Therapeutic Class Overview
Antidiabetic Agents (Dopamine Agonists)

Therapeutic Class

Overview/Summary: This review will focus on the antidiabetic dopamine agonist, bromocriptine mesylate (Cycloset®). Bromocriptine mesylate is the only dopamine agonist approved by the Food and Drug Administration (FDA) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.[1] Other formulations of bromocriptine are used for the treatment of Parkinson's disease, acromegaly, hyperprolactinemia and pituitary adenoma and will not be covered in this review.[2] Bromocriptine mesylate is a synthetic dopamine agonist that is chemically related to ergot alkaloids that acts on dopamine receptors throughout the body. The exact mechanism by which bromocriptine mesylate improves glycemic control is unknown.[1] Timed pulsed bromocriptine mesylate is thought to act upon the central nervous system to increase dopaminergic tone and decrease norepinephrine and serotonin release, thus improving control of peripheral metabolism in adipose tissue and liver.[2] Currently, bromocriptine mesylate (Cycloset®) is available as a 0.8 mg, brand-name only, quick-release tablet. Bromocriptine mesylate is administered once daily in the morning with food. The initial dose is 0.8 mg daily increased weekly by one tablet until maximum tolerated daily dose of 1.6 mg to 4.8 mg is achieved.[1]

The FDA approval of bromocriptine mesylate was based on the clinical evidence of safety and glycemic efficacy derived from four randomized, double-blind, placebo-controlled clinical trials in a total of 3,723 patients with type 2 diabetes.[1] Other clinical studies have since confirmed those results.[4-7] According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens.[8-11] Additionally, patients with high glycosylated hemoglobin (HbA_{1c}) will likely require combination dual or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. Guidelines currently rate bromocriptine mesylate as a second- or third-line agent due to its modest HbA1c reduction (~0.5 to 1%) and side effects profile, including nausea and orthostasis.[8-11] Several guidelines note that bromocriptine mesylate does not cause hypoglycemia or metabolic changes are preliminary data suggests that it may be useful to reduce the rate of cardiovascular events.[9,10]

The original new drug application (NDA) for the use of bromocriptine mesylate as an antidiabetic agent was denied by the FDA in 1998 due to a small treatment effect along with outstanding cardiovascular safety concerns. There were only a few cardiac events in the three pivotal trials submitted with the original NDA; however, the voluntary withdrawal of bromocriptine's indication for postpartum lactation due to postmarketing reports of cardiac events and seizures around the same time had also contributed to the final decision according to FDA's summary review of bromocriptine. The FDA issued an approvable letter in October 1999 conditional on the completion of a large, placebo-controlled, randomized trial to evaluate the potential for a significant increase in the risk of serious cardiac events in patients with type 2 diabetes treated with bromocriptine mesylate. Based on the results of this large safety clinical trial, the FDA issued an "approvable letter" for bromocriptine mesylate. Cycloset® is the first drug to be approved under the FDA requirement of evaluating cardiovascular risk in new antidiabetic therapies for the treatment of type 2 diabetes.[3]

Table 1. Current Medications Available in Therapeutic Class[3-7]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Bromocriptine mesylate (Cycloset®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 0.8 mg	-

Evidence-based Medicine

- The FDA approval of bromocriptine mesylate was based on the clinical evidence of safety and glycemic efficacy derived from four randomized, double-blind, placebo-controlled clinical trials in a total of 3,723 patients with type 2 diabetes.[1]
- As monotherapy, bromocriptine was shown to decrease in HbA_{1c} by 0.1% from baseline compared to an increase in HbA_{1c} of 0.3% from baseline in the placebo group (P=0.05). There was no change from baseline in the fasting plasma glucose (FPG) in the bromocriptine group compared to an increase in FPG of 23 mg/dL in the placebo group (P=0.005).[1]
- Combination therapy with bromocriptine was evaluated in two similarly designed studies. Patients treated with bromocriptine (and a sulfonylurea) in both the studies had a significantly improved HbA_{1c} compared to placebo (P≤0.001 for both studies). In addition, there was a significant improvement in FPG with bromocriptine compared with placebo (P=0.006).
- A safety study evaluated cardiovascular outcomes with bromocriptine use. The composite cardiovascular disease endpoint occurred in 37 (1.8%) patients in the bromocriptine-quick release (QR) group compared to 32 (3.1%) patients in the placebo group (hazard ratio [HR], 0.60; 95% two-sided CI, 0.37 to 0.96). Nausea was reported in 32.2% of bromocriptine-QR treated patients compared to 7.6% placebo-treated patients (P value not reported). Hypoglycemic adverse events occurred in 6.9% patients in the bromocriptine-QR group compared to 5.3% patients in the placebo group (P value not reported).[1,4]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[8-11]
    - Metformin remains the cornerstone of most antidiabetic treatment regimens.
    - Patients with high glycosylated hemoglobin (HbA_{1c}) will likely require combination or triple therapy in order to achieve glycemic goals.
        - Uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
        - Bromocriptine mesylate is generally considered a second- or third-line agent due to its modest HbA1c reduction (~0.5 to 1%) and side effects profile
- Other Key Facts:
    - Cycloset® is the first antidiabetic agent approved since the Food and Drug Administration (FDA) issued new guidelines requiring clinical trials of antidiabetic agents to demonstrate no increased cardiovascular risk.
    - No dose adjustments are needed for patients with moderate renal impairment (not cleared predominantly by the kidneys).
    - Gastrointestinal adverse events and nausea during dose titration period seems to be the chief reason for discontinuation of bromocriptine mesylate in clinical trials and may limit its use in patients with type 2 diabetes.
    - There is lack of evidence showing the benefit of using bromocriptine in combination with insulin, thiazolidinediones and other treatment alternatives for patients with type 2 diabetes (excluding metformin and sulfonylureas).
    - There are numerous drug interactions noted with bromocriptine mesylate due to its metabolic pathway.

References

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Overview/Summary

This review will focus on the antidiabetic dopamine agonist, bromocriptine mesylate (Cycloset®). Bromocriptine mesylate is the only dopamine agonist approved by the Food and Drug Administration (FDA) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.[1] Other formulations of bromocriptine are used for the treatment of Parkinson's disease, acromegaly, hyperprolactinemia and pituitary adenoma and will not be covered in this review.[2] Bromocriptine mesylate is a synthetic dopamine agonist that is chemically related to ergot alkaloids that acts on dopamine receptors throughout the body. The exact mechanism by which bromocriptine mesylate improves glycemic control is unknown.[1] Timed pulsed bromocriptine mesylate is thought to act upon the central nervous system to increase dopaminergic tone and decrease norepinephrine and serotonin release, thus improving control of peripheral metabolism in adipose tissue and liver.[2] Currently, bromocriptine mesylate (Cycloset®) is available as a 0.8 mg, brand-name only, quick-release tablet. Bromocriptine mesylate is administered once daily in the morning with food. The initial dose is 0.8 mg daily increased weekly by one tablet until maximum tolerated daily dose of 1.6 mg to 4.8 mg is achieved.[1]

The original new drug application (NDA) for the use of bromocriptine mesylate as an antidiabetic agent was denied by the FDA in 1998 due to a small treatment effect along with outstanding cardiovascular safety concerns. There were only a few cardiac events in the three pivotal trials submitted with the original NDA; however, the voluntary withdrawal of bromocriptine's indication for postpartum lactation due to postmarketing reports of cardiac events and seizures around the same time had also contributed to the final decision according to FDA's summary review of bromocriptine. The FDA issued an approvable letter in October 1999 conditional on the completion of a large, placebo-controlled, randomized trial to evaluate the potential for a significant increase in the risk of serious cardiac events in patients with type 2 diabetes treated with bromocriptine mesylate. Based on the results of this large safety clinical trial, the FDA issued an "approvable letter" for bromocriptine mesylate. Cycloset® is the first drug to be approved under the FDA requirement of evaluating cardiovascular risk in new antidiabetic therapies for the treatment of type 2 diabetes.[3]

The FDA approval of bromocriptine mesylate was based on the clinical evidence of safety and glycemic efficacy derived from four randomized, double-blind, placebo-controlled clinical trials in a total of 3,723 patients with type 2 diabetes.[1] Other clinical studies have since confirmed those results.[4-7] According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens.[8-11] Additionally, patients with high glycosylated hemoglobin (HbA_{1c}) will likely require combination dual or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. Guidelines currently rate bromocriptine mesylate as a second- or third-line agent due to its modest HbA1c reduction (~0.5 to 1%) and side effects profile, including nausea and orthostasis.[8-11] Several guidelines note that bromocriptine mesylate does not cause hypoglycemia or metabolic changes are preliminary data suggests that it may be useful to reduce the rate of cardiovascular events.[9,10]

Medications

Table 1. Medications Included Within Class Review[1]

Generic Name (Trade name)	Medication Class	Generic Availability
Bromocriptine mesylate (Cycloset®)	Dopamine Agonist	-

Indications

Table 2. Food and Drug Administration Approved Indications[1]

Indication	Bromocriptine mesylate
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	✔

Other formulations of bromocriptine are used for the treatment of Parkinson's disease, acromegaly, hyperprolactinemia and pituitary adenoma and will not be covered in this review. In addition, bromocriptine is used off-label for female infertility (In vitro fertilization).[12]

Pharmacokinetics[1]

Absorption
When administered orally, approximately 65 to 95% of the bromocriptine mesylate dose is absorbed. However, due to extensive hepatic extraction and first-pass metabolism, approximately 7% of the dose reaches systemic circulation. The time to reach peak concentrations is 53 minutes in the fasted state. The time to Cmax is increased to approximately 90 to 120 minutes with a high-fat meal and the relative bioavailability of bromocriptine mesylate is increased by approximately 55 to 65%.

Distribution
The volume of distribution of bromocriptine mesylate is approximately 61 L with 90 to 96% of bromocriptine mesylate bound to plasma proteins.

Metabolism
The major metabolic reaction in the metabolism of bromocriptine mesylate is by CYP3A4. Bromocriptine mesylate is extensively metabolized in the gastrointestinal tract and liver.

Elimination
The elimination half-life of bromocriptine mesylate is approximately 6 hours in healthy individuals. It is primarily eliminated in the bile and 2 to 6% of orally administered bromocriptine mesylate is excreted via urine.

Clinical Trials
The FDA approval of bromocriptine mesylate was based on the clinical evidence of safety and glycemic efficacy derived from four randomized, double-blind, placebo-controlled clinical trials in a total of 3,723 patients with type 2 diabetes. In all four clinical trials, patients in the bromocriptine group received an initial dose of 0.8 mg daily for one week and then increased by 0.8 mg each week for six weeks (4.8 mg/day final dose) if no intolerance occurred or until the maximum tolerated dose of ≥1.6 mg/day was reached.[1]

Monotherapy
Monotherapy with bromocriptine mesylate as an adjunct to diet and exercise was evaluated in an unpublished, 24 week, placebo-controlled monotherapy trial in 159 overweight patients (body mass index [BMI] ≥26.0 kg/m^2 for males and ≥28.0 kg/m^2 for females) with type 2 diabetes and inadequate glycemic control (HbA_{1c} 7.5 to 11%). There was a decrease in HbA_{1c} by 0.1% from baseline in the bromocriptine mesylate group compared to an increase in HbA_{1c} of 0.3% from baseline in the placebo group (P=0.05).

There was no change from baseline in the fasting plasma glucose (FPG) in the bromocriptine mesylate group compared to an increase in FPG of 23 mg/dL in the placebo group (P=0.005). The mean change in body weight from baseline was an increase of 0.2 kg in the bromocriptine mesylate group compared to 0.5 kg in the placebo group (P value not reported).[1]

Combination Therapy

Combination therapy with bromocriptine mesylate was studied in two similarly designed, unpublished, 24 week, randomized, double-blind, placebo-controlled trials (study K and study L) in patients with type 2 diabetes and inadequate glycemic control (HbA_{1c} 7.8 to 12.5%) on stable sulfonylurea (SU) therapy. The range of BMI was 26 to 40 kg/m^2 for men and 28 to 40 kg/m^2 for women with an approximate mean of 32 kg/m^2 in both the studies. Sixty-eight percent of patients in study K and 75% of patients in study L in the bromocriptine mesylate group achieved the maximum dose. In study K, the mean increase in body weight from baseline was 0.9 kg in the bromocriptine mesylate group compared to 0.5 kg in the placebo group (P value not reported). In study L, the mean change in body weight from baseline was an increase of 1.4 kg in the bromocriptine mesylate group compared to 0.5 kg in the placebo group (P value not reported). Patients treated with bromocriptine mesylate in both the studies had a significantly improved HbA_{1c} compared to placebo (study K: -0.1% bromocriptine mesylate plus SU versus 0.4% placebo plus SU; study L: -0.4% bromocriptine mesylate plus SU versus 0.3% placebo plus SU; P≤0.001 for both studies). Patients treated with bromocriptine mesylate in both the studies had significantly improved FPG concentrations compared to placebo (change from baseline: study K, 10 mg/dL bromocriptine mesylate plus SU versus 28 mg/dL placebo plus SU [P=0.02]; study L, 3 mg/dL bromocriptine mesylate plus SU versus 23 mg/dL placebo plus SU [P=0.006]).[1]

The overall safety including the cardiovascular safety of bromocriptine mesylate was evaluated in a 52-week randomized, double-blind, placebo-controlled trial (N=3,095) in patients with type 2 diabetes receiving various antidiabetic therapies (mean HbA_{1c} 8.3%). Serious adverse events (SAE) occurred among 176 (8.6%) patients in the bromocriptine-quick release (QR) group compared to 98 (9.6%) patients in the placebo group. The time to first all-cause SAE supports noninferiority between bromocriptine-QR and placebo groups (hazard ratio [HR], 1.02; 96% one-sided CI, 1.27). The composite cardiovascular disease endpoint occurred in 37 (1.8%) patients in the bromocriptine-QR group compared to 32 (3.1%) patients in the placebo group (HR, 0.60; 95% two-sided CI, 0.37 to 0.96). Nausea was reported in 32.2% of bromocriptine-QR treated patients compared to 7.6% placebo-treated patients (P value not reported). Hypoglycemic adverse events occurred in 6.9% patients in the bromocriptine-QR group compared to 5.3% patients in the placebo group (P value not reported). Mean baseline HbA_{1c} was 7.0% in both treatment groups. The least-squares mean change in HbA_{1c} from baseline to week 24 in the bromocriptine group was 0.0% and in the placebo group was 0.2%. Pre-specified subgroup analyses of glycemic efficacy were conducted in patients with an inadequate glycemic control on one to two oral antidiabetic therapies (baseline HbA_{1c} ≥7.5%). In this subgroup analysis, patients in the bromocriptine group had a decrease in HbA_{1c} of 0.4% from baseline compared to no change in HbA_{1c} for the placebo group at week 24 (P<0.001).[1,4]

Several other clinical trials published since then have confirmed these results.[5-7]

Table 3. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Gaziano et al[4] The Cycloset Safety Trial Bromocriptine-QR 0.8 mg QAM with morning meal (dose titrated up by 0.8 mg per day on a weekly basis until a maximum dose of 4.8 mg/day was achieved or until patient could not tolerate a higher dose) vs placebo QAM Patients were required to be on a stable antidiabetes regimen consisting of either diet, or oral hypoglycemic agents (no more than two) or insulin (alone or with no more than one oral hypoglycemic agent) for at least 30 days prior to randomization.	DB, MC, PC, RCT Patients between the ages of 30 and 80 years (mean age 59.7 years) with a BMI of <43 kg/m2 (mean BMI 32.4 kg/m2) and HbA_{1c} level ≤10.0% with type 2 DM (defined by the 2004 ADA guidelines)	N=3,095 52 weeks	Primary: Assessment of overall safety of bromocriptine-QR by measuring the frequency of SAEs and cardiovascular safety assessed by determining the frequency of major cardiovascular events (defined as a composite of first myocardial infarction, stroke, coronary revas-cularization, or hospitalization for angina or CHF that occurred after randomization) Secondary: Additional safety measures including laboratory measures (blood chemistries,	Primary: SAEs occurred among 176 (8.6%) patients in the bromocriptine-QR group compared to 98 (9.6%) patients in the placebo group. The time to first all-cause SAE support noninferiority between the bromocriptine-QR and placebo groups (HR, 1.02; 96% one-sided CI, 1.27). The composite CVD endpoint occurred in 37 (1.8%) patients in the bromocriptine-QR group compared to 32 (3.1%) patients in the placebo group (HR, 0.60; 95% two-sided CI, 0.37 to 0.96). The treatment effect did not change appreciably with the addition of the baseline covariates of age, duration of diabetes, insulin usage, sex, race, baseline HbA_{1c}, level and prior history of stroke or coronary revascularization. Adverse events occurred in 89% of patients in the bromocriptine-QR group compared to 83% of patients in the placebo group (P value not reported). Twenty-four percent patients in the bromocriptine-QR group compared to 11% patients in the placebo group discontinued their study medication (P value not reported). The most commonly reported adverse event among patients who discontinued bromocriptine-QR was nausea (7.6% of bromocriptine-QR vs 1% placebo, P value not reported). Nausea was the most common adverse event in the study population (32.2% bromocriptine-QR vs 7.6% placebo, P value not reported). Somnolence occurred in 4.3% of bromocriptine-QR treated patients compared to 1.3% placebo-treated patients and hypoesthesia occurred in 1.4% of bromocriptine-QR treated patients compared to 1.1% placebo-treated patients within the nervous system organ class (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			hematology and urine analyses) at weeks 0, 24 and 52 of the study and evaluation of ECGs at weeks 0, 24, 52 or early termination	Depression or depressed mood and anxiety was reported in 0.7% and 0.6% of bromocriptine-QR treated patients compared to 1.4% and 0.8% placebo-treated patients, respectively (P values not reported). Hypoglycemic adverse events occurred in 6.9% patients in the bromocriptine-QR group compared to 5.3% patients in the placebo group (P value not reported). Secondary: At week 52, heart rate decreased by ~1 bpm from a baseline study population mean heart rate of 68 bpm in the bromocriptine-treated patients compared to placebo-treated patients (P=0.02). The corrected QT interval decreased by 3.2 ms (baseline average 418 ms) in the bromocriptine-treated patients compared to 1.9 ms (baseline average 420 ms) at week 52 (P value not reported). The mean change in body weight from baseline to week 52 was 0.2 kg for the bromocriptine-QR group compared to 0.1 kg for the placebo-group.
Vinik et al[5] (Abstract) Bromocriptine-QR 1.6 to 4.8 mg QD vs placebo QD	PC, RCT Patients 18 to 80 years of age diagnosed with type 2 DM with baseline HbA_{1c} ≥7.5 and on one or two oral antidiabetic agents	N=515 24 weeks	Primary: Concomitant oral antidiabetic medication changes, HbA_{1c}, odds of reaching HbA_{1c} of ≤ 7.0% Secondary: Not reported	Primary: Significantly more patients (P<0.05) intensified concomitant antidiabetic medication therapy during the study in the placebo compared to the bromocriptine-QR arm. In subjects that did not change the intensity of the baseline diabetes therapy (72%), and that were on any one or two antidiabetic agents or on metformin with or without another antidiabetic agent, or on metformin plus sulfonylurea, the HbA_{1c} change for bromocriptine-QR compared to placebo was -0.47 versus 0.22 (between group delta = -0.69, P<0.0001), -0.55 versus 0.26 (between group delta = -0.81, P<0.0001) and -0.63 versus 0.20 (between group delta = -0.83, P<0.0001) respectively, after 24 weeks on therapy.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The odds ratio of reaching HbA_{1c} of ≤ 7.0% was 6.50, 12.03 and 11.45 (P<.0002) for these three groups, respectively. Secondary: Not reported
Aminorroaya et al[6] Bromocriptine-QR 2.5 mg QD with breakfast vs placebo QD with breakfast During the first week, patients received half the prescribed dose (half tablet) and daily dose was increased to one tablet by the second week.	DB, PC, RCT Obese patients (BMI >30 kg/m^2) between the ages of 32 and 70 years with type 2 DM uncontrolled on oral hypoglycemic agents (glyburide or its combination with metformin)	N=40 3 months	Primary: Changes in FPG, HbA_{1c} and BMI after three months Secondary: Not reported	Primary: At three months, the FPG concentration decreased from 10.59 ± 0.42 to 9.06 ± 0.41 mmol/L in the bromocriptine group (P<0.01). FPG concentration in the placebo group remained unchanged, 10.69 ± 0.52 to 10.6 ± 0.57 mmol/L. At three months, HbA_{1c} was reduced in the bromocriptine group from 9.9 ± 0.3% to 9.5 ± 0.2% (P=0.06) and there was an increase in HbA_{1c} in the placebo group from 10.2 ± 0.3% to 11.3 ± 0.6% (P<0.05). There was no statistically significant change in BMI from baseline in either bromocriptine group or placebo group during the study period (bromocriptine, 33.2 ± 1.2 vs. 33.2 ± 1.2 kg/m2; placebo, 31.8 ± 1.0 vs 31.9 ± 1.0 kg/m2). Secondary: Not reported.
Pijl et al[7] Bromocriptine-QR QD between 7:30 am and 8:30 am (dose titrated up by 0.8 mg per day on a weekly basis until a maximum dose of 4.8 mg/day was achieved after six weeks) vs placebo QD between 7:30	DB, PC, RCT Obese patients (BMI between 28 and 42 kg/m^2 for women and between 27 and 42 kg/m^2 for men) with type 2 DM; patients taking insulin or other drugs known to affect	N=22 16 weeks	Primary: Change from baseline in body weight, FPG, HbA_{1c}, cholesterol Secondary: Not reported	Primary: There was no statistically significant change from baseline in bromocriptine or placebo group during the study period in body weight (bromocriptine, 89.6 ± 2.8 vs. 90.0 ± 2.9 kg; placebo, 93.4 ± 5.7 vs. 94.3 ± 5.3 kg), fat mass, percentage fat mass or abdominal fat distribution. At 16 weeks, the FPG concentration decreased from 190 ± 13 to 172 ± 14 mg/dL in the bromocriptine group (P=0.02) and FPG concentration in the placebo group increased from 187 ± 22 to 223 ± 26 mg/dL (P=0.02). At 16 weeks, HbA_{1c} was reduced in the bromocriptine group from 8.7 ±

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
am and 8:30 am	insulin sensitivity were not eligible			0.4% to 8.1 ± 0.5% (P=0.009) and there was an increase in HbA_{1c} in the placebo group from 8.5 ± 0.5% to 9.1 ± 0.6% (P value reported as nonsignificant). The mean plasma glucose concentration during OGTT was reduced by bromocriptine (from 294 ± 14 to 272 ± 17 mg/dL, P=0.005) and was increased by placebo (from 289 ± 17 to 313 ± 28 mg/dL, P value reported as nonsignificant). There was no change in glucose disposal during the first step of the insulin clamp in both, the bromocriptine or placebo treated groups. During second insulin clamp set, the bromocriptine group had an improved total glucose disposal from 6.8 to 8.4 mg/min/kg fat-free mass (P=0.01) and nonoxidative glucose disposal from 3.3 to 4.3 mg/min/kg fat-free mass (P<0.05). Both these variables deteriorated in the placebo group (P≤0.02). The total plasma cholesterol concentration decreased from baseline in the bromocriptine group from 190 ± 7 to 178 ± 6 mg/dL (P=0.06) and remained unchanged in the placebo group. There were no significant changes in plasma LDL cholesterol, HDL cholesterol or triglyceride concentrations in either bromocriptine group or placebo group (P value not reported). The mean 24 hour blood pressure and the mean heart rate were not affected by either bromocriptine or placebo (P value reported as nonsignificant). Secondary: Not reported.

Drug regimen abbreviations: BID=twice daily, QAM=once daily in the morning, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: ADA=American Diabetes Association, DB=double-blind BMI=body mass index, CHF=congestive heart failure, CI=confidence interval, CVD=cardiovascular disease, DM=diabetes mellitus, FPG=fasting plasma glucose, HbA_{1c} =glycosylated hemoglobin A_{1c}, HDL= high density lipoprotein, HR=hazard ratio, LDL=low density lipoprotein, MC=multicenter, OGTT=oral glucose tolerance test, PC=placebo-controlled, QR=quick -release RCT=randomized controlled trial, SAE=serious adverse advents

Special Populations

Table 4. Special Populations[1]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Bromocriptine mesylate	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out. Safety and efficacy in children have not been established.	Not studied in renal dysfunction. Minor elimination pathway. Use caution in patients with renal impairment.	Not studied in hepatic dysfunction. Primarily metabolized by the liver. Use caution in patients with hepatic impairment.	B	Contra-indicated in women who are breastfeeding; bromocriptine inhibits lactation.

Adverse Drug Events

The adverse events reported more commonly in patients treated with bromocriptine mesylate than placebo in controlled clinical trials in at least ≥5% patients include nausea, fatigue, dizziness, vomiting and headache (Table 5). These commonly reported adverse events lasted a median of 14 days and were more likely to occur during the initial titration of bromocriptine mesylate.[1]

Table 5. Reported in Phase 3 Clinical Trials of bromocriptine meslyate in ≥5% patients[1]

	Bromocriptine mesylate, N (%)	Placebo, N (%)
Monotherapy (N=159)	***N=80***	***N=79***
Nausea	26 (32.5)	6 (7.6)
Rhinitis	11(13.8)	3 (3.8)
Headache	10 (12.5)	7 (8.9)
Asthenia	10 (12.5)	5 (6.3)
Dizziness	10 (12.5)	6 (7.6)
Constipation	9 (11.3)	3 (3.8)
Sinusitis	8 (10.0)	2 (2.5)
Diarrhea	7 (8.8)	4 (5.1)
Amblyopia	6 (7.5)	1(1.3)
Dyspepsia	6 (7.5)	2 (2.5)
Vomiting	5 (6.3)	1(1.3)
Infection	5 (6.3)	4 (5.1)
Anorexia	4 (5.0)	1(1.3)
Adjunct to Sulfonylurea (N=494)	***N=244***	***N=250***
Nausea	62 (25.4)	12 (4.8)
Asthenia	46 (18.9)	20 (8.0)
Headache	41 (16.8)	40 (16.0)
Flu syndrome	23 (9.4)	19 (7.6)

Constipation	24 (9.8)	11 (4.4)
Cold	20 (8.2)	20 (8.0)
Dizziness	29 (11.9)	14 (5.6)
Rhinitis	26 (10.7)	12 (4.8)
Sinusitis	18 (7.4)	16 (6.4)
Somnolence	16 (6.6)	5 (2.0)
Vomiting	13 (5.3)	8 (3.2)
Amblyopia	13 (5.3)	6 (2.4)
52-Week Safety Trial (N=3,070)	***N=2,054***	***N=1,016***
Nausea	661 (32.2)	77 (7.6)
Dizziness	303 (14.8)	93 (9.2)
Fatigue	285 (13.9)	68 (6.7)
Headache	235 (11.4)	84 (8.3)
Vomiting	167 (8.1)	32 (3.1)
Diarrhea	167 (8.1)	81 (8.0)
Constipation	119 (5.8)	52 (5.1)

In the monotherapy trial, hypoglycemia was reported by two patients in the bromocriptine mesylate group (3.7%) compared to one patient in the placebo group (1.3%). In the 52-week safety trial, the incidence of hypoglycemia was 6.9% in the bromocriptine mesylate group compared to 5.3% in the placebo group.[1]

Postmarketing reports of higher doses and other formulations of bromocriptine used for other indications include psychotic disorders, hallucinations, stroke and fibrotic-related complications (includes cases of retroperitoneal fibrosis, pulmonary fibrosis, pleural effusion, pleural thickening, pericarditis and pericardial effusions).[1]

Contraindications

Table 6. Contraindications[1]

Contraindication	Bromocriptine mesylate
Hypersensitivity to the drug or any component	✔
Hypersensitivity to ergot-related drugs	✔
Nursing Mothers	✔
Syncopal migraine	✔

Warnings/Precautions

Table 7. Warnings and Precautions[1]

Warning/Precaution	Bromocriptine mesylate
Hypotension, including orthostatic hypotension; can occur, particularly upon initiation of therapy or with dose escalation.	✔
Drug-drug interaction, other dopamine agonists; has not been studied with other dopamine agonists used for the treatment of Parkinson's disease or restless legs syndrome; concomitant use is not recommended	✔
Drug-drug interaction, dopamine antagonists; certain drugs that block the dopamine D2 receptor may reduce the effectiveness; concomitant use is not recommended	✔
Psychotic disorders; dopamine agonists may exacerbate the disorder or diminish the effectiveness of drugs used to treat the disorder	✔
Somnolence; refrain from driving or operating heavy machinery, particularly when initiating therapy	

Drug Interactions

Table 8. Drug Interactions[1]

Generic Name	Interacting Medication or Disease	Potential Result
Bromocriptine mesylate	Drugs that are highly bound to plasma protein (salicylates, sulfonamides, probenecid, chloramphenicol)	Bromocriptine is highly bound to serum proteins and may increase unbound fraction of other concomitantly used highly bound therapies, altering their effectiveness or side effects.
Bromocriptine mesylate	Dopamine receptor antagonists (neuroleptics [phenothiazines, butyrophenones, thioxanthenes] or metoclopramide	Concomitant use of a dopamine receptor antagonist may diminish the effectiveness of bromocriptine and vice versa.
Bromocriptine mesylate	Ergot-related drugs	May cause an increase in ergot-related side effects such as nausea, vomiting and fatigue and may reduce the effectiveness of the ergot to treat migraines.
Bromocriptine mesylate	CYP3A4 inducers	May decrease the exposure of bromocriptine, which may lead to subtherapeutic doses.
Bromocriptine mesylate	CYP3A4 inhibitors	May increase the exposure of bromocriptine, which may lead to supratherapeutic doses and increased side effects.
Bromocriptine mesylate	Sympathomimetic drugs (phenylpropanolamine and isometheptene)	May cause hypertension and tachycardia; concomitant use for more than 10 days is not recommended.

Dosage and Administration

Table 10. Dosing and Administration[1]

Generic Name	Adult Dose	Pediatric Dose	Availability
Bromocriptine mesylate	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Tablet: initial, 0.8 mg QD with food within two hours after waking in the morning; maintenance, 0.8 mg to 4.8 mg QD; maximum, 4.8 mg QD	Safety and efficacy in children have not been established.	Tablet: 0.8 mg

Drug regimen abbreviations: QD=once daily

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
American Diabetes Association: **Standards of Medical Care in Diabetes (2014)**[8]	Current criteria for the diagnosis of diabetes • Glycosylated hemoglobin (HbA_{1c}) ≥6.5%. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program certified and standardized to the Diabetes Control and Complications Trial assay; or • Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least eight hours; or • Two hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; or • In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L); • In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing. Prevention/delay of type 2 diabetes • Patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4% should be referred to an effective ongoing support program targeting weight loss of 7% of body weight and increasing physical activity to at least 150 min/week of moderate activity such as walking. • Follow-up counseling appears to be important for success. • Based on the cost-effectiveness of diabetes prevention, such programs should be covered by third-party payers. • Metformin therapy for prevention of type 2 diabetes may be considered in those with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%, especially for those with BMI >35 kg/m^2, aged, 60 years, and women with prior gestational diabetes. • At least annual monitoring for the development of diabetes in those with prediabetes is suggested. • Screening for and treatment of modifiable risk factors for cardiovascular disease (CVD) is suggested. Glucose monitoring • Patients on multiple-dose insulin or insulin pump therapy should do self-monitoring of blood glucose at least prior to meals and snacks, occasionally postprandially, at bedtime, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving. • When prescribed as part of a broader educational context, self-monitoring of blood glucose results may be helpful to guide treatment decisions and/or patient self-management for patients using less frequent insulin injections or noninsulin therapies. • When prescribing self-monitoring of blood glucose, ensure that patients receive ongoing instruction and regular evaluation of self-monitoring of blood glucose technique and self-monitoring of blood glucose results, as well as their ability to use self-monitoring of blood glucose data to adjust therapy.

Clinical Guideline	Recommendations
	• Continuous glucose monitoring in conjunction with intensive insulin regimens can be a useful tool to lower HbA_{1c} in selected adults (aged ≥25 years) with type 1 diabetes. • Although the evidence for HbA_{1c} lowering is less strong in children, teens, and younger adults, continuous glucose monitoring may be helpful in these groups. Success correlates with adherence to ongoing use of the device. • Continuous glucose monitoring may be a supplemental tool to self-monitoring of blood glucose in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes. HbA_{1c} • Perform the HbA_{1c} test at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control). • Perform the HbA_{1c} test quarterly in patients whose therapy has changed or who are not meeting glycemic goals. • Use of point-of-care testing for HbA_{1c} provides the opportunity for more timely treatment changes. Glycemic goals in adults • Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long-term reduction in macrovascular disease. Therefore, a reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. • Providers might reasonably suggest more stringent HbA_{1c} goals (such as <6.5%) for selected individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, long life expectancy, and no significant CVD. • Less stringent HbA_{1c} goals (such as <8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. Pharmacologic and overall approaches to treatment-type 1 diabetes • Recommended therapy consists of the following components: o Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous insulin infusion therapy. o Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. o For most patients (especially with hypoglycemia), use insulin analogs. o For patients with frequent nocturnal hypoglycemia and/or hypoglycemia unawareness, use of sensor-augmented low glucose suspend threshold pump may be considered. Pharmacologic and overall approaches to treatment-type 2 diabetes

Clinical Guideline	Recommendations
	• Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes. • In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the outset. • If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the HbA_{1c} target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin. • A patient-centered approach should be used to guide choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycemia risk, and patient preferences. • Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes.
American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012)**[9]	<u>Key points</u> • Glycemic targets and glucose-lowering therapies must be individualized. • Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. • Unless there are prevalent contraindications, metformin is the optimal first line drug. • After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. • All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. • Comprehensive cardiovascular risk reduction must be a major focus of therapy. <u>Initial drug therapy</u> • It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. • Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. • Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful.

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
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Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates.
Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection.

<u>Advancing to dual combination therapy</u>

If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required.
On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%.
If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted.
Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered.
It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration.
For all medications, consideration should also be given to overall tolerability.

<u>Advancing to triple combination therapy</u>

Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin.
Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit.
In using triple combinations the essential consideration is to use agents with complementary mechanisms of action.
Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence.

Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations
<table>
<tr><td>Initial Drug Monotherapy</td><td colspan="5">Metformin</td></tr>
<tr><td>Efficacy (↓HbA_{1c})</td><td colspan="5">High</td></tr>
<tr><td>Hypoglycemia</td><td colspan="5">Low risk</td></tr>
<tr><td>Weight</td><td colspan="5">Neutral/loss</td></tr>
<tr><td>Side Effects</td><td colspan="5">Gastrointestinal/lactic acidosis</td></tr>
<tr><td colspan="6">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td>Two Drug Combin-ations</td><td>Metformin + sulfonylurea</td><td>Metformin + thia-zolidinedione</td><td>Metformin + DPP-4 inhibitor</td><td>Metformin + GLP-1 receptor</td><td>Metformin + insulin (usually</td></tr>
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<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td></td><td>(TZD)</td><td></td><td>agonist</td><td>basal)</td></tr>
<tr><td>Efficacy (↓HbA_{1c})</td><td>High</td><td>High</td><td>Inter-mediate</td><td>High</td><td>Highest</td></tr>
<tr><td>Hypoglycemia</td><td>Moderate risk</td><td>Low risk</td><td>Low risk</td><td>Low risk</td><td>High risk</td></tr>
<tr><td>Weight</td><td>Gain</td><td>Gain</td><td>Neutral</td><td>Loss</td><td>Gain</td></tr>
<tr><td>Major Side Effects</td><td>Hypo-glycemia</td><td>Edema, heart failure, bone fracture</td><td>Rare</td><td>Gastro-intestinal</td><td>Hypo-glycemia</td></tr>
<tr><td colspan="6">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td>Three Drug Combin-ations</td><td>Metformin + sulfonylurea +</td><td>Metformin + TZD +</td><td>Metformin + DPP-4 inhibitor +</td><td>Metformin + GLP-1 receptor agonist +</td><td>Metformin + insulin therapy +</td></tr>
<tr><td></td><td>TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>TZD, DPP-4 inhibitor, or GLP-1 receptor agonist</td></tr>
<tr><td colspan="6">If combination therapy that includes basal insulin has failed to achieve HbA_{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents</td></tr>
<tr><td>More Complex Insulin Strategies</td><td colspan="5">Insulin (multiple daily doses)</td></tr>
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<tr><td>American Association of Clinical Endocrinologists: Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan (2011)[10]</td><td>
<u>Antihyperglycemic pharmacotherapy</u>

The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2009 American Association of Clinical Endocrinologists/ American College of Endocrinology Diabetes Algorithm for Glycemic Control.[59]
Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.
Antihyperglycemic agents may be broadly categorized by whether they predominantly target FPG or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making.
TZDs and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG.
When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia.
The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose.
When postprandial hyperglycemia is present, glinides and/or α-glucosidase

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Clinical Guideline	Recommendations
	inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. • When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia. • Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight. • Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. • Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained. • Most patients with an initial HbA_{1c} level >7.5% will require combination therapy using agents with complementary mechanisms of action.
American Association of Clinical Endocrinologists: American Association of Clinical Endocrinologists: **Comprehensive Diabetes Management Algorithm 2013 Consensus Statement (2013)**[11]	<u>Principles underlying the algorithm</u> • Lifestyle optimization is essential for all patients with diabetes; however, should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. • Achieving an HbA_{1c} ≤6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. • Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. • For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. • Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). • Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. • Rapid-acting insulin analogs are superior to regular insulin because they are more predictable. • Long-acting insulin analogs are superior to neutral protamine Hagedorn (NPH) insulin because they provide a fairly flat response for approximately 24 hours and provide better reproducibility and consistency, both between and within patients, with a corresponding reduction in hypoglycemia risk. <u>Monotherapy</u> • Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} ≤7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals

Clinical Guideline	Recommendations
	in a majority of patients. • In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: o GLP-1 receptor agonists. o DPP-4 inhibitors. o Alpha-glucosidase inhibitors. o Sodium glucose cotransporter 2 (SGLT-2) inhibitors. • TZD, sulfonylurea, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. <u>Combination therapy</u> • Patients who present with an initial HbA_{1c} ≥7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. • Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus: o GLP-1 receptor agonists, DPP-4 inhibitors, TZD, SGLT-2 inhibitors, Basal insulin, Colesevelam, Bromocriptine quick release, Alpha-glucosidase inhibitors, Sulfoureas and glinides. <u>Three-drug combination therapy</u> • Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months has a high likelihood of reaching target with a third agent. • Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. • Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfourea are used in conjunction with insulin. • Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus: o GLP-1 receptor agonists, TZD, SGLT-2 inhibitors, Basal insulin, DPP-4 inhibitors, Colesevelam, Bromocriptine quick release, Alpha-glucosidase inhibitors, Sulfoureas and glinides <u>Insulin therapy algorithm</u> • Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. • Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and

Clinical Guideline	Recommendations
	weight loss. • Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. • Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs. Basal insulin • Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. • Titrate insulin dose every two to three days to reach glycemic goals. • Basal insulin analogues (glargine and detemir) are preferred over NPH insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. Basal-bolus insulin regimens • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin. • A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. • Doses of insulin may be titrated every two to three days to reach glycemic goals. Basal insulin and incretin therapy regimens • Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. • The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.

Conclusions

Bromocriptine mesylate (Cycloset®) is a once-daily orally administered, ergot derivative which is Food and Drug Administration (FDA) approved to improve glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise. Bromocriptine has been used for over 30 years under Parlodel® for the treatment of Parkinson's disease and other indications (20 to 100 mg/day). The mechanism of action of bromocriptine mesylate by which it improves glycemic control is unknown.[1]

Notably, bromocriptine mesylate is the first drug to be approved since the FDA passed new guidelines that require clinical trials of diabetes therapies to demonstrate that they do not increase the risk of cardiovascular events. The average treatment difference in mean HbA_{1c} change from placebo was 0.5%

in the four double-blind, placebo-controlled clinical trials conducted to evaluate the safety and glycemic efficacy of bromocriptine mesylate. The HbA_{1c} reduction with the first line treatment options for patients with type 2 diabetes, metformin and sulfonylureas, is 1% to 2%.[1] Bromocriptine mesylate has a large number of drug-drug interactions and significant adverse events associated with its use. In the 52-week safety trial of 3,070 patients that received the study drug, 47% of patients stopped treatment of bromocriptine compared to 32% in the placebo group. The study investigators noted that gastrointestinal side-effects including nausea associated with dose titration to maximum tolerated dose of 4.8 mg/day may have contributed to this large discontinuation rate.[4]

Bromocriptine is formulated as quick release tablet that is dosed at 0.8 to 4.8 mg (one to six tablets) once-daily and should be given with food. Current guidelines recommend bromocriptine mesylate as a second- or third-line agent due to its modest HbA_{1c} reduction (~0.5 to 1%) and side effects profile.[8-11]

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