



the PRUDENT prescriber

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December 2022

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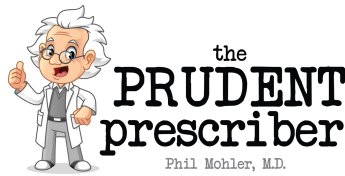
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Treating Type 2 Diabetes: What Drug Should You Add after Metformin?

The recently published GRADE Trial ([NEJM](#) 2022 September 22; 387:1063) offers some useful evidence for selecting the next drug after metformin in people with type 2 diabetes. Prior to this study there were few head-to-head comparisons of glucose lowering medications. This multicenter, comparative-effectiveness clinical trial was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health.

Methods:

The researchers selected participants who had type 2 diabetes for less than 10 years and who had received at least 500 mg of metformin per day for six months. Those patients who had received other glucose lowering medications in the previous six months were excluded, as were participants unwilling to receive injection therapy. During a run-in period of 6 to 14 weeks before randomization, the metformin dose was increased to at least 1000 mg per day, with a target maximal dose of 2000 mg per day. Eligible participants had a glycated hemoglobin (HbA1c) level of 6.8% to 8.5% at the end of the run-in period. The 5,047 participants were then randomized to one of four drugs: insulin glargine-100, the sulfonylurea - glimepiride, the glucagon-like peptide-1 receptor agonist (GLP-1) - liraglutide (Victoza), or a dipeptidyl peptidase inhibitor (DPP4i) - sitagliptin (Januvia). The participants were followed quarterly for an average of five years. The primary metabolic outcome was a glycated hemoglobin level (HbA1c), measured quarterly of 7.0% or lower? (I don't understand this goal). Many of the participants had underlying hypertension and dyslipidemias at the onset of the trial. Thiazolidinediones (TZD) and the



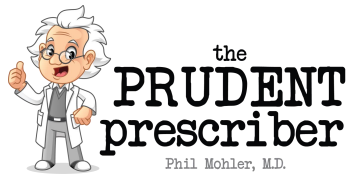
SGLT2 inhibitor class of glucose lowering medications were not included owing to safety concerns and FDA approval at the time of planning the trial.

Results:

- Participants attained a hemoglobin A1c value less than 7.0% with:
 - glargine 33%
 - liraglutide 32%
 - glimepiride 28%
 - sitagliptin 23%
- The mean HbA1c levels reached a nadir at six months in the glargine group and at three months in the other groups. At year 4, the absolute differences were small with mean HbA1c levels of 7.1 in the glargine and liraglutide groups as compared to 7.2% in the sitagliptin group and 7.3% in the glimepiride group.
- Incidences of major adverse cardiovascular events (non-fatal MI, stroke, or deaths from cardiovascular causes), hypertension, dyslipidemia, albuminuria or peripheral neuropathy were similar among groups.
- Severe hypoglycemia occurred most frequently in patients taking glimepiride (2.2%) versus approximately 1% in the other three groups.
- Participants who received liraglutide and sitagliptin had a mean weight loss of 3.5 kg and 2.0 kg, respectively, at four years, whereas the insulin and glimepiride groups had relatively stable weights.



- This large randomized controlled trial with fairly representative demographics for the US (19.8% Black and 18.6% Hispanic) suggests that all four medications when added to metformin decreased HbA1c levels. Glargine and liraglutide were significantly, albeit modestly, more effective in achieving and maintaining target HbA1cs.
- The trial is not generalizable to patients who have had diabetes for more than 10 years nor to those whose baseline control is not as good as those in this study (HbA1c >8.5%).
- The authors point out that the results of their trial highlight the difficulty in achieving and maintaining recommended HbA1c levels in patients with type 2 diabetes. During the mean five year follow up, the target HbA1c level of less than 7% was not reached or maintained in 71% of the participants who received approximately 2000 mg of metformin per day plus one of the four trial drugs. Participants had their medications provided at no cost.
- “What’s it going to cost?” is always the elephant in the exam room. This study probably overestimates the adherence of patients to their medications as they were provided all their study medications at no cost.



- Here’s a look at what a prescription for one of the four drugs in the GRADE Trial might cost at the pharmacy. My thanks to PharmDs Zach at RMHPs/UHC and Bev at Palisade Pharmacy for their assistance with these data.

Patient Costs for a One-Month Supply of the Four GRADE Trial Medications

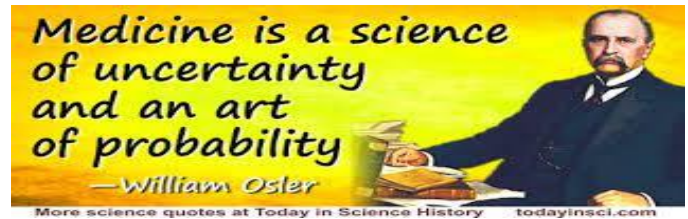
Drug	Average Out-of-Pocket Cost for RMHP/UHC Commercial Members <i>(Before the Member hits maximum out of pocket)</i>	Estimated Costs using: <ul style="list-style-type: none"> GoodRx Prices (November 26,2022) Three Least Expensive Pharmacies in Mesa County, Colorado Price may involve a “coupon”
insulin glargine	\$80	Vial with 1000 units: \$103-\$108 5 pre-filled pens with 1500 units: \$150-\$159
sitagliptin Januvia	\$142	\$524- \$548 25mg, 50mg and 100mg are flat priced
glimepiride	\$6	\$6-\$12
liraglutide Victoza	\$74	2 pre-filled pens 18mg/3ml: \$711-\$730 3 pre-filled pens 18mg/3ml: \$1112

Effective January 1, 2023, Medicare part D insulin will be capped at \$35 a month, no matter the type of insulin. For those who use insulin pumps the amount they pay will be no more than \$35, effective July 1. For more information, please visit www.medicare.gov/coverage/insulin.

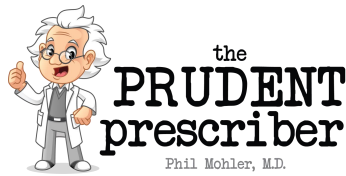
Physician Tolerance of Uncertainty: What It Means for Burnout

Preamble:

I’ll claim editorial privilege to bring this non-pharmaceutical study to your attention. Fifty years ago, this month I was introduced to Michael Balint’s “The Doctor, His Patient and the Illness.” The underlying theme of this book is the concept of the physician as a therapeutic entity (drug). How does the clinician decide how to dose oneself? What are the side effects of the “drug” physician? When does the clinician decide to stop the intervention?



This observational study from the Massachusetts General Hospital (MGH) in Boston (Journal of General Internal Medicine May 2022) explores the uncertainty that physicians face in their day-to-day practice of medicine. It focuses on the sequelae of that uncertainty for both clinicians and their patients. Earlier research shows an association between lower toleration of uncertainty and increased risk or presence of clinician burnout and work-related stress.



Methods:

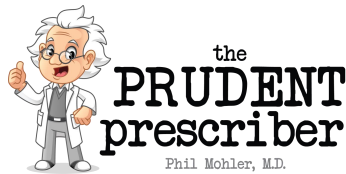
In May-June 2019, researchers administered a confidential online survey to all active clinical medical faculty at MGH. 93% of the 2,172 docs responded. Physicians were compensated \$167 to \$833 for their participation depending upon the amount of their clinical activity. As a part of an 18-page survey, they were asked a single item concerning medical uncertainty: “I find uncertainty involved in patient care disconcerting.” This single item has been shown to stratify tolerance of uncertainty among physicians. Other items ascertained professional and personal details and various well-being metrics (burnout, work engagement, overall career satisfaction).

Results:

- Of the respondents, 983 (49.3%) were male; 1186 (58.9%) practiced a medical subspecialty; 294 (14.6%) were primary care clinicians; 868 (43.1%) had 10 or fewer years of experience since training; and 998 (49.5%) had a trusted advisor.
- Lower tolerance of uncertainty was associated with:
 - female gender (odds ratio {OR} 1.23)
 - primary care practice (OR, 1.56)
 - lack of a trusted advisor (OR, 1.25)
 - more experience was associated with lower odds of low tolerance of uncertainty (OR, 0.99)
- Physicians with low tolerance of uncertainty were:
 - more likely to be burned out than those with high tolerance of uncertainty
 - less likely to be engaged at work
 - less likely to be satisfied with their career
 - more likely to have higher rates of exhaustion, cynicism and reduced personal efficacy
 - Adjusting for demographic and professional characteristics, physicians with low levels of tolerance of uncertainty were 3 times more likely to be burned out than physicians with a high tolerance of uncertainty.

Study authors' thoughts:

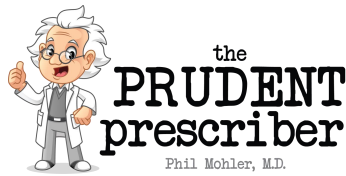
- “We found a strong relationship between tolerance of uncertainty and physician well-being, across specialties.”
- “Our findings generate a hypothesis that increasing tolerance of uncertainty might improve physician well-being.
- Evans and Trotter (Fam Med 2009. 41(5): p319-26) posit that a clinician’s ability to deal with uncertainty at a cognitive, emotional, and ethical level has been shown to influence the diagnostic process with potential for diagnostic error and impact on patient outcomes.
- It is estimated that 17% of excessive costs of medical care result from physicians’ anxiety related to how they manage uncertainty (Med Decis Making, 1998.18(3): p 320-9.), with



increased test ordering tendencies, and fear of malpractice litigation (Behav Med, 2001. 27(2): p 52-60).



- Recall that this study is observational in nature, and one should think “association,” not “causation.”
- Are these results from a big city academic center generalizable to family docs in the trenches? I’m uncertain.
- So, you’ve trudged through this review and are still looking for answers to the question, “How do you increase physicians’ tolerance of uncertainty?”
 - Begin et al., the authors of this study, suggest that “tolerance of uncertainty is amenable to change through an educational or experiential process.” Unfortunately, they don’t hone in on how to pull this off but suggest “further study.”
- Or, does it make more sense to find medical students who are born with tolerance of uncertainty?
- Travis Bradbury the author of “Emotional Intelligence” (Forbes December 21, 2015) proposes 11 ways successful people overcome uncertainty:
 1. They quiet their limbic systems.
 2. They stay positive.
 3. They know what they know and what they don’t.
 4. They embrace that which they can’t control.
 5. They focus only on what matters.
 6. They don’t seek perfection.
 7. They don’t dwell on problems.
 8. They know when to trust their gut.
 9. They have contingency plans.
 10. But they don’t ask, “What if?”
 11. When all else fails, they breathe.



2022-2023 Flu Vaccine Update

- The influenza vaccine for this season appears to be an excellent match with the circulating virus.
- All influenza vaccines are now quadrivalent.
- The ACIP voted in June 2022 to recommend Fluzone High-Dose, Flublok or Fluad as preferred influenza vaccines for ages 65 and older. No preference for one vaccine over the others. More mild to moderate local reactions than with the standard dose. In a two-year study with 31,989 participants (>65y) randomized to a high dose versus standard dose, the number needed to immunize (NNI) to prevent one case of flu using the high dose versus standard dose was 200. (NEJM 2014; 371:6 35-45)
- The live attenuated influenza vaccine (LAIV) trade name FluMist is back on the market (hiatus 2016-2018) for people ages 2-49 years. It has a new H1N1 component.

Looking for previous versions of the Prudent Prescriber newsletter? Good news, 10 YEARS of monthly editions are now available on rmhp.org.

Prudent Prescriber
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Distributed by Rocky Mountain Health Plans, a UnitedHealthcare Company