our next speaker today is dr daryl

pharmacological mechanismbased safety

program

of the office of clinical pharmacology

at the fda

he brings more than years of

experience in medicine pharmacology

including positions in academia practice

and research

prior to joining the fda he served as

chief scientific officer of the usp

daryl received his md and his phd from

the university of kansas in 9

he completed his residency in internal

medicine at the university of miami in

his postdoctoral training in clinical

pharmacology at mass general

daryls research interest includes the

effects on obesity

on peripheral drug distribution the

pharmacokinetics and pharmacodynamic

relationship of cardiovascular drugs and

aging

please enjoy this lecture

well good evening im darryl abernathy i

currently work over at the food and drug

administration my background is an

internist geriatric medicine and

clinical pharmacology

uh we spent much of a career in

academics

focusing on on geriatric cardiovascular

pharmacology so youll see some of that

tonight

and then well talk a little more

generally about effects of medications

in the older patient

some might consider the the older

patient and ill define that very

loosely as yet another special

population

uh if if you talk in terms of drug

development the special populations of

course are are patients with renal

dysfunction patients with liver

dysfunction

uh pediatric patients and and uh thats

about it

um

that is the older patient is not defined

as a special population

for those purposes and i happen to agree

with that because uh really the the

definition of what is geriatric

is quite unclear physiologic aging and

chronology chronological aging

certainly dont necessarily go in

parallel

and i usually say with a smile that

geriatric is really a few years older

than you are

so why dont we go ahead and

work through

some thinking about

the interface of drugs and older people

who have multiple illnesses

who have illnesses that have medications

uh which are clearly shown to be

effective for those illnesses

i i would say uh if if you want to

interrupt as we go along and with

questions thats just fine

so what well try to do is to

to point out these bullets

when we talk when you hear this term

polypharmacy used its oftentimes used

in conjunction with older patients

and the definition is fairly clearly

five

medications at one time

theres a newer term called

hyperpolypharmacy

and thats defined as more than 0 0 or

more medications than an older person at

one time

as well see

this is not such an uncommon sort of

occurrence

and quite honestly

thats totally understandable

considering the multiple disease

processes that older patients often have

secondly well talk about the changes in

cardiovascular function

that interface with drug responses and

show some examples of how that plays

itself out in terms of looking at

clinical outcomes

thirdly well describe the changes in

drug disposition in older people

and provide some examples

i would say parenthetically that either

the literature on pharmacokinetics and

aging is very large

uh the literature in drug effects and

aging is much much smaller

and then finally well talk about a tool

that weve developed over the past

decade to try to understand uh what we

believe are important effects on

functional status in older patients

with respect to

medication exposure

this is uh

simply one example of the multiple

illnesses that patients

in older age groups have

theres a burgeoning science of

multimorbidity and trying to understand

the role of

multimorbidity

in its interface with aging itself

you can see here that in this particular

study and this is just one of many that

maybe half of patients over the age of

have a diagnosis of arthritis

probably more than 0 hypertension go on

down the list and of course theres a

lot of overlap i think its probably

yeah theres a lot of overlap in these

illnesses so that any one patient may

well have three or four uh medically

important diagnoses all of which may

benefit from drug therapy

and so to get to the issue of

how much exposure to medications do

older patients have

this is one study of many this is taken

from a panel of

los angeles area nursing homes

so these would be nursing home residents

and you can see across a dozen nursing

homes a mean of around six or so

medications in each patient

now one can look at that and say gee

that looks like a bad thing

but

that needs to be put in the context that

these are patients who have multiple

diagnoses

and many of these medication exposures

may be really quite indicated and quite

appropriate

however this has to be linked to what

happens when multiple medications get

put into a patient

these are data from quite a while ago

but this has been replicated each decade

up until the present and so i show this

earlier data simply to say this is not

new information

its been replicated multiple times

that

the

the

incidence of adverse drug effect thats

ade

uh increases as a function of the number

of medications an individual is

concurrently taking

and

that we generally teach that the break

in that line is five medications

concurrently or more

and so thats uh how the definition of

polypharmacy came about

and that that has been confirmed and

really validated using roc curves

looking at the the characteristics of

patient function uh and and uh the

number of concurrent medications but as

you can see when the medication number

gets higher

that that its not a linear relationship

of the likelihood of an adverse drug

effect

so lets talk for a few minutes about

one particular uh important drug

set of drug targets that would be the

cardiovascular system

uh and so lets look at a few examples

of how age changes or it may impact on

the

pharmacodynamics of cardiovascular

medications

first whats the

landscape

these are data taken from the baltimore

longitudinal study on aging this is a

national institute on aging funded

project thats been going on for about

0 years now

simply

looking at individuals following them

through life and now following a number

of their offspring through life

and doing

repeated measurements every two years

on these individuals they come into the

center at the nia

and have a wide variety of

behavioral functional uh in this case

cardiovascular measurements made so this

is the goal of this study is to look at

quote normative aging

and as these patients develop illnesses

they continue in the study

but that thats really part of normative

aging the interface of

disease onset

and age so what are the cardiovascular

features

that relate to the older individual

first if we look at total intervascular

volume and somewhat decreased

peripheral vascular resistance is

increased

theres a tendency to decrease cardiac

output tendency is a very soft term the

reason for making it soft is that at

rest cardiac output in older patients

even up to fairly extreme of age

is not so different than younger

individuals however exercise cardiac

output or the ability to respond to

needing to have an increase in cardiac

output is impaired in older patients

importantly barrel reflexes are are

altered with decreased baroreceptor

sensitivity in older patients and well

see the consequences of that in a few

minutes

theres increased blood pressure

variability so beat to beat variability

and variability over the hour period

if we think in terms of the contracted

intravascular volume

that flies in the face of these patients

tend to be what we would call low renin

patients and so there too one can see a

physiologic change occurring

thats dissociating plasma renin

activity

in intravascular volume

and then finally well

look at some data that evaluates

vascular endothelial function

in older individuals

this is a

i believe the first demonstration that

beta adrenergic receptor

activation is impaired as a function of

age

this too has been replicated

many many many times

and interestingly even with many grants

and many studies the full mechanism of

this is not worked out but its there

and its clearly so

this particular study shows whats

called isoproterenol resistance so

giving isoproterenol a predominantly

beta adrenergic agonist increases the

heart rate

so the question here is how much

isoproterenol is required to increase

the heart rate beats per minute as a

function of increasing age

and you can see that the dosage of

isoproterenol goes up rather

dramatically

as a function of increasing age

as i say the conclusion from this is

that beta adrenergic function

is impaired with increased stage

and i wont show the data but but

workers at stanford some years ago

showed that beta adrenergic mediated

vaso peripheral vasodilation is also

blunted as a function of increasing age

now what about beta adrenergic function

and

we have to think about alpha adrenergic

function here as well

these are studies that we did some years

ago looking at the the responses to

label law in in this these are a

selected pair of younger and older women

and then looking at the change in heart

rate that would be the beta blocking

effect of libated law as a function of

drug concentration

you can see that in the younger

individual

at relatively low drug concentrations

rather than a dramatic decrease in heart

rate what one would expect from an

intravenous administration of a drug

like this and in the older individual

a much much greater exposure of labor

law required to achieve the same

reduction in heart rate

suggesting then that that the capacity

to suppress beta adrenergic function is

impaired uh as a function of increasing

age as well

now if we look at blood pressure

responses these are data from the same

study this is looking at systolic blood

pressure in younger and older

individuals

and we can see that

this is after an administration of an

oral dose of label law and the younger

individuals little change in systolic

blood pressure over time after this is a

single dose of oral or beta law

this would be typical if you think about

it of administering doses of an oral

betablocking drug

of any sort not much change in blood

pressure but if we look in the older

individual a rather

dramatic decrease in systolic blood

pressure over the first while after

exposure and then slowly returning to

to the baseline

so what is this suggesting

well its saying that we have that there

is blunted uh

capacity to respond to

an alphamediated vasodilating response

this is an alpha one blocker as well as

a beta blocker

and with that

incapacity to do that

and then the incapacity to have

with the peripheral vasodilation a

reflex tachycardia because of the

impaired beta adrenergic responsiveness

a really rather marked a decrease in

blood pressure as compared to younger

individuals

now lets move to an another uh target

uh that uh that is important with regard

to aging uh and and uh then uh look at

some data that uh relate to agerelated

changes

if we think about calcium flux from the

extracellular to the intracellular space

as demonstrated by this cartoon

calcium gets into the cell in a number

of ways but two very important ones are

through the the ltype calcium channel

and through the

receptoroperated calcium channel you

would say well what is this

the alpha receptor

is a great example

of of this particular chant

receptor that modulates the flux of

calcium

and so weve looked at

some data that indicate that there are

changes in this

potent this receptor operated calcium

channel lets look for a few minutes at

pharmacodynamic responses to drugs which

block the

ltype calcium channel

so first lets think about what the

structural changes are in older people

uh as we begin now to think about drugs

which act on uh on vascular function

these are data again accumulated from a

variety of sources

mostly autopsy but but then some biopsy

resources as well

what are the arterial changes related to

normal aging that would be not in

patients not with hypertension or other

marked atherosclerotic disease

for theres increased calcium and

collagen of course this is

accentuated in patients with

atherosclerosis or longstanding

hypertension

theres reduced arterial compliance in

other words impaired large large vessel

capacity to

dilate

with with cardiac function increased

pulse pressure we mentioned that in

other words a a

a greater difference between systolic

and diastolic blood pressure

we mentioned the barrel reflex

sensitivity and well talk a little bit

more about that

however

however if you want to put what barrel

reflex function is in a into a personal

context think about when you go from a

supine

posture to upright

and why your blood pressure

doesnt drop dramatically

and and your heart rate has a change

that allows you to maintain that blood

pressure an increase in heart rate in

older patients the capacity to have

those reflex functions is impaired

then in the small arteries and this is

this is most likely the

main reason for the increased peripheral

vascular existence in older patients

thickening of arterioles

and as we mentioned increased peripheral

vascular resistance

so what are the consequences of these

changes in thinking in a physiological

model

this is a a

idealized depiction but based on real

data

that michael orourke published in a

textbook some years ago

and it very nicely uh points up issues

that relate to younger and older

individuals

so this is a pulse wave that some of you

may be familiar with if one put a

catheter into

into an artery

particularly into a large artery one

would see something like this with each

heartbeat and

what does this represent well in the

younger individual thats what this is

meant to represent with a quote normal

blood pressure

theres a certain velocity of the pulse

wave going down the aorta after a

heartbeat

and then this will look familiar but

this would be the systolic part of the

heartbeat

and then with cardiac relaxation

diastole occurring

and then the incisiora

the

this lump here

represents an important component

in with cardiac function to permit

coronary artery filling this is

maintaining a pressure at the root of

the aorta where the coronary arteries

take off so we can see that this is

occurring during diastole when the heart

is relaxing allowing for an efficient

coronary artery filling in the older

individual with a stiff aorta a a

an aorta with decreased compliance a

broader a wider pulse pressure

resulting in a increased pulse wave

velocity so think of a an elastic tube

as compared to a rigid tube

and with the increased pulse wave

velocity this in shisha really

represents the reflection of the pulse

wave

from the bifurcation of the aorta back

to

the uh the root of the aorta and we can

see that this increased velocity results

then uh in the in the insister occurring

during systole

so that

when the heart is still in a contracted

state

is is a critical time for coronary

artery filling

and so this then results of course

in a decreased reserve

with regard to

to being able to maintain coronary

filling

so

based on that background of physiology

lets think about ltype calcium channel

blockers

and their their

effects in older individuals

this is a study again that we did some

time ago

looking at three age groups of normative

people

and so this is a pharmacokinetic curve

first of all this is giving a dose of

intravenous verapamil the same dose

in three different groups of individuals

and we can see in the younger individual

a

elimination rate that would be

consistent with many published studies

and that is fairly rapid and an older

individual some say slower and the older

the older yet individual some somewhat

slower yet

in this particular study i would say

that that the oldest individual in this

age group was 0 years old it was a

very charming

elderly gentleman

now we see that pharmacokinetic curve

which could be replicated well talk

about that in a little while across many

different kinds of drugs for apramil is

a cypa drug and this would be quite

typical for what one would expect in

terms of the disposition of the drug

what about its effects

first of all wrapper in addition to

being to causing peripheral vasodilation

also due to the ltype calcium channels

and atroventricular node of the heart

and the sinoatrial node of the heart has

effects there as well

that is that it blocks atroventricular

conduction

and then decreases heart rate slightly

not as much as a beta blocker but

decreases heart rate slightly due to the

sa node effects

now one might think and i have to say

when we were doing this study we

anticipated that the older individuals

would be more sensitive to the av nodal

blocking effect of a drug like verapar

mill

simply because of the fibrosis of the

conduction system thats well documented

with age

and here were the findings that we had

and that is that in the

here we go

in the

younger individual we saw

a concentration related prolongation of

the electrocardiographic pr interval

which is a surface measurement that

approximates av nodal conduction

and so we can see this delay and this

would be why the drug is useful for the

treatment of supraventricular

tachycardias

however instead of a heightened

responsiveness even with an increased

drug exposure if you remember from the

pharmacokinetic curve the older

individuals have less av nodal

conduction delay

and so theres a blunting of this

capacity

with regard to cardiac conduction as a

function of age

you might say then are these drugs less

effective for the treatment of

supraventricular tachycardias for

example as a function of increasing age

and to my my to my knowledge to the

state that study has never been done

now what about effects of this this

ltype calcium channel blocker its

peripheral vasodilating effects in the

same patient population or the same

subject population i should say

this is looking at the decrease in mean

blood pressure after a this would be the

first dose of rapper mill and younger

individuals some decrease in blood

pressure and older perhaps a greater

increase in in the much older perhaps a

somewhat greater increase yet with a

huge variability in all the groups

so youd say well does this say that the

older individuals have greater

peripheral vasodilation due to the

ltype calcium

channel blocking effect of the drug and

id pause that no thats not the case

here we can see the decrease in the

pardon me the change in heart rate uh at

the same time that these blood pressures

are measured so that the younger

individuals have a reflex tachycardia

protecting their blood pressure blunting

the decrease in blood pressure the older

individuals dont have any change in

heart rate

and thus without the increase in cardiac

output a greater decrease in blood

pressure and the much older individuals

actually have a decrease in heart rate

this is even after an acute intravenous

dose of wrapper milk

what we believe this this is showing is

uncovering the sinoatrial node

suppressing effects of verapamil in

these individuals

and we can see

that that with this

perhaps even decrease in heart rate

perhaps an even greater decrease

increase

in the drop in blood pressure

so the heart rate responses with the

ltype calcium channel

blocking exposures

decreased heart rate responses we

believe those are due to impaired reflex

sympathetic outflow and function

its possible and and they cant be

ruled out that there are parasympathetic

changes with age as well

those studies uh studies such as that uh

done in dogs with a by a colleague of

mine

from the past who works at uh san

francisco now suggested and in fact that

was true that that uh bagel withdrawal

it does change with age as well but

weve not been able to confirm that in

people

and then a hypothesis

that there may be differing sensitivity

to calcium channel blockade

at the sinus node in older individuals

now lets move uh

for a bit to the

to the peripheral vasculature and

particularly the vascular endothelium

and its interface with vascular smooth

muscle

we can see here then

paul van hoodas

view of what a vascular

endothelial cell looks like and how it

interacts with a vascular smooth muscle

cell

i would say at the outset this is a

highly simplified diagram that there are

many more

uh local interactions between these two

cell types that are shown here but were

going to focus on the nitric oxide

part of this interaction which appears

to be a very important one

so that

the the question is or the issue is

when when vascular endothelium are

stimulated by a variety of stimuli they

release nitric oxide

diffusing to the vascular smooth muscle

and then activating a cascade of events

via cyclic gmp mechanisms to result in

vascular smooth muscle relaxation thus

vasodilation and decrease in blood

pressure

so what happens is a function of

increasing age i want you to focus on

the dark blue bars

so the steady design here these are some

data that we generated again a while

back and this is looking then at one of

the the potent stimuli

for

endothelial mediated production of

nitric oxide and then resulting in

vascular smooth muscle relaxation

acetylcholine

now whats known uh and this was really

the first observation to get at

the role of endothelial relaxing factors

as it was very early called before it

was identified as nitric oxide

was that if if one administers

acetylcholine directly to vascular

smooth muscle it contracts

however the observation and this was by

bob fertscott

the observation in the early 90s was

that if one did that then to intact

vasculature once all relaxation and it

didnt make sense and so they worked and

they worked and then a group of three

people

ultimately got the nobel prize for

understanding the importance of

endothelial mediated function and

endothelial interactions with vascular

smooth muscle

so the study design here is looking at

younger and older individuals and their

responsiveness to acetylcholine

so whats the dose to cause a 0

maximal response of uh to acetylcholine

mediated vasodilation and younger as

compared to older individuals and the

point to be made here is a substantially

higher dose of acetylcholine is required

to result in maximal vasodilation in the

older individuals

now i would say that there are a number

of

other factors that that caused this same

sort of change and we attempted in this

study to control for

uh all of them uh and we hope that we

succeeded

uh but certainly cigarette smoking would

result in the same sort of finding

hyperlipidemia results in the same sort

of finding and patients with

longstanding hypertension have impaired

acetylcholinemediated

endothelial responses

now if we move this to another uh

important vascular set of vasculature

that would be the coronary system

we see similar sorts of findings

these are data that that were obtained

in individuals

who were referred for cardiac

catheterization and at the time of the

catheterization were found to have clean

coronaries

so first i would i would say that the

qualification would be these may well

not have been totally normal patients or

they wouldnt have had some sort of

atypical chest pain being referred for

cardiac catheterization

but secondly they did not have

atherosclerotic disease and so if we

look at

these individuals as a function of age

what this is showing is the percentage

increase in

coronary blood flow this would be the

maximal

increase in coronary blood flow to a

local

acetylcholine infusion into the coronary

artery and we can see in younger

individuals as much as a sixfold

increase in coronary blood flow with

this maximal vasodilating stimulus

however as the the uh with increasing

age this response appears to be uh

decreasing rather markedly actually and

so this these data are consistent with

what i showed you for the peripheral

vasculature

i didnt mention what the study design

was here but these studies are taken

from a peripheral arterial function

this is infusion of bastille choline

into the brachial artery and then

measuring forearm blood flow distal to

that acetylcholine infusion

now lets move from those form what i

would call pharmacodynamic changes of

aging uh to drug disposition in older

people

as i said theres a much larger

database for drug disposition probably

because drugs are easy to measure drug

responses are much harder to measure

first what happens to drugs i suspect

youve seen many variants of this slide

in this course already

but this is a very simple simple flied

point of view drug goes in its either

cleared by the kidney

or its chain its bio transformed by the

liver into metabolites which may be

active or inactive and then ultimately

cleared by some process and that is

shown here to be the kidney but it might

might also be via the gi tract with

biliary transport it might be

pulmonary with exhalation or so on but

the real the point is that the clearance

mechanism results

ultimately in the detoxification or the

removal of the drug from the system

so when we think about drug metabolism

and this would be the liver part of that

that

diagram

its generally split into these two

phase one drug biotransformations or

degradative biotransformations

in phase ii drug bio transformations or

synthetic or conjugative drug

biotransformations

well be talking primarily about the

phase one drug biotransformations

because these are the ones that change

as a function of increasing age uh the

phase two biotransformations dont

change much i suspect youve already

heard that with liver disease the same

is true uh and so that that appears to

be a consistent finding that uh these

these uh mechanisms of drug

biotransformation are more resistant to

disease

so what are some of the phase one drugs

that older people might get these are

just examples theres a huge long list

of them

for that

you could go to

this drug interaction table

at this website

i think thats been changed just in the

last month to the flockhart website this

is because the individual who developed

this

passed away last thanksgiving

in any case

looking at these examples you see some

fairly familiar drugs

the the

predominant drug of biotransformation

is

cyp

some people say

cypa but i i generally say that

there are other

isoenzymes of the a series that have

importance in some cases so to keep it

more general but then well see other

pathways of biotransformation as well

so lets look at a prototype cypa

drug in younger versus older individuals

this is from a study that we did a long

time ago

looking at triazolam or halcyon a

sedative hypnotic drug

and then looking at a typical

pharmacokinetic curve in a younger

versus

an older woman these were healthy

individuals

and of course these this pair was

selected because they represented

extremes not the mean but simply to

demonstrate that thinking about this

being a log plot

that in this case is a rather dramatic

difference in exposure to tries limb

after the same dose

now if we look at another sedative

hypnotic and a

conscious sedation drug midazolam trade

name versed

these again are data from a study that

we did some years ago

and this is a more typical cypa

change in older individuals

and here we can see if we look at young

younger men and younger women this was

defined as under the age of 0 older

men and older women defined as as over

the age of

that we can see that theres some

decrease in clearance of midazolam uh

in the these two

separate age groups

and the general teaching is probably

about a thirty percent decrease in cyp

mediated drug biotransformations if we

look across many different drug

substrates and many different studies

now what about drugs which undergo renal

excretion

these are drugs that are not metabolized

or excreted unchanged and so here are

some examples and some of these will

look familiar and some of them will look

quite dated

and so i suspect many or most of you

have seen this equation before but the

question is how do you

characterize renal function in

as a function of age or really as a

function of weight or what have you

there are many different

equations that have been developed and

variations of many different equations

this one is one thats widely used with

regard to drug development and drug

dosing uh

and

the the cockroft galt equation

many of you may be

more familiar with the mdrd equation

another equation thats been developed

that has some slight variation from this

equation but is frankly much more

complicated to to determine

both of these now are generally

generated on lab reports or the mdrd

report

equation result itself

generated in lab reports when the

relevant data are submitted with the

laboratory

in any case

what what

id like to have you take a look here

are what the elements of this

relationship are

so this would be an estimate of

creatinine clearance and so if we look

at this an important factor is age

a factor is weight and then serum

creatinine

and here the the standard approach is to

reduce the estimate of creatinine

clearance by in females as compared

to males why because serum circulating

serum creatinine is really a function of

lean body mass and lean body mass is

decreased in

in females that we look across in

population as compared to males

so the the changes in renal clearance uh

in renal function occur with age as you

can see

if we if we put this into a graph an x y

axis graph

decreases

across a population as a function of

increasing age and the clearance of

these renally cleared drugs decreases in

parallel with that

now its important to note

that

for example drugs which are not only

filtered at the kidney but secreted

actively like penicillins and others

that it appears that the active

secretory processes

of renal clearance go down pretty much

in parallel to

the the

nonactive

filtration sources so that these drugs

also decrease pretty much in parallel

with a decrease in in creatinine

clearance or measured or estimated

creatinine clearance

as a function of age

so if we did a summary of what are the

pharmacokinetic changes in older people

lets quickly run through them and ive

shown you data on some of these and not

on others for a reason

been a lot of studies done

looking at gastrointestinal absorption

changes with aging because its well

known that that

that

gastric acidity decreases with age

and its quite clear

looking across decades and many studies

that theres not a whole lot of change

in gi absorption of drugs

the central compartment volume of drugs

in other words this rapidly distributing

volume doesnt look like it changes very

much as a function of age

the peripheral compartment and those

this would be then the volume of

distribution uh that would be measured

uh and that you would see when thinking

in terms of uh the volume the

distribution of a drug

that moves really uh in relationship to

body composition and this is

irrespective of age so that drugs which

are relatively watersoluble uh will

have a decreased volume distribution

simply because the the uh proportion of

body fat and non nonfat mass changes

with age uh with with uh

lean body fat lean body mass decreasing

uh and fat mass increase in both males

and females here were not talking about

only obese individuals really across the

spectrum

and then

drugs which are highly fat soluble have

increased distribution uh in in

individuals with increased relatively

relative fat mass therefore in older

individuals as a group

much has been written about

protein binding of drugs because the

thought is that of course drugs the only

drug that is not bound to plasma

proteins is available for action

other than administering

single doses of drug

for example

the use of midazolam for onset of

anesthesia

or so on

this doesnt really make much difference

with regard to the disposition of drugs

and

although

albumin drug binding decreases with age

and alpha acid glycoprotein binding

may change with age thats frankly a

little unclear we published a paper

saying that that it goes up in aging

however its unclear whether thats

really inflammation or or the aging

process itself

but with chronic drug dosing which is

the usual circumstance its really the

the clearance of the drug is dictated by

the free concentration of the drug so

that these changes of in drug binding

and therefore changes in in circulating

total drug concentration uh really are

not relevant and its the clearance of

the free drug itself that is relevant uh

with regard to the drug

available so those changes in drug

clearance we talked about

would relate to then the free drug

now what about the biotransformation

reactions well we talked about cypa

reactions

decreasing in this range across a wide

range of substrates

here are other

important routes of phase one drug

biotransformation

this group have been studied rather

extensively and some of them change some

some of them not so much

youll see that that a couple or three

in here actually are polymorphic d c9

and c9 and i i think its important

to emphasize

the the polymorphic or the genetic

differences

are much much more important with regard

to drug clearance than any agerelated

change in any of these

enzyme activities

then as we mentioned phase ii drug

biotransformations are not much changed

in age

now lets talk for a few minutes about

the whole individual and

the kind of the real world circumstance

of that individual receiving uh either

one or many medications and what the

impact may be

so first this is simply looking at use

of medications the prevalence of

medication use

across different indications and this

would be then a surrogate really for the

incidence of of diagnoses

in individuals and so this is looking at

decades of age to and and

over

and we can see that taking any

hypertensive drugs 0 percent of

patients

hyper hypolipidemic drugs 0 or 0

percent and on down the list and this is

simply pointing out then that older

individuals will indeed be taking

multiple medications these are more

recent data and again

this can be replicated many times and

probably everybody in geriatrics has got

at least one publication

so

when we think about

the effects of of polypharmacy or

multiple medications an individual the

real question is whats important

well whats important really is the

patients functional status

and so

how can we

understand drug effects on the patients

overall functional status because its

quite clear

that that measures of functional status

are a much better marker of longevity

than specific physiologic measures

uh or other very individual measurements

so

as a nice example for patients with

congestive heart failure if we think

about the the determinants of mortality

their walking speed is more important

marker than their cardiac output

walking speed being then a very complex

composite functional measurement

now what drugs what drug groups and we

uh believe may have importance uh with

regard to changes in these functional

measurements

well there theres a fairly good

understanding that anticholinergic drugs

are

not the older persons friend

and an increasing understanding that

sedative drugs of one sort or another

are not the older persons friends and

so what we tried to do

was to develop a way of thinking about

this that could be then taken into the

population

so thats what we

mean by here to develop an

evidencebased model to assess

functional risk and benefit uh to

medication exposure in older patients

this is something called the drug burden

index there are a few other of these

measures

ill describe this one in some detail

partly because we developed but then

partly because weve we have validated

across multiple populations

and so the idea is

first of all

we believe based on literature and and

clinical experience that drugs with

anticholinergic effects

are drugs that we should think about

very carefully when i think

considering exposing older patients to

them

similarly drugs with sedative effects

and so then

rather than count medications how can we

put this in the context of drug exposure

and so what we did uh was to simply use

this relationship if you think about it

this is a variant of kind of an emax

concentration model or and

the idea is

what then is the dose that the patients

receiving

whats the minimum

recommended daily dose from the label of

the drug with the idea being that this

is probably not a maximal effect its

certainly probably not exactly an ec or

a dr a dose response at 0 percent uh

however its somewhere in between zero

and a hundred

and so putting

using this relationship

and then using an additive relationship

with drugs uh this is to

attempt to make some estimate of the

drug exposure and its relationship to

effect this is exposure based on drug

dose not not drug concentration because

those are the data that are really more

commonly available

and and

look across populations to understand

whether

information can be gleaned from this

kind of a parameter

so what are the functional measures that

that have been used and the data ill

show you first they were developed by

several investigators but really quite

predominantly by the national institute

on aging

and if you look at these functional

measurements and then think about them

for a bit they sort of make sense

the chair stance getting up and down

from a chair and the speed with which

you do it the time for a six meter walk

and then a time for a six meter walk

with a

narrow course

and then standing balance so these are

these are

complex uh functions that require the

the uh use of many different uh sensory

systems

and so

these have been turned then into

a composite measure

its called the health asian body

composition score why because a

longitudinal study again funded by nia

that looked at a large group of people

in memphis tennessee and pittsburgh

pennsylvania

and then related these functions over a

period of years to morbidity and

mortality in this population

and these were the things that fell out

changes in these functions were good

predictors of morbidity and mortality

this was validated then in another

population these pa these individuals i

would say are what we call high

functioning these are people in the

community who are seem to be getting

along reasonably well

at an earlier time there was a

very large multicenter study

with this name

its acronym is a pz of an unusual

acronym but one that i guess you can

remember but same idea except these are

lower functioning individuals patients

who are perhaps teetering on being able

to stay at home

and so it looked like that this works

across this particular

composite score works across a variety

of

different levels of of individual

function

what are the functional measures of

sedation

well that the digit symbol substitution

test taken out of the wechsler

intelligence scale is a very common one

and so it looks at a variety of things

psychomotor performance concentration

and so what are the findings this is

then looking

at the individuals in this health aging

and body composition study

this is about a thousand individuals

and looking then

at

using that drug burden index

and this then would be looking at drugs

which have anticholinergic effects these

are not only drugs that are administered

for their anticholinergic effects but

youll remember that a variety of other

drugs have anticholinergic effects as

offtarget effects for example

neuroleptics antidepressants and so

forth

so we looked at drugs which

do have anticholinergic effects and then

put them into the equation to develop

an anticholinergic burden and then

looked at that in relationship to the

health abc score

in these individuals in red

and the digit symbol substitution

test

in blue and we can see theres a fairly

clear relationship with increasing

anticholinergic burden and decreasing

health abc score and digit simple

substitution test

scoring

if we look at saturday burden

we again see

these are drugs then that have sedating

effects

however do not have anticholinergic

effects

if you think about it for a moment many

drugs which are anticholinergic are also

sedating in this particular study we

call them anticholinergic and then this

is separating out the others this would

include things like benzodiazepine and

other things which rather clearly dont

have anticholinergic effects but we see

perhaps a less dramatic association but

again the same general idea with

increasing exposure to sedative drugs

impairments in these functions

and so if youd say well

those lines look interesting but what do

they mean well look the development of

the particular

functional tests this health abc score

was rather comprehensive because uh the

interest of the investigators and this

study actually continues or evaluations

of the data due

the interest really had to do with with

disease associations with a whole

variety of psychosocial associations

with this score

and then we simply added the drug the

drug exposures on top of all of that but

with that other background

what what uh from the other studies have

been done

the changes we saw in in the health abc

score and the the

digit symbol substitution

test

would be approximately equivalent to the

patient having three additional physical

comorbidities things like hypertension

diabetes etc etc

or the same as patients with some

cognitive impairment depression or

anxiety so we believe that thats saying

a one point increase in drug burden

index probably is a meaningful thing to

the individual and we saw more than that

uh with increasing exposure to

anticholinergic and sedative drugs

now in addition to that we looked at

this that same population

thats a longitudinal study and so were

able to look at one three and five years

to look first at changes in drug burden

which werent much

and secondly what the cumulative

exposure was in other words simply doing

an area under the curve of the drug

burden index exposure over five years to

see

how that predicted then the functional

outcomes at year six and the the short

answer is it did quite well

so

youd say well thats interesting thats

in one study and memphis and pittsburgh

are not necessarily representative of

the world and i couldnt agree with you

more so it turns out that a collaborator

in this study who actually was doing a

fellowship with me at the time uh went

back to sydney australia and took a

faculty position

and

then

applied essentially the same methodology

to a

aging men project

in sydney australia looking at community

dwelling older men same finding

looking another

cohort in australia looking at

lowfunctioning individuals

and same finding and then looking

in

what the whats shown here is department

of fit uh veterans affairs uh

interestingly they would say these are

patients in repatriation hospitals i i

like that um but in any case again that

as these data have evolved

these findings were similar as well

now in the united states there is

another study this is headed up out of

johns hopkins

looking its called the womens health

and aging study

and so these are uh

individuals women in the city of

baltimore uh whove been characterized

as in the lower 0 percent of physical

function so these are people who are

barely hanging on being able to stay at

home

and so we did the same evaluation in

that study and again came up with the

same finding so we believe that that

with these what i guess id call

crosssectional

evaluations

that that this is a robust finding

and we also believe that this drug

burden index is a useful tool to think

in terms of drug exposure

thats being further evaluated now in

longitudinal studies uh one uh starting

in new zealand just now uh and another

one going on in australia and were

starting to work with the health uh the

world health organization

to see about incorporating this kind of

a a evaluation

because

in the world health organization

there are

first of all the essential medicines

list but then

optimal dosing uh

recommendations uh

across population so the countries with

less welldeveloped regulatory

organizatory authorities uh kind of

access to at least some information

so were working to see if if indeed

this might be useful to further inform

the dosage recommendations for that that

activity

so finally um

im sure that youve either read the

newspaper or youve read in journal

articles that old people are not

included in clinical trials we dont

know enough about how drugs work in old

people

why does the fda continue to allow drug

studies to occur which are looking

really only at healthy individuals and

then the drugs get put out in the

community

all i can say to the last comment is

that the guidelines

from both

the united states and the european union

this would be the european medicines

agency

are quite clear and that is that

patients over the age of with

multiple illnesses should be included in

studies patients with illnesses

consistent with what would be in the

community does that happen well probably

not as much as it should but theres a

continuing effort to try to

to try to improve

the exposure and the the understanding

of drug effects during the drug

development process

and this is simply a statement saying

yes the the patient should be uh

included in uh clinical trials

an important question of course is do

drug do older patients have the same

responses to

pick your class of medications but say

antihypertensives or hypolipidemics or

other medications to which theres a

high exposure

and the short answer is yes it looks

like that if you do stratified analyses

post hoc of data that the responses are

not so different

and so thats somewhat reassuring

however coupled with that uh uniformly

the adverse effect or the adverse event

profile is increased as a function of

increasing age

now this is saying should a trial be

powered to independently assess efficacy

and what were calling multiple chronic

condition or multi

multimorbidity patients

and thats an ongoing discussion because

of course that number one increases the

cost of the trial there for the increase

increases the cost of the drug

development program

and so on

now with regard to safety profile

at the moment thats mostly done uh in

older individuals after a drug has been

approved and is on the market can we do

better than that or learn more

at an earlier time point well perhaps

some

so what are the goals for for

therapeutics in the older patient well i

think these are obvious but

to have efficacy to decrease morbidity

and mortality as a function of the use

of medications

trying to minimize drug related problems

and improve quality of life

theres a very active effort going on uh

in in a number of parts of the world

really more in europe and australia than

in the united states uh called deep

prescribing initiatives

whats quite clear uh is that

when one goes into an older population

that

is exposed to fairly extreme

polypharmacy

and in a judicious way working with the

the primary caregivers starts removing

medications in general the patients will

do better with fewer medications not

more

and so i think if youre

saying well what are we going to hear

going forward uh theres theres going

to be really increasing emphasis on not

exposing older people to more

medications but trying to very

judiciously expose them to only the

medications that have a clear benefit

to that end theres another effort in

trying to modify treatment guidelines

treatment guidelines as they currently

exist early disease specific so theres

a treatment guideline for congestive

heart failure for diabetes and on down

the list

a

clever researcher over at johns hopkins

has been a lead but there are a number

of people working in this space

saying well what if we took the typical

0 year old person who had four or five

illnesses and we said okay lets follow

the treatment guidelines for each of the

illnesses they have well one ends up

with number one severe polypharmacy

number two drugs that interact with each

other

and number three clearly uh drugs that

when administered all together are going

to have an adverse outcome for the

patient

so theres a growing move to begin

thinking about patientcentered

treatment guidelines uh

taking the particular array of

morbidities that the individual patient

has and constructing treatment

guidelines around that so i would say

keep your ear to the wall for that

thats on the horizon

so anyway

this is one rather bleak view of the

older patient

whoops what do we do here anyway and

another happier view is that really the

the end of life can be a very rich time

so with that id be happy to try to take

any questions and

answer anything that i said that was

quite confusing thanks

im sad to report that since the filming

of the lecture you just saw

dr daryl bernathy has passed away a

pancreatic cancer

he was a true leader in the field of

clinical pharmacology and his leadership

will be missed

you