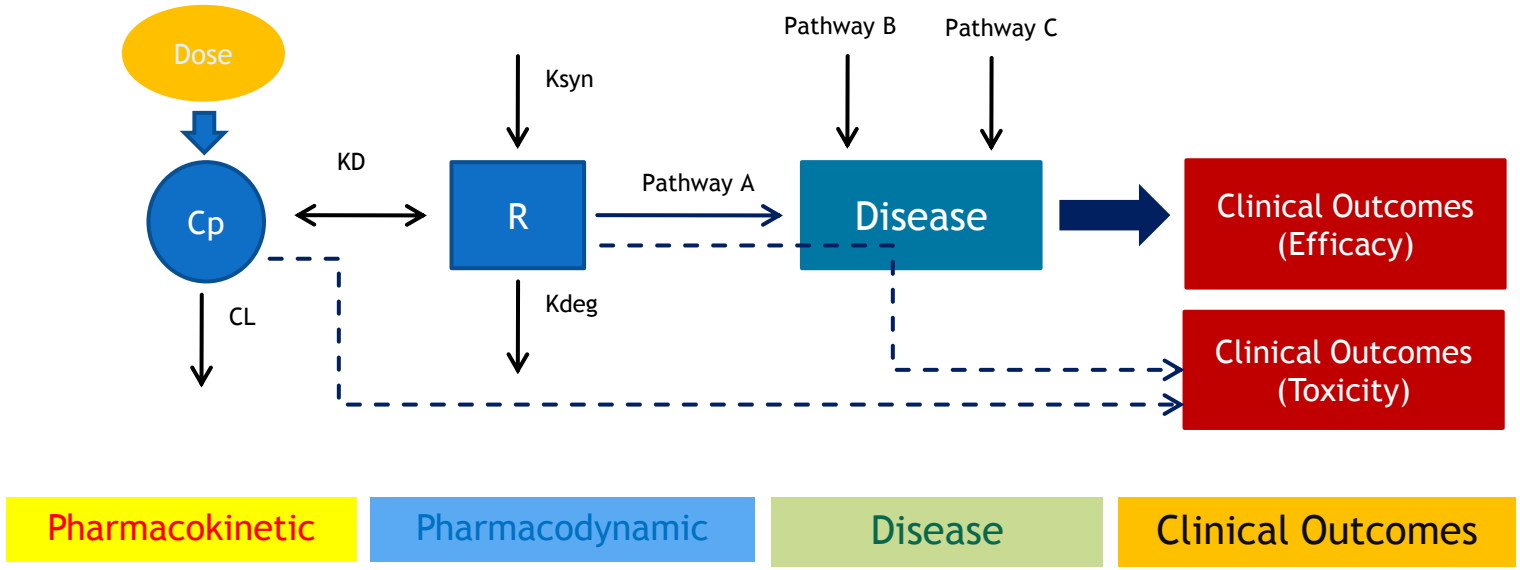

a
b
c
Nature Reviews | Drug Discovery

Pharmacologic programming

- Process whereby a drug (stimulus) applied during fetal or neonatal life has permanent effects on long-term development
- Structure and function of organ systems affected by interaction of drug with receptors during early crucial phases of development
- Can be *positive* (therapeutic) and *negative*
  - *E.g., in utero exposure to glucocorticoids adversely affects fetal renal and hepatic development as well as hypothalamus-pituitary axis development*
  - *In the developing brain, many neurotransmitters play a role entirely different from that which they play in the mature brain*

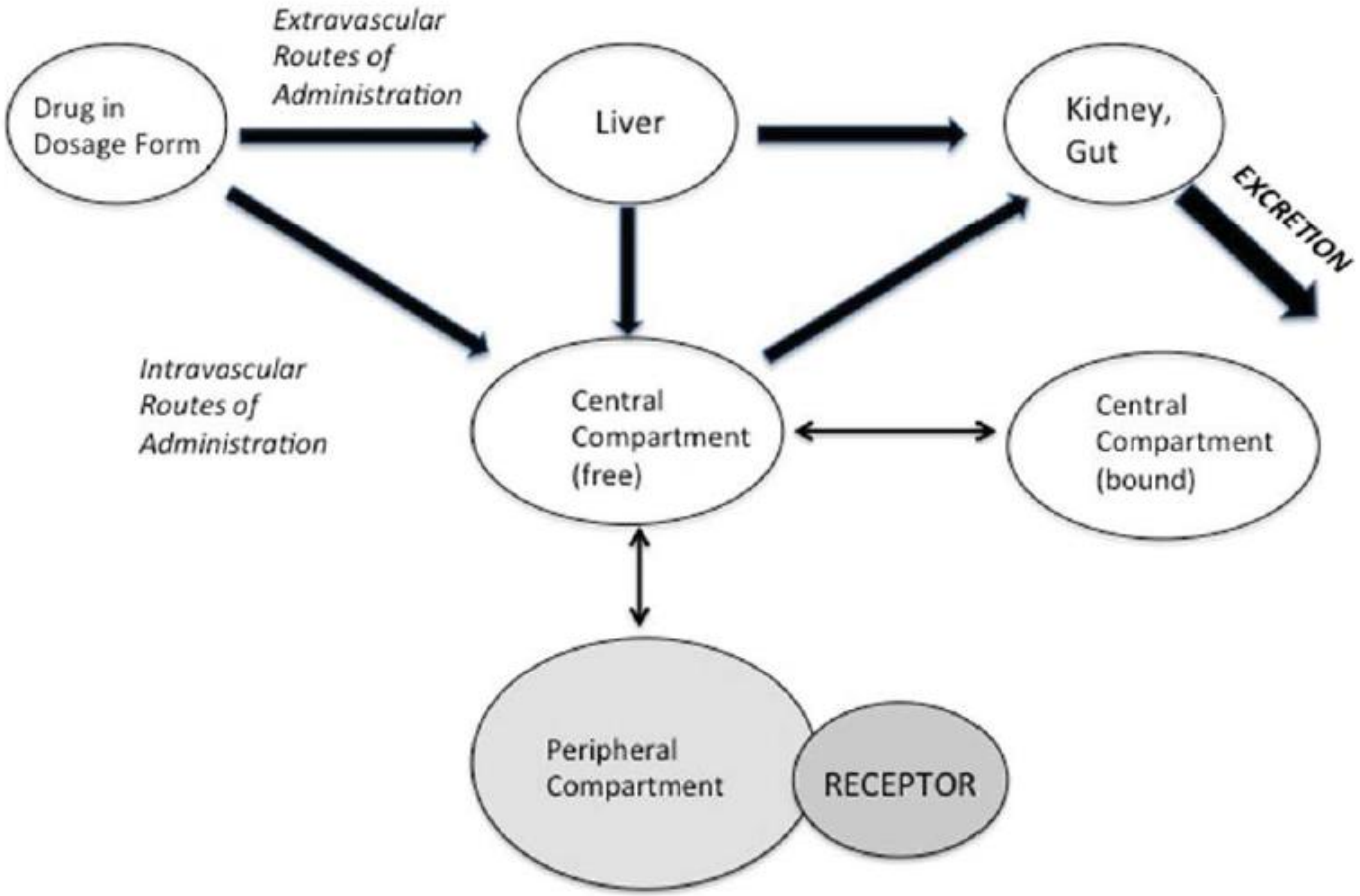
Mulla H. Paediatr Drugs. 2010 Aug 1;12(4):223-33.

Pharmacokinetic-Pharmacodynamic-Disease Relationships of Pharmacotherapy



Connecting dose-exposure-response

A hypothetical compartment model linking drug administration to effect

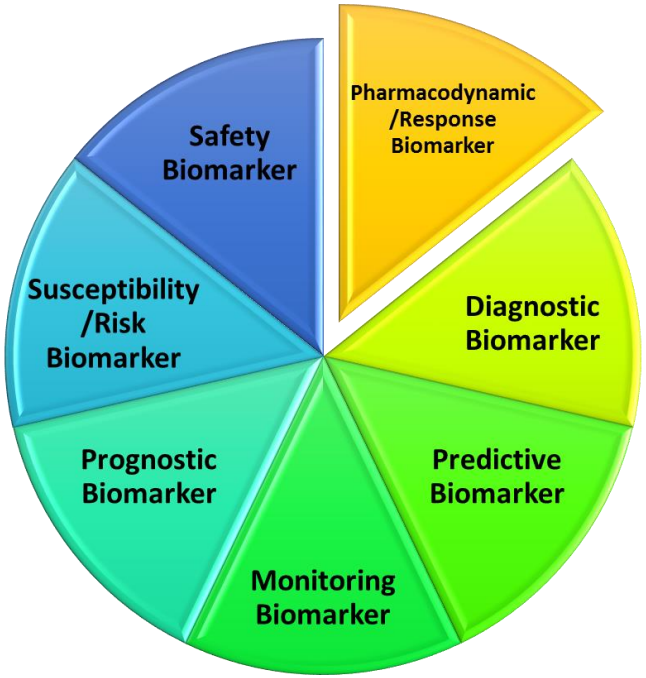


Assessing the Impact of Development on Drug Action and PD Will Require a New "Mouse Trap"

Biomarker Definition & Categories

NIH definition: “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention.”

https://www.ncbi.nlm.nih.gov/books/NBK326791/

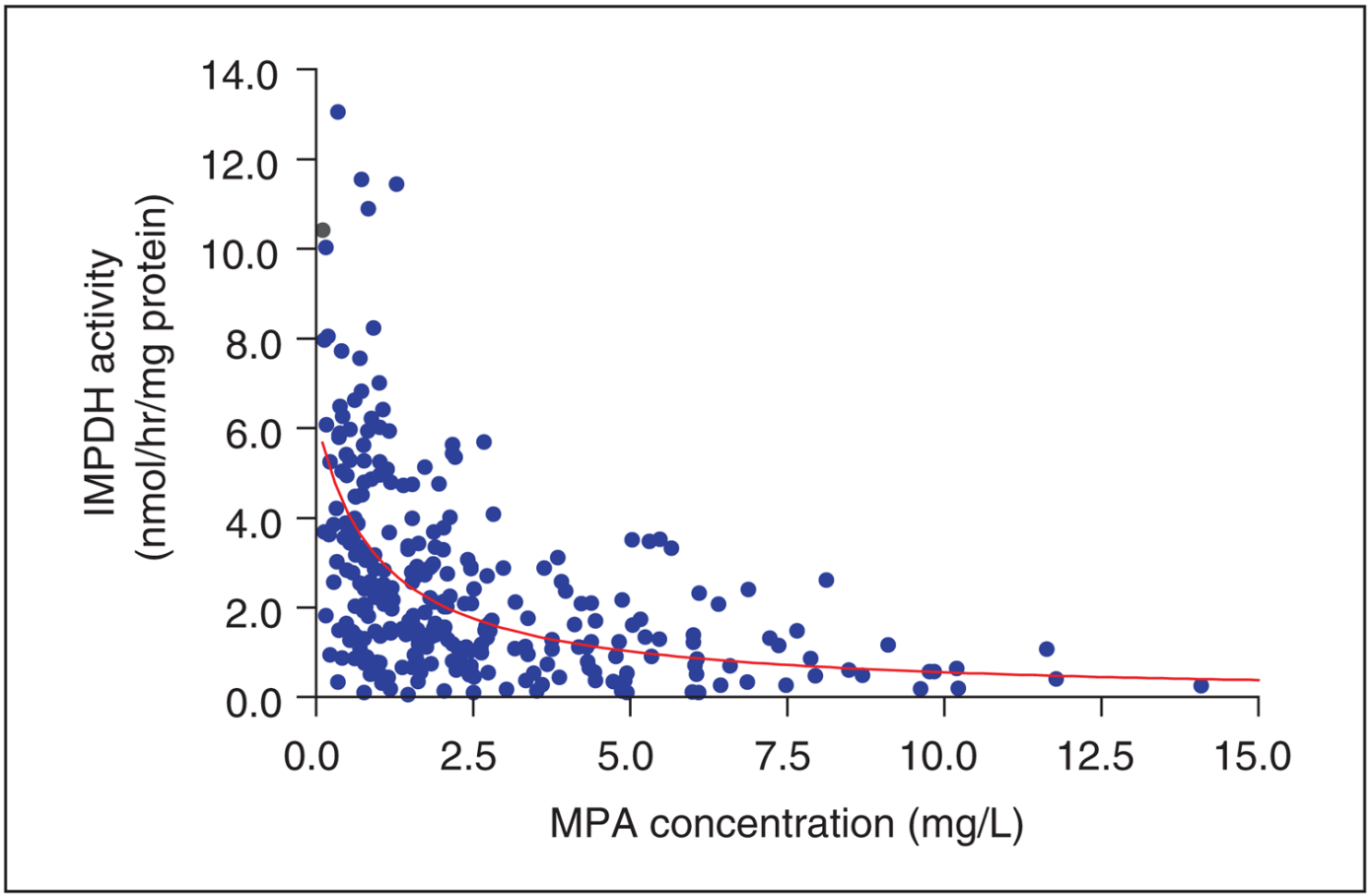


Categorization of Pediatric Biomarkers

Disease Progression or Response	Systemic Drug Exposure or Effect	Pharmacodynamic Biomarkers
Hemoglobin A1C (diabetes)	CYP2D6 (codeine response)	Plasma drug concentrations
C-reactive protein (inflammation)	TPMT (azathioprine or 6-mercaptopurine effect)	PET imaging and functional MRI
Alanine aminotransferase (hepatitis C)	VKORC1 (warfarin response)	Blood pressure
Exhaled nitric oxide (asthma)	CYP2C9 (warfarin metabolism)	Epicutaneous histamine response
MYCN (neuroblastoma)	Methotrexate polyglutamates (JIA response)	Esophageal pH monitoring (gastroesophageal reflux)
C reactive protein (inflammation)	CYP2C19 (proton pump inhibitors)	AUC / MIC ratio (antimicrobial effect)

Kearns GL and Artman M, 2015

Concentration vs. Effect – IMDPH activity as biomarker of mycophenolic acid immunosuppression



Fukuda T, et al. J Clin Pharmacol 2011;51:309-320

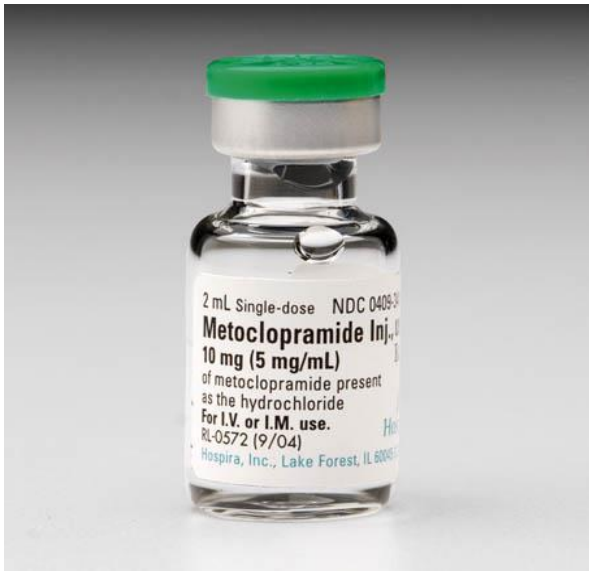
PD/Response Biomarker

- In clinical practice: The main utility is to guide dosing or continued use of a drug or other intervention
- In drug/device development: to establish proof-of-concept that a drug produces a pharmacologic response related to clinical benefit, and to guide dose-response studies

Children are "Biomarker Orphans"

- Compared to adults, relatively few validated biomarkers are available for pediatric patients
- Specific challenges to develop biomarkers for children:
  - Lack of validated endpoints in children – often extrapolated from adult
  - Avoid invasive and repeated sampling
  - Potential impact of development on the result (e.g. ontogeny of renal function)

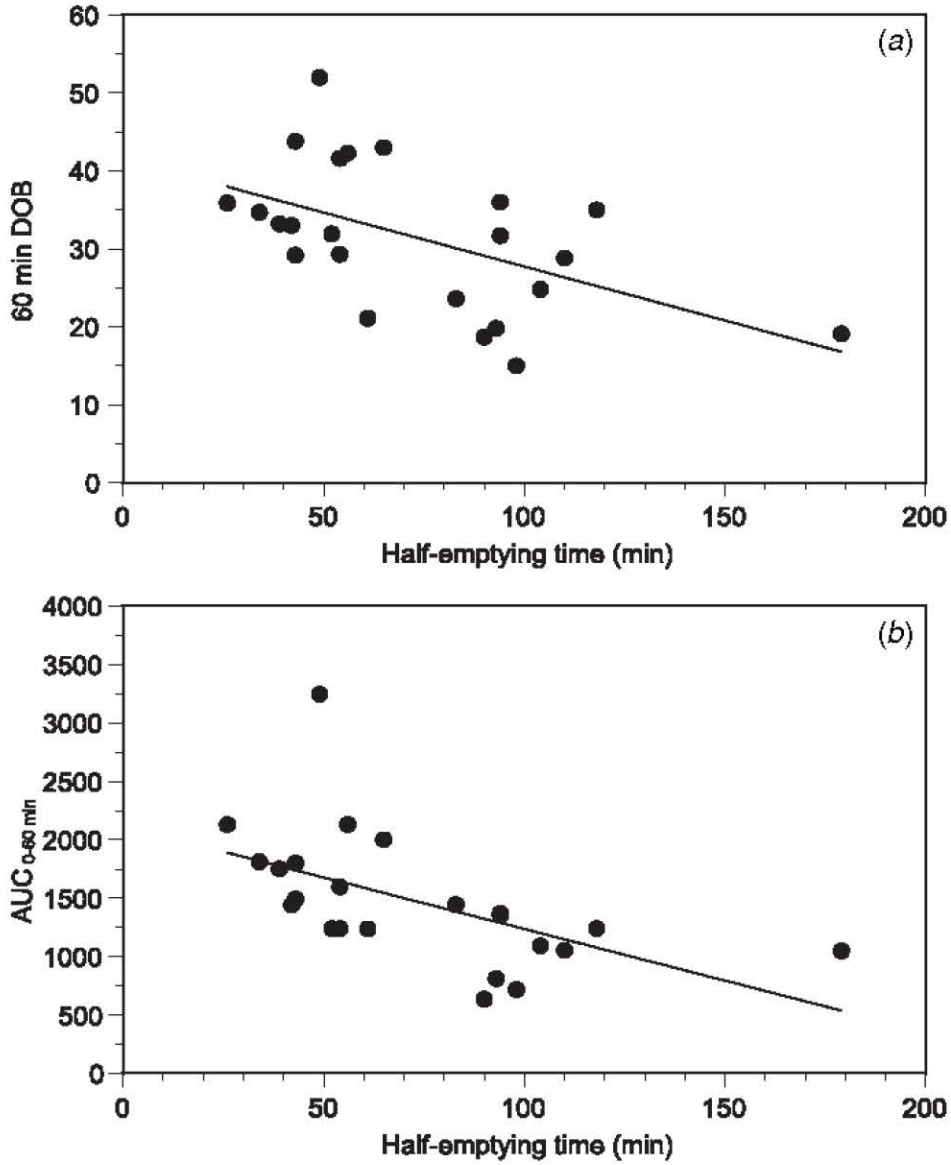
Savage and Everett. *Proteomics Clin Appl 2010*; 4: 915-21.



Of the 5 randomized, blinded trials, 2 showed no effect of metoclopramide on any outcome, and 2 showed a significant placebo effect. Four studies commented on adverse effects of therapy, with irritability being the most frequently reported potential adverse effect of therapy. Other reported adverse effects included dystonic reactions, drowsiness, oculogyric crisis, emesis, and apnea.

Hibbs AM, Lorch SA. *Pediatrics* 2006;118:746-752

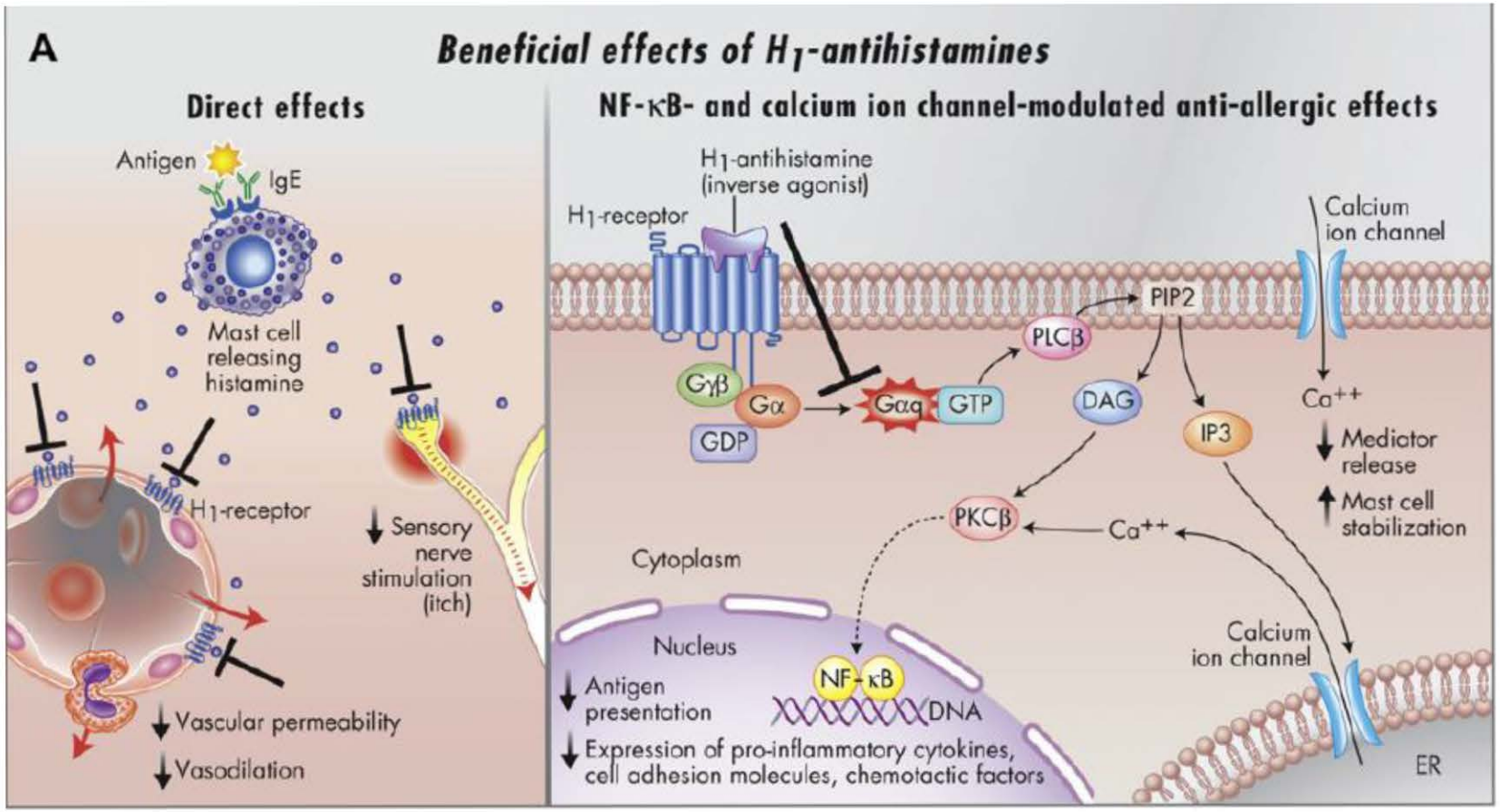
^{13}C Acetate Breath Test for Gastric Emptying



Jones BL, et al. *J Breath Res* 2009;3:1-6

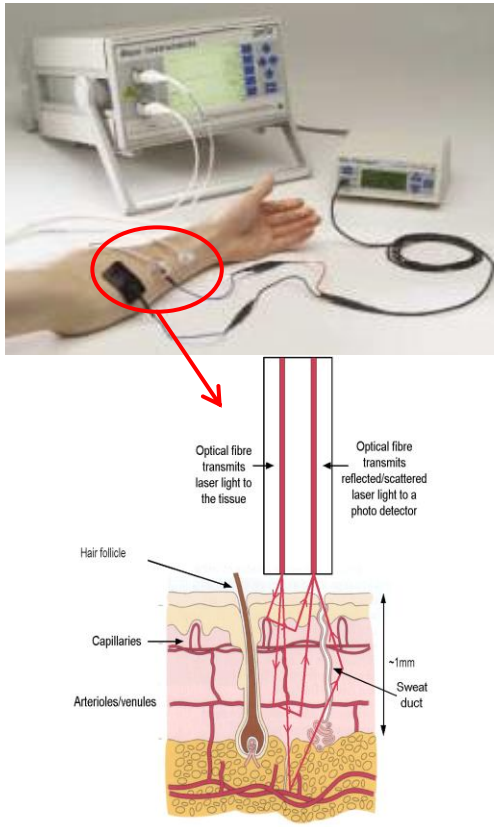
OTC Cough and Cold Products in Children

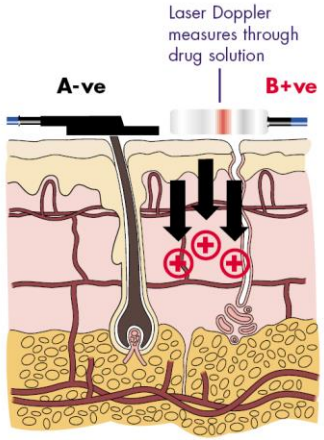
Public Health Advisory: FDA Recommends that Over-the-Counter (OTC) Cough and Cold Products not be used for Infants and Children under 2 Years of Age

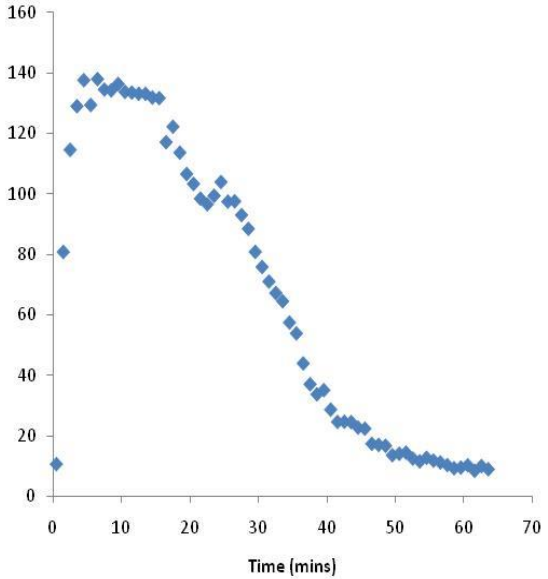


F. Estelle Simons et al, *J Allerg Clin Immunol,* 2011

Histamine Iontophoresis with Laser Doppler Flowimetry

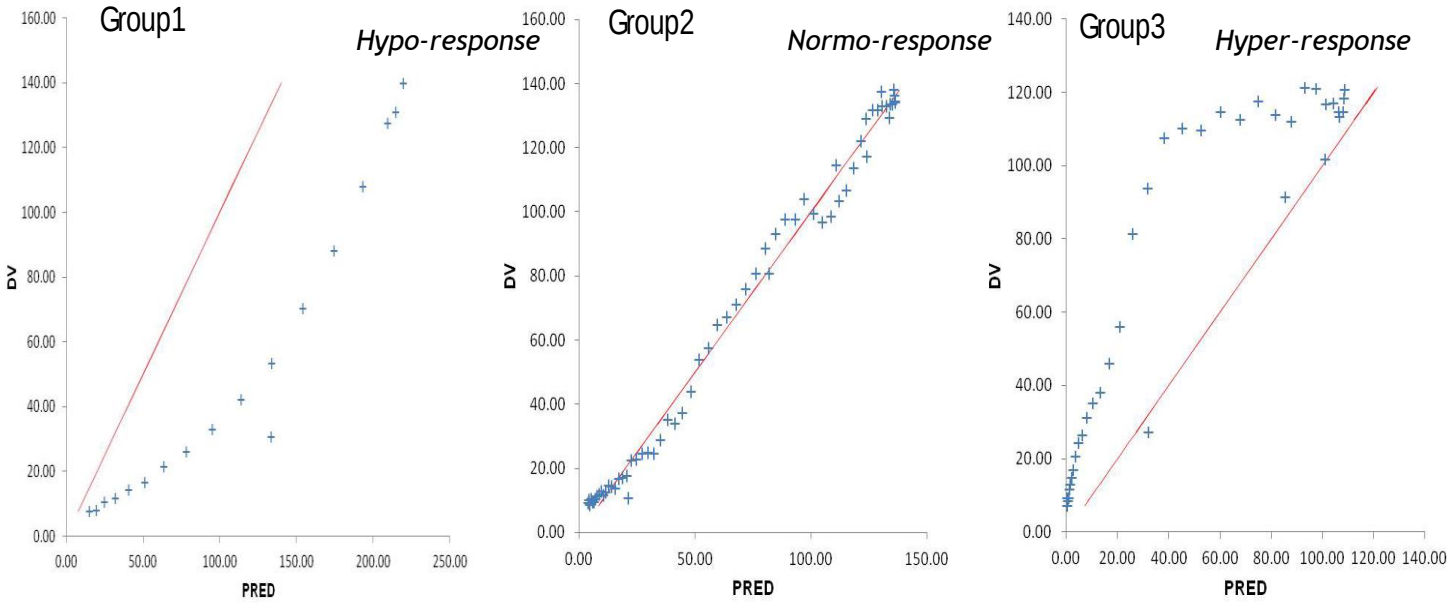






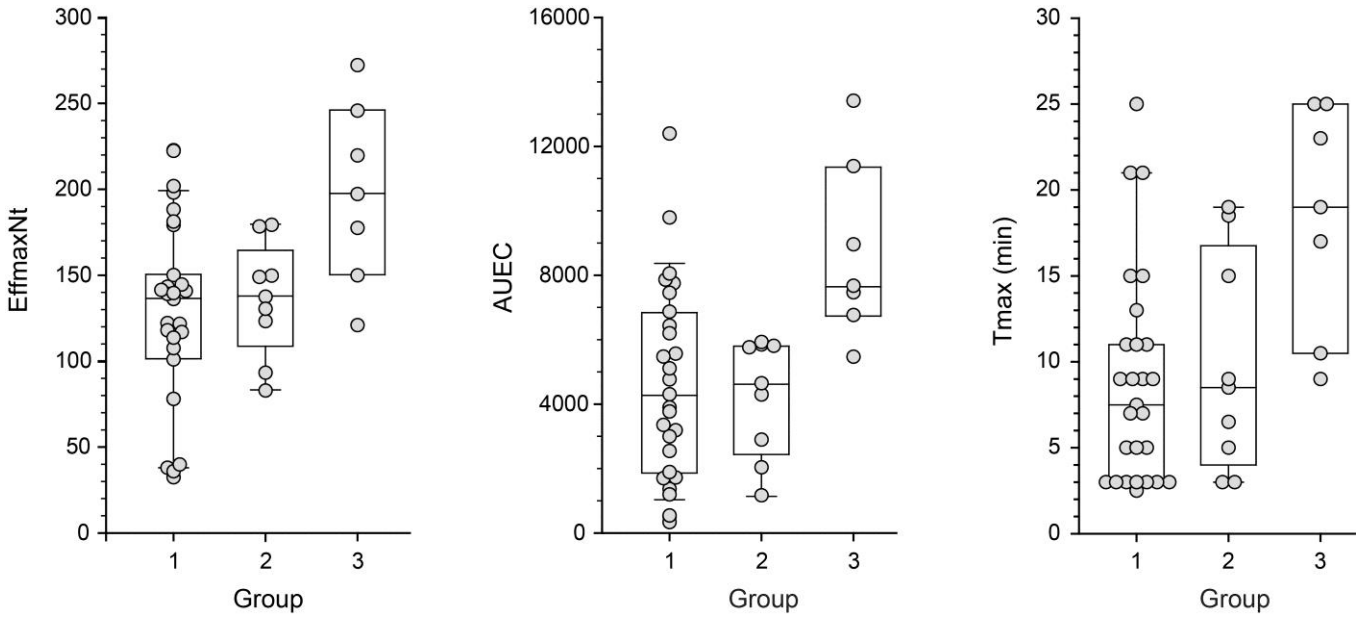
Histamine Response Phenotypes

Distinct Groups Identified from Predicted vs. Dependent Variable Plots for each subject



Jones, B et al., *Journal of Clinical Pharmacology*, 2013

Histamine Response Phenotypes



	Group 1	Group 2	Group3*
AUEC	4654±2997	4233±1819	8702±2776*
EffmaxNt	127±52	136±33	198±53*
Tmax	9±6	10±6	18±7*

Mean ± standard deviation values for each response group, *p<0.01

Jones B, et al. *Journal of Clinical Pharmacology*, 2013

Polymorphisms of Potential Importance to Determining Histamine Phenotype

HNMT	DAO	H_1 receptor	H_2 receptor
C314T*	A-594T	C-17T	G543A
A595G	C995T	G1045A	C826T
A929G	G1329A	T1522C*	G649A*
A1097T	C2970G	G1047T	G-1018A
T-1637C	T5052C*		
T-463C	C47T		
$(CA)_n$ repeat intron 5	C4106G		
BV677277$(CA)_n$	C-4586T		
	C2029G*		

H_3 receptor	H_4 receptor	HDC
C839T*	ss142022671*	G951A*
A280V*	ss142022677*	
	ss142022679*	

* Denotes that variation has been found to have possible clinical significance

B. Jones, Kearns GL, *Clin Pharmacol Ther*, 2011;89:189-197

Properties Required for Pediatric PD Biomarkers:

1. A predictive association with normal growth and development
2. Sufficient sensitivity to discriminate between time-dependent changes in disease pathogenesis and/or response to a treatment
3. Reasonable proximity with a drug's mechanism of action
4. Demonstration of accuracy and precision with regard to repeated measurement and sensitivity and specificity with respect to quantitation and discrimination

Goldman J, et al. *Biomarkers in Medicine*, 2011;5 (6):1-14

Properties Required for Pediatric PD Biomarkers: (Cont'd)

5. Not be subject to epigenetic changes which could influence the phenotypic expression of disease and/or drug response.
6. Be able to be accurately and repeatedly assessed in a pediatric patient so as to enable time- and concentration-dependent study of PD
7. Be non-invasive and non-noxious (i.e., well tolerated by the patient and parents)

Goldman J, et al. *Biomarkers in Medicine*, 2011;5 (6):1-14

Summary and Conclusions

- The use of pediatric biomarkers can add knowledge about effects of disease and ontogeny on PD
- Pediatric biomarkers require a capability of measuring drug response in both a time and age dependent fashion
- The development of pediatric biomarkers requires an integrated approach to insure that both growth and development are fully considered

Acknowledgements

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- World Health Organization
- Research collaborators at Children's Mercy Hospital and Arkansas Children's Hospital
- The Ross and Mary Whipple Family
- The staff of the Arkansas Children's Research Institute
- Research participants - patients and families