Original Investigation

Rapid Improvement of Acute Schizophrenia Symptoms After Intravenous Sodium Nitroprusside
A Randomized, Double-blind, Placebo-Controlled Trial

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IMPORTANCE The treatment of schizophrenia remains a challenge, and the currently available antipsychotic drugs are slow acting and produce a number of adverse effects.

OBJECTIVE To examine the effectiveness and safety of a single intravenous administration of sodium nitroprusside (0.5 μg/kg/min for 4 hours) on the positive, negative, anxiety, and depressive symptoms in patients with schizophrenia.

DESIGN Single-center, randomized, double-blind, placebo-controlled trial performed from March 9, 2007, to March 12, 2009.

SETTING University teaching hospital in São Paulo, Brazil.

PARTICIPANTS Twenty inpatients aged 19 to 40 years with a diagnosis of schizophrenia who were in the first 5 years of the disease who are taking antipsychotics.

INTERVENTION Sodium nitroprusside administration.

MAIN OUTCOME MEASURES The 18-item Brief Psychiatric Rating Scale and the negative subscale of the Positive and Negative Syndrome Scale.

RESULTS After the infusion of sodium nitroprusside, a rapid (within 4 hours) improvement of symptoms was observed. The placebo and experimental groups had significant differences in the 18-item Brief Psychiatric Rating Scale total score and subscale scores, which persisted for 4 weeks after infusion.

CONCLUSIONS The results clearly show a therapeutic effect of sodium nitroprusside. If this drug is approved for routine clinical use in patients with schizophrenia, this discovery will be an important advance in the pharmacologic treatment of this devastating disorder.

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Schizophrenia is among the world's top 10 causes of disability-adjusted life-years[1] and, despite recent advances, continues to be a major treatment challenge. Although the classic theories involving dopamine neurotransmission continue to be explored, more recent evidence suggests that other abnormalities exist in schizophrenia, including dysregulation of the glutamate-nitric oxide–cyclic guanosine monophosphate (cGMP) network.[2] Indeed, clinical studies have demonstrated that individuals with schizophrenia exhibit abnormalities at various levels of this pathway; glutamatergic dysfunction in schizophrenia is a commonly accepted phenomenon and is reviewed extensively elsewhere,[3] and patients with schizophrenia have been found to exhibit reduced nitric oxide metabolites[4-6] and cGMP[7] compared with healthy controls. Furthermore, it is well established that abnormalities in nitric oxide and glutamate signaling are involved in the development of abnormal rodent behavior resembling psychoses because pharmacologic inhibition or genetic abolition of glutamate and nitric oxide synthesis and transmission leads to psychosis-like behavior.[8-10]

Strikingly, in preclinical experiments we observed that sodium nitroprusside completely abolished the behavioral effects and c-fos expression induced by phencyclidine,[9] a blocker of *N*-methyl-D-aspartate (NMDA) glutamate receptors that induces psychosis-like behavior. The precise mechanism by which sodium nitroprusside produces such marked effects in phencyclidine-treated animals remains unclear; however, in addition to generating nitric oxide in the brain and increasing cGMP production, it may also modulate NMDA receptor activity.[11,12] These preclinical observations led us to develop the research hypothesis that sodium nitroprusside may improve symptoms of schizophrenia.

The therapeutic merits of sodium nitroprusside were first described in the late 1800s,[13] and the drug has been in clinical use since 1929 for severe hypertension.[14] Sodium nitroprusside is currently commercially available for intravenous administration, although its use is somewhat rare because of the possibility of ferrocyanide accumulation after multiple doses.[15] In this proof-of-concept study, we investigated the effectiveness of low-dose sodium nitroprusside (0.5 µg/kg/min for 4 hours) administered intravenously to patients with schizophrenia taking currently available antipsychotics and measured changes in positive, negative, anxiety, and depressive symptoms during the following 4 weeks. Given that the dose of sodium nitroprusside used is the lowest dose in the recommended range in humans (dose rates of 0.5 to 10 µg/kg/min are recommended for the treatment of hypertension),[16] it was expected that sodium nitroprusside infusion in the current study would produce therapeutic benefits with minimal adverse effects.

Methods

Participants

Participants were recruited from community mental health facilities in Ribeirao Preto, Brazil, and surrounding towns, with a catchment population of approximately 500 000. The management teams of these mental health facilities were instructed to contact the psychiatric ward at the university hospital in Ribeirao Preto when any patients with a diagnosis of schizophrenia in an acute psychotic episode presented to their services and required inpatient admission. These patients were then transferred to the university hospital, where they underwent a psychiatric assessment to be considered for inclusion in the study as an inpatient. Patients who met all the inclusion criteria and none of the exclusion criteria (**Table 1**) were invited in the presence of a family member to participate in the study. The patient and the patient's family were given complete information on the study procedures and details. If the patient and the patient's family provided consent to participate in the study, the patient was admitted to 1 of the 2 inpatient beds reserved specifically for this study in the university hospital. If the patient and/or family member did not provide consent to participate in the study, inpatient admission and treatment as usual (based on usual clinical guidelines) continued until the patient was discharged from inpatient services.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
18 to 65 years of age	Relevant medical illness (renal, hepatic, or cardiac) in the opinion of the investigators
Diagnosis of schizophrenia using *DSM-IV*	Prior history of intolerance to sodium nitroprusside
Within first 5 years of diagnosis	Presence of a seizure disorder, not including clozapine-induced seizures
Competent and willing to give informed consent	Currently taking clozapine
Able to complete the required evaluations	Any change of psychotropic medications within the previous 6 weeks
Female participants willing to have a pregnancy test before treatment	Diagnosis of substance abuse (except nicotine or caffeine) or dependence within the last 3 months according to *DSM-IV* criteria
Patients in an acute psychotic episode requiring full-time hospitalization according to clinical referral by the relevant mental health service	Pregnant or breastfeeding
	Used illicit substances or alcohol in the past 3 months
	History of any major medical illness

Twenty inpatients (14 men and 6 women; age range, 19-40 years) with schizophrenia were randomly assigned to receive either sodium nitroprusside or placebo. Participants underwent physical examination, electrocardiography, and blood and urine toxicologic screening.

Study Procedure

The experiment was a double-blind, placebo-controlled trial and was approved by the Research Ethics Committee of the Clinical Hospital of Ribeirao Preto Medical School, University of São Paulo. After a 48-hour period with no medication change, patients were randomly assigned using a pseudorandomization process to either the sodium nitroprusside or placebo group (allocation ratio, 1:1) and administered a single infusion. The randomization code was generated by a research assistant at the university hospital. A fully trained anesthetist (J.A.) and a cardiothoracic surgeon (P.R.E.) were present during each infusion to ensure safety during the experiment. Sodium nitroprus-

side was administered as an infusion of 0.5 μg/kg/min for 4 hours. The placebo was a 5% glucose solution that was infused over the same length of time. Experimental infusion standards and conditions were identical for both infusion (sodium nitroprusside and placebo) groups, and both patients and front-line study staff were masked to the assigned intervention.

Every hour for the 4 hours during infusion, the participant was interviewed by the same psychiatrist using the 18-item Brief Psychiatric Rating Scale (BPRS-18) and the negative subscale of the Positive and Negative Syndrome Scale (PANSS-negative subscale). The interrater correlation among the raters was 0.71, indicating sustained reliability throughout the study. Physiologic cardiovascular and pulmonary measures were also recorded every hour to assess the safety of sodium nitroprusside throughout the infusion. After the infusion was complete and the patient was disconnected from the monitoring equipment and the venous access was removed, the patient was asked how he/she felt during the infusion and if he/she experienced any unexpected bodily or psychological sensation or discomfort throughout the session. The patient was encouraged to ask questions related to the study procedures and to talk freely about anything he/she deemed to be important for the study or their treatment. Participants were allowed to rest 1 hour after the debriefing with the experimenter. Patients continued to be followed up in the inpatient unit at the university hospital. No changes in top-up medications were permitted for 48 hours after infusion, and no changes in antipsychotic drugs were permitted for 7 days after infusion. Participants remained as inpatients for the duration of the study (4 weeks after infusion).

Outcome Measures

The Structured Clinical Interview for *DSM-IV* (SCID) was used to confirm the diagnosis of schizophrenia. The BPRS-18 (Bech's version) and PANSS-negative subscale were used to measure the primary outcomes of this study (efficacy). The structured Udvalg for Kliniske Undersogelser (UKU) rating scale and the Abnormal Involuntary Movement Scale (AIMS), together with some physiologic measures, were used to assess the secondary outcomes of this study (safety and tolerability).

The BPRS-18 is one of the most widely used, validated, and sensitive scales in schizophrenia research. It is relatively short and easy to use and is appropriate for inpatient setting assessments.[17-19] Therefore, it was used to assess changes in severity of psychopathologic conditions. The scale used was Bech's version, which has 18 items with each item scored on a 5-point scale, which includes the following: 0, not present; 1, very mild or of doubtful presence; 2, present in mild degree; 3, present in moderate degree; and 4, present in severe or extreme degree.

Factor analysis has revealed that certain related items of the BPRS-18 can be grouped in clusters of symptoms, which present data regarding different dimensions of symptoms in schizophrenia. This approach acknowledges not only that schizophrenia symptoms are heterogeneous but also that the BPRS-18 is a test for the efficacy of pharmacologic intervention across all such different schizophrenia symptoms.[20] The 4 symptom subcategories are thinking disorder, anxiety-depression, withdrawal-retardation, and activation. The thinking disorder subscale is made up of suspiciousness, unusual thought content, hallucinations, conceptual disorganization, hostility, and exaggerated self-esteem, and the anxiety-depression subscale consists of self-deprecation and guilt feelings, anxiety (psychic), depressive mood, and somatic concern. The withdrawal-retardation subscale consists of psychomotor retardation, blunted or inappropriate affect, emotional withdrawal, disorientation and confusion, uncooperativeness, and specific motor disturbances, whereas the activation subscale consists of specific motor disturbances, anxiety (somatic), psychomotor agitation, and exaggerated self-esteem.

The PANSS is commonly used in clinical trials. It includes 7 positive subscale items, 7 negative subscale items, and 16 general psychopathology items.[21] The PANSS-negative subscale is designed to detect and rate symptoms that in schizophrenia represent a diminution or loss of normal functions. These symptoms include blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. The PANSS uses a 7-point severity scale (1, absent; 2, minimal; 3, mild; 4, moderate; 5, moderate-severe; 6, severe; 7, extreme). The PANSS-negative subscale was used to assess negative symptoms.

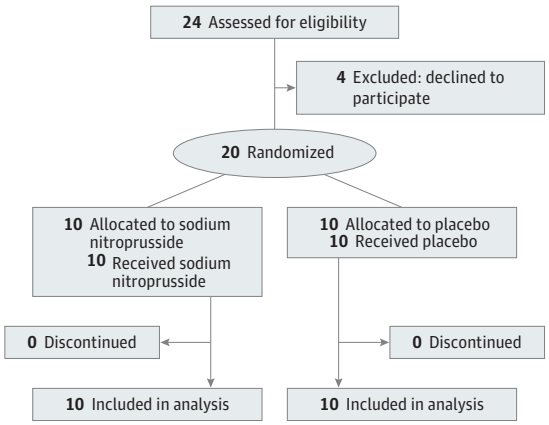
Safety and tolerability of the drug treatment were closely monitored throughout the study period by the clinical team, and cardiac function using an automated heart monitor (model 2020, Dixtal Medical), electrocardiography, blood pressure, and blood oxygen saturation levels were measured hourly throughout the experimental infusion sessions. The structured UKU rating scale[22] and the AIMS[23] were used to prospectively assess the treatment adverse effects during this study.

Statistical Analysis

Sample size determination was based on the assumption that for both the BPRS-18 and PANSS, a difference of 8 points, corresponding to an effect size of approximately 1.5 SDs between the placebo and treatment groups, would represent a clinically significant response. Calculations were based on the assumption of a 2-sample *t* test with independent groups and the probability of a type I error set at 0.05. Considering a 2-sided alternative hypothesis and a desired power value of 0.8, calculations indicated that a minimum of 8 individuals were required in each group.

An estimate of interrater reliability was obtained by 2 psychiatrists (J.P.M.d.O. and another psychiatrist). Training by the senior psychiatrist (J.E.C.H.) involved first familiarizing the other psychiatrist with the scales and related literature. Practice sessions were conducted in a room equipped with a unidirectional mirror where the roles of the observer and interviewer were alternated between sessions. After each practice session, the results and concerns were reviewed. Five interviews were conducted with inpatients from the psychiatric unit of the university hospital where the study was conducted. Rater agreement levels were above 75%, which is regarded as satisfactory for the use of these scales, and an interclass correlation coefficient of 0.71 between raters was obtained, indicating sustained reliability throughout the study. There were 3

Figure 1. Flowchart



Progress of the study participants throughout the study.

Table 2. Clinical and Demographic Characteristics[a]

Characteristic	Sodium Nitroprusside (n = 10)	Placebo (n = 10)
Age, mean (SD), y	25.5 (6.7)	25.6 (3.9)
Years of education, mean (SD)	7.9 (2.1)	8 (2.6)
Length of illness, mean (SD), mo	34.2 (27.6)	38.4 (31.9)
No. of hospitalizations, mean (SD)	1.5 (0.70)	1.3 (0.46)
Sex, No. (%)		
Male	7 (70)	7 (70)
Female	3 (30)	3 (30)
Marital status, No. (%)		
Single	10 (100)	9 (90)
Married	0	1 (10)

[a] There were no statistical differences in age, years of education, length of illness, number of hospitalizations, sex, and marital status of patient groups receiving sodium nitroprusside or placebo.

raters in all (J.P.M.d.O., J.E.C.H., and another rater), with 2 raters conducting the SCID and 2 raters conducting the symptom rating scales (therefore, 1 rater conducted both the SCID and the symptom rating scales). Clinical, demographic, and behavioral data were analyzed using SPSS statistical software, version 17.0 (SPSS Inc). For the clinical and demographic data, the χ^2 test was used when data were categorical, and independent 2-tailed *t* tests were used when data were continuous. For the BPRS-18 total score and subscores from its 4 subscales (anxiety-depression, activation, withdrawal-retardation, and thinking disorder) and the PANSS-negative subscale scores, separate repeated-measures analyses of variance were performed, with treatment (sodium nitroprusside or placebo) and time (every point of evaluation) as factors. If the analyses of variance were significant, an independent 2-tailed *t* test or a paired 2-tailed *t* test was used.

Results

Patient Characteristics

Patient recruitment and all study procedures occurred from March 9, 2007, to March 12, 2009. Twenty-four individuals initially agreed to participate and were assessed for eligibility; 4 individuals subsequently refused to participate, and 20 individuals were randomized to receive either sodium nitroprusside or placebo. All participants who were randomized completed the study procedures, and all patient data from randomized participants were included in the final analysis (**Figure 1**). The clinical and demographic data for the patients are given in **Table 2**, and medications present at the time of drug treatment are listed in **Table 3**. No significant differences in group characteristics were found.

Schizophrenia Symptoms

The statistical comparison between sodium nitroprusside and placebo revealed a rapid and statistically significant effect of sodium nitroprusside on BPRS-18 total score. This difference was evident from the second hour and persisted for the duration of the 4-week observation period (**Figure 2**). The BPRS-18 total score revealed a significant effect for treatment ($F_{1,18}$ = 12.91; P < .001), time ($F_{15,270}$ = 12.89, P < .001), and interaction between treatment and time ($F_{15,270}$ = 9.42, P < .001). The significant effect of sodium nitroprusside was not driven by only a small number of participants; **Figure 3** demonstrates that within the first 48 hours after infusion, individual BPRS-18 total scores were reduced in most participants who received sodium nitroprusside but not in participants receiving placebo.

Similar statistical differences between sodium nitroprusside and placebo were observed for the subscales of the BPRS-18, indicating improvement of a wide spectrum of symptoms of schizophrenia. Subscale scores for the placebo and treatment group are shown in **Figure 4**.

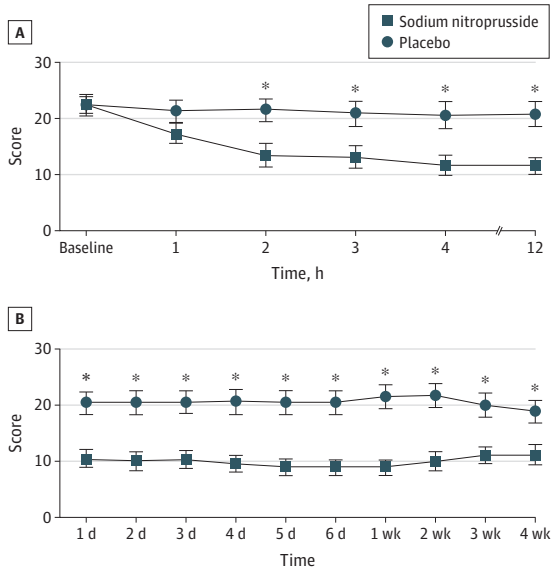
The score differences between the sodium nitroprusside and placebo groups on the thinking disorder subscale were obvious 3 hours after infusion and were still marked at 28 days after infusion, with sodium nitroprusside scores approximately half those of the placebo group. There was a significant effect for treatment ($F_{1,18}$ = 8.09, P = .01), time ($F_{15,270}$ = 15.96, P < .001), and interaction ($F_{15,270}$ = 6.32, P < .001). The anxiety-depression subscale results were similar to those of the thinking disorder subscale and revealed significant effects for treatment ($F_{1,18}$ = 4.73, P = .04), time ($F_{15,270}$ = 3.17, P < .001), and interaction ($F_{5,270}$ = 2.34, P < .001). Analysis of the withdrawal-retardation subscale did not reveal a significant effect for treatment; however, significant effects were observed for interaction ($F_{15,270}$ = 8.46, P < .001) and time ($F_{15,270}$ = 6.06, P < .001). Differences between the 2 groups were less obvious in the activation subscale. A significant difference was only observed for time ($F_{15,270}$ = 3.38, P < .001).

Analysis of the PANSS-negative subscale scores between the sodium nitroprusside and placebo groups also revealed significant differences. Significant effects were observed for interaction ($F_{15,270}$ = 7.25, P < .001), treatment ($F_{1,18}$ = 8.2, P < .001), and time ($F_{15,270}$ = 6.53, P < .001). **Figure 5** shows that, in contrast to the placebo group, the sodium nitroprusside group improved rapidly after infusion.

Table 3. Antipsychotic Drug and Dosage for Each Patient (Which Remained Unchanged for 48 Hours Before and 48 Hours After the Infusion of Sodium Nitroprusside or Placebo)

Patient No.	Medication on Day 1
Sodium nitroprusside group	
1	Risperidone, 8 mg, and levomepromazine, 75 mg
2	Olanzapine, 10 mg
3	Chlorpromazine, 300 mg
4	Chlorpromazine, 500 mg
5	Quetiapine fumarate, 150 mg
10	Ziprasidone, 240 mg
12	Quetiapine, 400 mg
13	Haloperidol, 7.5 mg
14	Aripiprazole, 7.5 mg
16	Haloperidol, 5 mg
Placebo group	
6	Risperidone, 2 mg
7	Haloperidol, 2.5 mg
8	Haloperidol, 5 mg
9	Risperidone, 4 mg
11	Haloperidol, 5 mg
15	Olanzapine, 30 mg
17	Risperidone, 3 mg
18	Risperidone, 4 mg
19	Olanzapine, 10 mg
20	Olanzapine, 10 mg

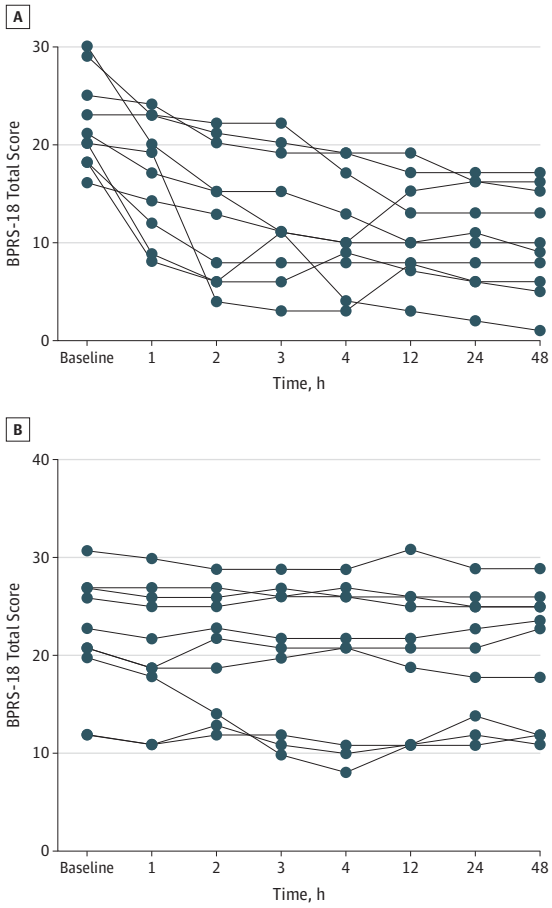
Figure 2. Mean Total 18-Item Brief Psychiatric Rating Scale Scores



A, Scores during the first 12 hours; B, scores at 4 weeks. Asterisks indicate statistically significant *P* values as given in the text; error bars, SEMs.

Overall, the significant interaction and time effects for the total and subscale scores of the BPRS-18 and PANSS-negative subscale can be attributed to the rapid improvement in the scores of the sodium nitroprusside group within the first 4 hours after infusion.

Figure 3. Individual Total 18-Item Brief Psychiatric Rating Scale Scores



Individual 18-item Brief Psychiatric Rating Scale (BPRS-18) total scores during the first 48 hours. A, Sodium nitroprusside group; B, placebo group.

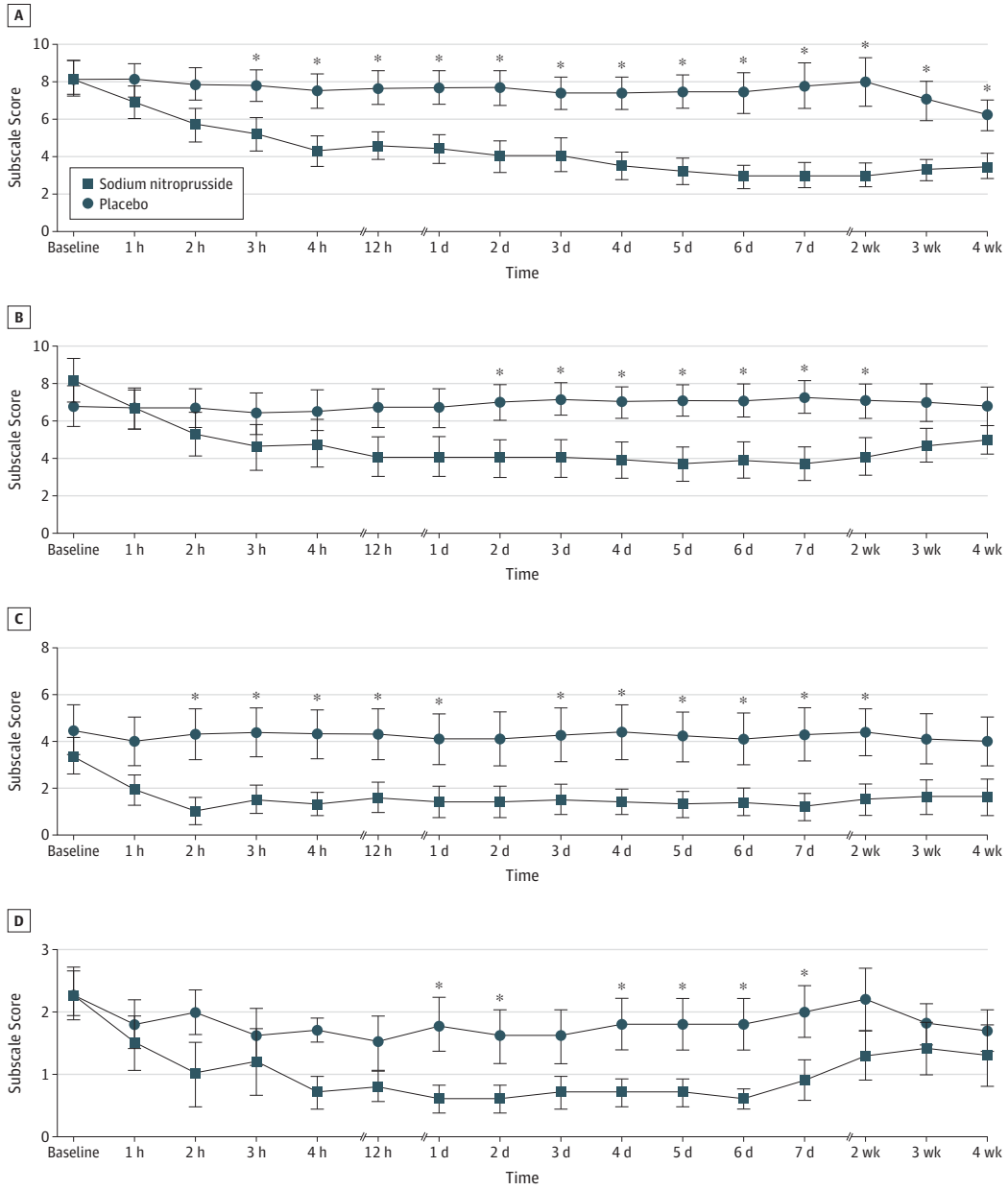
Safety

No statistically significant differences were found between the sodium nitroprusside and placebo groups in any of the physiologic parameters evaluated (systolic blood pressure, diastolic blood pressure, blood oxygen saturation level, and heart rate) at baseline and 60, 120, 180, and 240 minutes after injection (**Figure 6**).

Results for the AIMS in the pretreatment and posttreatment conditions revealed no differences between the sodium nitroprusside and placebo groups (data not shown); all participants received a rating of 0 (none) for all items with the exception of the 2 dental items, which received a rating of 2 (mild).

Results for the UKU indicated that, before treatment, 1 participant in the sodium nitroprusside group had 2 ratings of severe in the psychiatric items, corresponding to "asthenia/lassitude/increased fatigability" and "emotional indifference," and in the neurologic items received a rating of severe corresponding to "hypokinesia/akinesia"; on posttreatment testing these 3 ratings improved to mild. In the placebo group, 1

Figure 4. Mean 18-Item Brief Psychiatric Rating Scale Subscale Scores



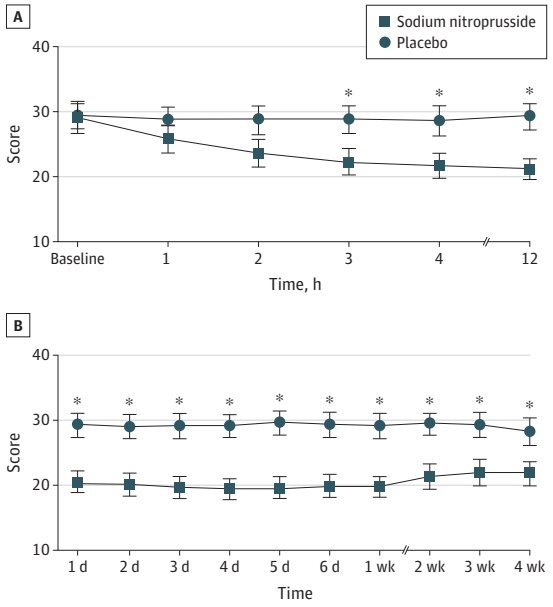
Mean 18-item Brief Psychiatric Rating Scale (BPRS-18) subscale scores during the first 48 hours and at 4 weeks. A, Thinking disorder scores; B, withdrawal-retardation scores; C, anxiety-depression scores; and D, activation scores. Asterisks indicate statistically significant *P* values as given in the text; error bars, SEMs.

participant had a severe rating in the psychiatric items, corresponding to "tension/inner unrest," which did not change after treatment. For the item categories corresponding to mild and moderate effects, the paired *t* test comparisons of the pretreatment and posttreatment means revealed statistically significant differences for the sodium nitroprusside group in the psychiatric category. These differences were associated with an improvement in the number of adverse effects as indicated by the ratings to the item categories of mild (t_9 = 4.07, P < .001) and not or doubtfully present (t_9 = 6.13, P < .001).

No patients in the study required any rescue psychotropic or medical treatment. After the infusion, all patients were transferred to their treatment-as-usual inpatient care for at least the duration of the study. Changes to antipsychotic drug regimens were permitted after 7 days. Fewer changes were noted in the sodium nitroprusside group compared with the placebo group; for patients receiving sodium nitroprusside, 3 participants did not require any medication change (compared with none of the patients in the placebo group), 5 participants had their antipsychotic dose increased (compared with 7 in the placebo group),

and 2 participants had their antipsychotic regimen changed (compared with 3 in the placebo group).

Figure 5. Mean Positive and Negative Syndrome Scale Negative Subscale Scores



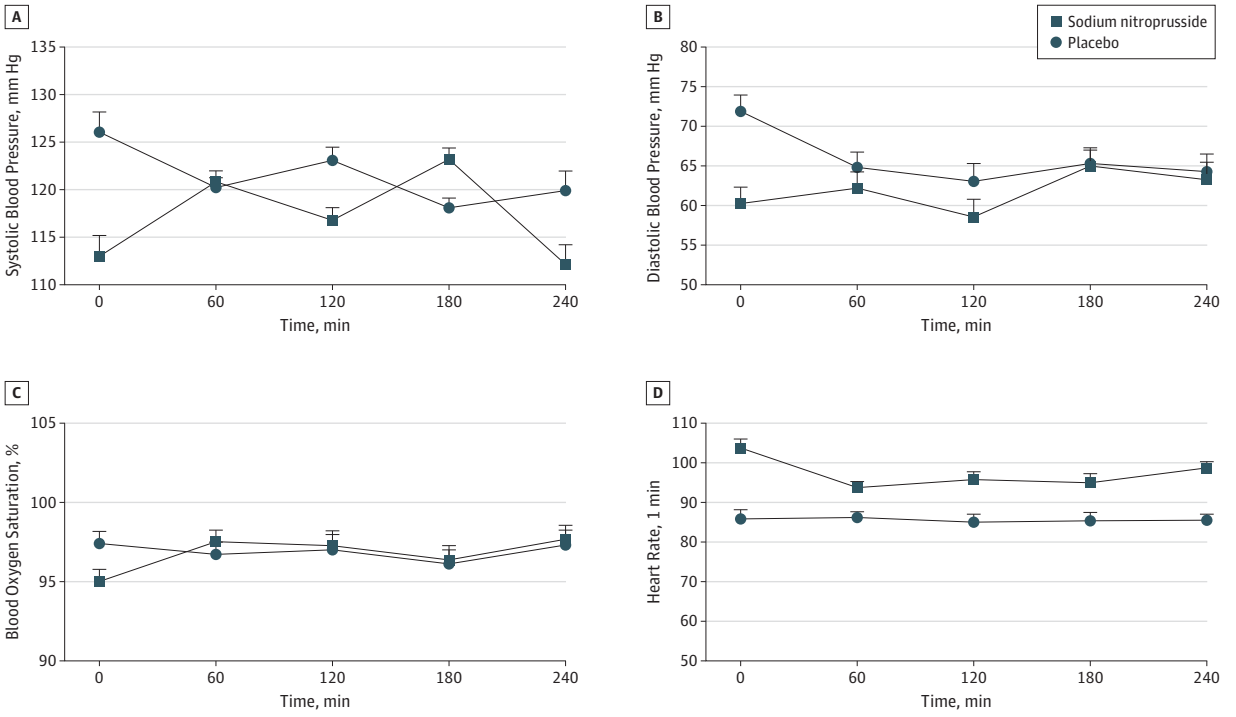
A, Scores during the first 12 hours; B, scores at 4 weeks. Asterisks indicate statistically significant *P* values as given in the text; error bars, SEMs.

Discussion

This randomized, placebo-controlled trial has for the first time demonstrated a safe, rapid (within hours), and long-lasting (several weeks) improvement of positive, negative, anxiety, and depressive symptoms in patients with schizophrenia after a single intravenous injection of sodium nitroprusside. These findings are important given that the medications currently available to patients are often ineffective in treating an acute psychotic episode in a reasonable time frame (if at all) without significant adverse effects. The improvements were observed across a number of symptom rating scales and subscales, suggestive of a robust therapeutic effect.

The antipsychotic mechanism of action of sodium nitroprusside is unclear at this time. The vasomotor effect of sodium nitroprusside could promote increased cerebral perfusion or some other vascular effect modulated by nitric oxide; however, this possibility is unlikely because a clear effect of sodium nitroprusside on the vascular system was not observed in the physiologic measures. This finding was not surprising because the dose used in this study was the minimum dose required for sodium nitroprusside to lower blood pressure in hypertensive patients, and it is well established that in normotensive individuals much higher doses of sodium nitroprusside are needed to lower blood pressure than for hypertensive patients. Because none of the participants in this

Figure 6. Physiologic Cardiovascular and Pulmonary Measures During the Infusion



No significant changes were determined that would require clinical intervention, including systolic blood pressure (A), diastolic blood pressure (B), blood oxygen saturation (C), or heart rate (D). Error bars indicate SEMs.

study were hypertensive, a higher dose than that used here would likely be required to show measurable vascular changes. In addition to this, the vasodilation properties of sodium nitroprusside are reported to last up to 10 minutes after infusion is stopped,[16] whereas the beneficial effects of sodium nitroprusside in this study remained for up to 28 days after the infusion was completed. A pharmacokinetic interaction between sodium nitroprusside and the antipsychotic drugs used by the patients is unlikely to contribute to the clinical benefits observed because the metabolic pathways of sodium nitroprusside and antipsychotic drugs differ.[24] Moreover, even if an interaction were to occur, it would not explain why the effect occurred regardless of the antipsychotic the patient was prescribed. A more plausible explanation for the observed effect of sodium nitroprusside is related to its capacity to modulate the NMDA-nitric oxide-cGMP pathway. The NMDA receptor is believed to be dysfunctional in schizophrenia,[3] and the modulation of NMDA receptor activity has been reported to exert therapeutic effects.[25] The level of cGMP was reported to be reduced in the cerebrospinal fluid of patients with schizophrenia relative to controls,[7] and treatment with antipsychotic medications was shown to increase cerebrospinal fluid cGMP relative to premedication levels.[26,27] Metabolites of nitric oxide have been reported to be reduced in the plasma[5] and cerebrospinal fluid[4] of patients with schizophrenia relative to healthy controls, and nitric oxide and its metabolites appear to be inversely correlated with the severity of negative symptoms.[6,28] A recent report by Brennand et al[29] clearly demonstrated that the NMDA-nitric oxide pathway via the connecting PSD-95 protein is crucially involved in schizophrenia. Sodium nitroprusside generates nitric oxide, increases cGMP production, and has also been suggested to exert modulatory effects on the NMDA receptor independent of its ability to generate nitric oxide[11,12]; as such, modulation of the NMDA-nitric oxide-cGMP pathway, perhaps even at multiple levels simultaneously, may underlie the clinically beneficial effects observed in this study. Further research is needed to determine how this pathway may be involved in schizophrenia and whether modulation of this pathway (or another, as yet unknown mechanism) underlies the therapeutic effect of sodium nitroprusside.

Although the current study design was blinded and placebo controlled, the results should be interpreted as preliminary at this time because of several limitations. The number of participants in the study was small, and the participants were relatively early in their disease course; further studies should examine the efficacy of sodium nitroprusside in more chronically ill patients. Furthermore, the BPRS-18 is not generally used for rapid serial assessment, although this scale was determined to be the most appropriate scale to use in this context because of its ability to capture a broad spectrum of schizophrenia symptoms. The major drawback to the current study is that we cannot definitely demonstrate the efficacy of sodium nitroprusside in patients with schizophrenia for longer than 48 hours because changes to supplemental medications (eg, benzodiazepines and analgesics) were permitted after 48 hours and changes to antipsychotics were permitted after 7 days, thereby introducing uncertainty to the antipsychotic effects of sodium nitroprusside alone at later time points; this undoubtedly needs to be studied in future work. Despite minimal changes to supplemental medications and modest changes to antipsychotic regimens (that were comparable between treatment groups), the BPRS-18 total and PANSS-negative subscale scores remained significantly improved 4 weeks after infusion in the sodium nitroprusside group relative to baseline but not in placebo-treated patients. Furthermore, scores on the thinking disorder, anxious-depressive, and withdrawal-retardation subscales remained significantly improved several weeks after sodium nitroprusside infusion relative to baseline, and scores on the activation scale became significantly different between treatment groups 24 hours after infusion and remained significantly improved for the first 7 days after infusion. On the basis of these promising observations, it can be strongly inferred that sodium nitroprusside is indeed effective in reducing symptoms for a clinically significant period, and future studies should confirm this hypothesis.

Despite the modest sample size and relatively short follow-up after sodium nitroprusside infusion before the permission of medication changes, these preliminary results are exciting in terms of effectiveness of the drug. Sodium nitroprusside administration significantly and rapidly improved the positive, negative, anxiety, and depressive symptoms of schizophrenia. At the dose tested, sodium nitroprusside did not produce any adverse reactions, which was not surprising because sodium nitroprusside has previously been shown to be safe in healthy volunteers[30-33] (which attests to a good safety profile for this drug when properly administered). In addition, there did not appear to be any negative interactions with any of the medications that were being taken by any patients at the time of the study. Approval of sodium nitroprusside infusions for the treatment of schizophrenia could significantly improve patient care in emergency and acute care settings, and the future development of alternative formulations more conducive to long-term use could be effective for maintenance therapy. Studies aiming to understand the mechanism of action of sodium nitroprusside could also lead to the development of sodium nitroprusside analogs as novel antipsychotic drugs. For the next step, further confirmatory studies, including ones in which a broader range of patients are followed up for longer than 48 hours with no other medication change, are required.

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