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Metabolic outcomes of bergamot polyphenolic fraction administration in patients treated with second-generation antipsychotics: a pilot study☆

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Abstract

Second-generation antipsychotics (SGAs) are notoriously associated with a marked increase in body weight and with a wide range of metabolic adverse effects, and their chronic use is related with an increased risk for the development of metabolic syndrome (MS). Different adjunctive treatments have been proposed to reduce SGAs-induced weight gain and/or metabolic abnormalities with inconsistent or too limited evidence to support their regular clinical use, thus suggesting the need to find new possible treatments. Bergamot polyphenolic fraction (BPF) has been proven effective in patients with MS, as demonstrated by a concomitant improvement in lipemic and glycemic profiles. The present study was aimed to explore the efficacy and safety of BPF treatment on metabolic parameters in a sample of subjects receiving atypical antipsychotics. Fifteen outpatients treated with SGAs assumed BPF at the oral daily dose of 1000 mg/day for 30 days. Fasting levels of glucose, glycated hemoglobin, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides were determined. BPF administration resulted in a statistically significant reduction of body weight (P=.004) and in a trend for body mass index decrease (P=.005). No significant differences in other and metabolic parameters were observed. Our findings suggest that BPF, at the daily dose of 1000 mg for 30 days, could be an effective and safe agent to prevent weight gain associated with atypical antipsychotic use. However, further clinical trials with adequately powered and well-designed methodology are needed to better explore the BPF effectiveness on the SGAs-induced weight gain and metabolic side effects.

Keywords: Bergamot polyphenolic fraction; Second-generation antipsychotics; Weight gain; Hyperlipemia; Hyperglycemia; Metabolic syndrome

1. Introduction

Second-generation antipsychotics (SGAs) are a class of drugs widely used in clinical practice due to their lower tendency to induce extrapyramidal symptoms compared to conventional antipsychotics [1,2]. However, SGAs are notoriously associated with a marked increase in body weight and with a wide range of metabolic adverse effects [3,4]; their chronic use is related with an increased risk for the development of metabolic syndrome (MS) [4–6]. Among SGAs, clozapine, olanzapine and quetiapine are particularly associated with weight gain, as well as with adiposity-dependent and possibly adiposity-independent glucose dysregulation and dyslipidemia [7].

A number of studies have examined the receptor-binding profiles of atypical antipsychotics to determine which sites are most closely linked with metabolic side effects. Affinity for H1, D2, 5-HT1A, 5-HT2C and α2-receptors is related with weight gain, whereas affinity for H1, M3 and 5-HT2C receptors is correlated with an increased risk of diabetes [8–10]. Conversely, the receptor-binding profiles involved with antipsychotic-associated dyslipidemia are unclear, although peroxisome proliferator-activated receptors and sterol regulatory element-binding protein may play a role [11,12].

Different adjunctive treatments have been proposed to reduce antipsychotic-induced weight gain and/or metabolic abnormalities with inconsistent or too-limited evidence to support their regular clinical use [13,14], thus suggesting the need to find new possible treatments.

The nutraceutical approach might be a promising strategy in the prevention of MS since different dietary supplements and nutraceuticals used in clinical practice have shown to be effective on the pathogenic mechanisms underlying dyslipidemia, diabetes mellitus and their complications [15].

Citrus bergamia (bergamot), a small tree belonging to the Rutaceae family, is an endemic plant of the Southern coast of Calabria region (Italy), which differs from other citrus fruits for flavonoids and flavonoid glycosides composition (neoeriocitrin, neohesperidin, naringin, rutin, neodesmina, roifolina and poncirina) and for their high amount [16,17].

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Various human studies have recently evidenced the therapeutic potential of bergamot derivatives: it was shown that bergamot polyphenolic fraction (BPF) has beneficial effects in patients with MS, as demonstrated by a concomitant improvement in lipemic and glycemic profiles [18–23].

On the basis of evidence from the literature, the present study was aimed to explore the efficacy and safety of BPF treatment on clinical and metabolic parameters in a sample of subjects receiving SGAs.

2. Methods

2.1. Study design

This was a 30-day, open-label, preliminary study aimed to evaluate the efficacy and safety of adjunctive BPF to atypical antipsychotics therapy. BPF [Bergamot Polyphenolic Fraction BPF, H&AD S.r.l-Bianco (RC), Italy] was administered in capsules at the oral daily dose of 1000 mg/day (500 mg twice daily) and was maintained unchanged until the end of the trial at day 30. The concentration of five main flavonoids per capsule was as follows: neoheriocitrin (55,535 mg), naringin (58,903 mg), neohesperidin (62,966 mg), melitidine (7958 mg) and brutieridine (24,371 mg); excipients of any type were not present. During the study, no additional medications, including aspirin or nonsteroidal anti-inflammatory drugs, were allowed. The patients were recruited from March 2016, and the follow-up was completed by June 2016. The study was carried out at the Psychiatry Unit of the University Hospital of Messina, Italy. The protocol has been approved by the ethics committee of the University of Messina.

2.2. Subjects

Fifteen outpatients, 9 men and 6 women, aged 20 to 58 years, in treatment with SGAs (clozapine, olanzapine, quetiapine and risperidone), were included in this study. All patients had been on monotherapy for at least 3 months; the dose had been stable for at least 1 month before the study and was left unchanged throughout the study. The patients did not receive any antidepressant or anticonvulsant drugs for a period of 2 months before the study. Furthermore, at enrollment, all subjects received standardized dietary advice in order to reduce the variability of their baseline metabolic values. Patients with any significant concurrent medical illnesses, organic brain disorder, mental retardation, pregnant or lactating women or a current diagnosis of alcohol/drug dependence were excluded. All the patients provided written informed consent after a full explanation of the protocol design, and the study was conducted according to the Declaration of Helsinki.

2.3. Assessment

Patients attended three visits: initial screening (week −1), inclusion (day 0), and final visit (day 30).

A physical examination was performed to measure blood pressure, heart rate, body weight and body mass index (BMI).

Standard laboratory methods were used to determine fasting levels of glucose, glycated hemoglobin (Hb1c), total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides. Low-density lipoprotein (LDL) cholesterol was determined by the Friedewald et al. calculation [24]: LDL=total cholesterol−(HDL+[triglycerides/5]).

Psychopathologic symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS) [25]. The BPRS was administered by two senior psychiatrists with at least 5 years of clinical experience and trained on rating scales; each patient had the same person conducting clinical interviews and administering psychometric test.

All physical information, laboratory measurements and data for clinical assessments were obtained at baseline and at the end of the study (approximately 30 days apart). Adverse effects, either observed or spontaneously reported, were recorded at each visit and classified in terms of onset, duration, severity, action taken and outcome. To monitor the adherence to the study protocol, weekly telephone calls during the study period and a pill count on the last day (day 30) were carried out.

2.4. Statistical analysis

Since this was a pilot study, no formal sample size calculation was performed. Due to the small sample size, the analyses were carried out by nonparametric tests. An intention-to-treat analysis with last-observation-carried forward (LOCF) was performed. Continuous data were expressed as mean ± S.D., and the within-group differences in efficacy ratings between baseline and final test were analyzed by the Wilcoxon rank sum test. To evaluate possible gender differences on the effect of BPF at end point, the Mann–Whitney *U* test for two independent samples was performed. To measure the magnitude of a treatment effect, effect size was provided by using Cohen's *d* statistic and was considered small when lower than 0.50, moderate when ranging from 0.50 to 0.79 and large when equal to or greater than 0.80. Taking into account that multiple correlations increase the risk of type 1 errors, a Bonferroni correction was applied, and a significance value of $P \leq .004$ was chosen. The statistical analysis was performed with SPSS 16.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

Baseline characteristics, duration of SGAs prior treatment, SGAs type and dose range in enrolled subjects are detailed in Table 1. Thirteen patients completed the study (86.6% completion rate); there were two premature dropouts: one due to treatment-emergent adverse effects (heartburn) and one due to noncompliance with the visits.

3.1. Treatment response

Table 2 shows the baseline and final values of the different clinical and metabolic parameters, and the effect size for the sample group: at day 30, within-group comparison revealed that BPF administration resulted in a statistically significant reduction of body weight ($P=.004$) and in a trend for BMI decrease ($P=.005$). No significant differences in other clinical (blood pressure, heart rate and BMI) and metabolic parameters (triglycerides, total cholesterol, HDL, LDL, glucose and Hb1c) were observed. Effect sizes were small in each explored clinical and metabolic parameters.

Table 3 shows the differences in clinical and metabolic parameters changes between male and female groups at the end of the study: no significant gender differences were found in mean scores change on explored variables.

Table 1
Demographic and clinical characteristics of the subjects enrolled

Patients entered (completers)	15 (13)
Sex (M/F)	9/6
Age (years), mean ± SD	44.5±9.1
Educational level (years), mean ± SD	10±2.5
Duration of prior AP treatment (months), mean ± SD	20.3±29.7
SGAs (dose range, mg/d)	***N***
Olanzapine (10–20 mg/d)	4
Clozapine (100–350 mg/d)	4
Quetiapine (50–100 mg/d)	4
Risperidone (3–4 mg/d)	3