ECHO Diabetes

Case Discussion

March 7, 2024

Clinical Question

- How can we improve this patient's diabetes management given the metabolic side effects of anti-psychotic use?

- New patient - A1c continues to increase.
  - Patient states that he ***struggles with compliance*** some days ***due to the amount of medications*** he is on.

Reasons for Poor Medication Taking Behavior

- **Fear/ Suspicious of the medication** (Fear of side effects / harm)
- **Out-of-Pocket Costs** (unaffordable)
- **Too many medications**
- **Perceived Treatment Inefficacy**
- **Lack of Physician Trust**
- **Failure of Communication and Lack of Comprehension** (not understanding)
- **Cultural Issues**
- **Psychosocial Stress** (complex and stressful living situations)
- **"Psychological" Issues** (denial, depression & severe psychiatric illness/psychosis.)
- **Secondary Gain**
- **Drug and Alcohol Dependence**

Compiled from AMA, BDI, Kaiser

Understanding Noncompliant Behavior: Definitions and Causes

Fred Kleinsinger, MD The Permanente Journal/ Fall 2003/ Volume 7 No. 4

- **"Psychological" Issues** (includes denial, depression & severe psychiatric illness such as psychosis.)
  - **Denial** is the process by which painful or upsetting thoughts and issues recede from consciousness—a very common response to bad news
  - Patients whose **depressed mood** causes a defeatist attitude reducing their ability to deal with their medical condition.
  - Patients who have more **severe depression** may engage in NCB that appears *suicidal.*
    - May lead to an abrupt and early death (e.g., a patient with insulin-dependent diabetes who will not self-monitor blood glucose levels and who is frequently hypoglycemic)
  - Patients with **bipolar disorders** - compliance varies, depending on their mood state.
  - Patients who are **clinically psychotic** or who have ***thought disorders with psychotic features present one of the greatest challenges to addressing NCB***
    - (E.g., a patient who is delusional and paranoid may refuse psychiatric care and …could refuse treatment for a serious disease)
- **Drug and Alcohol Dependence**
  - *"Stress and disorganization in the lives of many addicted patients—as well as health problems—create a formula for massive NCB and poor health outcome"*

MH Disorders & Insulin Resistance

- Evidence suggests that **mood disorder** is associated with ***insulin resistance and inflammation***.
  - Epidemiologic evidences showed that ***depressed adults*** have a ***37% increased risk of developing type 2 diabetes***
    - Some studies have demonstrated that depressed individuals had ***higher glucose levels and insulin resistance when they are symptomatic***

- ENDO 2023 symposia on MH and Diabetes
  - Investigator reported on improvement in refractory depression (in people without diabetes) by reducing insulin resistance with metformin

MH Disorders & Insulin Resistance

- There is an ***increased risk of diabetes*** *in patients with* ***schizophrenia*** and this risk is elevated by some antipsychotic medications.
  - The prevalence of diabetes in patients with schizophrenia was found to be higher than in the general population ***even before the use of antipsychotic medication***
    - ***Insulin resistance*** was reported in patients with schizophrenia over 55 years ago
  - It seems that the ***second-generation antipsychotic drugs*** may ***aggravate the insulin resistance*** that already exists in patients with schizophrenia.
    - While some of this is no doubt related to ***weight gain***, it has also been shown that antipsychotics ***inhibit glucose transport into muscle***.

Medication Contribution to IR & Diabetes

- Medications contributing to severe IR (In patients with severe insulin resistance, an effort should be made to discontinue such agents or switch to alternative medications if possible)
  - Glucocorticoids
  - Atypical antipsychotics
  - Calcineurin inhibitors
  - Protease inhibitors
  - Oral contraceptives

- The *metabolic side-effects* of second-generation(atypical) antipsychotics range along *a spectrum*, depending on the specific drug
  - The risk is greater with the atypical drugs clozapine and olanzapine
  - *Risperidone* is somewhere in the middle of the class – ***Paliperidone*** (9-hydroxyrisperidone) is the active metabolite of risperidone
    - Risperidone and paliperidone both exhibit ***pronounced insulin resistance***.
  - Newer second-generation drugs appear to have less metabolic impact

Medications with Potential for Weight Gain (Obesogenic)

Medication Classes Medications with Potential for Weight Gain

- Antipsychotics:
  - Quetiapine
  - Clozapine
  - Olanzapine
  - Risperidone → **Paliperidone**
  - Thioridazine
- Antidepressants:
  - Mirtazapine
  - Selective serotonin reuptake inhibitor (e.g., **paroxetine**, sertraline) (citalopram , escitalopram , fluoxetine)
  - MAOIs (e.g., phenelzine)
  - Tricyclic anti-depressants (e.g., **amitriptyline**, clomipramine, doxepin, imipramine, nortriptyline, protriptyline)
- Antiepileptics/Mood Stabilizers:
  - **Gabapentin** /Pregabalin
  - Carbamazepine
  - Divalproex
  - Lithium
  - Valproic acid
  - Vigabatrin

Medications that may be Weight Neutral or have Potential for Weight Loss

- Antipsychotics:
  - **Aripiprazole**
  - Haloperidol
  - **Ziprasidone**
- Antidepressants:
  - Bupropion
  - Desvenlafaxine
  - Venlafaxine
- Antiepileptics/Mood Stabilizers:
  - Topiramate
  - Lamotrigine
  - Zonisamide

Concern regarding polypharmacy

Medication Options to help Offset AAWG & Diabetes

- **Metformin** has been the main agent added to help offset AAWG (atypical antipsychotic weight gain) and diabetes (<20% patients >5% weight loss)

- Increasing evidence for use of **GLP1 RA** meds for AAWG & diabetes
  - "Initial evidence from our real-world clinical setting suggests that semaglutide may be effective in *reducing AAWG* in patients not responding to metformin."
  - "Our analysis revealed that GLP-1 RA treatment is safe and effective on ***cardio-metabolic parameters*** in antipsychotic-treated patients with schizophrenia."

- "Fusion clinics" (Severe Mental Illness & Diabetes)
  - Optimize medications for both MH and Metabolic factors
  - Commonly use GLP1 RA related medications
    - recent studies show **reduced anxiety and depression** symptoms with GLP1 RA - largest effect with ***tirzepatide*** *(~60% reduction in incidence vs placebo)*
      - The data suggests ***that GLP-1 medications may have a positive effect on mental health***; however, it ***does not identify a causational relationship*** between medication use and reduced rates of anxiety and depression [? more active, better sleep, etc.]
      - More insight is needed to evaluate the factors that contribute to these correlations.
    - **Semaglutide Use Linked to Lower Risk for Suicidal Ideation** - Endocrinology Advisor

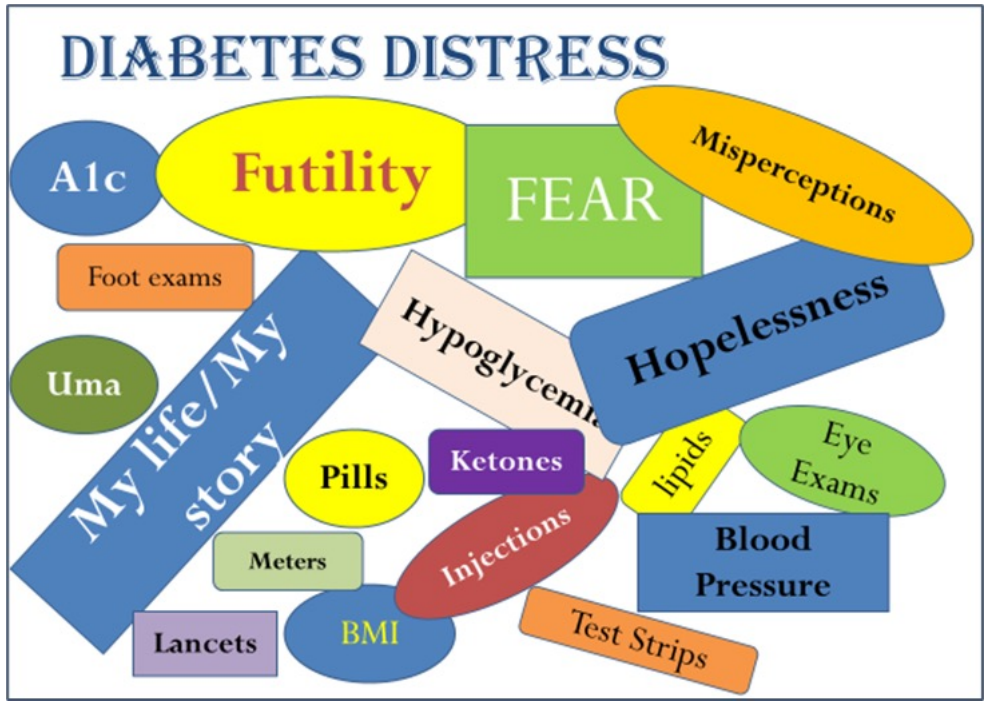
Consider Diabetes Distress

- Diabetes distress is ***not*** clinical depression - It is **emotional distress** that captures
  - the worries, concerns and fears among individuals struggling with a progressive and demanding chronic disease such as diabetes including
    - the emotional burden of self-management,
    - threats of complications and potential loss of functioning
  - ***DD often uncovered in patients w/ diabetes & refractory MH issues***

DD does not respond to antidepressants

The 7 major sources of DD

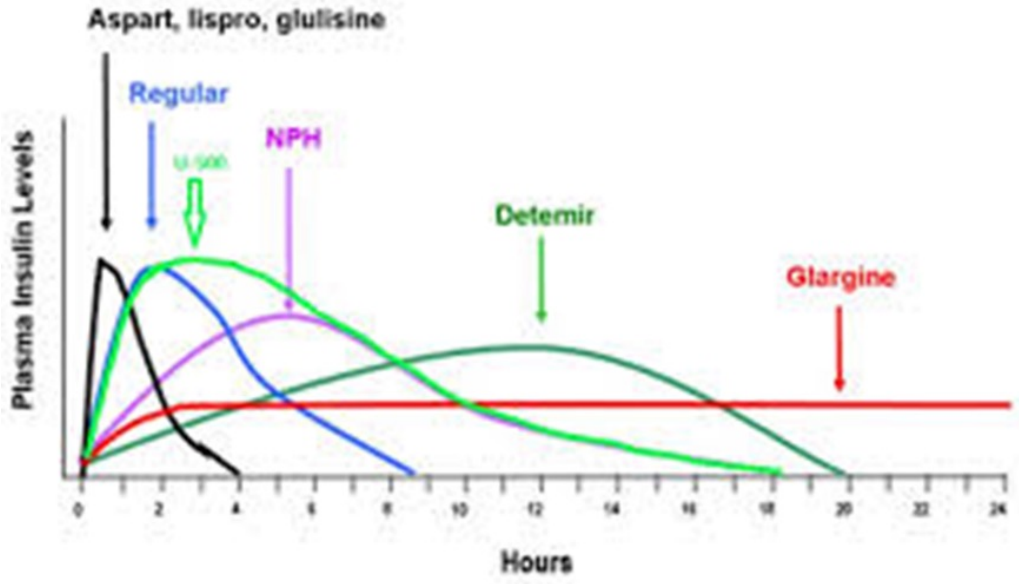
- **1. Powerlessness** (***hopelessness- pointless***)
- **2. Negative Social Perceptions** (***negative judgments of others***)
- **3. Physician Distress** (***don't get help I really need)***
- **4. Friend/Family Distress**
- **5. Hypoglycemia Distress**
- **6. Management Distress**
- **7. Eating Distress**



Meth - Both Hyper and Hypoglycemia

- Methamphetamine-Induced Hypoglycemia: A Case Report and Literature Review Cureus. 2023 May; 15(5): e39158. Henrik Ghantarchyan, et al
  - We believe that methamphetamine use or abuse can cause significant hypoglycemia, likely from pancreatic-stimulated insulin release.
  - Also, loss of appetite & loss of dentation – reduced food intake
- Methamphetamine use and the risk of diabetic ketoacidosis
  Medicine, Science and the Law 2022, Vol. 62(1) 39–42
  - In patients with Type 1 diabetes

Switching from U100 Insulin to U500 Insulin Dose Premeal similar to 70/30 Insulin



- The onset of activity for U-500 regular insulin is ~30–45 minutes, similar to U-100 regular insulin.
- However, the time to peak activity (4–6 hours) and duration of action (12–14 hours) for U-500 is most similar to NPH insulin
- Profile similar to Premixed 70/30 insulin

Diabetes Care. 2005;28(5):1240-1244.

200U or greater of insulin/day*

↓

U-500 exclusively

↓

200U-300U/day

↓

Twice daily
(Pre-breakfast & pre-dinner)

U500 Insulin likely not ideal for patient who takes insulin randomly - not best option for "correction insulin"
Would a long-acting basal insulin be of more benefit?
Once-weekly insulin on market soon & Combo "IcoSema" in testing

U500 Insulin transition to Basal Insulin

- If the dose of U500 insulin is known & is <200u/d & has been effective –
  - using 70/30 insulin model: calculate the basal component as 70% of the total dose – then reduce dose of analog basal insulin by 20%
  - For our patient – 140u U500 x 0.7 = 98u → 98 x.8 = **78.4(78) units** of **insulin glargine or degludec (max on pen is 80unit dose)**
- Since the required dose of U500 not reliably known for this patient
  - ? Past insulin requirements prior to U500 insulin
  - Likely marked insulin resistance (MH issues, AA use, gluco-toxicity)
  - Risk of hypoglycemia – meth effect & unreliable food intake
    - Continue gentle promotion of CGM for safety & effectiveness (curiosity regarding reluctance)
  - AACE guidelines: if A1c >8.5%, 0.2-0.3/kg (**30u/day starting dose basal analog insulin**)
  - Could go with in between dose (40-60u)/ work on adherence –step-wise – patient input on next-step priorities (symptoms of hyperglycemia –options daily insulin or pill)
- Titrate insulin dose up/down as needed – avoid inertia – frequent contact
  - ?? Use of correction insulin initially to get BGs down – basal insulin work better
- Continue efforts to reduce insulin requirements
  - Continue to titrate up semaglutide (consider tirzepatide – more “bang for buck” for BG)
  - Work with patient on taking empagliflozin (decrease insulin requirement) +/- metformin
  - MH meds with lower metabolic effects (balance with need for help with compliance)

How to help with your patient with Medication Taking

- Do make it easier (less burden) to remember & to take medications
  - **simplify** medication regimens
  - use once-a-day dosing whenever possible
  - provide pillboxes for patients or blister packs
  - use combination tablets when possible and appropriate
  - ensure necessary skills (e.g., how to give an injection)
  - align prescriptions for chronic care meds to be refilled at same time
  - provide 90-day supply x 4 for medications for chronic conditions when possible
    - Use computerized tracking systems for prescription refills
- Address reasons for not taking medications
  - ? "hopelessness" – connection with culture & community – also helpful for SUD
- Develop & reinforce *self-efficacy* & self esteem (help patient succeed)
  - reduce overwhelm – **simplify**
  - **use an *incremental* approach, with interim goals**
  - consider patient capacity

Be Sure to Screen for HCV

- Chronic HCV infection, even without cirrhosis, increases insulin resistance and can cause or worsen diabetes

- In many patients (unless extensive hepatic fibrosis or longstanding diabetes), SVR from treatment of HCV can improve glycemia and health outcomes and reduce medication requirements for diabetes.

UACR & SGLT2i med

- Elevated UACR may be related to markedly increased blood glucose
- Normal UACR is defined as <30 mg/g Cr (high UACR is defined as =/>30 mg/g Cr; very high =/>300 mg/g)
  - Because of high biologic variability in urinary albumin excretion, **two of three UACR specimens** collected within a ***3-to-6-month period*** should be abnormal before considering a patient to have high or very high albuminuria.
  - UACR can be *elevated independently of kidney damage* by
    - Exercise within 24-hour
    - Infection
    - Fever
    - **Marked hyperglycemia**
    - Marked hypertension
    - Menstruation

- Still favor use of SGLT2i to help glycemia (gluco-toxicity)
  - Can increase dose to help glycemia (slightly) without increasing number of pills
  - Larger BG lowering-effect with higher blood glucose levels
  - Maybe set up arrangement/agreement with him to take it daily
    - Ask if barriers such as fear of med in addition to MH/ MUD effects

Considerations

- Address Meth-Use -Disorder
  - See Indian Country ECHO resources https://www.indiancountryecho.org/
- Simplify medications as much as possible – incremental approach
  - One step (med) at a time
- Consolidate/deprescribe multiple antipsychotic meds
  - Preference to the most effective agent with the lowest metabolic impact
  - Consider Diabetes Distress as contributing to symptoms
    - https://diabetesdistress.org/surveys/t2-ddas/questions/?lang=en&view=0&start=1
- Consider less obesogenic SSRI
- Continue to increase GLP1 RA (tirzepatide if covered)
  - Potential metabolic & MH benefits
- Increase SGLT2i from 10 mg/d to 25 mg/d – shared decision making
  - Reduce gluco-toxicity / less risk hypoglycemia than insulin
- U500 insulin likely not best option for this patient
  - Would U200 Tresiba offer better coverage?? – once weekly insulin option later this year
  - See didactic on correction insulin
- Deprescribe any additional meds
  - Amitriptyline / Gabapentin / Hydroxyzine / other –(? not taking anyway)

Additional Resources for BH team

- Reclaiming Native Psychologic Brilliance Reclaiming Native Psychological Brilliance 2024 Registration (smartsheet.com)

- Journey to Health ECHO Journey to Health ECHO Program Sign-up

- https://www.indiancountryecho.org/resources/?_sfm_resources_program_relation=15022&_sft_resource_type=past-presentation

- Upcoming Webinars | Tele Education (ihs.gov)
- Webinar Archives | Tele Education (ihs.gov)

Extra slides

- PLoS One. 2021; 16(1): e0246211.
- Published online 2021 Jan 28. doi: 10.1371/journal.pone.0246211
- PMCID: PMC7842964
- PMID: 33508013
- A comparison of the metabolic side-effects of the second-generation antipsychotic drugs risperidone and paliperidone in animal models
- Fasting glucose levels were increased by all but the lowest dose of risperidone, but only with the highest dose of paliperidone. HOMA-IR increased for both drugs with all but the lowest dose, while the three highest doses decreased glucose tolerance for both drugs. Risperidone and paliperidone both exhibited dose-dependent decreases in the glucose infusion rate in the clamp, reflecting pronounced insulin resistance.

Review the patient's understanding and agreement with diagnoses and treatment goals and recommendations

- Ask the patient to describe how s/he understands his or her medical disorder in his or her own words
- Ask if the patient understands the purpose of treatment and the consequences of ineffective treatment
- Ask about beliefs about the disorder(e.g., diabetes) and/or the medications – help clarify
  - What do you see as the positives of the medication?
  - What do you see as the negatives of the medication?
- Have the patient explain the specific treatment recommendations you are agreeing on in detail [teach back, show me]
- Using open-ended questions, ask if the patient feels confident in following the treatment recommendations and if the patient sees any problems
- Offer new information
  - Addressing perceived necessity (PROs) – the why for taking the medication
  - Addressing perceived concerns (CONs) – patient tells you about their suspicions etc. – worthy of being discussed – clarify – provide new perspectives

Work to mutually find solutions to any problems with compliance that are identified

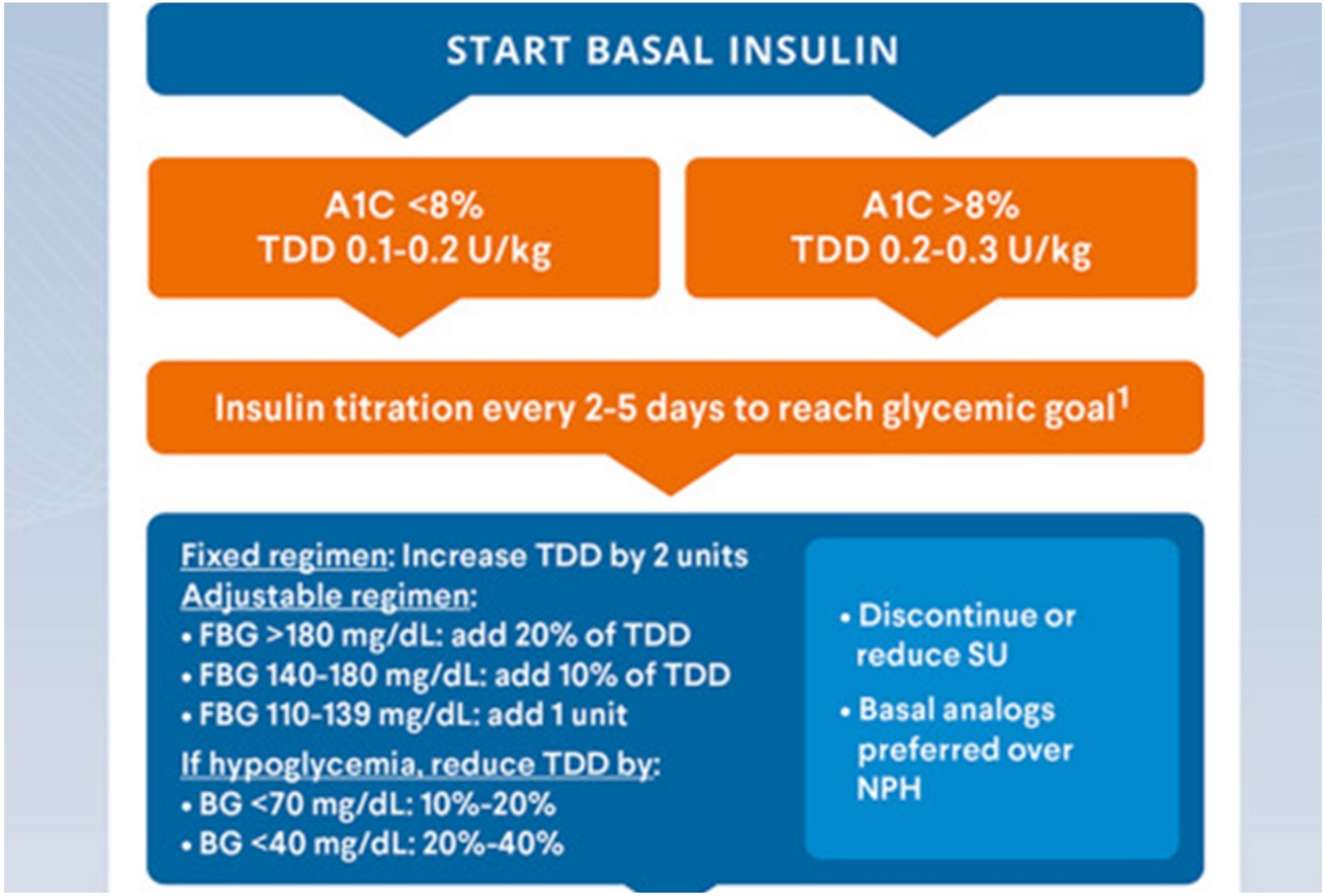
- Tailor the adherence solution to the individual patient.
  - E.g., Fear of Side Effects/ Fear of Harm is a common factor in medication non-adherence
    - Some physicians are worried that if they inform patients of potential side effects of a medicine, that scare them and add additional reasons for nonadherence.
    - Patients are entitled to know what might happen when they take a medicine.
    - Informing patients of potential side effects develops trust, engages the patient, and gives the patient the opportunity to develop the best treatment plan together with the physician.
    - Include the treatment plan and any potential side effects in the after-visit summary.
- Involve the patient in developing their treatment plan.
  - Patients who are included in decisions about the medications are more likely to adhere to their treatment plan. [Ownership vs Buy-in]
  - Enlist the patient in helping to monitor response (home BP checks, SBGM, etc.) [“discovery learning” – link the medication and monitoring – “see if it is doing the job for you”]

Is the stepping-down approach a better option than multiple daily injections in obese patients with poorly controlled Type 2 diabetes on advanced insulin therapy? https://onlinelibrary.wiley.com/doi/full/10.1002/edm2.204

Study Protocol:

- Patients on "advanced insulin therapy/MDI" - using insulin at least 2 times daily comprising both a basal and a prandial insulin or a premix insulin with or without other noninsulin medications
  - Continued or added metformin
  - Control group titrated MDI
  - Intervention group stopped mealtime insulin, continued & titrated basal insulin (starting at 80% dose) & ***added SGLT2i & GLP-1 RA meds***
    - If patients on Premix insulin - Calculated the dose for insulin glargine at **40% of total daily dose of premixed insulin (U500 insulin**)
    - For our patient – 80 units of U500 x 0.4 = **32 units of insulin glargine**
  - Intervention group A1c 9.7% → 7.3% (with 40% having A1c <7%) vs 10.3% → 9.5% MDI
    - weight 212#→ 196# vs no change for control MDI group (225#)
    - Total daily insulin requirement was reduced by over 50%
    - 45-point improvement in satisfaction score
    - CV & Renal benefits

AACE guidelines



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