

Medicine Update for Optometry.

John A. McGreal Jr., O.D.
McGreal Educational Institute
2019

JAM

1

John A. McGreal Jr., O.D.

Missouri Eye Associates
11710 Old Ballas Road
St. Louis, MO 63141
1.314.569.2020
1.314.569.1596 (Fax)
mcgrealjohn@gmail.com

JAM

2

Cataract Surgery in The Future

- Only guarantees in life are death & taxes....
 - Add Presbyopia & Cataracts
- Boomers fight aging and create an enormous unmet need
- “Holy Grail” is a presbyopic solution
- Options now include glasses, monovision CL, multifocal CL, monovision IOLs, multifocal IOLs, Accommodating IOLs, other surgeries and lifestyle treatments
- Bottom line: No perfect solution yet
- Challenge is to develop rewarding opportunities providing continuous vision

3

Cataract Surgery in The Future

- Growth in cataract cases is expected to increase to 38.5million by 2050
- Women comprise majority of cases today
- Caucasians comprise majority of cataracts but Hispanics will take lead by the 2040's as the amount of Caucasians decreases by this time

4

MKO Melt Alternative for Sedation

- Anesthetic pain pill is *IV free conscious sedation*
 - Sublingual. Lemon flavored turning to bitter, 5 minute melt
- Compounded formulation, single use, starts in 5-10 then maximal effect in 30-40mins
 - Midazolam 3mg (Versed/Roche) – rapid on/off, good anxiolytic
 - Ketamine 25mg- analgesia, euphoria. Ketamine “stare”
 - Ondansetron 2mg (Zofran/GSK) – nausea
- Benefits – no needles stick, bad veins, no hangover
- Dose – 2 pills (60-65), 1.5 (65-70), 1 (70-80), 0.5 for >80; younger and thinner need more than older overweight
 - IV preferred when more control needed, etoh, illicit drugs, benz

5

New Injectable Drugs for Cataract Pts

- Tri-Mox, Tri-Mox-Vanc, Dexi-Moxi, Dexi-Moxi-Ketor, Moxi / Imprimis Pharm (SanDiego)
 - Delivers a compounded mix of drugs trans-zonularly remains in the eye for a week
 - “drop-less” cataract surgery
 - Pharmaceuticals that do not mix are solubilized and micronized into uniform suspension optimized for isotonicity and pH for ophthalmic use
 - Sterility, endotoxin and potency testing on each batch

6

New Topical Drugs for Cataract Pts

- Pred 1%-Gati 0.5%
- Pred 1%-Brom 0.075%
- Pred 1%-Gati 0.5%-Brom 0.075%
- Gati 0.5%-Dex 0.1%
- Prednisolone acetate preservative free 1%
- Mydriatic 3 (Tropicamide/cyclopentolate/phenylephrine)
 - 1/1/2.5
- All sterile compounded formulations
- Optional delivery channels for doctors and patients
- Cost savings / compliance / cognitive issues

JAM

7

Immediately Sequential Bilateral Cataract Surgery (ISBCS)

- Paradigm changing as surgery gets safer
- 2/3rds schedule fellow eye surgery at 1-2 weeks post op
- Reasons to Consider – transportation issues, infirmity, terminal illness, anxiety, finances to patients & tax payer funded Medicare system
- Reasons for Concerns – bilateral endophthalmitis, bilateral TASS, monetary concern with reimbursement, refractive outcomes

JAM

8

Emerging Surgery Options for Presbyopia

- Extended Depth of Focus IOLs
 - Redistribute light rays to extend single focus in monofocal IOL to a range of foci
 - Create spherical aberration that increases depth of focus
 - Extension of multifocality with compensation of chromatic aberration to offset loss of contrast sensitivity
 - One focal point spread over 2D+ range
 - Can exploit “micromonovision” by being off 0.50D and be within 2D range so still keep 20/20 but read well
 - Clinical trials demonstrate 98% patient satisfaction
- Coming soon TechnisSymphony/AMO, Mplus/Oculentis, MiniWell/SifiMedtech, IC-8IOL/AcuFocus

JAM

9

Technis Symphony / Abbott Medical, IL

- Unilateral or bilateral, with or without astigmatism
- One piece acrylic design same as TechnisMF
- Diffractive echelette but ONE image on retina not 2 like other MFIOLs
- No glare or halo (similar numbers to monofocal IOLs)
- 20/25 @near 46%, @intermediate 91%, @distance 95%
- 20/40 @near 88%, @intermediate 99%, @distance 99%

JAM

10

Light Adjustable IOLs - LALs

- RxSight (formerly Calhoun Vision, Inc.)
 - Next generation “*adjustable*” material, unique, unstable, silicone, foldable
 - Cross-linked silicone polymer matrix - Mechanical and optical properties
 - Macromer - Low molecular weight links to photoreactive group
 - Photoinitiator - Organic molecule dissociates into free radicals, begins polymerization on exposure to special wavelengths, moving macromer down diffusion gradient into radiation area thickening the lens
 - 3 piece, foldable, silicone platform with 6mm square edged optic

JAM

11

Trifocal IOLs and Trifocal Toric IOL

- FineVision Trifocal (Phys-IOL) – 2 *overlapping* diffractive zones (1 for distance & near and 1 for distance & intermediate) with over 30 steps, near center design
- AT LISA Trifocal (Carl Zeiss Meditec) – *asymmetric* diffractive pattern that provides trifocal function from center to 4.34mm, bifocal pattern from 4.34-6mm
 - Distance = 50%, intermediate = 20%, near = 30%
 - Independent of pupil size (up to 4.5mm)!
- AcySof IQ PanOptix (Alcon) – extended intermediate focal point redirects light for amplified distance, intermediate at 60cm, near at 40cm, transmits 88% light

12

Supplementary IOLs

- XtraFocus Pinhole Implant (Morcher) – sulcus fixated, foldable, black, hydrophobic acrylic with a 1.3mm pinhole in center of optic
 - allowing straight rays of light through pupil reducing aberrations
 - corneal diseases
 - Iris abnormalities
 - Blocks visible light but allows infrared light and OCT
 - Can be piggybacked in normal eyes without corneal diseases
 - Increases depth of focus improving near vision without glasses

JAM

13

Loteprednol 1% (Kala Pharmaceutical)

- Nanoparticle design allows penetration of mucous for enhanced absorption
 - Mucous penetrating surface coating prevents adherence to mucous
- Better penetration into cornea and aqueous than traditional loteprednol
- Dose – 1st BID dose approved for cataract surgery
- Indicated – post-operative inflammation and pain after cataract surgery
- Available as – *Inveltys*

14

Adalimumab (Abbvie) for Uveitis

- 1st & only Anti-TNF for treating NI Uveitis
- Previously approved for psoriatic arthritis
- Steroid-sparing option proven to prolong time to a disease flare and decrease visual acuity
- Indicated – treatment of NI intermediate, posterior and panuveitis
- AE – URI, sinusitis, HA, rash, reactivation of HBV
- Warnings – TNF rarely cause CNS and peripheral demyelination (MS, Optic neuritis, Guillain-Barre)
- Available as – *Humira*

15

Intravitreal Insert for Uveitis

- Approved for treating chronic posterior NI Uveitis
- Developed to break the cycle of treatment-quiescence-recurrence-treatment that is hallmark of the disease
- Advantage – can be implanted in the office
- Builds on successes of previous platforms
 - Ozurdex (Allergan) 0.7mg dexamethasone injectable insert lasting 3 months
 - Retisert (B&L) long lasting fluocinolone implant requires surgery to implant
- AE – cataract, IOP increases
- Available as – *Yutiq (EyePoint Pharmaceuticals)*

16

Pazosin for PTSD Warnings

- Weak anti-hypertensive used by Veterans Administration since 2000 for PTSD at **high dosages** (45mg/D)
- Alpha-1 adrenergic blocking agent
- Indicated – treatment of trauma induced nightmares
- Warnings – suspect IFIS, since it's “cousin” tamsulosin (Flomax) is prescribed at 0.4mg/D
- NEJM 2018 – RCT demonstrated ineffectiveness in PTSD!
- Be watchful for “super Flomax” in cataract patients
- Available as – *Minipress*

17

Ocular Drug Delivery Challenges

- Requires high doses, frequent doses, side effects, intravitreal injections, compliance
- Nanyang Technical University (Singapore) – researchers found a better way (?)
 - Flexible eye patch made with array of detachable, double layer of methacrylated hyaluronic-based microneedles
 - Capable of releasing 2 drugs at different rates (biphasic release)
 - Applied like a contact lens, then microneedles detach from substrate and remain in eye while patch is peeled away
 - High bioavailability proven

18

Herpes Zoster: New Ways to Combat

- HZ is reactivation of varicella-zoster virus (pox)
- 1.2 million new cases annually in US
 - 10-20% involving CN I
 - 120,000-240,000 new cases of HZO in US annually
- Demographics are changing, new risk factors identified
 - Age of onset is decreasing
 - 90% affected are immunocompetent
 - Incidence increasing (worldwide also) – 2.5% per year since 1960, a four-fold increase
 - Not related to childhood vaccination practices
- Treatment-high dose oral anti-virals x 1 week w/in 72h

19

Herpes Zoster PHN

- Post-herpetic neuralgia (PHN) is pain beyond 3 months after onset of zoster, most common complication of HZ
 - Occurs in 30% of patients with HZO, particularly older
 - Most common cause of suicide due to pain in pts over 70
- Healthcare annual costs increase
 - \$1800 for HZ
 - \$7200 for PHN
 - \$1 billion HZ worldwide
 - \$2 billion PHN worldwide

20

Herpes Zoster Ocular Complications

- Vascular dermatitis, preceptal cellulitis, keratitis, neurotrophic keratopathy, uveitis, glaucoma, retinitis, choroiditis, optic neuritis
 - Treatment is complex, antivirals and steroids
 - Stromal keratitis is recurrent in 20% of HZO
- Rate of ocular involvement in HZO is 65%
 - Conjunctivitis is most common 57%
 - Vision threatening keratitis in 12%
 - 25% experience chronic or recurrent disease by 5 years out
 - Overall rate of recurrent eye disease is as high as 51% leading to *significant* morbidity

21

Herpes Zoster Ocular Complications

- Herpes Eye Disease Study informs decisions in management of HSV, no such study of HZ
- Recent study using low dose valacyclovir 500mg qd or acyclovir 400mg bid reduced recurrent episodes by 35% in HZ
 - Suggests that suppressive dosing may help prevent recurrences
- Zoster Eye Disease Study conceived to answer questions
 - Whether prolonged suppressive valacyclovir treatment reduces complications of HZO, including eye disease
 - And to test the treatment effect in reducing incidence, severity and duration of PHN

22

Herpes Zoster Vaccine

- 2016 – high potency live virus vaccine approved >60 yrs
- 2011 – live approved >50 yrs
- Shingles Prevention Study
 - Vaccine reduces incidence of HZV 51%
 - Reduces burden of illness by 66%
 - Reduces incidence of PHN by 66%
 - Not demonstrated to prevent repeat episodes of HZ in prior dz
 - Patients with immunosuppression 1.5-2 x higher incidence HZ
 - Duration not proven (booster?)

23

Herpes Zoster Vaccine (Merck)

- 2006 – zoster live attenuated vaccine for age 60 and over
- 2011 – lower age limit decreased to age 50
- Strong protection against shingles & PHN
 - 61% reduction in incidence of HZ, & 66% reduction in PHN
 - Efficacy wanes after 8 years to 4%
- Vaccination rates in US are low
 - 31% in 2015 and only 2% in individuals age 50-59
 - Not recommended –immunocompromised, immunosuppressed
- Recommended for naïve, past exposure prophylaxis, no evidence of immunity to varicella
- Available as – *Zostavax*

24

Herpes Zoster Vaccine (GlaxoSK)

- 2017 – zoster recombinant adjuvated subunit vaccine
- Age 50 and over
- Doses: 2 - 6 months apart IM injection
- Strong protection against shingles & PHN
 - 97% reduction in incidence of HZ in ages 50-69
 - 91% effective in incidence of HZ in age 70 and older
 - 91% effective against PHN
- Flu-like symptoms (17% grade 3), soreness at injection
- Recommended-naïve, past exposure, no evidence of immunity to varicella, or those who had Zostrix vaccine
- Available as – *Shingrix*

25

Plaquenil Screening Protocols - Update

- New guidelines recommend a maximum dose of 5.0mg/kg/day of real weight (not ideal wt)
 - Stored in adipose tissue and short statured or thin patients may be significantly overdosed
- 2011 toxicity prevalence – 1%
- 2016 AAO guidelines – 7.5%
- At new recommended dose risk of toxicity at 5 years is <1%, at 10 years <2%, but rises to 20% after 20 yrs
- Wider visual field test patterns are needed in Asians
 - Toxicity often manifests beyond the macula

26

Plaquenil Screening Protocols - Update

- New guidelines recommend testing VA, DFE, VF 10-2, VF 24-2 or 30-2 for Asians and one objective test, like SD-OCT, mfERG, FA
 - No longer recommend Amsler grid, color vision, photos
- Precautions for higher toxicity in patients with renal disease, concomitant tamoxifen use, macular disease
- Concomitant use of methotrexate can cause optic nerve damage and SD-OCT of optic nerve is indicated

27

Urology Drug Linked to Maculopathy

- Chronic exposure to pentosan polysulfate sodium (PPS)
- Drug used since 1996 for discomfort associated with interstitial cystitis (IC)
- Primarily affects the RPE in a patchy pattern
 - Subtle on exam but dramatic on FAF
- Thousands of patients diagnosed with macular disorders like Pattern Dystrophy, or macular degeneration AMD may actually have a preventable drug-associated maculopathy
- Emory Eye Center
- Available as - *Elmiron*

28

Obstructive Sleep Apnea and The Eye

- OSA affects 15-20 million in USA
- Ocular manifestations
 - Glaucoma, NAAION, keratoconus, AMD, Diabetic retinopathy
 - Strongest for diabetic retinopathy
- Non-ocular manifestations
 - HTN, stroke, MI, Afib, Diabetes
- WestSD Eye Disorders Associated with Obstructive Sleep Apnea Curr Opin Pulm Med. 2016; 22:595

29

Tobacco Use

- Single greatest health hazard existing in USA. 400,000 deaths per year related to cigarette use, mostly cancer of the lung or cardiovascular mortality.
- Estimated that an individual who smokes 1 PPD starting at age 15 loses approximately 7 minutes of life per cigarette inhaled.
- Also increased risk of cancer of the tongue, esophagus, stomach, colon, cervix, bladder. Increased risk of chronic bronchitis and emphysema.
- Passive smoking (second hand) has many risks (cancer, COPD, asthma) as well. Nicotine is addicting both physiologically and psychologically and recidivism after initially quitting is quite high

JAM

30

Lung Cancer

- Malignancies may be primary (75%) or metastatic (25%) cancer. Characterized by histologic characteristics of the tumor. Major types are
 - squamous cell carcinoma
 - Adenocarcinoma
 - large cell carcinoma
 - small cell carcinoma.
- Nearly 150,000 deaths per year in USA from cancer, most common cause of cancer death in men and just passed breast cancer in women . Single most important cause of cancer is cigarette smoking. Other causes include radon, radiation, vinyl chloride, hydrocarbons, asbestos
- Symptoms are localized and include dyspnea, cough, hemoptysis, chest pain, pneumonia, Horner's syndrome

JAM

31

Lung Cancer

- Most caused by cigarette smoke (90%)
- 25% of adult women smoke
- 30% of high school women smoke
- 13-22% of pregnant women smoke
- Cessation of smoking
 - Quit by 35 = 6-8 years of life expectancy
 - Quit by 44 = 6-7 years of life expectancy
 - Quit by 55 = 3-6 years of life expectancy
 - Quit by 65 = 1-4 years of life expectancy
 - 55% decrease in heart attack after quitting for one year!

JAM

32

Tobacco Use

- 10% of people over age 65 smoke
- 14.2 billion spent last year in Medicare to address smoking related illness
 - 10% of the entire Medicare budget
- New Medicare counseling program offered to beneficiaries to help with cessation programs
- Leading cause of preventable morbidity & mortality in US
- Cigarette smoking is significantly associated w new onset uveitis (Ophthal, 2015 122: 1257 Yuen,B et al)

JAM

33

Smoking Cessation

- 1-7% chance of quitting without help
- Antidepressants
 - Bupropion (Wellbutrin/Zyban)
- Nicotine replacement
 - Nicoderm CQ Patch (Transdermal Nicotine 21mg, 14mg, 7mg steps over 10 weeks)
 - Nicorette Gum (2mg if <25 cigarettes/D, 4mg if >25 cigarettes/D)
 - Nicotrol Inhaler
 - Nicotrol Nasal Spray
 - Nicotrol Patch

JAM

34

Smoking Cessation

- Best new option
 - Varenicline (Chantix/Pfizer)
 - 43.9% quit vs 29.8% quit on bupropion
 - Treatment is for 12 weeks, if successful take it 12 more weeks to lessen chance of smoking again
 - Blocks nicotine receptors in brain and stops “reward” associated with smoking again
 - Side effects – nausea is mild and tolerable but occurs at 32%, 3% discontinued

JAM

35

Roflumilast

- Indicated – treatment to reduce risk of COPD exacerbations in severe COPD associated with chronic bronchitis and history of exacerbations
- Side effects – psychiatric, usually suicide thoughts or depression
- Available as - *Daliresp*

36

Umeclidinium & Vilanterol

- Indicated – treatment of COPD and chronic bronchitis and emphysema in adults
 - Not approved for asthma
- One inhalation per day
- Side effects – sore throat, watch blood glucose and potassium
- Available as – *ANORO*

37

Psychiatric

- Insomnia – non diazepines
 - Zolpidem (AmbienCR)
 - Eszopiclone (Lunesta)
 - Zaleplan – (Sonata)
 - Ramelteon (Rozerem)
- Suvorexant (Belsomra) - first in class to target orexin neurons in brain arousal circuits (wakefulness center)
 - Speeds onset and reduces nighttime awakenings
 - 4 doses
- Restless Leg Syndrome
 - Ropinirol (Requip)

JAM

38

Neurologic / Psychiatric

- Headache
 - Sumatriptan (Imitrex NS, tablets, SQ stat)
 - Zolmatriptan (Zomig)
 - Naratriptan (Amerge)
 - Rizatriptan (Maxalt)
 - Eletriptan (Relpax)
- Migraine recognized as an organic disease
 - Brain lesions visible

JAM

39

Erenumab (Amgen)

- New approval for Migraine prevention and treatment
- 38 million Americans with migraine
- MOA – calcitonin gene-related peptide receptor antagonist (CGRP-R)
 - Disrupts mediator of migraine pathophysiology
- Dose – 70mg or 140mg once monthly by subq injection
 - Self administered
- Adverse events – injection site irritation
- Available as - *Aimovig*

JAM

40

Neurologic / Psychiatric

- Attention Deficit Hyperactivity Disorder (ADHD) – disorder of children and adults characterized by inability to concentrate, short attention span, hyperactivity, emotional lability, impulsivity, distractibility
- 1/3rd ADHD in children linked to tobacco smoke before birth or lead exposure afterward (environment)
- Treatment
 - Methylphenidate (Ritalin)
 - Clonidine (Catapres)
 - Dextroamphetamine (Adderall XR)
 - Atomoxetine (Strattera)
 - Methylphenadate (Concerta)
 - “black box” warnings for amphetamines recommended by FDA

JAM

41

Neurologic

- Multiple Sclerosis
 - Glatiramer (Copaxone)
 - Interferon B-1b (Betaseron)
 - Interferon B-1a (Avonex)
 - Interferon B (Rufab)
 - Side effects – macular edema, CRVO, CRAO, CWS, optic neuritis, papilledema
 - Flu-like symptoms are common for 2 weeks
 - Medications are given by injection
 - Annual costs range from \$12,000-\$33,000/year

JAM

42

Dimethyl fumarate

- Indicated – treatment of relapsing multiple sclerosis
- Oral
- SE – rare brain infection, white blood cell count decreases, flushing, stomach upset
- Available as - *Tecfidera*

43

Hepatitis-C Epidemic

- Chronic hepatitis C found in boomers ('45-'65)
- 3.5 million Americans have chronic HCV
 - Only half diagnosed
 - Only 9% successfully treated
 - Leading cause of liver transplant & liver cancer in US
- By 2007 HCV mortality surpassed HIV
- Before 2011 HCV treatment lasted one year, cure rate were 40%, now treat 12 weeks with cure rate of 95%
- CDC, AASLD, USPSTF recommend 1x screening of all boomers regardless of risk factors

JAM

44

Hepatitis-C Breakthrough

- Chronic hepatitis C virus genotype 1
- CURE rate 94-99%
- Interferon ribavirin free tablet
- Once daily
 - 8 weeks in treatment naive patients
 - 24 weeks in treatment experience patients
 - Side effects – fatigue, HA
 - High cure rates achieved even in cirrhosis, previous treatment, advanced age and high BMI
- Ledipasvir / Sofosbuvir – Harvoni

JAM

45

Neurologic

■ Optic Neuritis

- Controlled High-Risk Avonex Multiple Sclerosis Study (CHAMPS), Optic Neuritis Treatment Trial (ONTT)
 - Initial demyelinating episode (like ON) treated with interferon
 - Conclusively showed that treatment with interferon slowed rate of development of MS
 - Do not use oral steroids to treat ON
 - **Brain MRI obtained in all patients with ON**
 - If MRI abnormal IV/oral steroid regimen should be used
 - IV methylprednisolone 100mg q6h x 3d, followed by PO prednisone x 11 days
 - Abnormal MRI should be referred to neurologists for consideration of interferon treatment

JAM

46

Neurologic

■ Optic Neuritis

- Optic Neuritis Treatment Trial (ONTT)
- Archives Ophthalmology 2003
- Reported 10 year risk of developing MS is significantly higher if there is a **single brain lesion noted on MRI** scan at the time diagnosis (56% vs. 22%)
- The overall 10 year risk is 38%
- Male gender, no lesions on MRI and presence of disc swelling places a patient at lower risk of developing MS

JAM

47

Neurologic / Psychiatric

- Alzheimer's Dementia – chronic, progressive deterioration in global intellectual functioning. Familial tendencies, associated with B- amyloid and organic changes in the brain. 4.5 million Americans diagnosed
 - Research at Boston University
 - 2,581 patients
 - 79% reduction in risk of developing AD
 - Statins reduce cholesterol by blocking enzyme HMG Co-A reductase
 - Also interfere with production of B-amyloid
 - Current treatments target anticholinesterase, target amyloid production and gamma secretase

JAM

48

Neurologic / Psychiatric

- Alzheimer's Dementia
 - Donepezil (Aricept)
 - Tacrine (Cognex)
 - Rivastigmine (Exelon)
 - Galantamine (Reminyl)
- Experimental drugs with promise include Gleevec/Novartis which targets proteins that regulate secretase, sage extract, raloxifene, huperzin A (cholinesterase inhibitor, Chinese herb)
- Combinations with Memantine (Namenda) are safe and effective in moderate to severe AD
- Regular exercise in midlife reduce risk of AD by 50% (Lancet Neurol 2005)
 - 20-30 minutes of exercise twice a week

49

Memantine & Donepezil

- Indicated – treatment of moderate to severe AD
- Combination of two previously used individual drugs
- Dose – 14/10 or 28/10
- Once per day
- Side effects – slow heart beat, nausea and vomiting, HA most common, diarrhea, dizziness
- Available as – *Namzaric (Activis)*

50

Neurologic / Psychiatric

- Alzheimer's Dementia – 50% develop psychiatric and behavioral symptoms
 - Anxiety, aggression/violent outbursts, paranoid thoughts
 - Treatment trials and “off-label” use of Depakote
 - Inhibits tangles and plaques
 - May prevent psychiatric symptoms
 - Rule out UTI, thirst, hunger, pain, medication side effects

JAM

51

Alzheimer's Dementia Updates

- B-amyloid is hallmark of the diagnosis
 - Identified with PET scanning (not always available or affordable)
 - Diagnosed with PE, History, MRI (to R/O tumors and other diseases), neuropsychological examination
 - 70% accuracy of diagnosis
- Unmet need – non-invasive, easy, repeatable test
- Retina shows early AD with build up of plaque, and thinning of RNFL
- Odor identification may be useful screening tool

52

Alzheimer's Dementia Updates

- NeuroVisionImaging / NVI (Sacramento)
 - Proprietary formula of curcumin (turmeric) as fluorescent contrast agent
 - Absorbed by amyloid plaques, emits specific wavelengths of light allowing detection with sensors
- Reminiscent Memory Therapy – new concept
 - Beneficial coping strategy to compensate for other losses
 - Reduces social isolation and depression
 - Provide comfort
 - Reaches memories that reside in viable regions of the brain
 - reviews / evaluates / re-captures emotions / one to one or grp

53

Alzheimer's Dementia Updates

- Reminiscent Memory Therapy – enhances self-esteem
 - Allows participation of daily living
- Prompts for reminiscence
 - Music Therapy - popular, effective
 - Pictures / vintage posters (WWII, Korea, Vietnam) / Sears Catalogue / memory books / geneology / art therapy for curiosity and self valuation
 - Old cars
 - Smells / Foods
 - Old TV shows / Old movies
 - Old books

54

Neurologic / Psychiatric

- Acute Ischemic Stroke
 - 700,000/yr or one every 45 seconds
 - 500,000 new, 200,000 recurrent
 - 164,000 deaths/yr, 3rd leading cause of deaths
 - Cost \$56.8 billion in 2005
- Risk factors – HTN, smoking, DM, artery diseases, African-Americans twice prevalence
- Treatment
 - Alteplase (Activase)
 - Carotid artery stents – option in CA endarterectomy
 - Brain stents – Boston Scientific's Wingspan

JAM

55

Stroke Research

- Proceedings of the National Academy of Sciences
- University of Queensland Australia
- Spider venom (disulfide-rich peptide) reduces brain damage when given up to 8 hrs after CVA
- Australian funnel-web spider – *Hadronyche infensa*
- Precipitous decrease in brain pH activates acid-sensing ion channel 1a (ASICa)
 - a key mediator in stroke induced neuronal damage
- Results in improved neurologic function and motor

JAM

56

Antaging

- Calorie restriction (CR) – cutting normal calorie intake by 1/3rd boosts animal lifespans by 30-40%
- Resveratrol – proven at Harvard & National Institute on Aging to extend lifespan by 20%, slow aging process, even with high calorie diet
 - Studies in fruit flies, mice, fish, now humans
 - Present in red wine

JAM

57

Deoxycholic acid

- Indicated – treatment of submental fat
- Dose form - injection
- SE – injection site redness
- Available as - *Kybella*

58

Tavaborole 5%

- Indicated – toenail fungus
- Topical solution
- Not for children or pregnancy
- SE – redness at application site
- Available as - *Kerydin*

59

New Alcohol

- March 2015 Alcohol Tax & Trade Bureau approved powdered alcohol products (Palcohol) for sale in US
 - Absorbed into carbohydrate dextrin resulting in dry state
 - 50% by weight, if mixed according to package would yield 10% alcohol by volume
- Problems – higher dose mixes, binge drinking, undermining retail business, undermining taxation and regulation, spiking non alcohol beverages, easy concealment at facilities not permitting alcohol, promote smuggling over state lines, undermining retail responsibility laws, social issues & fatalities (100,000)

JAM

60

Opioid Crisis

- 63,632 deaths from drug overdoses in US in 2016 (CDC)
- 174 deaths/day, 1 death every 8.28 minutes, 66% opioids
- More deaths than those resulting from firearms, homicide, suicide, MVA
- Substance Abuse & mental Health Services Admin
 - National helpline 800 662 HELP
 - 24hr/7days/365days/English/Spanish/individual or families
 - Confidential/free
 - Helps find authorized opioid treatment program in your state
 - Dispensing methadone or buprenorphine
- Benefits of Narcan (Naloxone or Evzio) in rapid reversal

JAM

61

Antibiotic vs Appendectomy ?

- Assumed progression of appendicitis from mild disease to perforation with appendectomy as only means of preventing serious infection became established thought
- Several trials suggest that treating CT-confirmed uncomplicated appendicitis with initial round of antibiotic Ertapenem is successful in 73% over a one year period. Of those who did require surgery for failure to improve or presenting with recurrent appendicitis, there was no complication from receiving antibiotics
- JAMA 2015;313(23) Salminen, et al

JAM

62

Sepsis & Septic Shock

- Global healthcare issue – 15-19 million cases per year
- Leading cause of death from infection -1/3-1/2 of hospital deaths
- Early recognition required to prevent transition to septic shock (40% mortality)
- New approach – early use of IV vitamin C, thiamine, and corticosteroids
 - Effective in preventing progressive organ dysfunction and in reducing mortality (8.5% vs 40.4%) in severe sepsis and septic shock
- Chest, Marik et al 2016

JAM

63

Screening for Prostate Cancer

- Lifetime risk of diagnosis is 13%, lifetime risk of dying in 2.5%. Median age of death is 80yrs, 2/3rd over 75yrs
- PSA screening test was introduced in the 1980s but can be elevated in other conditions (10% false positives) including benign prostate hypertrophy and proctatitis
- Harms of biopsy include unnecessary biopsy, hematospermia, infection, pain, hospitalization, impotence, urinary incontinence, bowel domain problems, overdiagnosis and overtreatment
- USPSTF concludes with moderate certainty the net benefit of screening for prostate cancer in men 55-69 is very small and should be an individual decision

JAM

64

Screening for Prostate Cancer

- USPSTF recommends against screening for Prostate cancer in men over 70
 - 3 RCTs found no improved mortality in men over 70
 - Harms of screening far outweigh benefits
- African-American men have greater risk of prostate cancer than white men, younger age of onset, and positive family history increases risk
 - Based on available evidence the USPSTF is not able to make a specific separate screening recommendation for African-American men

JAM

65

Cardiovascular

- New Guidelines for Blood Cholesterol Treatment
 - Heart disease is the number 1 killer in this country
 - 65 million Americans should change life-style & diet (50)
 - 36 million should take medications to lower cholesterol (13)
 - Many more patients are now candidates for drug treatment than previous
 - many recent studies confirm a dramatic decrease in mortality and morbidity associated with decreased cholesterol levels
 - Framingham Heart Study “risk calculator”

JAM

66

Cardiovascular

- National Cholesterol Education Program Adult Treatment Panel (NCEP ATP-III) – lipid management in USA is less than desirable
 - <50% of even highest risk patients receive lipid lowering treatment
 - 1/3rd of treated patients achieve LDL goal
 - <20% of CHD patients achieve LDL goal
 - <50% of patients who are prescribed lipid lowering drugs are still taking it six months later, 30-40% after 12 months
 - 1 in 8 MI patients quit drugs only 1 month after discharge and are 3 times more likely to die in the year after MI

JAM

67

New Cardiovascular Concepts

- >20 years old = lipoprotein profile
 - LDL, HDL, Triglycerides, total cholesterol, and BP
- Guidelines

– Total cholesterol	<200	<190
– LDL	<130	<130
– LDL (high risk)	<130	<100 (70)
– HDL	>35	>40
- Risk Factors
 - Gender, age, smoking, high total cholesterol or LDL, low HDL, HTN, family history premature heart disease, & obesity

JAM

68

New Cardiovascular Concepts

- Risk Factors
 - Diabetes now singled out as so potent risk factor and assumes high risk category (same as for previous MI)
 - “metabolic syndrome” – new risk factor
 - requires three or more of the following
 - abdominal obesity - 40 in men/35 in women
 - low HDL - <40 men/<50 women
 - fasting triglycerides >150
 - HTN
 - fasting glucose >110
- New Concepts – C reactive protein, apolipoproteins, adiponectin protein, treat HDL & LDL together

JAM

69

Cholesterol Guidelines

- More than half of the coronary artery disease in the U.S. is attributable to abnormalities in the levels and metabolism of plasma lipids and lipoproteins. Diabetes, alcohol consumption, OCs, renal disease, hepatic disease, hypothyroidism can worsen hypercholesterolemia or worsen underlying hyperlipoproteinemia.
- $LDL = \text{total cholesterol} - HDL - \text{triglycerides} / 5$.
- Every 1% reduction in TC yields a 2% reduction in CAD risk!

JAM

70

Cholesterol Guidelines (ACC/AHA) 2013

- Pts with ASCVD inc MI, angina, previous coronary revascularization
- Pts w/o clinical ASCVD but w $LDL-C > 190\text{mg/dl}$
- Pts 40-75 yrs w/o clinical ASCVD but w DM and $LDL-C$ from 70-189mg/dl
- Pts 40-75 yrs w/o clinical ASCVD and DM but w $LDL-C$ from 70-189 and estimated 10 year ASCVD risk of 7.5% or higher
- For the first three groups there is universal acceptance of data
- The fourth group triggered immediate controversy
- JAMA 2015;(2):142-150 Pandya et al Cost Effectiveness of 10 yr Risk Thresholds of Statin Therapy for Primary Prevention of CVD

JAM

71

Cholesterol Guidelines (ACC/AHA) 2015

- Two new reports in JAMA 2015 suggest that the new risk factor threshold is reasonable and cost effective
- Suggest it may not even go far enough
- Included a more lenient and cost effective threshold taking into consideration patient preferences for daily pill, changes to statin prices, and risk of statin induced diabetes
- Could lead to massive treatment of billions of people worldwide
- We finally know who and when to treat with a cost effective primary prevention strategy

JAM

72

US Dietary Guidelines 2015

- USDA and HHS jointly release new guidelines every 5 years
- Far reaching influences on food supply across government cafeterias, schools, military, food assistance programs, agricultural products, restaurant recipes, industry food formulations; Revisions of guidelines is necessary for the health of millions
- Eliminates cholesterol as a nutrient of concern
 - No appreciable relationship between dietary cholesterol and serum cholesterol
- Absence of upper limit on total fat consumption
 - Dietry advice should emphasize optimizing types of fat not reducing total fat, since so often low fat is replaced w carbs

JAM

73

US Dietary Guidelines 2015

- Other policies need to follow suit but nothing is consistent
- Nutrition Fact Panel – separately regulated by FDA uses 30% fat limit obsolete for over a decade
- US Dept of Agriculture – should modernize the Smart Snacks in School standards removing 35% restriction on total fat
- Institute of Medicine – should update its report on dietary reference intakes for energy and macronutrients, now over 15 years old
- National Institute of Health guidelines recommends caution eating nuts, tuna canned in oil, olive oil, vegetables cooked w added fat, same category as chips, soda, and candy
- Natioanl School Lunch Program – bans whole milk, allows sugar sweetened non-fat milk

JAM

74

Lipids

- Cholesterol
 - Normal <200mg/dl
 - Cholesterol is used by the body to form steroid hormones, bile acids, and cell membranes.
 - Increased – cardiovascular disease and atherosclerosis, jaundice, uncontrolled diabetes
 - Decreased – malabsorption syndromes, stress, sepsis, liver disease, hyperthyroidism
 - Interfering factors – pregnancy, many drugs
- Framingham Heart Studies – 1/3rd of all MI patients have cholesterol <200. The implication is that “normal” levels are probably not normal at all

JAM

75

Lipids

■ Low Density Lipoproteins (LDL)

- Normal: 130mg/dl, High risk: 100mg/dl (70mg/dl since 7/04)
- LDL is the cholesterol rich remnants of the lipid transport vehicle, VLDL.
- Increased – coronary heart disease, atherosclerosis
- Modifications – losing weight, moderate alcohol consumption, niacin supplements, exercise, less red meat, less dairy, limit saturated fat, no fried foods, may all decrease LDL

JAM

76

Lipids

■ High Density Lipoproteins (HDL)

- Normal: 45mg/dl
- HDL is the cholesterol carried by alpha lipoproteins. A high HDL is an indication of a healthy metabolic system in a person free of liver disease. HDL serve as transporters of cholesterol and carry it from peripheral tissues to liver for catabolism and excretion. HDL probably inhibit uptake of LDLs.
- Increased – chronic liver disorders
- Decreased – in coronary artery disease, chronic physical inactivity, long distance runners, Lumigan??
- Modifications – losing weight, moderate alcohol consumption, lecithin supplements, exercise, less red meat may all increase HDL, torcetrapib not approved!

77

Lipids

■ Triglycerides

- Normal: 0-150/dl, lower in females, higher with age
- Triglycerides are produced in the liver from glycerol and fatty acids. They are used for production of energy. Excess levels of triglycerides are stored in adipose tissue.
- Increased – atherosclerosis, liver disease, pancreatitis, MI, hyperlipoproteinemias, toxemias, nephrotic syndromes
- Decreased – malnutrition, congenital lipoproteinemias
- Modifications – losing weight, low fat diet, exercise

78

Cholesterol Guidelines

■ Disorders of Lipid metabolism

- **Isolated Hypercholesterolemia** – TC>200, TG normal
 - Familial Hypercholesterolemia (FH) – genetic disorder, TC 275-500, TG normal, HDL normal or reduced
 - Familial Defective APO B – autosomal dominant, phenocopy of FH
 - Polygenic Hypercholesterolemia – mixed form, multiple genetic defects and environmental factors like age, sex, diet, exercise. TC<350
- **Isolated Hypertriglyceridemia** – TG>200 (chylomicrons or VLDL are increased)
 - Familial Hypertriglyceridemia
- **Hypercholesterolemia and hypertriglyceridemia**
 - Familial Combined hyperlipidemia (FCHL)

JAM

79

Cholesterol Lowering Drugs

■ Lipid Lowering – HMG Co-A reductase inhibitors

- Atorvastatin (Lipitor) – 9.2B
 - Lovastatin (Mevacor)
 - Pravastatin (Pravacol) – 2.8B
 - Simvastatin (Zocor) – 5.0B, 80mg dose risky
 - Fluvastatin (Lescol) – 0.73B
 - Rosuvastatin (Crestor) – 0.13B
 - Ezetimibe (Zetia) – alone or in combination (-23% reduction in LDL-C)
 - Ezetimibe (Vytorin) – combination of Zocor & Zetia
 - Desired effects – lower LDL, reduces inflammation in coronary arteries
 - Side effects - hepatic dysfunction (2%), myositis (1%), inc CPK
- HDL raising – torcetrapib not approved! Systolic BP 4mm higher

JAM

80

Pitavastatin

■ Indicated – treatment of cholesterol problems

- Reduce TC
- Reduce LDL-C
- Reduce ApoB
- Reduce TG
- Increase HDL-C

■ SE – low back pain, constipation, diarrhea

■ Available as - *Livalo*

81

Evolocumab

- Indicated – treatment of hypercholesterolemia in statin patients who are on maximal dose but need more lowering of LDL-C
- PCSK9 inhibitor
- Dose – 140mg/ml
- self injection under skin with single use autoinjector every 2 weeks or if monthly dose is preferred then 3 injections in a row within 30 minutes
- SE – sore throat, runny nose
- Available as - *Repatha*

82

Alirocumab

- Indicated – treatment of familial hypercholesterolemia in statin patients who are on maximal dose but need more lowering of LDL-C and in pts w heart attack or stroke
- PCSK9 inhibitor Dose – 75mg/ml
- self injection under skin with single use autoinjector every 2 weeks or if monthly dose is preferred then 3 injections in a row within 30 minutes
- SE – sore throat, runny nose
- Costly - \$560/injection or \$14,500 per year
- Available as - *Praluent*

83

Cardiovascular

- Lipid Lowering Margarines
 - Benecol (McNeil)
 - TakeControl (Unilever)
 - Smart Balance (Trans-fatty acids)
- Drug eluting stents
 - Boston Scientific – Taxus stent
 - Johnson & Johnson – Cypher stent

JAM

84

Cholesterol (TG) Lowering Drugs

- Nicotinic acid
 - Niacin 50-100mg tid initially, then increase to 1-2.5g tid
 - Side effects: flushing (ASA helps), arrhythmias, pruritis
- Bile acid –binding resins
 - Cholestyramine (Questran) 10g bid
 - Cholestipol (Cholestid) 10g bid
 - Side effects: constipation, bloating, discomfort
- Fibric acid derivatives
 - Clofibrate (Atromid)
 - Gemfibrozil (Lopid)
 - Fenofibrate (Tricor)
 - Side effects: gallstones, nausea
- No fat diet, fish oils also help lower TG

JAM

85

Innovative Approach to Diet, Exercise & Activity

- National Heart, Lung, Blood Institute, and NIH sponsor
- N = 471 (120 drop out) / Univ. of Pittsburgh
- Half - BodyMediaFitCoreTracker & monitored website
- Half – self-monitored diet and physical activity
- Activity is 300 min of vigorous activity per week
 - 45 minutes / day
- Results – self-monitored group lost more weight!
 - 13 lbs vs 7.7 lbs
- JakicicJM Effect of Wearable Technology Combined w Lifestyle Intervention on Long Term Wt Loss: IDEA RCT JAMA 2016; 316: 1161

86

Genetics, Lifestyle & Coronary Artery Disease

- 3 cohorts, one cross sectional study for 20 years
- N = 55,655
- Results
 - Healthy lifestyle mitigates genetic determinates of coronary heart disease across all risk categories
 - Unhealthy lifestyle negates genetic advantage
- KharaAV. Genetic Risk, Adherence to Healthy Lifestyle on Coronary Artery Disease. NEJM. Org. Nov. 13, 2016

87

Nail in the Coffin of Fish Oil Supplements

- N = 78,000 meta-analysis of 10 large RCTs involving history of heart disease (66%), stroke (28%), diabetes (37%), lasting 4.4 years compared fish oil with placebo or no treatment
- Fish oil supplements did not reduce risk of coronary heart disease deaths, non-fatal heart attacks, fatal or non-fatal strokes, revascularization procedures, or all-cause mortality
- Also they did not protect against major vascular events in any subgroup including history of heart dz, statin use, high cholesterol
- JAMA Cardiology 2018, January

88

Nail in the Coffin of Fish Oil Supplements

- Aggressive way heart dz is treated today-statins, B-blockers, ACEI, ASA along with procedures to restore blood flow may explain the dwindling benefit of fish oil over time
- Small benefit noted in 2 subgroups
 - Recent heart attack – 10% reduction in cardiovascular mortal
 - Heart failure – 9% reduction in all cause mortality
- Focus – monitor BP, lipids, lifestyle, diet and 2-3 servings fish a week
- Seafood consumption is rising - represents 5% protein in US diet , far less than 20% recommendation

89

Hypertension

- Characterized by chronic elevation of BP to 130/80. Etiology unknown in 90-95% (essential hypertension). Consider a secondary correctable form of HTN in pts under 30 or those who become HTN after 55. Isolated systolic HTN (systolic>160) and diastolic <90 most common in elderly due to decreased vascular compliance.
- Secondary HTN – causes include renal artery stenosis, renal disease, coarctation of the aorta, pheochromocytoma, hyperaldosteronism (hypokalemia), other causes (thyroid disease, acromegaly, OCs, Cushing's syndrome)

JAM

90

Hypertension

- Laboratory tests – creatinine, BUN, UA, CXR, ECG (LV hypertrophy suggests chronicity of HTN), blood tests may include CBC, glucose, cholesterol, triglycerides, calcium, uric acid.
- Treatment – goal is control with minimal side effects on monotherapy if possible. First line agents include *beta blockers* (effective in young), *ACE inhibitors* (well tolerated with low frequency of side effects, angioedema, rash, or non-productive cough, contraindicated in pregnancy), *calcium channel antagonists* (direct arteriolar vasodilators, may cause bradycardia so avoid combination with B-blockers), *diuretics* (thiazides preferred over loop diuretics because of longer action), and *alpha adrenergic* receptor blockers.

JAM

91

Prehypertension

- Guidelines for Blood Pressure Control
 - JAMA 5.21.03 National Heart, Blood, Lung Institute
 - *45 million Americans have “prehypertension”*
 - *BP = 120-139/80-90*
 - Risks are MI, kidney failure, stroke, CHF
 - Many more patients are now candidates for drug treatment than previous
 - Many recent studies confirm a dramatic decrease in mortality and morbidity associated with decreased BP levels. *Systolic blood pressure is far more important* risk factor > age 50. Damage occurs at 115/75, with each 20/10 increase doubling mortality!

JAM

92

Hypertension

- New ACC/AHA Guidelines for Blood Pressure Control
 - JAmCollegeCardiology & Hypertension
 - *ELIMINATES category of “prehypertension”*
 - Damage occurs at 115/75, with each 20/10 increase doubling mortality!
 - Framingham proves 90% of those with normal BP at age 55 eventually develop HTN.
 - DASH (dietary approach to stop hypertension) is endorsed
 - Recommends home BP monitoring devices
 - White coat HTN is HTN
 - Start treatment with thiazide diuretic - Low cost, generic

JAM

93

Hypertension

- New ACC/AHA Guidelines for Blood Pressure Control
- Normal <120/80
- Elevated 120-129 and 80
- Stage 1 130-139 or 80-90
- Stage 2 140 or 90
- HTN Crisis >180 and/or >120
- 46% of all US adults have HTN with greatest impact on younger patients
 - Triples prevalence in men <45
 - Doubles prevalence in females <45

JAM

94

Hypertension

- Only need to prescribe for Stage 1 if pt had MI, CVA, or at high risk based on age, DM, CKD, or risk calculator
- Recognition of need for 2 or more prescriptions to achieve goals, combination drugs preferred
- Identifies socioeconomic status & psychological stress as risk factors for HTN
- New Guidelines developed with 9 professional health organizations, written by panel of 21 experts after review of over 900 published studies

JAM

95

Prehypertension

- The Truth About Salt
 - Institute of Medicine lowered daily sodium to 1.5g/d (3.8g/d of salt) from 2.4g/d.
 - Av individual US consumption is 4g/d! (1.5 teaspoon)
 - Americans consume 3/4ths salt from packaged food and fast food
 - Only 11% comes from salt added at the table
 - Reading labels is important as products vary in salt content
 - Campbell Soup Tomato has twice salt of Organic Valley Tomato
 - Burger King Sm Fries has three times salt of McDonalds fries

JAM

96

Thrombolytics for MI

- Acute Coronary Syndromes
 - Reteplase (Retavase)
 - Eptifibatide (Integrilin)
 - Tirofiban (Aggrastat)
 - ASA (Bayer) 325mg chewed STAT
 - Drug-eluting stents
- Prevention
 - ASA 81mg (only 1/3rd of 62 million at risk in US use ASA)
 - Reduces 1st MI risk by 32%, 2nd MI risk by 20%
 - Caution in “vigorous” exercise which can contribute up to 17% of all sudden cardiac deaths

JAM

97

A New Look at Aspirin

- New England Journal of Medicine Sept 16, 2018
- Aspirin in Reducing Events in the Elderly (ASPREE) Trial
 - N = 19,114 >65 years of age, 5 years of follow up
 - Large, NIH sponsored randomized, double-masked trial
- Risks & benefits of low dose daily ASA in adults without previous cardiovascular events evaluated
- ASA did not prolong life in healthy independent living
- Guidelines note benefit of ASA in preventing MI, stroke in CAD
- More bleeding events in ASA group
- Study did not address ASA effect in <65 year olds

JAM

98

Belimumab / Human Genome Sciences

- Indicated – treatment of adult lupus
 - 1st new treatment in 50 years!
 - ASA in 1948
 - Plaquenil & steroids in 1955
 - Humanized IG G1y monoclonal antibody
 - Inhibits human B lymphocyte stimulator
- Dosed – IV infusion, in conjunction with standard therapies (steroids, NSAIDs, antimalarials, immune drugs)
- Available as - *Benlysta*

99

Diabetes Mellitus (DM)

- Hyperglycemia caused by metabolic disorders, with Type I and Type II replacing terms insulin dependent (IDDM) and non insulin dependent (NIDDM)
 - Type I – insulin deficiency and tendency to develop ketosis
 - Type II – heterogeneous group characterized by variable degree of insulin resistance, impaired insulin secretion, increased glucose production. Other type endocrinopathies (Cushing's, pheochromocytoma, hyperthyroidism, acromegaly), drugs (corticosteroids), pregn
- 27% increase in DM from 1998-2002 (6.5% of pop.)
- Nearly half a billion worldwide incidence (50% undiag)
- 5 million deaths in US in 2017 (50% < age 60)
- \$327 Billion in 2017-US, (1-in-4 dollars) 26% inc (2012)

100

Diabetes Mellitus (DM)

- Diagnosis of DM
 - **Fasting glucose >126mg/dl**
 - Symptoms of diabetes and a random blood glucose of >200mg/dl after a 75g oral glucose tolerance test
- Intermediate categories ("Prediabetes") – not DM but at substantial risk of developing type II DM and cardiovascular disease in the future
 - **Impaired fasting glucose (IFG) - (100-126mg/dl) or HbA1c of 5.7**
 - **Impaired glucose tolerance (IGT) – (140-200mg/dl)**
- Screening with fasting blood glucose – every 3 years >45years, or sooner if additional risk factors

JAM

101

Risk Factors for Type II DM

- Family history of DM
- Obesity (>20% desired body weight)
- Age >45years
- Race / ethnicity – ex. African American, Hispanic, Native American, Asian, American, Pacific Islander
- Previous identified IFG or IGT
- History of GDM or delivery of baby >9lbs
- HTN
- HDL <35mg/dl and/or TG>250mg/dl
- Polycystic ovary syndrome

JAM

102

Treatment - Diabetes Mellitus

- Education, control of multisystem complications
- Target HbA1c <7.0% (*trending lower to 6.0-6.6%*)
- Type I DM require 1.0U/kg/D insulin divided into multiple doses, typically combining intermediate and short acting insulins, given before morning and evening meals or continuous subcutaneous insulin infusion device
- Type II DM controlled with diet and exercise alone or in combination with oral agents, insulin or combinations of oral and insulin.

JAM

103

Treatment - Diabetes Mellitus

- Metformin as initial therapy is reasonable because of efficacy, low side effects and cost. Metformin lowers insulin resistance, reduces weight, improve lipid profiles and does not cause hypoglycemia with monotherapy. Combinations of 2 oral agents have additive effects with stepwise addition of bedtime insulin or 3rd oral agent if needed. Insulin as in Type I when needed. If >1U/kg/D is needed, consider combination therapy with thiazolidinediones or metformin
- Morbidity and mortality can be greatly reduced by timely and consistent surveillance procedures
- Icahn School of Medicine – Mount Sinai, NY evidence that metformin may delay cognitive decline and AD even in non DM

JAM

104

Newest Treatment Guidelines - T2DM

- ACP Guidelines
- Personalize HA1c goals – harms of drugs, patient preferences, health, life expectancy, treatment burden, cost, benefits
- Aim for HA1c between 7-8% in most T2DM
- Consider de-intensifying therapy in pts w T2DM and HA1c <6.5%
- Treat T2DM to minimize hyperglycemia symptoms & avoid targeting A1c levels in pts with life expectancy of <10 yrs due to age, nursing home residence, or end stage chronic conditions
- In conflict with ADA and AACE who still recommend A1c<7

JAM

105

Oral Drugs For DM

- Sulfonylureas - 1st generation
 - Acetohexamide (Dymelor)
 - Chlorpropamide (Diabinese)
 - Tolazamide (Tolinase)
 - Tolbutamide (Orinase)
- Sulfonylureas - 2nd generation
 - Glimepiride (Amaryl)
 - Glipizide (Glucotrol)
 - Glyburide (DiaBeta / Micronase / Glynase)

JAM

106

Older Oral Drugs For DM

- New evidence suggests that patients using older sulfonylureas (SFUs) may have as high as 45% more MAJOR cardiovascular events like MI, stroke or CV death
- Some suggest this borders on malpractice given new evidence based findings
- Examples include glipizide, glyburide

JAM

107

Drugs For DM

- Insulin Preparations
 - Short acting
 - Regular
 - Lispro Insulin (Humalog)
 - Intermediate acting
 - NPH
 - Lente
 - Long acting
 - Ultralente
 - Glargine

JAM

108

Drugs For DM

■ Combination Insulin Preparations

- 75/25-75%
 - NPH, 25% regular
- 70-30-70%
 - NPH, 30% regular
- 50/50-50%
 - NPH, 50% regular
- Strategy is to exploit different onset of actions, peak of actions, and effective/maximum durations of actions by combining products

JAM

109

Insulin Sensitizing Agents - DM

- Thiazolidinedione – these insulin sensitizing drugs allow dosages of insulin to be decreased and combination therapy with oral agents to achieve better glycemic control in pts with HA1c >8, on >30U of insulin/day
 - Troglitazone (Rezulin)
 - Rosiglitazone (Avandia) *
 - Pioglitazone (Actos) *
 - Repaglinide (Prandin)
- New combination – Avandaryl qd
 - Rosiglitazone (Avandia) & Glimepiride (Amaryl)

JAM

110

Guidelines for Ongoing Care of DM

- Self monitoring of blood glucose
- HbA1c testing 2-4 times per year
 - Each 10% decrease HA1c = 39% reduction in progression of DR
 - Lower A1C as fast as possible! (better long term even if “fall off wagon”)
- Limit post-prandial hyperglycemia to <5hrs
- Patient education & Nutrition education
- Eye examination – annual
- Foot examination – annual
- Screening for diabetic nephropathy (urine albumin)
- Blood pressure – quarterly
- Lipid profile - annual

JAM

111

Guidelines for Ongoing Care of DM

- Exercise 30 minute per day preferable in morning
- Use coffee and tea
- Maintain Vitamin D >40mg, Omega-3 500 mg/ day, MV
- No smoking
- Decreased processed meats, add probiotics
- Sleep more than 6 hrs/day but less than 9 hrs/day
- Lower thermostat
- Less light at night
- Alternate fasting and Paleo diet if obese
- Plant based diet (Mediterranean, healthy oils, nuts, veggies)
- More fiber
- Breast feeding

JAM

112

Metformin as Initial Oral Therapy

- 11 drug classes available as initial monotherapy for type 2 DM with vast choice of therapeutic mechanisms, costs and side effects
- Dispite guidelines recommending metformin as initial drug of choice, 57.8% of individuals began treatment with metformin
- Beginning with metformin was associated with reduced subsequent treatment intensification, without differences in rates of hypoglycemia or other adverse effects
- JAMA Intern Med 2014;174(2) 1955

JAM

113

Saxagliptin

- Indicated – treatment of adults to improve control of Type 2 DM
- Dose – one daily (weight neutral)
- Significant reductions in HbA1c partnered with oral anti-diabetic agents
- Available as - *Onglyza*

114

Saxagliptin / Metformin

- Indicated – treatment of adults to improve control of Type 2 DM
- First and only daily metformin & DPP-4 inhibitor combination
- Dose – one daily (weight neutral)
- Significant reductions in HbA1c partnered with oral anti-diabetic agents
- Available as - *CombiglyzeXR*

115

Linagliptin

- Indicated – treatment of adults to improve glycemic control in type 2 DM
- Only DPP-4 inhibitor at one dose for adults
- Significant reductions in HbA1c partnered with oral anti-diabetic agents
- Not for use with insulin
- Available as - *Tradjenta*

116

SGLT2 Drugs for Type 2 DM

- Major Breakthrough in DM care, preventing major cardiovascular events (MACE)
- Use of any SGLT2 increase urinary glucose
- Reduces all cause mortality by 49%
 - Decreased MI by 19%
 - Decreases stroke by 32%
- ADA Guidelines recommend SGLT2 as 2nd line therapy for type 2 DM after metformin
 - Especially in patients with pre-existing CVD
- Available as
 - Invokana (canagliflozin)
 - Jardiance (empagliflozin)
 - Farxiga (dapagliflozin)
 - Steglatro (ertugliflozin)

JAM

117

Dapagliflozin

- Indicated – treatment of type 2 DM
- Sodium glucose co-transporter inhibitor
- Dose – 5mg once daily
- SE – UTIs
- Benefits of distinction – reduces cardiovascular disease risks
- Available as - *Farxiga*

118

Canagliflozin

- Indicated – treatment of type 2 DM
- Sodium glucose co-transporter inhibitor
- Dose – 5mg once daily
- SE – UTIs
- Benefits of distinction – reduces cardiovascular disease including MI, stroke and death
- Available as - *Invokana*

119

Empagliflozin

- Indicated – treatment of adults to improve glycemic control in type 2 DM
- Approved for decreasing risk of CVD deaths in T2DM adults with CVD
- Significant reductions in HbA1c partnered with oral anti-diabetic agents
- Not for use with Type 1
- SE – yeast infections of penus, vagina, dehydration
- Available as – *Jardiance*
- *Jardiance & Tradgenta combination - Glyxambi*

120

Ertugliflozin

- Indicated – treatment of type 2 DM
- Alone or in fixed combination with metformin (Seglunet)
- Alone or in fixed combination with sitagliptin (Steglujan)
- Sodium glucose co-transporter inhibitor (SGLT2) – 4th
- Reduces glucose reabsorption, increases urine glucose excretion
- Reduces HbA1c 0.5-1%, decreases BP systolic by 3-6mm
- Available as - Steglatro

121

Empagliflozin / Linagliptin

- Indicated – treatment of adults to improve glycemic control in type 2 DM
- First in class medication simultaneously inhibit 2 proven targets – SGLT2 & DPP-4
- Not for use with Type 1
- Contraindicated in kidney failure
- SE – yeast infections of penis, vagina, dehydration and importantly pancreatitis
- Available as - *Glyxambi*

122

GLP-1 Analog Drugs for Type 2 DM

- Major Breakthrough in DM care
- Drives better BG levels
- Easy once weekly injections!
- Available as
 - Victoza (liraglutide)
 - Ozempic (semaglutide)
 - Trulicity (dulaglutide)

JAM

123

Liraglutide

- Indicated – treatment of adults to improve glycemic control in type 2 DM
- Gut – slows gastric emptying
- Liver - lowers glucose output
- Pancreas – improves insulin secretion
- Significant reductions in H_{A1c} partnered with oral anti-diabetic agents
- Available as - *Victoza*

124

Dulaglutide Injection

- Indicated – treatment of type 2 DM, not a first line Rx
- Glucagon-like peptide receptor agonist (GLP-1RA)
- Helps body release more of its own insulin, but not a substitute for insulin injections (it is not insulin)
- May lose weight, improves A1C and blood sugar levels
- Dose – injection pen; 0.75mg/0.5ml, 1.5mg/0.5ml
once weekly
- SE – nausea, vomiting, diarrhea, decreased appetite, pancreatitis, kidney failure
- Available as - *Trulicity*

125

Semaglutide

- Indicated – treatment of adults to improve glycemic control in type 2 DM
- Once weekly injection
- Significant reductions in H_{A1c} partnered with oral anti-diabetic agents
- Available as - *Ozempic*

126

Lixisenatide Injection

- Indicated – treatment of type 2 DM, not a first line Rx
- Glucagon-like peptide-1 receptor agonist
- Increases glucode dependent insulin release, decreases glucagon secretion and slows gastric emptying
- Does not increase likelihood of cardiovascular events
- Dose – daily at mealtime
- **Disposable prefilled pen**
- SE – nausea, vomiting, diarrhea, dizziness, hyoglycemia
- Available as - *Adlyxin*

127

Insulin Glargine Injection

- Indicated – adults w DM
- Long acting beyond 24 hrs with stable levels
- No peaks or wear-off betw doses
- Significant reductions in HAlc
- 3 times as much insulin in 1ml compared with standard insulin
- Not for use w alcohol
- Available as - *Toujeo*

128

Continuous Glucose Monitoring (CGM)

- Not a pump, worn under skin
- Available as
 - DexCom G-6
 - Freestyle Libre
 - Guardian 670G
 - Eversense
- 1/3rd use CGM in US, 1-3% worldwide type 1 use
- Popular in type 2 DM
- Results in mean reduction in A1c of 1%, less dose, no hyperglycemia, able to predict trends (up or down) saving lives!

129

Dexcom G6 CGM

- Under skin for 10 days
- No blood sticks
- Medicare approved for
 - Multiple daily doses
 - Pumps
- Auto applicator
- Slim, data to smart phone
- Approved > age 2

130

FreeStyle Libre (Abbott Medical)

- Under skin for 2 weeks
- Flash Glucose monitoring
- Upper arm
- Reader over sensor for BG
- No calibration
- Type 1 and 2 approved MC
- On insulin approved
- \$108-\$150/mos if not covered

131

Medtronic MiniMed 670G

- Hybrid loop pump
- Adjusts dose every 5 mins
- Targets 140mg/dl
- Good choice if A1c>7
- Customer service poor
- High maintenance,
- Calibration issues
- Closest thing to natural pancreas
- Uses IBM “Watson”- create strategies for personal care

132

Eversense Sensor CGM

- Implanted under skin
 - subQ
- Under local anesthesia
- Lasts 3 months
- Not visible on surface
- Biocompatible
- Fluorescent glucose sensor
- \$7/day

133

OmniPod Horizon CGM

- Closed Loop System
- Tubeless 2 part pump
- Bi-hormonal delivery
 - Novalog
 - Pramlintide (Amylin)
- Increases TIR by 3 hr/D

134

Continuous Glucose Monitoring (CGM)

- “Time in Range” is becoming the newest and most important metric in DM care
 - How long (what % of day) is blood glucose between 70-180
 - HAlc is not the whole story
 - Staying in-range results in less hyperglycemic & hypoglycemic episodes, less hospitalization, lower cost, less death, much lower DR or progression of existing DR
- If lower A1c not possible, increase TIR! (want 72%)
 - Ex. of hypoglycemia
 - \$1.25billion spent on hospital care (2009)
 - Newest treatment is fast acting Nasal Glucagon (easy/fast/life saver)

135

Interesting Recent Findings in DM

- Idea of “Triple Therapy” advancing in respected researchers
- Three agents simultaneously initiated at diagnosis of Type 2 DM
 - Metformin
 - Byetta (exenatide)
 - Actos (pioglitazone)
- Significantly reduces A1C, carotid intima media thickness (CMT) and severe hypoglycemia after 6 years of follow up compared to metformin, add-on sulfonylurea and insulin (Lantus)

136

Interesting Recent Findings in DM

- Air pollution and DM
 - 14% of all DM worldwide is due to particulate air pollution and emission
 - NASA research
- Alternate daily fasting for remission of DM
 - J. Fung, MD Toronto
 - Low carbohydrate paleo-type diet alternate days
 - Fast alternate days
 - For individuals >40lbs above ideal body weight
 - Demonstrated remission of type 2 DM!
 - Can be transitioned to Mediterranean diet after achieving goals

137

Lorcaserin (Arena Pharm)

- Indicated – treatment of obesity & overweight patients with one related health problem (HTN, DM, cholesterol)
 - Obesity >30 BMI, Overweight >27 BMI
- Approved 2012
- Prescribed with reduced calorie diet & exercise program
- SE: “serotonin syndrome”-produce excess serotonin, agitation, diarrhea, sweating, fever, spasms, mental changes
 - Antidepressants and migraine medications additive to these SE
 - No heart valve problems
- Available as – *Belviq*

138

Phentermine / Topiramate (Vivus, Inc)

- Indicated – treatment of obesity & overweight patients with one related health problem (HTN, DM, cholesterol)
 - Obesity >30 BMI, Overweight >27 BMI
- Approved 7/18/12
- Prescribed with reduced calorie diet & exercise program
- SE – tingling of hands/feet, constipation, insomnia, taste perversion, dry mouth
- Contraindications – glaucoma, hyperthyroidism, recent heart disease, stroke
- Available as – *Qsymia* (3.75/23, 7.5/46, 11.25/69, 15/92)

139

Phentermine / Topiramate (Vivus, Inc)

- 2 clinical studies confirmed benefit
- One year results = 7-9% weight loss
- 62-69% = 5% weight loss
- Safety concerns?
 - *Phentermine was half of fenfluramine (Fen-Phen) linked to heart valve damage and taken off market 1997*
 - *13 billion settlement*

140

Macular Degeneration in AIDS

- AIDS patients have a four fold risk of AMD
- Accelerated aging is found in patients with AIDS
- Accelerated aging is a consequence of chronic immune activation and inflammation
- Average age of cohort is 40 years old
 - ALL had intermediate AMD
 - Not usually seen until after age 50 years old
- JabsDA. Prevalence of Intermediate Stage AMD in Patients with AIDS. AmJOphtal. 2015; 159:1115

141

Thank you

JAM
