New York State Medicaid Prescriber Education Program

Metformin as a first-line medication

Treating type 2 diabetes mellitus

NEW YORK state department of HEALTH

SUNY The State University of New York

Key messages

1) **Metformin should be used as a first-line medication in almost every patient with type 2 diabetes.**
2) DPP-4 inhibitors and GLP-1 agonists should not be used first-line in patients with type 2 diabetes because metformin, sulfonylureas, and insulin are more efficacious.
3) HbA1C goals should be individualized for each patient with type 2 diabetes: less than 7% for most patients and less than 8% for specific high-risk subgroups.
4) Patients with type 2 diabetes should have an HbA1C test every three to six months.

Metformin

- Class: Biguanide
  - Only FDA-approved medication in its class
- Sites of Action
  - Primary: liver
    - Causes decreased hepatic glucose production
  - Secondary: muscle, adipose tissue
    - Increases glucose uptake, utilization
    - Improves insulin sensitivity
    - Decreases intestinal glucose absorption
- Lowers basal, postprandial glucose

Benefits of metformin use

- Expected HbA_{1C} decrease: 1% - 2%
- Oral medication
- Modest weight loss
- ↓ serum triglycerides
- ↓ total cholesterol
- ↓ LDL cholesterol

Two main disadvantages of metformin:

1. Gastrointestinal side effects:

Diarrhea	Indigestion	Upset stomach
Nausea	Flatulence	Metallic taste

2. Cannot use in renally impaired patients

   Lactic acidosis

While these are common concerns, neither should detract prescribers from using metformin in most patients with type 2 diabetes mellitus.

GI side effects

- Most common reasons for discontinuation
  - Of patients treated with metformin IR:
    - 53% experienced diarrhea
    - 6% had to discontinue medication due to diarrhea

- Tips to minimize GI disturbances:
  1. Switch to extended-release tablets
  2. Take metformin with food
  3. Initiate metformin using slow titration schedule

Glucophage® (metformin tablets) Prescribing Information. Accessed May 2, 2011.
Levy J, Cobas RA, Gomes MB. *Diabetol Metab Syndr. 2010;2:16.*

Metformin **IR**:

Recommended dosing titration to minimize GI side effects

SUN	MON	TUE	WED	THU	FRI	SAT
Week 1	500 mg once daily →					
Week 2	500 mg twice daily →					
Week 3	1,000 mg AM, 500 mg PM →					
Week 4	1,000 mg twice daily →					

- Recommended dose = 2,000 mg/day
- Maximum recommended dose = 2,550 mg/day

Metformin **ER**:

Recommended dosing titration to minimize GI side effects

SUN	MON	TUE	WED	THU	FRI	SAT
Week 1	500 mg once daily →					
Week 2	1,000 mg once daily →					
Week 3	1,500 mg once daily →					
Week 4	2,000 mg once daily →					

- Can split up into twice-daily dosing if easier for patient

Metformin contraindications

- Per the prescribing information, poor kidney function is a contraindication to metformin use
  - SCr ≥1.5mg/dl in males
  - SCr ≥1.4mg/dl in females
  - CrCl <60ml/min

Glucophage® (metformin tablets) Prescribing Information. Accessed May 2, 2011.

The concern about lactic acidosis

A concern exists that patients with poor renal function are at an ↑ risk of lactic acidosis:

- Review of studies shows a weak association between metformin use and development of lactic acidosis.
- No evidence from prospective comparative trials or observational cohort studies that metformin is associated with an ↑ risk of lactic acidosis
- Philbrick and colleagues recommend that elevated SCr levels should be a **risk factor** for lactic acidosis **not** an absolute contraindication

Philbrick AM, Ernst ME, McDanel DL, Ross MB, Moores KG. *Am J Health Syst Pharm. Nov 15 2009;66(22):2017-23.*

Monitoring parameters

- Renal function
  - At least annually
  - More frequent monitoring in renally impaired patients

- When to discontinue use:
  - Rapid decline in CrCl
  - Sharp increase in SCr
  - Prior to procedures requiring intravenous radiocontrast media
    - Hold for 48 hours afterwards

Summary

Metformin is a first-line medication in most patients with type 2 diabetes mellitus

- Associated with up to a 2% decrease in HbA_{1C}
- No correlation between metformin use and lactic acidosis
- GI side effects can be minimized or sometimes even eliminated with different treatment strategies
  - XR tablets
  - Take metformin with food
  - Slow titration