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Erectile dysfunction (ED) affects up to 30 million men in the United States. The only class of oral medication approved for ED is phosphodiesterase type 5 inhibitors (PDE5i). These include sildenafil, tadalafil, vardenafil and avanafil. Other pharmacologic options in the treatment of ED are delivered as an intraurethral suppository (alprostadil) or intracavernosal injection (alprostadil, papaverine, phentolamine, atropine). These are more invasive routes of administration. Men who fail to obtain benefit from a PDE5i or those who have a contraindication to this class of medication may ultimately avoid further pharmacologic treatment options. An alternative class of oral medication to treat ED may prove to be of benefit to a large population of underserved men.

There is in vitro evidence that beta-3 adrenergic receptors exist in human corpus cavernosum tissue. Activation of these receptors results in vasorelaxation, suggestion a potential pro-erectogenic effect is possible in vivo. Additionally, nebivolol, a beta-blocker, has pro-erectogenic effects noted in several studies. There is evidence that nebivolol exerts beta-3 adregenergic agonism, which may explain the mechanism by which these effects occur.

Mirabegron is the only available beta-3 adrenergic agonist in the United States. Its favorable safety profile and the potential for therapeutic efficacy in ED make it suitable for further investigation.

We hypothesize that beta-3 adrenergic activation offers a pharmacologic target for the treatment of ED. Men with mild, mild to moderate, or moderate ED and symptoms of overactive bladder (OAB) can be recruited with pre- and post- Mirabegron administration assessment of their ED to determine the validity of this hypothesis. Men with sever ED will be excluded as historical data shows they are less likely to benefit from oral pharmacologic therapy alone. Mirabegron is approved by the U.S. Food and Drug Administration (FDA) for the treatment of adults with OAB. Therefore, recruiting men with concurrent ED and OAB (rather than men with ED alone) will avoid the need for off-label administration of Mirabegron.

We propose a pilot study to be initiated at Johns Hopkins to investigate this hypothesis. If measurable positive effect on erectile function is noted, this can guide further investigation in a randomized, placebo-controlled blinded clinical trial.

For the observational pilot study, we will recruit 20 men with mild, mild to moderate, or moderate ED and symptoms of OAB who present routinely to the urology clinic at Johns Hopkins. This initial group of patients will allow a clinical assessment of Mirabegron’s possible in vivo effect on erectile function.

- Screening of erectile function status will be performed using the International Index of Erectile Function Questionnaire (IIEF). The Overactive Bladder questionnaire (OAB-q) will be used to assess the bother of OAB symptoms and its impact on health related quality of life. Currently, questionnaires such as the IIEF and the Sexual Health Inventory for Men (SHIM) are the primary tools guiding diagnosis and medical therapy of ED. Other validated tools or measurable physiologic correlates of ED are not yet available in current Urology clinical practice. More objective testing via a penile Doppler ultrasound is performed only for surgical candidates and does not guide medical therapy.
- Inclusion criteria will be: (1) men 18 to 70 years old, (2) presence of mild (score 22-25 out of 30 on the IIEF-Erectile Function domain), mild to moderate (score 17-21) or moderate (score 11-16) ED, (3) presence of OAB symptoms for at least 3 months with at least 3 micturitions per day and at least 3 episodes of urgency in a 3-day period. Past use of anticholinergic medications is acceptable.
- Exclusion criteria will be: (1) concurrent ED therapy, (2) prior pelvic surgery (including prostatectomy, cystectomy, transurethral procedures), (3) prior penile surgery (4) history of priapism, (5) history of neurologic disease (such as spinal cord injury, Parkinson's disease, multiple sclerosis), (6) uncontrolled hypertension (systolic blood pressure > 140mmHg or diastolic blood pressure > 90mmHg), (7) chronic kidney disease stage 4 or 5 (estimate creatinine clearance rate < 30ml/min), (8) moderate or severe hepatic impairment (Child-Pugh Class B or C) (9) concomitant use of CYP2D6-metabolized drugs (metoprolol, desipramine, thioridazine, flecainide, propafenone) or digoxin (10) post void residual greater than 150 ml, or (11) evidence of urinary tract infection on urinalysis and/or urine culture.

Internal review board approval will be obtained prior to patient screening. Following this, patients being seen routinely in the clinic setting will be screened for possible study participation. The initial clinic visit will consist of medical and surgical history, a physical exam (including blood pressure, postvoid residual measurement using a portable ultrasound machine specifically for this purpose as is routinely done in Urology clinical practice and urinalysis and/or urine culture) and administration of the IIEF and OAB-q questionnaires. A physician or clinical nurse participating in the pilot study will perform these tasks. Results will be recorded. A schematic of the protocol study design is shown below.

	Baseline	Week 2	Week 4	Week 8	Week 12
Vital Signs	X	X	X	X	X
Postvoid Residual (Ultrasound)	X		X	X	X
Urinalysis	X	X	X	X	X

IIEF	X	X	X	X	X
OAB-q	X	X	X	X	X
Clinical Interview	X	X	X	X	X

- Patients who meet inclusion criteria, do not meet exclusion criteria and are interested in participating in the study will discuss the risks and benefits of trial participation in detail. Informed consent will be obtained without monetary compensation.
- Time 0: Study participants will be provided with daily Mirabegron 25mg for 14 days (2 weeks. Astellas will supply the medication. Instruction for participants will include careful monitoring for any adverse effects of the medication, including those related to elevated blood pressure, nasal congestion, urinary tract infection, headache or other changes from baseline. Participants will receive contact information with 24-hour access to report any adverse reactions and to receive medical advice. Any concerning symptoms (at any stage of the study) will result in immediate discontinuation of the provided medication, medical assessment and recording of these findings. The FDA's MedWatch program and Astellas will be contacted to report such findings as well.
- Week 2: Study participants will return for evaluation by a physician or clinical nurse. Any noted adverse reactions will be recorded. Blood pressure and postvoid residual will be measured. IIEF and OAB-q questionnaires will be administered. If no adverse findings are noted, the participants will have the opportunity to dose-escalate if required to assess optimal benefit from use of the medication, Accordingly, they may either continue on Mirabegron 25 mg daily or proceed to receive Mirabegron 50mg daily to be taken for the next 10 weeks. Reduction in dosing will also be permitted during the course of the study (resumption of 25mg daily dosing) and will be recorded. Instructions to report any adverse reactions will be reinforced, as previously.
- Weeks 4 and 8: Study participants will return for interim evaluation by physician or clinical nurse. Reassessment of adverse reactions and clinical monitoring (blood pressure, postvoid residual) will be repeated, followed by re-administration of IIEF and OAB-q questionnaires.
- Week 12: Study participants will return for final evaluation by a physician or clinical nurse. Adverse reactions will be recorded. Blood pressure, postvoid residual IIEF and OAB-q questionnaires will again be assessed. Participants will be encouraged to contact study investigators with any concern of adverse effects following the conclusion of their participation.

Results from 20 subjects will be carefully tabulated. Adverse events will be recorded. Changes in blood pressure and postvoid residual will be evaluated. IIEF and OAB-q scores will be reviewed. The primary endpoint will be the change in IIEF-Erectile Function domain score

between Time 0, Week 2 and Weeks 4, 8 and 12. A measurable positive effect will be noted by a total mean increase of 4 or more points in the IIEF-Erectile Function domain score. Secondary endpoints will include OAB improvement, as reflected by a 10 point decrease in OAB-q symptom severity score.

This non-randomized single arm study will enroll 20 men with mild to moderate ED by IIEF criteria (scores 11-25) and symptoms of OAB. Pre-treatment IIEF and OAB scores will be compared to post-treatments scores at 4, 8, and 12 weeks. The primary analysis for both IIEF and OAB scores will be repeated measures analysis of variance (RMANOVA) if there are no missing time points, otherwise a mixed model will be used. The primary endpoint will be the TIME effect, i.e. to test for a change from pre-treatment value of IIEF or OAB. The minimum change considered clinically relevant is an increase in IIEF of 4 units, and a decrease in OAB of 10 units. In addition to absolute change I IIEF or OAB scores, we will also evaluate models of percentage change from pre-treatment value. If the overall effect of TIME is statististically significant we will use paired t-tests comparing pre-treatment to each of the post-treatment values, with a Bonferroni p-value adjustment, to determine the time at which an increase in IIEF of at least 4 points or a decrease in OAB of at least 10 points can first be detected. Covariates to be evaluated as potential confounding factors include age, comorbidity or cause of ED, body mass index, and other medications.

Although this is a pilot study and there are no data to suggest the magnitude of the effect of Mirabegron on ED, we performed power calculations for various scenarios of change in IIEF or OAB. The scenarios used a pattern of means with an absolute increase from pre-treatment to 12 weeks of 4 units for IIEF and absolute decrease of 10 units for OAB, and plausible conservative (higher than expected) values for the within-subject standard deviation that were increased until power fell below 80%. For both IIEF and OAB we evaluated power if the pre-treatment mean was the midpoint of the range of values eligible for study: IIEF = 18 (range 11-25), OAB = 50 (range 0-100). However, the power was not sensitive to the pre-treatment mean, and showed little variation according to the specific changes in mean score between time points, for a fixed overall change from pre-treatment to 12 weeks. The table below shows power to detect a 4 unit increase in IIEF and 10 unit decrease in OAB, with 20 patients evaluated at 4 time points, $\alpha = 0.05$, within-subject standard deviation and autocorrelation both constant over time. Power calculations were performed using PASS v. 11 (NCSS Software, Inc., Kaysville, UT), according to the method of Mueller (Mueller 1989).

Pattern of means over 4 time points				**Within-subject SD**	**Power**
Pre-test	**4 weeks**	**8 weeks**	**12 weeks**		
IIEF					
18	20	20	22	2	>0.99
18	20	20	22	3.5	0.88
18	20	20	22	3.8	0.81

OAB					
60	56	52	50	5	>0.99
60	56	52	50	8	0.87
60	56	52	50	10	0.84

Thus, despite the small size of the study, power is likely to be more than adequate to detect the minimum changes in IIEF (increase 4 units) and OAB (decrease 10 units) considered clinically relevant.

Should a measurable positive effect be noted, a more extensive randomized, placebo controlled, blinded and possibly multi-institutional trial be considered. The information obtained from the pilot study an help guide future studies if appropriate.

Rationale for the proposed drug doses:

Per the Mirabegron US package insert, 2015: The approved therapeutic dose of Mirabegron for OAB in the United States is 25mg once daily which may be increased to 50mg once daily based on individual tolerability. Mirabegron has been studied at doses ranging from 25mg to 200mg once daily in OAB patients and 25mg demonstrated statistical superiority compared to placebo for incontinence episodes and frequency.

Rationale for 12-week observation period:

Mirabegron has been studied extensively for at least a 12-week time period as this was the approximate time other classes of OAB drugs (eg. Antimuscarinics) were discontinued due to low tolerability (eg. Dry mouth). Mirabegron was found to be both efficacious and tolerable within this time frame.

Rationale for open label study design:

The proposed study is an observational pilot investigation. Results from this preliminary investigation will dictate the utility of a more resource consuming, future randomized controlled trial.

Discussion of the clinical effects and adverse effects of Mirabegron for its approved indication:

The approved indication is the treatment of OAB and the safety of the drug has been well characterized in phase 2 and 3 studies.

Potential adverse effects include QT prolongation with supratherapeutic doses or in high risk populations, increased heart rate and increased blood pressure, the risks of which are greater with increasing exposure. Cutaneous hypersensitivity reactions are also a potential risk. Changes in pulse rate and blood pressure are reversible upon discontinuation of the drug. The

most commonly reported adverse events include: hypertension, nasopharyngitis, urinary tract infection and headache. Other adverse events: constipation, upper respiratory infection, arthralgia, diarrhea, abdominal pain and fatigue.

Drugs that may interact with Mirabegron include:
Moderate to strong CYP2D6 inhibitors with narrow therapeutic index may interact with Mirabegron including: thioridazine, flecainide, propafenone, amitryptiyline, paroxetine, aripiprazole, donepezil, tramadol, imipramine, des/venlafaxine and terbinafine
Moderate to strong CYP3A4 inhibitors may also interact including: indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, Nefazadone, Saquinavir, Telithromycin,Cimetidine, Clotrimazole, Cyclosporine, Erythromycin, Fluconazole, Itraconazole

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