todays lecture is by dr sarah robertson

degree in chemistry from marquette

university followed by a doctorate of

pharmacy degree from the university of

wisconsin

she completed a pharmacy practice

residency at northwestern memorial

hospital in chicago and a fellowship in

clinical pharmacokinetics at the

national institutes of health

for six years dr robertson was a

reviewer in the office of clinical

pharmacology in the center for drug

evaluation and research at the fda

she is currently a director at vertex

pharmaceutical in the department of

clinical pharmacology and biomarkers

please enjoy todays lecture

hello im sarah robertson and today ill

be covering drug interactions

so as an overview

im going to be covering the

epidemiology and various categories of

drug interactions talking about the

mechanisms affecting drug absorption

distribution metabolism and modulation

of transport proteins

as well as alteration and renal

elimination of drugs well dive a little

bit into enzyme transport or interplay

and cover some complex drug interaction

issues

well discuss a clinical interpretation

and look at some examples of product

labeling

i have upfront some abbreviations ill

refer to throughout so this will be a

good point of reference im going to be

referring to the area under the

concentration time curve throughout and

that is a measure of drug exposure when

we look at a plasma concentration versus

time curve and ill look at well look

at some examples of those ill also be

using the terms substrate and modulator

so substrate just refers to the drug

being acted upon or the victim

whereas a modulator is a drug that

inhibits or induces

for instance drug metabolism or a

particular transport protein so the

modulator generally refers to the

perpetrator of a drug interaction

so the epidemiology of drug interactions

theyre not easy to quantify

particularly the clinical relevance of

them

i have a couple references here though

one was a review of medicaid records

between the years of 00009

in which it was discovered that nearly

of patients were found to have at least

one clinically significant drug

interaction

the risk of course increases in the

elderly are patients with comorbidities

or patients on multiple medications

a second publication here talks about an

fda review of ndas approved in 0 so

fairly recent

and that review found that majority of

compounds  percent were metabolized by

a cytochrome p0 enzyme

and about the same number showed

possible inhib inhibition or induction

of a metabolizing enzyme

and overall nearly 0 percent or

percent had a metabolism

metabolismbased drug interaction that

resulted in a change of clinical

significant

so the various types of interactions we

generally classify them or put them in

two categories pharmacodynamic which

related relates to a drugs effect on

target be it safety or efficacy and

pharmacokinetic which generally refers

to an impact on drug absorption

distribution metabolism basically

impacting the concentration of drugs

circulating in the body or acting at the

site of activity

so some examples of pharmacodynamic

interactions we have additive

combinations and some examples there

when you combine sedatives for instance

with pain medications

or antiseizure medications with pain

medications that can cause over sedation

a beneficial pharmacodynamic interaction

is that of ibuprofen and acetaminophen

used together in combination to treat

pain

a harmful example is i dont zydovidine

hiv medication used early in the

treatment of hiv with ganciclovir which

is an antiviral drug used to treat cmv

infection it was discovered early on

in the early

treatment of hiv that the two drugs in

combination cause severe neutropenia

a synergistic combination is when we

combine two drugs and we get a

beneficial effect above that of either

one

and a good example of this is

aminoglycosides with penicillin used to

treat grampositive infections

a harmful combination is obviously that

of barbiturates and alcohol or sedatives

and barbiturates or sedatives and

antiseizure medications

an antagonistic combination might be

where one

drug counter acts or blocks a

pharmacological effect of another

a beneficial antagonistic relationship

is the use of naloxone or narcan used to

treat opiate overdose

an example of a harmful one is that of

zidova

zydovidine and stabidine again two

antiviral retroviral medications used to

treat hiv

they actually compete with one another

for phosphorylation and its been shown

both in vitro and clinically

that using the tune combination actually

results in a lessening of antiviral

efficacy

some pharmacokinetic interactions we

generally put these in one of four

categories interactions affecting drug

absorption

distribution

metabolism

or elimination

so first well start with absorption

so ultra absorption might be impacted by

ph we know that a lot of drugs are

dependent on an optimal ph for their

solubility and hence permeability or

uptake into the into the absorption

increasing the ph in the gut for

instance using an h antagonist like

ranitidine or a proton pump inhibitor

can result in an increased or decreased

solubility of a drug

some examples include adesanovir and

reltegravir again to antiretroviral

medications they actually have two

different responses to ph adexanovir

absorption is decreased

with the use of proton pump inhibitors

whereas royal tegravir exposure is

increased

so the question is how clinically

relevant are these ph altering drug

interactions well theres an example

with urlot nib an

anticancer medication used to treat

pancreatic and nonsmall cell lung

cancer

in a retrospective review of patient

records actually found that use of acid

suppressing drugs in combination was

associated with a significant reduction

in overall survival after counting for

other factors up to nearly uh four

months

and thats in light of only a 0 percent

reduction in auc

another ddi affecting altered absorption

is the effect on gi motility

so use of narcotics such as methadone we

know decreased gi motility slow

transit of

medications through the gut and can

affect absorption

whereas other drugs like metaclopramide

otherwise known as reglan which is used

to treat nausea and other gi

issues

and

increases increases motility in the gut

can also affect absorption

so the example on the left here we are

using didenosine in combination alone in

combination with methadone or alone and

as you can see methadone again

decreasing gi motility had a significant

effect on didenosine absorption and

overall plasma exposure

whereas example on the right weve given

posaconazole a

a

antifungal agent in combination with

reglan or metoclopramide and we see

reduction in posaconazole absorption as

we increase uh motility

another example of altered absorption is

the effect of chelation and this is

basically irreversible binding of drug

in the gi tract which can happen to

certain phosphate medications certain

pro drugs

classic examples of these are the

tetracycline and quinolone antibiotics

are sensitive to combination with things

like antacids and dairy products calcium

containing products and in this example

we have a fluoroquinolone trobophloxacin

given with either malox which contains

magnesium and aluminum either separated

by two hours

or with malox given just 0 minutes

before and you can see a profound effect

on the absorption of trophofloxacin when

you give maalox just 0 minutes before

its not the

effect on

gastric secretion of

acid however because when you give

trophofloxacin with a proton pump

inhibitor theres no effect on

absorption so its really the chelation

with the magnesium and the

aluminum in this case

so were going to move on now to

mechanisms of interactions affected by

drug transport

so just to orientate everybody real

quickly in the gut we have passive

diffusion of drug and every drug

perfuses a little bit different with

different levels of permeability

some drugs are efluxed out more than

others by eflux proteins such as peak

glycoprotein

others rely on uptake by uptake

transporters most commonly in the gut we

think of oatp

and when we block either the efflux

transport

we can see less efflux of drug back into

the gut

and hence increased drug levels in the

blood

same two we could block up

uptake transporters such as oetp here

which would result in

increased drug back into the gut and

lower levels of drug in the blood

so again uptake and efflux transporters

in the gut can be inhibited or induced

that is increased

by

modulating drugs and these in turn can

increase or decrease the bioavailability

of drugs that rely on those transporters

and again it depends largely on the

compounds permeability the lower the

permeability of a compound the more its

absorption is affected by membrane

transporters in general

and of the money gut transporters we

looked at on the previous slide and

there are many the two most common

associated with clinically relevant drug

interactions include pglycoprotein or

pgp

and bcrp or breast cancer resistance

protein

a couple of examples of this is a

welldocumented interaction between

quinidine which is a pgp inhibitor in

digoxin

did jackson we described as a sensitive

substrate of pgp that is small

perturbations in pgp whether it be

induction or inhibition can result in

big changes in digestion exposure

so we often use digoxin as our substrate

of interest when we want to evaluate the

effect of another drug on p like

pglycoprotein

some clinically relevant

wellcharacterized pgp inhibitors

include cyclosporine erythromycin

verapamil etraconazole and

others now well move on to drug

interactions affecting drug distribution

specifically well talk first about

protein binding this is largely a

theoretical ddi and

generally its focused on restrictively

clear drugs so those are drugs in which

only a small fraction of drug is

extracted as it passes through the liver

or other eliminating organ

because only unbound drug is cleared you

would expect an increase in the fraction

unbound to lead to an increase in total

drug clearance and hence a decrease in

plasma concentrations

at the same time we know only unbound or

free drug is available to act upon the

pharmacologic target

but

because in general unbound plasma

concentrations return very quickly to

predisplacement levels after a

transient increase

these are rarely clinically relevant and

i have a quote here from a publication

that states the general clinical

importance of plasma protein binding

interactions has been largely overstated

and ill show this an example

so this is looking at warfarin morphine

is often cited as something potentially

sensitive to protein binding

distribution or protein binding rather

interactions because it is a

restrictively eliminated drug and its

got a narrow therapeutic window

so in the top plot we have the

pharmacodynamic response which is

bleeding or thrombin thyme on the bottom

we have warfarin concentrations in

plasma both free and total

and you can see when we add a displacing

drug so that is a drug that competes for

binding the plasma proteins with

warfarin we displace warfarin from

proteins and you get a spike in free

circulating warfarin

as a result you also see a small

increase in the prothrombin or bleeding

time

its quick and quite acute however

because we have more free drug

we also have more drug available to be

eliminated to the by the body so our

total drug concentration decreases and

overall those free levels of warfarin

also return to predisplacement levels

and all this is resolved in just a

matter of days

transport proteins as we talked about in

the god can also play a role in the

distribution of guts to other organ

systems most notably we think of organ

systems that are highly protected

like the bloodbrain barrier or the

placenta or kidneys

but also

organs of elimination like the liver

inhibiting or inducing these transport

proteins in these organs can affect the

distribution of drug

so in the first example we have here

loperamide and antidiarrhoeal

antidiarrheal medication

can cause cns side effects

its generally protected from getting

into the cns space by transport proteins

such as again p glycoprotein or pgp

but when you add an inhibitor like

quinidine that increases the cns

penetration of loperamide and puts

patients at risk for cns associated side

effects

same to our examples with digoxin again

this time with paroxetine as the

inhibitor which can increase the cns

penetration of digoxin

now lets move on to metabolism

youve probably learned a bit already

about drug metabolizing enzymes in the

system most notably cytochrome p0

enzymes

sip three four and five are probably the

by largely the most abundant and

promiscuous of the enzymes metaboli

metabolizing a large proportion of our

our medications

inhibition and induction of these

metabolizing enzymes most notably cepa

is also the primary source of most

adverse drug interactions

we can talk briefly about phase

enzymes but for the most part phase

metabolizing enzymes that cause

conjugation

are rarely associated with clinically

significant drug interactions

part of it is because the

prevalence of these enzymes theyre

available in such large quantities an

inhibition of a phase two enzyme rarely

translates into a very clinically

relevant drug interaction

so well focus for the most part

of

inhibition and induction of phase one

enzymes

so cytochrome p0 enzymes again as

youve probably learned already are most

prevalent in the liver but also in the

gi tract

and when we inhibit the inhibition we

can get a increase in substrate or

victim

concentrations which can result in

toxicity

usually the inhibition occurs by

competition to the enzyme site and its

generally a quick onset and offset of

effect when you add an inhibitor

but the time to the maximum effect

really depends on how long it takes for

the substrate drug to reach steady state

so if you consider a drug at steady

state these are the plasma

concentrations that peak in wayne from

peak to trough over the course of a day

when you add a sip inhibitor you slowly

start to gain a gain in concentrations

and the concentrations will increase

again until a new steady state is

reached

its important of course if youre going

to decrease the dose of a drug to bring

it back down to the preinhibitor levels

that you consider the withdrawal of the

inhibitor and the appropriate dose

increase back to be able to maintain

original substrate concentrations

so its not just the onset but also the

offset of inhibition

the effect of inhibition on a substrate

is of course greatest if that substrate

relies on only a single route of

metabolism so great example is midazzlam

which is a classic sensitive cip

substrate it relies only on ca and

its very extensively metabolized so it

doesnt take much inhibition of ca to

get a very profound increase in medazlam

exposure

drugs with more than one route of

metallic metabolism however like

voriconazole which relies on c9 c9

and a

are less sensitive

so if you inhibit ca voraconezval

still has sepc9 and 9 as pathways for

elimination

we talked about the most common method

is typically via competition to enzyme

binding site but theres another

mechanism and thats called

mechanismbased enzyme inactivation

and that results when reactive

metabolites form and they make a

inhibitory complex

we sometimes refer to this as

irreversible or

quasiirreversible inactivation of sip

it generally results in a more profound

and prolonged inhibition effect so even

after you withdraw the inhibitor the

inhibition can persist for some time do

the this metabolic inhibitory complex

some examples include the macrolide

antibiotics like clarithromycin and

erythromycin

as well as grapefruit juice

heres an example of strong syph

inhibition by retinovir norvir again an

antiretroviral drug used to treat hiv

on the left we have triazolam again a

very sensitive cepa substrate its

metabolized 00 by this enzyme and its

extensively metabolized and when you add

retonavir you see the profound increase

in the area under the concentration time

curve of 0 fold

on the other hand zolpiden or ambien is

metabolized by sip a and other sips

so when you add retanovir all you see is

a  increase in exposure relative to

the 0 fold we saw with triazolam

so flip into the other side lets talk

about induction of metabolizing enzymes

these occur by increased dna

transcription so drugs interact with

nuclear receptors most notably pxr car

pxr being responsible for the synthesis

of sip a a as well as pglycoprotein

interaction with this dna transcription

factor results in synthesis of new

enzyme

because it takes a couple weeks for

enzyme to be fully synthesized its a

slower onset and offset relative to

inhibition

we generally say that induction takes about a week to two weeks for its full effect

it also depends on the halflife of the inducer and the time to make the new proteins

this results in a decrease in substrate

as weve got greater metabolic turnover due to increase in sip enzymes and of course reduction in activity of the drug

we might also see the formation of toxic metabolites

when you remove the inducer without a dose adjusting the substrate you can get toxic concentrations of the substrate of course

so just as we talked about with the inhibitor you have to be mindful of both the onset and offset of inhibition and how you might be dose adjusting the substrate

same two with the inducer though of course a time course might be slightly different

unlike inhibition where

if a substrate had multiple enzymes to

metabolize it inhibition of one was not

so impactful

induction can be significant even when a

drug relies on multiple sip enzymes if

one of the pathways is induced

so this shows a time course of induction

again were at steady state with a

particular substrate when we add an

inducer its going to take between one

to two weeks to get to a full effect

until a new steady state is achieved

and this might require again a dose

increase and so we have to be thoughtful

about where youre going to introduce a

dose increase to maintain concentrations

during the course and onset of induction

heres an example of a strong inducer

like we talked about retinovir for

inhibition rifampin is a very strong

enzyme inducer of ca as well as some

other sip 0 enzymes

in this example it was paired with a

investigational agent

being developed for the treatment of

tuberculosis

this agent was metabolized only

partially bicepa only 0 percent

yet when we add rifampin we saw a

profound decrease in exposure of

percent up for the auc and  for the

trough with a half life shortened from

9 to  hours

this of course is potentially very

clinically significant since rifampin is

another tb drug

and might be something that would be

paired with this investigational agent

this table shows a number of classic and

common inducers and inhibitors of sip

0 enzymes just to point out in the

strong ciphering inhibitor list again we

have some macrolide antibiotics the

azole antifungals such as itraconazole

posaconazole voriconazole are classic

strong ca

inhibitors

in the deuce inducer side again we

talked about rifampin as a classic

strong enzyme inducer

carbamazepine and phenobarb are also

strong inducers that are often used in

drug interaction studies

and the herbal st johns wort is also

strong enzyme inducer

we also have moderate enzyme inducers

and inhibitors which can or cannot be

clinically relevant depending on the

drug in question

and we generally think of weak

inhibitors and weak inducers as not

being so clinically relevant drug

interactions

so now lets talk about altered hepatic

or biliary elimination via transport

proteins

so again we know of course that the

metabolizing enzymes are inside of

hepatocytes

certain drugs pass

uh permeably passively into the

paddocine dont rely on uptake transport

yet other drugs dont pass well by

themselves and rely on transport

proteins most notably oatpb

b and b is some common ones for

uptake into parasites

if these are blocked of course less drug

is going to get into the liver to be

metabolized and were going to get

higher systemic concentrations

a classic example of this are the

statins which rely on oatpb and b to

be taken up into the liver and well

look at a couple examples of the statins

theres also efflux proteins that push

drug from the parasite out into bile

these include again pglycoprotein

and bcrp

and if you inhibit these youre going to

have decreased biliary excretion you may

get higher systemic exposure or you may

might just get greater hepatic

metabolism if the drug is metabolized

extensively in the liver

so this is an example of gemfibrizil and

resuvastatin again rosuvastatin is a

substrate for oatp

uptake transporters in the liver and

brazil is an inhibitor in this example

weve seen  percent increase in

exposure over suvastent with gempibrazil

so as you might imagine after looking at

that diagram of the patocite we can get

some complex transporter sip enzyme

interplay

in this example were going to talk

about atorvastatin its a substrate for

cypa metabolism

its also efflux by pglycoprotein and

taken up by oatpb and b into the

liver

if you look at at the very bottom first

a drug like gemfibrisal which only

inhibits

oetpv you see about a  percent

increase

in atorvastatin exposure

however going to the very top when you

consider a drug that inhibits pgp

oatpb and is a weak hip inhibitor you

get a profound effect on a torvid statin

exposure of nearly nine fold

and somewhere in the middle such as

clarithromycin thats a strong sipa

inhibitor but it doesnt inhibit oatpb

and you only see about a  fold

increase in exposure

so this is where it gets really

complicated to predict and anticipate

what a drug interaction might cause

if you know that transport and and

metabolizing enzymes are involved

now well move on to renal elimination

much like in hepatocytes in the gut we

have active transporters taking up drug

from the blood putting it into the

kidney proximal tubules as well as

excreting drug into urine most notably

the oat and oct as well as p

glycoprotein transport proteins are

often cited in clinically relevant drug

interactions affecting renal elimination

so again if you inhibit uptake transport

you would decrease elimination of course

systemic exposure of the drug would

increase

some examples of this include some

editing over the overthecounter h

antagonists its an oct inhibitor and

its been shown to increase exposure of

drugs such as metformin

probenicid is another classic example

its an oat  and oat inhibitor and has

been shown to increase exposure of a

number of drugs that are renally

eliminated including saddafivir

ferocimide and acyclovir

lets talk about some more complex drug

interactions

there are certain compounds that

actually inhibit and induce enzymes at

the same time and a classic example of

this is return of iron step a

can result in really unpredictable and

potentially time defendant dependent

effect on substrates

whereas in the short term after two or

three dose days of dosing

you might see a huge spike in the

dazzling exposure however a week or two

later you may see a more nuanced effect

on midazolam exposure as induction

starts to kick in

we also talked about concurrent

inhibition reduction of both enzymes and

transporters at the same time

this can have a potentially additive or

antagonist effect on a substrate

elimination and these are very difficult

to predict as we looked at

you might have a combination of two

inhibitors acting on different enzymatic

pathways used by substrate

so we talked about the example of

voriconazole relying on multiple

enzymes for elimination if you inhibit

one theres not such a big effect but

imagine adding a cipc9 inhibitor on top

of sipa you can have an increased

effect on exposure of oriconazole or

other drugs

in addition

we have to consider

the

genetic polymorphisms of certain enzymes

we know that certain enzymes such as

sipc9 can be expressed differently in

different patient populations

a particular patient that has is a poor

metabolizer that is they carry a

genotype

conferring

lower enzymatic

potential of for instance sypc9 is

going to rely on other alternative

enzymes

and effect of for instance a cyph

inhibitor might be more profound

on voriconazole and somebody thats a

poor cipc9 and hip inhibitor or im

sorry septuccino metabolizer

in addition we have to think about

patients with altered baseline renal or

hepatic elimination due to kidney or

liver disease

so how do we predict these when we have

a new compound in development

well very early in drug development we

characterize the compound extensively in

vitro so first

we analyze that we look at preclinical

or animal studies and in vitro

experiments to characterize how the

drugs eliminated

is it renally is it through biliary

excretion is it through hepatic

metabolism if it is through metabolism

which enzyme is responsible is it one of

the sep0 enzymes one of the phase

enzymes

if its regionally eliminated is there

an active transport protein involved in

its elimination

after weve characterized clearly how

the drug is

eliminated that is characterize its

potential to be a victim of drug

interactions

we also evaluate whether the drug might

be a perpetrator

that is does it have the potential to

inhibit or induce enzymes or transport

proteins

if we do observe some inhibition or

induction in our in vitro systems we

characterize a probability of the

clinical significance of it so we look

at the in vitro ic0 value for example

if we look considering inhibition

reduction and compared to our clinical

exposures most notably we look at peak

or cmax concentrations

if our peak exposure i over ic0 exceeds

point one is a general rule we might

consider a clinical drug interaction to

characterize how extensively our drug in

development might inhibit or induce a

particular enzyme

or maybe we consider doing some

mechanistic modeling to evaluate the

potential for the clinical relevant drug

interaction

when we do conduct clinical drug

interactions we often conduct them with

wellcharacterized drugs

so for instance if our drug is

eliminated by ca and we want to know

how inducers and inhibit inhibitors

might impact it

in

patients well evaluate a well

characterized strong inhibitor like

itraconazole or wellcharacterized

inducers such as rifampin and well do a

drug interaction to see the impact of

those two sort of token inhibitors and

inducers on our substrate

if our were considering our drug to be

a potential perpetrator were going to

evaluate the effect on a sensitive

wellcharacterized substrate for

instance midazolam for sip a or digoxin

for pglycoprotein

or maybe resuvastan for oatpb

depending on the results of these

initial studies using probe inhibitors

inducers or probe substrates well

consider if we need to do any more ddi

studies

are there any common cominister drugs

in this patient population we should

consider

if the effect of the strong inducer

inhibitor is profound perhaps we need to

look at a more moderate inhibitor

inducer and characterize the effect

there

should we consider drugs with mixed

enzyme and transporter effects

does our drug rely on a particular ph

for solubility in that case we may want

to do a drug interaction study with a

proton pump inhibitor

when we evaluate the risk in the

clinical setting for drugs that are

hopefully have been well characterized

we consider the therapeutic index of the

victim drug so for example atorvastatin

its a relatively wide therapeutic

window if we see a 0 percent increase

in atorvastatin exposure that may not be

clinically significant

however

tacrolimus or prograph which is used in

following organ transplant as an

immunosuppressant has a much more narrow

therapeutic window and a 0 increase in

exposure can be clinically profound so

wed probably consider dose reduction or

therapeutic drug monitoring in that case

in looking at a clinical profile of of

drugs we also have to consider if

theres other potential perpetrators

involved or is it just a single drug

drug interaction

we have to think about the time course

of the interaction as we discuss whats

the onset of the inhibition or induction

when should we think about altering if

we need to the dose of our substrate

drug

and again as we talked about we have to

consider both addition and the

withdrawal of the potential perpetrator

also think about is this ddi class

effect or are there other options for

example rusuvistan and simpastan have

very different susceptibility to ddis

theyre both taken up by oatp but

simvasten is also extensively

metabolized by sipea whereas restuva

satin is not extensively metabolized it

also has a wider therapeutic index

relative to simvastatin

so that might be a good alternative for

somebody on a sipa inhibitor

and then we have to consider other

confounders that may magnify such as

organ impairment or older age

so looking at the us product label

ive highlighted here in the the index

those sections where we find drug

interaction information

in section 00 dosage administration

youll often see a dosage recommendation

in the setting of drug interactions

particularly if theres a very

clinically relevant or commonly used

drug thats used in combination with the

product

drug interactions might be described in

warning precautions

theyre certainly described in the drug

interaction section

and then the clinical pharmacology

section section  tends to have the

details of any ddi studies that were

conducted by a company during

development

so this is an example of a product that

i worked on this is colitico or iva

cafter used for the treatment of cystic

fibrosis

so if we look look in section seven

we describe here that ivacafter is a

sensitive septuary substrate its very

extensively metabolized and relies only

on ca for elimination

so we did a study with ketos conazal a

strong septuary inhibitor

and found an eight and a half fold

increase in auc or exposure

based on this we recommend a dose

reduction from 0 milligrams twice a

day to 0 milligrams twice a week when

we combine the drug with other strong

inhibitors and weve listed some here as

examples

in addition we did a study with a

moderate inhibitor fluconazole and also

saw a profound increase of threefold

so we have a dosage recommendation in

place to reduce from 0 twice a day to

once daily with moderate inhibitors

and we also have language in here about

trying to avoid grapefruit or seville

oranges that might be sipa inhibitors

and theres also warning about the

effect of strong inducers on the base of

a basis of a study we conducted with

rifampin in which we saw a ninefold

decrease in exposure

in section  of the label weve

characterized the result of all the drug

interaction studies that weve conducted

here on a forest plot so you can

actually see the magnitude of effect of

drugs on

um

on kolitiko

we also studied the effect of cletuco on

an oral contraceptive so this in that

case the oral contraceptive is a

substrate you can see here there was no

effect on the exposure of the progestin

or

estrogen component of the oral

contraceptive

lastly i have a slide which outlines

some resources and tools and references

that might be useful

thank you for your time i hope you found

that interesting and instructive and if

you have any questions please follow up

with the course coordinator