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"The Role of Minocycline in the Treatment of Negative Symptoms of Schizophrenia: A Systematic Review"

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Α. Περίληψη

Εισαγωγή: Η παραμονή των αρνητικών συμπτωμάτων στην σχιζοφρένεια παρά την θεραπεία των θετικών έχει απασχολήσει την σύγχρονη θεραπευτική. Λόγω των θεωριών που συνδέουν την ανάπτυξη της σχιζοφρένειας με ανοσολογικούς μηχανισμούς και λόγω της νευροπροστατευτικής δράσης που φαίνεται να έχει η μινοκυκλίνη σε άλλα νοσήματα του νευρικού συστήματος στηρίχτηκε η ανάπτυξη και δημιουργία κλινικών μελετών .

Στόχος: Ο στόχος της παρούσας μελέτης είναι η βιβλιογραφική ανασκόπηση των τυχαιοποιημένων κλινικών δοκιμών που αφορούν στην αποτελεσματικότητα της μινοκυκλίνης στην θεραπεία των αρνητικών συμπτωμάτων στην σχιζοφρένεια όταν προστίθεται στην ήδη λαμβάνουσα αντιψυχωτική φαρμακευτική αγωγή.

Μέθοδοι: Πραγματοποιήθηκε μια διαδικτυακή αναζήτηση σε βάσεις δεδομένων.

Αποτελέσματα: Δεδομένα εξήχθησαν από 6 τυχαιοποιημένες κλινικές δοκιμές που περιελάμβαναν συνολικά 596 ενήλικες ηλικίας 18 -65 ετών. Οι 4 στις 5 κλινικές μελέτες παρουσίασαν στατιστικά σημαντική διαφορά μεταξύ της μινοκυκλίνης και του placebo στην βελτίωση των αρνητικών συμπτωμάτων ενώ μόνο μία μελέτη δεν παρουσίασε στατιστικά σημαντική διαφορά.

Συμπέρασμα: Η μινοκυκλίνη φαίνεται να είναι αποτελεσματική στην βελτίωση των αρνητικών συμπτωμάτων. Λόγω όμως τη μεγάλης ετερογένειας των μελετών είναι επισφαλές να καταλήξουμε σε κάποιο συμπέρασμα. Απαιτούνται περισσότερες μελέτες. Η ανάπτυξη περισσότερων ανοσολογικών θεραπειών μπορεί να αποτελέσει στο μέλλον αποτελεσματική θεραπεία για την σχιζοφρένεια .

Λέξεις κλειδιά : μινοκυκλίνη, σχιζοφρένεια, τυχαιοποιημένη κλινική μελέτη

A. Abstract

Introduction: The persistence of negative symptoms in schizophrenia despite the treatment of positive has occupied modern therapy. Due to the theories that link the development of schizophrenia with immune mechanisms and due to the neuroprotective effect that minocycline seems to have in other neurological diseases; a number of clinical studies were developed.

Objective: The aim of the present study is to review the randomized clinical trials regarding the efficacy of minocycline in the treatment of negative symptoms in schizophrenia as an adjunctive therapy to the antipsychotic treatment.

Methods: An online search of databases was performed.

Results: Data were extracted from 6 randomized clinical trials involving a total of 596 adults aged 18-65 years. 4 out of 5 clinical trials showed a statistically significant difference between minocycline and placebo in improving negative symptomς while only one study did not show a statistically significant difference.

Conclusion: Minocycline appears to be effective on improving negative symptoms. However, due to the large heterogeneity of the studies, it is uncertain to reach a conclusion and more studies need to be developed. Advances in immunological therapies may in the future be an effective treatment for schizophrenia.

Keywords: minocycline, schizophrenia, randomized controlled trial

ABBREVIATIONS

CLZ	CLOZAPINE
DSM IV	(DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS , FOURTH EDITION)
PANSS	POSITIVE AND NEGATIVE SYMPTOM SCALE
RCT(s)	RANDOMIZED CONTROL TRIAL(s)
SANS	SCALE FOR THE ASSESSMENT OF NEGATIVE SYMPTOMS
SCZ	SCHIZOPHRENIA
TAU	TREATMENT AS USUAL

B. Introduction

Since early 1900s where schizophrenia was first described as a brain disease, little progress has been made for the investigation of its mechanisms and causes. Schizophrenia is characterized by severe psychotic symptoms that are accompanied by cognitive deficits and psychosocial dysfunction that leads to cognitive and functional impairment. For the treatment of schizophrenia drugs that antagonize D2-receptors have been used with sufficient results on positive symptoms but poorer on negative symptoms.

Negative symptoms, such as anhdonia, alogia, avolition, flattening of affection and disturbances of attention may be underestimated regarding their importance but they are the main reason of disability in schizophrenia as well as for the deterioration of social function. For the assessment of these symptoms rating scales have been proposed such as PANSS (positive and negative symptom scale) and SANS (scale for the assessment of negative symptoms). PANSS is a 30-item 7-point rating instrument; the patient is rated from 1 to 7 on 30 different symptoms. SANS evaluates five domains (affective flattening or blunting, alogia, avolition-apathy, anhdonia-asociality, attention) of negative symptoms. The patient is rated from 0 (absent) to five (severe) in each domain.

Several studies characterize schizophrenia as a neurodevelopmental disorder (1),(2). Studies have mainly focused on the investigation of these theories leading to the association of schizophrenia with activation of the immune processes (3, 4).These mechanisms seem to be mediated by genetic and environmental factors (5, 6). Negative symptoms of schizophrenia seem to be connected with inflammatory and glutamatergic pathways as well as dopaminergic signaling dysfunction (7).The negative symptoms of schizophrenia determine the prognosis and course of schizophrenia.

Minocycline is a second-generation tetracycline antibiotic, used for a variety of Gram-positive and Gram-negative bacteria such as *Mycoplasma*, *Chlamydia, Rickettsiae, Plasmodia,* and *amoebae*, that may influence the function of the central nervous system. Its mechanism of action include the modulation of glutamate-N-methylD-aspartate receptors, a decrease in oxidative and nitrosative stress as well as anti-inflammatory properties (8). It is also indicated that minocycline presents neuroprotective properties in other neurodegenerative disorders such as Parkinson's disease and ischemia (9).The mechanism of action of minocycline in schizophrenia has been extensively reviewed elsewhere (10). Minocycline may have beneficial effects in patients with schizophrenia in whom antipsychotic agents are insufficiently effective on neuroinflammation. Anti- psychotic drugs are mainly effective on positive symptoms acting on dopamine and serotonin pathways. Minocycline may improve negative symptoms that available antipsychotics seem to

be insufficient. Minocycline is investigated as an add-on treatment to traditional antipsychotics (11).

Ten previous systematic reviews and meta-analyses have investigated the effects of minocycline as an add-on treatment on schizophrenia. The most recent is reported last year (12). Overall, these studies have concluded that minocycline is superior to placebo in improving negative symptoms .The aim of the present study is to review the randomized clinical trials (RCTs) regarding the efficacy of minocycline in the treatment of negative symptoms in schizophrenia as an adjunctive therapy to the antipsychotic treatment. The primary outcome is to evaluate the change in the rating scales used for the assessment of negative symptoms in minocycline group and placebo group. The secondary outcomes aim to explore the differences in 3 different domains (cognition, functioning and positive symptoms) in these two groups. Ten systematic reviews and metanalyses have been conducted and only 3 (13-15) of them have investigated specifically minocycline and not generally anti-inflammatory drugs.

Based on current knowledge, this study is the first systematic review of RCTs that includes Deakin study (16) and the first one that aims at evaluating specifically the improvement of negative symptoms of schizophrenia regarding minocycline as an add-on treatment.

C .Methods

A literature advanced search was performed in the databases of MEDLINE, Cochrane Library, PUBMED, and Clinical Trials.gov. The terms used where ((minocycline) AND (Schizophrenia)) AND (randomized controlled trial). There were no date limits; the study language was English; and the studies were included in the systematic review according to the relevance of the subject.

Study selection and quality

Only randomized controlled trials with adults aged between 18 years and 65 years were included. Adults were eligible if they met the criteria of a diagnosis of Schizophrenia according to DSM IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition). The study quality was assessed according to the Oxford Quality Scoring System.

The primary outcome was to compare the efficacy of minocycline as an adjunctive treatment of negative symptoms in schizophrenia in comparison to placebo. The secondary outcomes were the measurement of functioning, cognition and positive symptoms using various rating scales.

D. Results

Studies identified through database searching were 301; 1 more were identified through references and after removal of duplicates the records were 111. Thirty-two studies were excluded because they did not meet the eligibility criteria (the subjects were animals, were not available in free texts) and fifty-eight were excluded because they were not RCTs. Sixteen RCTS were found and only ten of them were completed. Only seven of them met the eligibility criteria for this study and one of them was not retrieved. Studies eligible for this systematic review were RCTs that (1) compared minocycline with placebo; as an add on a TAU(treatment as usual-antipsychotic drug) (2) included patients diagnosed with schizophrenia according to structured clinical assessments; and (3) reported efficacy data using a standardized rating scale for the assessment of negative symptoms. The search was based on the PRISMA guidelines flowchart, which is presented in the Figure 1.

D.1 Study characteristics

In some studies, patients were recruited from psychiatric units (17, 18) other from health centers (19) or both (16, 20, 21). In two studies minocycline was used as an add-on to risperidone (19, 21, 22) while in two studies minocycline was an add on clozapine (20, 23) and in one study it was not limited to a certain antipsychotic (24).
The inclusion criteria regarding the diagnosis of schizophrenia varied from less than 5 years of symptoms to 2 -10 years of the disorder. Only one RCT included the efficacy of rating scale as a secondary outcome instead of primary (20).For the assessment of negative symptoms, SANS was used. Among the other studies, two of them used only SANS (20, 25), while two of them used the negative symptoms of PANSS (16, 18) and the other two used both these measurement scales.

The baseline characteristics of the treatment group and the control group were similar (gender, age, nationality, diagnostic procedure, rating scales, duration of symptoms) in all RCTs.

Patients that suffered from diseases such as renal, hepatic, heart disease, diabetes, anemia and dermatological disorders were excluded. No pregnant women were included or breastfeeding patients. Patients with substance abuse that could mislead in the diagnosis of schizophrenia were also excluded as well as patients with hypersensitivity to tetracyclines or treatment with them.

The adverse events were also marked in each study and the most frequent included gastrointestinal, dermatological, psychiatric, central nervous system symptoms such as headaches and constipation. In one study, admissions to hospital were recorded for patients that were included both to the minocycline group and the control group.

This fact was attributed to the remission of schizophrenia. In the same study, one patient from the control group was admitted with deepvenous thrombosis. No deaths occurred to any of the RCTS.

The attrition rates (overall and differential) were estimated separately for each study. Overall attrition rate varied between 4% and 55% for a time period of 3 to 15 months. The differential drop-out rate in two studies at the endpoint was almost 60%.

The duration of the studies ranged from ten weeks to fifteen months and the mean duration was about seven months.

The study characteristics are presented in Table 1. The name, number of participants with age, range, type of rating scale used, duration and the efficacy of the reduction of negative symptoms in 3, 6 months in both treatment and control group are depicted for each study.

Figure 1

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

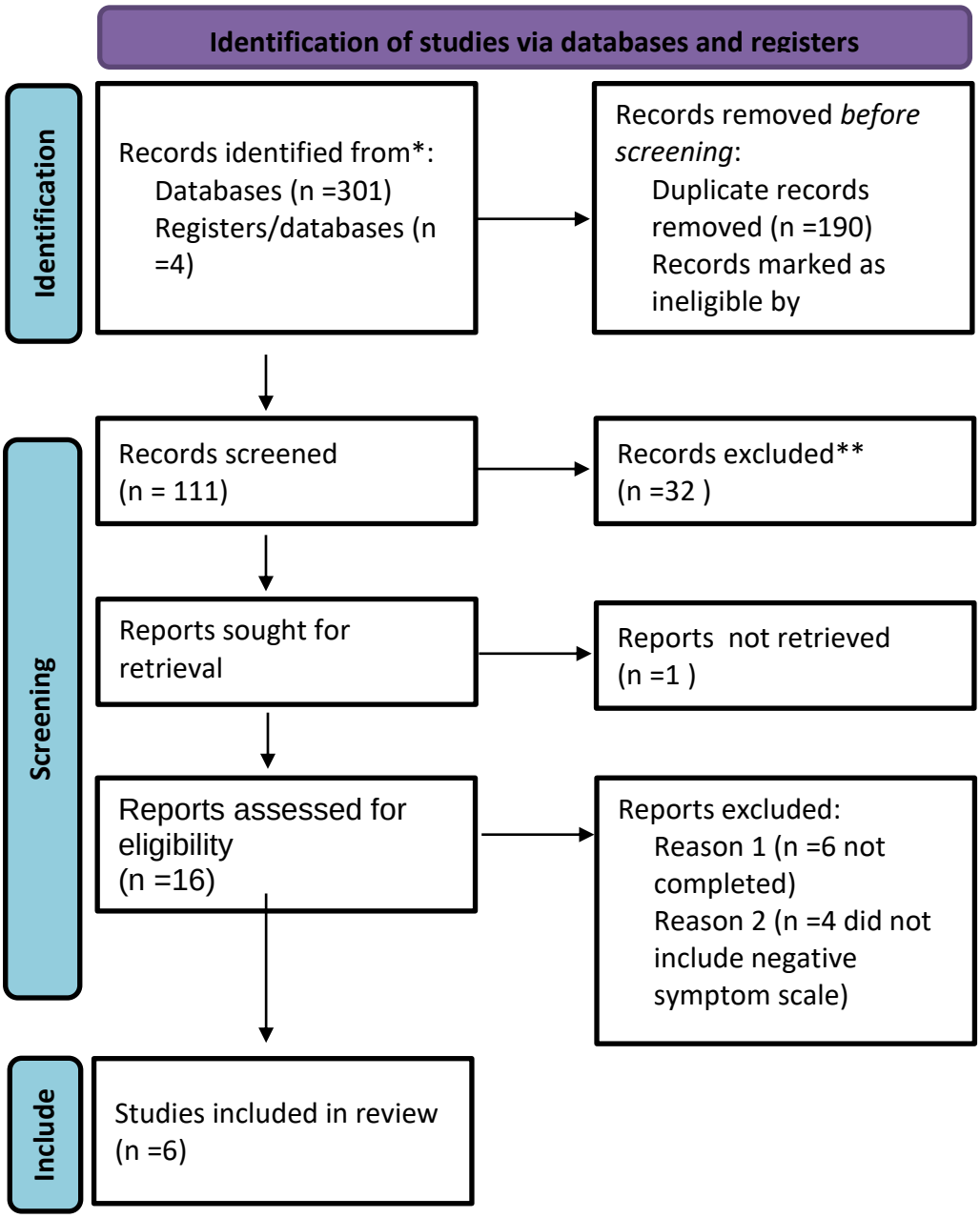

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TABLE 1 . RCTS that study impact of minocycline on negative symptoms of schizophrenia

Study	Participants	Type of add-on treatment	Duration period of the study	Negative symptoms improvement	Retention rate %	Comments
Liu et al., 2014	N=79(18-40 Yrs) Male 62% Female 38% Early stage schizophrenia Nationality :Chinese	Risperidone plus Minocycline N=39 Risperidone plus Placebo N=40	6 months	SANS total score Week 8→44.26 (p=0.015) Week 12→38.74 (p<0.001) Week 16→32.33(p<0.001) SANS total score Week 8→53.55 (p=0.015) Week 12→50.38 (p<0,001) Week 16→47.80(p<0.001) Response rate of SANS week 4→5.1% week 8→12.8% week 12→25.6% week 16 →43.6%	97% in minocycline group 14% of dropout Because of lost to follow-up, nonadherence, change of antipsychotic drug 15% of dropout Because of lost to follow-up, nonadherence ,change of antipsychotic drug	No difference between the two groups to cognitive function, Short course study, No follow up – unknown result after stop of use of minocycline

Levkovitz et al., 2010	N=54(18-35 Yrs) Male 80% Female 20% Early-phase schizophrenia Nationality :Israeli	Atypical antipsychotic plus minocycline	6months	Baseline→42.54 ±18.66 Endpoint→32.61 ±19.59 p<0,001	Total retention rate 38% 55% of dropout due to nonadherence, adverse events, withdrawal of consent, clinical deterioration	Low completion rates, The antipsychotic used was clozapine which needs monitoring , Small number of patients
		Atypical antipsychotic plus minocycline		Baseline→43.56±18.12 Endpoint→41.56±17.88	55% of dropout due to nonadherence, adverse events, withdrawal of consent	

Kelly et al., 2011;	N=52(18-65 Yrs) Male:74% Female:26% 6-month clozapine Nationality: American and English	CLZ plus minocycline N=29	10 week	SANS total score Week 0→29.7 ±13.3 (p>0.05) Week 10→28.2 ±12.4 (p>0.05) SANS avolition Week 0→2.5 ±0.9 (p=0.01) Week 10→2.2 ±0.9 (p=0.01)	Total Retention Rate 96% 6% of dropout due to pre-existing medical issues No drop out	Improvement of negative symptoms not the primary outcome, Patients receiving clozapine for 6 months, Short course,
		CLZ plus placebo N=23		SANS total score Week 0→33.3 ±10.3 (p>0.05) Week 10→35.1 ±10.7 (p>0.05) SANS avolition Week 0→2.4 ±0.8 (p=0.01) Week 10→2.6 ±0.8 (p=0.01)		

Deakin et al., 2018;	N=207 (16-35 Yrs) Male :72% Female:28% First episode schizophrenia, schizophrenicomorf, schizoaffective disorder Nationality: English	Any antipsychotic plus Minocycline group N=41	15 months	PANS negative subscale Baseline→17.7±5.9 2 months→16.4±5.6 6 months→15.8±6.5 9 months→15.9±6.3 12 months→16.4±6.2 Follow-up→15.6±6.6 (p>0.05)	Total retention rate 42% 53% of dropout due to lost to follow up, withdrawal, gastrointestinal adverse events(abdominal pain, vomit), epilepsy, visual disturbances	No difference in negative symptoms in comparison to previous literature,
				Baseline→16.8±5.5 2 months→15.1±5.8 6 months→15.7±5.8 9 months→14.5±.,9 12 months→14.2±5.2 Follow-up→14.0±4.9 (p>0.05)	60% of dropout due to lost to follow up, withdrawal, gastrointestinal adverse events(abdominal pain, vomit)	
		Any antipsychotic plus Placebo N=48				

Chaudhry et al., 2012;	N=94(18-65 Yrs) Male59% Female :41% First five years of diagnosis Nationality: Pakistan and Brazilian	Any antipsychotic plus Minocycline group N=46 Any antipsychotic plus Placebo N=48	12 months	PANSS negative scale score Pakistan baseline→ 22.26±8.12 6 months →16.53±5.22 12 months→12.51±4.53 Brazil baseline →23.07±8.60 6 months →16.46±5.64 12 months →13.77±6.50 PANSS negative scale score Pakistan Baseline→ 22.46±6.47 6 months→18.82±5.78 12months→15.54±9.23 Brazil baseline →17.80±6.57 6 months→18.09±7.52 12 months→18.45±7.15	Total Retention Rate 65% 35% of dropout due to non cooperative family, migration, side effects ,non compliance,death,lost to follow-up 34% of dropout due to non cooperative family, migration, treating doctor refused, extrapyramidal side effects, suicide, refused testing, lost to follow-up	2 different national groups, Random allocation of antipsychotic drug Scales used for different population may alter validity

Zhang& Zao ,2014	N=110(18-45 yrs) Male:27% Female :63% Early diagnosed Nationality: Chinese	Risperidone plus Minocycline High dose N=25	3months	SANS Score Month 1→56.68±6.18(p=0.003) Month 2→53.44±6.36 Month 3→51.08±6.76	Total retention rate 76% 28% dropout because of lost to follow-up and withdrawal of consent 20% dropout because of lost to follow-up and withdrawal of consent 24% dropout because of lost to follow-up and withdrawal of consent	First study to compare placebo group with different minocycline dosage group, No follow up study to compare results after stop of use of minocycline.
		Risperidone plus Minocycline low dose N=25		Month 1→57.80±5.82(p=0.003) Month 2→55.40±6.06 Month 3→53.88±6.20		
		Risperidone plus Placebo N=25		Month 1→59.12±5.11(p=0.003) Month 2→57.16±5.74 Month 3→55.72±6.44		

D.2 Study Quality

Adults were randomly assigned to the minocycline therapy group and the control group received the usual therapy. In all RCTs, there was blinding. The negative symptoms were assessed in most studies at baseline and at the endpoint except for three studies in which patients were assessed in each visit (19, 21, 24). The primary outcome in 5 out of 6 studies was the elevation of negative symptoms while in one study this was a secondary outcome. The secondary outcomes varied among assessment of cognition, functioning and evaluation of positive symptoms.

D.3 Study Outcomes

Primary Outcome

Data were extracted from 6 RCTs with a total of 596 participants aged between 18 to 65 years. In four out of the five studies, statistical significant differences were found between minocycline and placebo group regarding the decrease of scores in scales to measure the negative symptoms of schizophrenia. Only one study did not report any significant difference neither in the decrease of scores or in worsening the symptoms of placebo patients as it was anticipated. Specifically, in three studies, SANS total score was decreased after 3 months of treatment (in one of them after 8 weeks) and the response rates of SANS depicted significant differences in 12 and 16 week. One study showed no difference in the total score of PANSS between the two groups but revealed statistical significant difference in the avolition subscale between minocycline group and placebo group(p=0.003).

Secondary Outcomes

Adverse effects

The most common adverse events reported in the studies were gastrointestinal symptoms, central nervous system symptoms (headache, dizziness) and dermatological (rash, pigmentation). In two studies, no serious adverse events were reported and no significant difference between minocycline and placebo group. In Levkovitz et al (19), the indigestion and pigmentation of patients in the minocycline group was a reason to drop out from the study. In Kelly et al (20), side effects of minocycline group seem to be similar to the placebo. Headache and constipation were more common among the placebo group. In Deakin (16) et al, study 25 admissions were reported in both minocycline and placebo group due to deterioration of schizophrenia and one patient showed signs of deep-venous thrombosis. In Chaudry et al (18), patients suffered from nausea, anorexia, vomiting, headache, dizziness, skin reactions, tooth discoloration and visual disturbances. None of the patients from all studies have displayed any extrapyramidal symptoms.

Cognition

From the above studies, only two seem to relate minocycline with cognitive dysfunction such as working memory(26) and a decrease at CPT –IP score at the 16th week (21).

Functioning

Three of the above studies indicated an overall improvement in the rating scales of functioning (19).

Positive Symptoms

From the rating scales used for the assessment of the positive symptoms, Liu et al reported an overall association with all the PANSS subscales while the association found from Kelly et al of minocycline and BPRS score was not significant.

Retention Rates

All studies experienced withdrawals. Retention rates were estimated for all studies. The retention rate varied between 38% and 96%. The lower retention rate was observed in the study by Levkovitz et al (19). It is mentioned that the dropout rates reported to this study are similar to those found in other RCTs with antipsychotic drugs. Clinical trials involving antipsychotic drugs show low completion rates especially for studies with duration over 12 weeks, probably because of the difficulty of this group of patients to adhere to the treatment. In one study the principle reason for patients' drop-out was the uncooperative family while other patients were lost to follow-up, changes in the antipsychotic drug or presence of adverse events.

E. Discussion

E.1 Mechanisms of action

Minocycline is a tetracycline with sufficient diffusion into the brain. The potential of its use as an antipsychotic was first introduced for the treatment of a schizophrenic patient suffering from pneumonia (27).Minocycline seems to have anti-inflammatory and neuroprotective properties .Although the exact mechanism is still unknown, minocycline seems to inhibit the activation of microglia, attenuates apoptosis and suppresses the production of reactive oxygen species. This antibiotic has been associated in preclinical models with neuroprotection against several neurodegenerative diseases (28). The case for using minocycline in the treatment of schizophrenia relies on the ant inflammatory properties of minocycline and the theory that schizophrenia is related to neuroinflammation .Schizophrenia, for over thirty years, is associated with dysbalance in immune response, increased levels of pro inflammatory substances such as cytokines are found in the blood of patients with schizophrenia while intereleukines might provoke a dopaminergic dysfunction. A probable theoretical approach of minocycline use in the treatment of schizophrenia was that minocycline softens the hyperactivation of synaptic reorganization (8) that involve the overexpression of C4A complement factor that seems to be associated with increased risk of schizophrenia (29). That proposal could confirm a 1982-theory of a probable pathophysiological mechanism for schizophrenia (30) .Schizophrenia has also been affiliated with the activation of microglia . Minocycline has been shown to inhibit the activation of microglia, the proapoptotic caspases as well as the release of cytochrome C (8). Minocycline may also affect dopamine neurotransmission. Studies have shown that pretreatment of minocycline lead to the increase of dopamine levels in the frontal cortex and striatum following the administration of an NMDA antagonist (31). Moreover, minocycline may block nitric oxide-induced neurotoxicity which is related to NMDA receptor activation (32). The mechanism of action is shown in Figure 2.

E.2 Limitations

The main limitations of these studies were their heterogeneity. Studies presented different sample sizes and the doses of minocycline varied between studies. Moreover, there was heterogeneity among the anti-psychotic medications used in each study. Also, the sample size of the studies differed regarding the stage of schizophrenia. While in two studies chronic patients with schizophrenia participated, the other four consisted of early stage patients with schizophrenia.

E.3 Perspectives

In this study, the role of minocycline in the treatment of negative symptoms of schizophrenia was explored.

In literature, animal testing of doxycycline, a minocycline analog, has showed sufficient results that could also be used for future research as an adjunctive therapy (33). Doxycycline was tested on mice to treat amphetamine-induced schizophrenia-like symptoms. This experiment revealed that doxycycline might be an effective antipsychotic drug that could also prevent cognitive impairment.

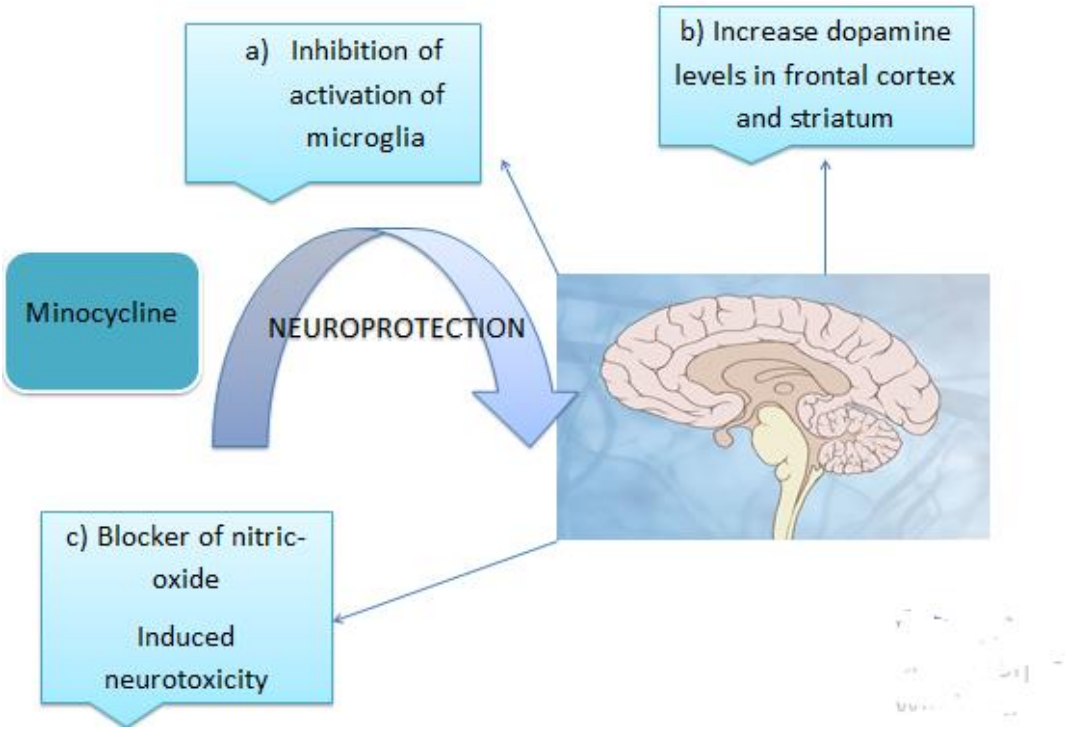

Figure 2.Mechanism of Action of Minocycline in Schizophrenia
a) Inhibition of activation of microglia, b) Increase dopamine levels in frontal cortex and, c) Blocker of nitric-oxide Induced neurotoxicity, d) Relation to glutamate pathway

F. Conclusion

In conclusion, although almost a century has passed since the first antipsychotic drug was first used, there has not been much progress in the treatment of schizophrenia. Several studies have been conducted including anti-inflammatory drugs such as minocycline as a potential treatment. This systematic review showed that minocycline could be used as an adjunctive therapy treatment in patients suffering from negative symptoms of schizophrenia although they already receive antipsychotic medication. Minocycline seemed to alleviate from negative symptoms early stage patients or patients that were diagnosed with schizophrenia the last five years. Patients included to this study showed satisfactory tolerance to the use of minocycline and no serious adverse events were recorded. Although most of these studies have indicated a positive role in the treatment of negative symptoms, their heterogeneity and the large number of drop outs cannot provide safe conclusions as per the role of minocycline in the treatment of negative symptoms. Further mechanistic studies as well as multicentric, larger RCTs are required to explore the clinical utility of minocycline in the treatment of negative symptoms in schizophrenia.

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