we are honored to have dr ann zick

dr zyck is a boardcertified

pediatrician and a pediatric clinical

pharmacologist who currently serves as

deputy director of the office of

clinical research at the nih

and received a bachelor degree in

pharmacy from duquesne university

and a doctorate of pharmacy degree from

state university of new york at buffalo

she then completed postdoctoral

fellowship training at saint jude

childrens research hospital

after that she served as assistant

professor at the university of colorado

school of pharmacy and a clinical

pharmacist at national jewish hospital

in 99

ann entered medical school

at the university of pittsburgh in 99

completed residency in pediatrics at

childrens hospital in pittsburgh

she practiced primary care pediatrics

for two years and then continued her

training in pediatric clinical

pharmacology at stanford university

she subsequently joined the fdas office

of clinical pharmacology and

biopharmaceutics

in 00 she joined the national

institute of child health and human

development

we know you will enjoy dr zychecks

lecture

hello my name is dr ann zicek and i will

be speaking to you about practical

pharmacology

the topics i want to talk about are

pharmacy abbreviations and prescription

writing uh common sense pharmacokinetics

in two equations

pharmacogenomics

and ill be focusing on codeine and the

thiopurines and

formulations

okay id like to start with the pharmacy

abbreviations

uh you may have seen these before but

maybe not

um i think theyre very helpful um

because at some point

most people watching these films will be

writing prescriptions and uh

its been my experience there isnt a

lot of training in exactly what the

pharmacy abbreviations are and how to

write a prescription so were going to

find that out today

i want to point out a couple of things

in these next four slides which have the

pharmacy abbreviations first of all

the ones that i flagged in red have been

flagged by

the international

excuse me institute for safe uh

medication practices and the ones in red

seem to have common problems um in terms

of when people are writing for them

the handwriting is not clear and there

are errors made in either what is

dispensed or the directions

the ones that i have

made a score through are ones that i

prefer that you not use because they

create a lot of confusion

with the parents and the patients

and i yellowed in the dispenses written

because were going to get at the end of

the lecture uh to formulations which

really

have to be dispensed as written and not

moved into a generic equivalent

okay

again some more red areas if youre

writing for something in a microgram

quantity millie equivalent quantity in

milligrams or milliliters there are

frequently

handwriting errors that make

the prescription difficult to read

lets see and again

the ones that ive scored through again

lead to confusion uh

incorrect use of the medications and the

one that i want to point out here

are the ones for example where

four times a day or qid

is written but that can be interpreted

in many ways it could mean that you take

it four times a day meaning at in the

morning 0 in the morning noon and

pm

or it could be

most appropriately a reworded as every

six hours

okay some more abbreviations

okay the format of the prescription im

sure you have seen prescriptions from

your physician or who have written them

should include the name of the patient

the date of birth or the age of the

patient

for pediatrics the weight of the patient

is very helpful

in the rx the name of the drug the

strength of the drug the amount of the

drug to be dispensed if its a scheduled

prescription for example something for a

narcotic the amount of the drug to be

dispensed should be written in english

or whatever your native language is not

just with the number of tablets

the sig is the directions to the patient

or parent on how much drug to take and

how frequently

if there are liquids as well point out

in a minute you should add a note that

the pharmacist should dispense the

liquid with an oral syringe

the number of refills and then again if

there is an issue about dispensing as

written in terms of the formulation

being written exactly how you intended

it to be

i cant stress enough that

you should speak with the patient before

you write the prescription to explain

exactly what youre writing for and how

its to be taken to avoid confusion i

think its also nice on the

prescriptions to perhaps add a diagnosis

so the pharmacist understands what

youre writing for as well this avoids a

lot of confusion and a lot of errors on

the part of the patient as well as the

pharmacist

as a former pharmacist i will also tell

you that if you get a call from the

pharmacy

asking about the prescription please be

helpful to the pharmacist about what

youre writing for and why

okay so one of those abbreviations or

two of them in that list was teaspoonful

and tablespoonful and i would urge you

not to use these directions in the

prescription and the reason i point this

out is uh because tablespoons and

technically a tablespoon is ml

and a teaspoonful is ml

but it is highly unlikely that the

teaspoon fulls or the tablespoon fulls

that the patient is taking it home will

in any way resemble those volumes so

these are pictures of the spoons in my

kitchen

so i pointed out in blue the tablespoons

which i will tell you neither of them

contain mls of water and the

teaspoons uh you can see there are all

kinds of flavors of teaspoons in the

kitchen

which technically are supposed to

contain mls typically do not in fact

contain ml

so i would urge you again to write for

metric units in liquids if you want

mls write mls not a teaspoonful and so

on

okay there are ways of doing this uh

theres an oral dosing spoon that you

can ask the pharmacist to dispense to

the patient uh which is calibrated in uh

ounces

as well as mls i think the oral syringe

is easier to go with um the patient is

instructed to just drop

uh the volume of liquid out of the

bottle that was dispensed and that is

leads to a

huge amount of uh of accuracy so again

if youre dispensing a liquid or writing

for a liquid

please write also on the script for an

oral dosing spoon or a syringe for

dosing accuracy

okay so this is a true story um

and this has to do with the use of the

term bid so we saw in the list of

pharmacy abbreviations that bid means

this and die twice a day okay so bd is

an year old male started on

carbamazepine 00 milligrams po per os

by mouth bid twice a day four days ago

in the early afternoon his son visits

and find

finds his father confused with

difficulty speaking what happened

okay

so on your differential diagnosis you

could think about you know did the

father have a stroke is there something

neurologic going on clearly there is

something neurologic going on

but after the sun talked to his father

for a while the upshot of this was that

his father had in fact taken the

carbamazepine 00 milligrams twice a day

but was taking it when he woke up at

oclock in the morning and taking it

again at oclock or excuse me at

noon

so when the sun came to visit him at one

or two oclock in the afternoon hed

already received his entire daily dose

of carbamazepine within four hours um so

again this just reiterates the point

that when you write for bid it is

better to write for every hours to

avoid this kind of

problem

okay

so here were going to write for a

prescription so here is the case

jd is a threeyearold 0pound girl

with a large red swollen tender area on

her arm

so she seems to have a cellulitis

she has no fever and appears well

otherwise a blood culture is drawn the

likely organisms causing the cellulitis

or staff and strep

the staff in your city has become

resistant to methicillin

oral antibiotic options include

clindamycin and trimethoprim

sulfamethoxazole

you decide to write for clindamycin

okay so number one were going to write

the prescription and number two what is

your plan for determining if the

infection is responding to the

antibiotic and i think this is what

makes pharmacology so interesting

because youve made a diagnosis youre

going to write for a medication and then

theres going to be interaction between

you

and the patient

or the parents of the patient to

determine whether the drug is working or

not working

okay so the format of the prescription

okay so with the name of the patient the

date of birth or the age of the patient

and in the case of a child the weight of

the patient and the reason this is

important is because you would really

like the pharmacist to double check what

you were writing for errors get made

theyre not intentional but its

important important to give the

pharmacist as much information as

possible to avoid a dosing error

okay and then the next part of the

prescription is the rx

so this this is what youre writing for

the name of the drug the strength of the

drug the amount of the drug to be

dispensed

and then the sig the signatura in other

words the directions to the patient or

parent on how to take the drug how much

and how frequently the number of refills

and then again if there is an issue

about

the formulation that you want the

patient to have you need to also include

the words dispense as written

okay so you decided to go with

clindamycin thats perfectly fine

um there are a couple of places to look

for the dosing

so number one the national institutes of

health national library of medicine

has a website for updated package

inserts its called dailymed

very helpful for you to know about okay

so you search under

in daily med for clindamycin granule and

it tells you that the label is for eight

to twenty five milligrams per kilogram

per day divided every six to every eight

hours

okay

now

the problem is that there are multiple

references for drug dosing the american

academy of pediatrics

red book

recommends 0 to 0 milligrams per kilo

per day divided every six to eight hours

okay so these recommendations from the

aap red book um which again may differ

from other references depending on where

youre looking

is updated on an annual basis so

for the purposes of this

discussion i will go with the

recommendations in the aap red book

and the duration of treatment is to

days for complicated skin and soft

tissue infections which is what this

little girl has

okay so your first problem is to figure

out

what

0 to 0 milligrams per kilogram per day

is so she weighs 0 pounds

there are pounds in a kilo so her

weight is kilos

kilos multiplied by

the dose of 0 milligrams per kilogram

per day equals milligrams per day

youre going to give it in three divided

doses i dont think anybody would ever

take anything four times a day

so thats milligrams per dose now

were obviously going to round this off

so

how is the drug supplied

its supplied as a 00 ml bottle

containing milligrams per ml which

again is the

sort of the ballpark of what a teaspoon

is

and milligrams divided by

milligrams per mls is about ml po

per os orally

q hours so every eight hours times

days

so your prescription is going to look

like this

so the name is her initials were jd

shes a threeyearold her weight is 0

pounds

clindamycin oral suspension

okay so this is the name of the drug

this is the concentration of the drug

milligrams per ml

and this is the amount youre going to

dispense now you can either calculate

the amount youre going to dispense and

you should also ask the pharmacist to

give a little bit extra because mills

will be lost here and there and its a

total of 00 ml so this is going to be a

lot this is seven bottles

you can also write for a day supply

and that is okay too if you dont want

to calculate out the number of mls

youre welcome to write day supply

uh the sig the directions to the patient

mls

po per os

qh so every eight hours

times days

um and

i sometimes find it helpful to explain

how it is you take something every eight

hours and typically am pm 0 pm

are good ballparks for what i think is

actually clinically reasonable to expect

somebody to do so when she first gets up

in the morning

sometime midafternoon

before bed

now in order to get the mls i would

not recommend a tablespoon full what you

want to do is to explain that the

pharmacist should dispense this with a

syringe with no refills now the other

alternative is to write for a sevenday

supply with one refill so your call but

anyway this is how the prescriptions

should look

now the thing you want to know also is

have you written for the right drug and

is she responding to it because you

dont want to send her home with a

prescription and

plan to see her at her four year well

visit okay so what you want to know is

is the size of the cellulitis getting

better so youre going to draw with a

with an ink pen around the cellulitis as

it is so that the parents and you can

see if its getting better or getting

worse

now shes a threeyearold so there are

a lot of soft signs for this girl also

so you want to know if shes sleeping is

she playing is she eating does she have

a fever is she complaining that she

needs either

acetaminophen ibuprofen some sort of

pain medication

so these are your signs or whether her

symptoms are improving

the other thing you want to ask about is

have if for example the cellulitis is

not getting better its still red its

still tender

is she taking the medication now when

you ask this question you need to ask it

in a nice way because if you ask it

in a

less nice way the parents are going to

say oh yes ive been taking it but

because clindamycin tends to taste awful

you should probably

you know ask you know is she bothered by

the taste is she able to take it

because if the cellulitis is not getting

better

and the parents admit that no in fact

shes not taking it she took the first

dose and now she refuses to take

anything else

then

youre going to need to either admit her

to the hospital on iv antibiotics or

switch her to back drum which has a

better taste than the clindamycin so

these are important questions to ask

the parents

okay id like to shift gears here to

practical pharmacokinetics

and this is im going to have present

two equations and this is going to be

all real common sense here

so its not high math its just looking

at some curves and making some

practical estimates of halflife and so

on okay

so first of all

these are the properties of a

concentration time curve for an oral

dose

we plot the time against the

concentration

so when the patient takes the drug the

concentrations in the blood are going up

and this is called the cmax the

concentration the maximal concentration

this is the t max so this is the time at

which

the concentration was the highest this

is the area under the concentration time

curve

so this gives you an idea of the time

course of drug concentrations

for an oral dose

for an iv dose the con this

concentration time curve looks a lot

different so this is the time at which

the infusion ended

this is the distribution phase this is

the elimination phase just to give you

an idea of what these concentration time

curves are going to look like

okay so this is equation number one

the steady state concentration is equal

to

the bioavailability factor times the

dose

divided by the clearance times the

dosage interval and what this is telling

you is that if the drug is well absorbed

and this bioavailability factor is

closer to one

then this will provide a higher steady

state concentration

if you increase the dose

then the steady state concentration will

increase this makes sense

if the clearance is increased in other

words the rate at which the patient is

eliminating the drug increases then the

concentration will drop

and if the dosage interval becomes

larger in other words the dose is spaced

out from every four hours to every eight

hours or eight hours to hours

then

the tau is a bigger number and the

steady state concentration will drop so

this is just real

common sense but its good to have that

in the back of your mind

okay clearance is the volume of

blood

cleared of drug per unit time

it can be mills per minute liters per

hour whatever and the reason that i

point this out is only to demonstrate

that there are sort of two flavors of

clearance theres first order clearance

zero order clearance first order

clearance theres a constant percent of

drug eliminated per unit time

and so the elimination rate constant

which were not going to spend a lot of

time on is the percent of drug

eliminated per time

most drugs fall into the first order

category

so if you double the dose for example

youll double the plasma concentrations

zero order elimination is a lot more

complicated theres a constant amount

of drug eliminated per unit time so what

this means is that the body is not good

at eliminating these drugs and theres a

lack of proportionality

between an increased dose or a decreased

dose and the plasma concentration

examples of this include ethanol

phenytoin

salicylate aspirin

and here theres no relevant halflife

because theres no

percentage of drug being eliminated per

unit time theres an amount per unit

time and so this creates a lot of

complications when youre trying to do

dose adjustments because again theres a

lack of proportionality

of increased dose and plasma

concentrations

okay so going back to these shapes of

the concentration time curves this is an

iv dose again we gave a big dose its

being distributed and then eliminated

and

this is for

oral dosing

so this is the cmax this is the tmax

when theres delayed oral absorption you

can see that the cmax this

concentration

may be the same

but the tmax is a lot later okay which

makes sense

now when you have

a concentration time curve that shows a

very small area under the curve this

could be due to two reasons

poor absorption

or rapid clearance

okay so this is question two

ab is a 0 year old female with epilepsy

which is not responded to several

antiepileptics

she started on phenytoin and again we

mentioned before that phenotoid is one

of those drugs eliminated by zeroorder

kinetics so she started 00 milligrams

twice a day

she comes to your office two weeks later

with nystagmus and ataxia

now you should recognize or you now

recognize that nystagmus and ataxia are

signs of

phenytoin toxicity

you draw a stat in other words emergent

to be run immediately phenytoin level

which comes back at 0 micrograms per

mil

and the usual therapeutic range is 0 to

0 micrograms per ml

so what is the first thing you should do

with her dosage regimen and when you see

anybody

with toxic concentrations of a drug

you hold the dose that is job number one

hold the dose okay

and then the second question which is

sort of a trick question is what is the

new maintenance dose which will provide

a steadystate phenotoid concentration

of micrograms per mil

so if phenytoin were one of the first

order uh drugs where there was a

percentage of uh drug cleared per time

youd say that if you wanted to go from

0 to youd half the dose so youd go

to 0 twice a day the issue here is

that because this is a zeroorder

elimination drug you dont really know

what the answer is um

my guesstimate would be to half the dose

and have her come back in a week and see

where she is but the problem is its

very difficult to judge this and theres

going to be a lot of trial and error

involved at getting her to a

concentration that controls her seizures

and

doesnt cause

adverse events

okay so this is equation number two its

the last one

and what this says is that the

concentration at a later time

is equal to the concentration at an

earlier time

using the function of the elimination

rate constant

and the time

and i have a graph to demonstrate this

but what this is telling you is that

theres a log linear decline

in drug concentrations that are related

to the slope of the decline this

elimination rate constant k

and the time

so this initial concentration

is most related to the dose you gave and

these later concentrations are related

to

the rate of decline of the

concentrations in other words the

elimination pathways in the body

and the time difference

okay so

if you plot

concentrations against time

on a regular cartesian piece of graph

paper

you get a curve

but if you plot them on semilog paper

so here we have

the regular

time differences here two hours and then

this is a log scale

we see that the slope of the decline is

a straight line and this is very helpful

because you can calculate the slope of

the line which was the elimination rate

constant which were not going to get

into and also you can

draw a line here to figure out when the

concentrations will be as low as you

want them to be and this is the case

were going to talk about next

okay

so this is how youre going to figure

out what the drug halflife is

so at hour two the concentration is 0

at hour four its ten

at hour six its five and at hour eight

its two and a half so

what is the halflife

okay and the halflife is the time it

takes for the concentration to drop by

half

so between 0 and 0

the time was two hours so the halflife

looks like its two hours okay again

here between ten and five took two hours

to drive from ten to drop from ten to

five so thats another two hours and

another two hours to get from five to

two and a half okay

and again this is the slope of the

decline of the concentration so again

the halflife is not a mystery

its just the time it took for the

concentration to drop by half so nothing

complicated here

okay one important

uh

piece of information also is how long

does it take to get to achieve steady

state concentrations and the answer

is five halflives so you can see after

one halflife the concentration has

gotten up to

dose third dose

fourth dose and so on and so by the time

you get to the fifth dose you can see

that you have arrived at steady state so

the time to achieve achieve steady state

is five halflives

okay so

heres the case question number three

mg is an year old 0 pound female

admitted three days ago with eurosepsis

okay so this is an elderly woman

a thin elderly woman

and she has a urinary tract infection

which ended up

producing positive blood cultures in her

blood

her labs include a white blood count of

000 which is elevated 0 bands so she

has a new infection

the bun and creatinine which are

estimates of her renal function are 0

and

and what you can get from that first of

all a bun should be somewhere probably

less than 0 so hers is elevated so

shes probably dehydrated

and this b under creatinine ratio

is about 0 also elevated it should be

less than 0 and this creatine of

which is an indicator you know for

example if you were a bodybuilder

might be perfectly fine because this is

related in part to muscle mass but you

have an year old woman who weighs 0

pounds probably

very thin

and so this

yeah slightly elevated in a 0 year old

male of might be fine but what this

is telling you she probably has kidney

function dysfunction

and the urine gram stain when she came

in showed gramnegative rods so she

probably has an e coli infection

she started on genomics in 0 milligrams

every eight hours the pecan trough

concentrations are drawn on day two

the half hour peak is 0 micrograms per

ml

target being somewhere between four and

eight and the trough is three

okay so what is your gestalt about what

you need to do here okay so the first

thing i think thats easier to

understand is to make a plot of these

numbers

so here is her peak the half hour peak

of 0

and the eight hour trough

of three

okay so lets look at these numbers

so it took seven and a half hours to get

from ten to three

so just as sort of a ballpark estimate

so this dropped from ten to five and

five to three in seven and a half hours

so her you know if youre going to

ballpark it the halflifes probably

around four hours

okay

and what you want to do is to figure out

how long you should wait to get to the

trough of less than two

and again this is just to reiterate the

drop from ten to three

was in seven and a half hours a ballpark

halflife is probably around four hours

and if the trough is three

at eight hours you probably need to wait

another four hours

to drop down

to one and a half

okay

so getting back to the hold the next

dose issue is that if you have

concentrations that are too high

you need to hold the dose

and then you need to restart

at an increased dosage interval

so that the concentration will drop

to somewhere in the ballpark of one and

a half

okay so the answer sort of is a

combination of bnc where you need to

increase the dosage interval yes that is

true but the first thing you need to do

is to hold the next dose

write the prescription again and have

her receive 0 milligrams every hours

and then redraw a peak in a trough in a

couple of days to make sure thats okay

okay the next thing i wanted to talk

about was the time course of drug effect

because

although its true that we want to make

sure that the concentrations are correct

we want to make sure that the drug is

working

okay so this is the emax model

of

drug effect so this is the log of the

dose

against the percent of maximum response

and in the best case scenario we would

like the efficacy

curve to be well separated from the

toxicity curve

okay which is the in the case

except for possibly chemotherapy this is

generally the case that it takes more

drug to produce toxicity

than the effective dose

okay so heres

one way of looking at this so

lets say i have a headache and i take

ibuprofen and this is the auc

of the oral dose of ibuprofen that ive

taken

and then

just after the peak concentration you

can see that my headache pain which was

not so good is now declining

really nicely over time

okay the other way to look at this

is to look at the log ibuprofen

concentration against the percent of

maximum reduction of headache pain

okay so as the concentrations increase

theres a bit of a lag and then i start

seeing that my headache pain

is getting a lot better and so my pain

relief which is pretty much now at 00

percent

is correlated to the ibuprofen

concentrations so its just a way of

looking at things so you could look at

this also as

i had a starbucks coffee this morning

and i ordered a decaf but they gave me

calf and then after about an hour after

the coffee i see that my heart rate is

increasing

so thatd be another way to look at it

and you can use this for anything um you

know having drinks alcohol

on an empty stomach there may be uh

less of the perception of being

intoxicated if its on an empty stomach

you may feel more intoxicated so you can

use this sort of uh

dose response for

a lot of practical situations

okay

two more topics uh one is

pharmacogenomics

okay

so we saw previously that there is

as youd expect a lot of

interindividual difference between

these concentrations

and the effect so the purpose of

pharmacogenomics was to try to develop a

genetic explanation of individual

variability in drug pharmacokinetics or

in drug response and i wanted to present

two

examples where this has been hugely

helpful the first was

one is

genetic variations in cytochrome p d

and codeine metabolism

including patients who were either ultra

rapid metabolizers or poor metabolizers

and a second example of thiopurine

methyltransferase activity

which has really become problematic in

children with leukemia and patients

receiving bioperines for inflammatory

bowel disease

okay

so this first example is a paper talking

about uh cytochrome p0 d genotype

and codeine therapy

so there are two

situations here now again none of these

are common um if they were common people

would have been working with

pharmacogenomics years before they did

um but in the case of uh codeine

codeine by itself is not active but its

metabolized like all the opioids are to

morphine so there are two situations

where patients are

poor metabolizers and therefore

uh

do not metabolize codeine to morphine

and therefore have no pain relief from

codeine

the other side of the spectrum is

patients who are ultra rapid

metabolizers

of codeine and instead of producing

lets say

or 0 percent of the codeine to

morphine

they produce eighty percent of the

codeine to morphine

okay and so therefore they have much

more respiratory depression

uh than uh people who are normal

wild type metabolizers

and so there are two outcomes here so

choice number one

is if you were an ultra rapid

metabolizer and you may have found out

found out the hard way that you were

because you had respiratory depression

or were very sedated from the codeine

dose you got and in this case the

recommendations are to avoid codeine

to avoid potential toxicity

but the other side of this is the poor

metabolizers

should avoid codeine because its simply

not going to work

so this is the example of codeine

now one other problem with this is that

women who are breastfeeding have been

treated with codeine as well for

uh postpartum pain for example

what they found was that if these women

were breastfeeding

um that there was a correlation between

the amount of sedation that the

breastfeeding mother was getting from

the codeine

as well as respiratory depression of her

neonate who was also getting the

morphine through the breast milk so

these are

other

issues that are typically not recognized

but are definitely problems in

people who are ultrarapid metabolizers

that its not just the pain the effects

on them but its also uh the effects on

a breastfeeding neonate

okay the second example i wanted to talk

about is uh genetic polymorphisms of

thiopurine methyltransferase

so thiopurine methyltransferase is an

enzyme which metabolizes six

mercaptopurine

and azathioprine to inactive metabolites

now the problem is that if you do not

have an active thiopurine

methyltransferase enzyme you will have

very high concentrations of six

mercaptopurine

causing

prolonged marrow applausia icu

admissions and on occasion uh fatalities

okay so here is the pathway of the

metabolism of isothioprine to six

mercaptopurine

and six mercaptopurine to inactive

metabolites again which is mediated by a

thiopurine

methyltransferase

and this is a nice review article uh by

william evans and therapeutic drug

monitoring pointing out the issue

that

given patients who are

deficient in

tpmt

wild type and so on given the same dose

of six mercaptopurine

wind up with very high toxicity levels

because of these very high

concentrations of six mercaptopurine

which cannot be metabolized

on the other hand if you

alter the dose based on the tpmt

activity you can reduce the toxicity

and then again you have better better

clinical outcomes in terms of toxicity

okay the last topic i wanted to talk

about had to do with formulations

um

the first thing i wanted to point out is

that many people have problems

swallowing solid oral dosage forms and

this is not just a pediatric problem

this is an adult problem

uh about it looks like from this curve

about a third of the uh population i

believe this was uh

happened in germany but the these same

results are in the us as well that a lot

of people have problems swallowing

tablets and its important that when

youre writing the prescription you talk

to the patient about whether he or she

has difficulty swallowing tablets

i have problems swallowing tablets its

very common so nobody should feel bad

about this but you need to know about

this before you write for something

just to let them know that there may be

other dosage forms that might be better

for them

okay i wanted to point out just for your

information the difference between a

solution a suspension so that were all

clear there uh salt water

uh water that has sugar in it thats

completely dissolved is a solution

suspensions on the other hand such as

this amoxicillin suspension is the

amoxicillin powder which is not

particularly soluble in water water is

added to the powder its shaken up and

so its important that uh when the

patient receives a prescription for a

suspension that he or she knows to

shake the bottle

okay

another question that frequently comes

up about

tablets is that can i cut a tablet in

half to get half the dose

and the answer typically is no

so this

middle figure

was a paper showing

the amount of metoprolol in various

tablets and what you can see is that

its not necessarily evenly dispersed so

if you were taking metoprolol for blood

pressure reduction and you decide to

take half of it and the tablet wasnt

scored

you may or may not wind up with half a

dose

this has been my experience when ive

cut tablets is that you wind up with

shards of tablet and theres probably

active drug over here so you may or may

not be getting

an accurate dose and maybe it doesnt

matter if the dose accuracy is not that

critical but if its critical you have a

problem

this is called a score so this is the

cut in the middle of the tablet so if

the tablet comes scored like this and

its easy to break it apart either with

a knife or with your fingers then half

the dose

is found in half the tablet but if the

tablet is not scored youre not going to

be getting half of the half of the drug

product so i just wanted to point that

out

because

tablet cutting is used fairly frequently

okay

the next slides are going to be about

modified release products so theres

sort of two general

flavors of release

in drug products theres immediate

release

which is standard release or faster

release such as orally disintegrating

dosage forms

and then theres modified release

theres extended release delayed release

these

terms are complicated

and they seem to vary from product to

product but just to let you know they

are immediate release products and

modified release

products okay um i guess the poster

child for problems with these

formulations came with bupropion

bupopion um has been around since i

dont know the 0s the 0s or something

um and the

innovator product was wellbutrin

in the late 990s or early 000s

there was a generic product that had

been approved by the fda

and there started to be

reports

of patients whose depression was not

being well managed

by this generic product and even though

the area under the curve were the same

for these two products and the cmax was

within

the acceptable range for the fda

clearly there was a clinical difference

here

and in fact it was a really nice

commentary by janet woodcock mansor khan

from in the new england journal of

medicine in 0

talking about how after the fda decided

to do its own investigation

to look at these differences that they

came to realize that in the case of this

drug which was used for depression these

differences even though they were within

the

acceptable range for fda were not

clinically acceptable and they asked

this generic company to remove this

generic from the market

so these differences if this were

amoxicillin it might not matter but for

some of these drugs that act on the

central nervous system these differences

are very critical

um

and and again have led to the uh the

removal of this generic product

okay so um im taping this the first

week of october of 0 and this past

sunday in the

uh new york times

was a very timely article about a person

who had been reading had a bipolar

disorder

and had been treated with

valproac acid

so

originally he had been treated with

the extended release product but was

switched to the delayed release product

the tablets looked different talked to

the pharmacist the pharmacist assured

him that the chemical product was the

same

but this patient had a really difficult

time and did not respond well to this

change in dosage form

so i just wanted to point out that even

though

it may seem that

yes the parent compound the valproic

acid in this compound was the same the

fact of the matter is that this patient

was very sensitive to these release

characteristics and this delayed release

compound and the extended release

compound were not the same for him and

he did very poorly until he was changed

back to the product he had been started

on in the first place

and this is a paper looking at the

evaluation of switching patients with

bipolar disorder from delayed release to

extended release valproic acid and the

upshot here is that

you can see that the bioavailability of

the extended release product is

significantly lower

than the delayed release product and the

recommendation actually was that if you

were switching

from one product to another

that the extended release product should

actually be bumped up and given extra

uh an extra dose of 00 milligrams of

drug product so again the extended

release the delayed release have

different release characteristics and

different bioavailability so just to be

cautious that when you write a

prescription for these again you use

those terms dispense as written so that

the patient is getting the exact same

drug product

not one with a different release

characteristic which may affect

behavior

okay these next uh three or four slides

talk about methylphenidate

so um this is a series this is a paper a

nice review paper

looking at uh

different release characteristics of

extended release products against

immediate release products

so the first thing i wanted to point out

to you which is funny is uh so theyre

comparing the immediate release

five milligrams every four hours but see

we have here five milligrams tid and so

this gets back to the tid in which case

theyre giving

three doses four hours apart okay which

is not every eight hours

and theyre comparing this against

concerta so what youre seeing with the

methylphenidate is you give a dose the

concentration goes up drops off you give

another dose concentration goes up drops

off give another dose

okay against the concerta which again is

a more uh

immediate or excuse excuse me

modified release product

where the concentrations are going up

go up again

and then drop off

this is a comparison of immediate

release

methylphenidate four hours apart so

these are the circles here so we give a

dose concentration goes up drops off

goes up again

drops off okay

and this is compared to

um

other modified release products

and there there are many of these um

they typically have a portion which is

an immediate release

and then

an extended release product is released

so this is with 0 milligrams

excuse me this is the 0 milligram dose

and then with twice as much with the 0

milligram dose okay and you can see

again which is very nice is that these

concentrations are sustained over time

and this is the last one so this is a

comparison again of the ritalin

immediate dose okay so weve got a dose

here concentrations go down another dose

is given here of the immediate release

and this is comparison in comparison to

the ritalin

long acting where you have

again the bump from the

portion of it that is immediate release

concentrations go down

and then they go back up again and then

drop off okay

so the importance of this is that if

youre giving a child

ritalin for attention deficit disorder

what you really want is not to give the

drug during the school day which is

disruptive and embarrassing

uh but you also want something thats

going to last throughout the time of the

day thats critical for the child

okay

so just to skip over the uh

the case for a second here is this eight

this is the time of day and this is the

behavior and so because the ritalin is

trying to control

the ability of the child to function at

school what you want is concentrations

that are going to be functional during

the school day so between lets say am

and pm

but then youd also like the child to be

able to finish his homework so that

brings you to pm but then you would

really like the concentration to drop

off so he can actually get some sleep

and the parents can get some sleep

so heres a story

abe is a sevenyearold boy who comes to

your office with his parents hes been

disruptive at school fighting with other

children in his class he had been

diagnosed with adhd a year ago and had

been doing relatively well on

methylphenidate during last school year

he was on a drug holiday this past

summer

and the reason i point this out is

because methylphenidate also reduces

appetite so a lot of these children end

up losing weight or not gaining weight

and not growing if theyre constantly on

methylphenidate so during the summertime

when it matters less that he can attend

to school

typically theres a drug holiday or the

drug is stopped

and were told that his growth which had

fallen off during the past school year

is now back at the 0th percentile so

thats good so he gained weight during

the summer time hes back on track

growthwise

the school year has now started and

given his behavior he will now need to

be restarted on methylphenidate

okay so question number one is would you

choose an immediate release or a

modified release product and i think

that we would all agree that probably

the modified release product is the way

to go because you dont want these peaks

and troughs in the concentrations which

will also be mirrored by changes in his

behavior and his attention span and

and

problems in the class

so i think modif we would all agree that

some sort of modified release product is

the way to go number two what

formulation and release characteristics

are you looking for okay so in terms of

formulation i guess my question there is

can he swallow a capsule

or would you prefer a chewable tablet

they also developed a liquid suspension

with such a sustain release suspension

liquid really interesting technology

and what release characteristics are you

looking for so hes seven he may or may

not be able to swallow a capsule but

its critical that you have a

conversation with his parents about the

best kind of dosage form for him

and i think we would all agree that the

release characteristics are probably

most critical for him during the eight

oclock in the morning to

lets say you know four or five in the

afternoon so you would like something

that would hold the methylphenidate

concentrations fairly stable during

those times of day but then again you

also want them to drop off in the

evening time because many of these

children who have sustained

methylphenidate concentrations in the

evening cannot sleep and that is not

good either so you want to make sure

that you have these release

characteristics that will be maximal

during the time that he can function at

school doing his homework

and then hes able to calm down and go

to sleep at night

number three how will you determine if

you chose the correct product and the

rect for real uh correct formulation and

then this goes back to number two

so if hes able to swallow the tablet

and he likes the dosage form and doesnt

mind taking it then you pick the correct

formulation

and in terms of the product what youre

going to be asking the teacher

and asking the parents is how his

behavior is

so i made this little chart

so

what the teacher

can do because the teachers are

obviously very involved in making sure

that hes receiving the right treatment

is to have the teacher make notes about

where

there may be problems in the day where

his behavior is changing and then

perhaps you can go back to

a psychiatrist or a colleague who would

have a lot of expertise in the area of

these dosage forms to figure out what

might be a different dosage form so that

hes able to function during the day and

get to sleep at nighttime

what side effects are you looking for

okay

so problem number one is an increase in

heart rate problem number two is an

increase in blood pressure and number

three is falling off the growth curve i

think those are the most common side

effects

some children may have hallucinations

may develop ticks so these are all

questions you want to ask the patients

about and when you examine the boy

see if any of these have occurred

okay so when you write the prescription

ritalin is a schedule controlled

substance in the united states

so youre going to write again the name

of the patient his date of birth or age

his weight

and the drug name

the strength

and when you write for the amount youre

required to spell it out so not just the

numbers but spell out in english or your

native language how many tablets or what

volume you are dispensing

the sig the directions for how much and

how often to take the medication

and again its important to make sure

that the parents are clear on how

theyre going to administer this drug so

theres no confusion

a schedule compound

does not have a refill so there will

never be refills on this

and then if you are concerned about the

specific formulation you wrote for in

terms of the release characteristics

write dispense as written on the bottom

of the prescription

okay and again daw that is exactly what

this is for dispensed as written do not

substitute other drug products

okay so in summary

youll need to take care when writing

prescriptions that you are clear with

the patient and the pharmacist regarding

what you are prescribing

and the directions for use

pharmacokinetics does not have to be

complicated and that pharmacogenomics is

an attempt to determine who will respond

to medications and who may need to have

his or her dose adjusted to prevent

overdosing and underdosing

thank you very much for your attention

i hope you found this information

valuable if you have any questions

please do not hesitate to contact the

program coordinator for this course

thank you