Original Paper

Glyceryl trinitrate in first-episode psychosis unmedicated with antipsychotics: A randomised controlled pilot study

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Abstract

Background: There is a pressing need for new classes of treatment for psychosis. A key therapeutic target for novel compounds is the NMDA receptor, which may be modulated by nitric oxide donors such as sodium nitroprusside (SNP). Recent studies of SNP in patients with psychosis have mixed results, and the drug has to be administered intravenously. Glyceryl trinitrate (GTN) is a well-established cardiovascular medicine that is also a nitric oxide donor, and can be given orally.

Aims: We explored the safety and potential effects of GTN in unmedicated patients with a first episode of psychosis.

Methods: This was a single-centre, randomised, double-blind, placebo-controlled trial from December 2016 to April 2019 (ClinicalTrials.gov identifier: NCT02906553). Patients received 3 × sprays of GTN or placebo for three consecutive days, and were re-assessed on Days 1, 2, 3 and 7. The primary outcome was cognition (Jumping to Conclusions task), secondary outcomes were symptoms (Positive and Negative Syndrome Scale (PANSS)), verbal memory (Hopkins Verbal Learning task), and mood (Bond–Lader Visual Analogue Scales).

Results: Nineteen patients were randomised, and 13 participants were included in the analyses. Compared with placebo, GTN was well tolerated, but was not associated with significant effects on cognition, symptoms, or mood. Bayesian statistics indicate that our results were 2× more likely under the null hypothesis than the alternative hypothesis, providing anecdotal evidence that GTN does not improve psychotic symptoms.

Conclusions: We found no indication of an effect of GTN on symptoms of psychosis or cognition.

Keywords

Clinical trial, psychosis, schizophrenia, sodium nitroprusside, glyceryl trinitrate

Introduction

Antipsychotic medications blocking the dopamine D2 receptor are the first-line treatment for psychosis (Leucht et al., 2012a). These medicines are effective in reducing symptoms and risk of relapse (Leucht et al., 2012b), but are ineffective in around a third of patients and have little impact on negative symptoms and cognitive deficits (Samara et al., 2019). Moreover, their use is associated with adverse effects including weight gain and diabetes (De Hert et al., 2012; Rummel-Kluge et al., 2010). There is thus a pressing need for new classes of treatment.

Nitric oxide donors are a candidate medicine targeting the NMDA receptor for glutamate, the function of which is thought to be altered in psychosis (Javitt and Zukin, 1991; Ripke et al., 2014), indicated by elevated brain glutamate levels in patients with psychosis (Merritt et al., 2016). Nitric oxide acts as a gaseous second messenger which activates guanylate cyclase in the brain. One downstream effect of this is the modulation of NMDA receptor activity (Hoyt et al., 1992; Manzoni et al., 1992; Pitsikas, 2015). Preclinical studies report that sodium nitroprusside (SNP, a nitric oxide donor) blocks the effects of an NMDA receptor antagonist in rats, suggesting that nitric oxide donors may be therapeutically beneficial in psychosis (Bujas-Bobanovic et al., 2000).

In 2013, Hallak and colleagues reported that SNP, delivered intravenously as an adjunct to antipsychotic medication, was effective in reducing acute psychotic symptoms in patients in the early phase of psychosis (Hallak et al., 2013a). However, subsequent studies in patients with chronic schizophrenia have not replicated this finding (Brown et al., 2019; Stone et al., 2016; Wang et al., 2018). It has been argued that SNP may only be effective in the early phases of psychosis in patients who have received relatively little antipsychotic treatment (Maia-De-Oliveira et al., 2017). This would be consistent with neuroimaging evidence that

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brain glutamate dysfunction in psychosis varies with stage of illness (Merritt et al., 2016), and preclinical data showing that novel compounds that act on glutamate/GABA function are only effective in rodents that have not been exposed to D2 receptor antagonists (Gill et al., 2014).

In previous trials, SNP was tested as an adjunct to antipsychotic medication, with the placebo-control condition consisting of patients receiving placebo in addition to antipsychotic medication. All trials showed an improvement in symptoms with SNP + an adjunct antipsychotic; however, the three negative trials also reported a significant improvement in symptoms for the placebo arm (those receiving placebo + antipsychotic) (Brown et al., 2019; Stone et al., 2016; Wang et al., 2018). Therefore, the efficacy of SNP may be masked by the response to the existing antipsychotic, and so there is a need to test nitric oxide donors in patients unmedicated with antipsychotics to determine its true efficacy.

The administration of SNP is logistically difficult, as it requires an intravenous infusion. Glyceryl trinitrate (GTN) has the same mechanism of action as SNP, by rapid breakdown to nitric oxide. However, GTN can be administered sub-lingually and as such could be more feasible in a psychiatric setting. Therefore, the present study aimed to investigate the safety and feasibility of conducting a trial of GTN in unmedicated patients experiencing an acute first episode of psychosis, and whether GTN could potentially be effective in reducing psychotic symptoms and improving cognition.

Methods

Trial design

The Nitric Oxide in Cognition Study was a single-site, 1 week, double-blind, randomised, placebo-controlled pilot study of GTN spray (ClinicalTrials.gov identifier: NCT02906553). The study was conducted at the Institute of Psychiatry, Psychology and Neuroscience, London, UK. Ethical approval was obtained from the London Bromley Research Ethics Committee (16/LO/1102), and the study adhered to the Declaration of Helsinki.

Participants

Between December 2016 and April 2019, 602 adults were assessed for eligibility (Figure 1). Participants were recruited from inpatient wards and community mental health teams within the South London & Maudsley Trust, alongside Participant Identification Centres in Central and North West London and East London NHS Foundation Trusts. Informed, written consent was obtained from all subjects. Capacity was assessed by the researcher and treating clinicians. Participants were asked to state the aim of the study and what it involved in their own words to ensure understanding. Inclusion and exclusion criteria are listed in Table 1.

Interventions

Participants received the maximum recommended dose of GTN: 3 × sprays of 400 µg per metered dose of active treatment (GTN & <100 mg ethanol per spray, Pharmasol Ltd, North Way), or the inactive placebo (96% ethanol, Pharmasol Ltd, North Way) for three consecutive days (Day 1, Day 2, Day 3). Drug administration was observed by the researcher (KM), and the spray was self-administered, sub-lingually. Study medication was prescribed by the study doctor (PM), and stored and dispensed by the Maudsley Hospital pharmacy. As headache is a common side effect of GTN, participants were asked if they wished to receive pre-treatment paracetamol (1 g) and ibuprofen (400 mg). The bioavailability of GTN following sublingual administration is ~40%. Plasma concentrations peak after ~3 min, biologically active metabolites have a half-life of approximately 40 min and it exerts a duration of action of ~25 min for cardiovascular effects (Divakaran and Loscalzo, 2017). In comparison, Hallak et al. administered a low dose of IV SNP (0.5 µg/kg/min) which has 100% bioavailability (Hallak et al., 2013b).

Assessments

Visits took place on the ward, or at the Clinical Research Facility based at King's College Hospital. Testing sessions occurred at five different time-points (carried out by KM): baseline (pre-dose), assessment 1 (day 1 following treatment), assessment 2 (day 2 following treatment), assessment 3 (day 3 following treatment) and assessment 4 (day 7 no treatment). Outcome measures were conducted 30 min post-dose, following the typical duration of action of GTN for cardiovascular effects and half-life of active metabolites (Divakaran and Loscalzo, 2017).

Outcomes

The following outcomes were measured at all assessments: (a) the emotionally salient version of the Jumping to Conclusions (JTC) task (Menon et al., 2006), (b) the Hopkins Verbal Learning Task – Revised (HVLT) (Shapiro et al., 1999), (c) Positive and Negative Syndrome Scale (PANSS) (videotaped) (Kay et al., 1987), (d) the Bond–Lader Visual Analogue Scales (Bond and Lader, 1974), (e) safety measures: side effects, blood pressure and heart rate. Demographic and recreational drug use data (historic use and Cannabis Experiences Questionnaire) were collected at baseline.

The primary outcome was the emotionally salient version of the JTC task, a version of the beads task, which was used to test the cognitive underpinnings of delusions. Performance on the JTC task improves with D2 receptor antipsychotic treatment (Menon et al., 2008). In the task, jumping to conclusions is defined as a draw score of less than 3 (Garety et al., 2013).

In the computerised JTC task (Psychopy V3.1.4), participants are presented with a scenario where a character 'Jack' is in court facing charges for crashing into a car. A solicitor has conducted a survey on 100 people from Jack's community, asking them to provide one word to describe Jack, to determine how well liked he is. Participants are informed that Jack is either mostly liked (60% said good words and 40% said bad words about Jack), or mostly disliked (40% said good words and 60% said bad words about Jack). Participants view the one-word opinions from the survey, one word at a time, and must select whether to view another word, or decide whether Jack was mostly liked or disliked. All previously viewed words appear on the bottom of the screen to eliminate working

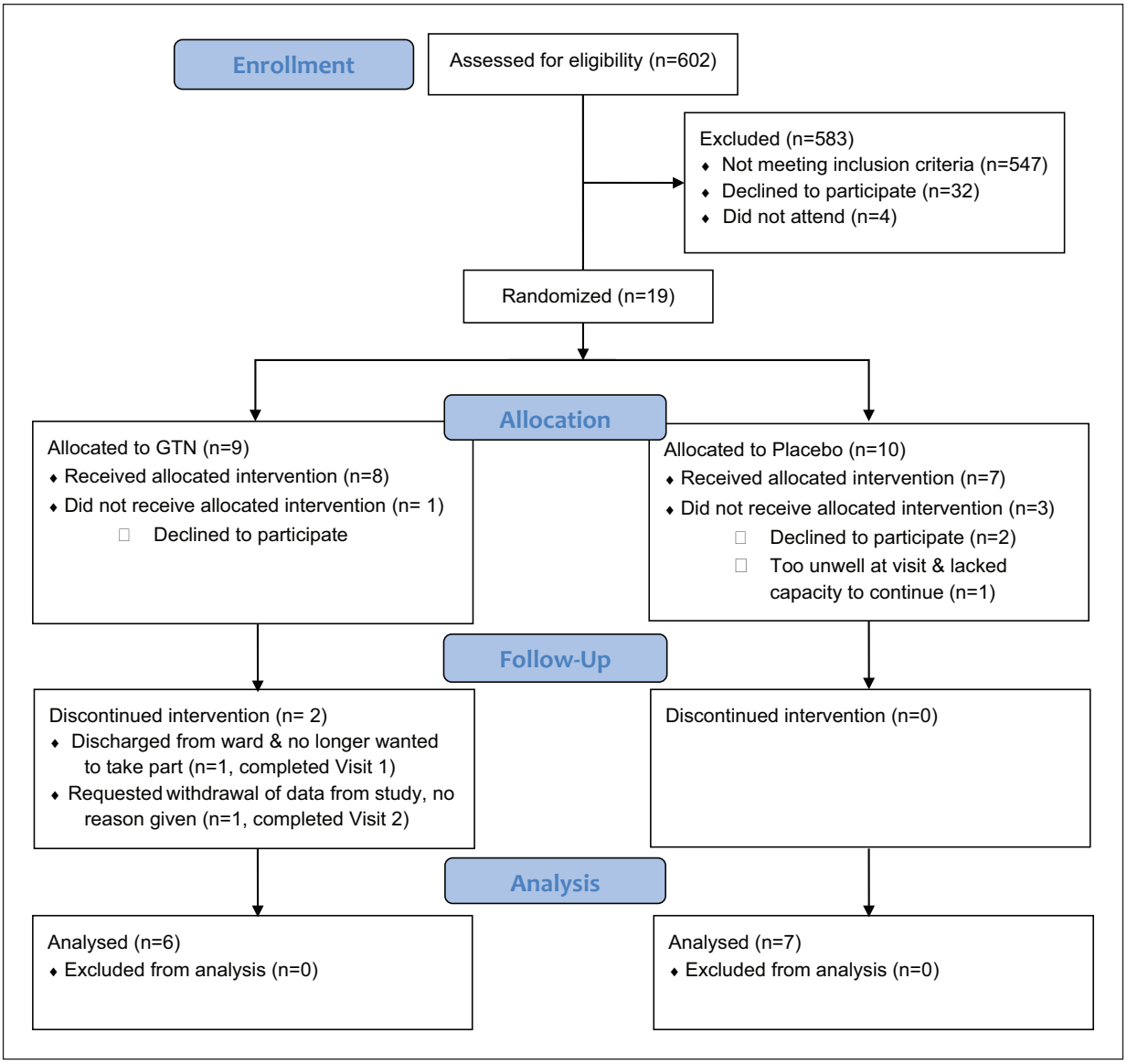

Figure 1. CONSORT flow diagram of participant recruitment.

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Patients undergoing an acute psychotic episode; defined as score >4 on question P1 Delusions or P3 Hallucinatory behaviour of the PANSS positive subscale	Prior history of intolerance to glyceryl trinitrate
Under clinical care of community early intervention team or ward	Systolic blood pressure below 90 mmHg, heart rate above 100 bpm
Capacity to give consent	Any major physical illness
18–45 years of age	Homicidal or suicidal
Currently unmedicated with antipsychotic medication	Pregnant or breast feeding

memory load. Up to 15 words can be viewed in total. Participants are instructed to select the finish button when they have viewed enough words to decide whether Jack was mostly liked or disliked, and are then prompted to enter their decision. The outcome measure is the number of words ('opinions') viewed, averaged over three trials. Participants repeat the JTC task three times each visit, with the same scenario using a different word list in a predetermined random order.

Secondary outcomes included: the PANSS assessment, the HVLT task, and the Bond–Lader Visual Analogue Scales. KM

conducted videotaped PANSS assessments with participants, from which the PANSS were scored by both the researcher (KM) and psychiatrist (AC). Discrepancies were discussed and final scores were reached by consensus. For the HVLT task, participants recall a list of 12 words read aloud to them. This is repeated a total of three times with the same word list, and 20–25 min later participants are asked to recall the word list. Immediate recall scores were averaged across the three recall conditions, and the delayed recall score was collected at each visit. Different word lists were used at each visit. The Bond–Lader Visual Analogue Scales consist of 16, 10 cm visual analogue scales which ask participants to rate their current mood (Bond and Lader, 1974). Scores are calculated for the following categories: alertness, calmness, and contentedness.

Sample size

As this was a pilot study formal power calculations are not required (Eldridge et al., 2016). In line with pilot study guidance recommending 30–55 participants (Lancaster et al., 2004), we initially intended to recruit 36 patients.

Randomisation and blinding

Randomisation was carried out by an independent member of staff in the King's Clinical Trial Unit using a bespoke web-based dynamic randomisation service, using block randomisation of varying sizes (2 and 4) stratified by whether participants had previously been treated with antipsychotic medication (yes/no). Treatment arm allocation emails were automatically sent to the Maudsley Hospital pharmacy where the medication was labelled and blinded before being dispensed. Researchers did not have access to the randomisation list, and a 24/7 emergency unblinding service was available from the pharmacy. Both investigators and participants were blind to treatment allocation. The placebo and active treatments were identical in appearance, taste and method of administration. On day 7, participants were asked which group they thought they were allocated to, to assess the maintenance of the blind.

Analysis

Bayesian statistics investigated the effect of GTN on positive PANSS score. The traditional *p*-value approach is able to disprove the null hypothesis (that there is no beneficial effect of GTN for psychotic symptoms); however, it does not allow us to infer whether there is enough evidence to support the null hypothesis (Quintana and Williams, 2018). To determine whether the data favour the null hypothesis compared with the alternative hypothesis (that GTN reduces psychotic symptoms), we conducted a Bayesian one-tailed independent samples *t*-test (Dienes, 2014; Jeffreys, 1998). Bayesian statistics were conducted using JASP (JASP Team, 2019), comparing slope values (change in PANSS positive score from baseline to Day 3, and baseline to Day 7) between treatment arms. The Cauchy prior was set according to the maximum effect size detectable versus placebo in the current study, based on the maximum possible improvement from baseline PANSS symptom score, average placebo response, and standard deviation of the change in score for each group. JASP compares this alternative model to a model of the null hypothesis set at an effect size of 0. Hedges *g* effect sizes are reported ('effsize' package on 'R' (v0.7.6, Torchiano)). Due to the small sample size of the study, frequentist statistical analyses (repeated measures ANOVA) of PANSS positive scores and JTC task responses are included in the supplemental material only, alongside a figure of the drug–placebo response curve (Faraone et al., 2000). Two-sample *t*-tests assessed differences in demographic and clinical factors between treatment groups at baseline, and repeated measures ANOVA assessed change in blood pressure and heart rate (SPSS version 24, SPSS inc. Chicago, IL, USA). Graphs were produced using the package ggplot2 (Wickham, 2009) within R 3.6 (R Core Team, 2014). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Participant flow and recruitment

In total, 19 participants were randomised, eight participants received GTN and seven participants received placebo. Four dropped out after baseline and did not receive an intervention: three declined further participation, and one was too unwell to continue (Figure 1). At follow-up a further two participants dropped out from the GTN arm; one requested withdrawal of all their data from study (no reason was given), and one was discharged from the ward and no longer wanted to take part (participant not included in intent-to-treat analysis as review of PANSS videotapes concluded that participant did not meet inclusion criteria for symptom severity). The final analysis included six participants in the GTN arm, and seven in the placebo arm.

After participation in the study, it emerged that one participant in the GTN arm had been prescribed olanzapine 10 mg and a monthly haloperidol 75 mg depot injection. Although this patient did not meet inclusion criteria of being unmedicated with antipsychotic medication, sensitivity analyses indicated that their inclusion did not change the results. No other participants were receiving antipsychotic medication at baseline: nine were antipsychotic naïve, and three reported previous antipsychotic treatment prior to the study. Of the latter, one received 5 mg olanzapine for 1 day, 4 days prior to baseline; one received chlorpromazine for 5 days, 4 years prior to baseline; and one participant received aripiprazole intermittently for 1.5 years, 4 months prior to baseline. For nine participants this was their first contact with a psychiatric ward or early intervention community team. During the study, one participant was started on 10 mg aripiprazole on Day 3, and one participant was started on 0.5 mg risperidone on Day 5.

Primary and secondary outcomes

At baseline there were no significant differences in demographics or any of the primary and secondary outcomes between the GTN and placebo treatment groups (Table 2).

To determine whether the data favoured the null hypothesis (that there is no beneficial effect of GTN on psychotic symptoms) compared with the alternative hypothesis (that GTN

Table 2. Baseline demographics and clinical characteristics of participants.

	GTN *n*=6 Mean (SD)	Placebo *n*=7 Mean (SD)
Age (years)	23.8 (7.1)	25.4 (6.8)
Male/Female	6/0	5/2
Education, years beyond 16	1.8 (1.6)	2.3 (1.5)
Currently employed Y/N/Student	0/3/3	0/5/2
Ethnicity (White/Black/Asian/Mixed race)	2/2/1/1	1/3/1/2
Previously treated with antipsychotic medication Y/N	2/4	1/6
Antipsychotic medication at Day 0 Y/N	1/5	0/7
Antipsychotic medication at Day 3 Y/N	2/4	0/7
Antipsychotic medication at Day 7 Y/N	2/4	1/6
Promethazine at Day 0 Y/N	0/6	0/7
Promethazine at Day 3 Y/N	0/6	2/5
Promethazine at Day 7 Y/N	0/6	1/6
Benzodiazepine/Zopiclone) at Day 0 Y/N	1/5	2/5
Benzodiazepine/Zopiclone at Day 3 Y/N	1/5	2/5
Benzodiazepine/Zopiclone at Day 7 Y/N	1/5	1/6
Current smoker or receiving NRT Y/N	3/3	4/3
Cannabis use Never / >1 year / >1 m / Last month	1/0/1/4	0/2/1/4
Other recreational drugs Never / >1 year / >6 m / Last month	3/0/0/3	2/2/1/2
Patient correct regarding Trial Arm Y/N	2/3 *n*=5	5/7
Primary outcome		
Number of draws on JTC task (Day 0)	10.8 (5.3)	14.4 (1.1)
Secondary outcomes		
PANSS Positive (Day 0)	21.5 (3.7)	19.1 (4.1)
PANSS Negative (Day 0)	10.2 (2.8)	11.7 (2.9)
PANSS General (Day 0)	29.0 (5.6)	33.6 (4.9)
PANSS Total (Day 0)	60.7 (7.8)	64.4 (8.8)
Mean learning trial recall HVLT (Day 0)	6.9 (1.5)	7.9 (2.6)
Delayed recall HVLT (Day 0)	7.2 (3.4)	7.4 (3.0)
Mood scale Alert (Day 0)	22.2 (14.5)	31.7 (6.1)
Mood scale Content (Day 0)	14.8 (8.6)	19.8 (1.5)
Mood scale Calm (Day 0)	5.1 (2.7)	6.1 (0.9)

There were no significant differences between GTN and Placebo treatment groups at baseline (Day 0). PANSS: Positive and Negative Syndrome Scale; higher scores indicate more severe symptom severity. HVLT: Hopkins Verbal Learning Test. Lower scores on mood scales indicate higher alertness, etc. NRT: nicotine replacement therapy.

reduces psychotic symptoms), we conducted Bayesian independent samples *t*-tests. Repeated measures ANOVA results are included in the Supplemental information.

For the change in PANSS positive score from baseline to Day 3 (treatment days only), the maximum effect size detectable (versus placebo) was d=2.1. The Cauchy prior distribution was centred around 0.5 (the therapeutic effect of newer atypical antipsychotics (Leucht et al., 2009)). The resulting Bayes Factor (BF_{+0}) was 0.445 (CI 0.025–1.058), indicating anecdotal evidence in favour of the null hypothesis that GTN has no beneficial effect on psychotic symptoms, as the data are 2.2× more likely under the null (H0) than the alternative hypothesis (H1). The magnitude of the effect size between groups (change in PANSS positive score from baseline to Day 3) was negligible; Hedges *g*=0.18 (CI −0.96 to 1.32).

For the change in PANSS positive score from baseline to Day 7 (final follow-up without treatment), the maximum detectable effect size was d=0.7 (smaller effect size due to larger placebo response on Day 7). The Cauchy prior distribution centred around 0.35 with a scale parameter of 0.12, corresponding to a probability of 80% that the effect size lies between 0 and 0.70. We found a Bayes Factor (BF_{+0}) of 0.468 (CI 0.035–0.634), indicating anecdotal evidence in favour of the null hypothesis that GTN has no beneficial effect on psychotic symptoms, as the data are 2.1× more likely under the null (H0) than the alternative hypothesis (H1). The reduction in PANSS positive symptoms between baseline and Day 7 was greater in the placebo group compared with the GTN group; Hedges *g*=0.68 (CI −0.49 to 1.84, Figure 2).

For the JTC task, only one participant demonstrated jumping to conclusions at baseline by viewing three or fewer words (Figure 2). Therefore Bayesian analyses to determine whether participants in the GTN group viewed more words over time are not applicable.

40% of patients in the GTN group correctly guessed that they received GTN and 71% in the placebo group correctly guessed they received placebo, indicating that patients were not unblinded during the study.

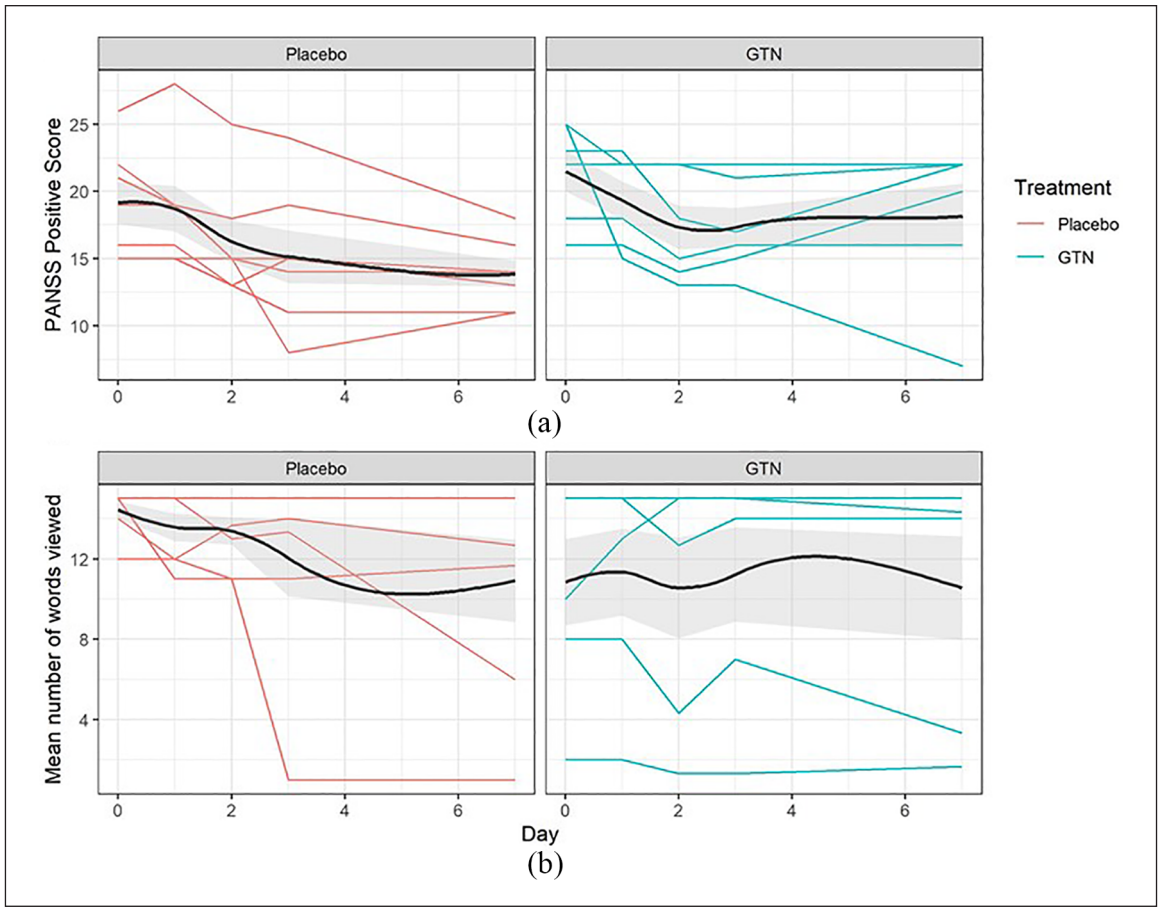

Figure 2. (a) Individual patient PANSS positive scores plotted over time. The change in PANSS positive score over time did not differ between treatment groups. Graphs are split based on treatment arm; the left panel shows patients receiving placebo, the right panel shows patients receiving GTN. (b) Number of words viewed by each participant during the JTC task over time (mean of three trials on each day). Only one participant demonstrated jumping to conclusions by viewing three or fewer words at baseline. Group mean at each visit is shown in black, grey ribbon indicates between-subjects standard error.

Safety measures

There were no serious adverse events and GTN was well tolerated. Reported side effects in the GTN group included dizziness (n=2), stinging sensation in mouth (n=1), nosebleed (n=1), fatigue (n=1) and headache (n=1). There was no significant difference in the number of side effects reported between the GTN and placebo treatment arms. GTN did not affect systolic or diastolic blood pressure (Table 3), but was associated with an increased heart rate (repeated measures ANOVA of change in heart rate pre and post drug, significant effect of group (F(1,9)=6.689, p=0.029, ηp2=0.426).

Discussion

This is the first study to investigate the feasibility and potential effects of GTN in patients with psychosis. We did not find any evidence of an effect of GTN over placebo on psychotic symptoms or cognitive performance. We demonstrated that GTN was well tolerated, with minimal side effects, and no effect on systolic or diastolic blood pressure, but an increase in heart rate.

Our results are consistent with data from recent studies of SNP in psychosis, which found no effect on symptoms or on spatial working memory (Brown et al., 2019; Stone et al., 2016; Wang et al., 2018), but not those from the first study of SNP in psychosis, which reported improvements in both positive and negative symptoms of psychosis (Hallak et al., 2013a). The former studies examined chronic patients who were receiving treatment with antipsychotic medication, and one explanation for the difference in their results compared with those from the first study is that it involved first-episode patients (Gill et al., 2014; Stone, 2011). This was a key driver for us investigating another nitric oxide donor in first-episode psychosis rather than chronic patients.

There was a significant reduction in psychotic symptoms over time, and a small but significant improvement on the HVLT immediate and delayed recall. This resulted in a large placebo response in our cohort, limiting the power of the study, alongside a small sample size. Bayesian statistics indicated that our results were 2× more likely under the null hypothesis than the alternative hypothesis, providing anecdotal evidence that GTN does not have a therapeutic effect at the magnitude seen with newer atypical antipsychotics (Leucht et al., 2009). Due to the small sample

Table 3. Blood pressure (BP) and heart rate measures at each timepoint for GTN and placebo groups.

	Day 1		**Day 2**		**Day 3**		**Repeated measures ANOVA**
	GTN (*n*=4)	Placebo (*n*=7)	GTN	Placebo	GTN	Placebo (*n*=7)	
Systolic BP change (mmHg)	−6.8 (6.7)	5.7 (23.7)	2.0 (2.7)	10.9 (22.9)	10.5 (18.5)	−6.7 (12.0)	Group: $F(1,9)=0.030$, $p=0.865$ Time: $F(1.1,10.3)=0.528$, $p=0.507$ Interaction: $F(1.1,10.3)=2.782$, $p=0.123$
Diastolic BP change (mmHg)	1.5 (6.8)	10.7 (21.7)	−0.8 (11.5)	−3.6 (4.5)	2.5 (14.2)	1.9 (8.9)	Group: $F(1,9)=0.166$, $p=0.693$ Time: $F(2,18)=1.035$, $p=0.375$ Interaction: $F(2,18)=0.622$, $P=0.548$
Heart rate change (bpm)	8.8 (8.3)	−0.6 (10.2)	6.5 (10.8)	−2.1 (5.1)	20.0 (20.3)	−4.6 (22.5)	**Group: $F(1,9)=6.689$, $p=0.029$** Time: $F(1.2,10.8)=0.408$, $p=0.573$ Interaction: $F(1.2,10.8)=1.046$, $p=0.344$

Mean and (Standard Deviation) presented.

size and large confidence intervals of the Bayes Factors, these results should be taken with a degree of uncertainty.

The 41% reduction in PANSS positive scores for the placebo group, and 16% reduction for the GTN group does not meet clinical significance for the majority of patients, although three patients were classified as borderline or no longer mentally unwell at the end of the study. This was the first contact with mental health services for the majority of patients, and so reinforces the value of an initial antipsychotic-free observation period. This initial assessment period where patients remain free of antipsychotic medication when first presenting with an episode of psychosis provided a suitable opportunity to recruit unmedicated patients into our study. A limitation of this approach, however, is that definitive diagnoses are not typically made during the first episode of psychosis.

Patients in the current sample did not demonstrate a 'jumping to conclusions' reasoning bias (defined as a word draw of less than three, whereas the mean word draw at baseline was 13), and so it was difficult to assess improvement on this task. This is in contrast to previous reports of a lower number of draws needed to reach a decision in patients with schizophrenia (McLean et al., 2016). We used an emotionally salient version of the task, performance on which has been shown to normalise following antipsychotic treatment (Menon et al., 2008). The absence of a JTC reasoning bias may result from the task being computerised, as this may enforce less social pressure to make a decision earlier. Moreover the presence of a memory aid has been found to abolish the difference in performance between patients with schizophrenia and healthy volunteers (Menon et al., 2006), but not in all studies (Dudley et al., 1997), indicating that JTC bias may result from poor working memory. Patients possessed an average PANSS delusion score of 5 at baseline ('moderate severe') yet did not show a JTC bias, suggesting that JTC bias may not be necessary for the formation of delusions. This is consistent with previous research showing that JTC bias is not related to positive symptom severity in first-episode psychosis patients (Catalan et al., 2015).

This study highlights the significant logistical challenges in recruiting unmedicated first-episode patients. A total of 606 patients were screened, but only 19 of these were randomised. The main barrier was that the majority of patients screened for the study were thought to require immediate treatment on presentation, and were started on antipsychotic medication before they could enter the trial. It is more feasible to examine novel antipsychotics as an adjunctive to anti-dopaminergic antipsychotic treatment, although when symptom improvement occurs in both trial arms (as seen with SNP), it is difficult to interpret this result and so trials in unmedicated patients are also needed.

Moving forwards, it would be beneficial if frameworks for testing new medicines were built into clinical services, to signpost patients showing a poor response to antipsychotics (estimated as 38% of patients (Samara et al., 2019)) and those not taking antipsychotic medication (upwards of 40% of patients (Lacro et al., 2002; Lieberman, 2007)) into clinical trials of alternatives. Clinical trials recruiting unmedicated patients should include clear criteria for treating patients with antipsychotics at early signs of clinical deterioration (Morrison et al., 2018); in the present study two patients were started on antipsychotic medication when clinicians deemed this necessary. The length of time needed to administer the experimental treatment should also be considered; a longer treatment period increases the confidence of detecting a treatment effect, but the amount of time not receiving treatment as usual should be minimised. In the present study we administered GTN for 3 days, whereas a longer duration of treatment may be necessary for efficacy. A shorter trial duration may also reduce drop out in the placebo group, which was low in the present study (n=0 discontinuation in placebo arm), but is common in placebo-controlled trials of antipsychotics (Fleischhacker et al., 2003). Future studies would benefit from using a sequential parallel comparison design to increase statistical power by reducing placebo-response data (Ivanova et al., 2011). An alternative method is to test novel drugs in participants at an ultra-high risk of schizophrenia. This population is not generally treated with antipsychotics, and so their involvement in clinical trials does not deny these patients of standard treatment.

It should be noted that GTN is a short-acting medication, and its ability to cross the blood–brain barrier has not been ascertained. Future studies of novel medicines should assess the drugs bioavailability in the brain through neuroimaging studies. Furthermore, novel medicines with glutamatergic targets should select patients with elevated brain glutamate levels, as determined by 1H-MRS scans (Egerton, 2019).

The results from our study show no indication of an effect of GTN on symptoms of psychosis or on cognition, and highlights the difficulties in recruiting unmedicated patients. These results,

along with the largely negative findings for SNP, suggest there is little evidence that nitric oxide represents a novel target that will yield a new class of antipsychotic drug.

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Author Contributions

RC, PM, and MT conceived and designed the study. All authors made substantial contributions to the data collection, analysis or interpretation. KM drafted the manuscript which was critically revised by all authors. All authors have approved the final version of the paper and agree to be accountable for all aspects of the work.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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