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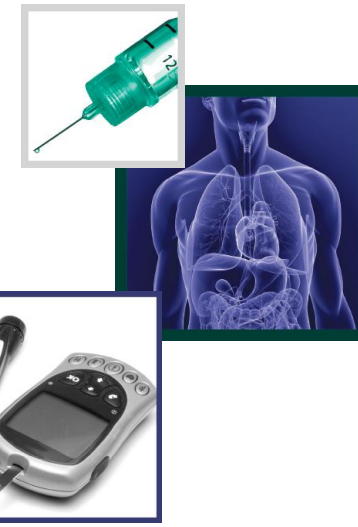

Bromocriptine mesylate QR in treatment of Type 2 diabetes

George Grunberger*

Practice Points

- Indication
  - Indication is for patients with Type 2 diabetes mellitus (T2DM) uncontrolled by diet and exercise. Given the unique mechanism of action of bromocriptine mesylate QR (CNS) it can theoretically be added to any other anti-DM agent(s).
- How to start
  - Timing is essential – bromocriptine mesylate QR has to be administered within 2 h of awakening and in the morning. Start with one 0.8 mg tablet and uptitrate by one tablet each week until either desirable improvement of glycemia occurs, or maximum dose of six tablets (4.8 mg) daily is reached. Some patients will not tolerate the maximum dose.
- When to expect results
  - Given its mode of action, results (predominantly improved postprandial glucose) should be noticeable rapidly (certainly by the end of the first month). Responders should see improvement after they are on 3–4 tablets a day (2.4–3.2 mg).
- Limiting factors
  - Most common adverse events limiting tolerance and dose escalation are gastrointestinal (mainly nausea but also vomiting, diarrhea or constipation), headache and dizziness. Nausea is quite frequent initially (up to 25–30% of patients) but dissipates after the first couple of weeks in most patients; 7.6% of patients in the largest study stopped bromocriptine mesylate QR because of nausea.
- When to stop
  - Discontinue the drug when either significant adverse reaction occurs or if no appreciable effect on A1c is seen at the 3-month check-up while the patient is on the highest tolerated dose of bromocriptine mesylate QR.

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SUMMARY There is a worldwide epidemic of Type 2 diabetes mellitus and practitioners everywhere are seeking optimal ways of approaching this complex and serious disease. Optimizing glycemic control to prevent long-term diabetic complications has been the holy grail of diabetes management. Bromocriptine mesylate QR is a sympatholytic dopamine D2 receptor agonist approved in the US for treatment of hyperglycemia in patients with Type 2 diabetes. It possesses a unique mode of action, acting centrally to enhance insulin sensitivity by resetting the circadian clock. In clinical trials it demonstrated lowering of A1c without the risks of hypoglycemia and weight gain. In addition, a possibility of cardiovascular benefit was raised in a large safety study. The major limitation of its use is the relatively high initial incidence of gastrointestinal events (nausea up to 30% and vomiting 8%). Among other adverse events, dizziness and headache were observed more commonly than in placebo-treated patients.

Background

Bromocriptine mesylate QR was approved in the US for treatment of hyperglycemia in patients with Type 2 diabetes mellitus (T2DM) in 2009. Its mode of action is unique among the drugs in clinical use for management of T2DM. Its effects appear to be mediated via resetting of dopaminergic and sympathetic tone within the CNS [1]. Several reviews of the subject have been published recently [2–5,101,102].

Briefly, it tends to normalize the level of dopaminergic tone at clock hypothalamic neurons in the morning, which then react by stimulating preautonomic neurons to reduce sympathetic outflow to the liver, fat, pancreas and vasculature, and by correcting aberrations in fuel-sensing neurons in the hypothalamus so that the liver can respond appropriately to a meal **(Figure 1)** [Cincotta AH, Pers. Comm.].

Of necessity, most studies have been carried out in animal models since it is impossible to sample human brain to document the neurotransmitter alterations in insulin resistant states.

Results showed that serotonin and noradrenergic levels and activities are increased in insulin resistant states [6–8]. Dopamine levels are low during the insulin-resistant state in animals and they return to normal as animals transition to insulin sensitive states [9,10]. Animal models of insulin resistance show reduced dopamine levels in the ventromedial hypothalamus (VMH) and lateral hypothalamic nuclei [6,11,12]. Infusion of norepinephrine and serotonin into VMH promotes insulin resistance and glucose intolerance in experimental animal models [13]. Conversely, systemic administration of bromocriptine mesylate to insulin resistant animals decreases the elevated VMH noradrenergic and serotoninergic levels. This results in decrease in hepatic gluconeogenesis, reduced adipose tissue lipolysis and improved insulin sensitivity [9,14,15]. Furthermore, bromocriptine mesylate reduces insulin resistance, glucose intolerance, hyperinsulinemic, and body fat stores in Syrian hamsters [16] and reduces body fat in pigs [17]. VMH functions as a central glucose sensor, able to induce hepatic glucose production via the autonomic and endocrine systems in response to central glucopenia [18]. Bromocriptine mesylate QR may improve insulin sensitivity more after a meal or during acute hyperglycemia than in fasting state, possibly owing to its effect on hypothalamic fuel-sensing centers [19,20].

Thus, bromocriptine mesylate QR given at an appropriate time (within 2 h of awaking) may act as a timed dopaminergic signal that in insulin-resistant states improves the sensitivity of brain fuel-sensing neurons to increased glucose and free fatty acid levels by activating dopamine receptors within hypothalamic neurons [1,20]. We know that insulin resistance is associated with reduction in central dopamine signaling in humans [21,22]. Agonist-elicited increase in dopamine activity improves glucose tolerance and insulin sensitivity, reduces adiposity and reduces triglycerides and free fatty acids [23–27]. Increase in dopaminergic activity is associated with reduced noradrenergic tone, especially in the hypothalamus and this effect lowers blood pressure, glucose levels, free fatty acid concentrations and appetite [9,28,29]. In humans, there is a reduction in dopaminergic activity in subjects with T2DM [30]. In initial human studies bromocriptine mesylate QR demonstrated a decrease in glycemia and dyslipidemia of insulin resistance [26,30,31].

Indications & usage

Bromocriptine mesylate QR is a dopamine receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The prescribing information specifically states that it should not be used

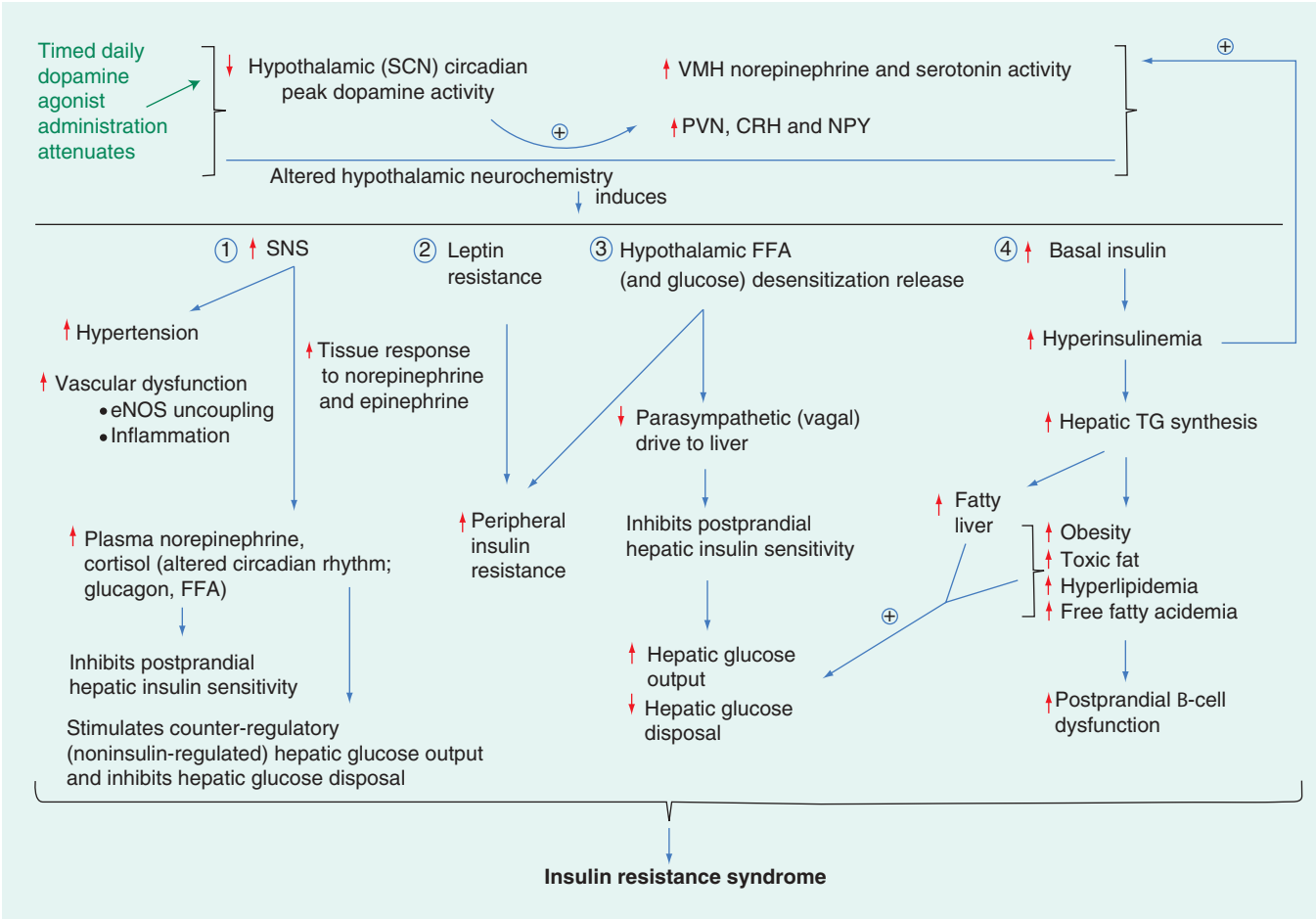

Figure 1. Proposed mechanism of action of bromocriptine mesylate QR. The scheme summarizes proposed relationships between the CNS and peripheral tissues in insulin resistance states. Bromocriptine mesylate QR (upper left) attenuates insulin resistance by its increase in dopaminergic tone.
CRH: Corticotropin-releasing hormone; FFA: Free fatty acid; NPY: Neuropeptide Y; PVN: Paraventricular nucleus; SCN: Suprachiasmatic nucleus; SNS: Sympathetic nervous system; TG: Triglyceride; VMH: Ventromedial hypothalamus.
Reproduced with permission from [1], [Cincotta AH, Pers. Comm.].

to treat Type 1 diabetes, that efficacy data in combination with thiazolidinediones are limited and that efficacy has not been confirmed in combination with insulin [103].

Dosage & administration

The drug should be taken orally within 2 h of waking in the morning with food, and the initial dose is one tablet (0.8 mg) daily, increased weekly by one tablet until the maximal tolerated daily dose of 1.6–4.8 mg (2–6 tablets) is achieved.

Clinical pharmacology

Mechanism of action

The precise mechanism by which bromocriptine mesylate QR improves glycemic control remains to be determined. The proposed mode was summarized above. Morning administration of the drug improves glycemic control in patients with T2DM without increasing plasma insulin concentrations. Once-daily morning administration of the medication to humans increases circulating levels of bromocriptine mesylate QR for 4–5 h after administration.

Structure

Cycloset® tablets (bromocriptine mesylate QR) contain bromocriptine mesylate, a dopamine receptor agonist. Bromocriptine mesylate is chemically designated (Ergotaman-3′,6′,18-trione, 2-bromo-12′-hydroxy-2′-[1-methylethyl]-5′-[2-methylpropyl]-,monomethanesulfonate [salt], [5′α]-). Molecular formula is $C_{32}H_{40}BrN_5O_5 \cdot CH_4SO_3$ and its molecular weight is 750.72 **(Figure 2)**.

■ Pharmacodynamics

Postprandial glucose & insulin response to a meal

Patients with T2DM and inadequate glycemic control on diet alone were randomized to bromocriptine mesylate QR or placebo in a 24-week monotherapy clinical trial. At baseline and study end, plasma samples for insulin and glucose were obtained before, 1 h and 2 h after standardized meals for breakfast, lunch and dinner. In this trial, once-daily (8 am) bromocriptine mesylate QR improved postprandial glucose (PPG) without increasing plasma insulin concentrations [103]. The mean reduction across the three meals averaged 37 mg/dl (from mean PPG at baseline of 272 mg/dl).

■ Pharmacokinetics

Absorption & bioavailability

When administered orally, approximately 65–95% of the bromocriptine mesylate QR dose is absorbed [32–35]. Due to extensive hepatic extraction and first-pass metabolism, approximately 7% of the dose reaches the systemic circulation. Under fasting conditions the time to maximum plasma concentration is 53 min. By contrast, following a standard high-fat meal, the time to maximum plasma concentration is increased to approximately 90–120 min. Also, the relative bioavailability of bromocriptine mesylate QR is increased under fed as compared with fasting conditions by an average of approximately 55–65% (increase in Area under the plasma concentration-time curve from time zero to infinity [AUC_{inf}]).

Distribution

Bromocriptine mesylate QR is 90–96% bound to plasma proteins. The volume of distribution is approximately 61 l [103].

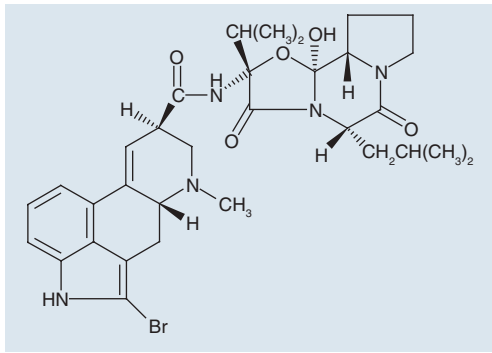

Figure 2. Structure of bromocriptine mesylate QR.

Metabolism

Bromocriptine mesylate QR is extensively metabolized in the gastrointestinal tract and liver. Metabolism by CYP3A4 is the major metabolic pathway. Most of the absorbed dose (~93%) undergoes first-pass metabolism. The remaining 7% reaches the systemic circulation [31–35].

Excretion

The major route of excretion of bromocriptine mesylate QR is via the bile with the remaining approximately 2–6% of an oral dose excreted in the urine. The elimination half-life is approximately 6 h. Prior consumption of a standard high-fat meal has little to no effect on the elimination half-life of bromocriptine mesylate QR [34,35].

Clinical evidence

■ Overview of clinical trials in Type 2 diabetes

Approval of bromocriptine mesylate QR was first sought in 1998 based on monotherapy and add-on to sulfonylurea (SU) studies performed in 1995–1996 with a drug formulation that is different from the one ultimately approved in 2009 [104] **(Table 1)**.

In a 24-week monotherapy study 159 obese patients (age: 54.9 ± 9.4 years) with poorly controlled T2DM (mean A1c: 9.0%; diabetes duration: 5 ± 6.2 years) were randomized to bromocriptine mesylate QR (n = 80) or placebo (n = 79) [30]. A total of 69% of the patients in the active arm reached the maximum dose of 4.8 mg/day. The active drug decreased A1c only by 0.1% (those on placebo saw rise in A1c of 0.3%). Fasting plasma glucose (FPG) was not decreased by bromocriptine mesylate QR (it rose by 23 mg/dl in the placebo group). Weight rose by 0.2 kg in the active group of whom 75% finished the 24-week long trial. Ten patients discontinued bromocriptine mesylate QR.

There were two different clinical trials in which bromocriptine mesylate QR was added to SU therapy in patients with uncontrolled T2DM [30]. Both of these studies lasted 24 weeks. In the first one (n = 245), 122 obese subjects were randomized to bromocriptine mesylate QR; all patients continued SU therapy. Use of bromocriptine mesylate QR resulted in a 0.1% decline in A1c (from baseline of 9.3%) while patients in the SU-only arm saw A1c rise by 0.4% (from baseline of 9.4%). A total of 75% of the patients reached the 4.8 mg/day dose

and 76% finished the study. FPG declined by 10 mg/dl (from baseline of 216 mg/dl) while weight increased by 1.4 kg.

In the second study, involving 249 patients (122 randomized to bromocriptine mesylate QR) the active drug led to a decline of 0.4% from the baseline A1c of 9.3% (in the placebo group A1c rose by 0.3% from baseline of 9.4%). In this study, 68% of the patients reached the maximum bromocriptine mesylate QR dose of 4.8 mg/day. FPG did not change and weight increased by a mean of 0.9 kg in the bromocriptine mesylate QR + SU group. Mean age and duration of T2DM were similar in both studies (age: 55; DM duration: 7 years). Any improvements in glycemic parameters in these trials would not be considered clinically significant.

Because of the improvement in glycemic control among patients on SU plus bromocriptine mesylate QR, a study was undertaken in 32 patients with T2DM already on insulin (minimum 25 units/day) [36]. Bromocriptine mesylate QR (as Ergoset® preparation) was given to 21, while 11 subjects received placebo for 12 weeks. The drug was started at 0.8 mg/day and uptitrated to a maximum of 4.8 mg/day over the initial 6 weeks. A1c decreased by 0.7% (from baseline of 9.2%) in bromocriptine mesylate QR treated patients while to it rose by 0.1% (from 9.5%) in those randomized to placebo. This improvement in glycemic control occurred even though patients reduced insulin dose by 8%. Diurnal glucose concentration (derived from nine time points of glucose levels) was decreased by 29 mg/dl by bromocriptine mesylate QR. Unfortunately, the study results were never published as a full paper. However, in a more recent effort to replicate the results, Roe and Raskin presented a study in an abstract form in 15 poorly controlled patients with T2DM on insulin (average almost 200 units/day) and metformin. They showed significant A1c lowering by bromocriptine mesylate QR (from baseline average 9.5–8%) over 3 months in the face of significant insulin dose reduction (to an average of 140 units/day) [Cincotta AH, Pers. Comm.].

The US FDA did not approve the drug in 1999, citing both the lack of efficacy and potential safety concerns (small imbalance in adverse cardiac events). The agency then requested a large safety study, which commenced in 2004. Interestingly, the drug formulation used in this 52-week safety clinical trial was different from both the one used in the initial studies as well as from the one eventually approved and used today.

Table 1. The original 24-week studies of bromocriptine mesylate QR.

Study	n	Baseline A1c (%)	Change in A1c (%)	Baseline FPG (mg/dl)	Change in FPG (mg/dl)
Monotherapy	B = 80 P = 79	B = 9.0 P = 8.8	B = -0.1 P = +0.3	B = 215 P = 205	B = 0 P = +23
Add-on to SU (study 1)	B = 122 P = 123	B = 9.3 P = 9.4	B = -0.1 P = +0.4	B = 216 P = 227	B = +10 P = +28
Add-on to SU (study 2)	B = 122 P = 127	B = 9.3 P = 9.4	B = -0.4 P = +0.3	B = 220 P = 226	B = +3 P = +23

B: Bromocriptine mesylate QR; FPG: Fasting plasma glucose; P: Placebo; SU: Sulfonylurea.
Data taken from [30].

Two trials assessing the effects of bromocriptine mesylate QR carried out more recently in different types of patients with T2DM deserve mention here. In a study of 105 newly diagnosed, drug-naive patients in Miraj, India, bromocriptine mesylate QR (2.4 mg/day) reduced fasting blood glucose significantly ($p < 0.05$) by 16 mg/dl (from 148 mg/dl), PPG by 14 mg/dl (from 184 mg/dl) and A1c by 0.46% (from 7.71%) over 12 weeks. When combined (at 1.6 mg/day) with metformin (500 mg twice daily), the improvements in glycemic parameters were larger: fasting blood glucose down by 44 mg/dl, PPG by 44 mg/dl and A1c by 0.74%. Patients randomized to the third arm and placed on metformin 500 mg twice daily saw results between those achieved in the two groups randomized to bromocriptine mesylate QR or its combination with metformin [37]. The adverse event profile was similar among all participants, with nausea, vomiting and headache being reported most commonly.

In a study of 40 patients with more advanced T2DM in Isfahan, Iran, bromocriptine mesylate QR (2.5 mg/day) was compared with placebo in a double-blinded fashion over 3 months [38]. These patients were all failing (baseline A1c for those randomized to bromocriptine mesylate QR 9.9%) on a therapy with metformin (average dose ~1000 mg/day) with or without glibenclamide (average dose ~16 mg/day). FPG fell from 10.59 to 9.06 mmol/l ($p < 0.01$) and A1c from 9.9 ± 0.3% to 9.5 ± 0.2 ($p = 0.06$) after 3 months among those assigned to bromocriptine mesylate QR therapy. These changes were significantly different from values seen among the placebo-treated subjects but not impressive clinically. Also, the authors do not mention the type of bromocriptine mesylate QR used in the study. They do point out that there was no change in weight and the drug was well

tolerated: all patients finished the study and only two patients on bromocriptine mesylate QR had mild transient nausea.

When an approvable letter for the bromocriptine mesylate QR application was issued by the FDA in October 1999 it contained the following:

> *"…Based on the data submitted to the NDA (New Drug Application), we remain concerned that treatment of patients with Type 2 diabetes with Ergoset may be associated with serious cardiac adverse events…"* [104].

In response to this concern, a large (n = 3095), double blind, placebo-controlled, parallel, prospective 52-week long trial was conducted in patients with T2DM receiving usual diabetes therapy and A1c ≤10% to determine whether Cycloset (new formulation of bromocriptine mesylate QR) resulted in all-cause rates of serious cardiovascular adverse events (myocardial infarction, stroke, coronary revascularization or hospitalization for unstable angina or congestive heart failure) that were not higher than that of placebo [39]. Patients were randomized in a 2:1 ratio to the active drug or placebo. Results of the study were published in 2010 [40], glycemic results shown in **Table 2** and showed that patients randomized to bromocriptine mesylate QR actually had fewer cardiovascular events than those in the placebo arm (1.8 vs 3.1%, respectively, resulting in a hazard ratio of 0.60 [95% CI: 0.37–0.96]). In absolute terms, there were 37 events (among 2054 patients) in the bromocriptine mesylate QR arm and 32 (among 1016 patients) for those randomized to placebo. There were significant reductions in every component of the composite cardiovascular disease (CVD) end point. A total of 47% of the patients on bromocriptine mesylate QR and 32% on placebo discontinued treatment before the final study visit. However, assessment for study end points was completed for 75% of the bromocriptine mesylate QR treated subjects and for 82% of those in the placebo group (patients not taking the drug any longer were either seen in the clinic or interviewed by phone at 52 weeks). The most common reason for discontinuation of bromocriptine mesylate QR was nausea (7.6 vs 1% for placebo). Nausea was overall the most common adverse event, described in 32.2% of bromocriptine mesylate QR versus 7.6% in placebo exposed subjects. None of the adverse events were classified as serious and they typically occurred during the initial titration phase and lasted for under 14 days. Diabetes therapies used by the patients at baseline included diet alone (12%), metformin (59%), thiazolidinedione (TZDs; 19%), SUs/glinides (37%) and insulin (15%). Furthermore, 39% were on monotherapy while 33% were on two oral agents, 8% took an oral agent and insulin and 6% were only on insulin.

Investigators have postulated explanations for the observed decrease in cardiac events. A comprehensive review by Bell [41] focused on two principal possibilities: first, decreased overactivity of the sympathetic nervous system, hypothalamic–pituitary–adrenal axis and the renin–angiotensin system, and second, improvement of the postprandial milieu resulting in lower glucose, triglycerides and fatty acids leading to lower inflammation and oxidative stress.

Given the diverse patient population enrolled in the safety trial it is not surprising that a number of *post hoc* analyses of secondary end points were published subsequently. In one such analysis, the 39% reduction of composite cardiovascular end points was seen regardless of age, duration of DM, race, gender or pre-existing CVD [42]. Based on 0.7% events among the bromocriptine mesylate QR treated patients versus 1.5% in the placebo-treated patients a 52% reduction in relative risk in major adverse cardiovascular events was reported.

In another analysis, effect of bromocriptine mesylate QR versus placebo on glycemic control was investigated over the initial 24 weeks among the 515 patients enrolled in the safety study who were on one or two oral agents (metformin, SU and/or TZD) and had A1c ≥7.5% [43]. Among patients whose DM treatment was not changed during the initial time, bromocriptine mesylate QR treatment led to decrease in A1c of 0.47% (from baseline of 8.22%) and 32% were able to achieve A1c ≤7%. Almost 33% of patients did not finish the 24 week treatment, with nausea being the major reason (20%) for discontinuation.

A subgroup taking a TZD at baseline with or without other anti-DM therapy (n = 495) was analyzed after 52 weeks of randomization to bromocriptine mesylate QR or placebo [44]. One hundred and twenty-two of those subjects had baseline A1c ≥7.5% (mean 8.2%) and they saw A1c reduction of 0.67%, fall in FPG of 13 mg/dl and 32% chance of reaching A1c ≤7%; all of these parameters were significantly better than for placebo-treated subjects. Among those whose

A1c at entry was below 7.5% (mean 6.4%) there was no improvement of glycemic control (A1c rose by 0.14%) after 52 weeks. However, more bromocriptine mesylate QR treated patients were at goal A1c ≤7% (83%) than among those randomized to placebo (72%). Far more patients had an occurrence of nausea when placed on bromocriptine mesylate QR than on placebo (44 vs 7%) and only 57% of patients randomized to bromocriptine mesylate QR finished the study (vs 72% of placebo-treated ones).

Given the fact that bromocriptine mesylate QR is supposed to improve insulin sensitivity, results of yet another *post hoc* analysis of results of the safety trial should not be surprising. Patients (n = 52) entering the study on SU with baseline A1c 9.4% had much better response to bromocriptine mesylate QR therapy if they had both elevated BP (≥130/85) and triglycerides (≥200 mg/dl). Placebo-adjusted A1c was decreased by 1.22%. Those (n = 33) who had the lowest BP (<120/80) and triglycerides (<150 mg/dl) saw only 0.15% placebo-adjusted decrease in A1c [45]. Finally, a question was asked whether bromocriptine mesylate QR could retard progression of CVD and glycemic deterioration (defined as A1c exceeding 7%) among those subjects who entered the safety trial in good control (A1c ≤7%). There were 586 patients in the active arm and 328 on placebo whose entry A1c averaged 6.3% and who had no change in concomitant therapy during the 1-year trial. Bromocriptine mesylate QR treatment reduced the time to first cardiovascular event by 50% (hazard ratio: 0.51; 95% CI: 0.28–0.96) and slowed down the progression of glycemic deterioration by 31% (from 26 to 18%; p = 0.006) [46].

Table 2. The 52-week safety trial: analysis at 24 weeks.

	n	Baseline A1c (%)	Change in A1c (%)
All patients	B = 2049 P = 1015	B = 7.0 P = 7.0	B = 0.0 P = +0.2
On 1–2 OHA and A1c ≥7.5	B = 376 P = 183	B = 8.3 P = 8.4	B = -0.4 P = 0.0
On Met + SU and A1c ≥7.5	B = 177 P = 90	B = 8.3 P = 8.3	B = -0.5 P = 0.0

Results shown for all randomized patents and separately for those considered uncontrolled at entry (i.e., A1c ≥7.5%) to assess the effect of bromocriptine mesylate QR in a population typically recruited into clinical trials. B: Bromocriptine mesylate QR; Met: Metformin; OHA: Oral hypoglycemic agent; P: Placebo; SU: Sulfonylurea.

Mechanistic clinical studies

To gain insight into possible mechanism of action 15 obese patients with poorly controlled T2DM (mean A1c: 8.7%) were placed on bromocriptine mesylate QR (double-blind study, with seven patients placed on placebo) for 16 weeks [26]. A1c declined on average by 0.6% (to 8.1%; p = 0.009), FPG by 18 mg/dl (from 190 to 172 mg/dl; p = 0.02) and mean plasma glucose level during oral glucose tolerance test by 22 mg/dl (from 294 to 272 mg/dl; p = 0.005). Furthermore, during the second insulin clamp step (377 µU/ml) bromocriptine mesylate QR increased total glucose disposal and nonoxidative glucose disposal. All parameters worsened among those subjects who were placed on placebo, leading the authors to conclude that bromocriptine mesylate QR improved overall glucose tolerance by ameliorating fasting and PPG levels as well as increasing insulin-mediated glucose disposal.

It has been postulated that bromocriptine mesylate QR reduces insulin resistance. Thus, it was logical to investigate its potential benefit among those with metabolic syndrome in absence of overt DM. A small such trial was reported in 1996 in which 17 obese subjects with impaired glucose tolerance took the drug (1.6–2.4 mg/day, n = 8) or placebo (n = 9) for 18 weeks. Significant weight loss (6.3 ± 1.5 kg; p < 0.01), 46% decrease in the area under glucose curve and 30% reduction under the insulin curve (during oral glucose tolerance test) were seen among those randomized to the active study arm [47]. The greatest effect of the drug was seen at the 1-h point with serum glucose reduction from mean 215 to 160 mg/dl while there was negligible reduction of serum glucose for those randomized to placebo.

Adverse reactions

These have been included in the description of individual trials in detail. Most common adverse event has been nausea, followed generally by dizziness, fatigue and headache in different studies.

Drug interactions

It is not recommended to use ergot agents within 6 h of administration of bromocriptine mesylate QR because side effects such as nausea, vomiting or fatigue could be increased. Bromocriptine mesylate QR is metabolized by the CYP3A4 pathway and is highly serum protein bound. Thus, CYP3A4 inducers can reduce the drug concentration and bromocriptine mesylate QR may increase the unbound fraction of other highly protein-bound medications (e.g., salicylates, sulfonamides

and phenytoin). Caution should be used when coadministering strong inhibitors, inducers or substrates for CYP3A4. Dopamine receptor antagonists (e.g., antipsychotics such phenothiazines, butyrophenones and thioxanthenes) or metoclopramide may diminish effectiveness of bromocriptine mesylate QR.

■ Use in specific populations

Bromocriptine mesylate QR is category B drug in pregnancy. Studies in pregnant women have not shown that bromocriptine mesylate QR increases the risk of abnormalities when administered during pregnancy. However, bromocriptine mesylate QR is contraindicated in women who are nursing their children. Bromocriptine mesylate QR contains bromocriptine, which inhibits lactation. The safety and effectiveness of bromocriptine mesylate QR in pediatric patients have not been established. In the clinical trials with bromocriptine mesylate QR 650 patients were older than 65 years. No overall differences in safety or effectiveness were observed between the elderly and younger patients [103].

Financial & competing interests disclosure

G Grunberger has served on the Santarus speakers' bureau. In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made at the discretion of the author and based on scientific or editorial merit only. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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