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An Open Study of Sulforaphane-rich Broccoli Sprout Extract in Patients with Schizophrenia

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Objective: Schizophrenia is a mental disorder characterized by severe cognitive impairment. Accumulating evidence suggests a role for oxidative stress in the pathophysiology of schizophrenia. Sulforaphane (SFN) extracted from broccoli sprout is an agent with potent anti-oxidant and anti-inflammatory activity. In this study, we attempted to evaluate the effect of SFN on cognitive impairment in medicated patients with schizophrenia.
Methods: We recruited a total of 10 outpatients with schizophrenia, all of whom gave informed consent. Participants took 3 tablets of SFN, consisting of 30 mg of SFN-glucosinolate per day, for 8 weeks. Clinical symptoms using the Positive and Negative Syndrome Scale (PANSS) and cognitive function using the Japanese version of CogState battery were evaluated at the beginning of the study and at week 8.
Results: A total of 7 patients completed the trial. The mean score in the Accuracy component of the One Card Learning Task increased significantly after the trial. However, we detected no other significant changes in participants.
Conclusion: This result suggests that SFN has the potential to improve cognitive function in patients with schizophrenia.

KEY WORDS: Schizophrenia; Sulforafan; Executive function; Clinical trial; CogState.

INTRODUCTION

Schizophrenia is a mental disorder characterized by severe cognitive impairment, as well as positive and negative symptoms.[1)] Cognitive deficits in schizophrenic patients are thought to be related to impaired dorsolateral prefrontal cortex function and, its interactions with other brain regions, such as the parietal cortex, thalamus and striatum, as well as the influence of neurotransmitter systems, such as dopamine, γ-aminobutyric acid (GABA) and glutamate.[2)] It can also be related to poor compliance with antipsychotic medication, a known risk factor for relapse and re-hospitalization.[3,4)] Importantly, cognitive impairment is highly relevant to the functional outcome of schizophrenic patients,[5)] making recovery from this state vital for improving the quality of life for sufferers.

There have been numerous attempts to treat cognitive deficits in patients with schizophrenia.[6)] Atypical antipsychotics improve several domains of cognitive function, especially working memory, executive function and attention, in schizophrenic patients.[7-9)] Adjunctive regimens with agents such as alpha-7 nicotinic acetylcholine receptor agonists,[10,11)] sigma-1 receptor agonists,[12,13)] selective estrogen receptor modulators,[14)] and D-amino acid oxidase inhibitors[15)] have been examined in clinical trials. However, no gold standard has been established, partly due to the lack of adequate efficacy for any of the tested agents.[16)]

Accumulating evidence suggest a role for oxidative stress in the pathophysiology of schizophrenia.[17-19)] Oxidative damage may precipitate a range of cognitive deficits in patients with schizophrenia,[20,21)] through decreased activity of plasma manganese superoxide dismutase[22,23)] and/or mitochondrial function.[24)] Based on this evidence, several studies evaluating the effect of antioxidants on schizophrenia have been conducted.[25)] Recent studies report

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on the possible positive effects of antioxidant treatments, such as *N*-acetyl cysteine,[26] vitamins,[27] extract of Ginkgo biloba[28] and essential polyunsaturated fatty acids.[29-32] However, to our knowledge there have been few reports of antioxidants improving cognitive deficits in schizophrenic patients. No alleviation of cognitive deficits was found in a placebo-controlled trial with omega 3 fatty acids,[33] whereas L-carnosine adjunctive therapy showed beneficial effects on some domains of cognitive function along with considerable adverse effects, in a placebo-controlled trial.[34]

Sulforaphane (SFN) is a molecule belonging to the isothiocyanate group of organosulfur compounds found in broccoli sprouts. It is known to have potent anti-oxidant and anti-inflammatory activity.[35] In clinical settings, SFN has been proposed as an alternative treatment against gastric tumors and other physical diseases.[36] Previously, we reported that SFN attenuated behavioral abnormalities in mice after administration of methamphetamine[37] or phencyclidine,[38] suggestive of a potential therapeutic potency in schizophrenia. Recently, we found that SFN improved cognitive deficits in phencyclidine-treated mice (Shirai *et al.*, in preparation). To date, there are no published reports examining the beneficial effects of SFN in schizophrenia. To evaluate the efficacy of SFN on cognitive function, we conducted an open trial of SFN augmentation, in stable patients with schizophrenia. In addition, we measured serum levels of brain-derived neurotrophic factor (BDNF) in patients at baseline and 8-weeks, since it was reported that BDNF shows neurotrophic activity against oxidative stress.[39,40]

METHODS

Study Design and Subjects

This is an open-label, preliminary clinical trial for patients with schizophrenia. The recruited outpatients from Chiba University Hospital were aged between 20 and 65 years of age, with a diagnosis of schizophrenia meeting criteria defined by the Diagnostic and Statistical Manual of Mental Disorders 4th edition text revised (DSM-IV-TR),[41] were being prescribed a single atypical antipsychotic drug (aripiprazole, blonanserin, olanzapine, paliperidone, perospirone, quetiapine, or risperidone) at a fixed dose, for at least 4 weeks before study entry. Both sexes were recruited; however, pregnant women and new mothers were excluded. Patients with intellectual disabilities, developmental disorders, attention-deficit hyperactivity disorders, delirium, dementia or other types of cognitive impairment, substance misuse disorders (except caffeine or nicotine), eating disorders, or personality disorders were excluded. Patients who had previously been administered SFN over 8 weeks were also excluded.

Measurement of Clinical Symptoms

After giving written informed consent, participants received 3 tablets of SFN prepared by Kagome Co., Ltd. (Nagoya, Japan), totaling 30 mg of SFN-glucosinolate per day, for 8 weeks. It is known that SFN-glucosinolate is metabolized to SFN in the body. We gave the each participant a recording sheet for them to confirm daily taking of SFN. We checked the sheet to evaluate their compliance in every visit.

We assessed each patient's medical condition every 2 weeks, using clinical interviews. Additionally, we performed blood tests at baseline, week 4, and week 8, to ensure the safety of SFN. Cognitive function was measured using the Japanese version of CogState (CogState Ltd., Connecticut, USA; http://cogstate.com) battery, which consists of a series of computed non-verbal tests.[42] In CogState, we chose the 5 subtests: Detection, Identification, One Card Learning, One Back Memory, and Two Back Memory. In Detection and Identification tasks, the primary performance measure was reaction time in milliseconds (speed), which was normalized using a log10 transformation. In the other tasks, the primary performance measure was the proportion of correct answers (accuracy), which was normalized using an arcsine square-root.[43]

In this trial, tests were performed at baseline and again at week 8. We also evaluated the psychiatric symptoms of participants using the Positive and Negative Syndrome Scale (PANSS),[44] and Clinical Global Impression (CGI)[45] at baseline, week 4 and week 8. In addition, we measured the serum levels of BDNF in each participant at baseline and week 8.

Measurement of BDNF Serum Levels

Serum samples from all subjects were collected between 9:00 and 15:00, and stored at -80^{o}C until use. Serum levels of BDNF were measured using the human BDNF ELISA kit (Aviscera Bioscience, Santa Clara, CA, USA). To minimize assay variance, serum levels of BDNF from each subject were measured on the same day. All experiments were performed in duplicate. Protocols were performed according to the manufacturer's instructions. The optical density of each well was measured using an automated microplate reader (Emax; Molecular

Devices, Sunnyvale, CA, USA).

Statistical Analysis

On completion of clinical assessments, we evaluated data using IBM SPSS Statistics ver. 22 (Essentials for R; IBM Co., Armonk, NY, USA), based on intention-to-treat analysis, with the adapting last observation carried forward concept for unmeasured scores in participants who dropped out of the study. Considering the small sample size, we adopted Wilcoxon signed-rank test for statistical analyses. Values of $p<0.05$ (two-tailed) were considered statistically significant in these analyses.

Table 1. Baseline demographics and clinical characteristics of participants

Variable	Data
Age (yr)	42.7±11.0
Gender (male : female)	4 : 6
Schizophrenia subtype	
Disorganized	2
Catatonic	1
Paranoid	7
Duration of illness (yr)	18.9±10.0
CGI-S	
2 (borderline)	1
3 (mildly ill)	2
4 (moderately ill)	1
5 (markedly ill)	5
7 (among the most extremely ill)	1
Chief medication (mg/day)	
Aripiprazole (15, 18, and 30)	3
Blonanserin (24)	1
Olanzapine (20)	1
Paliperidone (6 and 9)	2
Quetiapine (600)	1
Risperidone (2 and 3)	2

Values are presented as mean±standard deviation or number only.
CGI-S, Clinical Global Impression - Severity of Illness.

RESULTS

We recruited a total of 11 outpatients, who were given atypical antipsychotic mono-therapy against schizophrenia. This trial ran from October 2012 to July 2013. Of the 11 participants, one withdrew consent before initial assessments citing personal reasons, leaving a total of 10 patients. The baseline demographics, and clinical and treatment characteristics of patients are shown in Table 1. Three participants dropped out during the trial, whose scores of CGI-S were 5, 5, and 7. The reasons were: poor compliance with regular antipsychotic medication, withdrawal of consent to participate and the need to deal with other physical symptoms. No withdrawals were proven to be due to SFN related adverse events. Consequently, a total of 7 participants completed the trial. All completers took SFN with good adherence (over 90%).

The mean scores in the Accuracy component of the One Card Learning Task (OCLT) showed a significant increase from 0.88 to 0.95 (Wilcoxon signed rank test: $p=0.043$). The other scores in CogState battery did not change significantly. The mean PANSS total scores (91.7±16.2 at baseline, 91.6±16.6 after 4 weeks and 91.0±16.3 after 8 weeks; mean±standard deviation) showed no changes either. We also compared serum levels of BDNF after taking SFN for 8 weeks to baseline data in the completers, however no statistical differences were detected (Table 2).

DISCUSSION

These results highlight the possible use of SFN as an adjunctive therapy to improve cognitive function in patients

Table 2. Change of symptoms, brain-derived neurotrophic factor (BDNF) data, and cognitive function

	Pre-medication	8 Weeks	*p* value
PANSS (n=10, LOCF)			
Positive scale	20.5±3.8	20.3±4.2	0.705
Negative scale	25.2±8.6	24.0±8.5	0.102
General psychopathology scale	46.0±7.1	46.7±6.9	0.236
Total score	91.7±16.2	91.0±16.3	0.248
Serum BDNF (ng/mL)	31.5±2.89	23.9±9.26	0.063
CogState (n=10, LOCF)			
Detection (Speed)	2.66±0.16	2.68±0.15	0.149
Identification (Speed)	2.83±0.12	2.84±0.13	0.674
One Card Learning (Accuracy)	0.88±0.083	0.96±0.15	0.043*
One Back Memory (Accuracy)	1.20±0.23	1.21±0.22	0.528
Two Back Memory (Accuracy)	1.08±0.26	1.02±0.23	0.236

Values are presented as mean±standard deviation.
PANSS, Positive and Negative Syndrome Scale; LOCF, last observation carried forward. *$p<0.05$ (Wilcoxon signed-rank test).

with schizophrenia. To the best of our knowledge, this is the first report highlighting an effect for SFN augmentation in medicated patients with schizophrenia.

The CogState battery is a valid measurement of cognitive function, similar to the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia; http://www.matricsinc.org),[46,47] which is authorized as a standard evaluative tool for the components of cognitive impairment in patients with schizophrenia[48] and other diseases.[49,50] Its test-retest reliability is high enough for use in clinical evaluations,[43] while it was also assessed to have intermediate reliability and validity in a systematic review.[51] It is performed in Japanese patient cohorts with high validity.[42]

The OCLT is a continuous visual recognition learning task that primarily estimates visual recognition learning, attention and short-term memory.[52-54] Its accuracy score has negative association with scores from the Mini Mental Examination in healthy controls, which indicates it should be able to detect cognitive impairment with a considerable degree of sensitivity.[43] In this study, we found that SFN improved mean scores on the OCLT in patients with schizophrenia, implying that it may have the potential to enhance domains of cognitive function, such as attention-focusing.

On the other hand, other scores than OCLT did not change in this study. One Back Memory Task (OBMT) and Two Back Memory Task (TBMT) also reflect working memory and attention of examinees. In this study, the baseline accuracy rates of the participants were high enough (93% in OBMT and 88% in TBMT). Therefore, it was possible that the improvement of cognitive function could not be detected with these tasks because of ceiling effect.

SFN is also reported to attenuate oxidative stress caused by antipsychotics.[55] It is likely that SFN could offer safer and beneficial therapy, avoiding the chronic problems frequently induced by antipsychotic medication, in addition to improving cognitive function.

There currently lack of consensus around practice effects in the CogState battery. In a few studies using healthy volunteers and schizophrenic patients, no practice effects were observed at the one-month test-retest interval, in some measures of CogState battery.[56,57] In studies of patients with dementia, CogState showed acceptable stability, with no or minimal practice effects, even at short test-retest intervals.[58,59] On the other hand, a study in which some computerized neurocognitive assessment tools were adapted to an active duty military sample, there was a finding that the intraclass correlation score of the OCLT was not high, compared with other tasks in CogState.[60] An open label, multinational methodology study, reported that the composite score on CogState battery showed a moderate practice effect on the second administration compared to the first administration (effect size=0.28, 95% confidence interval [CI] −0.05 to 0.61); however, no further practice effect was observed between the second and the third administrations (effect size=−0.05, 95% CI −0.03 to 0.46), suggesting a saturation of practice effects at the second administration.[61] In contrast, another study in which repetitive examinations were performed over 12 months in elderly healthy people, there was a small improvement in group performance from baseline to the 12-month visit in the accuracy of performance in the OCLT, but the study failed to identify practice effects between the first two visits over a three month period.[52] To sum up, although practice effects in CogState cannot be ignored, it is highly unlikely to be a confounding factor in the results presented in this study.

Multiple data implicates BDNF in the pathophysiology of schizophrenia.[62,63] Some papers have specified a role for BDNF in cognitive deficits associated with schizophrenia.[64,65] Although we detected a recovery of some cognitive deficits, we found no change of serum BDNF in patients after eight weeks of SFN supplementation. A further study on the role of BDNF in the therapeutic mechanisms of SFN will be needed.

In summary, our clinical trial indicates that SFN has the potential to improve some domains of cognitive function in patients with schizophrenia. Further research is required including, randomized, double-blind, placebo-controlled trials, along with the measurement of potential biological markers for oxidative stress. Larger trials conducted over longer periods will be necessary to determine the efficacy and safety of SFN use in schizophrenia.

In conclusion, our pilot study suggests that supplementation therapy of SFN-rich broccoli sprout extract may have the potential to improve cognitive deficits in patients with schizophrenia.

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