The Journal of Clinical Psychiatry

Supplementary Material

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

Authors: Jing Huang, MD; AnMei Chen, MS; Hua Jin, MD; Fangkun Liu, MD; Gangrui Hei, MD PhD; Ziwei Teng, MD; Jingmei Xiao, MD; Renrong Wu, MD PhD; Jingping Zhao, MD, PhD; John M. Davis, MD; Ping Shao, MD, PhD; and Robert C. Smith, MD, PhD

DOI Number: 10.4088/JCP.24m15272

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