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Afrezza® (Technosphere® Insulin Inhalation System): Rapid-Acting Inhaled Insulin for the Treatment of Diabetes

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Diabetes affected an estimated 29.1 million Americans (9.3% of the United States population) in 2012, an increase from 25.8 million Americans (8.3% of the U.S. population) in 2010.[1] The vast majority of these patients have type 2 diabetes. Unfortunately, the prevalence of type 2 diabetes appears to be growing: in 2012, 1.7 million new cases of adult-onset diabetes were diagnosed. Importantly, diabetes is the 7th leading cause of death in the U.S. and 9th leading cause of death worldwide.[2] Nationwide, the overall treatment of diabetes cost an estimated $245 billion dollars in 2012.[1]

Despite being so common and relatively well-studied, a large percentage of people with type 2 diabetes remain uncontrolled, particularly those with more advanced or more severe disease. These people have often tried one or more oral antidiabetic agents and eventually most require exogenous insulin. According to National Health Interview Survey (NHIS) data, an estimated 2.9 million patients with diabetes (type 1 and type 2) use insulin only.[1] All currently-available insulin products require subcutaneous or intravenous injection; however, many people fear injections or find them cumbersome.[3] New routes of administration for insulin may help improve treatment adherence, thus improving glucose control, for those patients requiring insulin therapy.

Afrezza®, marketed by Sanofi, is a new rapid-acting inhaled insulin that was recently granted an FDA-approved indication for improving glycemic control in adult patients with diabetes mellitus. Hereafter, the term "Technosphere® inhaled insulin" or "TII" is used to refer specifically to Afrezza®; this product is different from the previously-available inhaled powder insulin (Exubera®), manufactured by Pfizer. The objective of this article is to review the pharmacology, clinical trials, contraindications, warnings, precautions, limitations, and dosing and administration of TII.

PHARMACOLOGY

Pharmacodynamics and Pharmacokinetics

TII is composed of recombinant human insulin (regular human insulin) and an inert excipient, fumaryl diketopiperazine (FDKP) that are administered with the breath-powered-Gen2 inhaler delivery device.[4] After pulmonary absorption into the systemic circulation, the elimination and metabolism of TII is comparable to regular human insulin. Following TII inhalation, the T_{max} is reached within 7.5 to 20 minutes (usually within 12 to15 minutes), independent of dose.[5] Serum insulin concentrations return to baseline approximately 180 minutes after administration. The median terminal half-life is 28 minutes following administration of 4 units, and 39 minutes following 32 units.[4] Compared with subcutaneous regular insulin or subcutaneous insulin lispro, TII has a rapid onset of action, which closely mimics endogenous insulin mealtime secretion, and a shorter duration of effect. The bioavailability of TII is estimated to be 30%.[4]

Special Populations

TII is considered a Pregnancy Category C medication.[4] However, to date, TII has not been studied in pregnant women or nursing mothers. Likewise, clinical studies to date have not included patients younger than 18 years of age.[4] A small number of patients aged ≥65 years have been included in clinical trials. However, additional studies assessing age-related changes in pharmacokinetic and pharmacodynamics effects on this medication are needed.[4] The effects of renal or hepatic impairment on the pharmacokinetics of TII have not been studied. Thus, more frequent monitoring may be necessary for this patient population.[4]

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Drug-Drug Interactions

The **Box** includes potential drug-drug interactions with subcutaneous insulin.[4] Whether and to what degree these drugs interact with TII is not known; however, pharmacodynamics interactions seen with subcutaneous insulin are likely to also occur with inhaled insulin.[4]

Clinical Trials

Unpublished Clinical Trials

TII has been studied in two pivotal phase III clinical trials, MKC-TI-171 and MKC-TI-175, neither of which has been published at the time of this writing. Both trials were presented at the American Diabetes Association Meeting in San Francisco, 2014 and thus have not been peer-reviewed. **Table 1** summarizes these trials.

Trial 171

The efficacy and safety of TII combined with basal insulin (N=174) was compared to insulin aspart combined with basal insulin (N=171) in Trial 171.[6] The patients included in this study were individuals that had a clinical diagnosis of type 1 diabetes mellitus for at least 12 months, body max index (BMI) ≤38 kg/m^2, stable dose of basal/bolus insulin therapy for at least 3 months with a fasting plasma glucose <220 mg/dL, HbA1c between 7.5% and 10%, nonsmoker for the preceding 6 months, fasting C-peptide ≤0.30 pmol/mL, negative urine cotinine test, and lung function tests (forced expiratory volume, FEV_1 ≥70%).[7] Patients were excluded from the study if they had a total daily insulin dose ≥2 IU/kg, a history of lung disease (e.g., COPD, asthma), severe complications of diabetes (in the opinion of the primary investigator), ≥2 unexplained severe hypoglycemic episodes within 3 months of screening, any hospitalization due to poor diabetic control within 6 months of screening, or were pregnant, lactating, or planning to become pregnant. The primary outcome was the change in HbA1c after 24 weeks. Important secondary outcomes included: fasting plasma glucose change from baseline and change in bodyweight from baseline.[7] TII plus basal insulin was found to be non-inferior to insulin aspart plus basal insulin in improving HbA1c, with similar mean reductions of 0.21% vs. 0.40% (between group difference at week 24 was 0.19% [95% CI 0.02 to 0.36]), respectively.[6] Patients on the TII plus basal insulin regimen had a fasting plasma glucose reduction of 25mg/dL from baseline to week 24, versus an increase in fasting plasma glucose of 10 mg/dL for those in the aspart plus basal insulin group, for a between group difference at week 24 of 35 mg/dL (95% CI -56.25 to -14.59; p=0.0009), favoring the TII group. Patients on TII plus basal insulin regimen experienced weight loss (-0.4 kg), whereas those in the aspart plus basal insulin group gained weight (+0.9 kg), for a between group difference at week 24 of 1.3 (95% CI -2.3 to -0.3; p=0.01), favoring TII, over the course of the study. Hypoglycemia events were frequent in both groups, although lower in the TII plus basal insulin intervention (9.8 vs. 13.97 hypoglycemic events per subject-month; p<0.0001).[6] It is unclear why those in the TII group had greater fasting glucose reductions, but fewer hypoglycemic events; these findings may be due, in part, to the timing of monitoring since TII has a faster onset of action than subcutaneous insulin, but shorter duration of action. A final noteworthy point is that these data have not been peer-reviewed or published fully to date, thus major limitations are difficult to assess.

Trial 175

Trial 175 was a multicenter, double-blind, placebo-controlled randomized clinical trial comparing prandial TII (N=177) versus a placebo Technosphere® inhalation powder (N=176) in insulin-naïve patients with type 2 diabetes mellitus that were poorly controlled with oral anti-diabetic agents.[8] The study duration was 24 weeks and inclusion criteria were patients with a clinical diagnosis of type 2 diabetes mellitus, 18 years of age or older, HbA1c of 7.5% to 10%, BMI ≤45 kg/m^2, nonsmoker (for at least 6 months before screening), currently receiving either metformin ≥1.5 grams daily or 2 or more oral anti-diabetic drugs (OAD) and on stable doses for at least 3 months before enrollment, no

Box | Potential drug-drug interactions with insulin.[4]

May increase risk of hypoglycemia
- Other antidiabetic agents
- ACE inhibitors
- Angiotensin II receptor blocking agents
- Disopyramide
- Fibrates
- Fluoxetine
- Monoamine oxidase inhibitors
- Pentoxifylline
- Pramlintide
- Salicylates
- Somatostatin analogs (e.g., octreotide)
- Sulfonamide antibiotics

May increase or decrease glucose lowering effect
- Alcohol
- Beta blockers
- Clonidine
- Lithium salts
- Pentamidine

May decrease glucose lowering effect
- Atypical antipsychotics (e.g., olanzapine, clozapine)
- Corticosteroids
- Danazol
- Diuretics
- Estrogens
- Glucagon
- Isoniazid
- Niacin
- Oral contraceptives
- Phenothiazines
- Progestogens
- Protease inhibitors

May diminish signs and symptoms of hypoglycemia
- Beta blockers
- Clonidine
- Guanethidine
- Reserpine

Table 1 | Summary of pivotal phase 3 clinical trials of Technosphere® inhaled insulin.[6-9]

Study Characteristic	Trial 171[6,7]		Trial 175[8,9]	
Design	Phase 3, multicenter, open-label, randomized, non-inferiority		Phase 3, multicenter, double-blind, randomized, placebo-controlled	
Duration	24 weeks		24 weeks	
Patient population	Type 1 diabetes		Type 2 diabetes insulin naïve	
Comparator	Insulin aspart with basal insulin		Technosphere® vehicle placebo	
Treatment Groups	**TII + basal insulin** (n=173)	**RAA + basal insulin** (n=171)	**TII** (n=177)	**Inhaled placebo** (n=176)
HbA1c (%)				
Baseline	7.94%	7.92%	8.25%	8.27%
Change (wk 0 to 24)	-0.21%	-0.40%	-0.82%	-0.42%
Fasting plasma glucose (mg/dL)				
Baseline	154	151	N/A	N/A
Change (wk 0 to 24)	-25	-10	11 mg/dL	4 mg/dL
Weight (kg)				
Baseline	75.50	73.54	N/A	N/A
Change (wk 0 to 24)	-0.39	+0.93	+0.49	-1.13 kg
Hypoglycemia incidence (%)				
Total hypoglycemia	96.0	99.4	N/A	N/A
Severe hypoglycemia	18.4	29.2	N/A	N/A
Hypoglycemia event rate				
Total (per patient-month)	9.80	13.97	1.16	0.50
Severe[a] (per 100 patient-months)	8.05	14.45	2.37	0.60
Glucose <36 mg/dL (per 100 patient-months)	11.64	25.57	N/A	N/A

+ signs indicate an increase in the variable; - signs indicate a decrease in the variable.
[a]Severe hypoglycemia requiring assistance.
RAA = rapid acting analog insulin; **TII** = Technosphere® inhaled insulin

previous or current treatment with insulin, FEV_1 ≥70%, forced vital capacity (FVC) ≥70%, and FEV_1/FVC at or greater than the lower limit of normal.[9] Patients were excluded if they had clinically important pulmonary disease (e.g., COPD or asthma), evidence of serious complications of diabetes, renal disease or dysfunction, significant cardiovascular dysfunction, a history of pulmonary embolism or deep venous thrombosis ≤12 months before screening, or a history of recent blood transfusions ≤3 months before screening, or had previous or current use of amiodarone, glucagon-like peptide analogs, thiazolidinediones, or weight loss drugs ≤3 months of screening. The primary outcome was change in HbA1c from baseline to week 24. Important secondary outcomes were proportion of patients achieving an HbA1c ≤7%, mean change in FPG from baseline to 24 weeks, incidence of hypoglycemia, and occurrence of adverse events.

TII was found to be superior to inhaled placebo in reducing HbA1c, with reductions of 0.82% and 0.42%, respectively, for a modest treatment difference of 0.40% (95% CI -0.57 to -0.23; p<0.0001).[8] Thirty-eight percent of patients in the TII group and 19% of patients in the inhaled placebo group achieved an HbA1c of ≤7% (p=0.0021). Mean FPG decreases were 11 mg/dL for TII and 4 mg/dL for placebo (p=0.17). Patients in the TII group had a mean weight gain of 0.5 kg, whereas those in the placebo group experienced a mean weight reduction of 1.1 kg (p<0.0001). As expected, hypoglycemia occurred more frequently among patients in the TII group (1.16 events per patient-month) than those in the placebo group (0.50 events per patient-month, respectively; p<0.0001). No statistically significant difference was observed between TII and placebo in event rates of severe hypoglycemia (2.37 vs. 0.60 events per 100 patient-months, respectively; p=0.20). The authors concluded that the addition of prandial TII to OADs is an effective treatment option in insulin-naïve patients with type 2 diabetes, who are not controlled on their current regimen.[8] As with Trial 171, these data have not been fully peer-reviewed or published, thus these findings must be taken with caution.

Published Clinical Trials

Rosenstock, et al. conducted a double-blind, randomized, placebo-controlled study to compare TII (N=61) versus placebo (N=62) in insulin-naïve patients with type 2 diabetes sub-optimally controlled with oral agents.[10] The inclusion criteria included age 18 to 80 years old, a clinical diagnosis of type 2 diabetes (with a duration of 2-12 years), treatment with at least 1 OAD (stable regimen for ≥3 months prior to enrollment), BMI <38 kg/m^2, HbA1c between 6.6% and 10.5%, baseline FVC and FEV_1 of 80% to 120%, and baseline single-breath carbon monoxide diffus-

ing capacity of the lung of 80-120% of predicted normal. The exclusion criteria included patients with severe diabetes complications, significant hepatic or renal disease, severe or multiple allergies, chronic pulmonary disease, AIDS, systemic autoimmune or collagen vascular disease, major psychiatric disorders, and myocardial infarction or stoke within the precious 6 months. The primary efficacy outcome was change in HbA1c from baseline to week 12. The secondary efficacy outcome was postprandial glucose at weeks 4, 8 and 12. This proof-of-concept trial showed that patients using TII had a modestly greater reduction in HbA1c than placebo (-0.72% vs. -0.30%, respectively; p=0.003) after 12 weeks of therapy. In addition, the mean postprandial glucose excursion AUC was reduced by 56% from 4,533 min*mg/dL at baseline to 1,977 min*mg/dL after 12 weeks of therapy (p<0.0001); in contrast, postprandial glucose excursions did not change from baseline to 12-weeks in the placebo group. Limitations of this study were that TII was not increased to the maximum allowed dose of 48 nominal units per meal (equivalent to 12.48 units of regular human insulin) in over 40% of patients and study sites did not have a structured titration algorithm to follow.[10]

Rosenstock et al. also conducted a randomized, open-label, parallel group study to compare prandial TII plus basal insulin glargine (N=211) versus twice daily biaspart insulin (N=237) in patients with type 2 diabetes that had previously been treated with insulin.[11] Inclusion criteria were age 18 to 80 years, type 2 diabetes with HbA1c between 7% and 11%, use of 2 to 3 subcutaneous injections of insulin per day, no smoking for ≥6 months, a baseline diffusion lung capacity of ≥70%, total lung capacity of ≥80%, and BMI ≤40 kg/m^2. The exclusion criteria included clinically significant diabetes complications, hepatic or renal disease, severe allergies, chronic pulmonary disease, present drug or alcohol abuse, major psychiatric disorders, myocardial infarction or stroke within the previous 3 months, or unstable diabetes. The primary efficacy endpoint was change in HbA1c from baseline to week 52. Important secondary endpoints were 2-hour postprandial glucose at week 52, and change in weight from baseline to week 52. The authors found that change in HbA1c was similar and non-inferior between TII compared to biaspart insulin (-0.68% vs -0.76%, respectively). Also, at 2 hours post-dose, glucose excursions were reportedly higher in patients taking TII plus insulin glargine than in those on the biaspart insulin, although these data were not published. Patients taking TII plus insulin glargine experienced less weight gain than patients using biaspart insulin (0.9 kg vs. 2.5 kg, respectively; p=0.0002). More patients taking TII plus insulin glargine reported a cough than those patients using insulin biaspart (33% vs. 6%, respectively), although no test of significance was reported.[11]

Adverse Events

Table 2 lists the adverse events that patients taking TII experienced in clinical trials. Hypoglycemia, cough, and throat pain or irritation, are the most common adverse reactions experienced by patients taking TII.[4] Serious adverse reactions that were reported were acute bronchospasm in patients with chronic lung disease, decline in pulmonary function, lung cancer, diabetic ketoacidosis, and hypersensitivity reactions.[4]

Raskin et al., conducted a randomized, open-label study in order to better understand the pulmonary safety of II (N=730), compared to usual anti-diabetes treatment (N=824) and a cohort of patients without diabetes that were not receiving any treatment (N=145).[12] Patients included in this study were aged 18 to 80 years, with a clinical diagnosis of type 1 or type 2 diabetes for ≥2 years, an HbA1c between 6.6% and 12%, a non-smoker (for at least 6 months prior), with a BMI <42 kg/m^2, FEV_1 and DL_{CO} ≥70% and total lung capacity (TLC) ≥80% of predicted. Patients excluded from this study were those with significant pulmonary, hepatic, renal or cardiac disease, history of malignancy within the past 5 years, severe complications of diabetes, current illicit drug or alcohol use, and past participation in an inhaled

Table 2 | Adverse events in clinical trials of inhaled insulin.[5]

Adverse Event	Inhaled Insulin (N=3017)	Non-placebo comparators (N=2198)
Acute Bronchospasm	<1%	N/A
Decline in pulmonary function	2.8%	1%
Lung cancer	2 cases reported in 2,750 patient years of exposure	N/A
Diabetic ketoacidosis	0.46%	N/A
Hypersensitivity reaction	N/A	N/A
Cough	25.6%-29.4%	4.9%-5.4%
Throat pain or irritation	4.4%-5.5%	0.9%-1.9%
Urinary tract infection	2.3%	1.9%
Headache	3.1%-4.7%	1.8%-2.8%
Diarrhea	2.7%	2.2%
Productive cough	2.2%	0.9%
Fatigue	2%	0.6%
Nausea	2%	1%
Bronchitis	2.5%	2%

insulin trial.[12] The primary endpoint of this study was change in pre-bronchodilator FEV_1 values from baseline to month 24 between the diabetes treatment groups. After an initial decline in lung function for patients on TII over the first 3 months of treatment, no further decline was observed during up to 2 years of follow-up. The most frequent adverse reactions were hypoglycemia (39.5% in TII vs. 39.1% in usual care) and a transient, mild, nonproductive cough that usually occurred ≤10 minutes after inhalation (more frequent with TII [27.8%] than usual care [4.4%]). A follow-on study that evaluated pulmonary function after up to 2 years of treatment showed that differences in pulmonary function tests resolved by 1 month following discontinuation of inhaled insulin. The authors concluded that any pulmonary function decline that was associated with the use of TII was observed early in treatment and remained non-progressive throughout the study duration.[12]

Contraindications and Precautions

Patients with chronic lung disease should not use TII due to risk of acute bronchospasm.[4] Prior to initiating TII, spirometry testing (FEV_1), a medical history, and a physical examination should be performed on all patients to detect potential lung disease, such as chronic obstructive pulmonary disease, asthma, or others. Patients with chronic lung disease were excluded in clinical trials and thus should not use TII. The use of TII is contraindicated in patients experiencing an episode of hypoglycemia or individuals with hypersensitivity to human insulin.[4] TII is not a substitute for long acting insulin for patients with type 1 diabetes. Likewise, TII is not recommended for smokers (or patients who recently stopped smoking) or for the treatment of diabetic ketoacidosis.[4]

Dosing and Administration

Route of Administration and Dosage Information

TII is available as single-use cartridges of 4 units or 8 units of delivered insulin; these single-use cartridges are administered either immediately before or within 20 minutes after starting a meal.[4] TII must be used along with basal insulin for patients with type 1 diabetes. However, TII may be used in patients with type 2 diabetes who use either basal insulin or oral anti-diabetic medications.[4]

Insulin naïve individuals should be started on 4 units of TII at each meal.[4] Patients who are non-insulin naïve should convert their subcutaneous mealtime insulin dose to TII using the conversion in **Table 3**. For patients switching from TII to injected mealtime insulin, the dose conversion is 1:1. For example, a patient using 4 units of TII should be transitioned to 4 units of injected mealtime insulin. For TII doses that exceed 8 units, multiple cartridges are necessary and a combination of 4 unit and 8 unit cartridges should be used to achieve the total necessary mealtime dose.

Monitoring

In clinical trials, TII use was associated with a small decline in lung function.[4] The full magnitude of the decline in lung function was typically seen within the first 3 months of therapy and persisted through the entire study. Thus, monitoring should include an FEV_1 test at baseline, and 6 months after starting therapy, and then annually thereafter, even if a decline in lung function is not detected. TII should be discontinued in patients with a decline in FEV_1 ≥20% during treatment.[4]

Table 3 | Switching from SC mealtime insulin to TII.[4]

SC mealtime insulin dose	TII dose
Up to 4 units	4 units
5-8 units	8 units
9-12 units	12 units
13-16 units	16 units
17-20 units	20 units
21-24 units	24 units

SC = subcutaneous; **TII =** Technosphere® inhaled insulin.

Summary

TII is a newly approved agent that delivers exogenous human insulin without the need for injections. TII is can replace rapid-acting inhaled insulin and is indicated for adult patients with diabetes mellitus, either type 1 or type 2. In one pivotal clinical trial of patients diagnosed with type 1 diabetes, TII caused weight loss, less hypoglycemia, greater reduction in FPG and was noninferior to insulin aspart in HbA1c reduction. In another clinical trial, of insulin-naïve patients with type 2 diabetes, TII compared to inhaled placebo was superior in reducing HbA1c and had greater reduction in FPG. However, patients gained weight and had more hypoglycemia events than the inhaled placebo group. Importantly, these trials have not been fully peer-reviewed or published, and these results should be taken with a degree of caution. Afrezza® is expected to be available in early 2015; accordingly, cost data were unavailable at the time of this writing.

References

1. "National Diabetes Statistics Report, 2014." *Centers for Disease Control and Prevention*. Centers for Disease Control and Prevention, 28 July 2014. http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf. Accessed: 10 Aug. 2014.
2. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2095-128.
3. Larkin ME, Capasso VA, Chen CL, et al Measuring Psychological Insulin Resistance: Barriers to Insulin Use. Diabetes Educ 2008;34(3):511-7.
4. Afrezza [package insert]. Danbury, CT: MannKind Corporation™; 2014. http://www.mannkindcorp.com/Collateral/Documents/English-US/Afrezza_PrescribingInformation.pdf.
5. Document, Briefing, Endocrinologic And Metabolic Drug Advisory Committee, 2014 April 01. Available at: http://www.fda.gov/ downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologic andmetabolicdrugsadvisorycommittee/ucm390865.pdf. Accessed: 10 Aug. 2014.

6. Bode BW, Lorber DL, Gross J, Yakusevich V, Chang PC, Bregman DB. Reduced hypoglycemia risk with an inhaled insulin compared to injected prandial insulin in type 1 diabetes. Presented at: 74th American Diabetes Association Scientific Sessions; June 14, 2014; San Francisco, CA. Oral presentation #127.
7. "Clinical Trial Evaluating Technosphere® Insulin Versus Insulin Aspart in Subjects With Type 1 Diabetes Mellitus Over a 24 -week Treatment Period." http://clinicaltrials.gov/ct2/show/record/NCT01445951. Accessed: 10 Aug. 2014.
8. Rosenstock J, McGill J, Franco D, Shumel B, Yuhui MA. Efficacy and safety evaluation of Technosphere insulin vs inhaled placebo in insulin-naïve type 2 diabetes. Presented at: 74th American Diabetes Association Scientific Sessions; June 14, 2014; San Francisco, CA. Oral presentation #128.
9. Comparison of Technosphere® Insulin Versus Technosphere Powder (Placebo) in Insulin-Naive Subjects With Type 2 Diabetes Mellitus. Available at: http://clinicaltrials.gov/ct2/show/record/NCT01451398?term=MKC-TI-175&rank=1. Accessed: 10 Aug. 2014.
10. Rosenstock J, Bergenstal R, Defronzo RA, et al. Efficacy and Safety of Technosphere Inhaled Insulin Compared With Technosphere Powder Placebo in Insulin-Naive Type 2 Diabetes Suboptimally Controlled With Oral Agents. Diabetes Care 2008;31(11):2177-82.
11. Rosenstock J, Lorber DL, Gnudi L, et al. Prandial Inhaled Insulin plus Basal Insulin Glargine versus Twice Daily Biaspart Insulin for Type 2 Diabetes: A Multicentre Randomised Trial. Lancet 2010;375(9733):2244-253.
12. Raskin P, Heller S, Honka M, et al. Pulmonary Function over 2 Years in Diabetic Patients Treated with Prandial Inhaled Technosphere Insulin or Usual Antidiabetes Treatment: A Randomized Trial. Diabetes Obes Metab 2012;14(2):163-73.

Contrave® (naltrexone HCL/ bupropion HCL): The Newest Combination Weight Loss Treatment

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Obesity – a body mass index (BMI) ≥30 kg/m^2 – was officially recognized as a disease by the American Medical Association (AMA) in 2013. Caloric intake that exceeds caloric expenditure in the body results in weight gain and, if excessive, obesity. Thus, in simple terms, obesity is often the result of consuming more energy than the body expends. However, many factors may contribute to obesity including genetics, lifestyle, medications, other health conditions, and perhaps an individual's microbiota. In the United States, more than 78.6 million adults are obese.[2] Obesity is more prevalent in non-Hispanic blacks than other races and more prevalent in adults aged 40-59 years than younger and older adults.[2] Obesity increases the risk of developing coronary artery disease (CAD), heart failure, hypertension, type 2 diabetes, gallstones, sleep apnea, and certain types of cancer. Obesity also increases the likelihood of having osteoarthritis or a stroke.[3] Using historical trends since the 1990s, one study projects that obesity will lead to more than 8 million cases of diabetes, 6.8 million cases of CAD and stroke, and 0.5 million cases of cancer in the next 20 years.[4] In 2008, the estimated total healthcare cost for obesity was $147 billion dollars.[2] The average annual medical costs of obese individuals are estimated to be $1,429 greater than for normal weight individuals.[3]

Current pharmacologic treatment options with FDA-approved indications for obesity include lorcaserin (Belviq®), phentermine, orlistat (Xenical®), and phentermine/topiramate (Qsymia®). Prior to approval, the FDA requires either a difference in mean weight loss of ≥5% between drug and placebo groups over one year or that the proportion of subjects who lose at least 5% of baseline body weight in the drug group is at least 35% and approximately twice that of the placebo group in addition to being statistically significant.[5]

Naltrexone/bupropion (Contrave®) has an FDA-approved indication for weight loss in individuals with a BMI ≥30 kg/m^2 or a BMI ≥27 kg/m^2 with one or more risk factors (diabetes, hypertension, or dyslipidemia).[6] This combination pill includes naltrexone, a mu-opioid receptor antagonist, and sustained-release bupropion, a weak inhibitor of neuronal uptake of norepinephrine and dopamine. The purpose of this manuscript is to review the pharmacology, efficacy, adverse events, and administration of naltrexone/bupropion for weight loss.

Pharmacology

Mechanism of Action

Bupropion stimulates hypothalamic pro-opiomelanocortin (POMC) neurons that release alpha-melanocyte stimulating hormone (α-MSH). α-MSH binds to MC4 receptors activating a cascade resulting in decreased energy intake and increased energy expenditure. Along with α-MSH, POMC neurons also release β-endorphin, a mu-opioid receptor agonist, when α-MSH is released acting as a negative feedback loop. Naltrexone blocks this negative feedback loop, potentiating POMC neuron activation. Bupropion and naltrexone act synergistically, creating a greater effect together than either medication used alone. Naltrexone and bupropion may also act on the mesolimbic reward pathway to decrease food intake.[6]

Pharmacokinetics

Select pharmacokinetic parameters are listed in **Table 1.** Although the pharmacokinetic data are provided for naltrexone and bupropion separately, the pharmacokinetic properties were analyzed using the combination medication. Naltrexone/bupropion is administered orally and reaches maximum concentration (C_{max}) in 2 to 3 hours. Ingestion of a high fat meal with naltrexone/bupropion increases the area under the curve (AUC) and C_{max} but does not affect the time to maximum concentration (T_{max}) of naltrexone and bupropion. As a result, naltrexone/bupropion should not be administered with a high fat meal. Naltrexone is minimally plasma protein bound, whereas bupropion is more highly plasma protein bound. Metabolism of naltrexone/bupropion occurs in the liver, to active metabolites, with bupropion being metabolized by CYP2B6 and naltrexone by dihydrodiol dehydrogenase. Naltrexone/bupropion is primarily excreted in the urine with some metabolites

Table 1 | Pharmacokinetics of naltrexone/bupropion.[7]

Parameter	Naltrexone	Bupropion
T_{max}	2 hours	3 hours
Elimination Half-life	5 hours	21 hours
Metabolism	Hepatic via dihydrodiol dehydrogenase	Hepatic via CYP2B6
Volume of Distribution	5,697 L	880 L
Elimination	79% in urine	87% in urine; 10% in feces
Protein Binding	21%	84%

being excreted in the feces.[7]

The pharmacokinetics of naltrexone/bupropion do not differ by sex or race. The pharmacokinetics of naltrexone/bupropion have not been evaluated in the elderly but a separate bupropion study suggests the elderly are at an increased risk of accumulation of bupropion.[8] Naltrexone/bupropion has not been studied in individuals with hepatic or renal impairment and the only available data are extrapolated from individual studies on naltrexone and bupropion. Naltrexone AUC is increased significantly in patients with liver cirrhosis, while bupropion AUC is unchanged when comparing individuals with mild-to-moderate cirrhosis to healthy individuals. Naltrexone C_{max} is increased in individuals with end stage renal disease (ESRD) requiring dialysis. Elimination of bupropion is decreased in individuals with renal impairment.

Clinical Trials

Clinical trials assessing the efficacy and safety of naltrexone/bupropion are summarized in **Table 2**. Two multicenter, randomized, double-blind, placebo-controlled, phase 3 trials were conducted comparing naltrexone/bupropion with placebo.[9,10]

The first study included 1,742 patients aged 18 to 65 years with a BMI of 30 to 45 kg/m^2 or a BMI of 27 to 45 kg/m^2 with concomitant controlled hypertension, dyslipidemia, or both. Patients were randomly assigned in a 1:1:1 ratio to one of three treatment arms: 32 mg naltrexone/360 mg bupropion (16 mg naltrexone/180 mg bupropion administered twice daily), 16 mg naltrexone/360 mg bupropion (8 mg naltrexone/180 mg bupropion twice daily), or matching placebo. All 3 arms included lifestyle modification consisting of a hypocaloric (500 kcal deficit) diet and exercise. The primary efficacy endpoints were percent change in body weight and proportion of patients with a decrease in body weight of ≥5% at week 56.[9] Secondary endpoints included proportion of patients with decrease in body weight of ≥10% and ≥15%, change in cardiometabolic risk factors, patient-reported measures of appetite, control of cravings, depressive symptoms, and weight-related quality of life.[9] Treatment with both doses of naltrexone/bupropion resulted in greater average weight loss and no increased safety risks concerning blood pressure or depression when compared to placebo. The primary efficacy results are summarized in **Table 2**. With the exceptions of LDL cholesterol, blood pressure, and depressive symptoms, treatment with 32 mg naltrexone/360 mg bupropion was associated with significantly greater improvements in the aforementioned secondary outcomes, relative to placebo treatment. No significant difference was observed between groups with regard to safety measures. The 16 mg naltrexone/360 mg bupropion treatment arm was associated with statistically significant improvements in all mentioned efficacy outcomes except for the cardiometabolic risk factors of LDL cholesterol, fasting insulin, and fasting blood glucose, and the safety endpoints of blood pressure and depressive symptoms.[9]

The second phase 3 study included 1,496 patients aged 18 to 65 years with a BMI of 30 to 45 kg/m^2 or a BMI of 27 to 45 kg/m^2 with concomitant controlled hypertension, dyslipidemia, or both. Patients were randomly assigned in a 2:1 ratio to receive 32 mg naltrexone/360 mg bupropion (16 mg naltrexone/180 mg bupropion administered twice daily) or matching placebo in addition to the same lifestyle changes mentioned above.[10] To evaluate safety and efficacy of a dose increase, patients who did not experience a ≥5% weight loss between weeks 28 and 44 were re-randomized in a 1:1 ratio to stay on the current dose or increase to 48 mg naltrexone/360 mg bupropion daily (administered in two divided doses as in the first phase). The primary efficacy endpoints were percent change in body weight and proportion of patients with a decrease in body weight of ≥5% at week 28. Secondary endpoints included the above endpoints at week 56, proportion of patients with ≥10% weight loss, change in cardiometabolic risk factors, patient reported measures of cravings, and weight-related quality of life at week 28. Tertiary endpoints included the listed secondary endpoints at week 56.[10] The active treatment group was found to have statistically significant improvements in all primary, secondary, and tertiary endpoints except fasting blood glucose, blood pressure, and depressive symptoms. Treatment with 32 mg naltrexone/360 mg bupropion resulted in greater average weight loss compared to placebo (**Table 2**). Blood pressure and depressive symptoms were no different when compared to placebo suggesting that treatment does not adversely affect these measurements. Patients re-randomized to 48 mg naltrexone/360 mg bupropion did not achieve a greater weight loss when compared to those re-randomized to continue their phase 1 dose (32 mg naltrexone/360 mg bupropion).

A third multicenter, randomized, double-blind, placebo-controlled trial included 793 patients aged 18 to 65 years with a BMI of 30 to 45 kg/m^2 or a BMI of 27 to 45 kg/m^2 with concomitant controlled hypertension, dyslipidemia, or both. Patients were randomly assigned to placebo or 32 mg

Table 2 | Summary of clinical trials of naltrexone/bupropion.[9-12]

Study	Treatment	Primary Endpoint	Results
Greenway (2010)[9]	• 32 mg naltrexone/ 360 mg bupropion (n=583) • 16 mg naltrexone/ 360 mg bupropion (n=578) • Placebo (n=581)	• % change in body weight at 56 weeks • Proportion of participants with ≥ 5% decrease in body weight at week 56	***% change in BW:*** • 32 mg naltrexone: -6.1%[a] • 16 mg naltrexone: -5.0%[a] • Placebo:-1.3% ***Proportion ≥5% BW decrease:*** • 32 mg naltrexone: 48%[a] • 16 mg naltrexone: 39%[a] • Placebo: 16%
Apovian (2013)[10]	• 32 mg naltrexone/ 360 mg bupropion (n=1001) • Placebo (n=495)	• % change in BW at 28 weeks • Proportion of participants with ≥5% decrease in BW at week 28	***% change in BW:*** • 32 mg naltrexone/360 mg bupropion: -6.5%[b] • Placebo: -1.9% ***Proportion ≥5% BW decrease:*** • 32 mg naltrexone/360 mg bupropion: 55.6%[b] • Placebo: 17.5%
Wadden (2011)[11]	• 32 mg naltrexone/ 360 mg bupropion + BMOD (n=591) • Placebo + BMOD (n=202)	• % change in BW at 56 weeks • Proportion of participants with ≥5% decrease in BW at week 56	***% change in BW:*** • 32 mg naltrexone/360 mg bupropion: -9.3%[b] • Placebo: -5.1% ***Proportion ≥5% BW decrease:*** • 32 mg naltrexone/360 mg bupropion: 66.4%[b] • Placebo: 42.5%
Hollander (2013)[12]	• 32 mg naltrexone/ 360 mg bupropion (n=335) • Placebo (n=170)	• % change in BW at 56 weeks • Proportion of participants with ≥5% decrease in BW at week 56	***% change in BW:*** • 32 mg naltrexone/360 mg bupropion: -5.0%[b] • Placebo: -1.8% ***Proportion ≥5% BW decrease:*** • 32 mg naltrexone/360 mg bupropion: 44.5%[b] • Placebo: 18.9%

BMOD = intensive behavior modification.
[a]p<0.0001 vs. placebo.
[b]p<0.001 vs. placebo.

naltrexone/360 mg bupropion (16 mg naltrexone/180 mg bupropion administered twice daily) in a 1:3 ratio.[11] Patients in both treatment groups received intensive behavior modification (BMOD) training from dieticians, behavioral psychiatrists, or exercise specialists in groups of 10 to 20 throughout the study duration. The primary efficacy endpoints were percent change in body weight and proportion of patients with a decrease in body weight of ≥5% at week 56. Secondary endpoints included weight loss of ≥10%, change in cardiometabolic risk factors, patient reported weight-related quality of life and safety measures. The naltrexone/bupropion group was found to have statistically significant improvements in both primary outcomes (**Table 2**), and all secondary outcomes except of LDL cholesterol, high sensitivity C-reactive protein (hsCRP), and fasting blood glucose, relative to the placebo-treated group.[11] Treatment with 32 mg naltrexone/360 mg bupropion resulted in greater average weight loss, a reduction in some cardiometabolic risk factors, including waist circumference, triglycerides, HDL cholesterol, and insulin levels, with no significant change in blood pressure or depressive symptoms when compared to placebo.

A fourth multicenter, double-blind, randomized, placebo controlled trial included 505 adults aged 18 to 70 years old with a BMI of 27 to 45 kg/m^2, an HbA_{1c} between 7% and 10%, and a fasting blood glucose <270mg/dL. Patients were randomly assigned to 32 mg naltrexone/360 mg bupropion (16 mg naltrexone/180 mg bupropion administered twice daily) or placebo in a 2:1 ratio with all patients advised on lifestyle modification as mentioned in previous trials. The primary efficacy endpoints were percent change in body weight and proportion of patients with a decrease in body weight of 5% or more at week 56.[12] Secondary endpoints included proportion of patients with ≥10% weight loss, change in cardiometabolic risk factors, change in glycemic control and safety endpoints of blood pressure changes and depressive symptoms. Active treatment, as compared to placebo, resulted in greater average weight loss and modest improvements in all secondary endpoints except fasting blood glucose, fasting insulin levels, insulin resistance, LDL, hsCRP, and blood pressure; safety outcomes were similar between groups.[12]

These clinical trials show that naltrexone/bupropion is more effective than placebo for weight loss in adults. The average weight loss and proportion of patients meeting specific weight loss goals with naltrexone/bupropion appear to

be similar to, or slightly better than, other newly approved weight loss medications; however, comparisons among active treatments across heterogenous trials should be done with caution. Calculated mean percent weight loss in the trials was 6.1%, 6.5%, and 5% when combined with a mild hypocaloric diet and 9.3% when combined with intense behavior modification.[8-11] Additionally, clinical trials found that 48%, 55.6%, and 44.5% of patients lost ≥5% of their body weight when naltrexone/bupropion was combined with a mild hypocaloric diet and 66.4% of patients lost at least 5% of their body weight when naltrexone/bupropion was combined with intense behavior modification.[9-12]

Adverse Effects

Clinical trials found that the most common adverse effects associated with naltrexone/bupropion use in clinical trials were nausea, constipation, and headache. These adverse effects occurred significantly more often in those treated with naltrexone/bupropion compared to placebo-treated patients.[9-12] The percent of patients experiencing any psychiatric adverse event was also greater in naltrexone/bupropion-treated patients compared with placebo. However, specific psychiatric adverse events were not significantly different between groups, likely because the trials were underpowered to detect differences in these variables. Adverse effect rates of treatment and placebo are summarized in **Table 3**. The Contrave® package insert has a black box warning for suicidal behavior and ideation and also warns of potential neuropsychiatric symptoms, seizures, increase in BP and heart rate, allergic reactions, and angle-closure glaucoma.[7]

Contraindications and Precautions

Contraindications to naltrexone/bupropion use are summarized in the **Box**. Caution should be used when considering use of naltrexone/bupropion in individuals with depression as suicidal behavior and worsening depression may occur.[7]

Dosing and Administration

Naltrexone/bupropion dosing is titrated over four weeks. Naltrexone/bupropion is supplied in 8 mg/90 mg tablets. The titration schedule for naltrexone/bupropion is shown in **Table 4**. The maximum daily dose of naltrexone/bupropion is 2 tablets twice daily (32 mg naltrexone/360 mg bupropion). Tablets should not be cut, chewed, or crushed. In clinical trials, naltrexone/bupropion was taken with meals but high fat meals should be avoided because of increased systemic exposure to both naltrexone and bupropion. If a patient has not lost ≥5% of baseline body weight after 12 weeks at the maintenance dose, naltrexone/bupropion should be discontinued because continued use is unlikely to generate weight loss in these individuals.[7]

The maximum daily dose of naltrexone/bupropion in patients with moderate-to-severe renal impairment is 8 mg naltrexone/90 mg bupropion twice daily (i.e., maximum total daily dose, 16 mg naltrexone/90 mg bupropion). Naltrexone/bupropion is not recommended in patients with ESRD. No specific dosing adjustments are recommended for patients with mild renal impairment; however, naltrexone/bupropion should be used with caution in these patients. The maximum daily dose in patients with hepatic impairment is 8 mg naltrexone/90 mg bupropion once daily. These recommendations are based on naltrexone and bupropion separately as studies on dose adjustments for renal and hepatic impairment have not been conducted for the combination pill.[7]

Drug-Drug Interactions

A washout period of at least 14 days should occur between discontinuing an MAO-I and beginning naltrexone/bupropion and vice versa as concomitant use increases the risk of hypertensive reactions.[7] The maximum daily dose of naltrexone/bupropion should not exceed 2 tablets when used concomitantly with CYP2B6 inhibitors. Naltrexone/

Box | Contraindications to use of naltrexone/bupropion.

- Uncontrolled hypertension
- History of seizures
- Bulimia or anorexia nervosa
- Chronic opioid use
- Abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepiliptics
- Monoamine oxidase inhibitor use
- Known allergy to naltrexone or bupropion
- Pregnancy

Table 3 | Percent of patients experiencing adverse effects in trials of naltrexone/bupropion.[10]

Adverse Event	Placebo	Naltrexone/bupropion
Any adverse effect	75.2%	85.9%
Nausea	6.9%	29.2%[a]
Constipation	7.1%	19.1%[a]
Headache	8.7%	17.5%[a]
Vomiting	2.0%	8.5%[a]
Any psychiatric event	15.2%	20.7%[a]
Depression	1.6%	1.3%
Anxiety	4.3%	4.8%

[a]p<0.05 comparing naltrexone/bupropion to placebo.

Table 4 | Titration schedule for naltrexone/bupropion.

Treatment Week	Dose
1	1 tablet in the morning
2	1 tablet twice daily
3	2 tablets in the morning and 1 tablet in the evening
4+	2 tablets twice daily

Table 5 | Cost of 30-day supply of available prescription-only weight loss medications.[13]

Medication	Cash Price	Discount card
Phentermine	$29.00 – $50.00	None
Lorcaserin (Belviq®)	$239.00 – $263.00	Free 15 day trial; pay as little as $50 with insurance or save $75 per month
Phentermine/Topiramate (Qsymia®)	$239.00 – $268.00	Free 14 day trial; $75 off per month
Orlistat (Xenical®)	$179.00 – $192.00	None

bupropion should be used with caution only after chronic opioid use has been stopped for 7 to 10 days to avoid withdrawal. If opioid therapy is needed temporarily, naltrexone/bupropion should be stopped during administration of the opioid. Naltrexone/bupropion should be used cautiously with CYP2D6 substrates as it may increase exposure to the substrate. A dose decrease of the CYP2D6 substrate may be warranted.[7]

Cost

The cost of Contrave® has not been established at the time of this writing as the drug is not yet commercially available; however, it may be reasonable to presume that Contrave® will be comparable in price to Belviq® and Qsymia®. Many insurance companies do not cover weight loss medications, making cost an important factor when considering treatment options. Brand name only medications often have trial discount cards available but long term discounts are minimal. **Table 5** shows current cash prices and discount cards for available weight loss medications already on the market.

Summary

Naltrexone/bupropion (Contrave®) is a newly approved drug that promotes weight loss via the synergistic actions of naltrexone and bupropion in the hypothalamic melanocortin system that controls appetite. At a dose of 32 mg naltrexone with 360 mg bupropion SR, this medication is indicated for weight loss in individuals with a BMI ≥30 kg/m^2 or a BMI ≥27 kg/m^2 with risk factors such as diabetes, hypertension, or dyslipidemia. In clinical trials, naltrexone with bupropion achieved ≥5% weight loss in 44% to 66% of patients, depending on concurrent diet and lifestyle modifications.[9-12] The most common adverse events reported were nausea, constipation, and headache.[9-12] Additional studies comparing naltrexone/bupropion to other weight loss medications may further define the role of this new medication in weight loss management.

References

1. AMA Adopts New Policies on Second Day of Voting at Annual Meeting. 2013. http://www.ama-assn.org/ama/pub/news/news/2013/2013-06-18-new-ama-policies-annual-meeting.page
2. CDC. Adult Obesity Facts. Accessed. 12 October 2014. http://www.cdc.gov/obesity/data/adult.html
3. National Institute of Health. Health Information for the Public: Overweight and Obesity. Accessed. Web. 12 October 2014. http://www.nhlbi.nih.gov/health/health-topics/topics/obe/
4. Wang YC, Mcpherson K, Marsh T, et al. Health and economic burden of the projected obesity trends in the USA and the UK. Lancet. 2011;378(9793):815-25.
5. Kim GW, Lin JE, Blomain ES, Waldman SA. Antiobesity pharmacotherapy: new drugs and emerging targets. Clin Pharmacol Ther. 2014;95(1):53-66.
6. Orexigen Therapeutics, Inc. Contrave Advisory Committee Briefing Document. La Jolla, CA: 2010 December.
7. Orexigen Therapeutics, Inc. Contrave Package Insert. La Jolla, CA: 2014 September.
8. Sweet RA, Pollock BG, Kirshner M, et al. Pharmacokinetics of single- and multiple-dose bupropion in elderly patients with depression. J Clin Pharmacol 1995;35(9):876-84.
9. Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2010;376 (9741):595-605.
10. Apovian CM, Aronne L, Rubino D, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). Obesity (Silver Spring) 2013;21 (5):935-43.
11. Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. Obesity (Silver Spring) 2011;19(1):110-20.
12. Hollander P, Gupta AK, Plodkowski R, et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. Diabetes Care 2013;36(12):4022-9.
13. "GoodRx: Qsymia; Phentermine; Belviq; Xenical." Accessed 12 October 2014. www.goodrx.com

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