SCOPING REVIEW OF LEVONORGESTREL PHARMACOKINETIC DATA IN SPECIAL POPULATIONS

FINAL PRESENTATION

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February 4th, 2025

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STRATEGIC ANALYSIS, RESEARCH & TRAINING CENTER
Department of Global Health | University of Washington

AGENDA

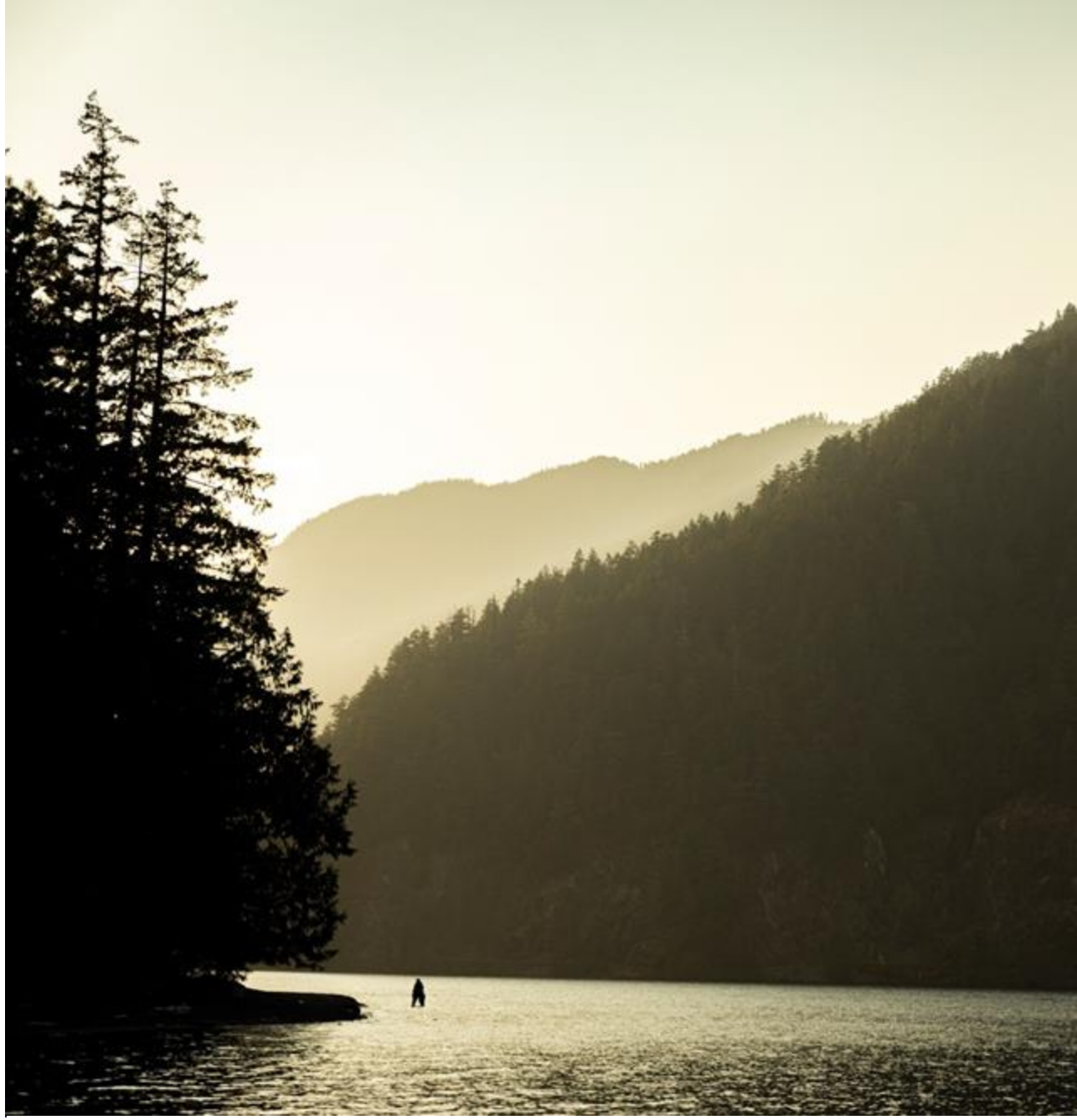
01 Project Background & Objective

02 Key Takeaways & Identified Gaps

03 Methods

04 More Detailed Results

05 Key Takeaways & Next Steps



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PROJECT TEAM

Ana Krause, RN, MSc (IPH)

PhD Student, Implementation Science

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MPH Student, Epidemiology

Research Assistant

Stephen Hawes, PhD, MS

Epidemiology, Global Health,

Faculty Lead & START Director

START OVERVIEW

Leverages leading content expertise from across the University of Washington

Provides high quality research and analytic support to the Bill & Melinda Gates Foundation and global and public health decision-makers

Provides structured mentorship and training to University of Washington graduate research assistants

PROJECT BACKGROUND

LEVONORGESTREL: MEETING GLOBAL NEEDS

Globally, approximately 407 million women use hormonal contraceptives (UN, 2019).

Levonorgestrel (LNG) is a hormonal contraceptive available in multiple forms, including pills and long-acting formulations such as IUDs, which has relevance in LMICs to reduce unintended pregnancies.

PROJECT BACKGROUND

LEVONORGESTREL: GAPS IN PHARMACOKINETIC RESEARCH

Pharmacokinetic research on LNG has historically focused on a narrow demographic, with the last comprehensive multi-route review published in 1995 (Fotherby, 1995).

Recent research on other drugs has identified limitations with this approach for populations in LMICs with different disease burdens that can impact drug absorption, distribution, metabolism, and excretion (Verrest et al., 2021).

KEY PROJECT OBJECTIVE

To conduct a scoping review to map existing literature on levonorgestrel in populations with altered physiology (e.g., undernutrition, liver disease, female reproductive tract abnormalities, GI illnesses) & identify any gaps and potentially relevant PK data.

PROJECT DELIVERABLES

I. A summary report outlining key findings from this scoping review.
- Supplemental files: data extraction sheet and article tables/figures

II. A presentation of findings.

KEY PROJECT TAKEAWAYS

LEVONORGESTREL SCOPING REVIEW

Levonorgestrel pharmacokinetic data for multiple special population groups **is scarce**, highlighting **abundant need** to learn more about the potential impacts of altered physiology on drug absorption, distribution, metabolism, and excretion.

Current data suggests **potentially different pharmacokinetic profiles** for levonorgestrel **among undernourished populations** and those with **gastrointestinal illnesses**, however more research is needed.

Due to insufficient data and methodological limitations, levonorgestrel physiologically based **pharmacokinetic (PBPK) models may be less precise** for particularly vulnerable populations in LMICs where different and overlapping disease burdens may impact drug efficacy.

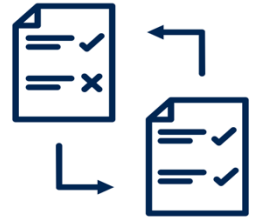
IDENTIFIED GAPS IN THE LITERATURE

BASED ON OUR SCOPING REVIEW

- SCARCITY OF LNG PK DATA FOR MULTIPLE SPECIAL POPULATIONS
- UNCLEAR INCLUSION & EXCLUSION CRITERIA
- VERY SMALL SAMPLE SIZES LIMIT DETECTION OF TRUE EFFECTS
- SHORT STUDY DURATIONS ONLY PROVIDE A SNAPSHOT OF DATA
- VARIABLE STUDY PROCEDURES LIMIT COMPARISONS







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LNG: levonorgestrel, PK: pharmacokinetic

METHODS

LITERATURE SEARCH

Initial Search

Met with UW Librarian to refine our search in PubMed, Embase, & Global Index Medicus

Literature Review Management

Set-up in Covidence for article screening, tagging, review, & data extraction

Title & Abstract Screening

81 unique articles identified, single reviewer screening

Full Text Review

28 articles advanced to full text review

Data Extraction

17 articles extracted & analyzed

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INCLUSION & EXCLUSION CRITERIA

	INCLUDED	EXCLUDED
POPULATIONS	Humans or animals treated with LNG Any abnormal pathophysiology that could impact PK[a] Any geography All ages	Only healthy women
INTERVENTIONS	Any route of non-emergency LNG administration	Emergency contraception Non-hormonal contraception Non-LNG contraception
COMPARATORS	Healthy controls or no comparator	N/A
OUTCOMES	Any LNG PK data* Clinical or pre-clinical	No LNG PK data
STUDY FEATURES	Any study design Any publication year	Protocols

a: see appendix

*Included outcomes: half-life, plasma concentration, Cmax, Cmin, AUC, clearance, bioavailability, volume of distribution, absorption, distribution, metabolism, excretion, etc.

ADDITIONAL SOURCES OF RELEVANT LNG PK DATA

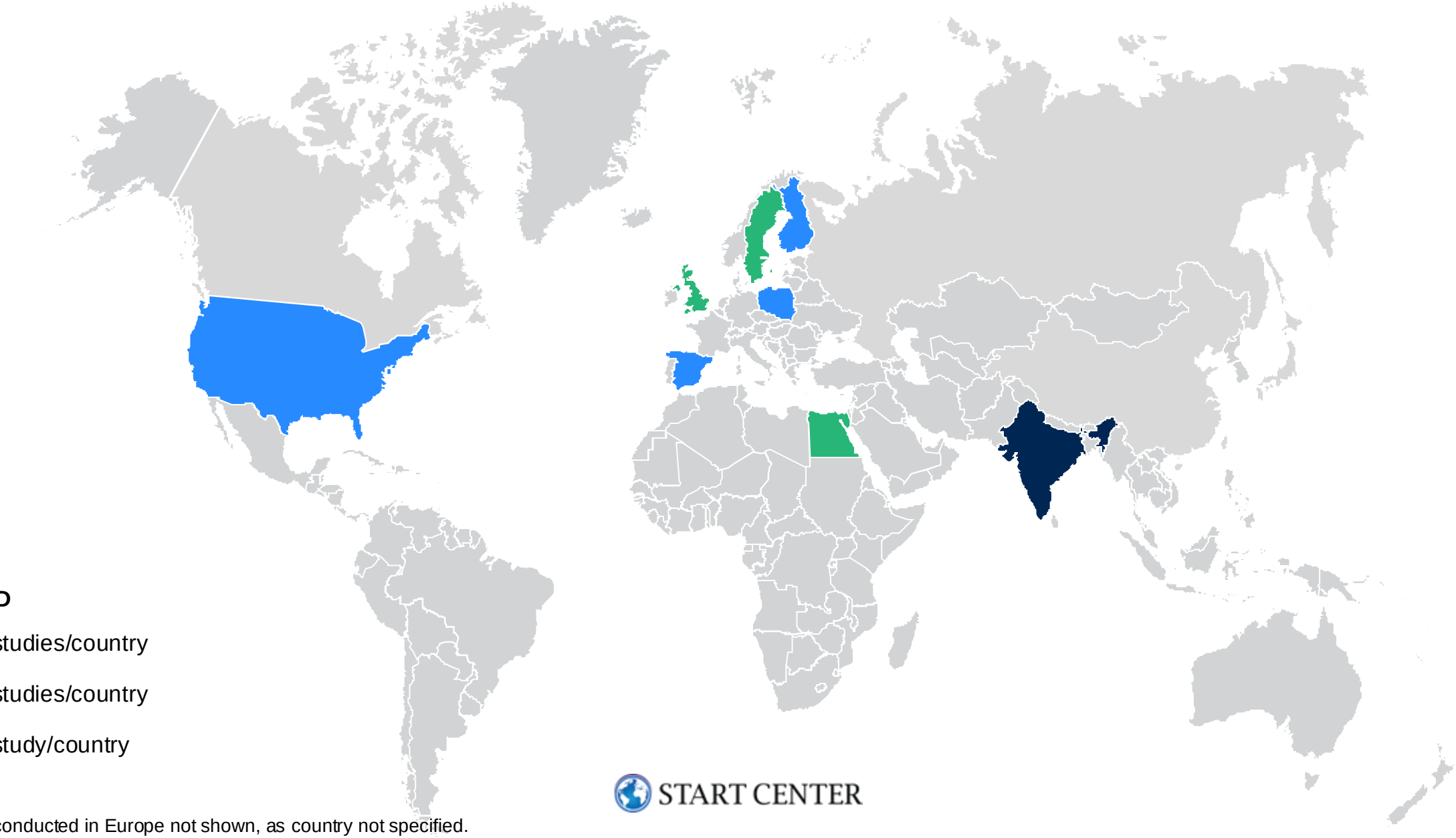
DRUG REGULATORY AGENCIES

To identify additional special population data, we explored 6 drug regulatory agencies:

- ✓ Limited our review of LNG PK data to the US FDA **Drugs@FDA** database due to richness of data relative to other agencies (FDA, 2024)
- ✓ Prioritized **non-oral contraceptives** due to relevance in lower resource settings

RESULTS

LOCATIONS OF INCLUDED PK STUDIES*



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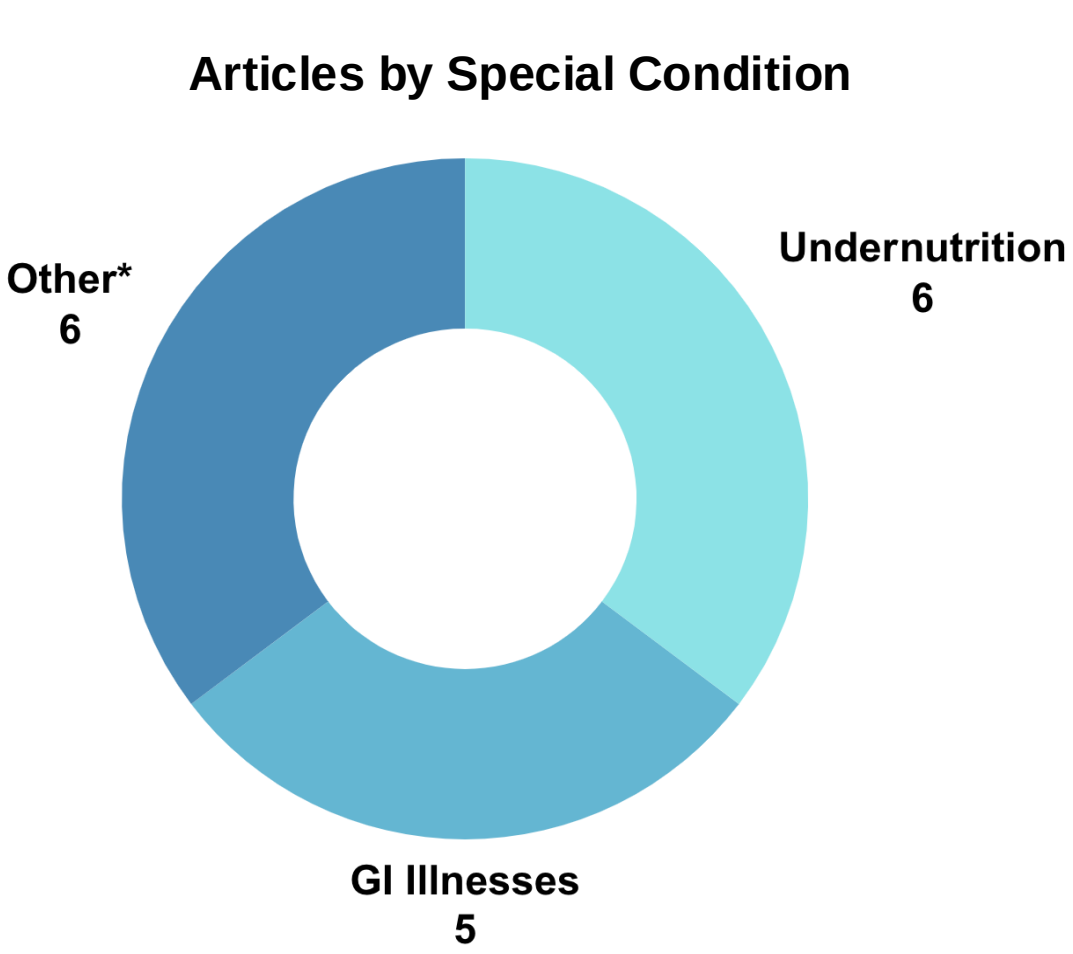
*One study conducted in Europe not shown, as country not specified.

DESCRIPTIVE RESULTS



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Articles included from scoping review:

- **Undernutrition** (6) - India
- **Gastrointestinal Illnesses** (5) - Sweden, UK, USA
- **Other** (6) - Egypt (liver disease, schistosomiasis) and Europe (cystic fibrosis, uterine fibroids, lung disease, B-cell malignancies)

FDA database search of non-oral LNG contraceptives:

- Only "special populations" mentioned were adolescents, post-menopausal women, and people with high BMI
- Found no data in populations with altered physiology that would be expected to impact PK

*Other: cystic fibrosis, liver disease, schistosomiasis, uterine fibroids, lung disease, and B-cell malignancies

DESCRIPTIVE RESULTS

Scarcity of published data in recent decades

Animal studies add context in populations lacking clinical data

Long-acting administration routes underrepresented or missing

Study Characteristics*			
Category	**No.**	**%**	**Characteristic**
Publication Year	14	82%	1979 – 1990
	1	6%	2010
	2	12%	2020 – 2021
Research Stage**	11	73%	Clinical (human)
	4	27%	Pre-Clinical (animal)
Route of Administration**	12	80%	Oral
	5	33%	IV
	1	7%	IUD
	1	7%	Intravaginal ring
	1	7%	Unknown
Formulation**	6	40%	LNG only
	10	67%	LNG-Estradiol or LNG-EE2
Healthy Controls**	11	73%	Yes
	4	27%	No

*Some studies had multiple characteristics within a single category
**Excludes 2 review articles

UNDERNUTRITION RESULTS 1/2

LNG PK DIFFERENCES

The high prevalence of undernutrition in LMICs can lead to severe impairments in hepatic function, substantially altering the metabolism of LNG (van Zutphen et al. 2021, Victora et al. 2021).

UNDERNUTRITION CORRELATES WITH FASTER LNG CLEARANCE AND SHORTER ELIMINATION HALF-LIVES IN BOTH HUMANS AND ANIMALS

UNDERNOURISHED RABBITS HAD FASTER LNG CLEARANCE (+20%), SHORTER HALF-LIFE (-46%), AND HIGHER URINARY EXCRETION (73.9% VS. 49.6%)[1,2]

IV dose daily for 5 days LNG-norethindrone

UNDERNOURISHED WOMEN SHOWED FASTER LNG CLEARANCE, SHORTER HALF-LIFE (-38%), AND ALTERED PLASMA DISTRIBUTION[3]

IVR continuous dose LNG-estradiol

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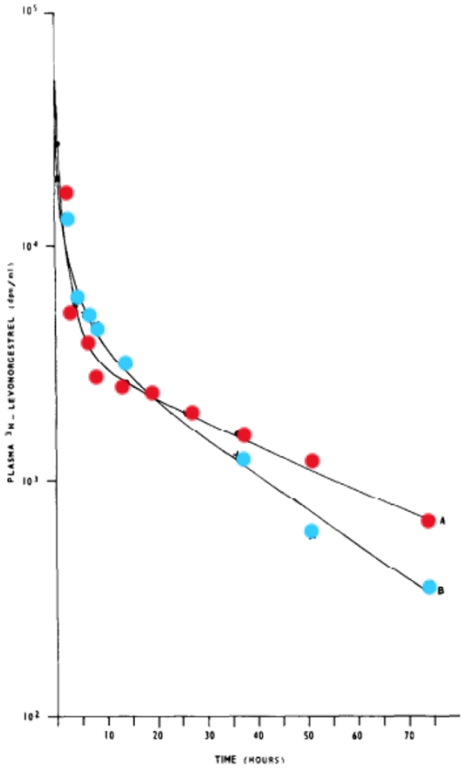
1. Nair et al., 1981, 2. Nair et al., 1988, 3. Nair et al., 1986

IVR: intravaginal ring

UNDERNUTRITION RESULTS 2/2

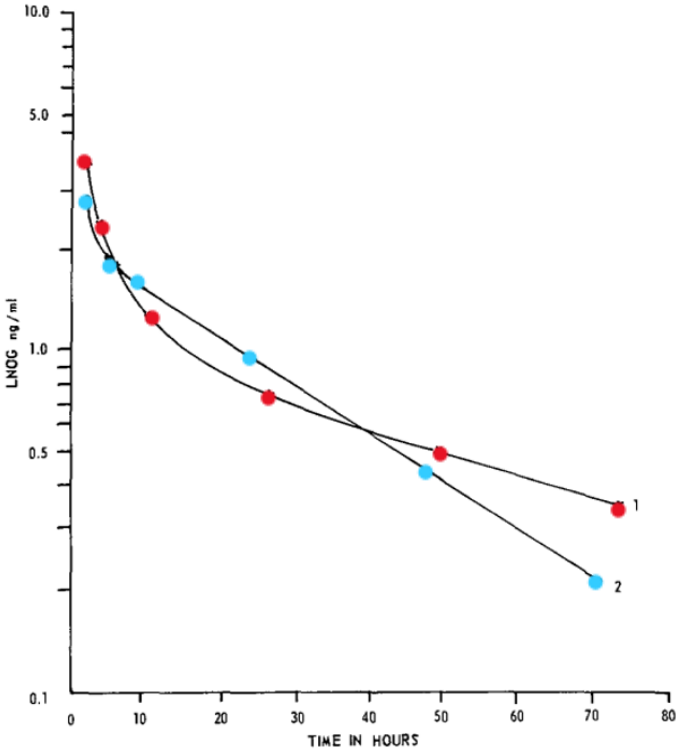
LNG PK DIFFERENCES COMPARED TO CONTROLS

Plasma curves suggest a shorter terminal half-life in undernourished animals (left) and humans (right)



ANIMAL STUDY: Plasma curves of levonorgestrel in control (red) and food restricted (blue) rabbits (Nair et al., 1981).

IV Single dose LNG



HUMAN STUDY: Plasma curves of levonorgestrel in well-nourished (red) and undernourished (blue) women (Nair et al., 1983).

Oral Single dose LNG-EE2

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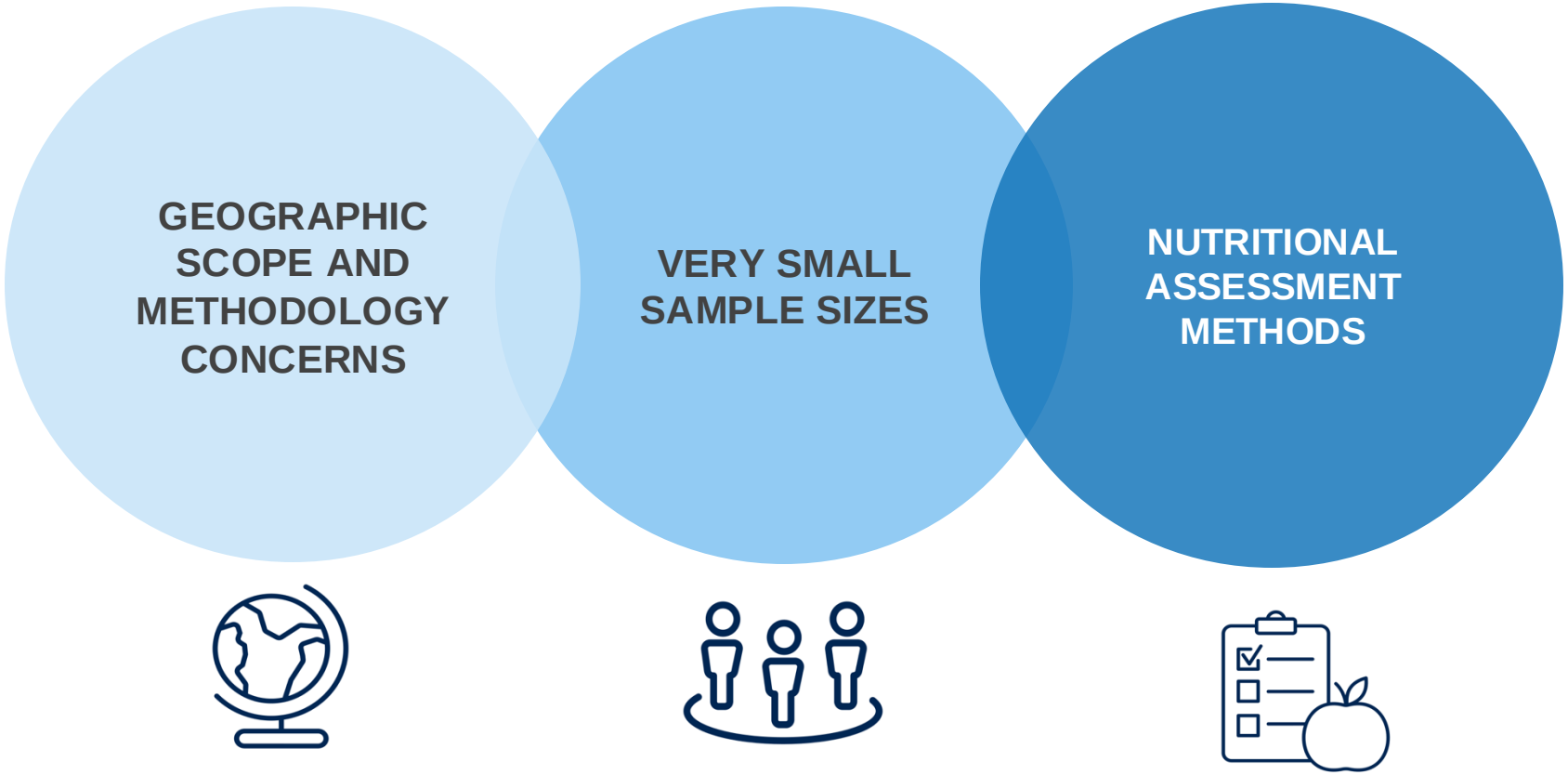
LIMITATIONS OF UNDERNUTRITION STUDIES



GI ILLNESS RESULTS 1/3

RATIONALE & OVERALL FINDINGS

Long-standing belief that GI illnesses can impact oral hormonal contraceptive absorption

Diarrheal diseases were the 2nd most incident cause of disease globally among females aged 15-49 years at 50,002 new cases per 100,000 in 2021[1]

NO DATA on levonorgestrel (LNG) pharmacokinetics and **enteric infections** was identified

The potential impact of GI illnesses on LNG pharmacokinetics is **difficult to ascertain**.

- 3 identified PK studies focused on women with well-controlled ulcerative colitis &/or undergoing bowel surgery.

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1. GBD Compare (2021), Level 3 causes of disease.

GI ILLNESS RESULTS 2/3

LNG PK DIFFERENCES

Despite study limitations and limited data, **different trends in key PK parameters** (plasma concentrations, bioavailability, volume of distribution) **between controls and those with inflammatory bowel disease or bowel surgery were observed***.

Compared to Controls

Oral Single dose LNG-EE

Mean Bioavailability

18.5% lower in ileostomy patients[1].

Mean Volume of Distribution

15.3% lower in ileostomy patients[1].

Mean AUC (oral)

13.9% higher in ileostomy patients[1].

Mean Plasma Levels (10-H)

25.0% lower in ileostomy patients[2].

LNG absorption thought to occur mostly in the small intestine. PK data in ileostomy patients may suggest greater involvement of the large intestine.

Mean AUC (IV)

45.9% higher in ileostomy patients*[1].

Mean Plasma Levels (10-H)

54.5% higher in ulcerative colitis patients (pre-op)*[2].

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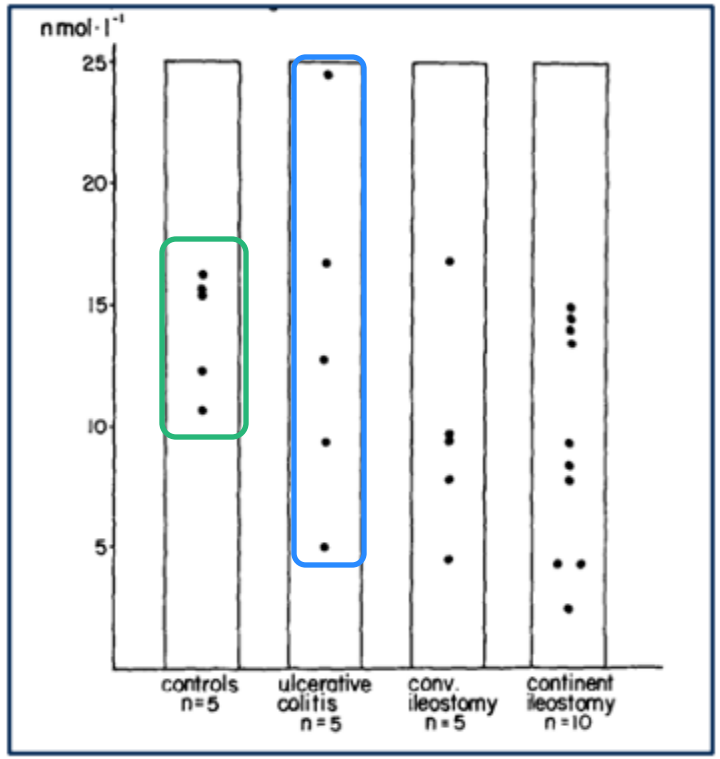
*p-value: <0.05. Interpret non-significant results with caution as very small sample sizes.

1. Grimmer et al., 1986 (ileostomy 4 yrs post-op); 2. Nilsson et al., 1985; (ileostomy mean 2.6 yrs post-op)

GI ILLNESS RESULTS 3/3

LNG PK DIFFERENCES COMPARED TO CONTROLS

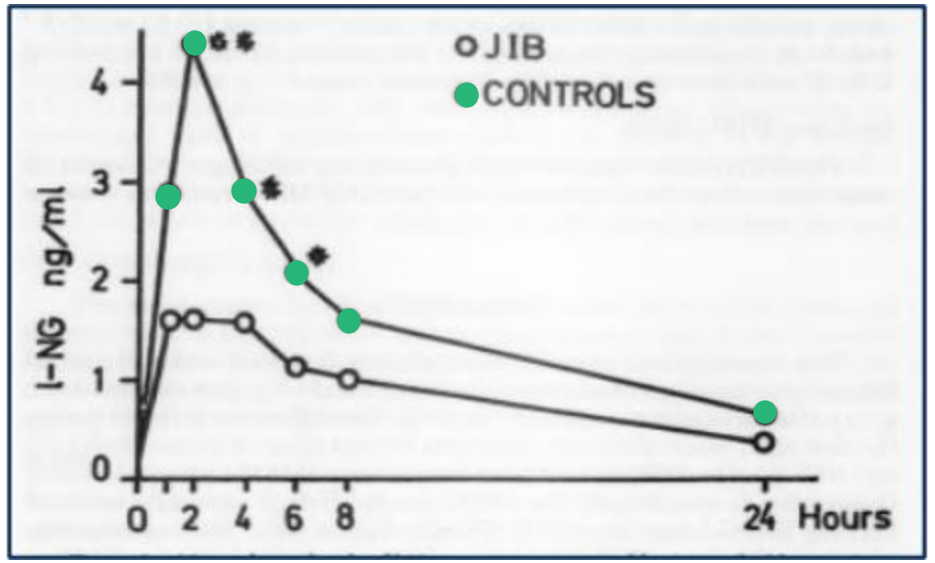
Controls **Ulcerative colitis**



Peak LNG plasma levels in different groups
(L-R: healthy controls, mild ulcerative colitis, conventional ileostomy, continent ileostomy)1

Oral Single dose LNG-EE

Controls (green) vs. Bowel surgery



Mean LNG plasma levels in different groups after oral 0.25mg LNG. **p<0.01, *p<0.05 (open circles: jejunoileal bypass; green circles: controls)2

Oral Single dose LNG

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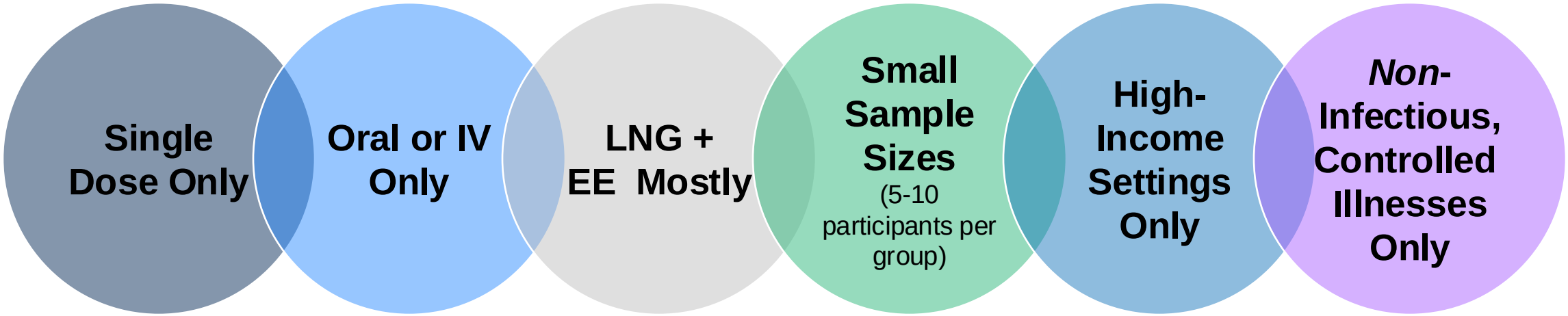
*Interpret non-significant results with caution due to the small sample sizes.

1. Nilsson et al., 1985; 2. Victor et al., 1987

LIMITATIONS OF EXISTING PK STUDIES

IN POPULATIONS WITH GI ILLNESSES



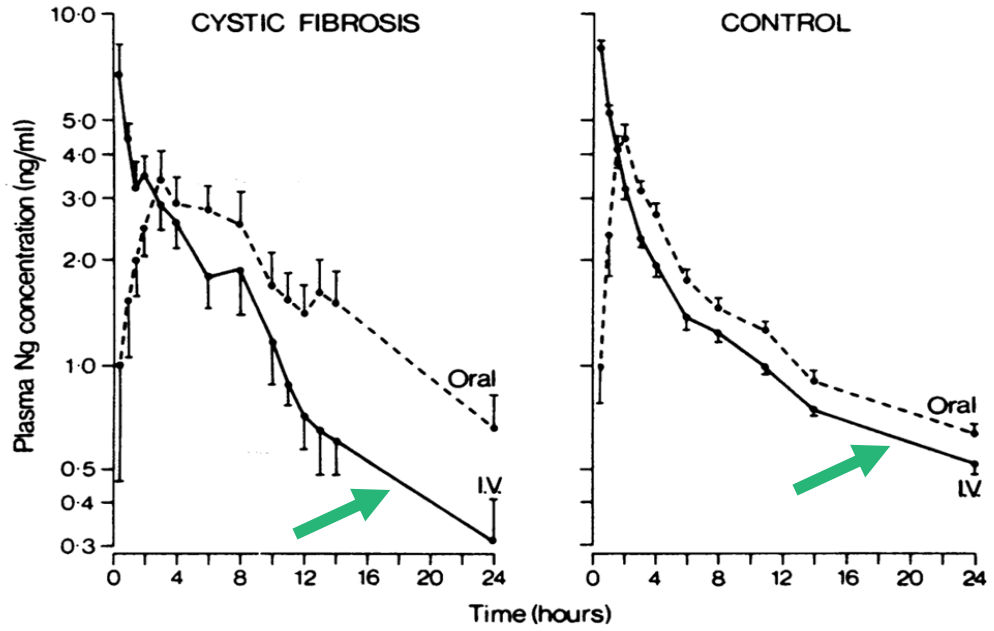
LNG: Levonorgestrel, EE: Ethinylestradiol

CYSTIC FIBROSIS

DIFFERENCES IN LNG CLEARANCE AND HALF-LIFE

Evidence that **cystic fibrosis** (CF) can impact absorption and disposition of drugs and their metabolites, likely driven by GI comorbidities[1,2]

Cystic fibrosis likely underreported and underdiagnosed in LMICs[3]



IV-administered LNG had

12% larger AUC
32% shorter half-life
45% faster clearance

in **CF patients** than in controls*[4] (Stead et al., 1987)

Need for additional research and larger studies to confirm and elucidate LNG PK differences in CF patients

Oral and IV Single dose LNG-EE

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*Interpret non-significant results with caution due to the small sample sizes.
1. De Sutter et al., 2020; 2. Jiao et al., 2018; 3. Da Silva Filho et al., 2021; 4. Stead et al., 1987

SCHISTOSOMIASIS

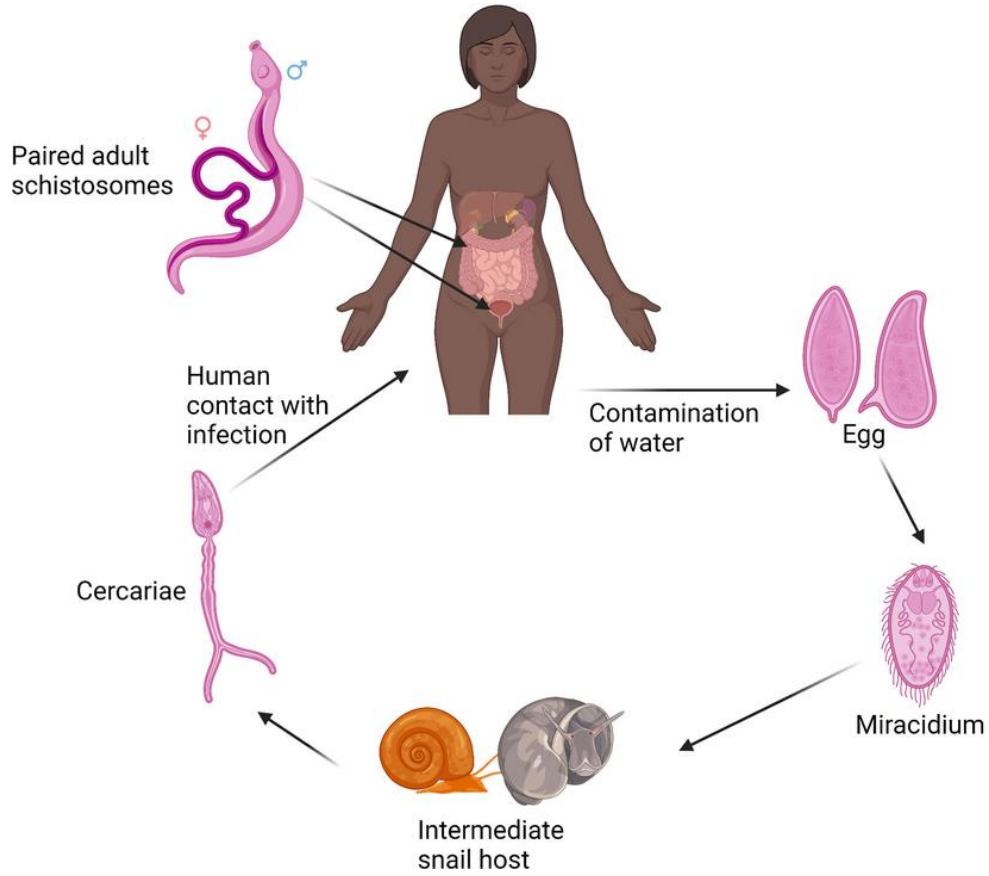
LNG PK DATA LIMITED TO EARLY DISEASE STAGES

16-56 million girls live with female genital schistosomiasis (FGS), which can cause liver enlargement or disease and scarring of genital tissues[1]

No notable PK differences observed

Unsurprising given early disease stage with **no evidence of liver impairment or other relevant pathophysiology[2]**

Larger studies with longer follow-up needed in **advanced schistosomiasis and FGS** where physiological changes and scarring are likely more pronounced



The lifecycle of *S. mansoni* and *S. Haematobium*[3]

Oral
Single dose LNG-EE

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1. Christinet et al., 2023; 2. El-Raghy et al., 1986; 3. Summers et al., 2022

LIVER DISEASE

NO HUMAN LNG PK DATA IN POPULATIONS WITH HEPATIC IMPAIRMENT

Impaired liver function is **known to impact drug PK**, potentially reducing efficacy as a result[1,2]

Liver diseases like Hep B and C are **highly prevalent and deadly in LMICs,** with fewer than 20% of affected people aware of their diagnosis[3,4]

Accounting for physiological differences in hepatically impaired populations is important for PBPK model accuracy[5]

Mice with induced hepatic necrosis had

20% faster clearance
12% shorter half-life

than healthy mice[6]
(statistically significant)

MAJOR GAP AND NEED FOR FURTHER RESEARCH

Further studies in humans with diverse liver diseases needed to confirm and elucidate this effect

Oral and IV
Single dose LNG

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1. Verbeek et al., 2008; 2. Armani et al., 2024; 3. World Health Organization, 2017;
4. Schweitzer et al., 2015; 5. Edginton and Willmann, 2008; 6. Gommaa et al., 1983

CONDITIONS WITH LIMITED FINDINGS

UTERINE FIBROIDS

High prevalence and DALYs from uterine fibroids in low-middle income regions[1]

POTENTIAL EFFICACY IMPLICATIONS:

pre-hysterectomy IUD expulsion in two women[2]

LNG measured directly in reproductive tissues of women with severe uterine fibroids or menorrhagia, but **no healthy controls** for PK comparison[2]

Need for additional PK studies in populations with **reproductive tract abnormalities or damage**

(e.g. fibroids, pelvic inflammatory disease, ectopic pregnancy)

Oral: single dose LNG-EE
IUD: continuous dose LNG

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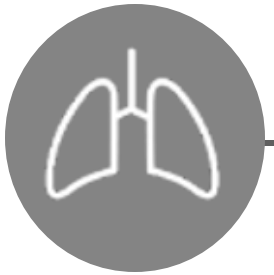
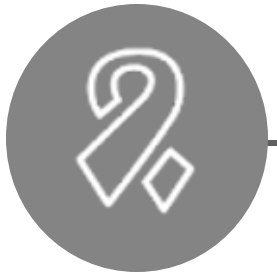
1. Li et al., 2023; 2. Nilsson et al., 1982

CONDITIONS WITH LIMITED FINDINGS

LUNG DISEASE AND B-CELL MALIGNANCIES



Chronic respiratory illnesses are a significant contributor to DALYs and deaths in LMICs[1]



LMICs bear a disproportionate cancer burden, with less access to preventative measures, resources, and care[2]

Drug-drug interaction studies contain LNG PK data in patients with interstitial lung disease (ILD)[3] and B-cell malignancies,[4] but

lack of healthy controls

limits comparison and conclusions[3,4]

Possible need for further studies in patients with:

- ILD and other **respiratory conditions** with high burden in LMICs
- various forms of **cancer**

that also include **proper control groups** for direct comparison of PK parameters

*Lung disease study also had second arm with 10-day continuous dosing

1. Boutros et al., 2024; 2. Stefan and Tang, 2023;
3. Vonk et al., 2021; 4. de Jong et al., 2020

SUMMARY OF FINDINGS

PATHOPHYSIOLOGY THEORIZED OR REPORTED TO IMPACT LNG PK

Abnormal Pathophysiology Included in Scoping Review Search Strings Across Three Databases			
Disease Category	**Specific Conditions/Terms**	**Potentially Impacted LNG PK Processes**	**Identified Data**
Liver Disease	Liver Failure, Hepatitis, Liver Cirrhosis, Liver Fibrosis, Nonalcoholic Fatty Liver Disease, Alcoholic Liver Disease, Liver Injury, Hepatic Steatosis	Metabolism	• **1** pre-clinical article
Infectious (Enteric) Diarrheal Diseases	Gastroenteritis, Rotavirus, E.coli, Salmonella, Shigella, Campylobacter, Norovirus, Giardiasis, Amebic Dysentery, Clostridium Infections, Vibrio Cholerae, Traveler's Diarrhea, Entamoebiasis, Entamoeba histolytica, Acute Diarrhea	Absorption, Metabolism	No articles/data
Non-Infectious Diarrheal Diseases	Chronic Diarrhea, Irritable Bowel Syndrome (IBS), Crohn's Disease, Ulcerative Colitis, Inflammatory Bowel Diseases (IBD), Microscopic Colitis, Functional Gastrointestinal Disorders, Celiac Disease, Fecal Incontinence, Colorectal Disease	Absorption	• **3** clinical articles (Ulcerative Colitis & Bowel Resections) • **2** review articles
Malnutrition/ Undernutrition	Malnutrition, Severe Acute Malnutrition, Starvation, Protein-energy Malnutrition, Nutritional Deficiency, Marasmus, Kwashikor, Starvation, Stunting, Wasting, Underweight	Distribution, Metabolism	• **3** pre-clinical articles • **3** clinical articles
Pelvic Scar Tissue, Adhesions, Venous Disorders	Pelvic Adhesions, Pelvic Scar Tissue, Venous Insufficiency, Venous incompetence, Varicose Veins, Venous Disorder, Venous Reflux	Absorption, Distribution	No articles/data
Pelvic Inflammatory Disease	Pelvic Inflammatory Disease, Salpingitis, Adnexitis, Oophoritis, Pelvic Inflammatory Disorder, Endometritis, Pelvic Peritonitis, Tubo-Ovarian Abscess	Absorption, Distribution	No articles/data
Uterine Fibroids	Leiomyoma, Uterine Neoplasms, Uterine Fibroid, Myoma, Fibroma, Uterine Tumor	Absorption, Distribution	• **1** clinical article
Schistosomiasis	Schistosomiasis, Female Genital Schistosomiasis, Bilharzia	Absorption, Distribution, Metabolism	• **1** clinical article (Early Schistosomiasis)
Ectopic Pregnancy	Ectopic Pregnancy, Tubal Pregnancy, Extrauterine Pregnancy, Ecdysis	Absorption, Distribution	No articles/data

TAKEAWAYS & NEXT STEPS

KEY PROJECT TAKEAWAYS

LEVONORGESTREL SCOPING REVIEW

Levonorgestrel pharmacokinetic data for multiple special population groups **is scarce**.

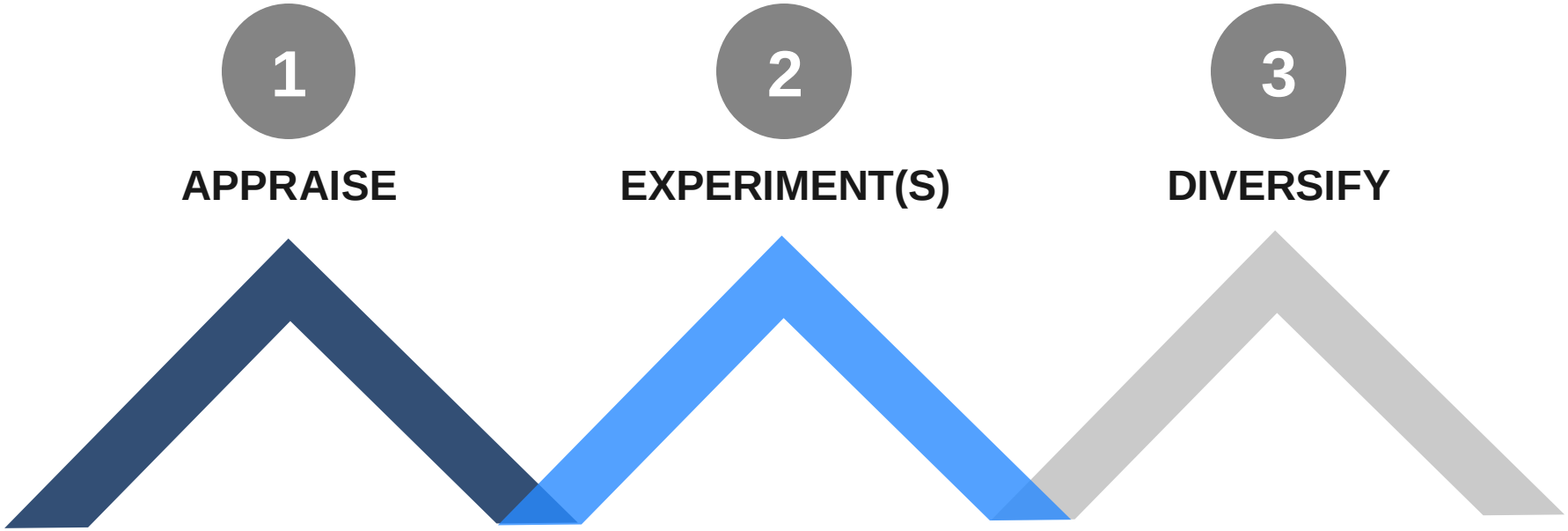
Current data suggests **potentially different LNG-PK profiles in undernourished populations** and those with **GI illnesses**, however more research is needed.

Due to insufficient data and methodological limitations, **LNG-PBPK models may be less precise** in LMICs where different and overlapping disease burdens may impact drug efficacy.

LNG: levonorgestrel, PK: pharmacokinetic, GI: gastrointestinal, PBPK: physiologically based pharmacokinetic

MOVING FORWARD

OPPORTUNITIES & CONSIDERATIONS



- Expand scoping review to consider other hormonal contraceptives & drug-drug interactions in special populations
- Could increase overall understanding of this issue

- Address evidence gaps through GF supported PK research in special population groups
- Include appropriate comparison groups

- Support more inclusive PK data by diversifying study geography and inclusion criteria and/or research policies

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PK: pharmacokinetic

DISSEMINATION OF FINDINGS

NEXT STEPS

START Website → Gates Open Research (START Gateway) → Academic Manuscript Drafting

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Department of Global Health | University of Washington

Gates Open Research
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QUESTIONS & DISCUSSION

THANK YOU

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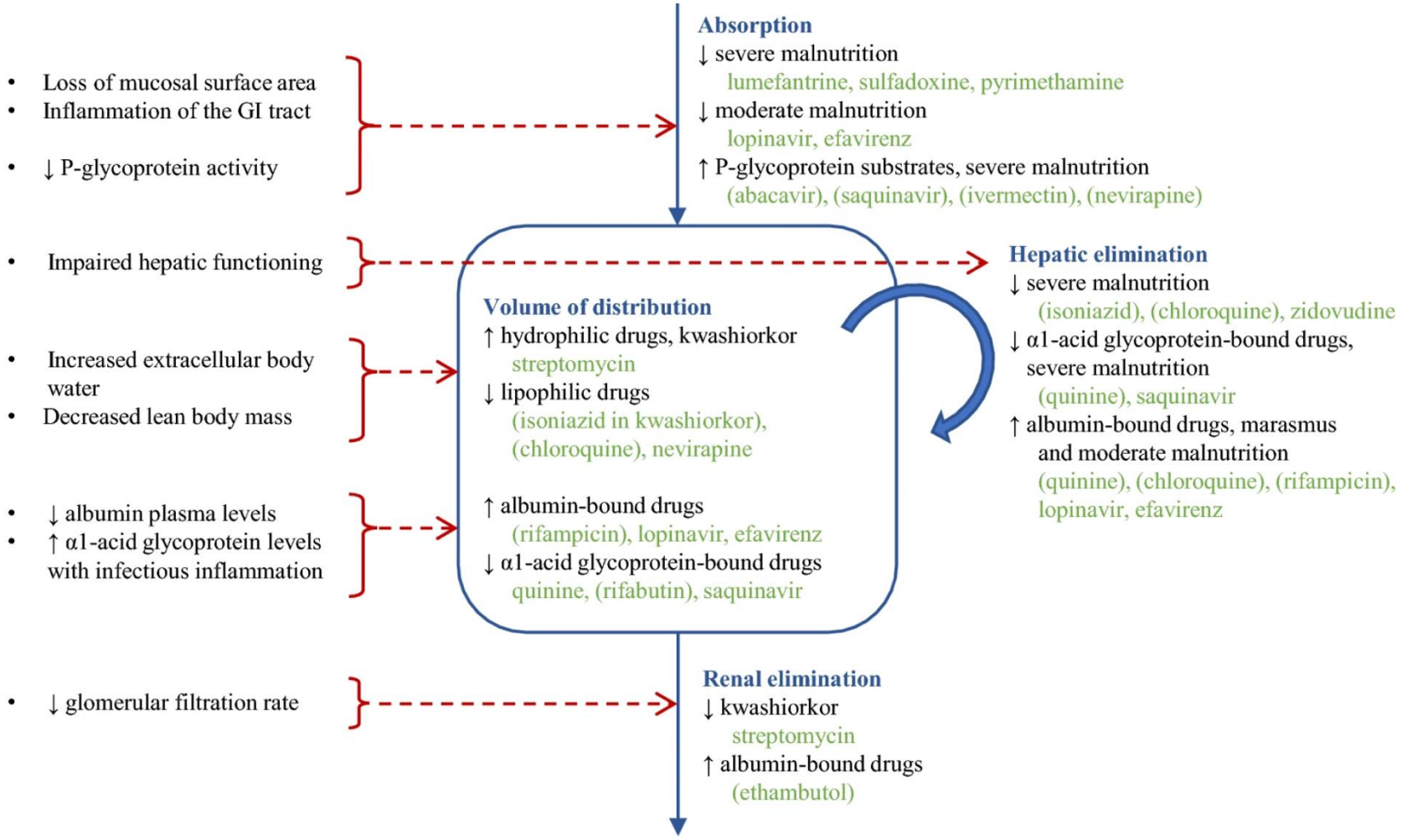
APPENDIX

DESCRIPTIVE RESULTS

Pathophysiology	Geography	Clinical vs. Pre-Clinical	Route of Administration	LNG Formulation	LNG Drug Name	Healthy Controls
Undernutrition (6)	India (6)	Clinical (3)	Vaginal Ring (1) Oral (3)	LNG-EE2 (1) LNG-Estradiol (2)	Primovlar-30 (1) WHO-LNB pill (2) Unclear/generic (1)	Yes (2) No (1)
		Pre-Clinical (3) (*in vivo*, rabbits)	IV (2) Unknown (1)	LNG only (3)	Unclear/generic (3)	Yes (3)
GI Illness (3*) * excludes 2 reviews	Sweden (2) USA (1) UK (1)	Clinical (3)	Oral (3) IV (1)	LNG only (1) LNG-EE2 (2)	Fillinett/Recip (1) Unclear/generic (2)	Yes (3)
Lung Disease (2)	Europe (1) UK (1)	Clinical (2)	Oral (2) IV (1)	LNG-EE2 (2)	Microgynon (1) Ovran (1)	Yes (1) No (1)
Liver Disease (1)	Egypt	Pre-Clinical (*in vivo*, mice)	Oral	LNG only	Unclear/generic	Yes
Female Genital Schistosomiasis (1)	Egypt	Clinical	Oral	LNG-EE2	Ovral	Yes
Uterine Fibroids (1)	Finland	Clinical	Oral and IUD	LNG-Estradiol (oral) LNG only (IUD)	Cyclabil (oral) Unclear/generic (IUD)	No
B-Cell Malignancies (1)	Poland and Spain	Clinical	Oral	LNG-EE2	Unclear/generic	No

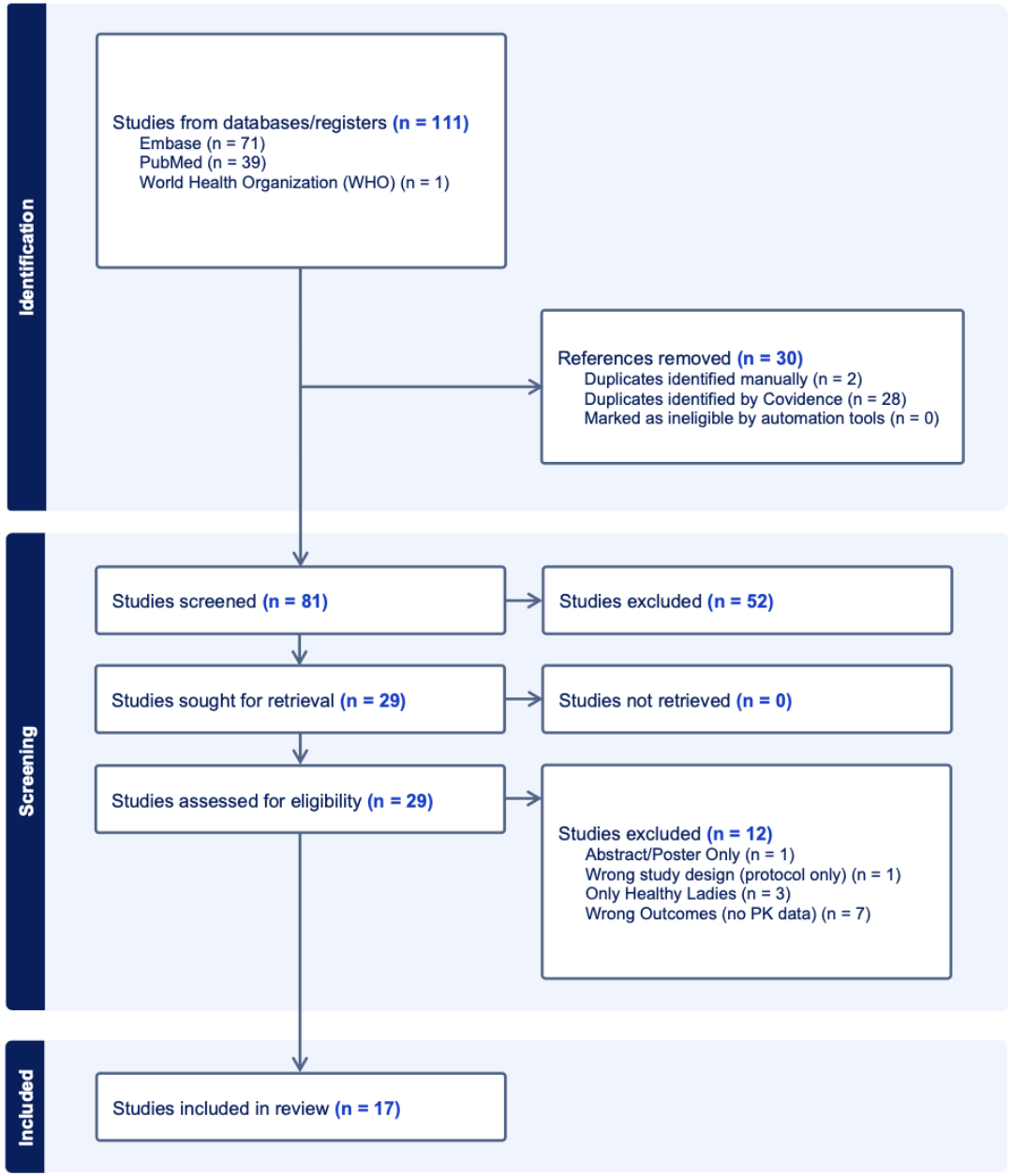
UNDERUTRITION ALTERED DRUG PHARMACOKINETICS



Alterations in drug pharmacokinetics by malnutrition. Figure summarizes the main pathophysiological changes (left) and the associated effects on drug pharmacokinetics in different pharmacokinetic stages, illustrated by the effects found for drugs against poverty-related infectious diseases (right). Drug names are mentioned when the evidence for the effect was considered strong, or mentioned in brackets when the evidence for the effect was considered weak

Verrest et al. (2021) Clinical Pharmacokinetics

COVIDENCE PRISMA FLOWCHART



In addition to the peer-reviewed literature captured in the PRISMA flowchart, we search the U.S. FDA database for PK data in special populations for non-oral LNG formulations.

BACKGROUND SLIDES

ADDITIONAL PROJECT CONTEXT

WHAT WE HEARD

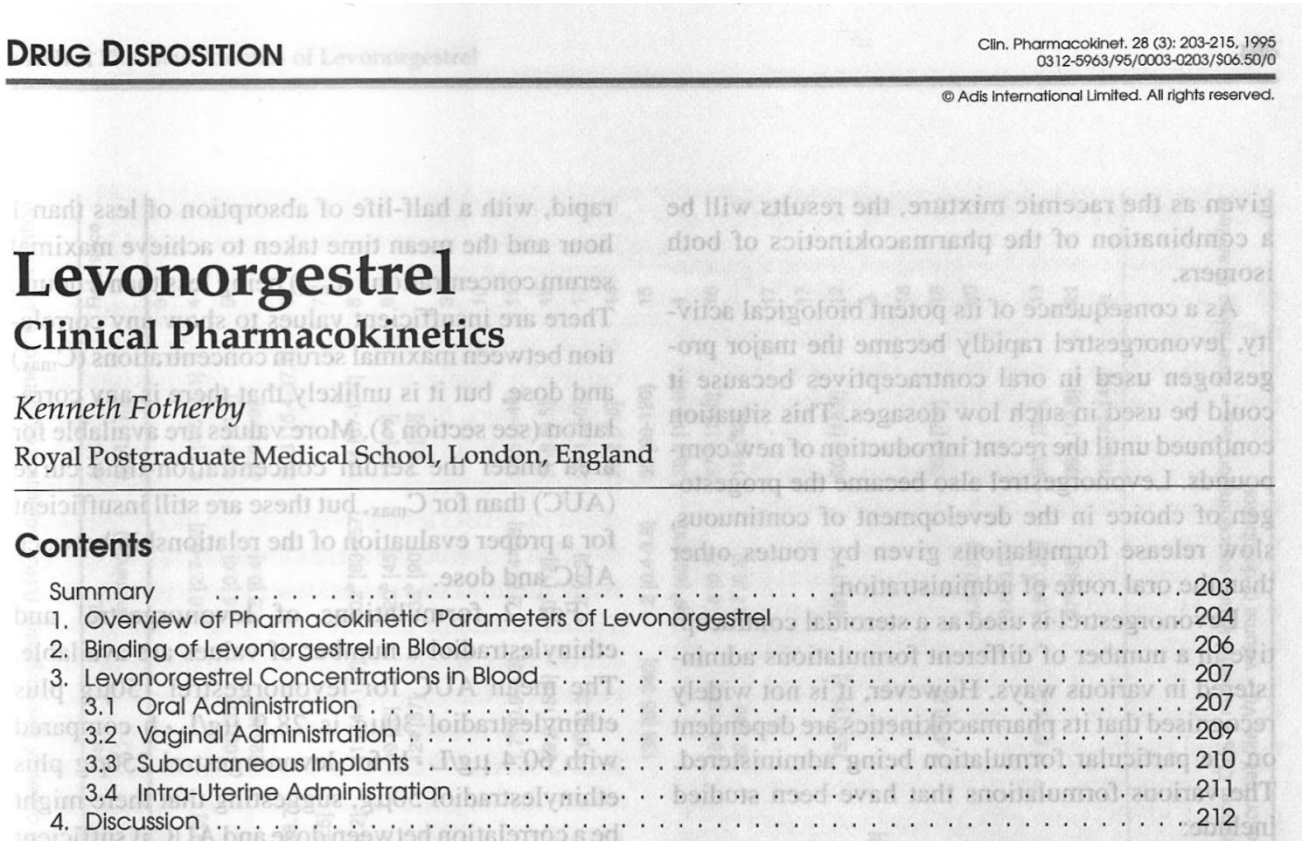
PBPK MODELS can help predict how a drug will behave in different populations.

WE ARE INTERESTED IN

? The extent to which levonorgestrel (LNG) PBPK models are tailored for LMIC populations/contexts.

LNG CLINICAL PHARMACOKINETICS

1995 REVIEW; A MORE RECENT MULTI-ROUTE REVIEW NOT FOUND



DRUG DISPOSITION

Clin. Pharmacokinet. 28 (3): 203-215, 1995
0312-5963/95/0003-0203/$06.50/0

Levonorgestrel

Clinical Pharmacokinetics

Kenneth Fotherby
Royal Postgraduate Medical School, London, England

Contents

Lack of diverse patient populations for clinical LNG PK data including:

- Age & bodyweight of participants covered a narrow range.
- Most studies involved Caucasian individuals.
- Several studies in Indian women reported vastly different ½ lives for distribution & elimination... author assumed values were erroneously derived.

HOW LEVONORGESTREL WORKS

WHAT WE KNOW

Absorption

- **ORAL:** absorbed via the GI tract
- **IUD:** absorbed via the endometrium
- **SUBDERMAL:** absorbed into interstitial fluids

BLOODSTREAM

Distribution

- **ORAL:** binds to plasma proteins to reach target organs
- **IUD:** acts locally on reproductive organs
- **SUBDERMAL:** binds to plasma proteins to reach target organs

Metabolism

PROCESSED BY THE LIVER
Specifically liver enzymes CYP3A4 & CYP3A5

- **ORAL:** first-pass metabolism
- **IUD:** not first-pass metabolism
- **SUBDERMAL:** not first-pass metabolism

Excretion

EXCRETED IN THE URINE

- **ORAL:** higher total LNG metabolites due to systemic action
- **IUD:** lower total metabolites due to more local action
- **SUBDERMAL:** lower total metabolites

CONDITIONS THAT COULD ALTER LNG ACTION

THEORIZED & SUGGESTED IN THE LITERATURE

Absorption

- **ORAL:** absorbed via the GI tract (small intestine) → **GI ILLNESSES**
- **IUD:** absorbed via the endometrium → **FEMALE REPRODUCTIVE PATHOLOGY**
- **SUBDERMAL:** absorbed into interstitial fluids

Distribution

- **ORAL:** binds to plasma proteins to reach target organs → **UNDERNUTRITION**
- **IUD:** acts locally on reproductive organs → **POSSIBLY ALTERED BLOOD FLOW FROM STRUCTURAL ABNORMALITIES**
- **SUBDERMAL:** binds to plasma proteins to reach target organs → **UNDERNUTRITION**

Metabolism

- **LIVER DISEASE(S)**
- **NUTRITIONAL STATUS** (up/down regulation of CY3A4& CYP3A5[1])

Per a 2020 Systematic Review[1]:
• weight loss increased CYP3A4 activity
• obesity might decrease CYP3A4/5 activity[1] & may reduce LNG efficacy[2]

Excretion

RENAL DISEASE

Reduced renal function could impact drug excretion & corresponding exposure[3]

START CENTER

1. Zarezadeh et al. (2020) 2. Curtis et al. (2024) 3. Masereeuw & Russel. (2001)

2016 U.S. BASED RECOMMENDATIONS

LIVER DISEASE

U.S. Selected Practice Recommendations for Contraceptive Use, 2016

Recommendations and Reports / July 29, 2016 / 65(4);1–66

Print

Please note: ***An update has been published for this report. To view the update, please click here.***

Kathryn M. Curtis, PhD[1]; Tara C. Jatlaoui, MD[1]; Naomi K. Tepper, MD[1]; Lauren B. Zapata, PhD[1]; Leah G. Horton, MSPH[1]; Denise J. Jamieson, MD[1]; Maura K. Whiteman, PhD[1] (VIEW AUTHOR AFFILIATIONS)

"U.S. guidelines state that screening for liver disease before initiation of the LNG-IUD is ***not necessary because of the low prevalence of these conditions*** and the ***high likelihood that women with liver disease already would have had the condition diagnosed***."

- U.S. women with liver disease in 2012: **1.3%**

Curtis et al. (2016) MMWR Recomm Rep

2016 U.S. BASED RECOMMENDATIONS

GASTROINTESTINAL ILLNESSES

2016 U.S. guidelines noted a **lack of evidence** addressing vomiting or severe diarrhea while using oral contraceptives.

- Recommendations for OC use with vomiting/diarrhea based on recommendations for missed pills

BURDEN OF DISEASE IN LMICS

SOME EXAMPLES OF POTENTIALLY RELEVANT EPIDEMIOLOGY

01

LIVER DISEASES:

- **<20% of the 325 million people** with chronic Hep B & C infections globally aware of their diagnosis; higher endemicity in the African region[1,2]

02

SCHISTOSOMIASIS/FEMALE GENITAL SCHISTOSOMIASIS (FGS):

- ~ 16 - 56 million girls living with FGS[3]: can cause liver enlargement/disease, scarring of genital tissues[4], etc. potentially impacting LNG distribution/metabolism.

03

UNDERNUTRITION & DIARRHEAL DISEASES:

- Rising prevalence in LMICs, with diarrhea being a leading cause of undernutrition[5].
- Could impact LNG absorption, distribution, metabolism, &/or overall drug efficacy.

1. Jaquet et al. (2021) Current Epidemiology Reports
2. Schweitzer et al. (2015) Lancet
3. Christinet et al. (2016) Intl Journal for Parasitology
4. Kjetland et al. (2012) Trends in parasitology
5. FAO, IFAD, UNICEF, WFP, & WHO (2024)

RECENT RELATED RESEARCH

2021 SYSTEMATIC REVIEW: IMPACT OF MALNUTRITION ON PK

- Reviewed the effects of malnourishment on the pharmacokinetics of drugs to treat HIV, TB, malaria, and NTDs.

KEY FINDINGS:

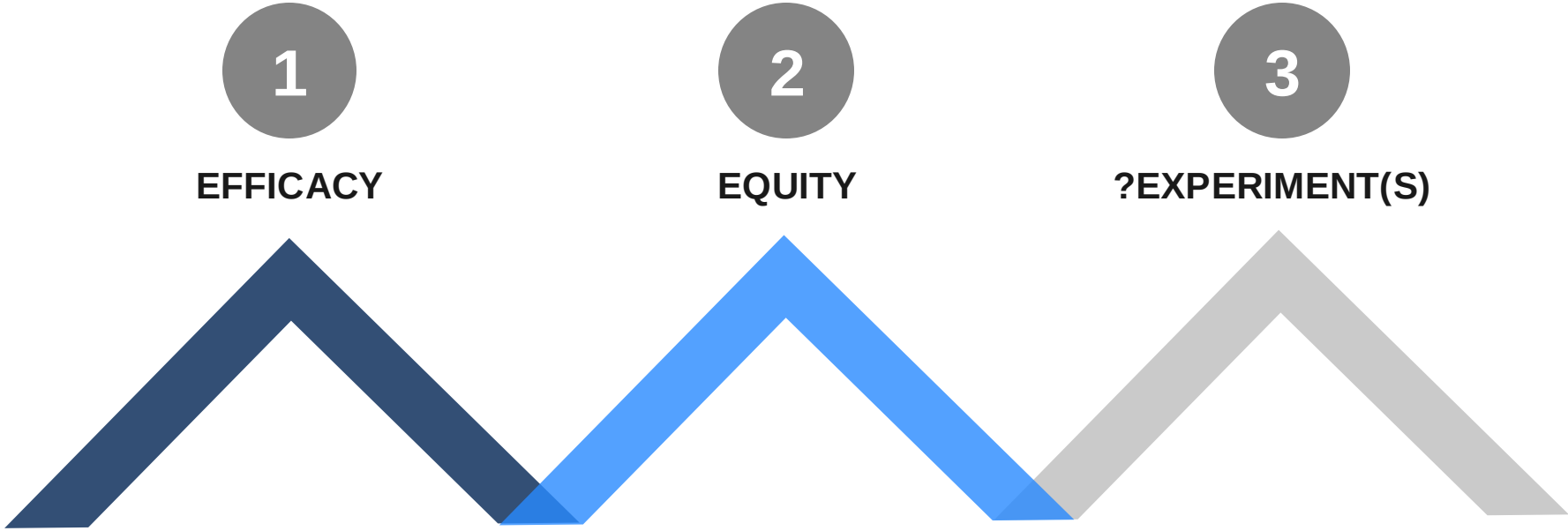
- Malnutrition leads to **physiological alterations that affect drug pharmacokinetics.**
- Pharmacokinetic knowledge for patients with NTDs and severe malnutrition **is lacking**.

LNG was not part of this review

Verrest et al. (2021) Clinical Pharmacokinetics

WHY THIS MATTERS

POTENTIAL PROJECT VALUE



- Drug efficacy may be reduced

- Young girls/women most affected by liver disease/ undernutrition/NTDs tend to be more vulnerable
- Avoiding unwanted pregnancies in this group particularly important

- This work could identify evidence gaps & inform possible future GF funded research

START CENTER

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