Berberine for antipsychotic-induced metabolic syndrome in patients with schizophrenia spectrum disorders: abridged secondary publication

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KEY MESSAGES

1. Antipsychotic therapy for schizophrenia spectrum disorders may induce metabolic syndrome.
2. Compared with placebo, berberine adjunctive treatment led to substantial reductions in body weight, body mass index, diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, fasting blood glucose, and glycated haemoglobin at 6 weeks, 12 weeks, or both (all $P<0.05$). The severity of psychotic and movement symptoms did not change in either group during the course of treatment. No serious adverse events were reported.
3. As an adjuvant, berberine is safe and effective in terms of reducing antipsychotic-associated weight gain and improving metabolic syndrome, without exacerbating psychotic symptoms or inducing other adverse effects.

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Introduction

Antipsychotic therapy for schizophrenia spectrum disorders (SSDs) may lead to various adverse drug reactions.[1] Metabolic syndrome (MetS) is associated with the use of atypical antipsychotics; its prevalence is 33.4% in patients with severe mental illness.[2] Berberine is a natural plant alkaloid isolated from the Chinese herbal medicine *Coptis chinensis*; it has weight-lowering, antidiabetic, and anti-hyperlipidaemic effects.[3] This study aimed to evaluate the efficacy and safety of berberine adjunctive treatment in terms of controlling weight gain and improving other anthropometric and metabolic variables in patients with SSDs who had MetS.

Methods

This randomised, double-blind, placebo-controlled trial was conducted between April 2018 and December 2020 at Queen Mary Hospital, Kowloon Hospital, Castle Peak Hospital, and The University of Hong Kong. Patients were invited to participate if they were aged 18 to 65 years with a primary diagnosis of SSD (based on the Classification of Mental and Behavioural Disorders, 10th version), had been receiving atypical antipsychotic treatment for ≥3 months, had a stable condition, and had developed MetS (based on the International Diabetes Federation criteria[4]). Patients were excluded if they had serious comorbid gastrointestinal or other unstable medical conditions, a history of suicidal attempts, any alcohol abuse or drug abuse in the past 3 months, and/or any investigational drug treatment in the past 6 months; patients were also excluded if they were pregnant or breastfeeding.

Participants were randomly assigned (at a 1:1 ratio) to the placebo or berberine group. All study medication was prepared in identical packaging and labelled with only a code. Participants continued their current atypical antipsychotic treatment as prescribed by their psychiatrist. Concomitant use of other psychotropic drugs (eg, antidepressants, anxiolytics, mood stabilisers, hypnotics, and anticholinergics) was allowed as usual, as was concomitant use of anti-hyperlipidaemic, antihypertensive, and antidiabetic treatment if the type and dosage of medication remained stable throughout the study.

Participants received additional treatment with either berberine or placebo tablets (0.3 g, twice daily before meals in the morning and evening) for 12 consecutive weeks. For participants taking psychotropic or other medications, an interval of at

least 2 hours was recommended between berberine/placebo intake and the use of other medications.

Berberine and placebo tablets were manufactured by Wah Kin Pharmaceutical Products Company, which registered the berberine tablets as over-the-counter drugs in Hong Kong. Berberine tablets were manufactured as yellow sugar-coated tablets, each containing 100 mg of berberine hydrochloride. Placebo tablets were manufactured with taste, appearance, and size identical to berberine tablets.

The primary outcome was the change in body weight from baseline to each time point. Secondary outcome measures were body mass index (BMI), waist circumference (WC), blood pressure, triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, fasting blood glucose (FBG), and glycated haemoglobin (HbA1c). The severity of psychotic symptoms, antipsychotic-induced movement symptoms, and adverse effects associated with therapy were also evaluated.

The intention-to-treat approach was used. A linear mixed-effects model was used to compare changes from baseline in terms of WC, BMI, blood pressure, biochemical variables, and scores on the Positive and Negative Syndrome Scale and its subscales. The model was established using time and group as categorical fixed factors and random intercepts within a scaled identity covariance matrix. Baseline LDL cholesterol was regarded as a covariate in the analysis of anthropometric variables (net weight gain, WC, and BMI). Respective baseline variables were regarded as covariates in analyses of blood pressure and metabolic variables. The Wilcoxon rank-sum test was used to assess differences in Extrapyramidal Symptom Rating Scale–Abbreviated scores. Student's *t* test was used to assess differences in continuous baseline variables between the two groups. Categorical baseline variables and adverse event incidences were analysed using the Chi squared test or Fisher's exact test. Statistical significance was defined as a two-tailed P value of <0.05.

Results

Of 286 patients screened, 113 agreed to participate and were randomly assigned to the berberine (n=58) and placebo (n=55) groups; 25 participants (17 in the berberine group and 8 in the placebo group) did not complete the 3-month study. The two groups were comparable in terms of all baseline variables, except for LDL cholesterol (Table 1).

Compared with the placebo group, the berberine group displayed significant decreases in body weight at 9 weeks (-0.47 vs 0.28 kg, P=0.031) and 12 weeks (-0.71 vs 0.37 kg, P=0.002). The placebo group displayed a slight increase in body weight (0.22 kg) at 12 weeks (Table 2). The berberine group displayed significant reductions in BMI (P=0.012), WC (P=0.034), and HbA1c (P=0.001) at 12 weeks; in triglycerides (P=0.038 and P=0.021), total cholesterol (both P<0.0001), and LDL cholesterol (both P<0.0001) at both 6 and 12 weeks; and in HDL cholesterol (P=0.001) and FBG (P=0.009) at 6 weeks. Compared with the placebo group, the berberine

TABLE 1. Baseline characteristics of participants

Variables	Berberine (n=58)*	Placebo (n=55)*	P value
Age, y	39.3±11.3	36.2±10.8	0.138
Sex			0.954
Male	25 (43.1)	24 (43.6)	
Female	33 (56.9)	31 (56.4)	
Marital status			0.389
Single/divorced/widowed	39 (67.2)	38 (69.1)	
Married	19 (32.8)	17 (30.9)	
Occupation			0.276
Professional or associate professional	24 (41.4)	19 (34.6)	
Skilled or non-skilled worker	14 (24.1)	18 (32.7)	
Others	20 (34.5)	18 (32.7)	
Antipsychotic regimen			0.997
Monotherapy	39 (67.2)	37 (67.3)	
Combination therapy	19 (32.8)	18 (32.7)	
Type of schizophrenia spectrum disorder			0.754
Schizophrenia	47 (81.0)	40 (72.7)	
Schizoaffective disorder	4 (6.9)	5 (9.1)	
Unspecific non-organic psychosis	6 (10.3)	9 (16.4)	
Persistent delusional disorder	1 (1.7)	1 (1.8)	
Duration of schizophrenia spectrum disorder, mo	138.4±113.9	120.3±107.2	0.386
Weight, kg	81.6±14.3	79.2±13.7	0.375
Waist circumference, cm	101.1±10.6	98.6±9.6	0.204
Body mass index, kg/m^2	29.3±4.5	29.2±4.2	0.827
Systolic blood pressure, mmHg	126.5±17.6	123.2±15.4	0.293
Diastolic blood pressure, mmHg	79.5±11.1	75.5±10.2	0.053
Triglycerides, mmol/L	2.3±1.4	2.2±2.1	0.873
Total cholesterol, mmol/L	5.4±1.1	5.0±1.2	0.072
High-density lipoprotein cholesterol, mmol/L	1.2±0.3	1.4±0.8	0.101
Low-density lipoprotein cholesterol, mmol/L	3.4±1.0	2.9±0.9	0.004
Fasting blood glucose, mmol/L	6.0±2.2	5.5±1.2	0.144
Glycated haemoglobin, %	6.1±1.3	5.8±0.7	0.170
Positive and Negative Syndrome Scale score	38.6±7.3	37.9±8.5	0.641

* Data are presented as mean ± standard deviation or No. (%) of participants; total may not equal 100% because of missing data.

TABLE 2. Clinical and biochemical variables after 12 weeks of treatment

Variables	Berberine (n=58)		Placebo (n=55)		P value
	Mean (95% confidence interval)	P value (vs baseline)	Mean (95% confidence interval)	P value (vs baseline)	
Net weight gain, kg					
Week 3	0.27 (-0.17, 0.70)	0.115	0.15 (-0.30, 0.60)	0.452	0.720
Week 6	-0.32 (-0.77, 0.12)	0.178	0.10 (-0.36, 0.56)	0.715	0.196
Week 9	-0.47 (-0.95, 0.01)	0.094	0.28 (-0.20, 0.74)	0.338	**0.031**
Week 12	-0.71 (-1.19, -0.23)	**0.017**	0.37 (-0.10, 0.84)	0.223	**0.002**
Change in body mass index, kg/m^2					
Week 3	-0.09 (-0.07, 0.24)	0.153	0.07 (-0.09, 0.23)	0.331	0.894
Week 6	-0.13 (-0.29, 0.03)	0.139	0.04 (-0.12, 0.20)	0.682	0.140
Week 9	-0.19 (-0.36, -0.02)	0.068	0.10 (-0.06, 0.27)	0.327	**0.018**
Week 12	-0.27 (-0.44, -0.10)	0.012	0.13 (-0.03, 0.30)	0.218	**0.001**
Change in waist circumference, cm					
Week 3	0.45 (-0.49, 1.38)	0.335	-0.07 (-1.02, 0.88)	0.832	0.454
Week 6	0.29 (-0.66, 1.23)	0.587	-0.82 (-1.79, 0.15)	0.161	0.111
Week 9	-0.28 (-1.33, 0.77)	0.716	-0.86 (-1.86, 0.15)	0.176	0.439
Week 12	-1.48 (-2.51, -0.45)	**0.034**	-1.13 (-2.12, -0.14)	0.081	0.635
Systolic blood pressure, mmHg					
Baseline	125.1 (122.6, 127.7)	-	124.6 (122.0, 127.2)	-	0.772
Week 6	124.3 (121.6, 127.1)	0.632	124.4 (121.6, 127.2)	0.916	0.970
Week 12	122.7 (119.7, 125.7)	0.213	125.5 (122.7, 128.3)	0.636	0.185
Diastolic blood pressure, mmHg					
Baseline	78.0 (76.2, 79.8)	-	77.4 (75.6, 79.2)	-	0.625
Week 6	77.8 (75.8, 79.7)	0.825	75.6 (73.6, 77.5)	0.137	0.119
Week 12	74.3 (72.2, 76.4)	**0.007**	77.8 (75.8, 79.8)	0.775	**0.019**
Triglycerides, mmol/L					
Baseline	2.19 (2.02, 2.36)	-	2.18 (2.01, 2.36)	-	0.949
Week 6	1.95 (1.76, 2.14)	**0.038**	1.93 (1.74, 2.13)	**0.034**	0.901
Week 12	1.89 (1.69, 2.09)	**0.021**	2.12 (1.93, 2.32)	0.629	0.101
Total cholesterol, mmol/L					
Baseline	5.18 (5.08, 5.28)	-	5.14 (5.04, 5.24)	-	0.569
Week 6	4.61 (4.50, 4.72)	**<0.0001**	5.15 (5.03, 5.26)	0.900	**<0.0001**
Week 12	4.61 (4.49, 4.73)	**<0.0001**	5.19 (5.07, 5.30)	0.509	**<0.0001**
High-density lipoprotein cholesterol, mmol/L					
Baseline	1.23 (1.20, 1.26)	-	1.24 (1.21, 1.27)	-	0.599
Week 6	1.16 (1.13, 1.19)	**0.001**	1.22 (1.19, 1.25)	0.303	**0.016**
Week 12	1.19 (1.16, 1.22)	0.094	1.22 (1.19, 1.26)	0.476	0.179
Low-density lipoprotein cholesterol, mmol/L					
Baseline	3.20 (3.11, 3.30)	-	3.14 (3.04, 3.25)	-	0.402
Week 6	2.74 (2.63, 2.85)	**<0.0001**	3.24 (3.13, 3.35)	0.144	**<0.0001**
Week 12	2.73 (2.61, 2.84)	**<0.0001**	3.24 (3.13, 3.35)	0.179	**<0.0001**
Fasting blood glucose, mmol/L					
Baseline	5.72 (5.50, 5.93)	-	5.66 (5.44, 5.88)	-	0.739
Week 6	5.33 (5.08, 5.57)	**0.009**	5.88 (5.63, 6.12)	0.150	**0.002**
Week 12	5.43 (5.17, 5.68)	0.087	5.57 (5.33, 5.82)	0.587	0.422
Glycated haemoglobin, %					
Baseline	5.94 (5.89, 6.00)	-	5.91 (5.86, 5.97)	-	0.446
Week 6	5.84 (5.77, 5.90)	0.006	5.90 (5.84, 5.97)	0.822	0.133
Week 12	5.80 (5.74, 5.87)	**0.001**	5.89 (5.83, 5.96)	0.662	**0.050**

group displayed greater decreases in BMI at 9 weeks (P=0.018) and 12 weeks (P=0.001), lower levels of total cholesterol and LDL cholesterol at 6 and 12 weeks (all P<0.0001), lower levels of HDL cholesterol (P=0.016) and FBG (P=0.002) at 6 weeks, lower levels of diastolic blood pressure (P=0.019) and HbA1c (P=0.016) at 12 weeks.

There were no significant differences in total and subscale scores on the Positive and Negative Syndrome Scale or the Extrapyramidal Symptom Rating Scale–Abbreviated, either within or between groups (data not shown). The berberine group had a lower incidence of drowsiness than the placebo group (P=0.008). No serious adverse events were reported.

Discussion

In patients with SSD experiencing typical MetS, berberine adjunctive treatment for 12 weeks led to reductions in body weight, BMI, diastolic blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, FBG, and HbA1c. Berberine had no effects on psychotic symptoms or involuntary movement symptoms. Participants receiving berberine had a lower incidence of drowsiness than those receiving placebo, suggesting that berberine can be used to manage sleep disturbances that often occur during antipsychotic treatment. These results confirm the weight-lowering and anti-MetS effects of berberine in patients with SSD who are receiving antipsychotic therapy.

Berberine adjunctive treatment led to 0.75 kg weight loss at 6 weeks and 1.08 kg weight loss at 12 weeks. These results are comparable with the 1.0 kg weight loss observed in patients with diabetes mellitus after 3 months of berberine treatment. In another study, approximately 2 kg weight loss was observed in patients with non-alcoholic fatty liver disease after 16 weeks of berberine treatment. The weight-lowering effect of berberine may be enhanced by extending the duration of treatment. The WC of participants on berberine was substantially lower at the end of the study, suggesting that berberine can help control central obesity.

Although berberine did not exacerbate psychotic symptoms or involuntary movement symptoms, there were more dropouts in the berberine group than in the placebo group (29.3% vs 14.5%). The main dropout reasons were inability to adhere to the treatment schedule and personal reasons, rather than berberine intolerance. No serious adverse events were reported during the study period. The findings suggest that berberine is a safe, orally administered agent.[4]

There were several limitations in the present study. First, the dropout rate of 22.1% was relatively high, but it is acceptable for a clinical analysis of patients with schizophrenia. Second, although baseline antipsychotic and other medication profiles were similar in the two groups, heterogeneous medication regimens could have led to inconsistent MetS severity. Further analysis is needed to determine whether the anti-MetS efficacy of berberine is associated with specific antipsychotic regimens. Third, the fixed berberine dosage was based on previous studies, in which the dosages ranged from 0.6 g to 1.5 g per day. Further investigations may be necessary to optimise the berberine dose for MetS. Fourth, the long-term efficacy of berberine was not evaluated. Long-term studies with larger sample sizes are needed to confirm the findings of this study.

Conclusion

Berberine effectively reduces antipsychotic-associated weight gain and improves MetS without exacerbating psychotic symptoms or inducing adverse effects.

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Disclosure

The results of this research have been previously published in:

1. Chan M, Qin Z, Man SC, et al. Adjunctive berberine reduces antipsychotic-associated weight gain and metabolic syndrome in patients with schizophrenia: a randomized controlled trial. Psychiatry Clin Neurosci 2022;76:77-85.

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