2018 ACCP Annual Meeting
North Bethesda, MD
Sept 23-25, 2018

U.S. FOOD & DRUG ADMINISTRATION

Intestinal Influx Transporters: A Missing Piece in the Puzzle?

Introduction

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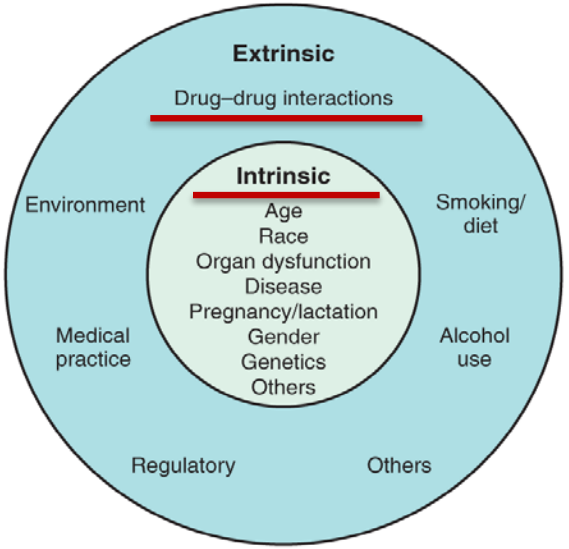
September 23, 2018

The views expressed in this presentation are that of the speaker and do not reflect the official policy of the FDA. No official endorsement by the FDA is intended nor should be inferred.

Drug Transporters: Contribute to Variability in Drug Concentration and Response

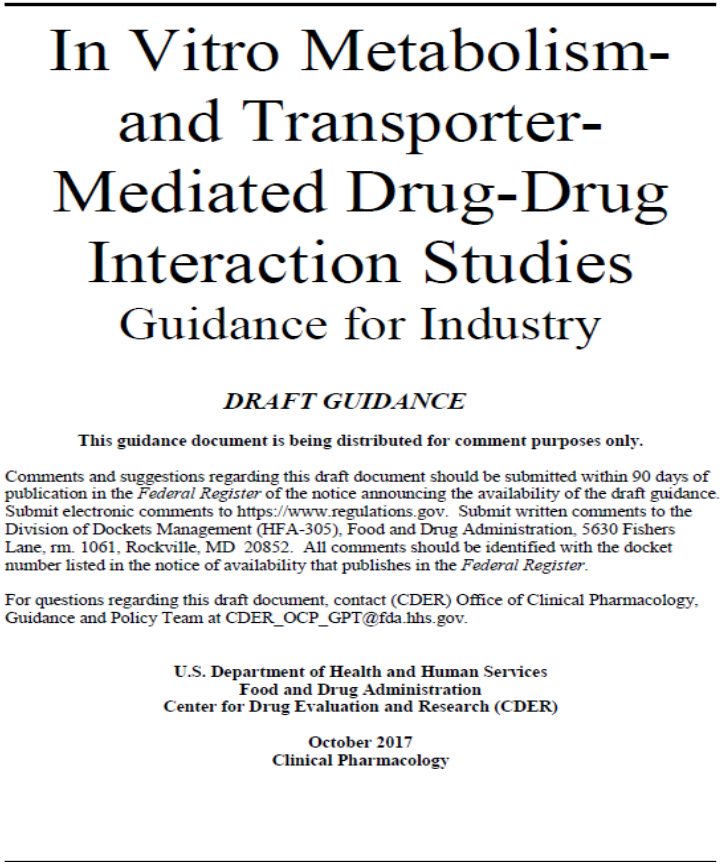
- **Pharmacokinetic** determinant
  - **A**bsorption
  - **D**istribution
  - **M**etabolism
    - by controlling drug's access to the enzymes
  - **E**xcretion



Huang S-M and Temple R, Clin Pharmacol Ther 84: 287-294, 2008

- **Pharmacodynamic** determinant
  - Delivery to site of action
  - Control of tissue concentrations
  - Discovery targets
    - Sodium-glucose co-transporter 2 (SGLT2) inhibitor for the treatment of Type 2 diabetes (e.g., canagliflozin, dapagliflozin, empagliflozin)
    - Urate transporter (URAT1) inhibitor in combination with an XO inhibitor for the treatment of gout (e.g., lesinurad)

FDA 2017 DDI Draft Guidances



In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies

Guidance for Industry

DRAFT GUIDANCE

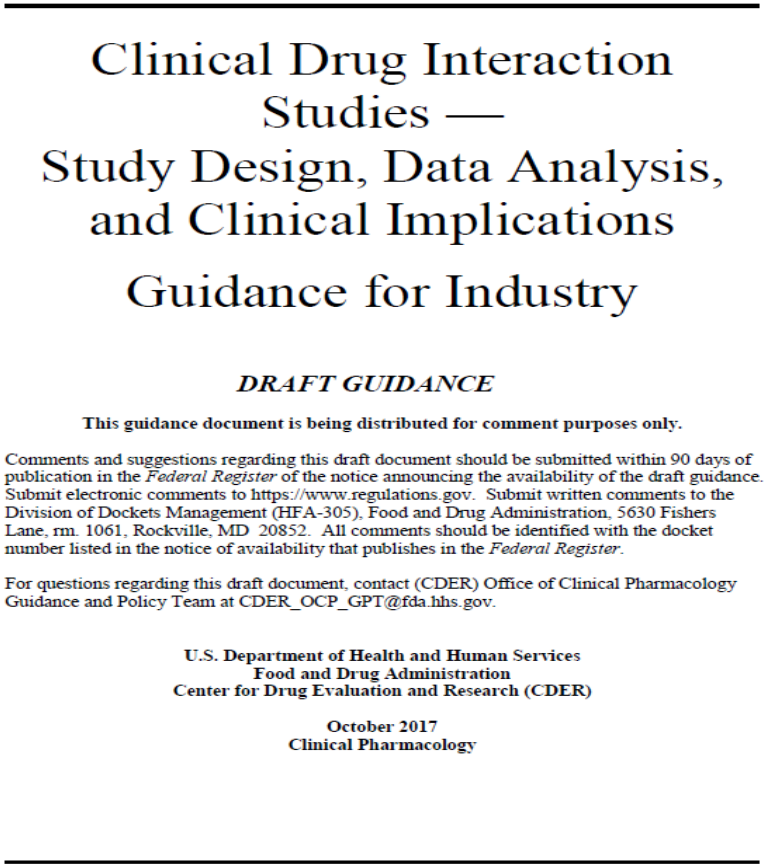
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Office of Clinical Pharmacology, Guidance and Policy Team at CDER_OCP_GPT@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2017
Clinical Pharmacology



Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications

Guidance for Industry

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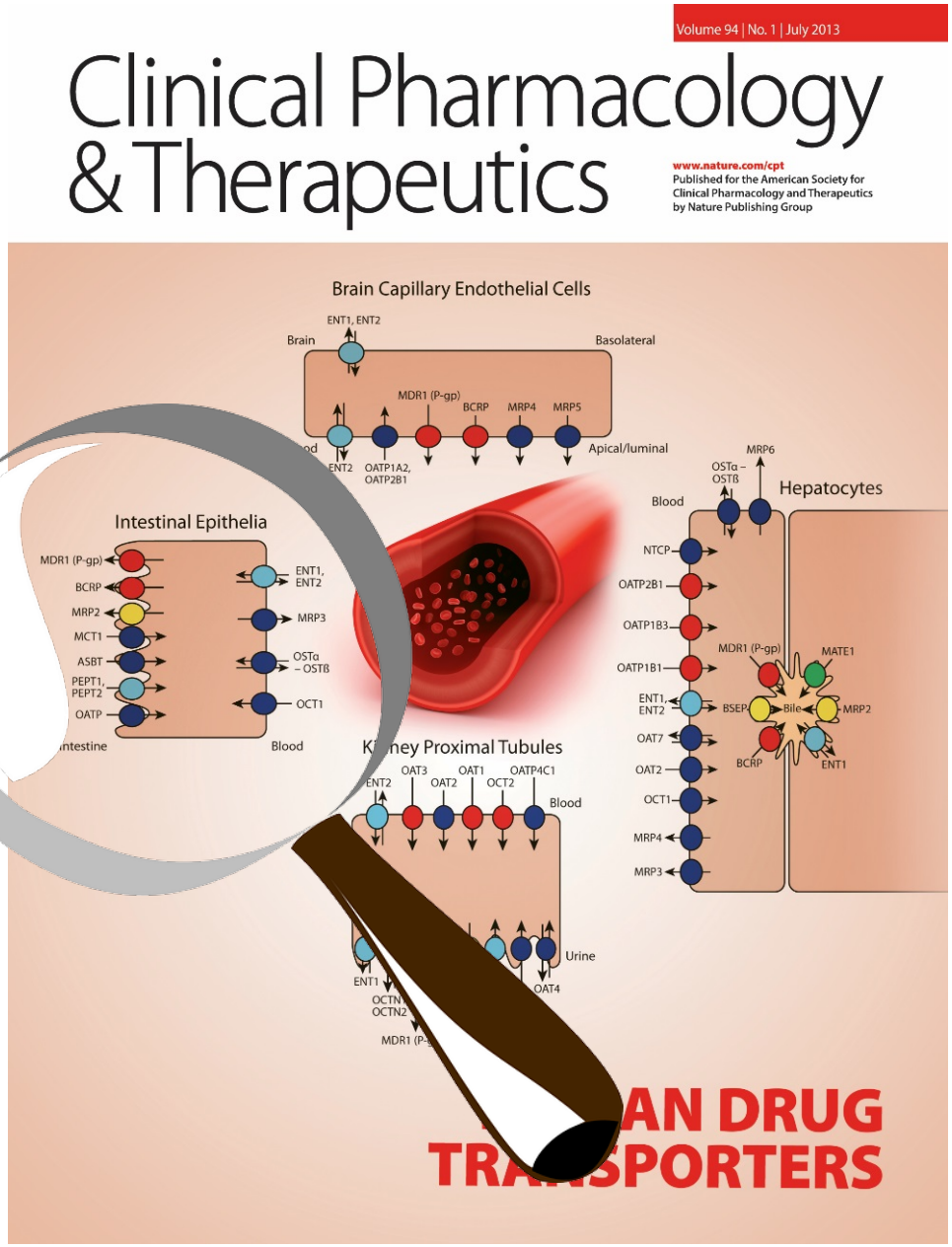
Both published in October 2017

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm



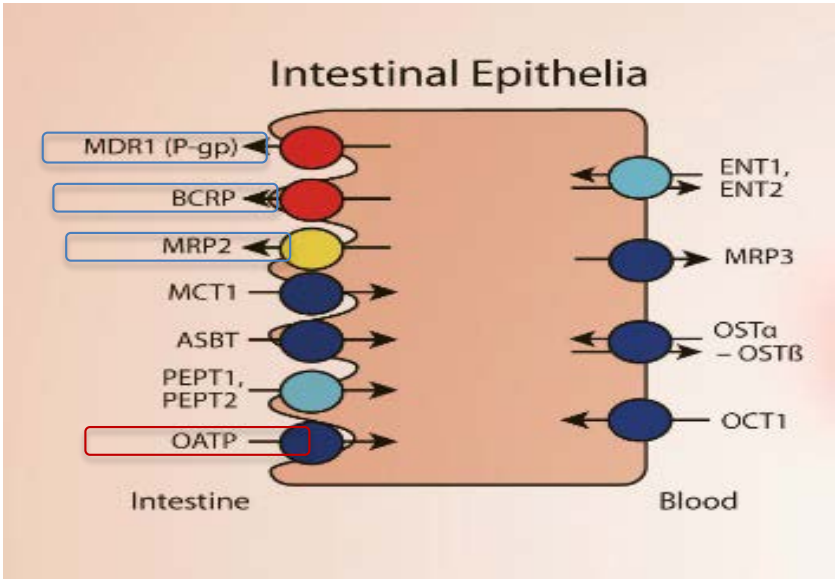
Giacomini and Huang, Editorial, Clin Pharmacol Ther. July 2013

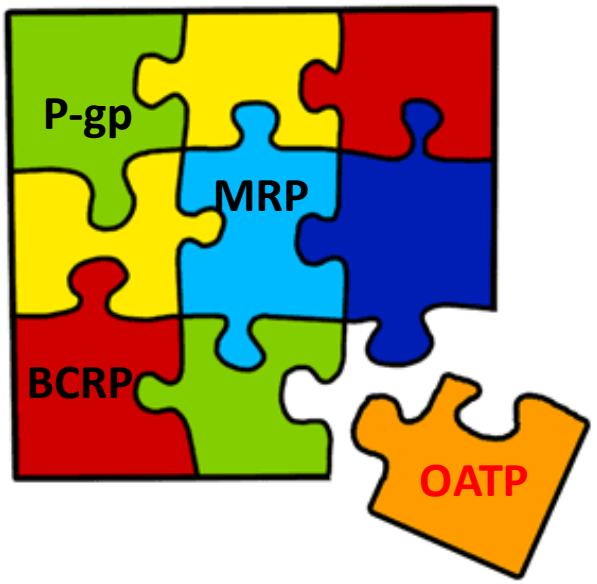
COMING SOON!

More transporter whitepapers will be published in the **November 2018 CPT** Theme Issue following the 3rd International Transporter Consortium Workshop (ITCW3) (held in March 2017).

Co-edited by:
Kathy Giacomini &
Shiew-Mei Huang

Intestinal Transporters





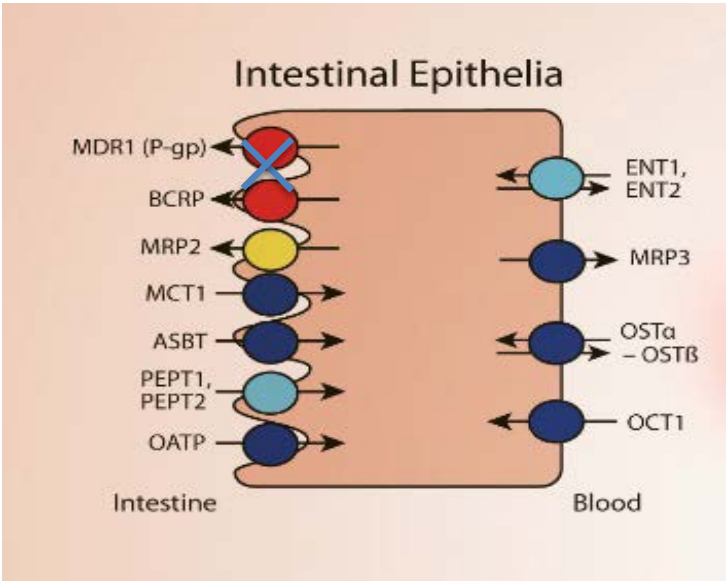
Transporters that affect drug absorption

- Efflux transporters
- Influx transporters?

Drug-Drug Interactions or Food-Drug Interactions

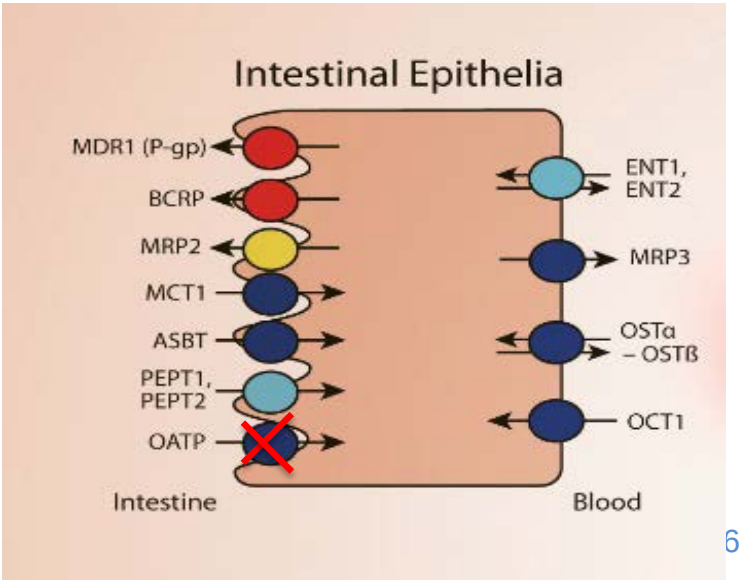
- Inhibition of intestinal efflux transporters

→ Substrate drug exposure



- Inhibition of intestinal influx transporters

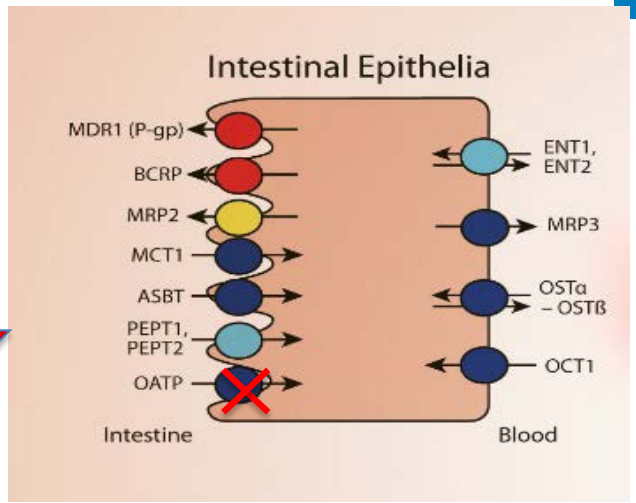
→Substrate drug exposure



Drug-Drug Interactions

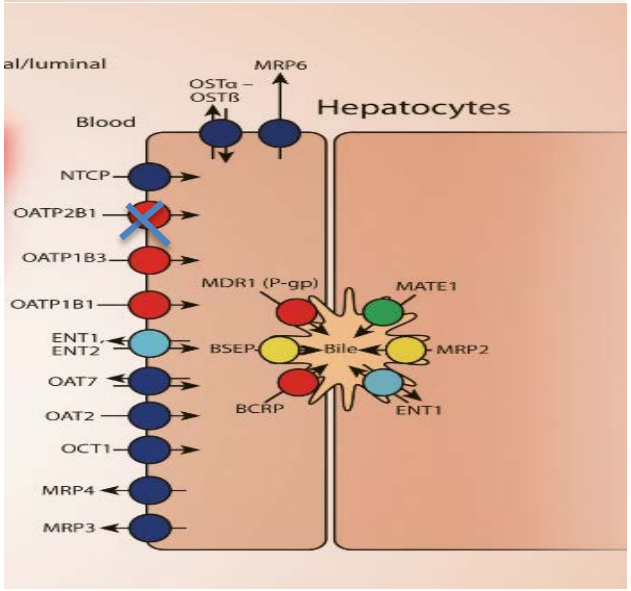
- Inhibition of intestinal influx transporters

→Substrate drug exposure



- Inhibition of liver uptake transporters

→Substrate drug exposure



What will be the overall DDI effect if the same transporter is expressed in both intestine and liver (e.g., OATP2B1)?

Possible Outcomes

- If inhibition of intestinal influx transporters is dominant

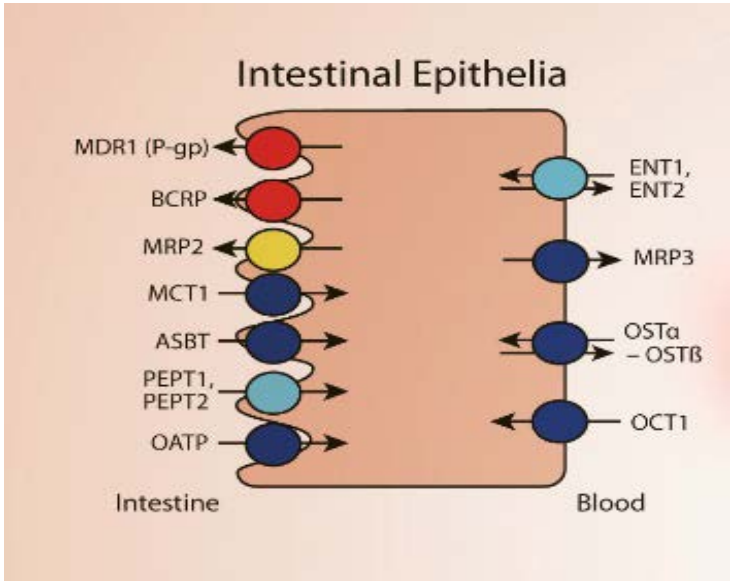
- If inhibition of intestinal influx transporters and liver uptake transporters is similar

- If inhibition of liver uptake transporters is dominant

Need a mechanistic understanding of various processes

Effect of Excipients on Intestinal Transporters?

- Can excipient differences between Product 1 vs. Product 2 affect the bioequivalence of these two products?
- What testing can be done?
- What products could be more vulnerable?



Objectives of this Symposium

- Describe main mechanistic findings and the clinical relevance of intestinal OATP2B1/1A2 transporters
- Explain the methodologies and mechanistic modeling strategy to evaluate these influx transporters during drug development
- Explore knowledge gaps and the regulatory perspective on the topic

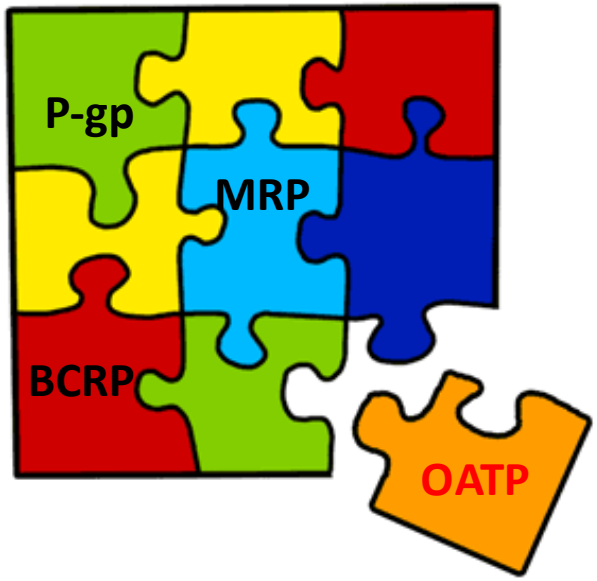
Agenda

- **Intestinal Drug Interactions Mediated by OATPs: A Systematic Review of Preclinical & Clinical Findings**
  - Isabelle Ragueneau-Majlessi, MD, MS, University of Washington
- **The Effects of Excipients on Intestinal Drug Transporters**
  - Kathy M. Giacomini, PhD, UCSF
- **Decoding the Contribution of Intestinal Influx Transporters to Clinical Drug-Drug Interactions: In Vitro, Preclinical & Physiologically-based Pharmacokinetic Mechanistic Modeling**
  - Manthena Varma, PhD, Pfizer
- **Regulatory Science Perspective on Intestinal Influx Transporters & Their Role in Drug-Drug Interactions**
  - Shiew-Mei Huang, PhD, FDA

- **Panel Discussion**

Acknowledgements

- Co-Chair
  - Zhu Zhou, PhD, University of the Pacific
- All speakers

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Possible Panel Discussion Questions

- Should OATP2B1 be studied routinely in drug development?
- How to disentangle OATP-associated interactions from other common mechanisms (such as intestinal P-gp/BCRP, hepatic OATP1B1/1B3)?
- What is the appropriate methodologies and mechanistic modeling strategy to understand the overall DDI effect if the same transporter is expressed in both intestine and liver?
- What is the applicability of the juice-drug interaction results to real world experience (some juice-drug interaction studies require a huge amount of juice consumed, might only prove the concept rather than reflect the real world experience)?

Should OATP2B1 be Studied Routinely in Drug Development?

REVIEW

Transporters in Drug Development: 2018 ITC Recommendations for Transporters of Emerging Clinical Importance

Maciej J. Zamek-Gliszczynski[1], Mitchell E. Taub[2], Paresh P. Chothe[3], Xiaoyan Chu[4], Kathleen M. Giacomini[5], Richard B. Kim[6], Adrian S. Ray[7], Sophie L. Stocker[8], Jashvant D. Unadkat[9], Matthias B. Wittwer[10], Cindy Xia[11], Sook-Wah Yee[12], Lei Zhang[13], Yan Zhang[14], on behalf of the International Transporter Consortium

https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.1112

ITC Perspective

- OATP2B1 can play a role in intestinal absorption and hepatic clearance of drugs.
- Present clinical evidence is insufficient to recommend prospective evaluation of OATP2B1 in drug development. As an emerging transporter, the role of OATP2B1 should be explored based on evidence of in vivo transport in the intestine or liver that cannot be attributed to more common mechanisms (e.g., intestinal P-gp/BCRP, hepatic OATP1B1/1B3). Intestinal OATP2B1 should be considered as a mechanistic explanation of DDIs or drug–fruit juice interactions upon observation of apparently decreased absorption of the substrate drug.

https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.1112

Effect of Excipients on Intestinal Transporters?

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