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ONLINE EXCLUSIVE

Bromocriptine: Its place in type 2 diabetes Tx

Patients intolerant of other diabetes medications or requiring minimal A1c reduction may benefit from bromocriptine.

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PRACTICE RECOMMENDATIONS

› *Reserve bromocriptine for cases in which only a modest reduction in A1c is needed.* (A)

› *Advise patients to take bromocriptine in the morning with food to maximize its bioavailability.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

For obese patients with type 2 diabetes (T2D) who do not tolerate other diabetes medications or for patients who need only a minimal reduction in glycosylated hemoglobin (A1c) to reach goal, bromocriptine may be a therapeutic agent to consider. Approved by the US Food and Drug Administration (FDA) in 2009, Cycloset is a quick-release formulation of bromocriptine mesylate, an ergot alkaloid dopamine D2 receptor agonist that has a faster onset of action than the customary formulation, Parlodel, which has been used to treat Parkinson's disease, acromegaly, and hyperprolactinemia.[1] In addition to its modest benefit in improving glycemic control, Cyclocet avoids undesirable side effects such as hypoglycemia and weight gain.

VeroScience, LLC holds the new drug application and related technologies for Cycloset and partnered with Santarus, Inc. and S2 Therapeutics to market it in September 2010.[2]

Bromocriptine's likely mechanism of action

Although its exact mechanism of action is unclear, bromocriptine does not stimulate insulin release, reduce hepatic glucose production, increase glucose transporter production, or increase or mimic glucagon-like peptide-1 activity as other T2D agents do.[3] Its contribution to glycemic control in T2D has been hypothesized to be due to adjustments in the neural control of seasonal and diurnal patterns of food intake and nutrient storage.[4]

Early hunter-gatherers and farmers are thought to have benefited from a "thrifty genotype" that favored fat deposition when food was seasonally abundant. With food in western society available year-round and often energy dense in both fat and carbohydrates, this same gene may lead to obesity and noninsulin-dependent diabetes mellitus.[5]

The hypothesis assumes that circadian rhythm, photoperiodism, and seasonal factors play a role in insulin resistance,

Bromocriptine may be suitable for obese patients with type 2 diabetes who are intolerant of other diabetes medications.

hepatic gluconeogenesis, and weight gain. In vertebrates, the neuroendocrine system plays an important role in synchronizing the animal with cyclic environmental changes. The hypothalamic suprachiasmatic nucleus (SCN) is known as the circadian pacemaker that maintains this rhythm. Oscillations in the SCN occur due to external cues such as changes in light or temperature. Circadian dopaminergic and serotonergic activities are likely responsible for modifying such oscillations, and neurotransmitters have been shown to regulate the dramatic seasonal alterations in body weight and body composition of all vertebrate classes.[6] Bromocriptine can reverse metabolic alterations associated with insulin resistance and obesity by resetting central (hypothalamic) circadian organization of monoamine neuronal activities.[7]

Proven anti-T2D effects. When administered systemically or into the cerebral ventricle at first light, bromocriptine prevents or reverses seasonal fattening, insulin resistance, and hyperinsulinemia, and it decreases endogenous (hepatic) glucose production in mammals.[8-11] Bromocriptine also decreases both fasting and postprandial triglyceride and free fatty acid levels.[1]

Clinical trials show modest benefit

Although bromocriptine has been studied since 1980 for its effects on hyperglycemia in T2D,[12] trials leading to the approval of the drug for clinical use with T2D have only been completed within the last 15 years. Randomized controlled trials of varying sizes and lasting from 6 to 52 weeks have shown absolute A1c reductions from 0.1% to 0.6%.[1,12–16] Compared with placebo, A1c reductions have ranged from 0.4% to 1.2% with monotherapy and in combination with other antidiabetes medications.[1,13-16]

The manufacturer assessed bromocriptine in 4 studies involving patients with T2D. In all 4 studies, the bromocriptine dose was titrated to a maximum of 4.8 mg/d.[16]

One study involved 159 overweight subjects who were not meeting glycemic goals.[16] Patients received either placebo or bromocriptine for 24 weeks in addition to diet and exercise. Mean baseline A1c was 9.0% in the bromocriptine group and 8.8% in the placebo group. After 24 weeks, A1c was reduced by 0.1% in the treatment group and increased by 0.3% in the placebo group. Mean fasting glucose was 215 mg/dL at baseline in the treatment group and was unchanged after 24 weeks. In the placebo group, fasting glucose increased from 205 to 228 mg/dL during the study. Weight increased by 0.2 kg in the treatment group and by 0.5 kg in the placebo group.

The next two 24-week manufacturer studies used similar designs to compare the addition of either bromocriptine or placebo to existing sulfonylurea therapy in patients with uncontrolled T2D.[16] One study assigned 122 patients to bromocriptine and 127 to placebo. The bromocriptine group demonstrated mean reductions of 0.4% in A1c and 3 mg/dL in fasting glucose. In the placebo group, A1c increased by 0.3% and fasting glucose rose by 23 mg/dL.

The other study assigned 122 patients to bromocriptine and 123 to placebo. Adding bromocriptine reduced A1c, on average, by 0.1% and fasting glucose by 10 mg/dL. In the placebo group, A1c increased by 0.4% and fasting glucose increased by 28 mg/dL. All of these results were statistically significant.

The last manufacturer-reported study evaluated the addition of bromocriptine to other diabetes treatments (diet or up to 2 antidiabetes medications).[13] While the primary intent of this study was to evaluate safety, it also assessed efficacy. This was a 52-week, randomized placebo-controlled trial involving 3095 patients.

Overall, after 24 weeks there was no change in A1c levels after adding bromocriptine. However, most patients in this study were already at goal (A1c <7.0%). A subgroup analysis of those with an A1c level >7.5% while taking other agents did show some improvement with the addition of bromocriptine. Adding bromocriptine to metformin and a sulfonylurea significantly reduced A1c by 0.5%, on average. Similar results were seen in those who received other combinations of diabetes medications. After 52 weeks, 25% of those receiving bromocriptine who originally had an A1c level >7.5% achieved an A1c level <7.0%. Of the patients who received placebo, 9% obtained an A1c level <7%.

In a 24-week study, bromocriptine titrated up to 4.8 mg/d was given to patients either on no other diabetes medication or on a sulfonylurea.[1] In individuals not on any current treatment, A1c decreased by 0.2% in those who received bromocriptine. In patients already on a sulfonylurea, A1c declined by 0.1%. A1c increased by 0.3% in those receiving placebo.

Bromocriptine most effective when taken with food

When bromocriptine is taken orally, 65% to 95% of the dose is absorbed; however, only 7% reaches systemic circulation due to extensive hepatic extraction and first-pass metabolism.[17] Bioavailability increases by 55% to 65% when the drug is taken with food, which is how it should be administered. The time to maximum plasma concentration is within an hour. With a high-fat meal, however, the time increases to 90 to 120 minutes. Bromocriptine is highly protein bound (90%-96%) and is metabolized extensively in the gastrointestinal (GI) tract and liver.[17] CYP3A4 is the major metabolic pathway.[1,18] Most excretion of bromocriptine is through bile, with approximately 2% to 6% of an oral dose eliminated via urine. The elimination half-life is approximately 6 hours.[17,18]

Dosing is once a day in the morning

Clinical trials investigating the use of bromocriptine in diabetes used doses ranging from 1.6 to 4.8 mg/d.[13-16,19] The FDA-approved dose range is 1.6 to 4.8 mg administered once daily with food, within 2 hours of waking in the morning.[16] In healthy individuals, central nervous system (CNS) dopaminergic activity peaks in the early morning. Thus, morning dosing attempts to mimic dopaminergic activity and circadian rhythms in healthy lean individuals.[6]

Titrate to maximum dose. The product is available in a 0.8-mg tablet (TABLE). Titration to the maximum dose is recommended to reduce GI adverse effects, particularly nausea. Start treatment with 1 tablet (0.8 mg) and increase the dose by 1 tablet per week until the patient reaches a maximum tolerated dose or the maximum allowable daily dose of 4.8 mg (6 tablets).

Precautions with renal or hepatic impairment. No pharmacokinetic studies of bromocriptine have been conducted with patients who have renal impairment, and the kidney is a minor elimination pathway for bromocriptine. The package insert offers no specific dose recommendations for such patients, although it does recommend caution when using this product in patients with renal impairment. Studies of bromocriptine in patients with liver dysfunction are also lacking. However, as bromocriptine is predominately metabolized in the liver, use caution in patients with hepatic impairment.[16]

Adverse effects are mostly GI related

In phase 3 clinical trials (bromocriptine n=2298; placebo n=1266), adverse events leading to drug discontinuation occurred in 539 (24%) of bromocriptine-treated patients and 118 (9%) placebo-treated patients.[16] This difference was mostly driven by an increase in GI adverse events with bromocriptine, particularly nausea. The most commonly reported adverse events from bromocriptine (nausea, fatigue, vomiting, headache, and dizziness) lasted a median of 14 days and were more likely to occur during the initial titration period. None of the reports of nausea or vomiting was considered serious.

There were no differences in the pattern of common adverse events across races or age groups (<65 vs >65 years old). Hypoglycemia occurred infrequently during the 52-week safety trial, with 6.9% of the bromocriptine patients and 5.3% of the placebo patients reporting an event.[13] In this same safety trial, 1.6% of bromocriptine patients experienced syncope vs 0.7% of placebo-treated patients. CNS effects (somnolence and hypoesthesia) were minimal. Serious adverse events affected 8.5% of bromocriptine patients and 9.6% of placebo-treated patients (hazard ratio=1.02; 96% one-sided confidence interval, 1.27). Fewer people in the bromocriptine group reported a cardiovascular disease endpoint (composite of myocardial infarction, stroke, coronary revascularization, hospitalization for angina, and hospitalization for congestive heart

Patients taking bromocriptine do not experience hypoglycemia or weight gain.

TABLE

Key prescribing information for bromocriptine[16]

How supplied	0.8-mg tablets
Indication	Adjunct to diet and exercise in type 2 diabetes mellitus
Dosing	*Initial*: 0.8 mg once daily with food, in the morning within 2 hours of waking *Titration*: Increase by 1 tablet (0.8 mg) per week until maximum dose or maximum tolerance is reached
Maximum dose	4.8 mg daily
Renal/hepatic impairment	Use with caution in patients with renal or hepatic impairment
Pregnancy; lactation	Pregnancy, category B; contraindicated for nursing women
Effectiveness	A1c reduced 0.1%-0.6% vs 0.3%-1.1% increase with placebo Fasting glucose reduced 0-10 mg/dL vs 23-28 mg/dL increase with placebo
Common adverse effects	Nausea, fatigue, headache, dizziness, vomiting
Adverse drug interactions	Highly protein-bound drugs Dopamine antagonists Drugs metabolized via CYP3A4 pathway Ergot-related migraine therapies 5-HT1B agonists (eg, sumatriptan)
Cost	$155.97 (90 tablets)*

*Pricing from www.drugstore.com.

Avoid giving dopamine antagonists or metoclopramide if prescribing bromocriptine.

failure) than did those in the placebo group (1.8% vs 3.2%, respectively).[13,16]

Postmarketing data link bromocriptine with hallucinations, fibrotic complications, and psychotic disorders. However, these adverse reactions were found with the use of much higher doses (30-140 mg/d) and with other indications for bromocriptine. These reactions have not been reported in clinical trials of bromocriptine used to treat T2D.[16]

Drugs to avoid (or use cautiously) with bromocriptine

Because bromocriptine is highly bound to serum proteins, it may increase the unbound fraction of other highly protein-bound drugs (eg, salicylates, sulfonamides, chloramphenicol, probenecid), which could alter their effectiveness or risk for adverse effects. Because bromocriptine is a dopamine receptor agonist, concomitant use of dopamine antagonists such as neuroleptic agents (clozapine, olanzapine) or metoclopramide is not recommended.[16]

Combining bromocriptine with ergot-related drugs (eg, migraine therapies) may increase the occurrence of ergot-related adverse effects such as nausea, vomiting, and fatigue, and may diminish effectiveness of migraine therapies. Dosing of the 2 therapies should occur at least 6 hours apart.[16]

Bromocriptine is extensively metabolized via CYP3A4. Potent inhibitors of this enzyme (eg, azole antimycotics, HIV protease inhibitors) or inducers (eg, rifampin, carbamazepine, phenytoin, phenobarbital) should be used with caution. Clinical trial data are limited regarding the safety of sumatriptan (5-HT_{1B} agonist) used concurrently with bromocriptine, so it is prudent to avoid using them together.[16]

Not for breastfeeding moms, migraine sufferers

Bromocriptine is contraindicated for patients

with syncopal migraine due to an increase in the likelihood of a hypotensive episode. It is also contraindicated for women who are breastfeeding due to its ability to inhibit lactation and to postmarketing reports of stroke in this population. Bromocriptine can lead to hypotension; monitor blood pressure during dose escalation and when a patient is taking antihypertensives.

Bromocriptine should not be used in patients with severe psychiatric disorders, as it may exacerbate their conditions or diminish the effectiveness of their treatment. Warn patients that somnolence can occur with bromocriptine, particularly during titration. No clinical studies have shown conclusive evidence of macrovascular risk reduction with bromocriptine or any other antidiabetic drug.[16] But neither has bromocriptine increased risk for cardiovascular events.[13]

Putting bromocriptine's usefulness into perspective

The larger studies of bromocriptine have shown absolute mean reductions in A1c of 0.1% to 0.6% and in fasting glucose of 0 to 10 mg/dL. When compared with placebo, mean A1c and fasting glucose differences were 0.4% to 1.2% and 23 to 38 mg/dL, respectively. While these findings were statistically significant when compared with placebo, they are clinically modest.

Although bromocriptine offers a few advantages, such as no weight gain, low risk of hypoglycemia, and possible beneficial effects on insulin resistance and triglyceride levels, its use should be limited at this time because it is less efficacious than other agents and long-term trials are lacking. Bromocriptine is not currently included in any treatment guidelines for the management of T2D. Cost is also a concern (**TABLE**). Because the medication is supplied only as 0.8-mg tablets, patients on the maximum dose would need to take 6 tablets once daily. JFP

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