Critical Appraisal of Drug Studies 6

A) Is the study valid? 6
1. Were patients randomized to treatment (tx) groups & was allocation concealed (AC)? (Without concealment, 37% bias in favor of tx)
   - Sealed, opaque envelopes or central registry used to attain AC) 6,9
2. Was everyone patients, physicians, investigators, assessors blinded to tx? (Especially important for assessors of subjective outcomes eg. Pain.)
3. Was the study controlled? (e.g. inclusion of placebo or active control group/arm; in an 'N of 1’ trial, patient is own control.)
4. Were treatment differences in prognostic factors for outcome of interest at beginning of study? If not, were adjustments made? Were all patients accounted for at end? (Missing patients addressed?)
6. Was data analyzed based on groups patients were initially randomized to? (Intent to treat or ITT: protects integrity of prognostic randomization; per protocol (PP) analysis may also be of interest (e.g. non-inferiority trials)
7. Were patient groups treated similarly except for study intervention?
8. How was the study funded? (Role of funding?) Was study stopped early?
9. Was active comparator drug & dose a good choice?

B) What are the study results?
1. What was the primary (1st) endpoint? What were the secondary (2nd) endpoints? Were endpoints & subgroups pre-specified? Avoid data mining
2. What was the difference between treatments? (Benefits & Harms)
3. What were the differences statistically significant? Clinically significant?
   - (What were the 95% confidence intervals (CI) or p values? Does the CI cross line of no effect?)
4. What are the absolute and relative risk reductions or increases?
5. What number needed to treat (NNT) or harm (NNH)?

C) Does this study matter to my patients?
1. How clinically relevant/importance are the outcomes?
2. Were the patients similar to those in my practice? (Consider inclusion & exclusion criteria; very sick, old, young, drug interactions & complicated/comp Morbid patients often excluded.)
3. Do treatment benefits outweigh the risks, costs & impact on life?

Types of Studies (from low to high level of evidence) 11

- Case-control study: a retrospective observational study which selects patients with the outcome of interest (cases) & patients without that outcome (controls); attempts to find exposures linked to the outcome.
- Cohort study: an observational study in which two groups (cohorts) are observed over time for an outcome of interest. One cohort has exposure to a condition or treatment that the other does not.

Strength of association: RR: 1:01-1:5 weak, 1:51-3: moderate, >3: strong 12

- Cross-sectional study: a design in which each patient receives both treatments in two phases separated by a washout period. Each patient serves as own control, thus smaller variability in outcomes, & smaller sample size required; period effects may limit findings.
- Randomized controlled trial (RCT): a prospective study in which patients are randomized to treatment or control groups (equal chance being assigned to any group). Groups are followed for outcome of interest.

- Systematic Review (SR): a systematic collection, review & presentation of available studies addressing a clinical question using specific criteria & methods; may include meta-analysis. e.g. Cochrane 10 & Campbell 14 Reviews

(Meta-analysis: the combining of studies meeting prespecified criteria & addressing a clinical question. Results are calculated from the data of each study. Data is then pooled. % sample size & statistical power useful if individual trials underpowered or subgroup analysis.)

Level of evidence: SR > RCT > observatory study > expert opinion.

Caution: Lots of low quality RCTs may not be better than a good quality RCT!

A low quality SR, or a SR of low quality trials does not constitute high-level evidence. 10,14

Do the study results matter to me & my patients?

- Clinical significance vs statistical significance: some studies may detect extremely small statistically significant differences between groups, however magnitude of effect (e.g. NNT) may be too small to make clinical change practice. Evaluate both 1) the endpoint, & 2) the NNT or NNH. (e.g. small cognitive score improvement not noticeable to patient.22,23

- Composite endpoints: combining endpoints can increase a study’s power allowing for smaller or shorter trials. Outcomes should have similar value. Examination of individual outcomes can be important in interpretation as one endpoint may be the primary driver. (e.g. in DREAM, outcome of diabetes diagnosis is the primary; death example of unequal endpoints. 21

- Surrogate endpoints: surrogate endpoints are related to biomarkers correlated with another endpoint (e.g. BP/IDL/1A1c for CV; CD4 cell count for HIV mortality). Clinical outcomes are more important since surrogate endpoints assume correlation with an outcome which may or may not always be true. 26 (e.g. lower A1C target in ACCORD; but 7 day, doxazosin ↓ BP ALATE instead of ↑HFistroke, & clorfenapine WHO-CLOF ↓ LDL but ↑ death.)

- Other considerations: What uncertainties remain? Has drug been studied in enough patients to detect serious rare adverse events? What duration of intervention is studied & what are the potential benefits & risks over a longer term of exposure? Does real-world experience appear to be consistent with clinical trial data? Cost? How benefits & risks are described will also affect decisions. 27

- What patient specific and societal values need to be considered?

Heads Up! Know what the numbers are telling you.

- Beware of the Relatives 10
  - Benefits are often given as relative numbers, whereas harms are often given as absolute numbers. This tends to exaggerate benefits & minimize the harms. 20 Look for NNTs & NNHs.
  (e.g. Vioxx monograph 2004: reported ~ 10% in GI complications with Vioxx vs older drugs. vs 0.93% Diclofenac vs 0.6% naproxen. Actual GI complications reductions 0.59% vs 1.37% (ARR=0.78; NNT=129); whereas thrombotic risk was worse (NNH=83).) (e.g. Oral contraceptives: risk of DVT in a younger, non-smoking woman may be 1/3000 but absolute risk is 1/50,000 & lower than risk in pregnancy.

- Non-Equivalent Durations & Risk/Benefit Perception
  - Benefits are often given for total duration of trial which may be several years, whereas harms are often given per year. (e.g. UKPDS-33: aggressive glucose control benefit on microvascular endpoints given to all patients; the risks of hypoglycaemia were given per year. 29

- Analysis: Pooling Together or Dividing Out
  - Discussing the multiple benefits of a composite endpoint while individually sorting out risks may minimize risk perception. (e.g. In WHI, risk of just breast CA with HRT was 8/100,000 per year; yet risk of any harm (DVT, CHD, stroke, PE & breast cancer) was 16/6 per 5 yrs.) 4,19

Calculated Examples: 1 yr trial

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<td>RR</td>
<td>(0.20 - 0.15)/0.20 X 100</td>
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</tr>
<tr>
<td>ARR</td>
<td>20% = 15% = 5%</td>
<td>20%</td>
</tr>
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<td>100 / 5%</td>
<td>20</td>
</tr>
<tr>
<td>NNH</td>
<td>100 / 33%</td>
<td>33</td>
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| NNT | 100 / 5% | 20 |
| NNH | 100 / 33% | 33 |


EVIDENCE-BASED MEDICINE (EBM) Overview: Notes on Validity, Precision & Contextualization of Results 12,3,4,5

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For references & downloadable info see: http://www.who.int/medicines/clinical trials/choice.pdf - in English
**Hypoglycemia**

ANTI-EFFECT ON WEIGHT

- ↓ Outcomes*
- ↓ Risk of HF findings/

Other comparisons between agents have not been done so one is left to evaluate each drug for its relative ad

**Risk of Death / Major CV†**

- ↓ MACE vs MF NNH=12/3yr (SPREAD-MICAD)
- ↓ MACE NNT=50/2.9yr, but 1° composite NS (RhypTIVCE)
- ↓ MACE (RIS) (pts with insulin resistance & recent CV/TIA)
- ↓ in IFG, MACE NNT=40/3.3yr, vs established CVD (Chinese) NS
- SAVOR-TIMI 53, TECOS, EXAMINE PROLOGUE, CARUMELINA, CAROLINA

**Risk of Hypoglycemia**

- ? less risk with MR formulation
- ? Severe, occurs at 1.4%/yr
- Low risk with monotherapy
- ? Risk when given with sulfonylurea or insulin
- ? XX Rate of 1.8%/yr

**Risk of HF /Edema**

- ↓22,23 1st line in HF with eGFR >30 mL/min (DCI18)
- ↓34 XX26 ↓ HF NNH=82/3.9yr edema NNH=8/2.3yr
- ↓25,27 XX25,27 ↓ HF NNH=15/3.5yr (RECORD), ↓ HF NNH=24/7yr (DREAM)
- ↓29 X730 ↓ HF saxagliptin NNH=14/2.3yr (SAVOR-ADOPT), liraglutide, sitagliptin & linagliptin + HF neutral
- Neutral: exenatide (EXSCEL), liraglutide (LEADER), lixisenatide (LIXEVA), dulaglutide (REWIND), semaglutide (SUSTAIN, PIONEER)
- ↓32 L-HF hospitalizations, empagliflozin (EMPA-REG) & canagliflozin (CANVAS)

**Effect on GL tolerability**

- X Start low & titrate
- ? rate of 1.8%/yr
- Nausea, vomiting, diarrhea
- Nausea/diabetes with dapagliflozin

**Cost**

- X X X X X X

**Other**

- X FDA +/- HC warning: 35 ↑ HF (see above), ↑ fractures (VITAL-WT, 30.5%)
- ↑ macular edema (conflicting data)
- Pjo: ↑ bladder ca >12 mos (27.5% excess/100,000 person yrs), avoid co-admin with dapagliflozin 36
- ⭐️ Resticted access in CDN (SK-EDS) (+ CV risk concerns) 37
- X TID dosing

**Overall**

- ? X

---

*Drugs that lower blood glucose come with various levels of evidence regarding their balance of benefits & harms. This chart relies on current evidence, especially from randomized controlled trials that have evaluated patient-oriented outcomes. Direct comparisons between agents have not been done so one is left to evaluate each drug for its relative advantages & disadvantages. **AIC** will vary depending on dose, combinations & initial AIC. **See next page for breakout GLP-1 & SGLT-2 data. See full version of this ANTI-HYPERGLYCEMIC DIABETES AGENTS: Outcomes Comparison Summary Table online for additional notes: [http://www.rxfiles.ca/rxfiles/uploads/Documents/Diabetes/AntiDiabetes-Comparison-Summary-Table.pdf](http://www.rxfiles.ca/rxfiles/uploads/Documents/Diabetes/AntiDiabetes-Comparison-Summary-Table.pdf). Also Boussageon et al. Meta-analysis. BMJ 2011;343:d4169)
**Glucagon-like peptide-1 (GLP-1) agonists**

- **Sitagliptin**: 50mg po daily
- **Saxagliptin**: 5mg po single daily
- **Linagliptin**: 2.5mg po daily
- **Alogliptin**: 4mg po double daily

**Initial Dose**
- Sitagliptin: 50mg po daily
- Saxagliptin: 5mg po single daily
- Linagliptin: 2.5mg po daily
- Alogliptin: 4mg po double daily

**Adverse Events**
- **Gastrointestinal**
  - Nausea, vomiting, diarrhea
- **Hypoglycemia**: For T2DM, may require ↓dose; For T1DM, with insulin may require ↓dose
- **Kidney**: ↑creatinine, ↑BUN
- **Liver**: ↑LFTs, hepatitis, liver failure
- **Pancreatic**: ↑pancreatitis
- **Skin**: ↑urticaria, ↑angioedema
- **Other**: ↑hypovolemia/hypotension, ↑urinary retention

**Contraindications**
- **Severe hepatic/renal impairment**: Use alternative agent
- **CNS depression**: Use alternative agent
- **Lactation**: Use alternative agent

**FDA-Approved Indications**
- Sitagliptin: T2DM: mono or combo ther with other T2DM agents
- Saxagliptin: T2DM: mono or combo ther with other T2DM agents
- Linagliptin: T2DM: mono or combo ther with other T2DM agents
- Alogliptin: T2DM: mono or combo ther with other T2DM agents

**Additional Considerations**
- Sitagliptin: Avoid with DPP-IV inhibitors (esp saxagliptin & sitagliptin)
- Saxagliptin: Avoid with DPP-IV inhibitors (esp saxagliptin & sitagliptin)
- Linagliptin: Avoid with DPP-IV inhibitors (esp saxagliptin & sitagliptin)
- Alogliptin: Avoid with DPP-IV inhibitors (esp saxagliptin & sitagliptin)

**Sodium-glucose co-transporter-2 (SGLT-2) inhibitors**

- **Canagliflozin**: 100mg po daily
- **Empagliflozin**: 10mg po daily

**Initial Dose**
- Canagliflozin: 100mg po daily
- Empagliflozin: 10mg po daily

**Adverse Events**
- **Urinary tract infection**: ↑frequency, ↑duration, ↑urgency, ↓volume
- **Decreased libido**: Women: ↑menstrual bleeding, ↓menstrual flow, ↓menstrual cycle
- **Ketoacidosis**: Most data liraglutide (Ketoacidosis may require ↓dose)
- **Other**: ↑hypoglycemia, ↑dizziness, ↓bone density, ↓renal function

**Contraindications**
- **Severe hepatic/renal impairment**: Use alternative agent
- **CNS depression**: Use alternative agent
- **Lactation**: Use alternative agent

**FDA-Approved Indications**
- Canagliflozin: T2DM: mono or combo ther with other T2DM agents
- Empagliflozin: T2DM: mono or combo ther with other T2DM agents

**Additional Considerations**
- Canagliflozin: Avoid with DPP-IV inhibitors (esp saxagliptin & sitagliptin)
- Empagliflozin: Avoid with DPP-IV inhibitors (esp saxagliptin & sitagliptin)

**Saxagliptin**: 5mg po daily

**Initial Dose**
- Saxagliptin: 5mg po daily

**Adverse Events**
- **Gastrointestinal**: ↑diarrhea, ↑vomiting, ↓appetite
- **Hypoglycemia**: T2DM: may require ↓dose; T1DM: with insulin may require ↓dose
- **Kidney**: ↑creatinine, ↑BUN
- **Liver**: ↑LFTs, hepatitis, liver failure
- **Pancreatic**: ↑pancreatitis
- **Skin**: ↓urticaria, ↓angioedema
- **Other**: ↓hypovolemia/hypotension, ↓urinary retention

**Contraindications**
- **Severe hepatic/renal impairment**: Use alternative agent
- **CNS depression**: Use alternative agent
- **Lactation**: Use alternative agent

**FDA-Approved Indications**
- Saxagliptin: T2DM: mono or combo ther with other T2DM agents

**Additional Considerations**
- Saxagliptin: Avoid with DPP-IV inhibitors (esp saxagliptin & sitagliptin)
A) General Considerations

1) Determine if the goal of dose reduction is reasonable (e.g. opioids have demonstrated some benefit), if complete discontinuation is more suitable (e.g. trial has been highly problematic/ineffective, or opioid induced hyperalgesia is a concern) or if patient presents with an opioid use disorder where a switch to opioid agonist therapy may be indicated.

2) If goal is to reduce dose, option to taper further & more gradually may be considered at a later point. Tapering plan may be paused/reassessed at any point if pain/function worsens or withdrawal symptoms persist for 1 mos or more. However, the “hold off on further taper & plan to restart taper” conversation should usually have a designated endpoint and be one conversation, not two!

3) Gradual tapers can often be completed in 1-6 months; some may benefit from a longer time frame of 12-24 mos. Literature & opinion varies. Some may benefit from opioid agonist therapy.

4) Set a start date! Initial reductions in daily dose in the range of 5-10% every 2-4 weeks may be reasonable. Once 1/3 of the original dose is reached, smaller dose reductions (e.g. 5% every 4-8 weeks) may be more optimal for a successful taperer. (May require a formulation change).

5) Long-acting formulations that offer small dose increments are useful for more gradual tapers once in the lower end of the dosage range. (Examples: morphine long-acting: M-ESLON 10mg cap q12h, KADIAN 10mg or 20mg cap q24h)

6) More rapid tapers are possible & sometimes desired. Use of an opioid withdrawal scale (e.g. SOWS, COWS) & corresponding protocols may be recommended, allowing for successful withdrawal within 1-2 weeks. (See links)3,3

7) Given the complexities in some cases, discussion with experienced colleagues & an interdisciplinary approach may help optimize management. Continue to use “best practice” tools (e.g. functional assessment, Opioid Manager, from Canadian guidelines, urine screen drugs, etc).

B) Timeline & Tips for Stopping or Tapering

- Allow for gradual dose reductions: e.g. q3 day, weekly, bi-weekly or monthly. Reassess as necessary. In general, the higher the dose & longer the duration of previous opioid therapy, the more time should be allotted for tapering.

- Consider switching to 50-75% of the MED of an alternate opioid +/- further taper

- May consider cross-over switch/rotation taper: e.g. switch to alternate opioid at MED of 50-75% equivalent dose (lower dose accounts for incomplete cross tolerance). Slowly over ~4 weeks up-titrates new opioid to ~50% MED/d while tapering off previous opioid.

- Tapering the last 20-60mg/day morphine equivalent (MED), may require more time.

C) Opioid Withdrawal Symptoms (See table to the right.)

- Many of these symptoms may not be seen with a more gradual taper!

- Physical withdrawal symptoms generally resolve over 5-10 days.

- Psychological withdrawal symptoms (dysphoria, insomnia) may take longer.

D) Management of Other Withdrawal Related Side Effects

- Aches/Pains/Myalgia: NSAID (e.g. naproxen 375-500mg twice daily or ibuprofen 400-600mg four times daily); useful for pain & withdrawal. (May give regularly initially.)

- Acetaminophen (650-1000mg q6h as needed) for aches, pains, flu-like symptoms

- Bowel Function (Constipation / Diarrhea): ensure adequate hydration

- Laxative - continue initially to prevent constipation; with time, reduce, hold & eventually stop laxative (See RxFiles Opioid Induced Constipation, page 61)

- Loperamide - used if necessary for diarrhea; may not need with gradual taper.

- Nausea/Vomiting: ensure adequate hydration

- Dimenhydrinate 50-100mg q6h PRN [others: haloperidol 0.5-1mg po q8-12h; prochlorperazine 5-10mg po q6-8h; haloperidol 0.25-0.5mg hs up to 0.5-1mg TID].

- Anxiety, Itchiness, Laxation, Cramps, Rhinorrhea, Diaphoresis, Insomnia:

- Hydroxyzine 25-50mg po TID PRN, or sometimes just needed at HS (short-term)

- Sweating: Oxybutynin 2.5-5mg po BID PRN (short-term); ensure adequate hydration

- Insomnia: encourage sleep hygiene (e.g. limit stimulation near bedtime: caffeine, alcohol, TV)

- Employ non-drug & sleep hygiene measures (e.g. CBT, regular bedtime & wake-up time; sleep restriction).6,7,7 If short-term pharmacologic tx necessary, options: trazodone 25mg po HS 531 up to 100mg, amitriptyline 10mg po HS 531, doxepin SILENOR 3-6mg po HS 530-50.

- Pain/Insomnia/Anxiety: (nabuloline: tx of nausea and anorexia in HIV-AIDS pts; : N/V cancer, palliative) gabapentin 300mg HS, pregabalin 75mg HS; nabuloline 0.25% -0.5mg HS up to 0.5-1mg TID

- Physical Withdrawal Sx’s (e.g. agitation) -- by sympathetic activity (e.g. adrenergic agonists):

- Clonidine 0.1mg BID PRN (some patients may need up 4 doses/day). Most patients may not require if gradual taper.

- May use SOWS (patient administered scale) for monitoring (e.g. score 10-20 take clonidine) see Pg 8. Caution: if SBP <100, orthostasis, HR <60. Duration (Cochrane): typical use for 7-14 days up to 30 days; however, some may need longer tx (e.g. high dose, >= 5 yrs of use, fentanyl). If used regularly, taper, over ~7-10 days, to stop. Some evidence that it may ↑duration of abstinence, decoupling stress from craving.5,10 [Lofexidine LUCYMERA (not available in Canada): 0.18 mg tabs, 0.54 mg po GID; similar & alternative to clonidine; less hypotension but ↑cost]

- (Tizanidine ZANAFLEX: : 2mg po HS, may ↑by 2-4mg/d to max. ~8mg q8h. Taper gradually!)

---

EARLY symptoms may include:

- anxiety / restlessness
- sweating
- rapid short respirations
- runny nose, tearing eyes
- dilated reactive pupils
- other: sympathetic/stimulation
- brief ↑ in pain (usually few days but up to 2-4wks)

LATE symptoms may include:

- runny nose, tearing eyes
- rapid breathing, yawning
- tremor, diffuse muscle spasms, bone/joint aches
- pilo-erection (gooseflesh skin)
- nausea & vomiting;
- diarrhea; abdomen. pain
- dysphoria;
- fever, chills
- ↑ white blood cells (if sudden withdrawal)

PROLONGED symptoms may include:

- irritability, fatigue, malaise, psychological/wellbeing (dysphoria, coping, craving)
- bradycardia
- decreased body temperature

Some with chronic pain will find that fatigue, function & general well-being improve over time with opioid tapered. In such cases, gradual, incremental gains in function will be possible & should be explored.
**PURINE ANTIMETABOLITES**

Cancer: Reports of newburneuxone monitor ANCA (anti-neutrophil cytoplasmic antibodies) in patients with Crohn's disease have made use of this drug as a potential treatment option.

- **CNS:** T-cell lymphocytopenia, neutropenia, thrombocytopenia, and decreased serum levels of vitamin D and vitamin E.
- **Thrombocytopenia:** Thrombocytopenia is a known side effect of this medication.

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12th Edition November 2019

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References available online at www.rxfiles.ca under the title/search terms: “REFERENCES: Geri-RxFiles – 3rd Ed”
Key Points to Remember When Managing Type 2 Diabetes in Older Adults

- The approach to diabetes management in older adults is distinctly different from that in younger adults, particularly in the elderly with multiple comorbidities, frailty, cognitive impairment, or with limited life expectancy. Medication therapy to achieve A1C values <7.0% in older adults with multiple medical conditions is now considered overtreatment.
- Avoidance of hypoglycemia is paramount in the older adult who has diabetes and other comorbidities such as dementia, heart disease, and/or frailty.
- Individualization of therapeutic approaches for management of diabetes requires assessment of the disease, other medical conditions, cognitive and psychological functioning, and ability to self-manage (or level of care) in order to determine targets for glucose, blood pressure and lipid levels.
- It is important to consider the expectations of the individual patient and family members or caregivers (and understand the patient’s goals of care) as medication therapy is de-intensified/simplified in order to ↓ risk of complications from intensive therapy. Education may be required to reassure patients and caregivers who have been advised for many years to achieve “perfect” blood sugars and A1C values of <7.0%.
- Diabetes is a risk factor for the development of dementia (Alzheimer’s disease and vascular dementia), resulting in a higher incidence of dementia in adults with diabetes. Older adults with diabetes should be monitored regularly for cognitive impairment (annual screening recommended by ADA), with additional cognitive assessment performed if there is a decline in clinical or functional status, and/or if there are concerns regarding medication adherence.
- Cognitive impairment is a risk factor for severe hypoglycemia. Adjust therapy accordingly if cognitive impairment is present.
- Complex medication regimens need to be simplified as changes occur in a patient’s cognitive function, ability to self-manage, and available nursing/caregiver support.
- Older adults with diabetic distal peripheral neuropathy are at ↑ risk of gait abnormalities and falls. Care should be taken to minimize the use of sedative drugs, and medications associated with orthostatic hypotension and hypoglycemia.
- Declining renal function in older adults needs to be considered. Most glucose lowering medications, including insulin, require dosing reductions when eGFR is <45 ml/min.

*Remember:* Healthy older adults with diabetes may be treated to achieve the same glycemic, blood pressure & lipid targets as younger adults with diabetes. However, the burden of treatment should always be considered along with burden of disease and time-to-benefit for drug therapies. For a strategy on how and when to deprescribe antihyperglycemic agents, see page 65 and 66 of this book.

Glycemic Control

- Consider the risk of hypoglycemia, and incorporate strategies to avoid it when selecting glycemic targets and medications to lower blood sugars.

Hypoglycemia is defined as blood glucose <4 mmol/L. Severe hypoglycemia = blood glucose usually <2.8 mmol/L, impaired consciousness, and require assistance to treat (i.e. the individual is unable to treat the hypoglycemia themselves and without assistance may suffer injury, seizure, coma, or a CV event).

Key Points Related to HYPOGLYCEMIA to Consider

- Hypoglycemia is associated with ↑ morbidity and mortality in older adults with both type 1 and type 2 diabetes. **hypoglycemia can kill**
- Moderate to severe hypoglycemia may result in falls, confusion, seizures, cardiac arrhythmias, and cardiac ischemia.
- If an individual with type 2 diabetes has established CVD or is at high risk for CVD, and has ≥1 episode of severe hypoglycemia, he/she is more likely to have a CV event and die in next 5 years. **
- Severe hypoglycemia has been linked to increased risk of dementia. **A1C <6.5% is associated with increased risk of fractures.**
- Hypoglycemia is more common in older adults with diabetes due to: ↓ renal function (↓ clearance of glucose-lowering medications and endogenous insulin); age-related reduction in glucagon production; autonomic neuropathy and reduced stress hormone response to low blood sugars; cognitive impairment with ↓ awareness and/or ability to respond to early symptoms of hypoglycemia; variable food intake; altered intestinal absorption.
- Older adults may not experience typical neurogenic symptoms of hypoglycemia (tremor, sweating, palpitations, tachycardia, nausea) due to autonomic neuropathy and/or effect of medications such as beta-blockers. Asymptomatic hypoglycemia is best assessed by continuous glucose monitoring (a system that uses a device with a sensor inserted subcutaneously to measure glucose concentrations in the interstitial fluid), in the elderly diabetic population.
- Risk of severe hypoglycemia has been shown to increase by 2 to 3 times with tighter glycemic control (A1C <7.0%).
- Medications with a higher-risk for hypoglycemia include: insulin, sulfonylureas, meglitinides.

*Remember:*...glycemic targets may be different in older adults as compared to younger adults, and they will change as an individual ages or experiences a change in health status. The glycemic target and the risk of hypoglycemia influence the aggressiveness of medication therapy and the complexity of treatment regimens.
### Sliding Scale Insulin

(insulin regimens containing only short- or rapid-acting insulin dosed according to current blood glucose levels without concurrent use of basal or long-acting insulin)

Insulin is a class of medication that is well known to cause adverse events. Approach insulin therapy with caution in older adults. Avoid hypoglycemia by addressing glycemic lows first.

In frail older adults or older adults with cognitive impairment &/or multiple comorbidities, avoidance of hypoglycemia is more important than achieving tight glycemic control. Use of scheduled basal (long-acting insulin), bolus/prandial (short-acting insulin) & correction.supplemental (short-acting insulin used in addition to the daily regimen) is recommended rather than sliding scale insulin. Basal/bolus insulin therapy is proactive & allows for more flexibility of insulin dosing & ↓ hypoglycemia.

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<th>When a Medication Could be Problematic for Older Adults</th>
<th>Clinical Concern</th>
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<td>In <strong>DIABETES MELLITUS WITH FREQUENT HYPOGLYCEMIC EPISODES</strong></td>
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<td><strong>NOTE:</strong> benefit may outweigh risk in individuals with a strong indication for beta-blockers (e.g. post-MI, angina, HF with ↓EF)</td>
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<td></td>
<td>• Risk of suppressing hypoglycemia symptoms. e.g. hunger, shakes, tremor &amp; tachycardia but NOT sweating</td>
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<td>• The benefit of a beta-blocker post-MI, in angina, or in HF with ↓EF almost always outweighs the risk of masking hypoglycemia.</td>
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<td>Biguanide</td>
<td>With an <strong>eGFR &lt;30mL/min</strong></td>
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<td><strong>NOTE:</strong> see earlier discussion regarding some flexibility for this cut-off (e.g. if lower dose, stable patient)</td>
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<td>• Risk of lactic acidosis.</td>
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<td>o Risk factors include conditions that cause hypoxemia: acute cardiovascular condition, acute renal condition, acute hepatic condition, respiratory failure, sepsis, &amp; hypovolemia</td>
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<td>Sulfonylureas (SU), long-duration</td>
<td>With <strong>TYPE 2 DIABETES</strong></td>
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<td>Chlorpropamide</td>
<td><strong>QE = High; SR = Strong</strong></td>
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<td>Glimepiride</td>
<td><strong>qe = Moderate; sr = Strong</strong></td>
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<td>Glyburide•</td>
<td><strong>Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting. Avoid insulin regimens that include only short- or rapid-acting insulin dosed according to current blood glucose levels without concurrent use of basal or long-acting insulin. This recommendation does not apply to regimens that contain basal insulin or long-acting insulin.</strong></td>
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<td></td>
<td>• Poor efficacy.</td>
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<td>• The use of sliding scale insulin treats hyperglycemia after it has occurred; it has a <strong>tendency to cause more hypoglycemia, &amp; fluctuating blood glucose levels</strong> regardless of care setting.</td>
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<td>• May cause cognitive impairment, dementia, ↓ motor or visual skills.</td>
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See the RxFiles Drug Comparison Charts for more detailed medication information.
Chronic obstructive pulmonary disease (COPD) is most commonly the result of progressive exposure to cigarette smoke and other lung irritants. Lung damage takes time to manifest; thus, the prevalence of disease increases with age. Symptoms include shortness of breath (dyspnea), chronic cough, and sputum (phlegm) production. People with COPD often have difficulty exhaling - their damaged lungs have lost elasticity, and no longer can contract properly. The result is airflow limitation.

Airflow limitation can be measured through spirometry, and this is how COPD is diagnosed. An individual has COPD if, after taking a bronchodilator, the volume of air exhaled in 1 second (FEV₁) is less than 70% of the total amount of air that leaves the lungs with full exhalation (FVC). (Another way of saying this is that FEV₁/FVC < 0.7). Unlike in asthma, the airflow limitation in COPD is “persistent” - using a bronchodilator results in only a minimal increase in FEV₁.

The goals of therapy in COPD are to reduce exacerbations, reduce symptoms, and improve ability to do physical exercise & activities of daily living.

### Approach to COPD Management in Older Adults (see page 156 for AECOPD)

- **Encourage smoking cessation.**
  - Quitting smoking conveys a mortality benefit (decreasing the risk of death by ~40%) AND slows decline in lung function (decreasing the rate of decline by ~40%). See Figure 1.7

- Refer to **RxFiles Tobacco / Smoking Cessation Pharmacotherapy** for the therapeutic alternatives available to help people quit smoking (e.g. nicotine replacement therapy, bupropion, varenicline, nortriptyline).

- **Ensure influenza vaccination is up to date.**
  - A flu shot should be given each autumn since it decreases COPD mortality by 50% and respiratory disease hospitalizations by 40%. See Figure 1.7

- **Ensure pneumococcal vaccination is up to date.**
  - The pneumococcal vaccine PPSV23, PNEUMOVAX, is covered x 1 dose in Saskatchewan for individuals with COPD or anyone >65 years. (A repeat dose after 5 to 10 years in high risk individuals may be given; however, this second dose is not covered in SK, ~$65). An additional pneumococcal vaccine PCV13, PREVANAR 13 is available for adults >65yrs & may be considered 1yr after, or 8 weeks before, PPSV23 immunization. However, PCV13 is not covered in SK ($100), and there are no trials comparing combination PCV13 and PPSV23 vaccination to PPSV23 vaccination alone. See pg 204 of this book.
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