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Title: Trial of an intervention to Improve Metformin Persistence and Adherence

Coordinating Center: Weill Cornell Medicine, Department of Medicine

Primary Investigator: Leon I. Igel, M.D.

Coinvestigator: James H. Flory, M.D.

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Version 1	01/29/2018
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Study Overview:

This protocol outlines the design for a randomized controlled trial entitled, "Trial of Restarting and Tolerating Metformin (TreatMet)". Metformin is a safe and effective first-line drug for type 2 diabetes that is also widely recommended for weight loss and diabetes prevention. But, metformin is associated with gastrointestinal and other side effects which prevent its use in 10-20% of patients and appear to limit the usable dose in others. This study is an N-of-1 trial design that will recruit 20 previously metformin-intolerant patients for re-challenge with metformin in a double-blind scenario. In this setting, 'intolerant' means either unable to take metformin at all, or unable to increase the dose past 1,000 mg despite the treating physician's recommendation to do so. Patients will be assigned to take their baseline medication regimen plus 2 weeks of 250 mg per day of metformin extended release, followed by 500 mg metformin XR, 750 mg, and 1,000 mg metformin XR with each treatment period separated by a 2-week course of placebo. Initial treatment, placebo or metformin XR, will be decided randomly. At the end of each two-week treatment period, participants will complete questionnaires assessing overall satisfaction with the medication, gastrointestinal symptoms, and adherence. Six months after the conclusion of the intervention, follow-up will establish if patients are continuing metformin at a higher dose than upon entry to the trial. This trial has two aims. First, to test the hypothesis that medication satisfaction will be the same during periods of placebo treatment and during periods of treatment with the active drug. The second aim is to test the hypothesis that > 30% of metformin-intolerant patients in an N of 1 crossover trial are able to tolerate higher-dose metformin at 6-months.

Relevant Scientific Background:

Despite 60 years of clinical use, and approximately 20 years in which it has been the consensus first-line drug for type 2 diabetes, there are still unresolved translational science questions about metformin. Metformin has only a 50% rate of use among patients with diabetes, and far lower rates of use in patients with obesity and pre-diabetes. In all these groups, poor tolerability related to gastrointestinal side effects is seen as a significant barrier to use. Intolerance can result in non-persistence, poor adherence, or the inability to titrate the dose up to that shown to be efficacious in major studies. One question about metformin intolerance is how often it results from reproducible physical side effects and how often it results from subjective symptoms that are either transient or attributable to placebo effect ("psychogenic intolerance"). Anecdotally, some metformin-exposed patients experience dramatic, objective gastrointestinal side effects that preclude (or dose-limit) its use, while other patients experience vaguer malaise that may be psychogenic. Statin therapy provides a useful analogy: while some statin users experience objectively verifiable myopathy with creatine kinase elevations, others discontinue statin therapy due to much more subjective symptoms. Joy and colleagues found a group of eight patients with a history of statin intolerance could not reliably distinguish between statin and placebo in a crossover re-challenge study, and that half of these patients persisted with statin use long-term after the re-challenge.[1] Particularly in diabetes prevention, the perception by

patients that metformin is worsening their quality of life may be a substantial barrier to long-term use. Research is needed to characterize how often this concern is based on reproducible side effects and how often it is a form of placebo effect. For patients in whom it is due to placebo effect, simple interventions (for example, demonstrating that the side effects are the same with the drug and with a placebo) might eliminate this psychogenic intolerance and make the patient more comfortable with long term use of metformin. For patients who do have reproducible symptoms from metformin use, more research into the risk factors and causes for such side-effects is needed to support development of interventions to make metformin more tolerable.

There are over 14 million unique prescriptions for metformin in the U.S annually, and it is widely regarded as a very safe medication for the treatment of type 2 diabetes mellitus; though side effects do occur. The most frequent adverse events attributable to metformin are primarily gastrointestinal, including nausea, diarrhea, and GI upset. Metformin contains a black-box warning for lactic acidosis, however cases of this occurring nearly are nearly non-existent. One study (Salpeter) found, "There is no evidence to date that metformin therapy is associated with an increased risk of lactic acidosis or with increased levels of lactate compared with other antihyperglycemic treatments if the drugs are prescribed under study conditions, taking into account contraindication".[2] Furthermore, risk of hypoglycemia is near zero with metformin. The package insert for metformin produced by the FDA states, "hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas) or ethanol".

From a pragmatic point of view, it has been proposed that for patients who are strongly motivated to use a medication but experience subjective discomfort when using it, an n-of-1 placebo-controlled trial can be a therapeutic intervention. For patients who are having difficulty assessing whether their quality of life is worsened by exposure to a drug like metformin or a statin, undergoing a placebo-controlled double-blinded crossover study and finding that they cannot distinguish between the two could reduce concerns about purely subjective, placebo-driven side effects, and allow patients to use the drug without experiencing those effects. Conversely, if side effects are clearly reproducible with exposure to drug over placebo, patients and their providers could confidently conclude that the drug really is not tolerable for that patient. This idea has been developed to a limited extend in statin use, but has not been applied to diabetes treatments.

Methods:

Patients will be recruited at Weill Cornell Medicine and will be eligible if they have a diagnosis diabetes, pre-diabetes, or obesity, previously attempted to take metformin for one of these indications, and have a history of intolerance to metformin. Intolerance may manifest either as the inability to take metformin at all, or the inability to titrate the dose past 1,000 mg due to side effects. Intolerance will be defined based on the treating

physician's assessment that a history of metformin intolerance (defined as the inability, due to side effects, to use metformin at the otherwise medically appropriate dose) exists, confirmed by the patient's recollection of the same history .

Subject will be recruited that currently have a diagnosis of diabetes, pre-diabetes, or obesity, and possible related comorbidities, but who are ambulatory, independent, and neither seriously nor terminally ill.

Electronic medical records will be reviewed for patients who have been prescribed metformin hydrochloride and for whom the medical record indicates that metformin intolerance occurred and limited the patient's ability to take metformin.

Physicians involved in the clinical trial will identify eligible patients. Once identified, the physician will approach the patient in the clinic at their next appointment and discuss participation in the study. With the permission of other providers at WCMC, such as primary care providers, physicians involved in TreatMet or other study personnel in TreatMet may contact patients by telephone to invite them to participate in this study. Physicians will receive an email, or personal contact inquiring whether they are willing to give the investigators permission to contact specific patients, or to contact patients themselves. Only after obtaining physician approval, patients will be contacted via telephone to invite them to participate in TreatMet. Patients will be contacted during normal office hours. If a patient declines participation, they will not be contacted again. If patients do agree, an in-person meeting for written informed consent will be scheduled. Patients are free to opt-out at any point in this process.

Study Design:

This trial is a self-controlled, double blind crossover study enrolling patients with a clear history of metformin intolerance. Intolerance is defined here as the inability, despite the recommendations of the treating physician, either to take metformin at all, or to increase daily metformin dose beyond 1,000 mg. The study intervention is the addition of 250 mg, 500 mg, 750 mg, and 1,000 mg of metformin daily, to the patient's existing regimen. Up to twenty patients will be enrolled for ten months. For one two-week block they will have 250 mg of metformin extended-release added to their existing regimen, followed by two-week blocks of 500 mg, 750 mg, and 1,000 mg metformin XR, each separated by two-week periods of placebo. The order of treatment assignments will be double-blinded and randomized, except that the 250 mg, 500 mg, 750 mg, and 1,000 mg blocks will always occur in order, smallest to largest.

Primary Objectives:

For aim 1 of this study, the primary objective is to test the hypothesis that patients will have similar treatment satisfaction on metformin and on placebo. The primary outcome of this portion of the study will be the results of the Treatment Satisfaction Questionnaire for Medication. For aim 2 of this study, the primary objective is to test the hypothesis

that > 30% of the patients enrolled in this study are able to tolerate higher-dose metformin at 6 months.

Secondary Objectives:

For aim 1, the secondary objectives are to test the hypotheses that scores on a gastrointestinal symptom questionnaire are not significantly different between placebo and intervention periods; that adherence is not significantly different between periods; and that the answer to the question 'Were you taking placebo or metformin for the past two weeks' is correct no more often than would be predicted by chance.

Statistical Considerations:

With respect to sample size for aim 1, by Lehr's approximation, a sample size of 16 would be needed to identify a 1 standard deviation difference in the mean score on the Medication Treatment Satisfaction Questionnaire. The target sample size is 20 patients to account for possible patient dropout. With respect to sample size for aim 2, by Lehr's approximation, a sample size of 20 provides 95% confidence intervals of approximated +/- 20% around most reported percentages. If the reported rate of success in increasing metformin dose is 30%, the 95% confidence interval around that estimate will range from 10% to 50%. If the reported percentage is 0%, the 95% confidence interval will be approximately 0-15%. We think these are sufficiently precise estimates to help clinicians decide whether n-of-1 clinical trials are a useful intervention for overcoming metformin intolerance.

Inclusion/ Exclusion Criteria:

Patients will be eligible if they are between the ages of 18 and 100. Patients will be recruited in an outpatient setting. Subjects will be enrolled regardless of gender, though a 50:50 ratio of male to female subjects is desirable.
Patients will be ineligible if they have a contraindication to metformin (ie, advanced renal or liver disease, a history of lactic acidosis attributed to metformin, or advanced heart failure). Pregnant women will be excluded from this study due to risk of confounding; pregnant women frequently have nausea and vomiting, changing over time, which if included may invalidate the results of the study.

Assessing Safety and Efficacy:

No data will be collected systematically to monitor safety or efficacy, only tolerability. However, the gastrointestinal symptom questionnaire will serve to quantify gastrointestinal adverse events every 2 weeks. Patients will be educated on potential side effects and risks of metformin and encouraged to both stop the medication and contact the investigators if they experience intolerable side effects or any severe adverse reactions

Interim and Complete Stopping Rules:

Due to the small sample size, short duration, and limited risks of this study, statistical stopping rules are not specified. Patients are encouraged to speak with their physicians and study coordinators regarding any medication-associated adverse events that may occur as a result of participation in this study.

Adverse Events Collection:

Adverse events that may cause termination or dropout of a subject include hypoglycemia, lactic acidosis, and severe gastrointestinal effects including severe nausea, vomiting, and diarrhea.

Metformin has a well-established safety profile in this clinical setting and no active monitoring for adverse events is planned. Patients who are using diabetes drugs associated with hypoglycemia (sulfonylurea, insulin, or meglitinide) will be advised of the potential for metformin to increase risk of hypoglycemia by potentiating the action of those drugs, and to immediately report any occurrence of hypoglycemia both to the study team and to their regular physician

Adverse events will be graded according to the "Common Terminology Criteria for Adverse Events (CTCAE) v4.0" scale produced by the United States Department of Health and Human Services and the National Institutes of Health. The CTCAE scale rates potential adverse events on a scale from 1 to 5, and is a commonly accepted method of grading adverse events. All adverse events will be recorded on the Office of Research Integrity's "Adverse Event & IND Safety Reporting Cumulative Table". We will report all required adverse events and incidents to NYPH-WCM Patient Services, Risk Management, and/or the Department of Health.

In addition to the IRB, all adverse events recorded during this trial will be reported to Dr. James Flory, and Dr. Leon Igel.

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[1] Joy TR, Monjed A, Zou GY, Hegele RA, McDonald CG, Mahon JL. N-of-1 (Single-Patient) Trials for Statin-Related Myalgia. *Annals of Internal Medicine.* 2014;160(5):301-310

[2] Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2010;2010(4):Cd002967.