Efficacy and Safety of Sulforaphane Added to Antipsychotics for the Treatment of Negative Symptoms of Schizophrenia: A Randomized Controlled Trial

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Abstract

Objective: There are few established treatments for negative symptoms in schizophrenia, which persist in many patients after positive symptoms are reduced. Oxidative stress, inflammation, and epigenetic modifications involving histone deacetylase (HDAC) have been implicated in the pathophysiology of schizophrenia. Sulforaphane has antioxidant properties and is an HDAC inhibitor. We conducted a 24-week, double-blind, placebo-controlled study, in Hunan, China, to assess the effect of high-dose sulforaphane (Nutramax extra strength sulforaphane tablets glucoraphanin content 30 mg/tablet) on reducing negative symptoms in antipsychotic-treated patients with schizophrenia.

Methods: Participants were recruited from August 2020 to August 2022 and met *DSM-5* criteria for schizophrenia. Participants were randomly assigned (2:1) to receive antipsychotics plus sulforaphane (1,700 mg Avmacol Extra Strength sulforaphane daily) or antipsychotics plus placebo for 24 weeks. Fifty-three patients treated with sulforaphane and 24 patients treated with placebo who had at least 1 postintervention clinical scale evaluation were analyzed. The primary outcome measure was change in the Positive and Negative Syndrome Scale (PANSS) negative symptoms.

Results: Sulforaphane-treated patients showed a significantly greater decrease in PANSS negative symptom total score ($P = .01$) and PANSS negative factor score ($P = .02$) than placebo-treated patients, with the most prominent difference occurring at 24 weeks ($P \leq .001$) with a large effect size at this time point ($d = 0.8$). Sulforaphane's effect on decreasing negative symptoms was not mediated by changes in scores of depression or cognitive factors on the PANSS.

Conclusions: The results of this study suggest that add-on high-dose sulforaphane may reduce negative symptoms in patients with schizophrenia. The clinical significance of this reduction in negative symptoms needs further evaluation.

Trial Registration: ClinicalTrials.gov identifier: NCT04521868.

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Schizophrenia is a severe mental illness, characterized by recurrent positive symptoms, persistent negative symptoms, and marked cognitive deficits,[1] with a prevalence of approximately 1%.[2] Antipsychotics, the mainstay of treatment, act predominantly on the dopaminergic system and show amelioration of positive symptoms. However, antipsychotics have lower efficacy in treating negative symptoms, which emerge during the prodromal phase and persist the entire lifespan and result in functional disability. The etiology of negative symptoms is complex and unknown; they can be primary to the disease itself, or be secondary to positive symptoms or depressive symptoms, or worsened by antipsychotic-induced side effects.[3–5] Although amisulpride, cariprazine, and blonanserin show advantages over other antipsychotics in alleviating negative symptoms,[4,6,7] to date no medication has been approved for the treatment of negative symptoms by the FDA.

Sulforaphane (SFN), as a plant-active substance, has antioxidant and anti-inflammatory, neuroprotective, and metabolic regulation effects. Both animal and clinical studies revealed that SFN has the potential to improve symptoms, behaviors, and cognitive impairment in

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Clinical Points

- Antipsychotics exhibit substantial efficacy in treating positive symptoms but have limited efficacy in treating negative symptoms.
- Sulforaphane, in higher doses, can be added as a safe and viable supplement to improve negative symptoms, but its effect should be evaluated during several months of treatment.

psychiatric diseases.[8,9] Though the pathogenesis of schizophrenia remains unclear, inflammation and oxidative stress appear to play an important role in the pathology of schizophrenia.[10] Cell-mediated immune activation was found in schizophrenia patients. Maes et al[11] reported that the plasma concentrations of the inflammatory cytokine interleukin-6 were significantly higher in schizophrenia patients than in healthy participants. In a positron emission tomography brain imaging study, participants with subclinical symptoms at ultra-high risk of psychosis and patients with schizophrenia were found to show elevated microglial activity.[12] Meta-analyses showed that some oxidative stress markers (thiobarbituric reactive substances and nitric oxide) were increased, while antioxidant markers (superoxide dismutase and glutathione) were decreased in schizophrenia patients.[13,14] These results were consistent with 1 large meta-analysis which concluded that patients with schizophrenia have a lower antioxidant capacity and increased proinflammatory state.[15]

Animal studies have provided evidence of the therapeutic effects of SFN on schizophrenia. In a phencyclidine (PCP)-induced schizophrenia mice model, the dendritic spine density and the proportion of PV-positive cells were decreased in the medial prefrontal cortex and hippocampal CA1 of the schizophrenia mouse models, while the proportion of 8-hydroxy-2'-deoxyguanosine (a marker of DNA oxidative damage)–positive cells were increased in the above 2 brain regions.[16] This study further observed that the above changes induced by PCP can be attenuated by pretreatment with SFN. Early intervention using SFN may reduce the onset of subsequent transition to schizophrenia.[16,17] However, our previous study evaluating SFN's effects in first-episode schizophrenia patients or early episode with acute exacerbation of symptoms did not show statistically significant differences in the Positive and Negative Syndrome Scale (PANSS) positive or negative symptoms between SFN and placebo treatment.[18] Another study in patients with schizophrenia also failed to show a difference in PANSS scores.[19] However, these previous studies did not set inclusion criteria based on the specific symptoms and used relatively lower doses of SFN in Nutramax tablets compared with a higher dose tablet available more recently. Further, randomized clinical trials may need to be conducted to explore the effects of SFN in specific clinical subsets of schizophrenia and find optimal therapeutic doses.

The primary objective of this study was to investigate the efficacy of SFN in the treatment of negative symptoms in schizophrenia patients. The study also assessed the safety of SFN treatments through clinical and laboratory evaluations.

METHODS

Study Design and Participants

The study was a randomized, double-blind, placebo-controlled study. Participants were recruited from August 2020 to August 2022 at the Second Xiangya Hospital of Central South University. The inclusion criteria were as follows: (1) met the criteria for schizophrenia of the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*); (2) aged 18–50 years old; (3) disease duration ≤10 years; (4) total score greater than or equal to 20 on the sum of the 7 items constituting the PANSS negative symptoms; at least 1 item of PANSS negative symptoms with a score of >3; (5) taking 2 or fewer antipsychotics; (6) with antipsychotic medication remaining unchanged during the study period.

The exclusion criteria were as follows: (1) have a history of substance dependence or abuse or whose symptoms are caused by other diagnosable mental disorders; (2) have a history of traumatic brain injury, seizures, or other known neurological diseases of the central nervous system; (3) take antidepressants, stimulants, or mood stabilizers or received modified electroconvulsive therapy[20] or repetitive transcranial magnetic stimulation during the past 3 months; (4) have current suicidal or homicidal thoughts or any safety concern by research staff that cannot be managed during the trial; (5) take dementia-related drugs, minocycline, and other drugs that may affect cognitive function; (6) laboratory tests indicated significant abnormalities in blood routine, liver and kidney function, or other metabolic results; (7) pregnant or lactating women.

The study was approved by the local ethics committee, written informed consent was obtained, and the study was registered at ClinicalTrials.gov (identifier: NCT04521868).

SFN and Placebo Administration

Participants were randomly assigned (2:1) to receive antipsychotics plus SFN or antipsychotics plus placebo using a computer-based random number generator. Both the clinical evaluators and patients as well as treatment team members were blinded to the treatment. Patients in the SFN group received 1,700 mg Avmacol

Extra Strength SFN (obtained from Nutramax though a Chinese supplier) once daily as an add-on treatment for 24 weeks; measured glucoraphanin content was more than 30 mg/tablet in each tablet, and the SFN group received 2 tablets once daily. Each Avmacol Extra Strength tablet contains ≥30 mg glucoraphanin and has an SFN potential of at least 12 mg (approximately 68 μmol) of SFN per tablet. Therefore, participants in this study received ≥60 mg glucoraphanin with an SFN potential of 24 mg (approximately 136 μmol) of SFN daily if they followed study procedures (see Supplementary Material for statement on quality control). Patients in the placebo group received placebo tablets (matched in color and size) once daily as an add-on treatment for 24 weeks. Adherence to medication was calculated as the percentage of the actual drug dose to the total administered dose. An independent research staff member counted the pill counts distributed and returned and contacted the participants for follow-up visits. Although it is possible there could be differences in taste between the SFN and placebo pills, the independent researcher, who had no role in the evaluations, dispensed the pills, and any complaints regarding taste could be directed solely to her. Once contacted by phone, participants attended one-on-one follow-up without opportunities for interaction among themselves. The antipsychotic medications remained at a fixed dose as baseline levels throughout the course of treatment. We set 3 time points for assessment: baseline, week 12, and week 24. Clinical evaluations and blood tests were included at each time point. Psychopathology was assessed using the PANSS[21] and the Clinical Global Impression Scale (CGI).[22,23] The Treatment-Emergent Symptom Scale (TESS)[24] was used to monitor treatment safety to evaluate adverse events at each clinic visit.

Outcome Measures

The primary outcome measures were the PANSS negative symptoms, both the PANSS negative sum score and the 5-factor PANSS negative symptom score (sum of N1, N2, N3, N4, and N6) at the relevant time points. The 5-factor PANSS scores were derived from factor analysis described in previous studies.[25,26] Secondary outcome measures were the PANSS total score, PANSS 5-factor scores except negative factor (positive, excitement, depression, and cognitive). Additional outcome measures were the CGI scale, and the safety and tolerability evaluation included reporting adverse events, electrocardiogram, laboratory tests, and Treatment Emergent Symptom Scale (TESS) scale.

Statistical Analysis

Statistical analysis utilized SPSS 25, SAS 9.4, and R programs for a mediation analysis. The main analysis of PANSS scale outcome data utilized mixed model analysis using SAS 9.4 process mixed, to deal with missing data from dropouts or other causes. The main analysis of PANSS scores was a mixed model analysis of difference scores from baseline with baseline scores ratings, duration of illness, sex, age, and converted antipsychotic equivalent dose as covariates or factors. Additional analyses used mixed model original values at baseline, 12 weeks', and 24 weeks' time points with duration of illness, sex, age, and converted antipsychotic equivalent dose as covariates or factors. Comparison of baseline characteristics between SFN and placebo groups used *t* tests, Mann-Whitney *U*, and χ^2. Details of statistical analysis and sample size calculation are shown in Supplementary Material.

RESULTS

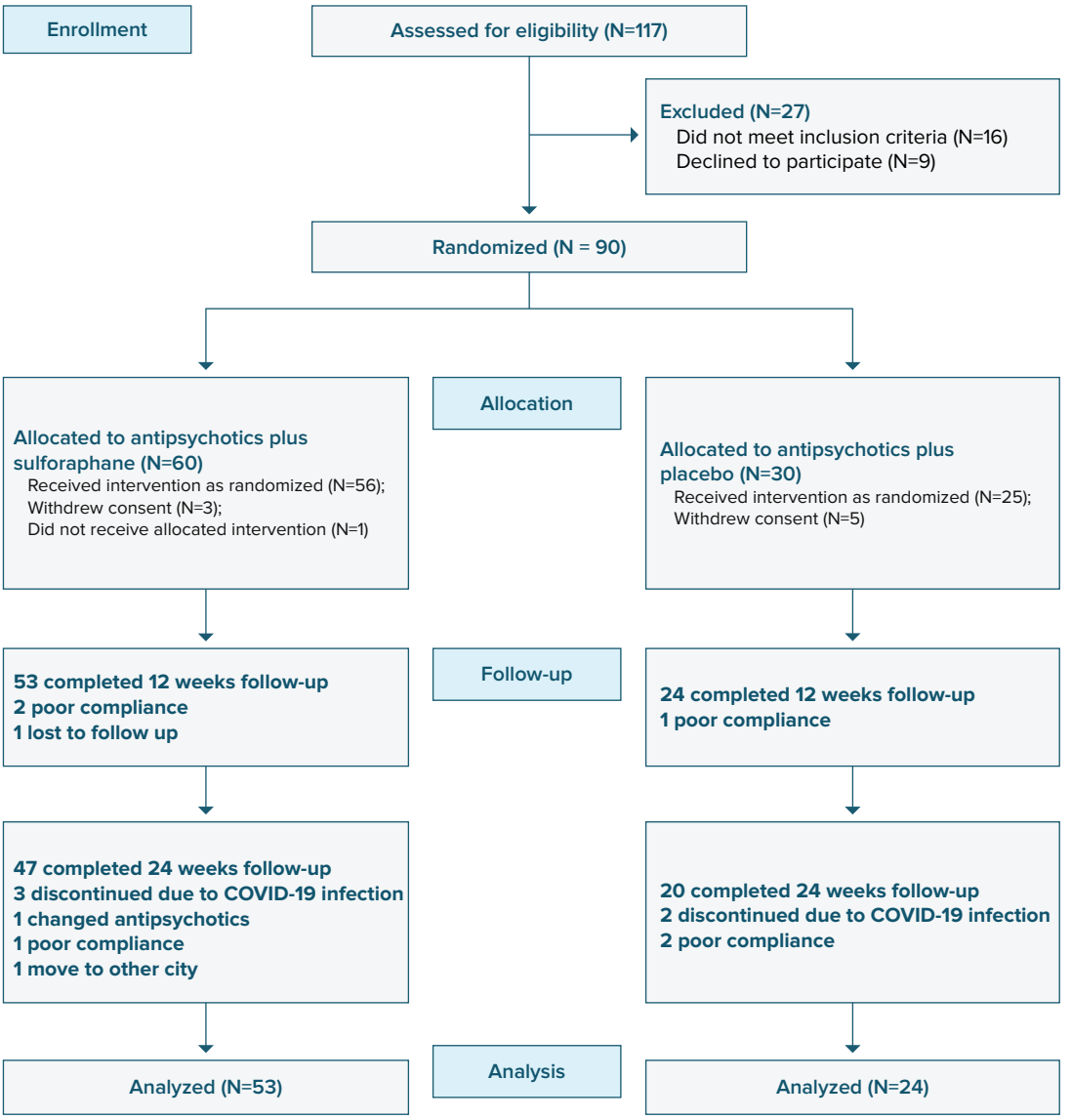
Participant Characteristics

There were no differences in demographic and related characteristics (age, sex, and duration of illness) of the participants assigned to SFN or placebo (Figure 1; Table 1). The sample included both patients with first-episode schizophrenia (70%) and multiepisode schizophrenia (30%), but there were no differences in the distribution between SFN and placebo participants. The patients had mean total PANSS scores of 74–77 in the 2 groups and a mean PANSS total negative symptom score of 24–25 in both groups; 95% of participants had higher total negative symptoms than positive symptoms and 84% having a negative symptom score ≥21. There was no significant difference in PANSS total or negative symptom scores between the 2 groups, but the placebo patients had higher positive symptoms (mean 16) than the SFN-treated patients (mean 12). The patients were treated with a variety of antipsychotic drugs, and the most frequently used antipsychotic medication administered was risperidone (see Supplementary Material for antipsychotic drug treatment distribution). However, there was no significant difference in the calculated olanzapine equivalent antipsychotic dose between the placebo and SFN groups.

Effects of SFN on PANSS Scores

The SFN-treated group showed a significantly greater reduction in negative symptoms than the placebo group, and this effect was prominent at the 24-week treatment time point (see Figure 2 and Tables 2 and 3). This was evident in the analysis of PANSS negative symptom estimated mean scores at the evaluated time points (Figure 2, treatment × time overall effect $F = 4.69$, $df = 1, 59$, $P = .01$) and the analysis of the estimated mean decrease in scores from baseline (Tables 2 and 3). Both the decreases in PANSS negative symptom sum scores and the PANSS 5-factor negative symptom scores showed significant overall treatment effects (PANSS negative symptom sum score $F = 6.78$, $df = 1, 58$, $P = .01$ and

Figure 1.
Flowchart of the Trial[a]



[a]Eligible participants were screened and randomized to receive antipsychotics plus sulforaphane or antipsychotics plus placebo for 24 weeks. Clinical evaluation and laboratory tests were conducted at baseline, after 12 weeks of treatment, and at the end of the trial at week 24.

PANSS 5-factor negative symptom score $F = 6.22$, $df = 1$, 58, $P = .02$). At the 24-week time point, the difference between SFN and placebo groups was highly significant ($P \leq .001$) with about a 3-point greater decrease in the SFN group than in the placebo group. Effect size at the 24-week time point was high ($d = 0.83–0.86$). There was no difference in drug vs placebo effects on PANSS total scores, but there was a trend ($P < .10$) for positive symptoms to decrease more in the placebo group than in the SFN-treated group with a significant ($P < .05$) difference at the 24-week time point. Although PANSS 5-factor excitement and cognitive factors did not show overall drug effects, there were some significant differences between SFN and placebo groups at 12 or 24 weeks. There was a correlation between the decrease in PANSS negative and cognitive factor scores at 24 weeks ($r = 0.40$, $P < .01$) suggesting that decreases in cognitive deficits may accompany decreases in negative symptoms. However, a mediation analysis of the 5-factor PANSS negative symptom score showed that neither PANSS depression factor nor PANSS cognitive factor significantly mediated the decrease in negative symptom decrease at the 24-week time point ([Average Causal Mediation Effect] ACMEs *P*s > .57).

Previous studies and meta-analysis showed that amisulpride had a significant effect on reducing negative

Table 1.
Participants Characteristics in Sulforaphane and Placebo Groups[a]

Characteristic	Sulforaphane	Placebo	Test statistics
Age	23.75 ± 6.21	23.68 ± 6.32	$T = 0.042$, $df = 68$, $P = .97$
Sex (male/female)	28/25	12/12	$\chi^2 = 0.053$, $df = 1$, $P = .82$
First-episode/multiepisode schizophrenia	37/16	17/7	$\chi^2 = 0.008$, $df = 1$, $P = .93$
Inpatient/outpatient	10/43	5/19	$\chi^2 = 0.041$, $df = 1$, $P = .84$
Duration of illness (mo)	44.2 ± 35.22	43.43 ± 47.64	$T^w = 0.073$, $df = 35.7$, $P = .94$
Antipsychotic treatment			
First generation	1	0	…[b]
Second generation (not clozapine)	36	21	
Clozapine	1	2	
Two or more antipsychotics	10	3	
Olanzapine equivalent antipsychotic dose	15.24 ± 9.88	12.71 ± 3.57	$T^w = 1.636$, $df = 71.3$, $P = .11$
PANSS total sum	73.83 ± 11.88	76.67 ± 12.60	$T = 0.952$, $df = 75$, $P = .34$
PANSS negative sum	24.70 ± 4.24	24.42 ± 4.03	$T = 0.274$, $df = 75$, $P = .79$
PANSS positive sum	12.06 ± 3.83	16.33 ± 5.95	$T^w = 3.230$, $df = 31.9$, $P = .003$

[a]Ns are subjects who were included in analysis. Ns sulforaphane 48–53 and placebo 22–24; different Ns because of missing data on selected subjects. Each number entry is either mean ± SD or number of subjects.
[b]Chi-square test cannot be accurately calculated because of n < 5 in several cells.
Abbreviations: *df* = degrees of freedom, PANSS = Positive and Negative Syndrome Scale, *T* = *t* test, T^w = Welch *t* test for unequal variances, X^2 = chi-square test.

symptoms in schizophrenia,[4,6] and there was an imbalance in this antipsychotic treatment in the 2 groups in the current study. Seventeen patients in the SFN-treated group had amisulpride as their main or accessory antipsychotic, whereas only 1 patient in the placebo group was treated with amisulpride. We therefore performed additional statistical analyses to try to determine whether amisulpride treatment influenced the effect of SFN on negative symptoms. Results of a mediation analysis that we performed showed that amisulpride did not mediate the effects of SFN on reducing negative symptoms (PANSS negative sum difference at 24-week ACME = 0.56, $P = .30$ and PANSS negative factor difference at 24-week ACME = 0.19, $P = .68$). In additional mixed model analyses, in which amisulpride treatment was added as a factor, the amisulpride × group × time effect was not significant. Furthermore, in the SFN-treated patients, those not treated with amisulpride had a greater decrease in negative symptoms by week 24 than those treated with amisulpride (PANSS negative sum difference at 24 weeks [mean ± SD], participants not on amisulpride −9.59 ± 4.63, participants on amisulpride −6.18 ± 3.76, *t* test $T = 2.58$, $df = 44$, $P = .01$). These results support the contention that amisulpride was not a confounding factor explaining SFN's effect on negative symptoms, but the marked imbalance in the number of participants on amisulpride in the SFN group vs placebo group may create problems in interpreting the statistical analyses and make our conclusions less certain.

We also examined whether SFN treatment affects some types of negative symptoms more than others. Comparing the difference in decrease in scores at 24 weeks, compared to baseline, items assessing blunted affect, emotional withdrawal, passive apathetic social withdrawal, and lack of spontaneity in flow of conversation showed a significant ($P < .05$) effect of SFN vs placebo group; poor rapport, difficulties in abstract thinking, and stereotyped thinking showed no significant effect of SFN (see Figure 2).

Safety and Tolerability

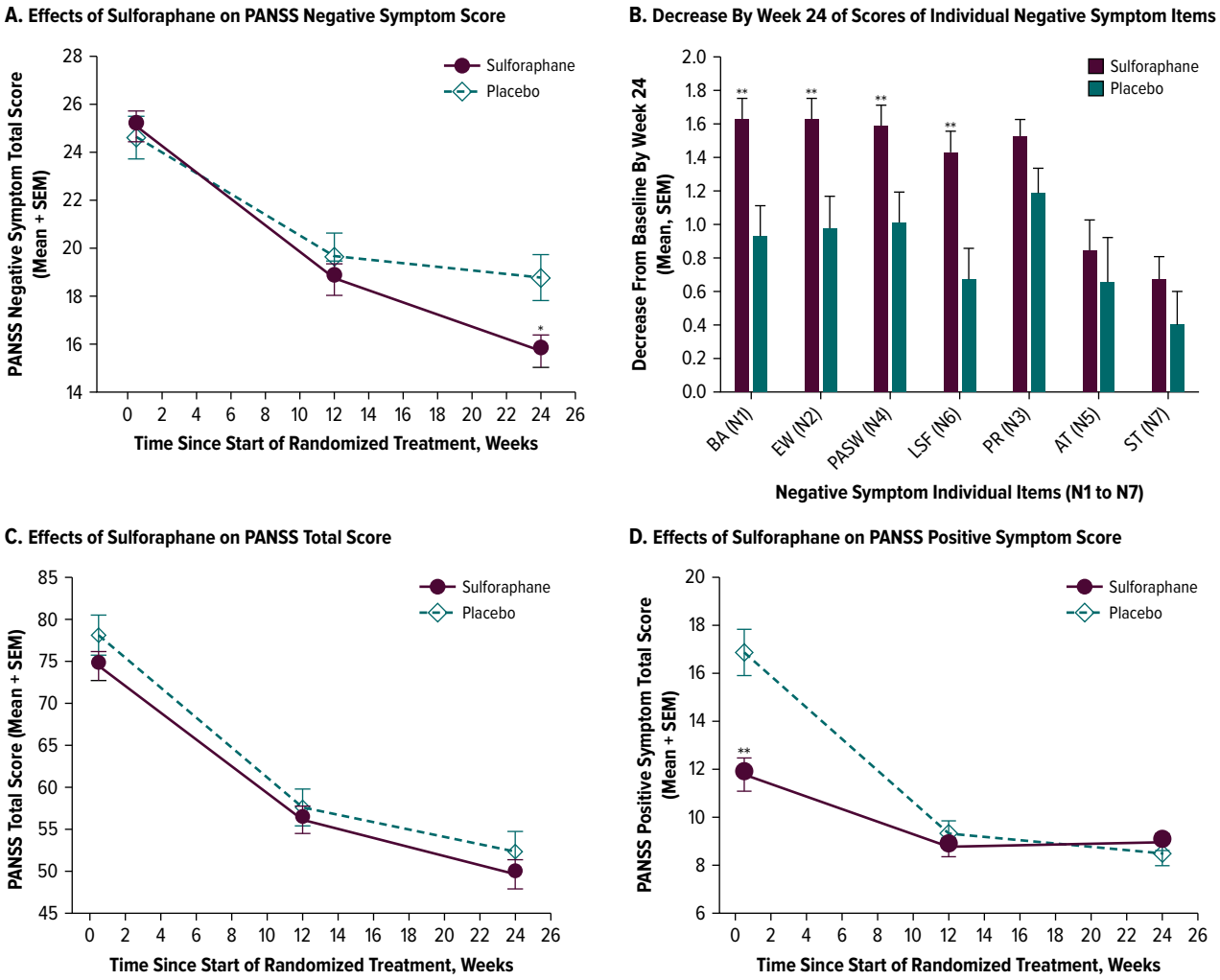
SFN was well tolerated compared to placebo as evaluated by the TESS scale and metabolic measures (see Supplementary Material for details).

DISCUSSION

The treatment of negative symptoms remains a challenge in the management of schizophrenia. These symptoms can be the most persistent, intractable, and disabling element of the illness for many patients. This study showed a significant effect of SFN compared to placebo on reducing negative symptoms in patients with schizophrenia. The effect on decreasing negative symptoms occurred with longer term treatment and was prominent at 24 weeks, but not 12 weeks of SFN treatment, with a large effect size at the 24-week time point. The SFN effect appeared to be specific for negative systems as measured by the PANSS. There were no changes in the overall global improvement as assessed by the CGI scale, and the decrease in negative symptoms was not mediated by changes in depression or cognitive symptoms or differences in amisulpride treatment. The placebo group had significantly higher positive symptoms at baseline than the SFN group, and this may have influenced the effects on their greater decrease in

Figure 2.

Effects of Sulforaphane on PANSS Symptom Scores



For parts A, C, and D, scores represent least squares mean and SEM at each time point in patients who received either sulforaphane or placebo, using mixed model analysis as described in the statistical methods section. In part B, scores are mean and SEM decrease from baseline at week 24 for each negative symptom item. Statistical significance between sulforaphane and placebo at specific time point: **P* < .02, ***P* < .01. Ns for each point in the graphs are sulforaphane = 53 and placebo n = 24 with means derived from mixed model analysis. Overall treatment × time effect: (A) $F = 4.69$, $df = 2, 59$, $P = .013$; (C) $F = 0.41$, $df = 2\ 59$, $P = .67$; (D) $F = 10.63$, $df = 2, 59$, $P < .001$.

Abbreviations: AT(N5) = difficulty in abstract thinking, BA(N1) = blunted affect, EW(N2) = emotional withdrawal, LSF(N6) = lack of spontaneity in flow of conversation, PASW(N4) = passive apathetic social withdrawal, PR(N3) = poor rapport, SEM = standard error of the mean, ST(N7) = stereotyped thinking.

positive symptoms. The covariate of baseline positive symptoms was statistically significant in the mixed model analysis. However, since the analysis controlled for baseline positive symptoms and still found a decrease in positive symptoms in the placebo group, the higher baseline positive symptoms in this group cannot be the entire explanation for the greater decrease in the placebo group.

The relationship between decreases in negative symptoms and changes in cognition could not be fully evaluated because we did not employ more comprehensive measures of cognitive function and only could utilize the cognitive factor from the 5-factor PANSS. Although there was a positive correlation between decreases in the PANSS negative factor and cognitive factors, additional medication analysis showed that changes in the cognitive factor scores did not mediate decreases in negative symptoms.

The results of the current study differ from the findings of our earlier report of SFN effects in first- or early episode schizophrenia.[18] In that study, we reported no effects of SFN on any PANSS scale measure. The differences in effect may be due to several differences between the 2 studies. The sample characteristics were different—a mixture of multiepisode schizophrenia and first-episode schizophrenia in this study, acute exacerbation with more severe total PANSS scores in the original study sample (approximately 90 in that earlier sample vs 73–76 in the current sample), and slightly higher baseline negative

Table 2.

Effects of Sulforaphane on Psychopathology Scores in Patients[a]

Scale score	Treatment	Baseline score (mean ± SEM)	Adjusted estimated difference from baseline at specified time point (mean ± SEM)		Overall treatment effect
			12 wk	24 wk	
PANSS total	Sulforaphane	73.83 ± 1.63	−19.13 ± 1.38	−25.90 ± 1.49	$F = 0.28$, $df = 1, 58$, $P = .60$
	Placebo	76.67 ± 2.57	−18.81 ± 1.84	−23.83 ± 2.10	
PANSS positive	Sulforaphane	12.06 ± 0.53	−4.37 ± 0.36	−4.20 ± 0.37*	$F = 3.06$, $df = 1, 58$, $P = .09$
	Placebo	16.33 ± 1.22	−4.94 ± 0.49	−5.77 ± 0.54	
PANSS negative	Sulforaphane	24.70 ± 0.58	−6.26 ± 0.62	−9.35 ± 0.57***, $d = 0.86$	$F = 6.78$, $df = 1, 58$, $P = .01^B$, $d = 0.22$
	Placebo	24.42 ± 0.82	−5.05 ± 0.82	−5.82 ± 0.81	
PANSS general	Sulforaphane	37.09 ± 1.14	−8.82 ± 0.81	−12.59 ± 0.80	$F = 0.55$, $df = 1, 58$, $P = .46$
	Placebo	35.92 ± 1.50	−8.28 ± 1.07	−11.27 ± 1.14	

[a]Sulforaphane N = 53 and placebo N = 24. Results are from mixed model analysis of change scores with baseline score and age, illness duration, and olanzapine equivalent dose as covariates and sex as factor. Overall treatment effect is overall group (sulforaphane vs placebo) effect of the difference score. *T* test values at specific time point between sulforaphane and placebo, significance: *$P < .05$, ***$P < .001$; for negative symptoms 24 wk, $T = -3.54$, $df = 58$, $P < .001$; for positive symptoms 24 wk, $T = -2.27$, $df = 58$, $P = .027$.

Abbreviations: B = met Benjamini-Hochberg protected significance level (α = .05), *d* = effect size, PANSS = Positive and Negative Syndrome Scale.

Table 3.

Effects of Sulforaphane on PANSS 5-Factor Scores in Patients[a]

PANSS factor scores	Treatment	Baseline score (mean ± SEM)	Adjusted estimated difference from baseline at specified time point (mean ± SEM)		Overall treatment effect
			12 wk	24 wk	
PANSS positive	Sulforaphane	8.08 ± 0.43	−3.39 ± 0.25	−3.53 ± 0.27*	$F = 3.75$, $df = 1, 58$, $P = .06$
	Placebo	10.50 ± 0.90	−4.08 ± 0.35	−4.53 ± 0.39	
PANSS negative	Sulforaphane	19.13 ± 0.49	−4.79 ± 0.49	−7.84 ± 0.49*** d = 0.83	$F = 6.22$, $df = 1, 58$, $P = .02$, $d = 0.27$
	Placebo	18.67 ± 0.92	−4.00 ± 0.66	−4.92 ± 0.70	
PANSS excitement	Sulforaphane	4.00 ± 0.19	−0.85 ± 0.20	−0.84 ± 0.20*	$F = 2.46$, $df = 1, 58$, $P = .12$
	Placebo	5.33 ± 0.51	−1.08 ± 0.26	−1.58 ± 0.29	
PANSS depression	Sulforaphane	5.70 ± 0.26	−1.32 ± 0.20	−1.65 ± 0.18	$F = 2.34$, $df = 1, 58$, $P = .13$
	Placebo	5.25 ± 0.40	−1.60 ± 0.26	−2.19 ± 0.26	
PANSS cognitive	Sulforaphane	5.70 ± 0.24	−0.99 ± 0.19*	−1.72 ± 0.26	$F = 2.52$, $df = 1, 58$, $P = .12$
	Placebo	5.83 ± 0.42	−0.29 ± 0.25	−1.37 ± 0.37	

[a]Sulforaphane N = 53 and placebo N = 24. Results are from mixed model analysis of change scores with baseline score and age, illness duration, and olanzapine equivalent dose as covariates and sex as factor. Overall treatment effect is overall group (sulforaphane vs placebo) effect of the difference score. *T* test values at specific time point between sulforaphane and placebo, significance: *$P < .05$, ***$P \leq .001$; for negative factor 24 weeks, $T = -3.39$, $df = 1, 58$, $P = .001$; for positive factor 24 wk, $T = -2.05$, $df = 1, 58$, $P = .05$.

Abbreviations: *d* = effect size, PANSS = Positive and Negative Syndrome Scale.

symptom scores in the current sample. Thus, the current sample had lower total and lower positive psychotic symptoms on the PANSS, and most of the participants had negative symptom scores higher than the positive symptom scores although they may not have met all criteria for the designation as predominantly negative symptom patients. The patients in this sample also likely received a much higher dose of SFN produced by the Extra Strength Avmacol SFN tablets used in this study (estimated SFN content ingested approximately 136 μmol/day) than in the previous SFN study (estimated SFN content ingested in the low-dose and high-dose SFN groups approximately 66 and 99 μmol/day). The treatment phase in the current study was slightly longer, and the main effect on decreasing negative systems was most prominent at the 24-week time point.

Two second-generation antipsychotic medications, cariprazine and amisulpride, have relatively strong evidence for having an effect on reducing negative symptoms in schizophrenia according to a recent meta-analysis.[6] The mean difference of approximately 3 points greater decrease in PANSS negative symptoms by SFN compared to placebo in this study is greater than the 1.46 difference in negative symptom decrease in the cariprazine vs risperidone study,[27] which could suggest a larger effect of SFN augmentation in our study. However, we cannot fully assess whether the 3-point difference in our study is clinically meaningful. In the Nemeth et al[27] study, the patients on cariprazine also showed improvement in CGI and in several functional outcome measures on the Personal and Social Performance Scale (PSP), whereas the current study showed no significant improvement in CGI-I or CGI-S scales, and we did not include additional measures for assessing functional outcomes. The fact that in the current study, global evaluation of improvement and total PANSS symptoms did not change more in the SFN group than in the placebo group, and the fact that positive

symptoms decreased slightly more in the placebo group raises potential questions about the overall clinical benefit of the high-dose SFN.

Side effects of SFN were low compared to placebo, and only drowsiness decreased less in the SFN group from baseline to week 24. Items on the TESS scale related to extrapyramidal symptoms (akathisia, tremor, motor symptoms, etc) showed no significant change compared to the placebo, and this supports the contention that the change in negative symptoms was not related to changes in extrapyramidal symptoms.

This study has several limitations that may influence the interpretation of results. Although we had procedures for blinding patients and evaluations of the placebo or SFN medication administration, we did not have a questionnaire evaluation assessing the effectiveness of the blinding. Our choice of only 3 time points for measurements of symptoms during the course of the 24-week study may be insufficient to capture full fluctuations in PANSS measures. We did not include quantitative scales measuring EPS symptoms (such as the Simpson-Angus Scale or Barnes Akathisia Scale) which would have allowed a better assessment of the changes in extrapyramidal symptoms and their relationship to changes in negative symptoms. A lack of functional outcome measures such as the PSP makes it more difficult to assess the clinical meaning of the statistically significant decrease in negative symptoms. Although all patients' medications remained unchanged during the trial, we did not collect precise data on doses of anticholinergic EPS medications on our patients. Moreover, the Avmacol Extra Strength SFN tablets also contain additional elements (Moringa leaves and β-glucans), so we cannot be certain that the total effect on decreasing negative symptoms was only due to SFN. Furthermore, we did not measure the concentration of SFN in plasma or blood cells. We did not control the diets of our participants, and it is possible that some participants consumed foods with broccoli extracts. However, the strong heating of the food before consumption, which is common in China, would likely destroy this SFN content in the diet.

CONCLUSIONS

The results of the current study showed that high-dose SFN had statistically significant effect in reducing negative symptoms in patients with schizophrenia. The changes induced by SFN in negative symptoms were not mediated by changes in depression or cognition changes as assessed from the PANSS 5-factor scale. However, the substantial clinical import of this decrease in negative symptoms is tempered by the lack of SFN's effect on measures of global improvement and the slightly greater decrease in positive symptoms in the placebo group. Additional studies are needed to confirm SFN's effects and its clinical treatment implications.

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Data Availability: The data and statistical analysis that support the findings of this study are available on request from the corresponding authors, primarily Dr Robert Smith.

Supplementary Material: Available at Psychiatrist.com.

References

1. McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia: an overview. *JAMA Psychiatry*. 2020;77(2):201–210.
2. Saha S, Chant D, Welham J, et al. A systematic review of the prevalence of schizophrenia. *PLoS Med*. 2005;2(5):e141.
3. Bobes J, Arango C, Garcia-Garcia M, et al. Prevalence of negative symptoms in outpatients with schizophrenia spectrum disorders treated with antipsychotics in routine clinical practice: findings from the CLAMORS study. *J Clin Psychiatry*. 2010;71(3):280–286.
4. Danion JM, Rein W, Fleurot O. Improvement of schizophrenic patients with primary negative symptoms treated with amisulpride. Amisulpride Study Group. *Am J Psychiatry*. 1999;156(4):610–616.
5. Carpenter WT Jr, Heinrichs DW, Wagman AM. Deficit and nondeficit forms of schizophrenia: the concept. *Am J Psychiatry*. 1988;145(5):578–583.
6. Krause M, Zhu Y, Huhn M, et al. Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci*. 2018;268(7):625–639.
7. Davidson M, Saoud J, Staner C, et al. Efficacy and safety of roluperidone for the treatment of negative symptoms of schizophrenia. *Schizophr Bull*. 2022;48(3):609–619.
8. Vanduchova A, Anzenbacher P, Anzenbacherova E. Isothiocyanate from broccoli, sulforaphane, and its properties. *J Med Food*. 2019;22(2):121–126.
9. Elkashty OA, Tran SD. Sulforaphane as a promising natural molecule for cancer prevention and treatment. *Curr Med Sci*. 2021;41(2):250–269.
10. Leonard BE, Schwarz M, Myint AM. The metabolic syndrome in schizophrenia: is inflammation a contributing cause? *J Psychopharmacol*. 2012;26(5 suppl):33–41.

11. Maes M, Bosmans E, Calabrese J, et al. Interleukin-2 and interleukin-6 in schizophrenia and mania: effects of neuroleptics and mood stabilizers. *J Psychiatr Res*. 1995;29(2):141–152.
12. Bloomfield PS, Selvaraj S, Veronese M, et al. Microglial activity in people at ultra high risk of psychosis and in schizophrenia: an [(11)C]PBR28 PET brain imaging study. *Am J Psychiatry*. 2016;173(1):44–52.
13. Zhang M, Zhao Z, He L, et al. A meta-analysis of oxidative stress markers in schizophrenia. *Sci China Life Sci*. 2010;53(1):112–124.
14. Das TK, Javadzadeh A, Dey A, et al. Antioxidant defense in schizophrenia and bipolar disorder: a meta-analysis of MRS studies of anterior cingulate glutathione. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;91:94–102.
15. Fraguas D, Díaz-Caneja CM, Ayora M, et al. Oxidative stress and inflammation in first-episode psychosis: a systematic review and meta-analysis. *Schizophr Bull*. 2019;45(4):742–751.
16. Shirai Y, Fujita Y, Hashimoto R, et al. Dietary intake of sulforaphane-rich broccoli sprout extracts during juvenile and adolescence can prevent phencyclidine-induced cognitive deficits at adulthood. *PLoS One*. 2015; 10(6):e0127244.
17. Hashimoto K. Recent advances in the early intervention in schizophrenia: future direction from preclinical findings. *Curr Psychiatry Rep*. 2019;21(8):75.
18. Hei G, Smith RC, Li R, et al. Sulforaphane effects on cognition and symptoms in first and early episode schizophrenia: a randomized double-blind trial. *Schizophr Bull Open*. 2022;3(1):sgac024.
19. Dickerson F, Origoni A, Katsafanas E, et al. Randomized controlled trial of an adjunctive sulforaphane nutraceutical in schizophrenia. *Schizophr Res*. 2021;231:142–144.
20. Wang J, Jiang Y, Tang Y, et al. Altered functional connectivity of the thalamus induced by modified electroconvulsive therapy for schizophrenia. *Schizophr Res*. 2020;218:209–218.
21. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
22. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare, Public Health Service; 1976.
23. Berk M, Ng F, Dodd S, et al. The validity of the CGI severity and improvement scales as measures of clinical effectiveness suitable for routine clinical use. *J Eval Clin Pract*. 2008;14(6):979–983.
24. Health NIM. TESS (treatment emergent symptom scale-write-in). *Psychopharmacol Bull*. 1985;21:1069–1072.
25. Davis JM, Chen N. The effects of olanzapine on the 5 dimensions of schizophrenia derived by factor analysis: combined results of the North American and international trials. *J Clin Psychiatry*. 2001;62(10):757–771.
26. Jiang J, Sim K, Lee J. Validated five-factor model of positive and negative syndrome scale for schizophrenia in Chinese population. *Schizophr Res*. 2013;143(1):38–43.
27. Nemeth G, Laszlovszky I, Czobor P, et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. *Lancet*. 2017; 389(10074):1103–1113.

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Supplementary Material

Article Title: Efficacy and Safety of Sulforaphane Added to Antipsychotics for the Treatment of Negative Symptoms of Schizophrenia

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Material

1. **Antipsychotic Drug Treatment of Participants**

Supplementary Table 1 - Drug Treatment of Participants in Study

Antipsychotic Drug	***Sulforaphane***	***Placebo***
Risperidone	29	8
Olanzapine	5	11
Aripiprazole	3	5
Amisulpride	17	1
Clozapine	1	2
Perphenazine	1	0
Paliperidone	1	0

Sulforaphane 53 participants. Placebo 24 participants. 13 participants were on 2 antipsychotic medications.

2. **Quality Control Procedures for Avmacol Extra Strength Tablets by Nutramax**.

At Nutramax Laboratories, Quality Control chemists qualify each lot of Avmacol Extra Strength by measuring the level of glucoraphanin and performing a conversion assay demonstrating presence of active myrosinase and promotion of production of sulforaphane that must meet our strict release criteria.

3. **Mediation Analysis**

Mediation analysis general description of procedure

In this paper, we examine whether the reduction in depression symptoms or the reduction in cognitive symptoms mediates the effects between add-on sulforaphane to antipsychotic treatment and the reduction of negative symptoms, using causal mediation analysis with a model-based approach employing an R package called Mediation. For each analysis, we fit two ordinary least squares regression models: the mediator model and the outcome model. To examine the mediation effect of the reduction in depression symptoms of add-on sulforaphane on the reduction of negative symptoms, we fit the models with the potential mediator as the change in depression symptoms, the exposure as the treatment group (i.e., sulforaphane or placebo), and the outcome as the change in negative symptoms. Similarly, for the

mediation effect of add-on sulforaphane's reduction in cognitive symptoms on the reduction of negative symptoms, we utilize the change in cognitive symptoms as the potential mediator, along with the exposure treatment group and the change in negative symptoms as the outcome. All models control for covariates or factors such as age, sex, illness duration, baseline scores of depression symptoms or cognitive symptoms, and olanzapine equivalent dose. We use the "mediate" function in both analyses to estimate the average causal mediation effect (ACME) and the average direct effect (ADE) of the fitted models.

4. Additional Analysis of TESS Side-Effects Scale

Supplementary Table 2. TESS Side-Effect Scale -Statistical Analysis of Difference Between Sulforaphane and Placebo Treatment Groups

TESS Item	**Treatment Week Score or Difference Score**			
	Baseline (Week 0)	**Week 12**	**Week 24**	**Difference Score Week 24 -Week 0**
Toxic Confusion	P=1.00	P=1.00	P=.53	P=.56
Excitement or Agitation	P=.20	P=.80	P=.86	P=.56
Affective depression	P=1.00	P=1.00	P=1.00	P=1.00
Increased Activity	P=1.00	P=1.00	P=1.00	P=1.00
Decreased Activity	P=.96	P=.61	P=1.00	P=.92
Insomnia	P=.70	P=.47	P=.18	P=.25
Drowsiness	**P=.015 P>S**	P=.53	P=.052	**P=.011 S>P**

Abnormal blood test	P=.14	P=1.00	P=1.00	P=.12
Abnormal Liver function test	P=1.00	P=1.00	P=1.00	P=1.00
Abnormal urine test	P=1.00	P=1.00	P=1.00	P=1.00
Myotonia	P=.09	P=.13	P=.53	P=.34
Tremor	P=.31	P=.15	P=.91	P=.37
Torsional movement	P=1.00	P=1.00	P=1.00	P=1.00
Akathisia	P=.39	P=.48	P=.37	P=.21
Dryness in Mouth	P=.59	P=.77	P=.22	P=.86
Stuffiness	**P=.017 P>S**	P=.17	**P=.003 P>S**	**P=.003 P>S**
Blurred vision	P=.93	P=.36	P=.46	P=.96
Constipation	P=.52	P=.78	P=.25	P=.70
Hypersalivation	P=.66	P=.99	P=.37	P=.65
Sweating	P=.44	P=1.00	P=.25	P=.51
Nausea and vomiting	P=.49	P=.99	P=.53	P=.86
Diarrhea	P=.39	P=.97	P=1.00	P=.88
Decreased Blood pressure	P=.11	P=.17	P=.53	P=.90
Dizziness and fainting	P=.27	P=.95	P=.83	P=.97

Tachycardia	P=.72	P=.97	**P=.029 P>S**	P=.091
Hypertension	P=1.00	P=1.00	P=1.00	P=1.00
Abnormal EKG	**P=.009 P>S**	**P=.044 P>S**	P=1.00	**P=.007 S>P***
Dermatological signs	P=.179	P=.48	**P=.007 P>S**	P=.28
Weight gain	P=.14	P=.38	P=.92	P=.17
Weight loss	P=.50	P=.21	P=.86	P=.64
Decreased appetite or anorexia	P=.91	P=.75	P=.37	P=.46
Headache	P=.59	P=.36	P=.46	P=.58
Tardive Dyskinesia	P=1.00	P=1.00	P=1.00	P=1.00
Obsessive Thinking	P=1.00	P=1.00	P=1.00	P=1.00
Compulsive Behavior	P=1.00	P=1.00	P=1.00	P=1.00
Others	P=1.00	P=1.00	P=1.00	P=1.00

Each P= is the probability of a difference between sulforaphane and placebo scores for the indicated item at the indicated time point analyzed by Mann-Whitney U test. The final column is the difference score from baseline at 24 weeks of treatment with significance of difference analyzed by Mann-Whitney U test. The tests analyzed all subjects who had values for the side effects item at the indicated time point(s). For the individual time points (week 0,12,24) if there was a significance difference (i.e. P≤.05), we examined the data distribution and ranks. P>S means Placebo had higher scores for the item than sulforaphane. There were no side-effect items at the individual time points where sulforaphane had higher side effect score than placebo. For the difference scores, P>S indicates that placebo had higher positive scores (less decrease from baseline) than sulforaphane. S>P indicates that sulforaphane had higher positive scores

(less decrease from baseline) than placebo. * However, for the item abnormal EKG change all sulforaphane subjects showed no change in EKG (all their change scores were "0"), but placebo subjects showed decreased scores in EKG abnormality. Placebo subjects had shown higher scores (more abnormal EKG) for this item at baseline (Week 0) compared to sulforaphane subjects.

5. Changes in Routinely Assessed Metabolic Lab Values During Sulforaphane Trial

Supplementary Table 3. Comparison of Routine Lab Metabolic Values in Patients Treated with Sulforaphane or Placebo at Three Time Points

Metabolic Measure	Time Point	Sulforaphane	Placebo	T-Test
Glucose	Baseline	5.04 ± 0.69	4.63 ± 0.73	T=2.337, df=69, P=.022
HDL	Baseline	1.22 ± 0.33	1.21 ± 0.32	T= .160, df=66, P=.87
LDL	Baseline	2.42 ± 0.62	2.23 ± 0.59	T= 1.180, df=66, P=. 24
Triglyceride	Baseline	1.33 ± 0.66	1.27 ± 0.76	T= .326, df=66, P= .75
Cholesterol	Baseline	4.20 ± 0.80	3.73 ± 0.68	T= 2.342, df=66, P= .022
Glucose	12 week	4.97 ± 0.78	4.74 ± 0.77	T= 1.122, df=62, P= .27
HDL	12 week	1.19 ± 0.28	1.34 ± 0.33	T= 1.847, df=63, P= .069
LDL	12 week	2.59 ± 0.62	2.49 ± 0.85	T= .467, df=63, P= .64
Triglyceride	12 week	1.34 ± 0.57	1.66 ± 1.20	T^w= 1.234, df= 27.5, P= .29
Cholesterol	12 week	4.36 ± 0.89	4.23 ± 0.95	T= .567, df=63, P= .57

Glucose	24 week	4.86 ± 0.52	4.76 ± 0.63	T= .624, df=63, P= .54
HDL	24 week	1.18 ± 0.21	1.21 ± 0.27	T= -.361, df=63, P= .72
LDL	24 week	2.41 ± 0.60	2.52 ± 0.79	T= -.612, df=63, P= .54
Triglyceride	24 week	1.29 ± 0.66	1.71 ± 1.13	T^w= -1.584, df=26.648, P= .13
Cholesterol	24 week	4.17 ± 0.86	4.19 ± 0.95	T= .080, df=63, P= .94

Each number is Mean ± S.D. expressed as mmol/L. T=T-test , T^w=welch t-test for unequal variances.

N's Sulforaphane - 42-47 at different time points Placebo = 21-24 at different time points.

Supplementary Table 4. Change in Routine Metabolic Parameters After 24 Weeks of Treatment With Sulforaphane or Placebo

Metabolic Measure	Sulforaphane Difference 24 weeks - Baseline	Placebo Difference 24 weeks - Baseline	T-Test
Glucose	-0.17 ± 0.58	+0.16 ± 0.76	T= -1.855, df= 59, P= .07
HDL	-0.04 ± 0.28	+0.04 ± 0.23	T= 1.091, df=57, P= .28
LDL	0.05 ± 0.56	0.35 ± 0.57	T= 1.981, df=57, P= .05
Triglycerides	0.07 ± 0.71	0.38 ± 0.60	T= 1.687, df=57, P= .10
Cholesterol	0.05 ± 0.72	0.52 ± 0.85	T= 2.221, df=57, P= .03