



A selective neurokinin-1 receptor antagonist in chronic PTSD: A randomized, double-blind, placebo-controlled, proof-of-concept trial

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A Selective Neurokinin-1 Receptor Antagonist in Chronic PTSD: a Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Trial

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Abstract

The substance P-neurokinin-1 receptor (SP-NK₁R) system has been extensively studied in experimental models of stress, fear, and reward. Elevated cerebrospinal fluid (CSF) SP levels were reported previously in combat-related PTSD. No medication specifically targeting this system has been tested in PTSD. This proof-of-concept randomized, double-blind, placebo-controlled trial evaluated the selective NK₁R antagonist GR205171 in predominately civilian PTSD. Following a 2-week placebo lead-in, 39 outpatients with chronic PTSD and a Clinician-Administered PTSD Scale (CAPS) score ≥ 50 were randomized to a fixed dose of GR205171 (N=20) or placebo (N=19) for 8 weeks. The primary endpoint was mean change from baseline to endpoint in total CAPS score. Response rate ($\geq 50\%$ reduction in baseline CAPS) and safety/tolerability were secondary endpoints. CSF SP concentrations were measured in a subgroup of patients prior to randomization. There was significant improvement in the mean CAPS total score across all patients over time, but no significant difference was found between GR205171 and placebo. Likewise, there was no significant effect of drug on the proportion of responders [40% GR205171

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vs. 21% placebo ($p=0.30$)]. An exploratory analysis showed that GR205171 treatment was associated with significant improvement compared to placebo on the CAPS hyperarousal symptom cluster. GR205171 was well-tolerated, with no discontinuations due to adverse events. CSF SP concentrations were positively correlated with baseline CAPS severity. The selective NK₁R antagonist GR205171 had fewer adverse effects but was not significantly superior to placebo in the short-term treatment of chronic PTSD. ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00211861) Identifier: NCT 00211861, NCT 00383786)

Keywords

NK₁; substance P; PTSD; clinical trial; randomized

INTRODUCTION

Despite the enormous societal impact of posttraumatic stress disorder (PTSD), few pharmacotherapies are associated with consistently robust improvements in all three symptom domains (i.e., reexperiencing, avoidance/emotional numbing, and hyperarousal). U.S. practice guidelines have endorsed cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) as first-line treatments (Benedek et al., 2004). However, the only two U.S. Food and Drug Administration (FDA)-approved medications, sertraline and paroxetine, have modest effect sizes (Stein et al., 2006), and a minority of patients in short-term clinical trials achieve remission (Mathew et al., 2009). Moreover, SSRI medication may provide limited benefit in subgroups of PTSD patients such as combat veterans (Benedek et al., 2004; Friedman et al., 2008). In light of these findings, coupled with substantial evidence for the efficacy of exposure-based psychotherapies, recent influential reports have recommended that pharmacotherapy should not be routinely used as a first-line treatment for PTSD due to lack of sufficient evidence for efficacy (National Institute for Clinical Excellence (NICE), 2005; Committee on Treatment of Posttraumatic Stress Disorder (Institute of Medicine), 2007). Thus, it is imperative to identify novel therapies that improve upon and are mechanistically distinct from existing pharmacological treatments.

The neurotransmitter substance P (SP) together with its preferred neurokinin₁ receptor (NK₁R) may serve important roles in the modulation of stress and anxiety (Ebner and Singewald, 2006). NK₁R are broadly distributed in neural regions implicated in stress responsivity, including the hypothalamus, basolateral amygdala, hippocampus, nucleus accumbens, and frontal cortex (Gobert et al., 2009; Hietala et al., 2005; Nakaya et al., 1994). In preclinical experiments, immobilization stress induced activation of NK₁R by SP in the amygdala was associated with increased anxiety-like behavior (Ebner et al., 2004), whereas pharmacological or genetic inactivation of NK₁R inhibited the associated behavioral responses in several models (George et al., 2008; Holmes et al., 2003; Varty et al., 2002; Santarelli et al., 2001).

Few clinical studies have investigated the SP-NK₁R system in stress-related anxiety disorders. Significant elevations in SP concentrations in cerebrospinal fluid (CSF) were found in male combat veterans with PTSD, as well as phasic increases in SP following symptom-provocation (Geraciotti et al., 2006). Patients with panic disorder studied with positron emission tomography and [¹⁸F]SPA-RQ showed widespread reduction (12-21%) of NK₁R binding in multiple brain regions, potentially consistent with repeated release of SP (Fujimura et al., 2009). Fear provocation in phobic patients was associated with reduced NK₁R availability in the amygdala, indicating increased release of endogenous SP (Michelgard et al., 2007). A pharmaco-fMRI study with the NK₁R antagonist LY686017

found reductions in BOLD response to aversive images in two brain regions (inferior frontal cortex and insula) relevant to anxiety and reward regulation (George et al., 2008). Finally, the selective NK₁R antagonist GR205171 reduced state anxiety, distress, and heart rate during a stressful public speaking task, and attenuated amygdala responses to social threats in patients with social phobia (Furmark et al., 2005).

In this proof-of-concept, 8-week, randomized, double-blind, placebo-controlled trial, we tested the hypothesis that the NK₁R antagonist GR205171 would be effective in reducing symptoms associated with chronic PTSD. The relationship between CNS concentrations of SP and symptom severity was also explored.

EXPERIMENTAL PROCEDURES

Study Design

This trial was conducted at 2 U.S. sites, and used a fixed dose, randomized, double-blind, parallel-arm, placebo-controlled design comparing GR205171 (5 mg/day) with placebo in chronic PTSD. The study was funded by the National Institutes of Health, and designed in collaboration with the drug manufacturer, GlaxoSmithKline. Enrollment began in September 2005 and ended in December 2008. Initial eligibility was ascertained by telephone screening. Eligible patients underwent a 2-week placebo lead-in period during which a subgroup received a lumbar puncture (LP), detailed below. After the lead-in period, patients who continued to fulfill eligibility criteria were randomly assigned in a 1:1 ratio to receive either placebo or GR205171 treatment for 8 weeks. The randomization scheme was generated by a Mount Sinai School of Medicine (MSSM) pharmacist who assigned individuals across both sites using a permuted-block 1:1 randomization list. Patients were assessed weekly for efficacy and side effects, including weekly blood tests of hepatic function. All study personnel, investigators, and patients were blinded to treatment assignment until completion of the entire study.

Participants

Patients (aged 18-65) were recruited from media advertisement (86%) or clinician referral (14%). Diagnoses were made with the Structured Diagnostic Interview for DSM-IV performed by an experienced research clinician, along with an independent interview by a psychiatrist. A primary diagnosis of chronic PTSD, signifying an illness duration ≥ 3 months, was required. A score ≥ 50 on the Clinician Administered PTSD Scale (CAPS) (20), and ≥ 4 on the Clinical Global Impression (CGI) Scale severity item (Guy, 1976) was required at screening and baseline. The Life Events Checklist (Gray et al., 2004) was used to identify traumatic stressors; the event identified as causing the most distress or generating the PTSD symptoms was the focus for CAPS ratings. Comorbid DSM-IV depressive disorders (specifically, major depressive disorder, dysthymic disorder, and depressive disorder NOS) and anxiety disorders (except obsessive-compulsive disorder) were permitted if the onset of illness post-dated the traumatic event and was not the primary focus of clinical attention. Patients were required to be free of all psychotropic medications for at least 1 week before starting placebo lead-in (5 weeks for fluoxetine). Exclusionary criteria included bipolar disorder, schizophrenia, schizoaffective disorder, or psychotic symptoms; current anorexia or bulimia nervosa; alcohol or drug abuse or dependence within the past 3 months (except nicotine); unstable medical or neurological illness; and for females of child-bearing potential, pregnancy. Physical and neurological examination, vital signs, weight, ECG, standard blood tests, urinalysis, and urine toxicology confirmed absence of unstable medical illnesses and recent illicit substance use. The protocol was approved by the Institutional Review Boards at MSSM and the Intramural Research Program at the National Institutes of Mental Health (NIMH-IRP), and all participants provided written informed

consent before trial entry. The study was monitored by a NIMH Data Safety and Monitoring Board. Participants received compensation of \$20 for each completed assessment.

Experimental Drug Protocol

Patients completing the 2-week placebo lead-in period and who continued to meet all eligibility criteria (including CAPS ≥ 50) entered the 8-week double-blind treatment protocol and were randomly assigned to GR205171 (5 mg capsule) or identical-appearing placebo capsule. This dose was selected because of repeated dose safety data in healthy volunteers and patients with social phobia (Furmark et al., 2005; GSK, data on file). Each week, participants received a pill bottle containing 10 capsules. At the following visit, patients returned the pill bottle, with the number of remaining capsules documented for adherence testing. Patients were assigned to study medication for 8 successive weeks or until drop-out. Participants were discontinued from the study if there was an increase of greater than 30% in CAPS scores from baseline at any assessment. In addition to weekly ratings, participants were evaluated by a study psychiatrist, who conducted medication management focusing on symptoms, adherence, and side effects. No psychotherapy was permitted during the trial.

Efficacy and Safety Assessments

The primary outcome measure was change in total CAPS score from baseline to the last observation. Secondary efficacy outcomes included rates of response ($\geq 50\%$ reduction in CAPS total score from baseline) and remission (CAPS ≤ 20) (Davidson, 2004), and percentage of patients with CGI-I scores of 1 or 2, signifying “very much improved” or “much improved.” Additional secondary outcome rating scales included the self-report Davidson Trauma Scale (DTS) (Davidson et al., 1997), Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), CGI-S, and the Sheehan Disability Scale (SDS) (Sheehan et al., 1996). Safety evaluations included vital signs and weight, physical and neurological examinations, 12-lead ECG, and laboratory tests, including weekly liver function tests. Side effects were elicited at each visit by a blinded rater who administered a checklist of 87 symptoms on a scale of 0 (none) to 3 (severe). Intraclass correlation coefficients for raters for the CAPS and MADRS were 0.986 and 0.824, respectively.

Lumbar Puncture

Cerebrospinal fluid for determination of SP was collected at the MSSM site during the final week of the 2-week placebo lead-in period, prior to randomization to GR205171 or placebo. Patients were given instructions for a modified diet and activity schedule in the 24 hours preceding the LP. The LP was performed at approximately 9:00 am by an experienced anesthesiologist as the subject sat upright (arms and head leaning on tray table) or lay in the lateral decubitus position. After routine sterilization of the skin with an antiseptic solution, lidocaine (Xylocaine) was injected into the skin and subcutaneous tissue. A 20-gauge introducer needle was inserted to penetrate the superficial tissues, followed by insertion of a Sprotte 25-gauge-pencil point spinal needle into the subarachnoid space between the L3-4 or L4-5 interspace. Approximately 30 cc of CSF was removed, divided into 3 mL aliquots and frozen at -80°C until assayed. Samples were stored at the Mount Sinai General Clinical Research Center before being shipped to Emory University for analysis.

CSF Substance P Assay

CSF substance P immunoreactivity was determined with solid phase radioimmunoassay in CSF samples using a highly specific substance P antibody (see Supplementary Table S1 for methods).

Statistical Analyses

The sample size was based on *a priori* power calculations for hypothesized CAPS response rates from previous pilot studies with a similar design (Davidson et al., 2003; Zohar et al., 2002), and assumed a large drug-placebo response rate difference (response rate to placebo of 20%, and response rate to GR205171 of 60%). Assuming a dropout rate of 30%, 26 patients per treatment group were required to detect a 40% maximum response rate difference assuming $\alpha = 0.05$ and $\beta = .14$ (power of 86%). Twenty-three patients per group ($n=46$) were required for $\beta = .20$ (power of 80%).

Primary statistical analyses for efficacy and safety were performed for the modified intention-to-treat (mITT) population, defined as randomized patients who received at least one dose of trial medication and for whom CAPS total score ratings were available at baseline and week 1. Additional analyses were conducted for all randomized participants. A linear mixed model with restricted maximum likelihood estimates and an autoregressive moving average covariance structure was used to examine the CAPS scores with main effects for time, drug, and site, an interaction for time and drug, and a fixed intercept. Secondary efficacy analyses included response and remission rates for CAPS total; response analysis for the CGI improvement item; and change from baseline on the DTS, MADRS, CGI-S, and SDS score. The size of treatment effects was calculated with Cohen's *d*, and when appropriate, number-needed-to-treat (NNT). Patients were compared on baseline characteristics using chi-square tests or Fisher's exact test for categorical variables and independent t tests for continuous variables. Adverse events were compared using Fisher's exact test for newly incident or worsened symptoms compared to baseline. Pearson's product moment correlations were computed to examine relationships between CSF SP concentrations and symptom severity. All statistical tests were two-tailed, with an alpha value of 0.05. Statistical analyses were performed by a study biostatistician (D.A.L.), and were independently confirmed by a biostatistician not affiliated with the study (M.P.). No interim analysis was performed.

RESULTS

Of 235 potential participants screened for eligibility, 171 (73%) were excluded prior to placebo lead-in (Fig 1). Sixty-four patients began placebo lead-in, of whom 47 patients (73%) were randomized, with 22 randomized to GR205171 and 25 randomized to placebo. Of 47 randomized patients, eight patients (two receiving GR205171 and six receiving placebo) did not receive ratings at the first post-baseline assessment at week 1, and were discontinued from the study. The remaining 39 patients (20 receiving GR205171, and 19 receiving placebo) were included in primary efficacy and safety analyses detailed below. There were no significant differences between treatment groups in baseline characteristics, except for higher rates of past substance abuse or dependence in the GR205171 group (Table 1). Five patients randomized to GR205171 reported "accidental injury" as their most significant traumatic event compared to none in the placebo group.

The study sample was predominately civilian (non-military), minority, and female, with a mean baseline CAPS total score of 73.0 (SD=13.7; range=51-106), which did not differ between treatment groups (Table 1; Supplementary Table S2). Sixty-four percent of patients met current criteria for major depressive disorder, dysthymic disorder, or depressive disorder NOS. No baseline group differences were found for DTS, MADRS, CGI-S, or SDS (Supplementary Table S2). Thirty-one patients (66%) completed the 8 week double-blind protocol. There was a trend for higher retention in the active treatment arm, with a 82% completion rate for patients in the GR205171 group versus a 52% completion rate in the placebo group ($p = 0.09$, Fisher's Exact Test) (Fig 1). Adherence determined by capsule

counts and medication review at each visit was greater than 97% in both groups (GR205171 = 98.2%; placebo = 97.7%).

Primary Efficacy Outcome

The mixed-model analysis for CAPS total score showed a significant improvement in CAPS scores over time [$F(8,160)=9.86$, $p<0.001$], which was not influenced by drug [$F(1,39)=1.28$, $p=0.27$]. There was no significant interaction between time and drug [$F(8,160)=0.78$, $p=0.62$]. The mean change from baseline to week 8 was -31.7 ($SE=5.1$) and -25.2 ($SE=5.7$) for GR205171 and placebo, respectively, with a mean treatment difference at week 8 of 7.6 ($SE=7.2$; 95% CI -6.7 to 21.9). The mean (SE) CAPS total score at week 8 was 43.5 (5.1) for the GR205171 group versus 51.1 (5.7) for the placebo group (Fig 2). When the analysis was repeated including all randomized patients (non-protocol adherent), the results were similar [Time: $F(8,166)=10.07$, $p<0.001$; Time \times drug: $F(8,166)=0.72$, $p=0.67$].

Secondary Efficacy Outcomes

Forty percent (8 of 20) of patients randomized to GR205171 met CAPS response criteria at endpoint, compared to 21% (4 of 19) of patients randomized to placebo ($p=0.30$). At endpoint, 25% (5 of 20) of patients treated with GR205171 met CAPS remission criteria, versus 11% (2 of 19) of patients treated with placebo ($p=0.41$). A numerically higher but not significant proportion of patients treated with GR205171 were responders on the CGI-I scale at endpoint compared to patients treated with placebo (55% versus 42%; $p=0.53$).

Linear mixed models indicated significant improvement over the course of the trial for DTS ($F(8,131)=13.64$, $p<0.001$), MADRS ($F(8,164)=3.95$, $p<0.001$), CGI-S ($F(8,140)=7.21$, $p<0.001$), and SDS ($F(2,40)=7.39$, $p=0.002$). However, treatment assignment did not significantly alter the time course of change: [DTS: $F(8,131)=0.81$, $p=0.59$; MADRS: $F(8,164)=1.37$, $p=0.21$; CGI-S: $F(8,140)=0.76$, $p=0.64$; SDS: $F(2,40)=1.20$, $p=0.31$].

Exploratory Analyses

The mixed-model analysis on CAPS subscales showed significant overall change in all scores (Reexperiencing: $F(8,145)=6.04$, $p<0.001$; Avoidance/Numbing: $F(8,164)=6.92$, $p<0.001$; Hyperarousal: $F(8,175)=6.56$, $p<0.001$). The hyperarousal symptom cluster changed differentially based on treatment group, with patients randomized to GR205171 showing greater improvement than patients randomized to placebo [$F(8,175)=2.08$, $p=0.04$; $d=0.25$, 95% CI $[-0.16$ to 0.65 ; Supplementary Table S3]. No differential effects of treatment were found for reexperiencing ($F(8,145)=0.60$, $p=0.77$) or avoidance/numbing [$F(8,164)=0.50$, $p=0.71$].

Safety and Tolerability

There were no drug-related serious adverse events, and there were no discontinuations due to adverse events. No adverse effect occurred in the GR205171 group with an incidence of 10% and twice the rate of placebo (Supplementary Table S4). The most frequently reported adverse effects associated with GR205171 treatment were headache, tiredness/fatigue, irritability, and appetite decrease; none of these differed in frequency from placebo. Lower frequencies of nausea and vomiting ($p's < 0.02$) were associated with GR205171 treatment compared to placebo (Supplementary Table S4).

No clinically meaningful changes in systolic or diastolic BP, pulse, liver function tests (alanine aminotransferase, aspartate aminotransferase, bilirubin), or ECG were found. Baseline-to-endpoint mean change in weight for the GR205171 group was -2.0 lbs,

compared to + 1.4 lbs for the placebo group. No patient experienced a clinically significant weight gain (7% of body weight).

CSF Substance P Analyses

Of 50 patients from the MSSM site who began the placebo lead-in period, lumbar puncture was performed in 21 patients (9 females). There was no significant association between age and CSF substance P concentrations ($p=0.15$). Mean CSF substance P concentrations did not significantly differ between males (mean=23.16 fmol/ml, SD=4.0) and females (mean=21.66 fmol/ml, SD=3.3; $p=0.36$). CSF substance P concentrations significantly correlated with pre-treatment CAPS total scores, in both age-adjusted ($r=0.53$, $p=0.015$) and unadjusted ($r=0.47$, $p=0.031$) analyses (Fig 3).

DISCUSSION

This proof-of-concept double-blind placebo-controlled trial is the first report to our knowledge of a selective NK₁R antagonist in patients with chronic PTSD. There was no statistically significant difference between GR205171 and placebo in CAPS total score at week 8, although GR205171 was associated with a numerically greater reduction in severity (7.6 point mean difference). The drug treatment was well tolerated, and side effects were transient and generally mild or moderate in severity. In patients who underwent LP prior to randomization, we found a significant association between PTSD symptom severity and SP concentrations in CSF. Overall, these findings potentially support SP-NK₁R dysregulation as a pathophysiological mechanism in PTSD, but fail to support the efficacy of this specific compound in this small Phase II study at the dose used.

In comparing these results to previous short-term pharmacotherapy trials in PTSD, the CAPS effect size of 0.22 is consistent with the small effect sizes reported for short-term randomized controlled trials of pharmacotherapy in PTSD (Stein et al., 2006). Nevertheless, given the chronicity of illness of study participants, the response to placebo was slightly higher than anticipated. It is possible that repeated weekly administration of the CAPS, generally conducted by the same rater throughout the trial, served to attenuate overall drug-placebo differences. We also adopted a conservative definition of response (50% or greater reduction in baseline CAPS) compared to many previous acute pharmacotherapy trials, which have generally defined response as a 30% or greater reduction in CAPS. Finally, the recruitment of study participants primarily via media advertisement rather than clinical care settings might have contributed to the placebo responsiveness of this sample.

In the only previous published report of a NK₁R antagonist in anxiety disorder patients, GR205171 (5 mg/day) was administered for 28 days in a small sample of patients with social phobia (Furmark et al., 2005). In that trial, 42% of patients receiving GR205171 were responders by CGI-I criteria, compared to 50% of patients taking citalopram and 8% of patients randomized to placebo (Furmark et al., 2005). The safety and tolerability profile was similar to the current study in PTSD. Preclinically, GR205171 was recently shown in gerbils to display anxiolytic-like properties in the elevated plus maze test, and attenuated contextual fear-potentiated startle (FPS) (Heldt et al., 2009). While animal and human response in a FPS paradigm may not fully approximate the exaggerated startle in PTSD patients (Morgan et al., 1995), it is noteworthy that in the current study GR205171 showed greater efficacy than placebo on the CAPS hyperarousal symptoms, which include items for exaggerated startle, sleep disturbance, irritability, difficulty concentrating, and hypervigilance. This finding is consistent with individual item analyses demonstrating significant improvements in sleep and cognitive disturbance with the selective NK₁R antagonist L-759274 in patients with major depressive disorder (Kramer et al., 2004). As a

caveat, however, our study was insufficiently powered to detect effects on specific PTSD symptom clusters, and the significant result was exploratory in nature.

The CSF analyses performed in a subgroup of trial participants showed that CSF SP levels were significantly associated with overall PTSD symptom severity. The only previous investigation of CSF SP in PTSD, conducted in a male Vietnam War veterans, found an association between self-reported increases in anxiety ratings following symptom-provocation, and phasic increases in CSF SP levels (Geraciotti et al., 2006). Basal elevations in CNS SP were also observed in the PTSD patients compared with healthy volunteers, suggesting a role for SP in both the modulation of the acute stress response and in disorder expression (although it should be noted that elevations of SP were also observed in patients with major depressive disorder, limiting the specificity of this finding). Using the same assay methodology, our study extended this report by characterizing an association between PTSD symptomatology and basal levels of SP. The small number of patients undergoing LP who subsequently met criteria for the ITT sample did not permit meaningful analyses of baseline CNS SP concentrations and trial outcome.

There was no significant impact of GR205171 treatment on comorbid depressive symptoms. Although several NK₁R antagonists have shown antidepressant activity and the development of highly selective NK₁R antagonists remains a focus for drug development for mood disorders (Mathew et al., 2008), the clinical utility of NK₁R antagonists for depressive disorders is uncertain. In the largest series of studies in major depressive disorder to date, involving over 2500 patients, the NK₁R antagonist aprepitant failed to demonstrate efficacy (Keller et al., 2006). Further understanding of post-traumatic depressive symptoms in the context of PTSD is necessary.

Methodological strengths of this study include the enrollment of a socioeconomically and racially diverse sample of PTSD with significant mood and anxiety disorder comorbidity, illness chronicity, and previous substance abuse or dependence histories. Further, study participants had experienced a wide range of traumatic events, enhancing the generalizability of the trial findings. The use of mixed models enabled a rigorous evaluation of the impact of attrition on outcome.

Limitations include the small sample size and brief duration of the trial, as 8 weeks might have been insufficient to test the efficacy of GR205171 for chronic PTSD. Regarding sample size, 46 randomized participants was the minimum number required for 80% power based on *a priori* hypothesized CAPS response rates. While continuing enrollment to the original proposed sample size of 52 would have increased power to 86%, the slow rate of subject accrual necessitated early termination once the minimum threshold was achieved. Therefore, if GR205171 is an effective molecule but does not have efficacy of this magnitude, then it is likely that more subjects would be required to reach a clinically meaningful effect.

Baseline differences between groups in past substance abuse or dependence could have mitigated against a more robust response to GR205171. Attrition was notably greater in the placebo group compared to the GR205171 group. Finally, the fixed dose design and lack of pharmacokinetic data allowed the possibility that individual differences in drug metabolism could have impacted outcome. It is possible that a higher dose of GR205171 would have been more efficacious. However, the fixed 5 mg dose was mandated by the limited amount of safety data at higher doses.

Conclusions

In this proof-of-concept clinical trial in chronic PTSD, the selective NK₁R antagonist GR205171 did not meet its primary efficacy endpoint. Exploratory analyses showed a significant improvement in hyperarousal symptoms. The drug was well tolerated and not associated with changes in weight, vital signs, or hepatic function. Further trials are necessary to determine whether selective NK₁R antagonists are an effective treatment option for PTSD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Flowchart of Patients Through the Study

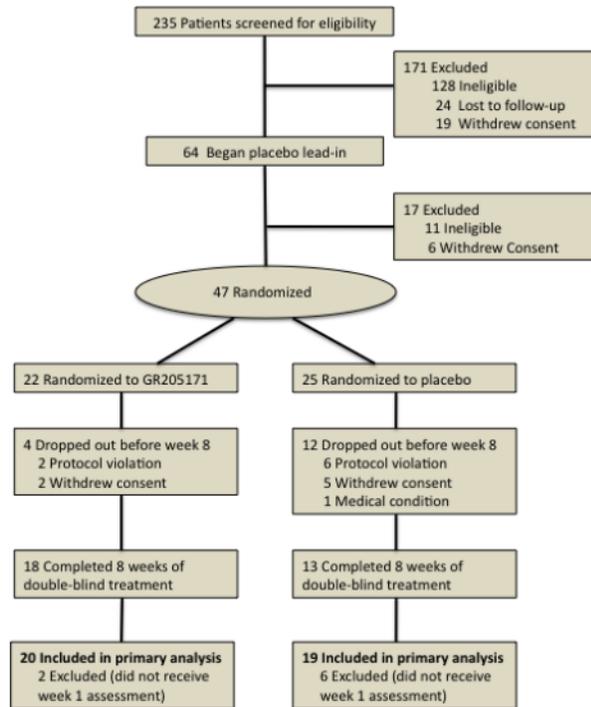


Fig 1.
CONSORT Diagram of Participant Flow

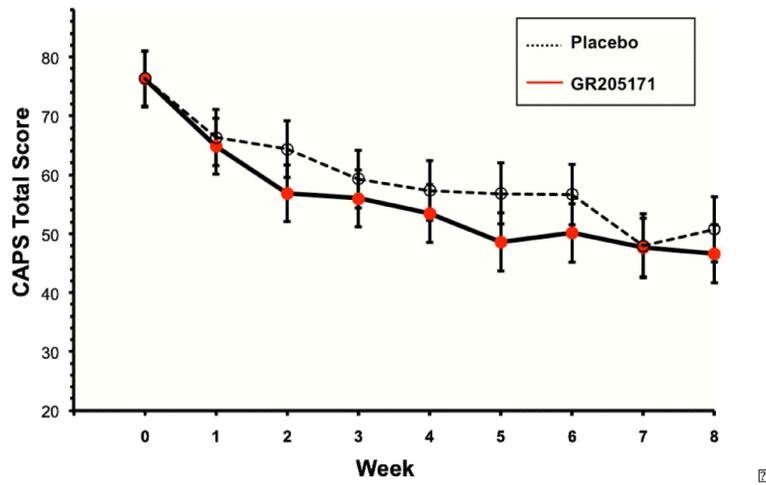


Fig 2.
Mean Change in Scores on the Clinician-Administered PTSD Scale for Patients Randomized to Placebo or GR205171^a
^a No significant difference between groups over time [F(8,160)=0.78, p=0.62].

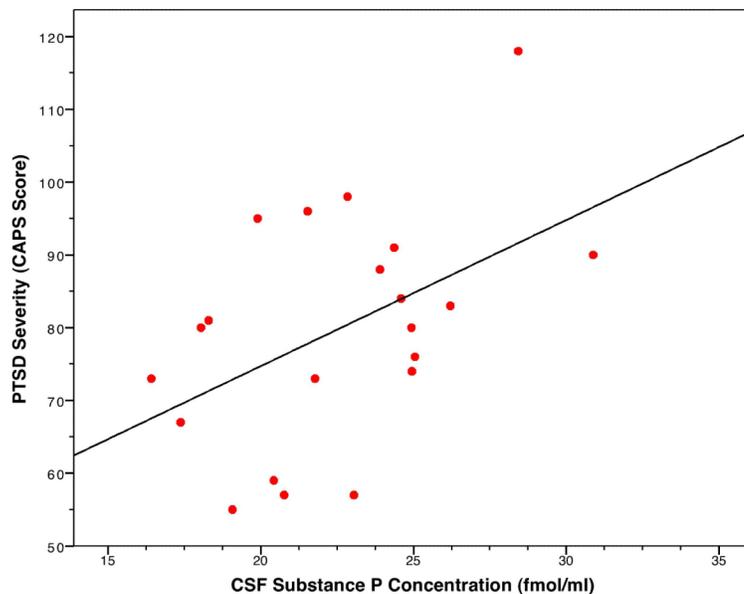


Fig 3.

Association Between CSF Concentrations of Substance P and PTSD Severity^a

^a PTSD severity determined by Clinician Administered PTSD Scale (CAPS) prior to 2-week placebo lead-in. Lumbar puncture was performed in participants (n=21) during the placebo lead-in period prior to randomization. A significant positive correlation was found ($r=0.47$, $p=0.03$).

TABLE 1

Baseline Characteristics of Randomized Patients with PTSD^a

Characteristic	Placebo (N=19)	GR205171 (N=20)	P Value ^b
Female, No., %	12 (63.2)	11 (55.0)	0.75
Age, mean (SD), years	43.0 (11.5)	38.7 (12.3)	0.26
Race, No., %			
Black	7 (36.8)	7 (35.0)	0.41
Hispanic	3 (15.8)	7 (35.0)	
White	8 (42.1)	6 (30.0)	
Asian	1 (5.3)	0 (0.0)	
Marital status, No., %			
Currently married or living with partner	5 (26.3)	4 (20.0)	0.53
Never married	8 (42.1)	12 (60.0)	
Divorced or separated	6 (31.6)	4 (20.0)	
Education, No., %			
High School Degree of Lower	7 (36.8)	5 (25.0)	0.09
Partial College Education	5 (26.3)	12 (60.0)	
College Degree of Higher	7 (36.8)	3 (15.0)	
Employment, No., %			
Unemployed	5 (26.3)	8 (40.0)	0.42
Part-Time	5 (26.3)	6 (30.0)	
Full-Time	7 (36.8)	6 (30.0)	
Retired	2 (10.5)	0 (0.0)	
Duration of illness, mean (SD), years	12.2 (15.4)	10.6 (13.0)	0.72
Time from traumatic event, mean (SD), years	14.5 (16.9)	11.6 (13.7)	0.60
Current depressive disorder^c, No., %	10 (52.6)	15 (75.0)	0.19
Current anxiety disorder, No., %	6 (31.6)	9 (45.0)	0.51
History of alcohol dependence/abuse, No., %	1 (5.3)	4 (20.0)	0.34
History of substance dependence/abuse, No., %	0 (0.0)	5 (25.0)	0.047
Current nicotine use, No., %	3 (15.8)	7 (35.0)	0.27
Body mass index, mean (SD), kg/m²	27.3 (5.4)	26.6 (5.7)	0.71
Type of Trauma, No., %			
Sexual Abuse	7 (36.8)	7 (35.0)	0.15
Nonsexual Abuse/Violence	9 (47.4)	5 (25.0)	
Combat	1 (5.3)	2 (10.0)	
Unexpected Death	2 (10.5)	1 (5.0)	
Accidental Injury	0 (0.0)	5 (25.0)	

^aModified intention-to-treat sample

^bGroup comparisons calculated with Chi-square, Fisher exact test or independent t-test

^cincludes major depressive disorder, dysthymic disorder, and depressive disorder NOS