REVIEW ARTICLE

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Efficacy and Safety of Bromocriptine-QR as an Adjunctive Therapy on Glycemic Control in Subjects with Uncontrolled Type 2 Diabetes Mellitus: A Systematic Review and Meta-analysis

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Abstract

Introduction. There has been an increasing awareness of the effects of combining bromocriptine-QR with other medications for diabetes mellitus type 2. This study aimed to assess the efficacy and safety of bromocriptine-QR as an adjunctive therapy for patients with uncontrolled type 2 diabetes mellitus.

Methodology. This systematic review is registered at the International Prospective Register of Systematic Reviews (CRD42022360326). Literature search was done via MEDLINE, NCBI, Google Scholar, Science Direct, Europe PMC and Cochrane Library databases. We included randomized controlled trials with participants 18 years old and above with uncontrolled type 2 diabetes mellitus. The primary outcome of interest is the efficacy and safety of bromocriptine-QR as an adjunctive therapy for glycemic control. Case reports, case series, reviews and animal studies were excluded. The risk of bias was reviewed using the Cochrane Risk of Bias tool. Meta-analysis was performed using Review Manager 5.4 and presented as a weighted mean difference and 95% confidence interval for changes from the baseline level.

Results. Nine studies were included in the systematic review with a total of 2709 participants. The baseline HbA1c in the bromocriptine-QR group was 7.42% and 7.51% in the control group. The bromocriptine-QR group was favoured, outperforming the control group in terms of reducing hemoglobin A1c(HbA1c), with a statistically significant difference (weighted mean difference -0.6%; 95% CI [-0.83,-0.36]; p<0.00001). The most common side effects were nausea (33.75% vs 6.92%), fatigue (13.11% vs 5.94%), and headache (11.17% vs 6.87%).

Conclusion. Administration of bromocriptine-QR at a dose range of 1.6 to 4.8 mg/day as an adjunctive therapy reduced HbA1c and FBG in patients with uncontrolled type 2 diabetes mellitus (T2DM). However, there were also statistically greater odds of the occurrence of adverse events such as nausea, vomiting, and headache compared to controls.

Key words: bromocriptine-QR, type 2 diabetes mellitus, HbA1c, side effects, glycaemic control, dopaminergic

INTRODUCTION

Diabetes mellitus can cause end-organ damage, leading to significant morbidity and mortality, such as cardiovascular disease (CVD), cerebrovascular events, renal failure, amputation and vision loss. Type 2 diabetes mellitus (T2DM) accounts for the vast majority (over 90%) of diabetes worldwide. The International Diabetes Federation 2021 stated that around 536.6 million people in the world live with diabetes, and is predicted to increase further by 2045. According to estimates, 19.5 million Indonesian people have diabetes, making it the country with the fifth greatest prevalence.[1]

Current recommendations from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) include lifestyle modifications and oral hypoglycemic drugs (OHDs) as first-line therapy. Metformin, a biguanide, is the most recommended therapy for patients with T2DM. The selection of an add-on medication to metformin depends on patient preference and clinical characteristics, including comorbidities.[2]

The Food and Drug Administration (FDA) approved Bromocriptine-Quick Release (QR), a centrally-acting dopamine D2 receptor agonist, as the first medication to improve glycemic control by targeting dopamine activity in patients with T2DM. The dopaminergic pathway affects glucose and lipid metabolism, while patients with T2DM have been reported to have lower hypothalamic dopaminergic tone in the morning.[3] Dopamine agonists, such as Bromocriptine-QR, activate the dopaminergic

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pathway responsible for metabolic control, thus improving glucose and energy metabolism in patients with T2DM.[4]

Recognizing the effects of bromocriptine-QR has increased awareness of the possible role of combining this agent with other therapies for T2DM management. Hence, this study aimed to assess the efficacy and safety of bromocriptine-QR as an adjunctive therapy for glycemic control in people with uncontrolled T2DM.

METHODOLOGY

Eligibility criteria

This systematic review and meta-analysis are reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[5] The protocol of this review has been registered on the International Prospective Register of Systematic Reviews (PROSPERO) database with the registration number CRD42022360326.

We included randomized controlled trials (RCTs) with the population consisting of patients over 18 years old with uncontrolled type-2 diabetes mellitus (T2DM), defined as having HbA1c test results over 7.5% despite receiving standard regimens of oral hypoglycemic drugs, insulin, or both with stable doses. The bromocriptine group included patients who received bromocriptine-QR as an add-on to their respective anti-diabetic regimen. The comparators in the included studies (control group) were patients who were not given any additional treatment or those given a placebo. The primary outcome was to assess the efficacy and safety of bromocriptine-QR as an adjunctive therapy in patients with uncontrolled T2DM. The glycemic efficacy of bromocriptine-QR was evaluated based on the changes in baseline HbA1c and fasting plasma glucose (FPG) between the bromocriptine-QR group and the control group. All adverse effects reported by the included studies were also extracted to assess the safety and tolerability of bromocriptine-QR. We included studies with a duration of at least 12 weeks to assess the glycemic control of bromocriptine-QR adequately. The dose of bromocriptine-QR used in the included studies must be within 1.6 to 4.8 mg/day as approved by the Food and Drug Administration (FDA).[6]

Case reports, case series, reviews and animal studies were excluded. We also did citation and hand-searching to ensure that all available studies were included.

Search strategy and study selection

The literature search was conducted on September 5, 2022, and was finished on the same day. We systematically searched and obtained the papers from MEDLINE, NCBI, Google Scholar, Science Direct, Europe PMC and Cochrane Library. The search terms used included (“bromocriptine-QR") AND ("diabetes mellitus" OR "diabetes mellitus type 2" OR "diabetes mellitus type II") AND (“uncontrolled” OR "poorly controlled" OR "inadequately controlled"). The details of the Medical Subject Heading (MeSH) terms are listed in Table 1. All records were then inputted into Rayyan software, which can detect duplicates and allow all authors to collaborate in selecting relevant studies. Three authors (CLB, MM, SC) conducted the initial search and imported all studies from various academic databases to the Rayyan software. Another author (TY) would then cross-check all the initial searches. All authors independently screened all available studies. All conflicts met during the screening process were resolved by discussion among the group until a conclusion was reached. If any missing or further data were needed, corresponding authors were sent an email of inquiry once.

Data extraction and quality assessment

The data extraction process was done independently by three authors (CLB, MM and SC) and was checked by TY. The authors recorded study characteristics (author, year of publication, location, study design and study period),

Table 1. Medical subject heading (MeSH) terms used in each database

Database	Medical subject heading	Number of studies found
Pubmed	("bromocriptine"[MeSH Terms] OR "bromocriptine"[All Fields] OR "bromocriptin"[All Fields] OR "bromocriptine s"[All Fields] OR "bromocriptine-qr"[All Fields] OR ("bromocriptine"[MeSH Terms] OR "bromocriptine"[All Fields] OR "bromocriptin"[All Fields] OR "bromocriptine s"[All Fields] OR "cycloset"[All Fields])) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields] OR ("diabetes"[All Fields] AND "mellitus"[All Fields] AND "type"[All Fields] AND "ii"[All Fields]) OR "diabetes mellitus type ii"[All Fields]) OR ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields] OR "diabetes mellitus type 2"[All Fields])) AND ("uncontrollability"[All Fields] OR "uncontrollable"[All Fields] OR "uncontrollably"[All Fields] OR "uncontrolled"[All Fields] OR ("poorly"[All Fields] AND "controlled"[All Fields]) OR (("inadequate"[All Fields] OR "inadequately"[All Fields] OR "inadequates"[All Fields]) AND "controlled"[All Fields]))	12
NCBI	((bromocriptine) OR (bromocriptine-qr)) AND ((diabetes mellitus) OR (diabetes mellitus type 2) OR (diabetes mellitus type II))	1000
Google Scholar	(bromocriptine-qr) AND ("diabetes mellitus" OR "diabetes mellitus type 2" OR "diabetes mellitus type II") AND (uncontrolled OR "poorly controlled" OR "inadequately controlled")	181
Science Direct	(bromocriptine-qr OR dopamine agonist) AND (uncontrolled) AND (diabetes mellitus type II)	183
Medline	((bromocriptine) OR (bromocriptine-qr)) AND ((diabetes mellitus) OR (diabetes mellitus type 2) OR (diabetes mellitus type II))	10
Europe PMC	((bromocriptine OR bromocriptine-qr) AND ("diabetes mellitus") AND (uncontrolled or "poorly controlled")	127
Cochrane Library	((bromocriptine) OR (bromocriptine-qr)) AND ((diabetes mellitus) OR (diabetes mellitus type 2) OR (diabetes mellitus type II))	9

baseline HbA1c level, change of HbA1c level, treatment given to the intervention and control group, adverse effects, and baseline variables, including age, sex, body mass index (BMI) change, blood pressure (BP) change, creatinine, duration of T2DM and previous diabetic treatment regimens. Data presented as mean and standard error of the mean (SEM) were converted into mean and standard deviation using the Cochrane method.[7]

All authors independently assessed the quality of each included study using the Jadad Scale Assessment,[8] where a score of four and higher indicated higher-quality studies. We included moderate to high-quality studies. As for the risk of bias, we used the Cochrane Risk of Bias tool.[9] The overall certainty of evidence for each outcome was assessed using the Grading Recommendations Assessment, Development and Evaluation (GRADE) approach.[10] High certainty effects were characterized as the outcome effect, moderate certainty using "probably," low certainty using "may," and very low certainty using "uncertain." Any discrepancies were sorted internally until an agreement was attained.[11] Funnel plot was not generated as there was insufficient study.

Data synthesis

Review Manager 5.4 software was used to perform this meta-analysis. The primary outcome for glycemic control in this study is the change in HbA1c from baseline, and the secondary outcome is the fasting plasma glucose level. We calculated the weighted mean difference and 95% confidence intervals for changes from the baseline level in the bromocriptine-QR add-on group vs the control group. A fixed effect model was used when $I^2 \leq 50\%$ and $p > 0.1$, and a random effect model was used to merge the data when $I^2 > 50\%$ or $p < 0.1$. The degree of heterogeneity was assessed based on the I^2 statistic. A value of I^2 less than 25% was considered low heterogeneity, 26 to 50% was considered moderate heterogeneity, and greater than 50% was deemed high heterogeneity.[12,13] Subgroup analyses were done based on previous treatments to analyze the efficacy of adding bromocriptine to standard regimens.

RESULTS

Study selection and characteristics

The initial search yielded 1522 records, and 1357 were screened after removing duplicates. A total of 1190 studies were excluded after title and abstract screening, leaving 167 reports that were further assessed for eligibility. Animal studies, studies with incorrect study designs and outcomes, without full papers and those in non-English languages were excluded. Studies on patients with controlled diabetes and on the use of bromocriptine-QR as monotherapy were also excluded, leaving a total of seven studies. Additional hand-searching yielded two studies from Pijl et al.,[4] and Aminorroaya et al.[14] A total of nine studies were included in the systematic review and eight were eligible to be included in the meta-analysis (Figure 1).

Quality assessment

The studies included in this review were assessed using the Modified Jadad scale. All included studies were rated "high quality" based on the criteria (Table 2). In conclusion,

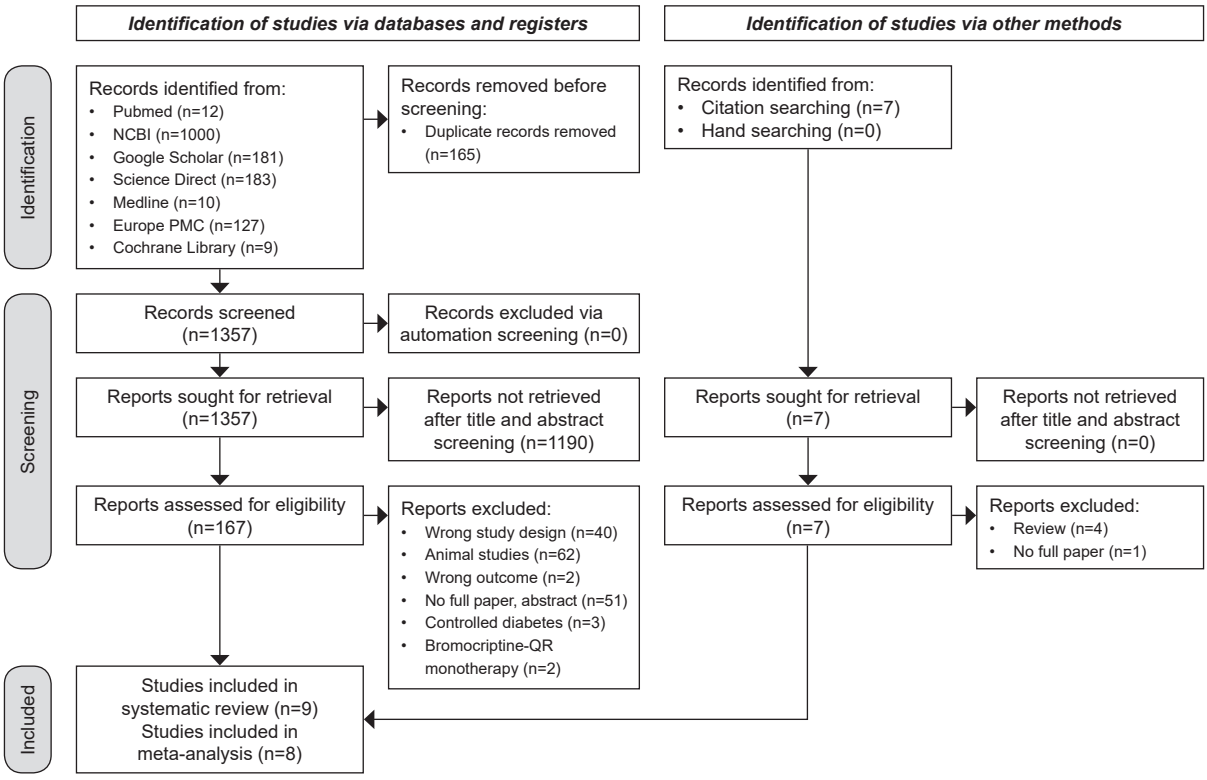

Figure 1. PRISMA flowchart for selection of included studies.

all studies were included in the review. The risk of bias is presented in Table 3.

Study characteristics and demographic data

The summary of each study and the summary of demographic data are presented in Tables 4 and 5, respectively. This review included 2709 patients, with 1800 patients in the bromocriptine-QR group and 909 in the control group. The mean (SD) age was 58.84 (8.87) years in the bromocriptine-QR group and 59.24 (8.98) years in the control group. Most participants in both groups were males, and the mean BMI was above 30. The mean (SD) duration of diabetes was 8.11 (6.46) years in the bromocriptine-QR group and 8.21 (6.2) years in the control group. Most patients in both groups used metformin monotherapy as their previous treatment (72.33% in the bromocriptine-QR group and 71.29% in the control group), and less than one percent of patients in both groups used sulfonylurea monotherapy as their previous regimen.

HbA1c outcome

The baseline mean HbA1c values in the bromocriptine-QR and control group were 7.42% and 7.51%, respectively. All studies reported a decline in HbA1c from baseline in the bromocriptine-QR group, while only three studies reported a decrease in HbA1c level in the control group. Meta-analysis favoured the bromocriptine-QR group in terms of HbA1c lowering when compared to the control group. The difference was deemed statistically significant (weight mean difference -0.6%; 95% CI [-0.83, -0.36]; p<0.00001). Moderate heterogeneity was found in the analysis (I^2 = 46%; random-effects modeling). Subgroup analysis was done to measure changes in HbA1C with metformin as previous anti-diabetic treatment (metformin + bromocriptine-QR vs. metformin/metformin + placebo). Analysis revealed no significant changes upon addition of bromocriptine-QR to metformin (weight mean difference –0.4%; 95% CI [–0.86, 0.060; p = 0.09, high certainty). Subgroup analysis using other previous anti-diabetic regimens was not performed due to a lack of data.

Fasting plasma glucose outcome

The baseline mean FPG values in the bromocriptine-QR and control groups were 152 mg/dL and 152.08 mg/dL, respectively. All studies reported a decreased FPG levels from the baseline in the bromocriptine-QR group. Meta-analysis showed a result favouring the bromocriptine-QR group in lowering FPG when compared to the control group, with a statistically significant difference (weight

Table 2. Quality appraisal of studies included in the meta-analysis using Modified Jadad scale assessment

Study	Was the research described as randomized?	Was the approach of randomization appropriate?	Was the research described as blinding?	Was the method of blinding appropriate?	Was there a description of with-drawals and dropouts?	Was there a presentation of the inclusion/ exclusion criteria?	Was the method used to assess adverse effects described?	Was the approach of statistical analysis described?	Total	Interpre-tation
Briones-Aranda, et al. (2018)[36]	1	1	0	0	0	1	1	1	5	High quality
Chamarthi, et al. (2017)[37]	1	1	1	1	0	1	1	1	7	High quality
Chamarthi, et al. (2016)[27]	1	1	1	1	0	0	1	1	6	High quality
Ghosh, et al. (2013)[38]	1	1	0	0	0	1	1	1	5	High quality
Vinik, et al. (2012)[15]	1	1	1	1	1	1	1	1	8	High quality
Florez, et al. (2011)	1	1	1	1	1	1	1	1	8	High quality
Ramteke, et al. (2011)[33]	1	1	1	1	0	1	1	1	7	High quality
Aminorroaya, et al. (2004)[4,14]	1	1	1	1	1	1	0	1	7	High quality
Pijl, et al. (2000)[4]	1	1	1	1	1	1	1	1	8	High quality

Table 3. Risk of bias in included studies based on Cochrane Risk of Bias Tool

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete complete data	Selective reporting	Other bias
Aminorroaya 2004	Low	High	High	High	High	High	Unclear
Briones-Aranda 2018	Low	High	Low	Low	High	High	Unclear
Chamarthi 2016	Low	High	High	High	High	High	Unclear
Chamarthi 2017	Low	High	High	High	High	High	Unclear
Florez 2011	High	Low	High	High	High	High	Unclear
Ghosh 2013	High	High	Low	Low	High	High	Unclear
Piji 2000	Low	High	High	High	High	High	Low
Ramteke 2011	High	High	High	High	High	High	Low
Vinik 2012	Low	Low	High	High	High	High	Unclear

Table 4. Summary of studies included

Author (year)	Study duration (week)	Study design (RCT)	Age, (years), mean ± SD		Baseline HbA1c level, mean ± SD (%)		Intervention (n)	Control (n)	HbA1c Change, % mean (95%CI)	
			B-QR	Control	B-QR	Control			B-QR	Control
Briones-Aranda, et al.(2018)[36]	12	Open-labeled	49.80 ± 20.36	50.50 ± 13.47	9.0 ± 1.13	9.3 ± 1.55	Metformin 850 mg + B-QR (gradually increased from 1.25 mg to 2.5 mg per day (10)	Metformin 850 mg (10)	-1.0 (0.08, 1.41)[c]	-0.6 (0.005, 1.14)[d]
Chamarthi, et al. (2017)[37]	12	Double-blind	59 ± 6.63	58 ± 12	8.31 ± 0.66	8.1 ± 0.8	Basal-bolus insulin + metformin + B-QR 1.6-4.8 mg/day (44)	Basal-bolus insulin + metformin + placebo (16)	-0.73 ± 1.06[a] (−1.05, −0.41)	+0.40 ± 1[a] (−0.14, 0.94)
Chamarthi, et al. (2016)[27]	12	Double-blind	59.5 ± 9.9	59.8 ± 9.7	[3]7.5	[3]7.5	Metformin + B-QR 1.6-4.8 mg/ day (1,208)	Metformin + Placebo (583)	-0.68[a]	-0.09[a]
Ghosh, et al. (2013)[38]	12	Open-labeled	50.92	48.1	7.90 ± 0.56	7.97 ± 0.56	Metformin 500 mg + B-QR 0.8 mg first weeks, others 1.6 mg (51)	Metformin 1000 mg/day (23)	-1.09[d]	-0.42[d]
Vinik, et al. (2012)[15]	24	Double-blind	57.9 ± 0.5	59.1 ± 0.7	8.28 ± 0.04	8.37 ± 0.06	One or two OAD (sulfonylurea/ thiazolidinedione/ alpha-glucosidase inhibitor/ meglitinide/ metformin) + B-QR 0.8-4.8 mg/day (341)	One or two OAD (sulfonylurea/ thiazolidinedione/ alpha-glucosidase inhibitor/ meglitinide/ metformin) (174)	-0.45[a] (-0.56, -0.34)	+0.06[a] (-0.1, 0.21)
Florez, et al. (2011)	52	Double-blind	56.4 ± 11	59.6 ± 10.9	8.2 ± 0.6	8.4 ± 0.7	Thiazolidinedione + B-QR 1.6-4.8 mg/day (78)	Thiazolidinedione + placebo (44)	-0.62 (-0.9, -0.34)[b]	+0.04 (-0.33, +0.42)[b]
Ramteke, et al. (2011)[33]	12	Double-blind	N/A	N/A	7.75 ± 0.50	7.73 ± 0.48	Metformin 1000 mg/day + B-QR 1.6 mg/day (33)	Metformin 1000 mg/day (32)	-0.74[c]	-0.63[d]
Aminorroaya, et al. (2004)[14]	12	Double-blind	50.6 ± 2.1	52.4 ± 2.0	9.9±0.3	10.2 ± 0.3	Glibenclamide or its combination with metformin + B-QR (gradually increased from 1.25 mg to 2.5 mg) (20)	Glibenclamide or its combination with metformin + placebo (20)	-0.4 (-1.7, 0.9)[d]	+1.1 (0.2, 1.9)[c]
Pijl, et al. (2000)[4]	16	Double-blind	56 ± 2	50 ± 3	8.7 ± 0.4	8.5 ± 0.5	Sulfonylurea + B-QR (15)	Sulfonylurea + placebo (7)	-0.6	+0.6

B-QR, bromocriptine-quick release; OAD, oral anti-diabetes drug; RCT, Randomized Controlled Trial; [a]$p \leq 0.001$; [b]$p < 0.01$; [c]$p < 0.05$; [d]$p \geq 0.05$

mean difference -1.08%; 95% CI [-1.62, -0.53]; p = 0.0001). High heterogeneity was found in the analysis (I^2 = 89%; random-effects modeling). In addition, subgroup analysis was performed to measure the change in FPG with metformin as previous anti-diabetic treatment (metformin + bromocriptine-QR vs. metformin/metformin + placebo), which yielded no significant changes (weight mean difference -1.31%; 95% CI [–2.73, 0.1]; p = 0.007, moderate certainty). The lack of data did not allow for all other planned subgroup analyses using other previous anti-diabetic regimens.

Certainty of evidence

The overall certainty of evidence for each outcome is described in Table 6.

Safety and tolerability

Adverse events that occurred more frequently in the bromocriptine-QR group than in the control group included nausea (33.75% vs. 6.92%), fatigue (13.11% vs. 5.94%), headache (11.7% vs. 6.87%), vomiting (9.06% vs. 3.08%), constipation (6.37% vs. 4.76%) and hypoglycemia (6.52% vs. 4.53%). Hypotension was rarely found in both groups (2.05% of the bromocriptine-QR group and 1.15% of the control group). Although not specified, the overall serious adverse events (SAEs) between the bromocriptine-QR group versus control were 5.79% and 7.72%, respectively. Serious adverse events in the cardiovascular system occurred less frequently in the bromocriptine-QR group than in the control group, as reported by Vinik et al.[15] (1.8% vs. 3.4%). Both studies also mentioned that SAEs in other organ systems occurred infrequently and had a similar percentage between the bromocriptine-QR and control groups. Meta-analysis showed that bromocriptine-QR has significantly greater odds of several adverse effects, such as nausea (OR 6.86; 95% 5.11 to 9.21, p < 0.0001), vomiting (OR 3.07; 95% 1.99 to 4.76, p <0.0001) and headache (OR 1.71; 95% 1.24 to 2.36, p = 0.001). However, side effects related to hypoglycemia (OR 1.45; 95% 0.99 tl 2.13, p = 0.06) and fatigue (OR 1.97; 95% 0.90 to 4.31, p = 0.09) are insignificant.

DISCUSSION

Bromocriptine mesylate is an ergot derivative that acts as a sympatholytic D2-dopamine receptor agonist, proposed as a novel centrally-acting antidiabetic agent.[4] This meta-

Table 5. Demographic data of the patients and reported adverse effects

Variable	Number of data available		n (%)	
	Bromocriptine-QR group	Control group	Bromocriptine-QR group	Control group
Age (years), mean ± SD	1716	854	58.84 ± 8.87	59.24 ± 8.98
Sex	1716	854		
Male, n (%)			977 (56.93)	510 (59.72)
Female, n (%)			739 (43.07)	344 (40.28)
BMI (kg/m²), mean ± SD	541	303	32.47 ± 3.28	31.77 ± 3.76
Systolic BP (mm/Hg), mean ± SD	1681	827	130.01 ± 12.58	129.23 ± 11.89
Diastolic BP (mm/Hg), mean ± SD	1681	827	77.15 ± 8.03	76.9 ± 8.06
Creatinine (mg/dL), mean ± SD	1262	609	1.01 ± 0.2	1 ± 0.2
Duration of diabetes (years), mean ± SD	1696	834	8.11 ± 6.46	8.21 ± 6.2
HbA1c (%), mean ± SD	1800	909	7.42 ± 1.06	7.51 ± 1.19
Fasting plasma glucose (mg/dL), mean ± SD	1790	899	152 ± 37.68	152.08 ± 38.38
Previous diabetes treatment	1800	909		
Metformin			1302 (72.33)	648 (71.29)
Thiazolidinedione			78 (4.33)	44 (4.84)
Sulfonylurea			15 (0.83)	7 (0.77)
Metformin and sulfonylurea			20 (1.11)	20 (2.2)
Two OADs, unspecified			341 (18.94)	174 (19.14)
Insulin basal-bolus and OAD			44 (2.44)	16 (1.76)
Serious adverse effects (SAEs)	673	337	39 (5.79)	26 (7.72)
Adverse effects				
Hypoglycemia	1671	817	109 (6.52)	37 (4.53)
Nausea	1600	780	540 (33.75)	54 (6.92)
Vomiting	1600	780	145 (9.06)	24 (3.08)
Hypotension	341	174	7 (2.05)	2 (1.15)
Headache	1549	757	173 (11.17)	52 (6.87)
Constipation	1549	757	88 (6.37)	36 (4.76)
Fatigue	1549	757	203 (13.11)	45 (5.94)

OAD, oral anti-diabetes drug

Table 6. GRADE Evidence Summary

Certainty assessment							No. of patients		Effect			
No. of studies	Study Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bromocriptine	Control	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
HbA1C Changes												
8	randomized trials	not serious	not serious	not serious	not serious	none	952	326	–	SMD **0.6 SD lower** (0.83 lower to 0.36 lower)	⨁⨁⨁⨁ High	Important
FPG Change												
7	randomized trials	not serious	serious[a]	not serious	not serious	none	582	316	–	SMD **1.08 SD lower** (1.62 lower to 0.53 lower)	⨁⨁⨁◯ Moderate	Important

CI: confidence interval; SMD: standardized mean difference

Explanation
a. High I^2 statistics due to study differences

analysis showed a significant difference in HbA1c and FPG decline between the bromocriptine-QR and control group. These findings signify that oral bromocriptine-QR is superior to placebo for glycemic control in patients with uncontrolled T2DM. A study by Liang et al.,[16] found a similar conclusion, with bromocriptine-QR treatment lowering HbA1c more than the control group (weighted mean difference, -6.25 mmol/mol; 95% CI [-8.07, -4.97]).

The metabolic system of vertebrates during a food shortage inspired the use of bromocriptine for diabetes treatment. In such conditions, many develop obesity and insulin resistance. During the insulin-resistant state, dopamine levels are found to be low and later increase to normal after returning to the insulin-sensitive state.[17] Hence, reduced dopaminergic tone may be involved in the pathology of insulin resistance.[18] The development of an insulin-resistant state in animals closely resembles the changes in T2DM patients.[17] It is thought that people with type 2 diabetes experience a morning dip in dopaminergic tone, leading to increased sympathetic activity.[19] In addition, plasma prolactin is high in insulin-sensitive individuals during sleep. However, it was noted that in obese insulin-resistant individuals, daytime plasma prolactin levels were twice as high,[20] consistent with reduced dopaminergic tone.[21]

The possible mechanism driving the beneficial effects of bromocriptine-QR as adjunctive therapy in diabetes is the central modulation of dopaminergic and sympathetic tone.[21] Previous studies found that intracerebral injection of bromocriptine in insulin-resistant mice reduces noradrenergic and serotonergic levels, thereby improving

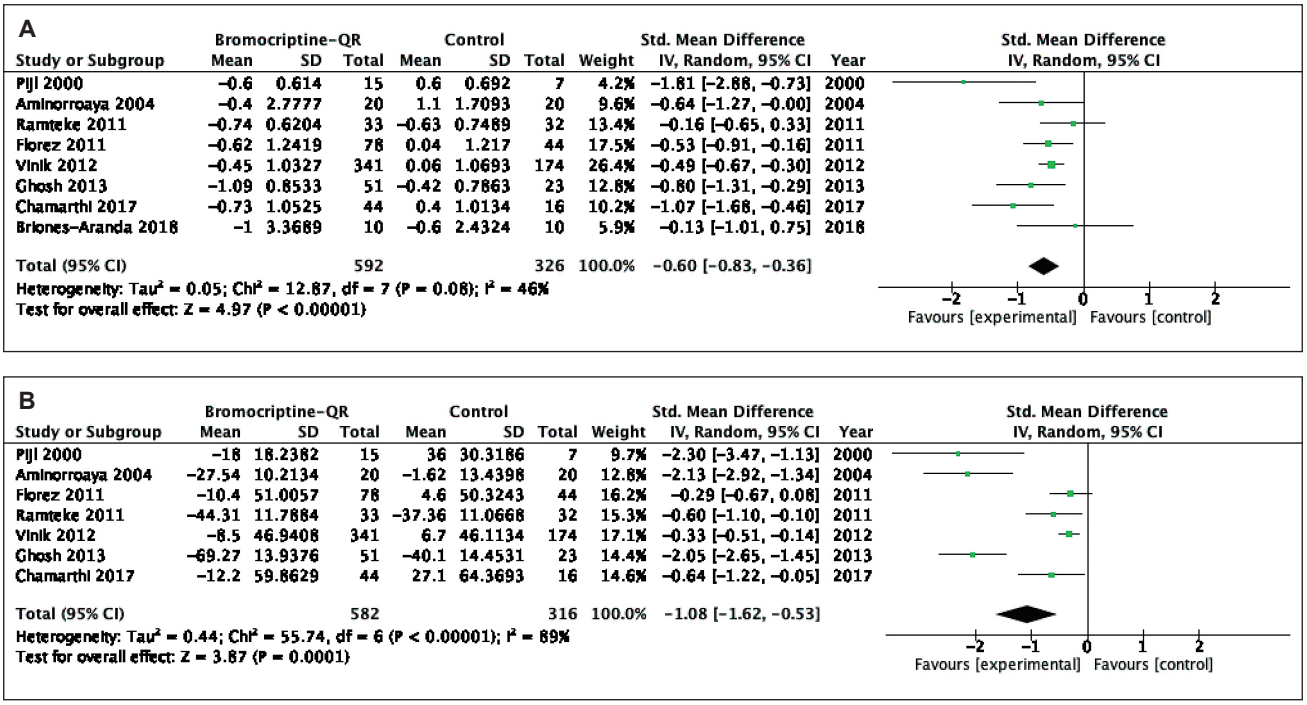

Figure 2. Forest-plot analysis for changes in HbA1c **(A)** and changes in fasting plasma glucose **(B)** in bromocriptine-QR and control group.

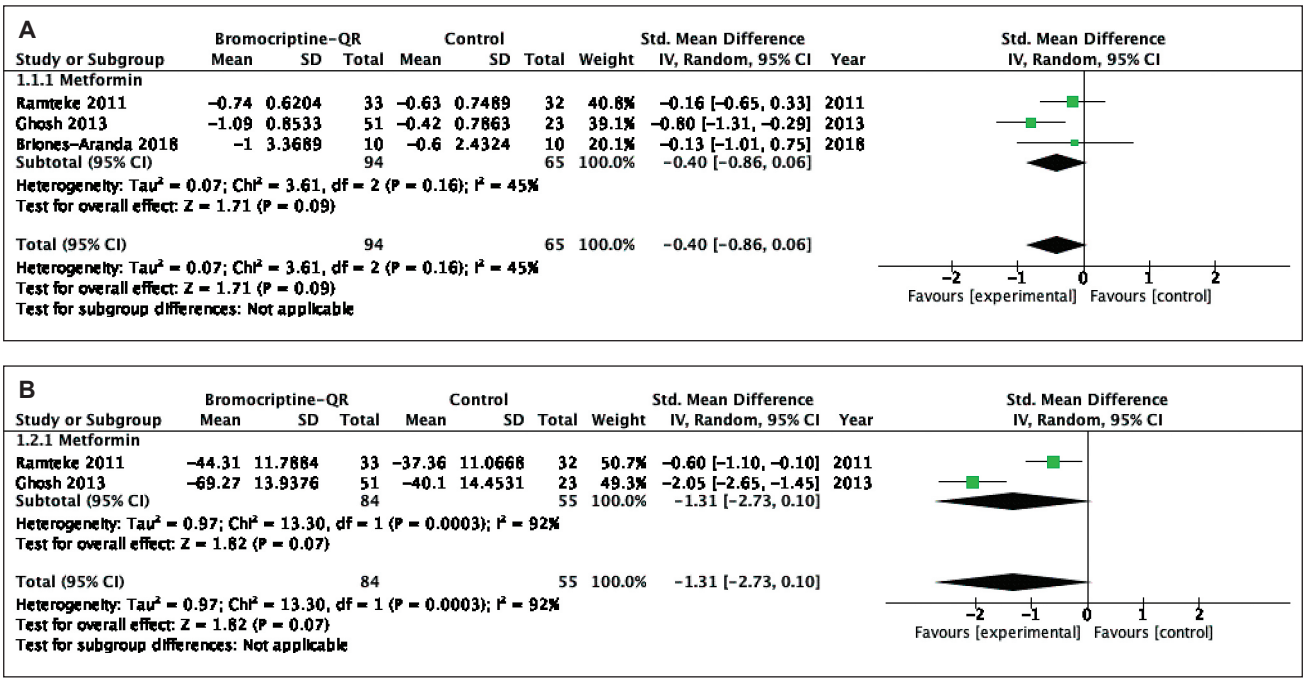

Figure 3. Subgroup analysis for changes glycemic index (HbA1c and fasting plasma glucose) based on metformin as previous anti-diabetic treatment (metformin + bromocriptine-QR vs metformin / metformin + placebo). **(A)** Changes in HbA1c value and **(B)** changes in fasting plasma glucose.

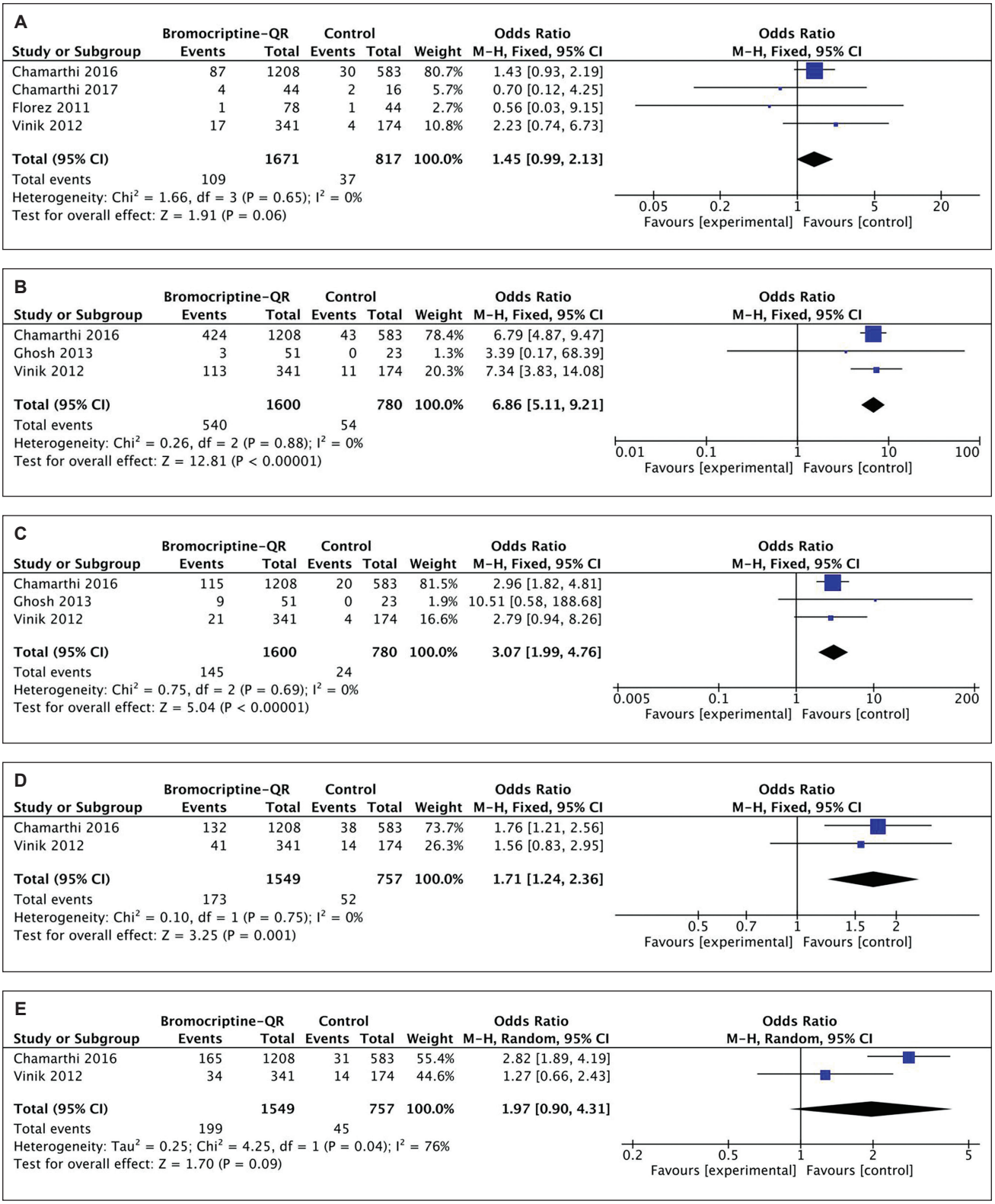

Figure 4. Forest-plot analysis for each adverse events of bromocriptine-QR group compared to control. **(A)** Hypoglycemia, **(B)** Nausea, **(C)** Vomiting, **(D)** Headache, **(E)** Fatigue.

insulin sensitivity and reducing plasma glucose.[22] The use of bromocriptine was assumed to increase dopaminergic activity in the morning and decrease sympathetic and serotonergic activity, leading to a decrease in insulin resistance and a decline in hepatic glucose output, hence improving glucose tolerance.[17,21]

Other mechanisms have been theorized regarding the use of bromocriptine-QR to improve glycemic control. It has been shown to inhibit glucose-stimulated insulin secretion by directly activating alpha2-adrenergic receptors in pancreatic beta cells. It also improves insulin sensitivity in hyperglycemic conditions by stimulating D2 receptors in beta cells. Reduced insulin resistance may also affect the gastrointestinal tract by suppressing hunger and enhancing satiation.[18]

It is well known that bromocriptine is used to treat Parkinson's disease and prolactinoma; however, bromocriptine used to treat T2DM is different.[17] Bromocriptine-QR was designed to provide a timed pulse of dopamine activity centrally by circulating brief daily intervals of bromocriptine at a particular time of the day. It differs from conventional bromocriptine, which is dosed several times daily and results in higher circulation of dopamine agonists, as used in Parkinson's disease. Bromocriptine-QR normalizes abnormal hypothalamic functions, decreases sympathetic tone and improves HPA axis circadian activity when administered at the appropriate time by restoring normal central dopaminergic activity in insulin-resistant subjects.[23]

This meta-analysis found a similar percentage of overall SAEs in both groups. The occurrence of SAEs in the cardiovascular system was less in the bromocriptine-QR group compared to the control group. Previous studies revealed that bromocriptine-QR has the potential for protective cardiovascular effects when given to T2DM patients.[23–27] Studies found that administration of bromocriptine-QR in T2DM subjects results in 40 to 55% relative risk reduction in CVD.[23,25–27] The promising cardiovascular benefit of bromocriptine-QR was also tested among children and adolescents with type 1 diabetes (T1DM) who are at risk of having vascular dysfunction and, therefore, present with a lifetime risk of CVD. A study found that bromocriptine-QR significantly reduces blood pressure and normalizes central and peripheral aortic stiffness over four weeks in youth with T1DM.[28]

The cardiovascular effects of bromocriptine-QR are not only explained by the reduction of fasting plasma glucose, HbA1c, plasma lipids, or blood pressure. The elevated sympathetic tone has been implicated in the pathophysiology of CVD. Bromocriptine-QR can reduce sympathetic activity by stimulating presynaptic dopamine receptors to inhibit norepinephrine release.[29,30] Moreover, evidence suggests that bromocriptine-QR has an anti-inflammatory effect by reducing endoplasmic reticulum (ER) stress genes, oxidative stress response genes and toll-like receptor (TLR) pro-inflammatory genes to substantially reduce the pro-oxidative/pro-inflammatory state in the development of CVD.[24] Bromocriptine-QR suppresses the vascular inflammations that lead to endothelial dysfunctions that are drivers of CVD.[31]

Other adverse events that occurred more frequently in the bromocriptine-QR group than in the control group include gastrointestinal effects (nausea, vomiting and constipation), fatigue, headache and hypoglycemia. These reported side effects were classified as mild to moderate. The relatively lower doses of bromocriptine-QR used in the treatment of T2DM compared to the usual doses in hyperprolactinemia or Parkinson's disease play a part in reducing the risk of adverse effects. The common adverse effects can be minimized by gradual weekly titration of the bromocriptine-QR dosage.[32] Although hypoglycemia was found more frequently in the bromocriptine-QR group than in the control group, the episodes were mild, transient and resolved spontaneously after food intake.[15,33] The mild adverse effects may limit bromocriptine-QR use in some patients; however, studies mentioned that bromocriptine-QR has several favorable clinical properties, such as a low degree of weight loss or weight gain, and it is not strongly associated with hypoglycemia.[4,34,35] The low rate of hypoglycemia is explained by how bromocriptine-QR does not stimulate insulin secretion but improves insulin sensitivity.[21]

The results of this meta-analysis should be seen in the light of a few limitations. Some studies included had limited data on the safety and tolerability of using bromocriptine-QR in T2DM patients. The included studies also appear to be short-term observations; hence, bromocriptine-QR needs further evaluation for long-term efficacy, safety and tolerability. Based on the I^2 value, this meta-analysis has moderate to high heterogeneity. Small study effects, clinical variations such as the time of HbA1c or plasma glucose measurement and sampling methodology may be the source of unexplained heterogeneity. The wide range of HbA1c values and various types of adjunctive therapy in combination with bromocriptine-QR used among the included studies may have also introduced heterogeneity in this study.

Despite these limitations, our study also has its merits. We included nine studies with over 1700 uncontrolled T2DM patients receiving bromocriptine-QR as an adjunctive treatment. This is considered a large analysis comparing the addition of bromocriptine-QR to the standard of care. In addition, we also included clinical trials to give more complete data about the efficacy and safety of bromocriptine-QR as an anti-diabetes drug.

CONCLUSION

This meta-analysis found that administration of bromocriptine-QR at a dose range of 1.6 to 4.8 mg/day as an adjunctive therapy has favourable outcomes in T2DM

as it significantly reduces HbA1c and fasting plasma glucose compared to placebo. Although bromocriptine-QR led to numerically greater adverse events such as nausea, vomiting and headache, they are generally mild. It is relatively safe and tolerable among T2DM patients under short-term surveillance. Bromocriptine-QR may reduce the risk of adverse cardiovascular events in T2DM. From these findings, it can be an alternative candidate to further expand well-established treatment options in T2DM patients, especially those on injectable medications.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
TAY: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing – original draft preparation, Writing – review and editing, Supervision, Project administration, Funding acquisition; **CLB:** Conceptualization, Methodology, Validation, Formal analysis, Resources, Investigation, Data Curation, Writing – original draft preparation, Writing – review and editing, Supervision; **MPM:** Software, Investigation, Resources, data Curation, Writing – original draft preparation, Writing – review and editing, Visualization; **SC:** Software, Investigation, Resources, data Curation, Writing – original draft preparation, Writing – review and editing, Visualization.

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