New Insights on Common Problems—Pain Management and Diabetes Care

Activity Number: 0217-0000-16-149-L01-P, 1.50 hours of CPE credit; Activity Type: A Knowledge-Based Activity

Wednesday, October 26, 2016
9:45 a.m. to 11:15 a.m.
Great Hall 5

Moderator: Ann M. Philbrick, Pharm. D., BCPS, BCACP
Associate Professor, University of Minnesota College of Pharmacy, Minneapolis, Minnesota; Bethesda Family Medicine Clinic, St. Paul, Minnesota

Agenda

9:45 a.m.  Clinical Dilemmas in Pain Management—Transitions of Care, Opioid Misuse, and Symptom-Directed Pain Management
Chris M. Herndon, Pharm. D., BCPS, CPE
Associate Professor, Southern Illinois University Edwardsville, Edwardsville, Illinois

10:30 a.m.  Diabetes: New Ideas About an Old Disease and Its Complications
Brian K. Irons, Pharm. D., FCCP, BCPS, BCACP, BC-ADM
Professor of Pharmacy Practice; Division Head—Ambulatory Care, Texas Tech University Health Sciences Center, Lubbock, Texas

Conflict of Interest Disclosures
Chris M. Herndon: no conflicts to disclose
Brian K. Irons: no conflicts to disclose
Ann M. Philbrick: no conflicts to disclose

Learning Objectives

1. Discuss the pain management strategies in patients taking agonist-antagonist opioids in transitions to acute care settings.
2. Describe the impact of opioid rescheduling and state regulations of daily dose limitations.
3. Compare and contrast multimodal pain management strategies for common acute and chronic pain conditions.
4. Discuss the current evidence regarding drug treatment of pre-diabetes including factors associated with success.
5. Describe new mechanisms for diabetic macular edema and compare and contrast new therapies with older regimens.
6. Discuss current knowledge surrounding mechanisms for kidney complications of diabetes and new approaches to therapy.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am
Clinical Dilemmas in Pain Management
Transitions of Care, Opioid Misuse, and Symptoms

Chris Herndon, PharmD, BCPS
Southern Illinois University Edwardsville
Edwardsville, IL
Oct 26, 2016
cherndo@siue.edu

Conflict of Interest
No financial conflicts of interest to disclose

Learning Objectives
• Discuss the pain management strategies in patients taking agonist-antagonist opioids in transitions to acute care settings
• Describe the impact of opioid rescheduling and state regulations of daily dose limitations
• Compare and contrast multimodal pain management strategies for common acute and chronic pain conditions

The Problem......

7.3%

The other problem....

Meet Brent from MA
• Injured back in motor vehicle accident, 2009
• Numerous back surgeries without relief
• Currently takes 10-12 oxycodone 15mg tablets daily
• No other adjuvant analgesics
• Frequently runs out early

MA: Massachusetts
Is Brent a Drug Addict?

- Aberrant drug taking behaviors
  - any departure from prescription
- Misuse
  - departure with therapeutic intent
- Abuse
  - departure without therapeutic intent
- Addiction
  - Neurobiologic disease characterized by cravings, compulsion, withdrawal syndrome, and loss of control

MEDD:

- Aberrant
- KT,
- Neurobiologic disease

What went wrong with Brent?

Prescription opioids and heroin

- Quantitative questionnaire using street outreach, venue-recruitment, and needle-exchange advertisement (n = 123)
- Median age 29 yrs (75% male, 53% white, 28% Hispanic, 19% black or other)
- 39.8% reported problematic prescription opioid use prior to first heroin use
**Back to Brent**

- Turned to prescription opioids purchased on street
- Supplemented with heroin when necessary
- Sought treatment when wife threatened to leave
- Now on buprenorphine / naloxone SL 16-4mg daily
- Will eventually be weaned and transitioned to naltrexone

How does this complicate future acute pain control?

**MOR Binding Affinities & Displacement (not equianalgesic dosing)**

<table>
<thead>
<tr>
<th>Select Opioid</th>
<th>K, nM binding affinity</th>
<th>KD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>1.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>1.5</td>
<td>.18</td>
</tr>
<tr>
<td>Morphine</td>
<td>5.7</td>
<td>2.0</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>19.8</td>
<td>not found</td>
</tr>
<tr>
<td>Meperidine</td>
<td>193</td>
<td>not found</td>
</tr>
</tbody>
</table>


**Brent requires surgery....**

- Should buprenorphine / naloxone be stopped 3-7 days prior to surgery?
- Is buprenorphine / naloxone reasonable for acute pain control in Brent?
- What if he is on naltrexone?
- Methadone?

**What non-opioid alternatives could we offer Brent?**

- CBT: cognitive behavioral therapy
- NMDA: N-methyl-D-aspartate receptor
- TCA: tricyclic antidepressants
- SMRs: serotonin reuptake inhibitors
- NSAIDs: nonsteroidal anti-inflammatory drugs

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SNRIs
- Venlafaxine
- Desvenlafaxine
- Duloxetine
- Milnacipran
- Levomilnacipran

TCAs

<table>
<thead>
<tr>
<th>Tertiary Amines</th>
<th>Secondary Amines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nortriptyline</td>
<td>Imipramine</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Clomipramine</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>Clomipramine</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>Desipramine</td>
</tr>
</tbody>
</table>

Anticholinergic Activity, Kᵢ (nM)

SMRs
- Antispasmodics
  - Cyclobenzaprine
  - Methocarbamol
  - Baclofen
  - Dantrolene
- Antispasticity Agents
  - Tiagabine
  - Gabapentin
- Oral Anticonvulsants
  - All equally effective for short-term relief of low back pain
  - Not more effective than NSAIDs for acute low back pain
  - Poor supporting data

Topical Analgesics
- Lidocaine
- Capsaicin
- Diclofenac
- Nitroglycerin
- Select opioids
- Ketamine
- Amitriptyline
- Gabapentin
- Baclofen
- Many others with no supporting data

* must be compounded

Anticonvulsants with data in pain (excluding animal models)

<table>
<thead>
<tr>
<th>1st Generation</th>
<th>2nd Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Eslicarbazepine</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Ezogabine</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Levetiracetam</td>
</tr>
<tr>
<td>Valproate</td>
<td>Oxcarbazepine</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Zonisamide</td>
</tr>
</tbody>
</table>

MeSH terms used included “drug name” combined with “pain” or “neuropathy”
All entries reviewed on www.clinicaltrials.gov
Search performed 16 Aug 2016

NMDA Glu Receptor Antagonists
- Dextromethorphan
- Ketamine
- Memantine

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Back to Brent....

- Long term pain management should be multimodal
- Continuation of opioid maintenance therapy should be carefully considered given risk of recidivism
- Consider combination of non-opioid adjuvants / co-analgesics selected on patient-specific variables
- Absolutely incorporate CBT, physical therapy, and other non-pharmacologic modalities as tolerated
- DISCUSS REALISTIC TREATMENT GOALS / EXPECTATIONS
Diabetes: New Ideas About an Old Disease and Its Complications

Brian K. Irons, PharmD, FCCP, BCACP, BC-ADM
Professor and Division Head – Ambulatory Care
Texas Tech University Health Sciences Center – School of Pharmacy

October 26th, 2016

Learning Objectives

1. Review alternative prognostic biomarkers and approaches to care of diabetes kidney disease
2. Describe new mechanisms of diabetic macular edema and compare and contrast new therapies with older regimens
3. Discuss the current evidence regarding drug treatment of pre-diabetes including factors associated with success

Diabetic Kidney Disease

Diabetes Kidney Disease: Prognostic Biomarkers

- Kidney damage/progression due to diabetes is multifactorial – oxidative stress primary factor
- Albuminuria not very sensitive / specific marker for progression of nephropathy
  - Better screening tool for identifying/detecting damage than actual progression
- How to ID patients with DM at greatest risk for vascular complications / progression of disease?
  - Varying degree of susceptibility to DM complications
  - Familial aggregation of DM complications
  - Genetic susceptibility very likely
  - ? Difference in genetic antioxidant capacity?

Haptoglobin (Hp) Genotype in Diabetic Nephropathy

- Hp binds ‘free’ hemoglobin (key factor in oxidative tissue damage)
- Two most common Hp alleles (1 and 2)
- Genotypes: Hp 1-1, Hp 2-1, Hp 2-2
  - Leads to different Hp protein polymers with varying degree of hemoglobin affinity
  - Hp 1-1 (dimer) >> Hp 2-1 (linear polymer) >> Hp 2-2 (cyclic polymer) in Hgb affinity
- Prevalence: Hp 1-1 ~ 15%, Hp 2-1 ~ 45%, Hp 2-2 ~40%

Conflict of Interests

Dr. Irons has no conflicts of interest to disclose
Haptoglobin (Hp) Genotype in Diabetic Nephropathy

- Hp Genotype between patients with and without DM not different
- DM patients Hp genotype (Hp 2-2) may determine susceptibility to vascular complications (NOT seen in patients without DM)
  - More susceptible to LDL oxidation?
  - Accelerated endothelial dysfunction/injury?
  - Hemoglobin penetration in glomerulus increased?
  - Function of glycosylated hemoglobin-Hp interaction?

Haptoglobin Genotyping Ready for Prime Time?

- Some ethnicities may be affected while others are not?
- Could antioxidant therapy (e.g. Vit E) be simple (and cheap) intervention in genetically susceptible DM patients to limit kidney damage??
- 2016: new commercially available testing for Hp genotype

Other Potential Biomarkers: microRNAs

- Short, noncoding RNA regulate gene expression
- Binds to target messenger RNAs, complex can result in loss of protein expression
- Transforming growth factor (TGF)- β1 = known pathogenic cytokine in DM nephropathy
- Serum TGF- β1 regulated miRNAs (5 types)
  - 2 found to be associated with significant increase in nephropathy progression in T1DM
  - 2 found to be associated with a 50% less chance of nephropathy progression
- Need for large studies to assess real sensitivity/specificity
- ? Intervention if found to be highly sensitive?

Other Potential Biomarkers: Haptoglobin

- Urine haptoglobin: creatinine levels
- As a single biomarker only marginally better to level of albuminuria:creatinine
- Together (urine Hp:Cr and Alb:Cr) provide for increased sensitivity to predict early renal fxn decline
  - But not more specific
- Same issue of larger sensitivity/specificity and what to do with it to intervene?

Hp 2-2 Association with Nephropathy

- Type 1 DM: Epidemiology of Diabetes Complications (EDC) 2009 study and DCCT/EDIC 2013 study
  - Hp 2-2 associated with higher risk for eGFR decline and progression to ESRD compared to Hp 1-1 (not associated with urine albumin concentrations)
- Type 2 DM: Smaller studies
  - Egyptian and Israeli Studies: Higher Hp 2-2 in pt with macroalbuminuria
  - No association in Japanese, Brazilian, or Spanish patients
  - ? Power / Limitations

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Diabetes 2015;64:3063  Diabetes 2015;64:3285

Kidney International 2013;83:1136
**Diabetes Kidney Disease**

**Is there a role for statins here too?**

- Not a new concept per se
- Dyslipidemia = risk factor for both development and progression of diabetes kidney disease
- Possible pleiotropic effects beyond cholesterol
- Improved endothelial function
- Reduced inflammation

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**PLANET Studies**

- Randomized, double-blind, parallel-group
  - Multinational, 52 week study
- Planet 1: 353 T1 or T2DM patients with urine protein:creatinine (PCR) 500-5000 mg/g (mean 1200)
- Planet 2: Similar but without DM (n=237)
- In addition to ACE-1 or ARB tx
  - Rosuvastatin 10 mg(n=107) or 40 mg (n=116)
  - Atorvastatin 80 mg (n=102)
- Primary Endpoint: Change in urine PCR from baseline

*Lancet Diabetes and Endocrinology 2015;3:181-190*

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**Diabetes Kidney Disease**

**Is there a role for statins here too?**

- Rosuvastatin reduced eGFR while Atorvastatin no sig dif despite better LDL reduction
- Lot of limitations to PLANET Studies
  - PLANET 1 not powered for between group differences
  - Not very large study and not placebo controlled

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**Diabetes Kidney Disease**

**Is there a role for statins here too?**

- Older data suggesting no or mixed effect have big limitations
  - Meta-analyses (mixed results, not DM focused)
  - Cochrane review (‘uncertain effects’)
  - Post-hoc data from CVD studies (e.g. CARDS,TNT)
- Prospective studies
  - Small n / Varying degrees of proteinuria
  - Most not specific to DM patients
- Need for studies specific to patients with DM and increased albumin excretion

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**PLANET Studies**

(% change from baseline PCR)

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**Diabetes Kidney Disease**

**Is there a role for statins here too?**

- Can’t crucify rosuvastatin
  - Drop in eGFR similar to estimated yearly decline
  - Some prospective short-term data specific to DM
  - No change in eGFR but did decrease urine albumin excretion rates
- Need for large, placebo-controlled and comparative data between statins on robust nephropathy outcomes (change in eGFR, doubling Cr rate to ESRD etc)
Diabetic Macular Edema

Diabetic Macular Edema (DME) Treatments
- Photocoagulation shown to be effective in reducing risk of severe vision loss in DME since the 1980s and remains common intervention
- Some benefit in decreasing macular thickness too
- Vitrectomy (usually reserved for tx failures)
- Limitations
  - Not effective in reversing existing vision acuity problems
  - Laser scarving, visual field defects, retinal fibrosis

Newer DME Agents – Intraocular Steroid Therapy
- Intravitreal triamcinolone acetonide (IVTA) injections
  - Frequency of injection ~16 weeks
  - Short-term benefit compared to photocoag
- Vitreal steroid implants (slow, sustained release): 2014 approvals
  - Fluocinolone acetonide (36 months of drug release)
  - Dexamethasone (36 months of drug release)
  - Lower frequency of intervention

Other DME Treatment Options
- Intravitreal NSAID (diclofenac)
- Comparable reduction in macular thickness and visual acuity to IVTA
- Benefit over IVTA: Reduced IOP

Diabetes and Sight-Threatening Complications
- Diabetic retinopathy
  - Proliferative
  - Non-proliferative
- Retinal artery/vein occlusions
- Retinal detachment
- Diabetic macular edema (DME)
  - ~7-12% of DM population (>25% with DM > 20 years)
  - 1-3% with visual impairment
  - Primary cause of vision loss from DM retinopathy
- Very dependent on the duration of DM, glycemic and blood pressure control
Bevacizumab

Role of Vascular Endothelial Growth Factor (VEGF) in DME

- Lowered retinal blood circulation from DM stimulates retinal cytokine VEGF
- VEGF stimulates new blood vessel production in the retina (angiogenesis)
- New vasculature of tiny, fragile blood vessels >> leak, bleed and increase fluid accumulation in the retinal macula (key to central and color vision) = DME

Anti-VEGF Therapy in DME

<table>
<thead>
<tr>
<th>Agent</th>
<th>MOA</th>
<th>FDA approved for DME?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranibizumab</td>
<td>Monoclonal antibody binds to all VEGF isoforms / fragments</td>
<td>Yes (2014)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>As above</td>
<td>No</td>
</tr>
<tr>
<td>Afibercept</td>
<td>Recombinant protein also binds all VEGF isoforms/fragments</td>
<td>Yes (2014)</td>
</tr>
<tr>
<td>Pegaptanib</td>
<td>RNA aptamer binds selectively to VEGF-165 isoform</td>
<td>No</td>
</tr>
</tbody>
</table>

Anti-VEGF vs Laser vs IVTA: (1 yr outcomes)

- Visual Acuity Change
  - Laser Alone: 25
  - Ranibizumab + Laser: 10
  - IVTA + Laser: 5
  - NS

- Retinal Thickness Change
  - Laser Alone: -140
  - Ranibizumab + Laser: -80
  - IVTA + Laser: 0

Relative Efficacy Between Anti-VEGFs (1 year)

- Visual Acuity Change (all)
  - Aflibercept: 14
  - Bevacizumab: 10
  - Ranibizumab: 6

- VA Change with poor baseline
  - Aflibercept: 15
  - Bevacizumab: 10
  - Ranibizumab: 5

Anti-VEGF Risks/Limitations

- More Common
  - Increased IOP shortly after injection
  - Conjunctival hemorrhage, eye pain, vitreous floaters
- Rarer
  - Posterior vitreous detachment – Suggest using IVTA or implants if exists at baseline
  - Endophthalmitis (general ocular tissue inflammation)
  - ? Increased cardiovascular risk?
- Frequency of dosing – Effects are limited in duration
- Cost: Ranibizumab and aflibercept >>>> Reformulated bevacizumab

Anti-VEGF for Proliferative DM Retinopathy

- Photocoagulation standard for 40+ years
  - Most retinal specialists use as initial tx (w/o DME)
- Compared to photocoagulation (JAMA 2015;314:2137)
  - Similar visual acuity changes
  - Less frequent vitrectomy frequency
  - Less likely to progress to DME
- Who to use one or the other treatment??
  - Must be adherent to anti-VEGF therapy else will increase risk advanced retinopathy / vision loss
  - Panretinal laser photocoagulation may have better chance for sustained success
Screening and Control Still Key
- DME can be preventable
- Appropriate screening key to identifying early disease
- Glycemic control
- Blood pressure control
- Lipid control?

Haptoglobin Genotype in Retinopathy
- Less data than with nephropathy / CVD
- Mixed results
  - Several studies show association Hp2-2 and retinopathy or a protective association with Hp1-1
  - Mostly small studies (45-100)
  - Some show no association
  - Still likely an ethnic factor in determining Hp 2-2 risk
- Prospective study with antioxidant therapy to prevent development or progression of retinopathy needed

Prediabetes
- Current CDC estimates suggest 37+% of US adults have pre-DM
  - 86 million US adults / 90% unaware
- Pre-DM should be considered a disease or risk factor?
  - Development Type 2 DM
  - Early kidney and retinal damage
  - Increased hospitalization rates

Issues / Problems in Diabetes Prevention
- Diet/Exercise work to reduce risk T2DM development
  - Few are successful long-term
  - < 25% of pre-DM patients receive ‘treatment’ (often limited to counseling on lifestyle)
- Medications work: Different mechanisms
  - Reducing obesity
  - Improving beta-cell function or insulin sensitivity
  - Reducing degree of hyperglycemia

Issues / Problems in Diabetes Prevention
- TZDs, glucosidase inhibitors, metformin effective
  - Stop the medication, rate to develop T2DM returns to pre-intervention rates
  - Timeframe is medication dependent
- Metformin underutilized
  - Well tolerated and cheap
  - As little as 3.7% of eligible patients receive it
  - Dose rarely optimized (want DPP dose 850 mg bid)
Lifestyle and/or DM Meds in PreDM

<table>
<thead>
<tr>
<th>Study</th>
<th>n'</th>
<th>Duration (yr)</th>
<th>Risk Reduction to DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Prevention Program (DPP)</td>
<td>3234</td>
<td>2.8</td>
<td>Lifestyle: 58%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Metformin: 31%</td>
</tr>
<tr>
<td>Finnish Diabetes Prevention Study (FDPS)</td>
<td>522</td>
<td>3.2</td>
<td>Lifestyle: 58%</td>
</tr>
<tr>
<td>STOP-NIDDM</td>
<td>714</td>
<td>3.3</td>
<td>Acarbose: 25%</td>
</tr>
<tr>
<td>ACT NOW</td>
<td>602</td>
<td>2.4</td>
<td>Pioglitazone: 72%</td>
</tr>
</tbody>
</table>

Diabetes Prevention vs Delay

• True prevention = zero progression to T2DM
• Landmark studies show continued rising risk
• Some subsets of patients show minimal progression
  • Very compliant with lifestyle modifications
  • FDPS: Near zero progression if compliant with 4 or 5 goals tx
  • DPP: > 90% reduction in DM w/ wt loss and lifestyle targets met

Diabetes Prevention

• Factors associated with intervention success
  • Long-term adherence (lifestyle and/or meds)
  • Lifestyle Intervention: Degree of weight loss and lower baseline impaired glucose tolerance
  • Metformin: Higher BMI and lower FBG
  • TZD: Greatly improved insulin sensitivity

Diabetes Prevention

• Issues we still want answers to:
  • Impact on future DM or CVD related hard outcomes
  • Implications to future glycemic control success
  • Ultimate success will require societal changes in disease prevention
  • 2016 push to increase awareness

Anti-obesity Agents and Diabetes Prevention

• Reduced weight a key factor in intervention success (if maintained)
• Many would rather take a pill than change diet/exercise to the degree needed for sustained weight loss
• Increased number of anti-obesity agents approved in the last few years
### Existing Chronic Anti-Obesity Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat (Zenical/Alli)</td>
<td>Gastric lipase inhibitor</td>
<td>2007</td>
</tr>
<tr>
<td>Lorcaserin (Belviq)</td>
<td>Selective serotonin 2C agonist</td>
<td>2012</td>
</tr>
<tr>
<td>Phentermine / Topiramate</td>
<td>Sympathomimetic amine anorectic / antiepileptic</td>
<td>2012</td>
</tr>
<tr>
<td>(Qsymia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naltrexone/Bupropion</td>
<td>Opioid antagonist / dopamine reuptake inhibitor</td>
<td>2014</td>
</tr>
<tr>
<td>(Contrave)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide (Saxenda)</td>
<td>GLP-1 Agonist</td>
<td>2014</td>
</tr>
</tbody>
</table>

### Anti-Obesity Agents in PreDM (Subgroup or post hoc analyses)

<table>
<thead>
<tr>
<th>Agent/Study</th>
<th>N</th>
<th>Duration (yr)</th>
<th>% patients with &gt;5% weight loss</th>
<th>DM-Related Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat (Zenical/Alli)</td>
<td>3,465</td>
<td>4</td>
<td>53</td>
<td>37% reduction in development of DM</td>
</tr>
<tr>
<td>Lorcaserin (Belviq)</td>
<td>1,265</td>
<td>1</td>
<td>56</td>
<td>36% reduction in development DM</td>
</tr>
</tbody>
</table>

### Anti-Obesity Agents and Diabetes Prevention: Issues

- Considered chronic medications
- Quit medications the weight comes back
- Long-term safety and efficacy unknown
- Costly mode of treatment
- Impact on hard DM and CVD-related outcomes needed

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Questions ???