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The effect of minocycline on symptoms in schizophrenia: Results from a randomized controlled trial☆

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ABSTRACT

Background: Studies have hypothesized that immunological abnormalities might contribute to schizophrenia, and basic science studies, as well as several clinical trials suggest that minocycline could be efficacious in ameliorating both positive and negative symptoms of schizophrenia. In this study we examined the effect of minocycline on schizophrenia in a large randomized controlled trial.
Methods: We performed a 16-week, multi-center, double-blind, randomized, placebo-controlled study on 200 subjects with schizophrenia or schizoaffective disorder randomized to receive either minocycline (200 mg/day, n = 100), or placebo (n = 100) as an add-on to anti-psychotic treatment. The primary outcome measure was the PANSS total score.
Results: Mixed models for repeated measures showed no significant difference between minocycline and placebo for total PANSS (p = 0.862), PANSS subscales, CGI or BACS.
Conclusions: Minocycline did not improve symptoms or cognition in schizophrenia.

1. Introduction

Minocycline is a second-generation tetracycline that exerts anti-inflammatory and antimicrobial effects, and is hypothesized to have neuroprotective activity. It decreases macrophage/microglial activation, cytochrome *c* release, and diminishes damaging MAPK signaling (Jordan et al., 2007; Kim and Suh, 2009). Minocycline also affects the glutaminergic system through inhibition of nitrous oxide (nNOS) and blocking of NO- induced neurotoxicity (Du et al., 2001; Kraus et al., 2005), and for these reasons has been suggested as a potential treatment for schizophrenia. A study on rats indicated that minocycline decreased rearing behavior and stereotypic behaviors in a way similar to chlorpromazine (Dokuyucu et al., 2014). Several published clinical trials (Chaudhry et al., 2012; Ghanizadeh et al., 2014; Kelly et al., 2011; Khodaie-Ardakani et al., 2014; Levkovitz et al., 2010; Liu et al., 2014) found that add-on treatment of 200 mg/d of minocycline in addition to antipsychotic treatment was beneficial for negative symptoms and cognition in schizophrenia. A meta-analysis from 2014 did not find significant improvement in patients receiving minocycline vs. placebo (Sommer et al., 2013). A more recent meta-analysis has presented results from clinical trials showing improvement in positive symptoms in patients receiving minocycline (Xiang et al., 2017), including a study by Miyaoka et al. (Miyaoka et al., 2008) which administered open-label 450 mg/day minocycline.

Based on these encouraging data, the objective of the current study was to perform a large, multi-center double-blind, parallel group, placebo

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controlled add-on study in patients with schizophrenia, in order to test minocycline's effects on symptoms and cognition in schizophrenia.

2. Materials and methods

This study was part of a larger study testing the effects of minocycline, pramipexole or aspirin, vs. placebo as add-on to antipsychotic medication, with each arm including 100 patients. For the purposes of the current analysis we used 100 patients receiving minocycline and compared them to 100 patients receiving placebo. Subjects (n = 200, Table 1) were either inpatients (≥3 days after admission) or outpatients recruited from 30 sites located in Romania and the Republic of Moldova, between January to June 2011. The duration of the trial for each participant was 16 weeks. Key inclusion criteria were ages 18 to 65, with a DSM-IV-TR schizophrenia or schizoaffective disorder diagnosis, use of an antipsychotic drug for at least 2 weeks prior to the baseline visit; a score of ≥4 (moderate or worse) on 2 or more of the following PANSS items- delusions, hallucinatory behaviors, conceptual disorganization or suspiciousness/persecution and/or a total PANSS negative symptoms score of 18 or above; and a CGI-S score of ≥4 (moderate or worse) at screening. Patients receiving any of the study medications were excluded from the study. The study received ethical approval from the respective local and national regulatory authorities and each patient provided informed consent. Study participants were randomized to receive minocycline 200 mg/day or placebo both in divided doses taken twice daily. The use of 200 mg/day was based on previous studies, which tested minocycline for schizophrenia.

Table 1
Baseline demographic and clinical characteristics for patients in the minocycline and placebo groups (n = 100 for each group).

Characteristic	Placebo		Minocycline		p-Values
	Mean or count	SD or %	Mean or count	SD or %	
Age, mean (SD), y	43.5	(9.7)	43.4	(10.5)	0.92[a]
Gender					0.57[b]
Female	54	(54%)	58	(58%)	
Male	46	(46%)	42	(42%)	
Marital status					0.79[b]
Never married (Single)	50	(50%)	56	(56%)	
Presently married	18	(18%)	15	(15%)	
Divorced/Separated	26	(26%)	25	(25%)	
Widowed	6	(6%)	4	(4%)	
Formal education					0.80[b]
1–8 years	11	(11%)	12	(12%)	
8–16 years	83	(83%)	84	(84%)	
>16 years	6	(6%)	4	(4%)	
Inpatient (%)	14	(14%)	20	(20%)	0.64[b]
Psychiatric diagnosis					
Schizophrenia (%)	90	(90%)	79	(79%)	0.03[b]
Schizoaffective disorder (%)	11	(11%)	21	(21%)	0.05[b]
Number of hospitalizations, mean (SD)	15.6	(15.3)	18.2	(19.8)	0.30[a]
Age at onset of psychiatric illness, mean (SD), y	26.3	(7.7)	26.2	(8.4)	0.88[a]
Baseline PANSS score, mean (SD)					
Total PANSS score	96.5	(16.0)	94.6	(14.3)	0.36[a]
Positive scale	23.6	(4.7)	23.9	(4.9)	0.67[a]
Negative scale	25.8	(6.2)	24.5	(4.7)	0.11[a]
General Psychopathology scale	47.1	(9.5)	46.1	(8.7)	0.44[a]
Baseline CGI-severity score, mean (SD)	4.8	(0.8)	4.7	(0.7)	0.11[a]
BACS (z-scores)					
Total Verbal Memory	−2.2	(1.6)	−2.0	(1.5)	0.49[a]
Digit Sequencing	−2.4	(1.7)	−2.1	(1.5)	0.29[a]
Token Motor Task	−1.8	(1.6)	−1.5	(1.4)	0.26[a]
Total Fluency	−2.3	(1.0)	−2.2	(0.9)	0.51[a]
Symbol Coding	−3.0	(2.0)	−3.0	(1.9)	0.99[a]
Tower of London	−1.9	(2.2)	−1.8	(2.3)	0.68[a]
BACS Composite	−3.6	(2.1)	−3.4	(1.8)	0.43[a]

[a] Two-tailed two-sample *t*-test.
[b] Two-tailed chi-square test.

Psychopathological symptoms were assessed at baseline and at predetermined intervals using the PANSS scales (Kay et al., 1987), the Clinical Global Impression Scale-Severity (CGI-S) and Global Impression Scale- Improvement (CGI-I) (Guy, 1976), and the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2008). Structured assessments of side effects were performed using the Simpson- Angus Scale (Simpson and Angus, 1970) and the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating (Lingjaerde et al., 1987). Compliance was monitored through capsule and bottle counts and interviews at weeks 1, 3, 4, 6, 7, 9, 10, 11, 13, 14 and 15. A minimum of 75% adherence was required for participants to be considered compliant. Blood samples for biomarkers of inflammation were collected at baseline, week 8 and end of study visits.

The primary outcome measure of the study was PANSS total score at the end of the trial. Because this study tested aspirin, pramipexole and minocycline all of which have been reported to affect positive, negative or both types of symptoms, PANSS total was used as the primary outcome measure. Secondary outcome measures were PANSS positive, negative and general psychopathology scales, Clinical Global Impression Scale-Severity (CGI-S) and Global Impression Scale-Improvement (CGI-I), Brief Assessment of Cognition in Schizophrenia (BACS) and rates of drop outs before the end of the trial.

According to the power analysis performed at the beginning of the study, the number of proposed subjects in each drug treatment group (n = 100) allowed power of >85% in order to detect a medium (d = 0.5) or larger effect size response, corresponding to a mean 15% change from baseline within the active treatment group, and very little change over time within the placebo group.

The randomization was done in blocks of 4, with 1:1:1:1 pramipexole/minocycline/acetylsalicylic acid/placebo. A randomization list was provided by data management to the study drug manufacturer, which assigned the medication according to the randomization list. Randomization at individual sites was done according to the study medication label number. Raters were GCP trained and board certified. All principal investigators were involved in a number of previous international clinical trials (Davidson et al., 2009).

2.1. Statistical analysis

Data analyses were conducted using Stata version 14, the statistical analysis code is available upon request. Since this RCT was designed as a four-arm trial with three active treatments being compared to a single control group, all p-values are adjusted for the three pair-wise comparisons using the Šidák method. We used mixed models for repeated measures to determine the effect of minocycline (vs. placebo) on the PANSS, CGI-S, and BACS outcomes. Models included interaction terms for visit * group were calculated using restricted maximum likelihood, and included random effects for visit. In addition, as a sensitivity analysis, we estimated the effect of minocycline vs. placebo on each outcome at 16 weeks post-randomization using ANCOVA (with the respective baseline outcome as covariate). This was done in two different ways: using an intention-to-treat approach (last observation carried forward) and a completers-only approach using data from all subjects with observed data at 16 weeks.

We also used mixed models to conduct exploratory subgroup analyses examining whether baseline PANSS, demographic factors, and/or medications used during the study modified the effect of minocycline vs. placebo on PANSS at week 16 (presented as a forest plot). Medications were then analyzed according to use of risperidone, use of clozapine, and low vs. high potency anti-psychotics. When possible, subgroup categories were defined according the median value. Likelihood ratio (LR) tests were used to assess the addition of three-way interactions of time * intervention * modifier. When a baseline variable changes the outcome of drug in a materially different manner than

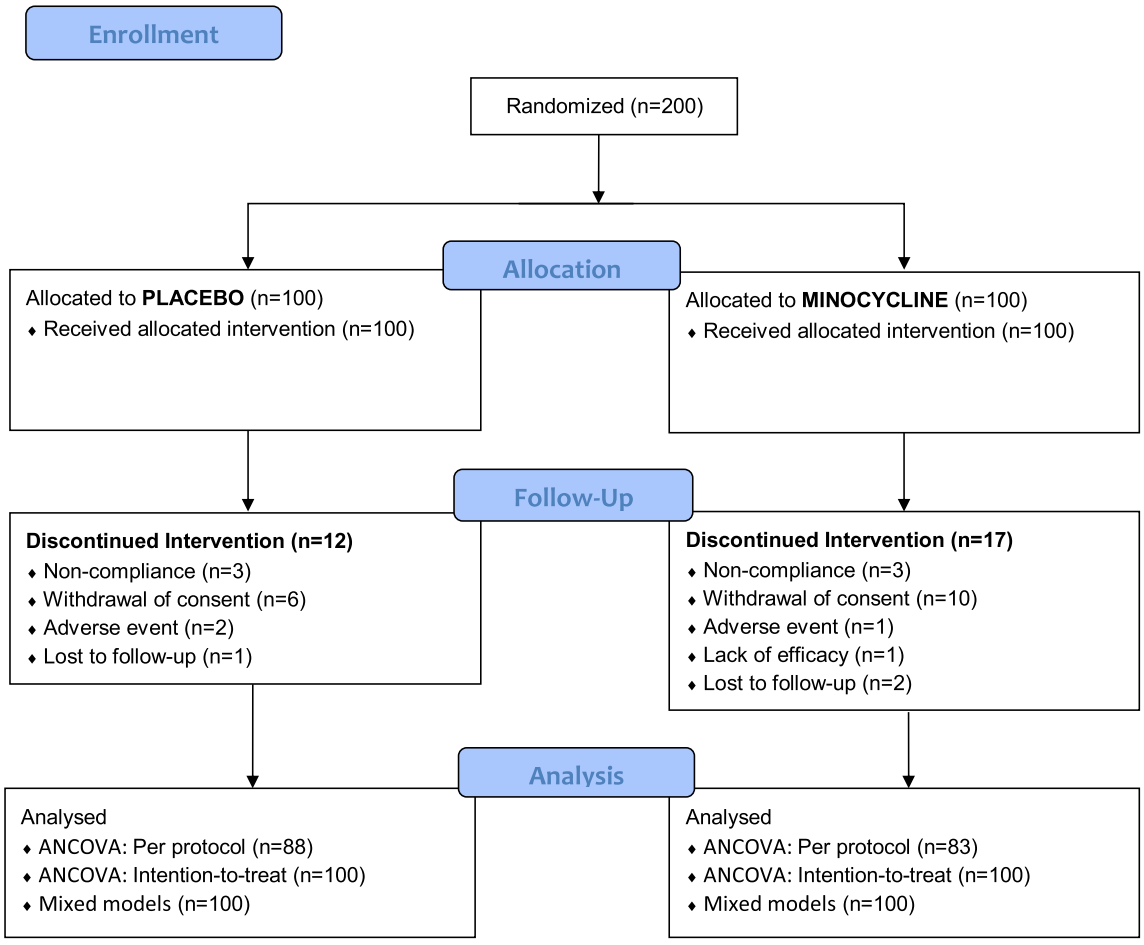


Fig. 1. CONSORT diagram.

that of placebo, it suggests that this variable may to some degree mediate this outcome rather than a moderator variable which affects both drug and placebo equally. A low LR test p-value can be interpreted as evidence for this. If there were mediation, the confidence difference between each horn of the dichotomy would not overlap.

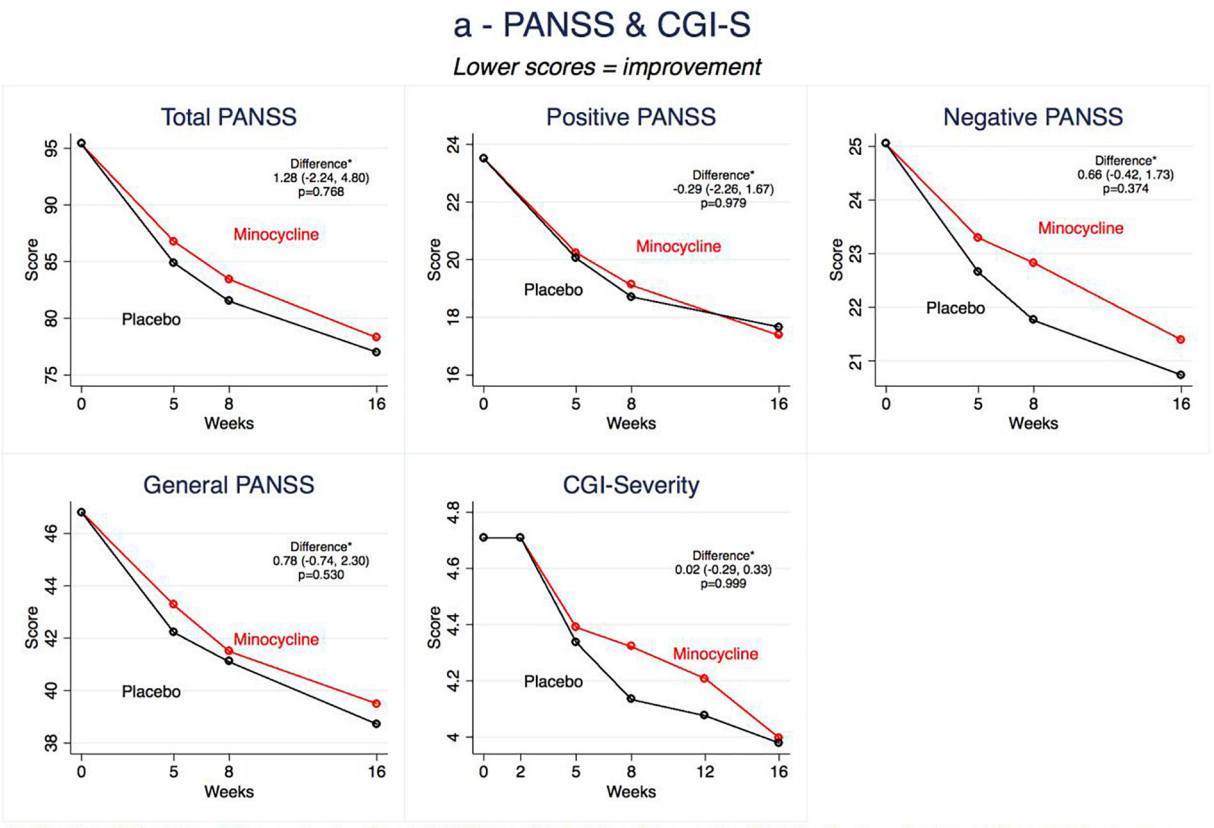
3. Results

A total of 200 patients were randomized to the trial (see CONSORT diagram, Fig. 1). The mean age of patients was 43, 56% were females, 17% were inpatients, mean duration of illness was 13 years. Mean PANSS total score at baseline was 95.5, mean CGI at baseline was 4.8 (Table 1).

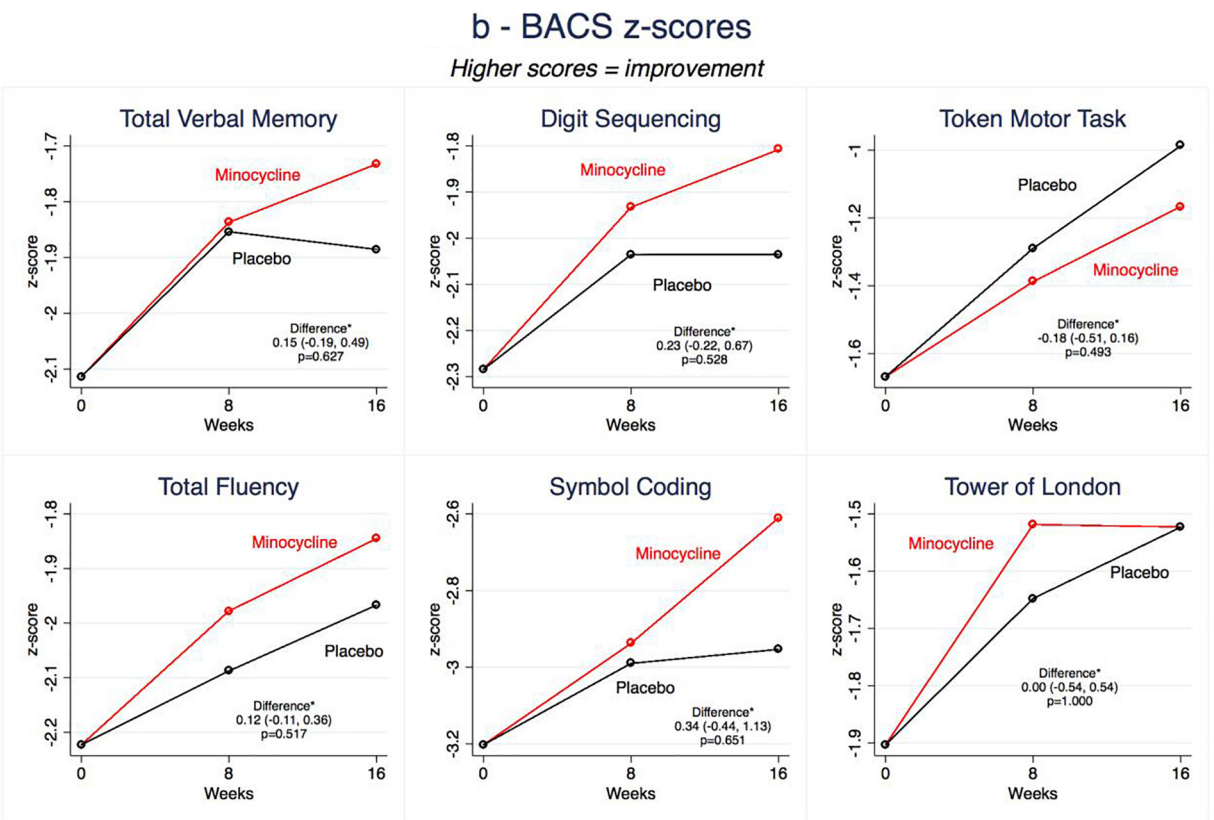
Table 2
Differences at week 16 for minocycline vs placebo §.

	Mixed Model for Repeated Measures (MMRM)			Analysis of covariance					
				LOCF			Per protocol		
	Diff	95% CI	p-Value	Diff	95% CI	p-Value	Diff	95% CI	p-Value
PANSS total	1.32	(−3.19, 5.83)	0.862	1.89	(−2.55, 6.34)	0.667	1.60	(−3.02, 6.21)	0.791
Positive Symptoms	−0.33	(−1.92, 1.26)	0.944	0.21	(−1.30, 1.73)	0.982	−0.20	(−1.74, 1.34)	0.985
Negative Symptoms	0.86	(−0.58, 2.30)	0.392	0.63	(−0.71, 1.98)	0.594	0.76	(−0.67, 2.19)	0.499
General Symptoms	0.85	(−1.53, 3.23)	0.779	0.98	(−1.27, 3.23)	0.651	0.97	(−1.43, 3.36)	0.704
CGI-severity	0.11	(−0.21, 0.42)	0.807	0.12	(−0.16, 0.40)	0.684	0.09	(−0.21, 0.39)	0.840
BACS (z-scores)									
Total Verbal Memory	0.13	(−0.23, 0.49)	0.765	0.15	(−0.17, 0.47)	0.591	0.13	(−0.22, 0.49)	0.754
Digit Sequencing	0.22	(−0.20, 0.64)	0.498	0.22	(−0.15, 0.59)	0.397	0.23	(−0.19, 0.64)	0.482
Token Motor Task	−0.19	(−0.57, 0.20)	0.563	−0.14	(−0.49, 0.22)	0.731	−0.18	(−0.57, 0.20)	0.592
Total Fluency	0.12	(−0.14, 0.37)	0.614	0.08	(−0.15, 0.30)	0.797	0.15	(−0.11, 0.40)	0.417
Symbol Coding	0.41	(−0.08, 0.90)	0.127	0.43	(−0.01, 0.87)	0.060	0.37	(−0.12, 0.86)	0.192
Tower of London	−0.02	(−0.48, 0.45)	1.000	−0.03	(−0.44, 0.37)	0.996	0.00	(−0.46, 0.46)	1.000
BACS Composite	0.18	(−0.23, 0.58)	0.654	0.17	(−0.20, 0.53)	0.609	0.18	(−0.23, 0.59)	0.629

§ A positive difference means the minocycline group had a higher score than the placebo group. For example, as calculated using a MMRM, the minocycline group had a Total PANSS score 1.32 points higher than the placebo group. For PANSS and CGI-S, a low score equals improvement in well−being; for BACS a high score equals improvement in well-being.
† Confidence intervals and p-values are Sidak-adjusted to account for the two other interventions.
Abbreviations: CI = confidence interval; Diff = difference between groups; LOCF = last observation carried forward.



* Estimated effect of minocycline vs. placebo at week 16 (95% confidence interval in parenthesis) derived from a mixed model for repeated measures. P-values and confidence intervals are Sidak-corrected.



* Estimated effect of minocycline vs. placebo at week 16 (95% confidence interval in parenthesis) derived from a mixed model for repeated measures. P-values and confidence intervals are Sidak-corrected.

Fig. 2. Change from baseline to week 16: (A) PANSS & CGI-S, (B) BACS z-scores, (C) BACS composite z-score.

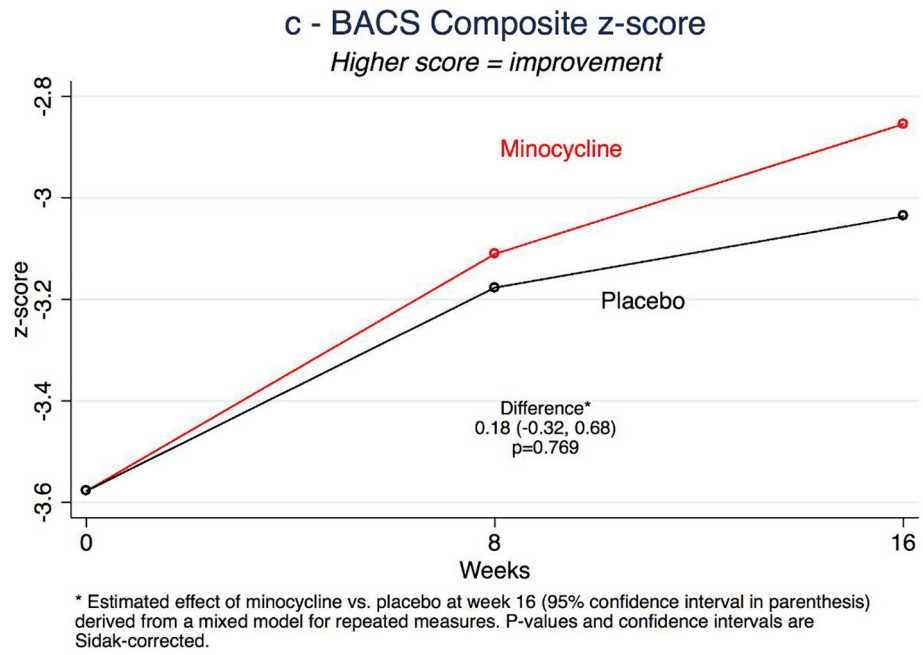


Fig. 2 (*continued*).

Mixed models for repeated measures comparing minocycline to placebo showed almost no difference on significance for total PANSS scores with the outcome on placebo being 1.3 PANSS points better than minocycline ($p = 0.862$), with similar findings for the positive ($p = 0.944$), negative ($p = 0.392$), and general psychopathology ($p = 0.779$) scales (Table 2, Fig. 2a). Differences between baseline and week 16 assessments on psychiatric and cognitive symptoms (Table 2) showed that the improvement with minocycline was almost identical to that of placebo augmentation, generally favoring placebo, although both drugs improved due to treatment with anti-psychotics that all patients received (see Figs. 1, 2). Comparisons for the CGI-severity scale did not show any trend for significance ($p = 0.807$) (Fig. 2a). Comparisons of the BACS cognition scale did not show any trend for significance for the BACS composite z-score, $p = 0.654$, Fig. 2b, c. This being said, looking at the individual BACS scores does show a non-significant numerical improvement for 5/6 BACS items and for the composite score in the minocycline group either at week 8 or 16 or both.

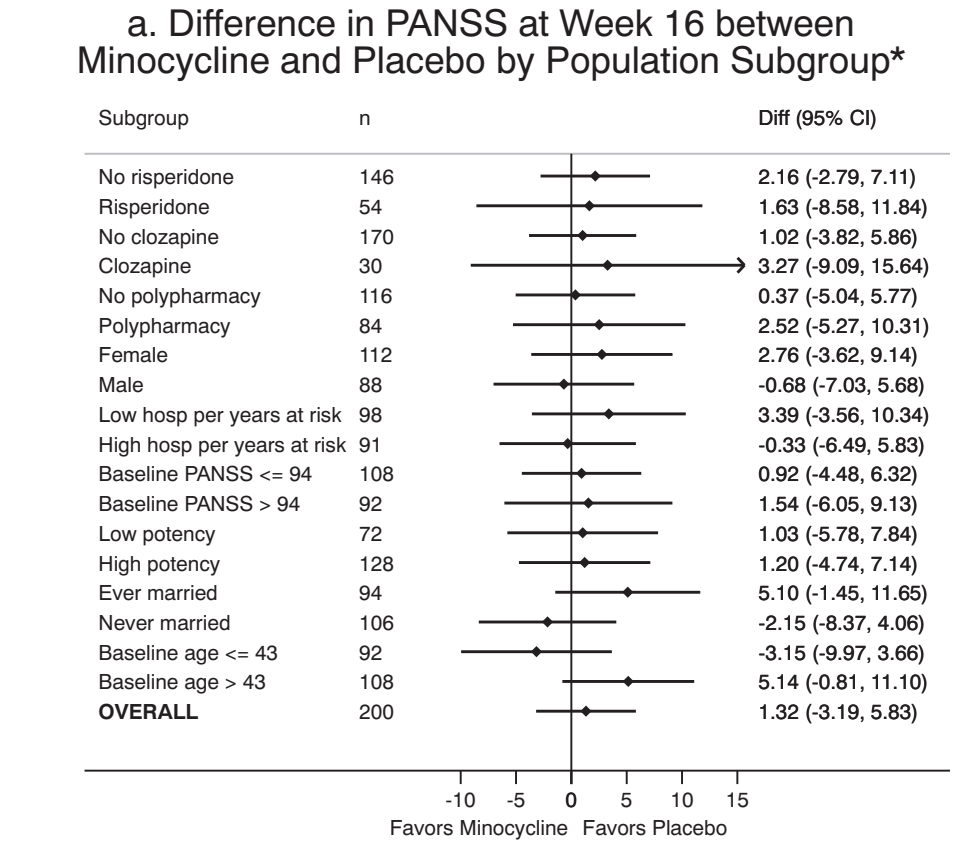
Analyses on the difference in PANSS scores at week 16 between minocycline and placebo by population subgroup revealed no difference between males and females, patients with more rather than less hospitalizations, baseline PANSS scores, marital status, low vs. high potency medications, use of risperidone or clozapine, and age (Fig. 3a). No significant difference was found in the BACS composite z-score at week 16 between minocycline and placebo by subgroups of education status (Fig. 3b). CRP levels were not significantly different between the study groups. Additional analyses on additional biomarkers are ongoing and will be published in a separate paper.

No significant difference was found between groups in adverse events, as can be seen in Table 3.

4. Discussion

This study utilized clinical data in assessing the potential effects of minocycline as a potential treatment for schizophrenia, based on the dopaminergic mechanisms which are known to be involved in schizophrenia. Previous literature on preclinical data on minocycline shows that minocycline has a protective effect against nigrostriatal dopaminergic system dysfunction (Meulendyke et al., 2012). Based on these pre-clinical data, minocycline would not be expected to improve positive psychotic symptoms, at least not analogously to antipsychotic drugs that block D2 receptors. Alternatively, it could be hypothesized that minocycline's effect on dopaminergic activity might lead to improvement in negative symptoms (Murray et al., 2008), but this is not supported in the current study, as minocycline was not efficacious in treating negative symptoms or cognition. Our negative results are similar to those of a recently published clinical trials of add-on minocycline in schizophrenia (Deakin et al., 2018). These results contradict those of other authors who reported that minocycline is efficacious for negative symptoms (Chaudhry et al., 2012; Ghanizadeh et al., 2014; Kelly et al., 2011; Khodaie-Ardakani et al., 2014; Levkovitz et al., 2010; Liu et al., 2014; Miyaoka et al., 2008), meta-analyzed in Oya et al.'s paper (Oya et al., 2014). Some of these studies also showed efficacy for PANSS total and PANSS General Psychopathology (Khodaie-Ardakani et al., 2014; Liu et al., 2014), our results did not. Although overall the results on cognition were not statistically significant, there was an improvement in scores in weeks 8 or 16 or both. These results are not significant but they might reflect changes at the upper limit, or greater practice effects, especially when compared with placebo.

Possible explanations for these discrepancies include that many of these previous studies treated patients in earlier stages of schizophrenia (Kelly et al., 2011; Khodaie-Ardakani et al., 2014), whereas this current study treated more severe, chronic patients. This suggest that minocycline's protective effect might occur early in the natural course of schizophrenia, but once the illness enters the chronic phase, minocycline is no longer efficacious. Additionally, previous studies gave minocycline for a longer period of time. Levkovitz et al. administered 200 mg/daily for 6 months, and Chaudhry et al. administered 200 mg/daily for up to one year, whereas we gave study medication for four months only. However, we do not know of any psychotropic medication which is not active after four months and is active after six. It is also important to note that minocyclince has caused worsening of symptoms in other diseases, such as amytrophic lateral sclerosis, in which patients on minocycline showed worsening signs (Gordon et al., 2007), and multiple sclerosis, in which patients did not show improvement after 6 months (Metz et al., 2017). More importantly, this is a large, multi-center trial while most of the positive trials were single center trials. While it could be claimed that unwanted variability and



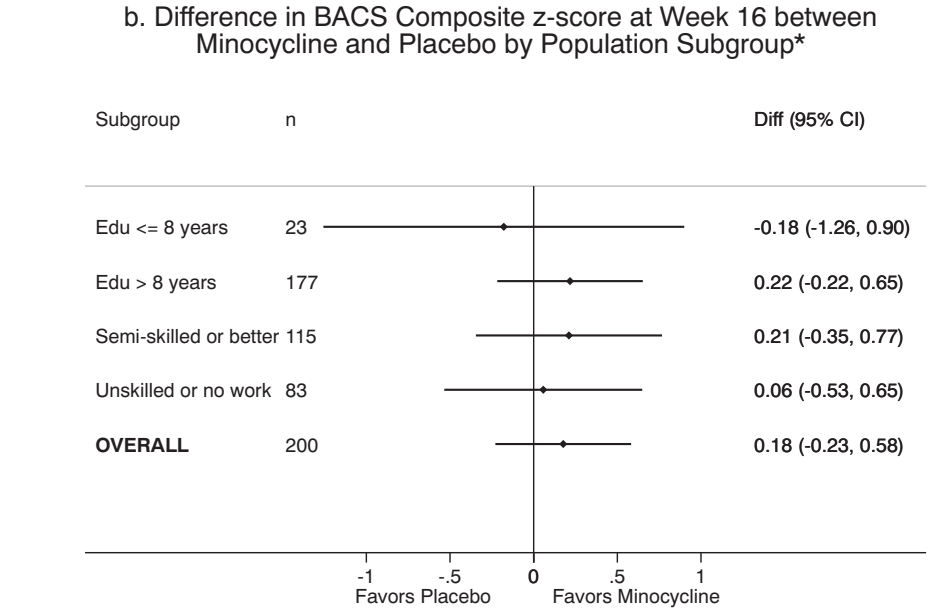


Fig. 3. Difference at week 16 between minocycline and placebo by population subgroup: (A) PANSS, (B) BACS composite z-score.

placebo effects are larger in multi-center trials (Kemp et al., 2008), it has also been claimed that many positive single center trials do not replicate in multi-center, larger samples trials (Bellomo et al., 2009). It is common for small sample studies to yield larger results than large studies, the so call small study effect (Collaboration, 2008). Our experience at the Clinical Trials program of the Stanley Medical Research Institute is that small single center studies are often not replicated in much larger multicenter trails.

Table 3
Adverse events experienced at least once during the study (n = 197).[a]

Adverse event	Minocycline (n = 99)	Placebo (n = 98)	p-Value[b]
	No. (%)	No. (%)	
Gastrointestinal disorders	15 (15)	17 (17)	0.85
Nervous system disorders	8 (8)	11 (11)	0.63
Psychiatric disorders	3 (3)	7 (7)	0.33
General disorders and administration site conditions	1 (1)	4 (4)	0.37
Vision disorders	1 (1)	3 (3)	0.62
Cardiac disorders	1 (1)	2 (2)	>0.99
Renal and urinary disorders	0 (0)	2 (2)	0.50
Investigations	11 (11)	15 (15)	0.53
Blood and lymphatic system disorders	0 (0)	3 (3)	0.25
Reproductive system and breast disorders	1 (1)	0 (0)	0.50
Infections and infestations	9 (9)	11 (11)	0.81
Ear and labyrinth disorders	0 (0)	2 (2)	0.50
Skin and subcutaneous tissue disorders	1 (1)	5 (5)	0.21
Injury, poisoning and procedural complications	1 (1)	1 (1)	>0.99
Hepatobiliary disorders	1 (1)	0 (0)	0.50
Respiratory, thoracic and mediastinal disorders	4 (4)	3 (3)	0.72
Musculoskeletal and connective tissue disorders	3 (3)	2 (2)	0.68
Metabolism and nutrition disorders	1 (1)	0 (0)	0.50
Vascular disorders	2 (2)	0 (0)	0.25
Any adverse event	42 (43)	48 (48)	0.48

[a] Three subjects had no follow-up visits.
[b] Fisher's exact test (two-tailed).

5. Limitations

In this randomized controlled trial, participants were chronic patients who have been ill for many years with relatively high levels of symptoms. Therefore, this current study cannot relate to the possibility of administrating minocycline to patients with less severe symptoms or during earlier stages of the illness, and for longer period of time. However, stratifying the analyses for frequency of relapses, baseline PANSS, and a number of other variables showed no difference.

In summary, minocycline is not efficacious in the largest RCT to date of schizophrenia. However, since minocycline is safe, inexpensive and easily accessible, a future study looking at the benefits on practice-related learning and improvements with minocycline should be contemplated.

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The authors declare no conflict of interest.

Contributors

Prof. Mark Weiser takes responsibility for the integrity of the work as a whole, from inception to the published article. Prof. Weiser conceived and designed the study, participated in analysis and interpretation of the data, critically revised it for important intellectual content and approved the final manuscript. Linda Levi and Dr. Shimon Burshtein have been involved in all the steps of the study, starting from the grant proposal and the protocol writing, and including data analysis and intensive work in writing the manuscript. Dr. Chirita and Dr. Cirjaliu were involved in data collection and recruiting subjects. Dr. Gonen was responsible for the organization of the trial both in Romania and in Moldova. Prof. Robert Yolken was highly involved in the planning of the trial and in the analysis of data. Prof. Michael Davidson participated in the design of the study, commented on statistical analyses and made important contributions to the manuscript. Daisy Zamora has run many of the statistical analyses and has prepared all of the figures and tables for the manuscript submission. Prof. John M. Davis helped design the study and assisted with the statistical analyses, as well as the writing process of the manuscript.

Conflicts of interest

All authors declare that they have no conflict of interests.

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