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PHOSPHODIESTERASE-5 INHIBITORS FOR ERECTILE DYSFUNCTION

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Until recently, sexual health has not been at the forefront of medical research. Over the last 8 years, new medications have been introduced that are safe and effective for the treatment of erectile dysfunction (ED). ED is defined as the recurrent inability to obtain and/or maintain an erection sufficient for sexual activity for at least 3 months.[1] Due to the ambiguity of the definition, the exact estimate of its prevalence is unknown. ED is a common disorder affecting over 150 million men worldwide. Approximately 52% of men between 40 and 70 years of age suffer from ED. In addition, the risk of ED increases 2-3 fold with each decade of life.[2] Unfortunately, 70-90% of men with ED do not receive treatment. ED not only affects the patient's quality of life, but also their partner. For example, it is estimated that ED is at least partially responsible for 20% of marriage failures.[3]

Any condition which impairs blood-flow to the penis may cause ED, while vascular disorders account for the majority of physiological causes.[4] Table 1 lists possible etiologies of ED. According to the MMAS (Massachusetts Male Aging Study), ED has a strong correlation to cardiovascular disease (CVD) and patients with CVD should be routinely screened for ED and vice versa. In fact, ED may be the initial manifestation of underlying vascular disease.[5] Regardless of the etiology, phosphodiesterase-5 inhibitors (PDE5i) are safe and effective oral agents routinely used for treatment of ED. This summary will focus on the similarities and differences between commercially available PDE-5 inhibitors: sildenafil (Viagra®), vardenafil (Levitra®), and tadalafil (Cialis®).

Pathophysiology

Obtaining an erection involves a complex cascade of neurovascular events modulated by hormonal and psychological factors. An erection is maintained by smooth-muscle tone of the corpora cavernosa. In the absence of sexual stimulation, contractile factors, endothelin-1 and PGF2a, are favored. These factors induce vasoconstriction and limit blood flow to the penis.

Upon sexual stimulation, penile vasculature and tissues change from a contracted to a blood-filled, relaxed state. The parasympathetic pathways amplifies the relaxant effects of nitric oxide (NO), which causes the corpora caversona to swell with blood. Cyclic guanosine monophosphate (cGMP) [second messenger of nitric oxide], through downstream me-

INSIDE THIS ISSUE:

Table 1. Etiologies of erectile dysfunction

Lifestyle	Disease states	Psychogenic	Medications
Smoking	Hypertension	Stress	Thiazide diuretics
Obesity	Dyslipidemia	Relationship difficulties	Beta-blockers
High-fat diet	Diabetes Mellitus	Performance anxiety	SSRIs
Sedentary	CVD		Anti-arrythmics
Alcohol/ drug abuse	Depression		

diators, leads to reduced cytosolic concentrations of calcium. Decreased availability of calcium leads to smooth muscle relaxation. Premature degradation of cGMP by PDE5 is key in detumescence.[3] Selective inhibition of PDE5 by sildenafil, vardenafil and tadalafil increases the availability of cGMP; thus, promoting smooth muscle relaxation and a sustained erection.

PDE5 is part of a protein superfamily of nucleotides which are divided into at least 11 families of related enzymes. Although structurally and functionally related, they show some differences in primary structure as well as tissue distribution. PDE5-inhibitors show a high selectivity towards PDE5, with minor selectivity differences between agents. Localization and reduced selectivity account for certain adverse effects of PDE5i. For example, PDE-6 is localized in photoreceptor cells in the rods and cones of the eye. When inhibited, visual disturbances, such as color changes, blurred vision, and loss of vision, may occur. Tadalafil's increased PDE5 selectivity may account for a reduced incidence of visual side effects.[6-8]

Pharmacokinetics

The pharmacokinetics of sildenafil, vardenafil, and tadalafil are summarized in table 2. Subtle differences exists between agents with half-life and period of response with tadalafil being clinically significant.

Efficacy

Sildenafil, vardenafil and tadalafil are highly effective in enhancing erectile function in a wide range of patients with many co-morbidities. Due to differences in study designs, comparisons of the three agents are difficult. Each agent improves general scores on function, intercourse satisfaction by the patient and partner, and overall satisfaction with therapy.[9] Night-time erections in men with and without ED, rigidity, and orgasmic function also show significant improvement. However, several randomized controlled trials (RCTs) show no improvement in libido when compared to placebo.[10, 11]

Each agent is effective in treating patients with a history of diabetes mellitus (DM). Tadalafil is an effective treatment for those DM patients with microvascular complications, such as diabetic retinopathy, or microabuminuria. RCTs for sildenafil and vardenafil excluded DM patients with a history of microvascular problems.[12-14] Although usually taken on demand, there is recent data to support daily administration of sildenafil. This type of administration seems to have a beneficial effect on endothelial function in diabetic patients due to amplification of tissue oxygenation during more frequent nocturnal erections.

In an open label study, authors investigated whether 50 mg of sildenafil at bedtime would have long-term improvements over "as-needed" use. After 1 year of treatment, both groups had similar erectile function domain scores. After a 4 week washout period, 59% of patients dosed nightly continued to have erectile domain scores in the normal range compared to only 9% of the on-demand group. Extended functionality after drug discontinuation may be secondary to improved endothelial function.[15] Future studies are needed to determine the role of daily administration for ED.

Safety

Table 2. Pharmacokinetics of PDE inhibitors [6-8]

	Sildenafil	Vardenafil	Tadalafil
Dosing (mg)	25, 50, 100	2.5, 5, 10, 20	5, 10, 20
Bioavalability (%)	40	15	NR
Onset (min)	14	10	16
Half-life (h)	4	4.5	17.5
Period of response (h)	4	NR	36
Δ Cmax with high-fat meal	▼29	▼18	No change

NR = none reported, ▼ = decrease

Safety of all three PDE5 inhibitors has been established through large clinical trials. Most adverse effects may be attributed to the inhibition of PDE5 in nonpenile tissues. Common adverse effects include rhinitis, myalgia/back pain, flushing, dyspepsia, headache, and abnormal vision. In an recent review, flushing was more common in patients taking vardenafil and sildenafil, while back pain and myalgia were more common with tadalafil. All adverse effects were typically transient and abated with time. Discontinuation rates were low with each agent at less than 3%.

Clinical trials of sildenafil, vardenafil and tadalafil included patients with stable cardiovascular disease (CVD) and DM. Trials did not include patients with unstable CVD, unstable angina, recent myocardial infarction, uncontrolled arrhythmias, uncontrolled hypertension, and heart failure. Guidelines exist for risk-stratification and counseling of ED patients with CVD. Patients who experience cardiac symptoms during sexual activity should seek immediate medical attention.

Drug Interactions

CYP 3A4 is the predominant enzyme responsible for metabolism of PDE5 inhibitors. Any potent inhibitor of 3A4 may increase the systemic exposure by 2-16 fold, which may increase adverse effects.[6-8] Concomitant use of organic nitrates and PDE5 inhibitors constitutes an absolute contraindication due to a PDE5 inhibitor's ability to potentiate the hypotensive/vasodilator effects of NO donors. Postural hypotension has been reported when sildenafil was administered together with doxazosin, an α-blocker commonly used for treating BPH and hypertension. According to the package insert (PI), sildenafil doses greater than 25 mg should not be taken within 4 h of an α-blocker.[6] Co-administration of an α-blocker is a precaution for patients taking vardenafil and tadalafil.[7,8] When co-administered with alcohol (a mild, systemic vasodilator), both sildenafil and vardenafil did not show an increase in hypotensive side effects in healthy patients with mean maximum blood alcohol levels of 0.08%.[6,7]

Treatment Success

Incorrect use of any of the PDE5 inhibitors could lead to treatment failure. To optimize treatment success, providers should educate patients that sexual arousal as well as multiple attempts may be required to obtain an erection. The majority of patients respond to treatment after 1 or 2 doses; however, some patients may need to undergo 6-8 separate attempts prior to success. Practitioners should educate patients not to be discouraged or give up before a sufficient number of attempts on the maximum dose is attempted. If a PDE5 inhibitor fails, an alternative PDE5 inhibitor should be attempted. In a review of patients with ED, investigators found the cumulative chance of successful intercourse increased from 54% on the first attempt to 86% after 7-8 attempts.[16]

Summary

ED is a consequence of aging. With several available treatments and additional emerging options, PDE5 inhibitors continue to be the most widely prescribed agents. Overall, PDE5 inhibitors are relatively safe and efficacious in about two-thirds of patients. Treatment success depends on the dose of medication, number of attempts, and, if necessary, switching drugs. Most often, patient preference is the key determinant to predict successful treatment.

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Table 3. Cost of therapy[2]

Sildenafil	Avg price[1]	Range[1]	**Vardenafil**	Avg price[1]	Range[1]	**Tadalafil**	Avg price[1]	Range[1]
25 mg	116	107-131	2.5 mg	107	98-115	5 mg	134	126-148
50 mg	116	107-131	5 mg	107	98-116	10 mg	134	126-148
100 mg	116	107-131	10 mg	114	107-127	20 mg	134	126-148
			20 mg	114	107-128			

[1]Rounded to the nearest dollar [2] Prices obtained for 10 tablets from 4 community pharmacies in Gainesville, FL

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Rimonabant (Acomplia®): The first endocannabinoid receptor antagonist for the treatment of obesity

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Globally there are over 1 billion adults who are overweight; as many as 300 million are obese. Obesity is considered a major risk factor for developing chronic diseases, such as type 2 diabetes, cardiovascular diseases, hypertension, stroke, and certain forms of cancer.[1] While genetics play a role in obesity, societal influence and nutritional habits, such as increased consumption of saturated fats and sugars, also contribute. The prevalence of health risks associated with obesity pose an extensive economic burden on society. It is estimated that obesity costs the United States over $117 billion each year including both direct and indirect costs, such as diagnosis, treatment, hospitalizations, and loss of productivity.[2] Costs associated with obesity are now estimated to be comparable to that associated with smoking.

The cannabinoid-1 (CB1) receptor is one of two known receptors of the endocannabinoid system associated with the intake of food and tobacco dependency. Preliminary evidence indicates that blocking the CB1 receptor increases satiety resulting in weight reduction.[3] Currently, there are only a few FDA approved medications for treatment of obesity: a lipase inhibitor (i.e. orlistat) and a central nervous system agents (i.e. sibutramine, phentermine, diethylpropion). However, adverse effects limit the use of these agents.[4] Development of investigational weight loss agents has concentrated on serotonin and noradrenaline reuptake inhibitors, lipase inhibitors, and leptin sensitizers. In addition, development should focus not only on reducing fat mass (adiposity), but also on correcting adipose tissue dysfunction (adiposopathy).[5]

Rimonabant (Acomplia® [ä kôm' plE ä]) is the first selective cannabinoid-1 (CB1) receptor blocker with an approvable letter from the FDA.[6] The European Union approved rimonabant on June 21, 2006 for the

treatment of obesity in addition to diet and exercise. This paper will review the efficacy, safety, cost, and convenience of rimonabant.

Pharmacology and Pharmacokinetics

High concentrations of endocannabinoid receptors are synthesized in the GI tract. Endocannabinoid receptors found in the brain and intestine are responsible for integrating feeding behavior, metabolism, and energy balance. Specifically, CB1 receptors are found throughout the enteric system, in spinal and vagal afferents from the gut, and in adipocytes. Endocannabinoid concentration in the hypothalamus increases during short-term fasting and declines during feeding.[7] Rimonabant works on the premise that if endocannabinoids induce hunger, antagonists at the CB1 receptor will help reduce appetite and stimulate weight loss.

Absorption of rimonabant exhibits linear kinetics up to a 20 mg dose, or target dose, after which there is a decline in absorption. In healthy and obese subjects, mean peak plasma concentrations (Cmax) were similar and ranged from 188 ng/mL in obese volunteers to 196 ng/mL in healthy volunteers. Time to maximum concentration (tmax) occurred 2 hours after oral administration. Steady-state concentration was achieved in 25.5 days. The terminal elimination half-life of rimonabant is 6-9 days in healthy subjects and 16 days in obese subjects due to a larger peripheral volume of distribution.[8] Gender has no impact on the pharmacokinetics of rimonabant.[9] No dosage adjustment is required for renal impairment or mild to moderate hepatic disease. Of note, rimonabant has not been studied in severe hepatic disease.

Clinical Trials

There are numerous trials investigating the effects of rimonabant on weight loss, lipids, atherosclerosis, smoking cessation, diabetes, alcoholism, and other cardiometabolic factors. Three trials are complete and published, while others are currently enrolling patients.

Rimonabant in treatment of obesity in North America

The Rimonabant in Obesity-North America (RIO-NA) trial was a two year, randomized, multicenter, placebo-controlled, double-blinded study that evaluated the effects of rimonabant on overall weight reduction from baseline.[10] RIO-NA is the largest clinical trial of rimonabant to date with over 3,000 subjects, and is the most recent segment completed for the rimonabant phase III trials. After a 4 week, placebo plus diet (600kcal/d deficit) run-in period, patients were randomized to receive either 5 mg or 20 mg of rimonabant or placebo once daily. In the second year, patients were re-randomized to either the same dose of rimonabant or switched to placebo. The main outcome measures included body weight change in the first year, and prevention of weight gain over the second year. Secondary outcome measures were changes in waist circumference, plasma lipid levels, and other cardiometabolic risk factors.

All patients lost a mean of 1.9 kg in the 4 week placebo run-in period. After randomization to 5 mg, 20 mg, or placebo, weight loss in the rimonabant groups was significantly greater than those randomized to placebo. The percentage of patients achieving 5% or greater weight loss at one year was 26.1% in the 5 mg rimonabant group (P=0.004), 48.6% in the 20 mg rimonabant group ($p<0.001$), and 20% in the placebo group. Patients achieving or exceeding 10% weight loss was 25.2% of patients in the 20 mg rimonabant group and 8.5% of placebo patients ($p<0.001$). In the second year of the study, patients were re-randomized to either rimonabant 20 mg or placebo. Patients treated with rimonabant 20 mg once daily for 2 years achieved an average 7.9 lbs greater weight loss than the placebo group ($p<0.001$). In contrast, patients switched from active drug to placebo for the second year of treatment regained the majority of weight lost in the previous year.

Rimonabant effects on metabolic risk factors

The Rimonabant in Obesity-Lipids (RIO-Lipids) trial was a 12 month, double-blinded, randomized, placebo-controlled trial that evaluated the effects of rimonabant on body mass index (BMI).[11] The trial also measured secondary effects, including changes in cholesterol, insulin resistance, glucose tolerance, and the prevalence of metabolic syndrome. Patients were obese (BMI of 27 to 40 kg/m^2), had untreated dyslipidemia, and were non-diabetic. Study subjects were randomized to receive 5 mg or 20 mg of rimonabant, or placebo, in addition to a hypocaloric diet (600kcal/d deficit). Follow up with a dietician occurred every 2 weeks for the first two visits, then monthly for the duration of the study. Clinical endpoints included 5% and 10% weight loss from baseline. Each group lost 2 kg initially. The placebo

Table 2. RIO-Lipids: Changes from Baseline† for Secondary Endpoints in the Intention to Treat Population (Last-Observation-Carried-Forward Method)[12]

End point	Placebo	Rimonabant 5mg		Rimonabant 20mg	
			p value		p value
HDL cholesterol (mg%)	11.0 ± 15.8	14.2 ± 17.6	NS	19.1 ± 20.9	<0.001
Total cholesterol:HDL ratio	-0.14 ± 0.68	-0.23 ± 0.82	NS	-0.72 ± 0.93	<0.001
Fasting glucose (mmol/L)	-0.05 ± 0.62	-0.01 ± 0.62	NS	-0.08 ± 0.58	NS
Fasting insulin (microunits/ml)	0.09 ± 15.9	0.04 ± 10.3	NS	-1.7 ± 12.4	0.011
Adiponectin (mcg/ml)	0.7 ± 1.9	1.0 ± 2.0	NS	2.2 ± 2.5	<0.001
Leptin (ng/ml)	-0.3 ± 6.0	-2.3 ± 7.9	<0.001	-4.1 ± 7.4	<0.001
C-reactive protein (mg/L)	-0.4	-0.2	NS	-0.9	0.02
Systolic blood pressure (mmHg)	-0.3 ± 10.1	0.4 ± 11.8	NS	-2.1 ± 12.3	0.048
Diastolic blood pressure (mmHg)	-0.2 ± 7.4	0.1 ± 8.3	NS	-1.7 ± 8.5	0.011
QTc (msec)*	-1.8 ± 15.3	-3.7 ± 16.9	ND	-4.6 ± 15.7	ND
Depression*	0.2 ± 2.7	-0.2 ± 2.8	ND	0.1 ± 3.1	ND
Anxiety*	0.1 ± 2.7	-0.1 ± 3.5	ND	0.3 ± 3.0	ND

† Plus-minus values are means ± SD, NS = Not significant, ND = Not determined
* No statistical test was performed; measured according to the institution's anxiety and depression scales

group had a further 2.3 kg weight loss over the entire 12 months compared to a weight loss of 4.2 kg in the 5 mg group and 8.6 kg in the 20 mg group($p<0.001$). The proportion of patients who reached or exceeded the weight loss endpoint of 5% was 19.5% in the placebo group and 58.4% in the 20 mg group ($p<0.001$). The proportion of patients who achieved or exceeded 10% weight reduction was 7.2% in the placebo group and 32.6% in the 20 mg group ($p<0.001$). Weight loss occurred in the first 9 months and stabilized without regain for the duration of the study.

In addition to decreased weight and waist circumference, there was also a wide array of cardiometabolic risk factors that improved in RIO-Lipids (Table 2).

Safety

Overall discontinuation rates were similar among the three treatment groups in each trial, but more patients discontinued treatment due to adverse events in the 20 mg rimonabant group than in other groups. In the first year of the RIO-Lipids trial when compared with placebo, adverse effects that were reported in 5% or greater of patients receiving 20 mg rimonabant included upper respiratory tract infection, nasopharyngitis, nausea, influenza, diarrhea, arthralgia, anxiety, insomnia, viral gastroenteritis, dizziness, depressed mood, and fatigue.[8] In the second year, study withdrawals, and adverse event-related study withdrawal were lower than in the first year and there were no differences among the treatment groups.

In Rio-NA, serious adverse events occurred in 5.2% of the 5 mg group, 4.0% in the 20 mg group, and 2.3% in the placebo group. Adverse events that occurred in 5% or greater of each treatment group, in decreasing order of frequency, were nausea, dizziness, influenza, anxiety, diarrhea, and insomnia, and occurred more often in the 20 mg treatment group. The most common adverse events in the treatment groups compared with placebo that resulted in discontinuation included depression, anxiety, and nausea.[9] Other safety measures were similar in all groups except for blood pressure which was decreased in the rimonabant 20 mg group, and occurred more often in patients that were hypertensive at baseline.[9]

Dosing and Cost

Rimonabant is in phase III clinical trials and is not currently marketed in the United States. If approved, rimonabant will be available as 20 mg tablets with once daily administration. Long term effects are unknown at this time. Information regarding the du-

ration of therapy is pending further investigation. Pricing information from Europe projects the cost of rimonabant to be about $82 for 28 days of therapy. Rimonabant is projected to be available in late 2006.

Summary

Rimonabant is the first endocannabinoid receptor antagonist for treatment of obesity. It increases satiety and causes weight reduction through activity at the CB1 receptor. Phase III clinical trials (RIO-NA and RIO-LIPIDS) demonstrated positive results of rimonabant-induced weight loss and decreased waist circumference, as well as improvements in other cardiometabolic risk factors. At high concentrations, rimonabant blocks calcium and potassium channels, and may directly affect cellular gap junctions through the CB2 receptor. Actions through this alternative mechanism may soon initiate human clinical trials for myocardial infarction, endotoxemia, and attenuating shock due to hemorrhage. Ongoing clinical trials are currently investigating the effects of rimonabant on smoking cessation, diabetes, and reduction of alcohol consumption.

The use of current weight loss agents is limited due to their significant side effect profile. Rimonabant may be an alternative to these agents in obese patients. In addition to a limited side effect profile, rimonabant's effect on weight loss and cardiometabolic risks may prove useful in patients with metabolic syndrome.

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