were excited to have Dr Juan latora

his medical medical degree from the

National University of the Northeast in

Argentina and received a PhD in

Pharmacology from Tulane University Dr

latora is currently an Adjunct professor

of Madison at Duke University and

Louisiana State University previously Dr

lotura was a faculty member at the

clinical pharmacology Center

Northwestern University between 9 and

00 he was professor of medicine and

pharmacology at Tulane University School

of Medicine

Dr LaTour joined the NIH clinical Center

in 00 as the Director of clinical

pharmacology program and led this course

the principles of clinical pharmacology

until his retirement from the NIH in

0 please enjoy the presentation

welcome to principles of clinical

pharmacology

uh my name is Juan lartora and today I

will present an overview of the

discipline of clinical pharmacology and

I also will introduce

the basic concepts in pharmacokinetics

and its clinical applications

the focus of the course

traditionally has been on the scientific

basis of drug use

development and evaluation

we do not consider this to be a course

in Therapeutics but of course there will

be relevant examples of applications of

clinical pharmacology in in Therapeutics

we will discuss general principles that

are applicable to both old and new drugs

uh there is a textbook that has been

used for this course for a number of

years principles of clinical

pharmacology the lead editor is Dr

Arthur J Atkinson Jr

so uh let us see an outline of what I

would like to cover for you today uh in

the first part uh we will have an

overview

addressing the general scope of the

discipline

uh

some brief Historical Notes

we will talk about what

do clinical pharmacologists engage in as

professionals

we will emphasize the topic of

variability in drug response as an area

of great interest in our field

also adverse drug reactions and their

impact both in terms of drug development

and clinical use of drugs and finally a

brief overview of drug development so

lets move on then and Define

pharmacology as the study of drugs and

biologics and their actions in living

organisms

uh generally when we talk about drugs we

think of small molecules chemical agents

when we talk about biologics were

thinking about large molecules

peptides and antibodies

the most

basic definition of our field is that

clinical pharmacology is the study of

drugs and biologics in humans

the discipline really spans the spectrum

of drug Discovery drug development drug

utilization and Drug regulation

we aim in clinical pharmacology we aim

at advancing Therapeutics in humans with

mechanistic understanding of drug

actions this is an area term

pharmacodynamics

and also drug disposition and that is of

course the subject of pharmacokinetics

now

you know of course

the concept of translational sciences

and how much it has been emphasized for

the last decade or so

basically we talk about knowledge

that has been acquired in animal or in

Silicon models of disease

or through exvivor studies in human

tissues

or in Vivo studies in healthy or disease

humans that then is translated into

effective treatment for patients

clinical pharmacology is a translational

discipline

essential for drug development and

Therapeutics in humans

now a bit of History

focusing on the founders of American

clinical pharmacology

Im talking about doctors Harry gold and

Dr Walter Modell at Cornell University

and this is a partial list of their

accomplishments and fundamental

contributions

introducing the doubleblind clinical

trial design in 9

initiating the Cornell conference on

therapy a couple of years later

and in the early 0s

analyzing detoxing effect kinetics to

estimate the absolute bar availability

as well as the time course of the

chronotropic effects of digoxin welcome

back to this example later in the talk

and in 90 they founded the journal

clinical pharmacology and Therapeutics

which is today of course a leading

journal in the discipline

now at the NIH we should mention Dr

Albert scherzman who headed the

experimental experimental therapeutic

Branch at the national Heart Institute

from 9 through 9 he trained

individuals of the stature of Luke

Gillespie John Oates Leon Goldberg

Richard crowd Ken Melbourne and many

others that subsequently became leaders

in the discipline as well

their research focus on serotonin and

the carcinoid syndrome

theochromocytoma antihypertensive drugs

and and many other contributions

now what are the professional goals of

clinical pharmacologies

well we are interested in the discovery

development evaluation of new medicines

and how their uses regulated by the Food

and Drug Administration in the United

States and other regulatory agents in

other countries

we are also interested in optimizing the

use of existing medicines and often

finding new indications for all drugs

but as I mentioned in our initial

outline

a critical area of interest to clinical

pharmacologies is to define the basis

for variability in therapeutic and toxic

responses to medicines

uh and this is an example uh looking at

the exposure to Two antidiabetic drugs

uh bioglitason on the left side of the

slide and Metformin on the right hand

side and were looking at drug exposure

in terms of the area under the plasma

concentration time versus time curve and

this is an AUC area under the curve that

has been normalized to a milligram

dose of bioglitos on

and a 00 milligram dose of Metformin

and also normalize to 0 kilograms of

body weight for a human patient and you

see the great variability that we see in

drug exposure both in females and males

in the case of both of these

antidiabetic agents so thats one of

the challenges clinical pharmacologists

face in trying to understand the basis

for this variability in drug exposure

and how it may impact on the therapeutic

actions of the drug

another source of variability in drug

exposure May relate to underlying

genetic variants in this instance we are

using the example of nortriptyline a

tricyclic antidepressant that has been

in use for many years

and the impact of cytochrome

p D polymorphism

and here we are plotting plasma

concentration of nortriptyline after a

milligram dose over time and then we

see the impact of the number of

functional genes for cd

the first curve on top

indicates a higher exposure for an

individual that does not express cipd

and actually by definition is a very

slow metabolizer of this drug and then

the

progressively smaller area and the curve

with increasing numbers of cd

functional genes this over here at the

bottom is an individual with copies

of the gene

that is also an ultra rapid metabolizer

of this drug so another source of

variation in drug exposure and of course

potentially on therapeutic efficacy of

drugs uh in terms of these

pharmacogenetically determine

variation in drug exposure

now lets turn to another major area of

interest in clinical pharmacology namely

adverse drug reactions

some toxicities of drugs

can be managed

and may be acceptable

based on a risk benefit ratio

but other adverse reactions and

toxicities by their nature and severity

are really unacceptable and those drugs

either have to be removed from Clinical

use or used with great caution and

adherence to

significant

and close monitoring of the patients

uh we need to understand of course that

risk benefit is contextual

depending on the drug and the disease

that we intend to treat

it is not the same to consider a

potentially serious toxicity for a drug

intended to treat hypertension which is

a condition that needs lifelong therapy

compared to say treatment of cancer

a disease that is potentially lethal

over the short term and that requires a

very intense treatment with

combination of drugs that have very

significant toxicity so again risk

benefit is contextual and we must

consider the drug in question and the

disease that we are

intending to treat

now again in terms of genetics

as

it may relate to severe drug toxicity

now this is a condition or situations if

you will wear an underlying genetic

variant May predispose individuals to

severe toxicity from drugs here we have

the examples of HLA

b0

individuals that carry this HLA variant

are at very high risk of a back of your

hypersensitivity a back of there is a

drug used in the treatment of HIV

infection and AIDS and prior to

instituting treatment with a back of ear

every patient is first tested for this

variant

hlab0 if they have the variant they

cannot be treated with that drug and an

alternative must be found

uh the next example that we show here is

that of HLA

b0

predisposing to severe carbon mazepine

induced Stevens Johnson syndrome this is

a serious cutaneous adverse drug

reaction that actually can be fatal so

once again

the

underlying genetic variants

conferring

predisposition to severe drug toxicity

another example of unacceptable drug

toxicity is that of course at the points

what were showing here is an

electrocardiographic

record

of heart rhythm in a patient that

suffered from an episode of this

polymorphic ventricular tachycardia this

is a very abnormal Rhythm you can see

here in normal beat if you will in the

electrocardiogram preceding these runs

of polymorphic

ventricular tachycardia that is actually

drug induced so this is another example

of a potentially lifethreatening

adverse reactions from drugs

and uh here

um showing terphenidine which

historically was

the first

nonsedating

antihistamine that was introduced uh in

the United States Market under the brand

name of celldane but was subsequently

withdrawn from the market because of the

risk of drug induced arrhythmias now

look at the metabolic transformation of

terphenidine in humans and the

production of terphenidine carboxylate

as a metabolite very interestingly this

metabolite is active it also has this

antihistamine pharmacological action

and its also a nonstating

antihistamine but terphenidine which is

marketed as Allegra does not have the

risk of a drug inducer rhythmia like

tors at the point and this again brings

us to consider and remember the

importance of studying drug metabolism

and

assessing whether metabolites are also

pharmacologically active or are

otherwise inactive ones bio

transformation has taken place

let me bring you the example of

thalidomite

again in terms of

unacceptable drug toxicities but

actually with a very interesting history

as I will show you in a moment

thalidomide was introduced in the 90s

as a sedative

and actually was prescribed as an

antinosia medication to pregnant women

unfortunately and fortunately in many

countries although not in the US

because

thalidomide was not approved in the

United States and actually was not

allowed to enter the market at the time

because of the discovery of some severe

toxicity to

unborn children due to prenatal drug

exposure uh this led to an epidemic

worldwide of for Camellia children born

with severe defects in terms of their

limbs and and of course this is a very

uh unfortunate outcome of the use of

that drug in pregnant women

now there were consequences to this

thalidomide crisis

for one thing the uh United States

Congress approved the kefauver Harrys

amendments in 9 that instituted new

and more strict FDA regulations to

establish whether drugs were on the one

hand effective but safe and and the

process that

has been modernized over the years but

again emphasizing safety and

demonstrating efficacy of drugs before

theyre allowed into the market The

Institute of medicine and the National

Academy of Sciences began to review

therapeutic claims at that time

and also more research on the causes of

adverse reactions was encouraged and the

National Institute of General Medical

Sciences created a number of clinical

pharmacology centers in the United

States to

again

Implement rational drug development to

establish a scientific basis of drug use

in in clinical medicine and

again sadly as a consequence of this

major

thalidomide crisis

so our discipline is

imminently

involved in the development and

evaluation of new drugs

we start with drug Discovery and this is

a process in itself that we will be

addressing detail in another session of

this course

then we have preclinical

meaning

animal testing of candidate drugs and

eventually clinical evaluation to

demonstrate safety in humans and whether

or not the drug is effective in a given

clinical condition

uh but then we also have post marketing

studies once the drug enters the market

we continue to evaluate uh for the

possibility of rare adverse reactions

that were not discovered uh in the uh

preapproval stage and also

performing studies in special

populations like the elderly and and in

in children

now this is a schematic of premarketing

drug development uh you see here the

face of preclinical development we have

animal models we have assay development

we study pharmacokinetics and

pharmacodynamics in animals we of course

begin to study animal toxicology in the

short term and the long term if the drug

is intended for chronic use and once a

package of information is developed that

indicates that the candidate drug May in

fact be promising an investigation of

new drug application the IND is filed

with the Food and Drug Administration or

other Regulatory Agencies and then we

begin the process of evaluating drugs in

humans

typically considered as phase one

first those in human studies those

escalations to assess tolerance phase

two when we do the proof of concept

studies treating patients with the

condition that may benefit potentially

from the drugs and phase three the large

randomized clinical trials comparing the

new drug to a placebo or to a previously

established therapy and that then leads

to the submission of a new drug

application or NDA

where the sponsor as the regulatory

agents to review this body of evidence

and request approval for marketing the

drug and to begin

using the drug in clinical practice

uh one way to look at the faces of drug

development is with the learn and

confirm paradigm

the late Dr Lou Shiner and his

colleagues advocated this approach phase

one and phase two are the learning

phases of drug development phase three

is the confirmatory phase

and phase four again is the post Market

in Phase but learning continues uh

focusing on rare adverse drug reactions

and special populations if required

now lets talk for a moment about drug

repurposing this is an area where the

National Institutes of Health and and

other academic investigators

have been very interested in and that

has to do with finding new biological

targets and new therapeutic indications

for all drugs

what are the potential advantages of

this approach well for one thing it may

shorten drug development time

we already know

a lot about the safety of the drug and

we also have data in terms of the human

pharmacokinetic behavior of the drug and

Drug repurposing then and this is the

concept of of Dr Austin at ncats

is Illustrated

in this fashion now typically we have a

process of drug screening of thousands

of compounds and the whole process may

take 0 years between

identifying the target agent and

Performing all the political and

clinical phases of drug development that

may then lead to drug approval

what if then

through repurposing of a much smaller

number of drugs that have been in use

for other indications

could perhaps

shorten the period of drug development

to a couple of years now this is ideal

but conceptually again very important

and we do have examples of a number of

drugs that have been repurposed and very

interestingly we have again thalidomide

extremely toxic and forbidden

in pregnant females but nevertheless

through the

clinical observation of a physician in

the 90s

it became a very useful agent to lead or

rather to treat a complication of

leprosy called erythema nodosum leprosa

so again a drug that otherwise was

banned from marketing becomes Now useful

in the clinical condition like erythema

and the doors on the proso

years later the drug was actually

studied in the condition of multiple

myeloma again a form of cancer

this time through targeted drug

development in any case these are now

two FDA approved indications this is an

immunomodulatory agent marketing is done

under a very special and very restricted

distribution program

referred to as system for thalidomide

education and prescribing but a very

good example of drug repurposing

and in this slide I show you a list of

drugs that were approved originally for

a different indication but now our FDA

approved for indications uh that for

example for sildenafil uh include

pulmonary hypertension

Lamotrigine being used for bipolar

disorder and and so forth so again

repurposing as a viable and and

potentially very important way to look

at finding new indications for all drugs