http://doi.org/10.47626/1516-4446-2025-4185

Supplementary Material S1 Search strategy

Search strategy PubMed – Date: March 21, 2022

Terms	**Search**
Schizophrenia Results: 23.086	("schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields] OR "schizophrenias"[All Fields] OR "schizophrenia s"[All Fields] OR ("psychotic disorders"[MeSH Terms] OR ("psychotic"[All Fields] AND "disorders"[All Fields]) OR "psychotic disorders"[All Fields] OR "psychosis"[All Fields]))
Toxoplasma Results: 3.124	("toxoplasmosis"[MeSH Terms] OR "toxoplasma"[MeSH Terms] OR ("toxoplasmosis"[MeSH Terms] OR "toxoplasmosis"[All Fields] OR "toxoplasmoses"[All Fields]))
Therapeutics Results: 729.793	("therapeutics"[MeSH Terms] OR ("drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR ("pharmacological"[All Fields] AND "treatment"[All Fields]) OR "pharmacological treatment"[All Fields]))
Search strategy Results: 32	("schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields] OR "schizophrenias"[All Fields] OR "schizophrenia s"[All Fields] OR ("psychotic disorders"[MeSH Terms] OR ("psychotic"[All Fields] AND "disorders"[All Fields]) OR "psychotic disorders"[All Fields] OR "psychosis"[All Fields])) AND ("toxoplasmosis"[MeSH Terms] OR "toxoplasma"[MeSH Terms] OR ("toxoplasmosis"[MeSH Terms] OR "toxoplasmosis"[All Fields] OR "toxoplasmoses"[All Fields])) AND ("therapeutics"[MeSH Terms] OR ("drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR ("pharmacological"[All Fields] AND "treatment"[All Fields]) OR "pharmacological treatment"[All Fields]))

Search strategy SCOPUS – Date: March 21, 2022

Terms	**Search**
Schizophrenia Results: 263,178	("schizophrenia" OR "psychotic disorders")
Toxoplasmosis Results: 46,987	("toxoplasmosis" OR "toxoplasma" OR "toxoplasmosis")
Therapeutics Results: 776,468	("therapeutics" OR "drug therapy" OR "pharmacological treatment")
Search Strategy Results: 9	("schizophrenia" OR "psychotic disorders") AND ("toxoplasmosis" OR "toxoplasma" OR "toxoplasmosis") AND ("therapeutics" OR "drug therapy" OR "pharmacological treatment")

Search strategy LILACS – Date: March 21, 2022

Terms	**Search**
Esquizofrenia Results: 2,700	((Espectro de Esquizofrenia y Otros Trastornos Psicóticos) OR (Esquizofrenia))
Toxoplasma Results: 2,045	(Toxoplasmosis)
Terapeutica Results: 37,609	(Farmacoterapia)
Search strategy Results: 0	((Espectro de Esquizofrenia y Otros Trastornos Psicóticos) OR (Esquizofrenia)) AND (Toxoplasmosis) AND (Farmacoterapia))

http://doi.org/10.47626/1516-4446-2025-4185

Supplementary Material S2 Statistical code for R

```
install.packages("readxl")
install.packages("dmetar")
install.packages("metafor")  # dmetar depende de metafor
library(readxl)
library(dmetar)
library(metafor)

# variables: autor (author),
# puntaje basal sujetos en intervención (pbi),
# desviación estándar de puntaje basal sujetos en intervención (dbi),
# n de sujetos en intervención (ni),
# puntaje final sujetos en intervención (pfi),
# desviación estándar puntaje final sujetos en intervención (dfi),
# puntaje basal sujetos en grupo control (pbc),
# desviación estándar de puntaje basal sujetos en grupo control (dbc),
# n de sujetos en sujetos en grupo control (nc),
# puntaje final sujetos en grupo control (pfc),
# desviación estándar puntaje final sujetos en grupo control (dfc).
# país (Country)
# tiempo de seguimiento en semanas (Time)

getwd
setwd ("/Users/juanfernandocanoromero/Documents/Doctorado/RS/")
data <- read_excel("baseRS.xlsx")

head(data)
data$pfi <- as.numeric(data$pfi)
data$dfi <- as.numeric(data$dfi)
data$ni <- as.numeric(data$ni)
data$pfc <- as.numeric(data$pfc)
data$dfc <- as.numeric(data$dfc)
data$nc <- as.numeric(data$nc)
data$pbi <- as.numeric(data$pbi)
data$dbi <- as.numeric(data$dbi)
data$pbc <- as.numeric(data$pbc)
data$dbc <- as.numeric(data$dbc)
data$Time <- as.numeric(data$Time)
str(data)

data$change_i <- data$pfi - data$pbi  # Cambio en el grupo de intervención
data$change_c <- data$pfc - data$pbc  # Cambio en el grupo de control

data$sd_change_i <- sqrt(data$dbi^2 + data$dfi^2)  # Esto es una simplificación
data$sd_change_c <- sqrt(data$dbc^2 + data$dfc^2)

data <- escalc(
  measure = "MD",
  m1i = change_i,
  sd1i = sd_change_i,
  n1i = ni,
  m2i = change_c,
  sd2i = sd_change_c,
  n2i = nc,
  data = data
)
meta_random <- rma(yi, vi, data = data, method = "REML")
summary(meta_random)
xlim <- par("usr")[1:2]
print(xlim)
```

```
forest(meta_random, xlab = "Standardized Mean difference", slab = data$author)

het_text <- paste0(
  "Heterogeneity: τ² = ", round(meta_random$tau2, 3),
  "; I² = ", round(meta_random$I2, 2), "%, Q = ", round(meta_random$QE, 2),
  " (df = ", meta_random$k - 1, ", p = ", round(meta_random$QEp, 3), ")"
)
par(mar = c(5, 4, 4, 2) + c(0, 0, 1, 0))  # Aumentar margen superior si es necesario
text(x = (xlim[1] + xlim[2]) / 2, y = -6, labels = het_text, pos = 1, cex = 1, xpd = TRUE)


#### Meta-analysis minocycline

data1 <- read_excel("baseRS2.xlsx")
head(data1)
data1$pfi <- as.numeric(data1$pfi)
data1$dfi <- as.numeric(data1$dfi)
data1$ni <- as.numeric(data1$ni)
data1$pfc <- as.numeric(data1$pfc)
data1$dfc <- as.numeric(data1$dfc)
data1$nc <- as.numeric(data1$nc)
data1$pbi <- as.numeric(data1$pbi)
data1$dbi <- as.numeric(data1$dbi)
data1$pbc <- as.numeric(data1$pbc)
data1$dbc <- as.numeric(data1$dbc)
data1$Time <- as.numeric(data1$Time)
data1$change_i <- data1$pfi - data1$pbi  # Cambio en el grupo de intervención
data1$change_c <- data1$pfc - data1$pbc  # Cambio en el grupo de control
data1$sd_change_i <- sqrt(data1$dbi^2 + data1$dfi^2)  # Esto es una simplificación
data1$sd_change_c <- sqrt(data1$dbc^2 + data1$dfc^2)
data1 <- escalc(
  measure = "MD",
  m1i = change_i,
  sd1i = sd_change_i,
  n1i = ni,
  m2i = change_c,
  sd2i = sd_change_c,
  n2i = nc,
  data = data1
)

meta_random1 <- rma(yi, vi, data = data1, method = "REML")

summary(meta_random1)

xlim <- par("usr")[1:2]
print(xlim)
forest(meta_random1, xlab = "Standardized Mean Difference", slab = data1$author)
het_text <- paste0(
  "Heterogeneity: τ² = ", round(meta_random$tau2, 3),
  "; I² = ", round(meta_random1$I2, 2), "%, Q = ", round(meta_random1$QE, 2),
  " (df = ", meta_random1$k - 1, ", p = ", round(meta_random1$QEp, 3), ")"
)
par(mar = c(5, 4, 4, 2) + c(0, 0, 1, 0))  # Aumentar margen superior si es necesario

text(x = (xlim[1] + xlim[2]) / 2, y = -5, labels = het_text, pos = 3, cex = 1, xpd = TRUE)


#### - Time as moderator
data$yi <- (data$pfi - data$pfc)  # Diferencia de medias entre intervención y control
data$vi <- (data$dfi^2 / data$ni) + (data$dfc^2 / data$nc)  # Varianza del tamaño del efecto
meta_moderator <- rma(yi, vi, mods = ~ Time, data = data, method = "REML")
```

```
summary(meta_moderator)
data$effect_size <- (data$pfi - data$pbi) / sqrt((data$dfi^2 + data$dbi^2) / 2)
meta_time_adjusted <- rma(yi, vi, mods = ~ Time, data = data, method = "REML")

summary(meta_time_adjusted)
forest(meta_moderator, xlab = "Adjusted Mean Difference", slab = data$author)

meta_moderator <- rma(yi, vi, mods = ~ Time, data = data, method = "REML")
summary(meta_moderator)

par(mar = c(5, 4, 6, 2) + 0.5)  # Ajusta los márgenes si es necesario

forest(meta_moderator,
       xlab = "Adjusted Mean Difference",
       slab = data$author,
       order = "obs",              # Ordenar por el orden de los estudios
       ylim = c(-4, length(data$yi) + 3))  # Ajustar límites para dar espacio al polígono

intercept <- coef(meta_moderator)[1]              # Intercepto (efecto promedio cuando Time = 0)
ci_lb <- intercept - 1.96 * meta_moderator$se[1]    # Límite inferior del IC 95%
ci_ub <- intercept + 1.96 * meta_moderator$se[1]    # Límite superior del IC 95%

usr <- par("usr")  # Obtener los límites actuales del gráfico

addpoly(intercept,
        ci.lb = ci_lb,
        ci.ub = ci_ub,
        row = -2,             # Coloca el polígono en una fila por debajo de los estudios
        col = "black",          # Color del polígono
        mlab = "Time-Adjusted SMD",  # Etiqueta para el polígono
        cex = 1.0,              # Tamaño del texto
        efac = 0.8)           # Factor de expansión para el ancho del polígono
tau2 <- meta_moderator$tau2
I2 <- meta_moderator$I2
Q <- meta_moderator$QE
Q_p <- meta_moderator$QEp
het_text <- paste0(
  "Heterogeneity: τ² = ", round(tau2, 2),
  ", I² = ", round(I2, 1), "%, Q = ", round(Q, 2),
  " (df = ", meta_moderator$k - 1, ", p = ", round(Q_p, 3), ")"
)

text(x = usr[1] + 0.5 * (usr[2] - usr[1]),
     y = ylim[1] - 2,  # Ajusta la posición en y para colocar el texto debajo del gráfico
     labels = het_text,
     cex = 1.0,
     col = "black",
     xpd = TRUE,       # `xpd = TRUE` permite que el texto se muestre fuera de los límites del plot
     pos = 1)          # Alinea el texto al centro horizontalmente

data1$yi <- (data1$pfi - data1$pfc)  # Diferencia de medias entre intervención y control
data1$vi <- (data1$dfi^2 / data1$ni) + (data1$dfc^2 / data1$nc)  # Varianza del tamaño del efecto
meta_moderator1 <- rma(yi, vi, mods = ~ Time, data = data1, method = "REML")

summary(meta_moderator1)

data1$effect_size <- (data1$pfi - data1$pbi) / sqrt((data1$dfi^2 + data1$dbi^2) / 2)
meta_time_adjusted1 <- rma(yi, vi, mods = ~ Time, data = data1, method = "REML")

summary(meta_time_adjusted1)
meta_moderator1 <- rma(yi, vi, mods = ~ Time, data = data1, method = "REML")
summary(meta_moderator1)
```

```
par(mar = c(5, 4, 6, 2) + 0.5)  # Ajusta los márgenes si es necesario

forest(meta_moderator1,
       xlab = "Adjusted Mean Difference",
       slab = data1$author,
       order = "obs",              # Ordenar por el orden de los estudios
       ylim = c(-4, length(data$yi) + 3))  # Ajustar límites para dar espacio al polígono
intercept <- coef(meta_moderator1)[1]              # Intercepto (efecto promedio cuando Time = 0)
ci_lb <- intercept - 1.96 * meta_moderator1$se[1]    # Límite inferior del IC 95%
ci_ub <- intercept + 1.96 * meta_moderator1$se[1]    # Límite superior del IC 95%
usr <- par("usr")  # Obtener los límites actuales del gráfico
addpoly(intercept,
        ci.lb = ci_lb,
        ci.ub = ci_ub,
        row = -2,              # Coloca el polígono en una fila por debajo de los estudios
        col = "black",           # Color del polígono
        mlab = "Time-Adjusted SMD",  # Etiqueta para el polígono
        cex = 1.0,             # Tamaño del texto
        efac = 0.8)            # Factor de expansión para el ancho del polígono
tau2 <- meta_moderator1$tau2
I2 <- meta_moderator1$I2
Q <- meta_moderator1$QE
Q_p <- meta_moderator1$QEp
het_text <- paste0(
  "Heterogeneity: τ² = ", round(tau2, 2),
  ", I² = ", round(I2, 1), "%, Q = ", round(Q, 2),
  " (df = ", meta_moderator1$k - 1, ", p = ", round(Q_p, 3), ")"
)
text(x = usr[1] + 0.5 * (usr[2] - usr[1]),
     y = ylim[1] - 3,  # Ajusta la posición en y para colocar el texto debajo del gráfico
     labels = het_text,
     cex = 1.0,
     col = "black",
     xpd = TRUE,       # `xpd = TRUE` permite que el texto se muestre fuera de los límites del plot
     pos = 1)          # Alinea el texto al centro horizontalmente



### Sensitivity analysis
unique_follow_up <- unique(data$Time)

for (time in unique_follow_up) {
  subset_data <- subset(data, Time == time)

  meta_subgroup <- rma(yi = subset_data$yi, vi = subset_data$vi, data = subset_data, method =
"REML")

   forest(meta_subgroup, main = paste("Follow-up time:", time), xlab = "SMD")
}


## Funnel  Plots
library(metafor)

funnel(meta_random, main = "Funnel Plot - Random Model")
# Perform Egger's test
egger_test <- regtest(meta_random, model = "lm")

print(egger_test)

funnel(meta_random, yaxis = "sei", main = "Funnel Plot with Egger's Test - Random Model")
trimfill_model <- trimfill(meta_random)
```

```
funnel(trimfill_model, main = "Funnel Plot with Trim-and-Fill - Random Model")
unique_follow_up <- unique(data$Time)

# Loop through each unique follow-up time to create a funnel plot
for (time in unique_follow_up) {
  # Subset the data
  subset_data <- subset(data, Time == time)

  # Re-run the random-effects meta-analysis for the subset
  meta_subgroup <- rma(yi = subset_data$yi, vi = subset_data$vi, method = "REML")

  # Create the funnel plot for this subgroup
  funnel(meta_subgroup, main = paste("Funnel Plot - Follow-up Time:", time))
}
```

```
# Funnel Plot para subgrupo Minocycline

# Basic funnel plot for the meta_random model
funnel(meta_random1, main = "Funnel Plot - Minocycline studies")
# Perform Egger's test
egger_test1 <- regtest(meta_random1, model = "lm")

# Print the result of Egger's test
print(egger_test1)

# Funnel plot with standard error on the y-axis (common in Egger's test)
funnel(meta_random1, yaxis = "sei", main = "Funnel Plot with Egger's Test - Minocycline studies")

# Perform trim-and-fill analysis
trimfill_model <- trimfill(meta_random1)

# Funnel plot after trim-and-fill adjustment
funnel(trimfill_model, main = "Funnel Plot with Trim-and-Fill - Minocycline studies")

# Assuming follow_up_time is a variable in your data
unique_follow_up <- unique(data$Time)

# Loop through each unique follow-up time to create a funnel plot
for (time in unique_follow_up) {
  # Subset the data
  subset_data <- subset(data, Time == time)

  # Re-run the random-effects meta-analysis for the subset
  meta_subgroup <- rma(yi = subset_data$yi, vi = subset_data$vi, method = "REML")

  # Create the funnel plot for this subgroup
  funnel(meta_subgroup, main = paste("Funnel Plot - Follow-up Time:", time))
}
```

http://doi.org/10.47626/1516-4446-2025-4185
Efficacy of anti-*Toxoplasma* medications on symptom severity and cognition in patients with schizophrenia or schizoaffective disorder: systematic review and meta-analysis – Cano JF et al.

Supplementary Table S1 Data from all included articles

	Demographics of participants			Study methodology							Interventions		Outcomes Qualitative			Outcomes Quantitative		
Author, country	**Age range**	**Sex distribution**	**Participants**	**Setting**	**Study type**	**Sample size**	**Randomization**	**Outcome**	**Instrument/ Scale**	**Limitations**	**Intervention**	**Comparator**	**Intervention**	**Comparator**	**Intervention**	**Comparator**	**Conclusions**	**Other (funding, conflicts of interest)**
Chaudhry et al.,[1] Brazil and Pakistan	Placebo: 26.59 (SD, 8.26) years Minocycline: 25.87 (SD, 7.07) years	Placebo (n=73): 38.34% female Intervention (n=70): 42.86% female	Patients with schizophrenia onset < 5 years	Stable outpatients on medication for the previous 4 weeks	Randomized double blind, placebo-controlled trial	Placebo group: 73; intervention group: 71	Separate, computerized randomization list	Positive and negative syndrome ratings with the PANSS	PANSS	No controlled antipsychotic medication. Validity and reliability of the cognitive measures in two different racial groups and cultures may have inflated variability and obscured the drug's effects.	50 mg increments of minocycline over an 8-week period up to a dose of 200 mg daily for 1 year	Matching placebo	Adding minocycline led to greater improvement in negative symptoms than placebo		Negative symptoms improved by 9.2 points in the minocycline group and by 4.7 points in the placebo group, an adjusted difference of 3.53 (SE 1.01) 95% CI: 1.55, 5.51; p < 0.001 in the intention-to-treat population		Adding minocycline to treatment as usual early in the course of schizophrenia generally improves negative symptoms.	Funded by the Stanley Medical Research Institute (Grant 04T-583)
Ibrahim et al.,[2] Egypt	18-50 years	Valproate: 18 female/ 28 male; placebo 19 female/29 male	Patients with schizophrenia according to DSM-IV criteria; illness duration < 5 years; receiving a stable dose of risperidone for ≥ 1 month, PANNS score ≥ 4	Outpatients from clinics of the Mansoura University Hospital, Egypt, from March 2013 to August 2016.	Randomized controlled trial (20 weeks)	109 patients with schizophrenia	A dynamic treatment allocation procedure was used. Balancing on sex, age, and residence	Cognitive function domains estimated using the Arabic version of the Penn Computerized Neurocognitive Battery	Arabic version of the Penn Computerized Neurocognitive Battery PANNS, GAF, HDRS, NEO	The relatively small sample restricted the power to detect small effects. All patients were stabilized on antipsychotic medications when they consented to the trial	Valproic acid adjusted to therapeutic levels (50-100 ug/ml) as an adjuvant to risperidone	Risperidone + placebo tablets identical in shape to the valproate tablets provided by the manufacturer	No significant effects between the valproate and placebo groups regarding CNB test scores. Marginally significant difference independent of serologic status in emotion differentiation test speed and short fractal N back test speed but not accuracy		PANNS 51.78 (SD 24.90)	PANNS 49.77 (SD, 24.08)	Valproate may not be beneficial for cognitive dysfunction in schizophrenia or toxoplasmosis infection.	Funded in part by grants from the Stanley Medical Research Institute (07R-1712 and 11 T-06), and from the National Institutes of Health (MH093246, D43 TW009114, MH63480, D43TW008302)
Deakin et al.,[3] England	Placebo 25.7 (SD, 5.1) years Intervention: 25.5 (SD, 5.2) years	Placebo (n=103): 20.13% female Minocycline (n=104): 25.96% female	Patients with schizophrenia or schizoaffective disorder for < 5 years	Outpatients	Randomized double blind, placebo-controlled trial	207 patients. Intervention: 104; placebo: 103	Permuted blocks algorithm	PANSS negative at months 2, 6, 9, and 12	PANSS - Negative subscale	Poor treatment adherence in any group is a a further potential source of bias	200 mg/day of minocycline for 2 weeks, then 300 mg for 12 months	Matching placebo	Adding minocycline had no effect on negative symptom ratings.		Treatment effect difference -0.19 (95%CI -1.23 - 0.85)		Minocycline does not benefit negative or other symptoms of schizophrenia over and above adherence to routine clinical care in first-episode psychosis.	National Institute for Health Research Efficacy and Mechanism Evaluation program, in partnership with MRC
Dickerson et al.,[4] USA	18-65 Years Mean age 43.9 (SD 10.4) years	Female: 15 (54%)	Stable outpatients with schizophrenia or schizoaffective disorder on antipsychotic medication, with moderately severe symptoms according to PANNS score and detectable IgG antibodies	Outpatients	Randomized clinical trial	28 patients with schizophrenia. Intervention: 13; placebo: 15	Randomized, but insufficient information	PANNS positive, negative and general Score	PANNS	No limitations section	Adjuvant azithromycin 600 mg	Placebo-controlled adjuvant	No significant effects on PANSS positive, negative, or general scale scores in 16 weeks of follow-up		Results shown in a graph, no table	Results shown in a graph, no table	No significant effect on toxoplasma seropositive schizophrenia	Pfizer, Inc provided the azithromycin and placebo

Author, country	Demographics of participants			Study methodology							Interventions		Outcomes Qualitative			Outcomes Quantitative		Other (funding, conflicts of interest)
	Age range	Sex distribution	Participants	Setting	Study type	Sample size	Randomization	Outcome	Instrument/ Scale	Limitations	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Conclusions	
Dickerson et al.,[5] USA	18-65 years Mean age 47.3 (SD, 9.3) years	Male: 38 (58%)	Schizophrenia or schizoaffective disorder according to DSM-IV criteria, outpatient, psychotic symptoms, moderately severe as evidenced by PANNS positive symptoms scores ≥ 1 and/or PANNDS negative scores ≥ 4	Outpatients who previously received at least 8 weeks of AP	Randomized controlled trial (12 weeks)	66 patients with Schizophrenia. Placebo: 33; artemisinin 33	Randomized, but insufficient information	PANNS positive, negative, and general score (Week 0,2,4,6,8,10, and 12)	PANNS Positive, negative, and general scores (Week 0,2,4,6,8,10, and 12) RBANS (Week 0 and 12)		Adjuvant artemisinin capsules 100 mg twice a day	Adjuvant Placebo capsules	No differences between the two groups in PANNS or subscale scores. Decreased levels of gliadin antibodies. No changes in toxoplasma antibodies.		Results shown in a graph, no table	Results shown in a graph, no table	No clinical benefits on for schizophrenia symptoms from adjunctive artemisinin	Funded by the Stanley Medical Research Institute
Liu et al.,[6] China	Mean age Intervention: 27.05 (SD, 5.68) years; Placebo 27.7 (SD, 7.27) years	Intervention (n=39): 64.1% male; Placebo (n=40) 60% male	Patients with schizophrenia for < 5 years	Outpatients	Randomized placebo-controlled trial	Intervention: 39; placebo: 40	Random number table	Cognitive and negative symptoms in schizophrenia	SANSS; PANSS, CGI, Cognitive Test Battery based on MATRICS	Short treatment duration, no follow up after study, small sample	200 mg/d minocycline for 16 weeks added to risperidone	Matching placebo added to risperidone	The intervention group had greater improvement in the SANSS and PANSS negative subscale. Higher treatment response rates. No difference in cognitive domains		SANSS week16: 32.33 (SD 15.29) PANSS total week 16: 52.46 (SD 9.25) PANSS positive week 16: 9.41 (SD 2.43) PANSS negative week 16: 15.59 (SD 4.93) PANSS general week 16: 27.31 (4.79)	SANSS week 16: 47.80 (SD, 15.29) PANSS total W16: 59.98 (SD, 10.01) PANSS positive week 16: 9.63 (SD, 3.36) PANSS negative week 16: 20.80 (SD, 4.9) PANSS general week 16: 30.50 (6.17)	Adding minocycline to atypical antipsychotics in early schizophrenia was significantly efficacious for negative symptoms but only had a slight effect on the attention domains	
Kelly et al.,[7] USA	Mean age Intervention 42.9 (SD 14.2) years Placebo: 42.3 (SD 11.0) years	Intervention (n=28): 71% male Placebo (n=23): 78% male)	Schizophrenia and schizoaffective patients with persistent positive symptoms receiving clozapine	Inpatients	Randomized placebo-controlled trial	52 patients: placebo 23; intervention 29	Permuted blocks algorithm	Primary positive and cognitive symptoms	BPRS, MATRICS	Small sample size, only 10 weeks of follow-up.	Minocycline dosed at 50 mg twice daily for the first week and 100 mg twice daily for weeks 2-10	Matching placebo	No significant differences in BPRS. No difference in global functioning in MATRICS, but significant improvement in working memory.		BPRS week 10: 39.6 (SD 7.3) in the intervention group and 43.2 (SD 8.1) in the placebo group. CGI week 10: 3.6 (SD, 0.6) in the intervention group and 4.0 (SD, 0.7) in the placebo group.		Minocycline's effect on composite MCCB score and positive symptoms were not significant, but significant improvements were found in working memory, avolition, and anxiety/depressive symptoms in a chronic population with persistent symptoms	Funded by NIMH R21MH091184-01A1
Khodaie-Ardalani et al.,[8] Iran	Mean age Intervention: 41.05 (SD 7.47) years Placebo 38.95 (SD 7.78) years	Intervention: (n=20) 70% male Placebo: (n=20): 75% male	Patients diagnosed with schizophrenia for ≥ 2 years and treated with a stable dose of risperidone for ≥ 8 weeks	Outpatients	Randomized placebo-controlled trial	Intervention 20; placebo 20	Computer-generated code	Positive and negative symptoms	PANSS	Small sample size, short therapy duration (8 weeks)	The initial dose of minocycline was 100 mg/day for the first week, followed by 200 mg/day for 7 weeks	Matching placebo	Intervention group improved in negative, general psychopathology, and positive subscales		Mean difference in PANSS positive = 0.90 (95%CI 0.24-1.55); PANSS general psychopathology = 2.70 (95%CI 0.83-4.56); PANSS total = 8.95 (95%CI 6.05-11.84)		Minocycline seems to be an efficacious and tolerable short-term add-on to risperidone for treating negative and general psychopathology symptoms of schizophrenia	Prof. S. Akhondzadeh received a grant (no.: 11921) from the Tehran University of Medical Sciences

Author, country	Demographics of participants			Study methodology							Interventions		Outcomes Qualitative			Outcomes Quantitative	Conclusions	Other (funding, conflicts of interest)
	Age range	Sex distribution	Participants	Setting	Study type	Sample size	Randomization	Outcome	Instrument/ Scale	Limitations	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator		
Levkovitz et al.,[9] Israel	Mean age Treatment 25.14 (SD, 4.77) years; Placebo 24.67 (SD, 4.24) years	Intervention: 69.44% male Placebo: 83.33% male	Patients with Schizophrenia whose disorder had begun within the past 5 years	Outpatients	Randomized placebo-controlled trial	Initial sample: 36 intervention, 18 placebo. Completers: 13 intervention, 8 placebo	Yes	Cognitive and negative symptoms of schizophrenia	SANSS; PANSS, CANTAB cognitive	A small number of patients with each AP; 6 months follow-up; low completion rate and high dropout rate	22-week add-on phase with minocycline	Matching placebo	Beneficial effects on positive and negative symptoms and general outcome (CGI); similar benefits in cognitive function, especially working memory, cognitive shifting, and cognitive planning		SANSS endpoint = 32.61 (SD, 19.59); PANSS Positive endpoint = 10.67 (SD, 2.42); PANSS negative endpoint = 17.19 (SD, 5.91); PANSS total = 67.40 (SD, 10.25)	At endpoint: SANSS = 41.56 (SD, 17.88); PANSS positive = 11.19 (SD, 4.69); PANSS negative = 20.32 (SD, 6.53) PANSS total = 63.80 (SD, 18.09)	Minocycline was associated with improvement in negative symptoms and executive functioning	Funded by the Stanley Medical Research institute
Zhang et al.,[10] China	Intervention High dose: 33.24 (SD, 6.48) years; Intervention Low dose: 33.04 (SD, 7.78) years; 33.68 (SD, 6.48) years	High dose (n=25): male 48%; Low dose (n=25): 52% male Placebo: (n=25): 48% male	Patients with schizophrenia; onset 2-10 years	Outpatients	Randomized placebo-controlled trial	25 patients in each group	Random number table	Change in negative schizophrenia symptoms and biomarkers	SANSS, PANSS, IL-6 IL-1β	Short follow-up; no other data on proinflammatory confounders; 3 cytokines were measured	High dose: 200 mg/d; Low dose: 100 mg/day. 3-month trial	Matching Placebo	High dose associated with greater improvement in SANSS and PANSS negative subscale and reductions in IL 1B and IL-6 compared with placebo and low dose		Low dose at week 12: SANSS = 53.88 (SD, 6.20); PANSS total = 62.28 (SD, 7.40); PANSS positive = 11.04 (SD, 1.90); PANSS negative = 22.00 (SD, 2.92); PANSS general = 29.24 (SD, 3.33) High dose at week 12: SANSS = 51.08 (SD, 6.76); PANSS total = 13.32 (SD, 1.52;) PANSS positive = 11.64 (SD, 2.02); PANSS Negative = 20.68 (SD, 3.05) PANSS general = 29.16 (SD, 4.27)	Change at week 12: SANSS = 55.72 (SD, 6.44); PANSS total = 63.12 (SD, 8.00); PANSS positive = 10.88(SD, 2.26); PANSS negative = 22.68 (SD, 2.64); PANSS general = 29.56 (SD, 3.85)	Significant improvement in negative symptoms with the addition of minocycline to risperidone. Pro-inflammatory cytokine reduction may play an important role in the potential mechanism for efficacy.	
Shibre et al.,[11] Ethiopia	Age range 15-49 years Mean age: 34.3 (SD, 8.0) years	100% male	Male patients diagnosed with severe schizophrenia and confirmed with ICD		Double-blind, randomized, placebo-controlled trial	91 Patients; 80 cases (87.9% positive)	Randomization list generated using a random number table which was then transferred to a series of sealed envelopes	Change in PANNS score	PANSS Scale	Average illness duration ~13 years. Small sample size, no objective measure of medication compliance	Adjuvant trimethoprim 200 mg/d, for 6 months	Placebo: Medication identical in appearance and taste (lactose monohydrate).	No difference in PANSS scores at the end of the second and fifth months. Both showed lower overall PANNS scores		PANNS: baseline 78.5 (SD 14.9) month 1: 75.4 (SD, 21.0); month 6: 61.9 (SD, 18.0)	PANNS: Baseline = 79.6 (SD, 17.6); month 1 = 74.6 (SD, 28.1); month 6 = 65.5 (SD, 17.6)	In patients with chronic schizophrenia, trimethoprim as adjuvant treatment was not superior to placebo	Funded by the Stanley Medical Research Institute

	Demographics of participants			Study methodology							Interventions		Outcomes Qualitative		Outcomes Quantitative			
Author, country	**Age range**	**Sex distribution**	**Participants**	**Setting**	**Study type**	**Sample size**	**Randomization**	**Outcome**	**Instrument/ Scale**	**Limitations**	**Intervention**	**Comparator**	**Intervention**	**Comparator**	**Intervention**	**Comparator**	**Conclusions**	**Other (funding, conflicts of interest)**
Wang et al.,[12] China	Age range 16-40 Years	Intervention group (N=50): 23 (46.0%) male' Placebo group: (N=50): 24 (48.0%) male	DSM-IV diagnosis of schizophrenia by 2 senior Psychiatrists; illness duration ≤ 24 months; antipsychotic naive; inpatients or outpatients; *T gondii* seropositivity (IgG or IgM positive); PANNS score >/= 60	Renmin Hospital, Hubei province	Double-blind, randomized, placebo-controlled trial	100 *T. gondii*-seropositive participants with schizophrenia	Yes, but method unexplained	Change in PANNS, CGI, and BACS scores	PANSS Scale and Subscales BACS (Week 8) Clinical Global Impression Scale	The sample size was relatively small. Artemether dosed for malaria, since there is no recommendation for chronic *T. gondii* infection	Risperidone 0.5 mg bid, titrated to a maximum of 6 mg/day + artemether 80 mg/day during the second week (8-14) and the fourth week (22-28)	Risperidone 0.5 mg bid, titrated to a maximum of 6 mg/day + placebo, same protocol as artemether	Greater reduction in PANSS negative symptom and CGI scale scores. No significant differences in PANSS positive symptom and general psychopathology scales. No differences in BACS scores		PANNS general: week 2 = 32.7 (SD, 4.7); week 6 = 22.9 (SD, 4.3); week 8 = 20.5 (SD, 3.5) PANNS positive: week 2 = 19.8 (SD, 4.2); week 6 = 12.1 (SD, 3.8); week 8 = 10.8 (SD, 3.3) PANNS negative: Week 2: 16.1 (SD 4.2); Week 6 10.9 (SD: 2.9), Week 8: 10.4 (SD: 2.4) CGI: Week 2: 4.3 (SD: 0.7); Week 6: 3.0 (SD: 0.6), Week 8: 2.7 (SD 0.6)	PANNS general: week 2 = 33.7 (SD, 3.8); week 6 = 22.8 (SD, 4.9); week 8 = 20.9 (SD, 4.2) PANNS Positive: week 2 = 20.1 (SD, 4.1); week 6 = 12.0 (SD, 3.7); week 8 = 10.6 (SD, 2.8) PANNS negative: week 2 = 17.4 (SD, 4.7); week 6 12.6 (SD, 5.2); week 8 = 11.9 (SD, 4.6) CGI: week 2 = 4.5 (SD, 0.5); week 6 = 3.4 (SD, 0.6); week 8 = 2.9 (SD, 0.7)	Combined artemether and risperidone is safe and well tolerated, but, as an adjunct to risperidone, artemether does not appear to alleviate schizophrenia cognitive deficit.	Funded by the Stanley Medical Research Institute (Grant ID: 06T-776) and the National Nature Science Foundation of China (Grant ID: 0300108).
Weiser et al.,[13] Moldova	Mean age Intervention: 43.4 (SD, 10.5) years Placebo: 43.5 (SD, 9.7) years	Intervention (n=100): 42% male Placebo (n=100): 46% male	Patients diagnosed with schizophrenia or schizoaffective disorder	Inpatients and outpatients	Randomized placebo controlled trial-Secondary analysis	100 patients in each group	Yes	Symptom change measured by total PANSS scores	PANSS, CGI-S, CGI-I, BACS	Long disease history, high level of symptoms	200 mg/d of minocycline added to the antipsychotic (16 weeks)	Matching placebo	No significant differences between minocycline and placebo in any scale		Difference between groups at week 16: PANSS total = 1.32 (−3.19, 5.83) PANSS positive =: −0.33 (−1.92, 1.26) PANSS negative = 0.86 (−0.58, 2.30) PANSS general = 0.85 (−1.53, 3.23); CGI = 0.11 (−0.21, 0.42)	BACS differences between groups: Total Verbal Memory = 0.13 (−0.23, 0.49) Digit Sequencing = 0.22 (−0.20, 0.64); Token Motor Task = −0.19 (−0.57, 0.20); Total Fluency = 0.12 (−0.14, 0.37); Symbol Coding = 0.41 (−0.08, 0.90); Tower of London = −0.02 (−0.48, 0.45); BACS Composite = 0.18 (−0.23, 0.58)	Minocycline did not improve symptoms or cognition in schizophrenia	Funded by the Stanley Medical Research Institute.
Fond et al.,[14] France	Mean age 35.69 (SD, 11.45) years	Female 32/114 (28.1%). Seropositive 28/74 (37.8%), Seronegative 4/40 (10%)	Patients with schizophrenic or schizoaffective disorder who met DSM-IV criteria in the DIGS interview	Patients from 2 university-affiliated psychiatric departments in France (Mondor Hospital, Créteil, University Paris-Est and Fernand Widal Hospital, Paris, University R Diderot)	Cross-sectional	114 schizophrenic and schizoaffective patients, stable for > 4 weeks before the study	NA	Differences in PANNS scores, past mood episodes, and hospitalizations	PANNS Scale Age of Illness Onset # hospitalizations and duration Number of depressive and manic episodes	Only the current treatment was studied. Recruitment bias due to often recruiting patients after a hospitalization. Responders/non-relapsing patients may not have been included in this study. The length of current treatment was not recorded, and IgG levels were not assessed before TATA was administered	Exposure: antipsychotic use with anti-TATA effect at the time of the study	Drugs without this effect used at baseline	No differences in mood symptomatology, suicidal behavior, psychotic symptomatology or illness severity between the TATA+ and TATA- treatments		PANNS General = 33.51 (SD, 11.27); PANNS positive = 16.46 (SD, 6.81); PANNS negative = 19.46 (SD, 7.67). Mean hospitalizations = 5 (range, 1-21). Mean hospitalization duration = 15.45 (SD, 25.42) days	PANNS General = 29.41 (SD, 6.56). PANNS positive = 14.17 (SD, 5.95); PANNS negative = 18.83 (SD, 7.54). Mean hospitalizations: 6 (range, 2-20). Mean hospitalization duration = 19.64 (SD, 21.99) days	No differences between the anti-TATA+ and anti-TATA- groups	Supported by Agence Nationale pour la Recherche (Project V.I.P.), the Institut National de la Santé et de la Recherche Médicale, Assistance Publique des Hôpitaux de Paris, and the Fondation Fondamental (RTRS Santé Mentale)

Author, country	Demographics of participants				Study methodology						Interventions		Outcomes Qualitative			Outcomes Quantitative		Other (funding, conflicts of interest)
	Age range	Sex distribution	Participants	Setting	Study type	Sample size	Randomization	Outcome	Instrument/ Scale	Limitations	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Conclusions	
de Witte et al.,[15] Denmark	Mean age 22.4 (SD, 4.5) years	44.32% Female	Patients diagnosed with schizophrenia in the Danish registries	Outpatients	Cohort Study	11,157	NA	Disability pension (functional outcome)	NA	Prescription data defined exposure to tetracycline antibiotics. Adherence was not recorded and, treatment indication missing in almost half of the patients.	Exposure: doxycycline prescription	Non-brain-penetrant or no tetracyclines	Lower incidence rate of disability for those exposed to doxycycline vs those not exposed to tetracycline or brain-penetrant tetracycline	Rate not lower in non-brain-penetrant tetracycline	IRR: 0.68 (95%CI 0.56-0.83) for doxycycline vs no tetracycline; IRR 0.69 (95%CI 0.55-0.87) for non-brain-penetrant tetracycline		Doxycycline exposure is associated with a reduced incidence of disability pension.	Funded by the National Institutes of Mental Health R21 MH123913
Krynicki et al.,[16] England (Deakin et al data)	Mean age 25.76 (SD, 5.21) years	73% male (n 149); 27% female (n=56)	Patients with schizophrenia or schizoaffective disorder; onset < 5 years	Outpatients	Secondary analysis of a randomized placebo-controlled trial		Used Deakin et al.	Inflammatory markers (IL-6 and TNFα); PANSS symptoms	PANSS	Used Deakin et al.	Used Deakin et al.	Used Deakin et al.	Minocycline did not affect any individual symptom or subdomain in the full sample or the immune active subgroup				Minocycline continues to show very little promise as a treatment for any symptom dimension of early schizophrenia.	
Chaves et al.,[17] Brazil	Mean age Placebo; 25 (SD, 6.37) years Intervention: 24 (SD, 5.02) years	Placebo: 21.4% female Intervention: 18.8% female	Patients with schizophrenia; onset < 5 years	Outpatients	Secondary analysis of randomized double-blind placebo-controlled trial	16 in minocycline group; 14 in placebo group	Separate computerized randomization list	Brain morphology and cerebral perfusion; PANSS	PANSS		Minocycline 200 mg/day for 12 months (same group)	Matching placebo	According to VBM analysis of MRI scans the placebo group had significantly smaller gray matter volumes in the mid-posterior cingulate cortex and the precentral gyrus in comparison with the patients in the minocycline group. Improvements in PANSS general and subscale scores compared to placebo		Results shown in a graph, no table	The optimal dose of minocycline for neuroprotection in humans is still unknown. Structural and functional brain evaluations were only performed after the clinical trial	Minocycline may protect against gray matter loss and modulate fronto-temporal areas involved in the pathophysiology of schizophrenia.	
Liu er al.,[18] China	Mean age Intervention 26.7 (SD, 5.5) years; Placebo 28.9 (SD, 7.0) years	Intervention (n=27) 59.3% male; placebo (n=28): 57.1% male	Patients with schizophrenia for ≤ 5 years	Outpatients	Secondary analysis of randomized placebo-controlled trial	27 in minocycline group, 28 in placebo group	Yes	Changes in schizophrenia symptoms and biomarkers	SANSS, PANSS, IL-1β, TNFα, Nitric Oxide	Small sample, short treatment duration, confounders of inflammatory response	200 mg/d of minocycline added to risperidone for 16 weeks	Matching placebo added to risperidone	The intervention group had significantly lower SANSS, PANSS total and negative subscale scores, as well as lower nitric oxide metabolites, but not other biomarkers		SANSS Change W16: -31.2 (SD 25.5) PANSS Total W16: -32.9 (SD 17.1) PANSS Positive W16: -8.5 (SD 5.9) PANSS Negative W16: -10.8 (SD 4.93) PANSS General W 16: -14.5 (9.9) Nitric Oxide: -8.19 (SD 18.09)	SANSS Change W16: -14.8 (SD 20.2) PANSS Total W16: -25.3 (SD 12.8) PANSS Positive W16: -7.5 (SD 4.7) PANSS Negative W16: -6.2 (SD 4.2) PANSS General W 16: -11.8 (8.1) Nitric Oxide: 4.37 (SD 15.53)	The beneficial effect of adjunctive minocycline on negative symptoms might occur through mechanisms other than the nitric oxide pathway.	Funding: National Key R&D Program of China (2016YFC1306900)

Author, country	Demographics of participants				Study methodology						Interventions		Outcomes Qualitative			Outcomes Quantitative		Other (funding, conflicts of interest)
	Age range	Sex distribution	Participants	Setting	Study type	Sample size	Randomization	Outcome	Instrument/ Scale	Limitations	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Conclusions	
Zhang et al.,[19] China	Mean age Intervention High dose: 34.22 (SD, 6.73) years Intervention Low dose: 33.60 (SD, 7.73) years Placebo: 34.68 (SD, 6.43) years	High dose (n=18): 50% male; Low dose (n=20): 50% male; Placebo (n=19): 52.6% male	Patients with schizophrenia for 2-10 years	Outpatients	Secondary analysis of randomized placebo-controlled trial	High dose = 18, Low dose = 20; Placebo = 19	Yes	Cognitive functioning change after treatment.	MCCB; Biomarkers,	Short study duration, only 3 cytokines, small sample	High dose: 200 mg/d; Low dose: 100 mg/day. 3-month trial	Matching placebo	High dose associated with greater improvement in cognitive function and reduced IL-6 and IL-1β		LOW DOSE (Month 3) TMT : 51.36(12.64) BACS: 40.45(6.45) Verbal Fluency: 12.35(2.72) Attention/ Vigilance (CPT-IP): 2.00(0.86) Spatial Span:11.90(2.75) HVLT-R: 14.25(3.68) BVMT-R: 16.95(3.69) Maze: 11.15(3.69) IL-1β 22.18(4.85) IL-6: 25.11(4.36) TNFα: 31.64(7.42) High dose (Month 3) TMT: 50.86(14.33) BACS: 42.94(7.02) Verbal Fluency: 13.78(2.44) Attention/ Vigilance (CPT-IP): 2.06(0.87) Spatial span:12.39(2.85) HVLT-R: 14.72(3.74) BVMT-R:18.11(3.86) Maze: 12.22(3.70) IL-1β 20.12(4.50 IL-6: 24.18(4.86) TNFα: 31.51(7.22)	PLACEBO (Month 3) TMT : 53.86(12.25) BACS: 43.26(8.01) Verbal Fluency: 13.05(3.01) Attention/ Vigilance (CPT-IP): 1.84(0.69) Spatial Span: 12.26(2.64 HVLT-R: 13.74(4.28) BVMT-R: 16.32(3.42 Maze: 12.32(3.45) IL-1B 23.39(4.97) IL-6: 26.41(4.55) TNFα: 33.09(8.53)	Adjunctive minocycline treatment improved cognitive deficits in patients with schizophrenia.	Funding: National Key Research and Development Program (Grant No.2016YFC1306900), the National Natural Science Foundation of China (Grant Nos. 81571310, 81630033, 81471363), the Natural Science Foundation of Guangdong Province (Grant No. 2017A030313809).

AP = antipsychotics; BACS = Brief Assessment of cognition in Schizophrenia; BPRS = Brief Psychiatry Rating Scale; BVMT = Brief Visuospatial Memory Test; CGI = Clinical Global Impressions; CGI-I = CGI of Improvement; CGI-S = CGI of Severity; CNB = Computerized Neurocognitive Battery; CPT-IP = Continuous Performance Test, identical pairs version; DIGS = Diagnostic Interview for Genetic Studies; GAF = global assessment of functioning; HDRS = Hamilton Depression Rating Scale; HVLT-R = Hopkins Verbal Learning Test-Revised; ICD = International Classification of Diseases; IgG = immunoglobulin G; IL = interleukin; IRR = inter-rater reliability; MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia; MCCB = MATRICS Consensus Cognitive Battery; MRC = Medical Research Council; MRI = magnetic resonance imaging; NA = not applicable; PANSS = Positive and Negative Syndrome Scale; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SANSS = Scale for the Assessment of Negative Symptoms; TATA = Treatment with anti-toxoplasmic activity; TMT = Trail Making Tests; TNF = tumor necrosis factor; VBM = Voxel-based morphometry.

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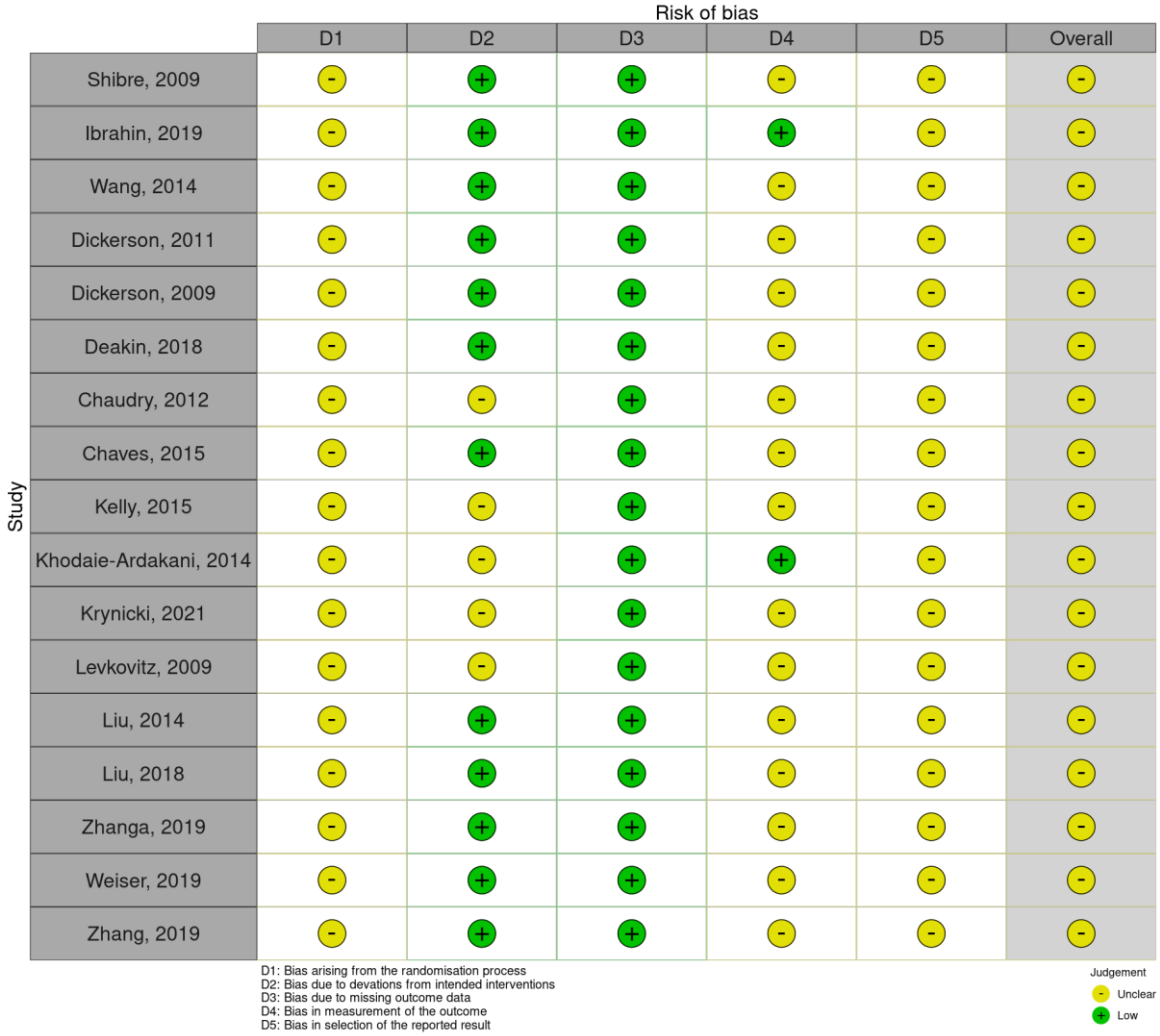
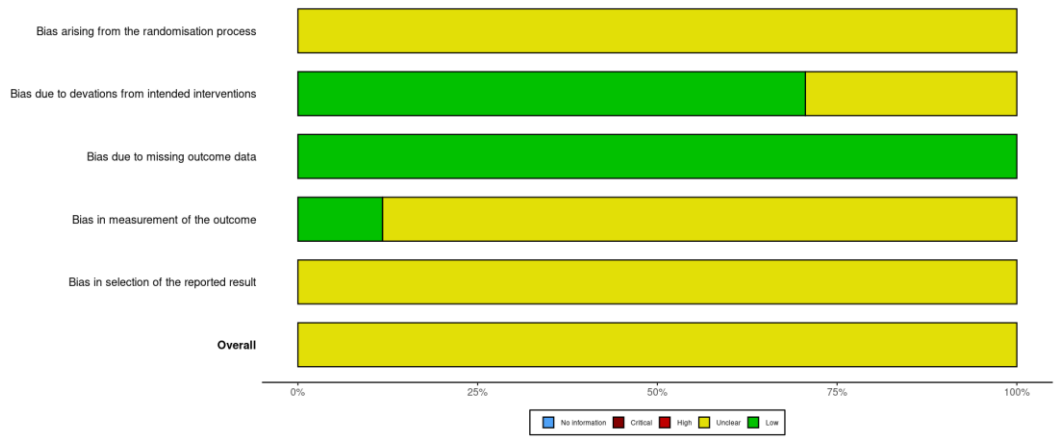
http://doi.org/10.47626/1516-4446-2025-4185

Supplementary Figure S1 Risk of bias - randomized clinical trials





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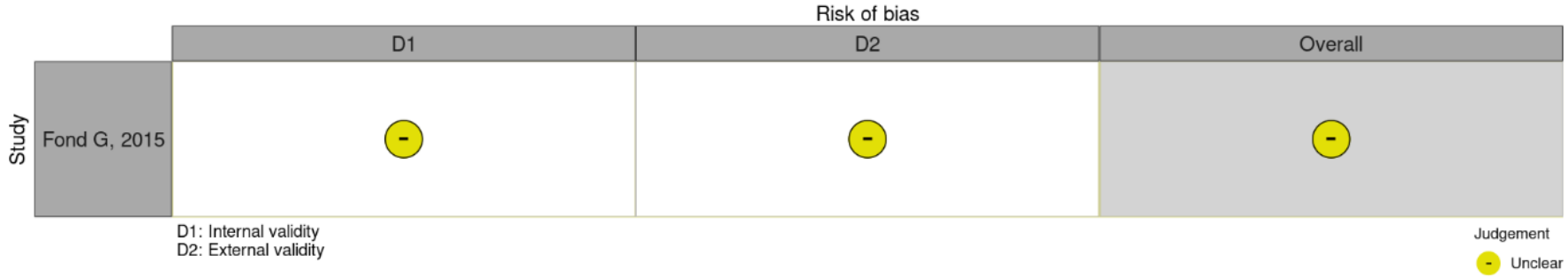
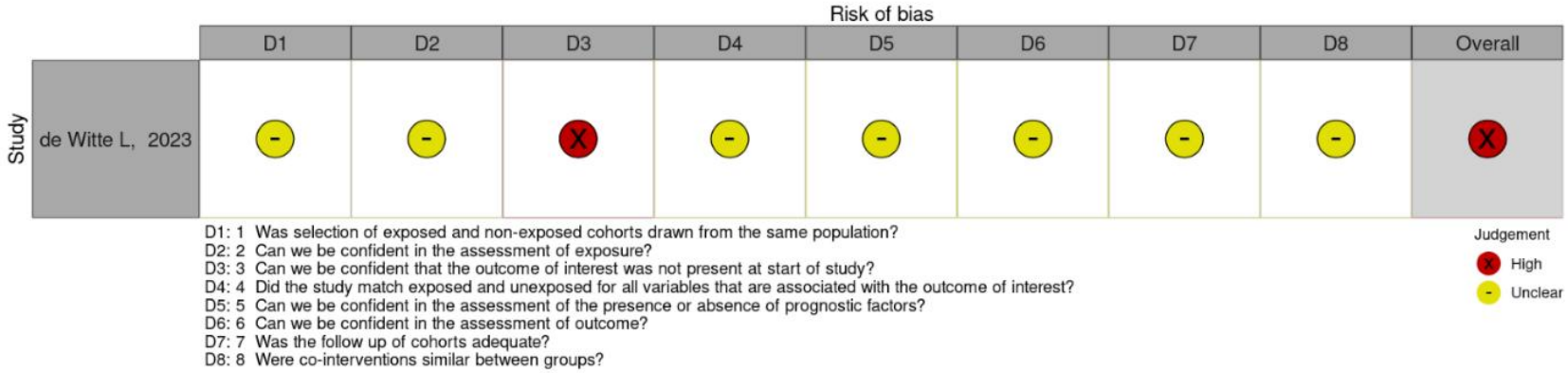
Supplementary Figure S2 Risk of bias – Observational studies



Supplementary Figure S3 Risk of bias – Cohort studies



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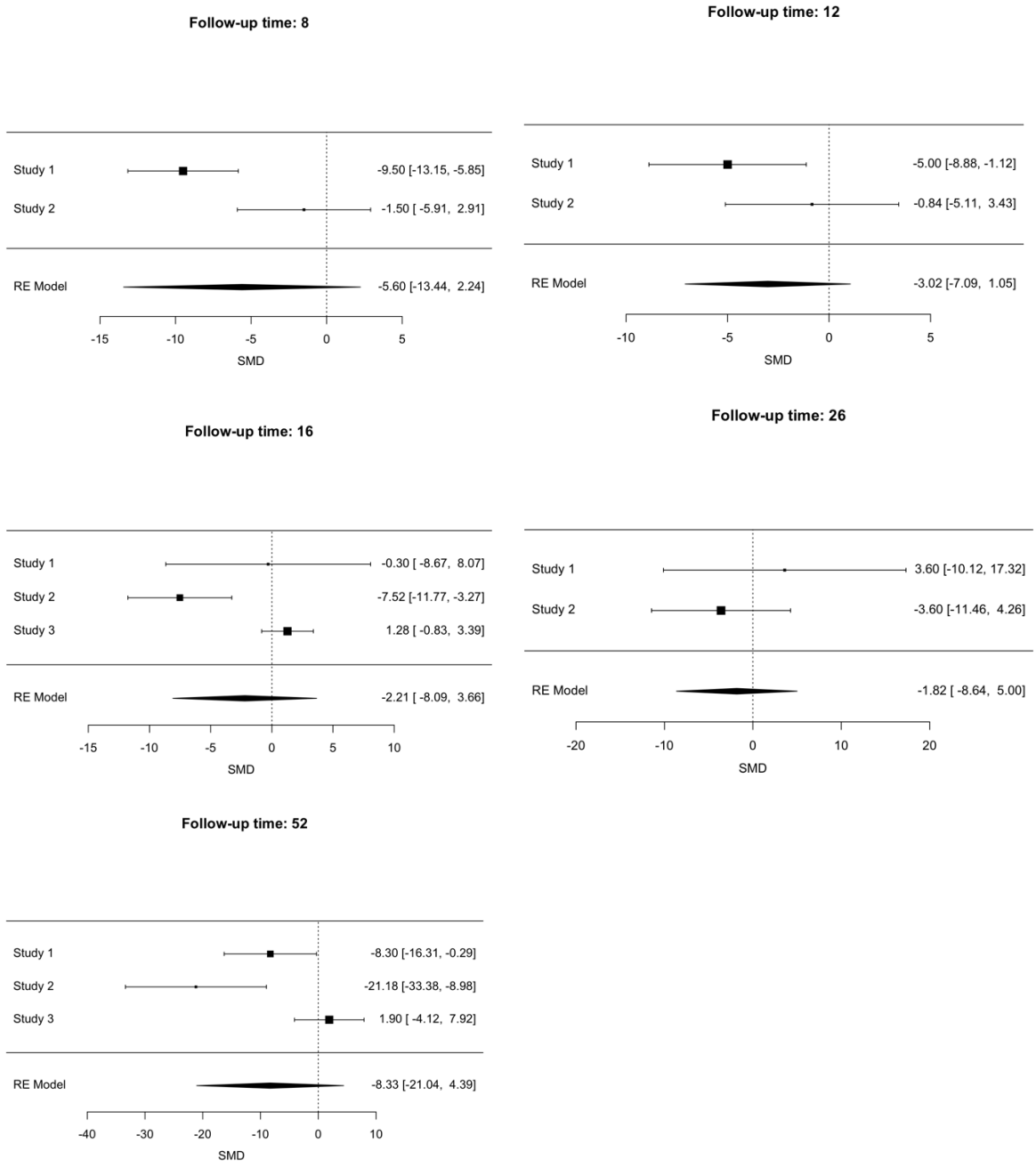
Supplementary Figure S4 Forest plots for all treatments adjusted by follow-up time (in weeks)



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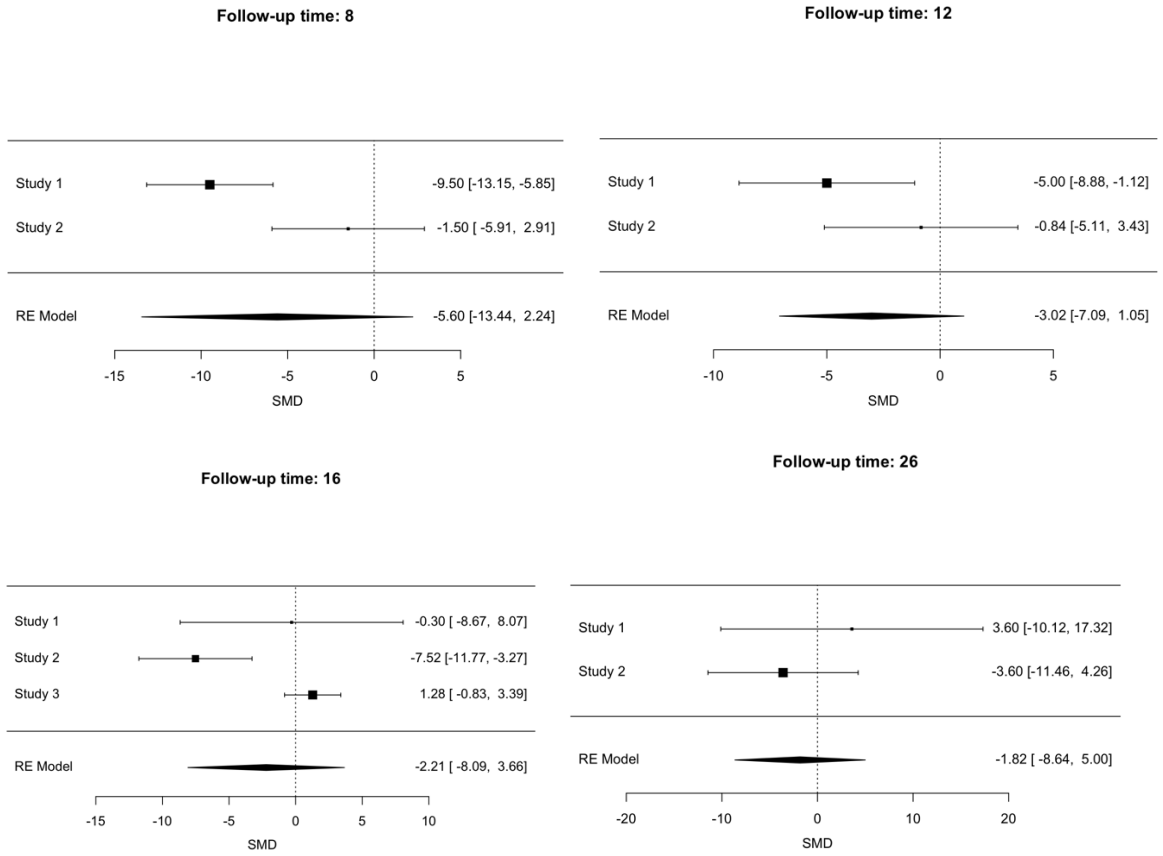
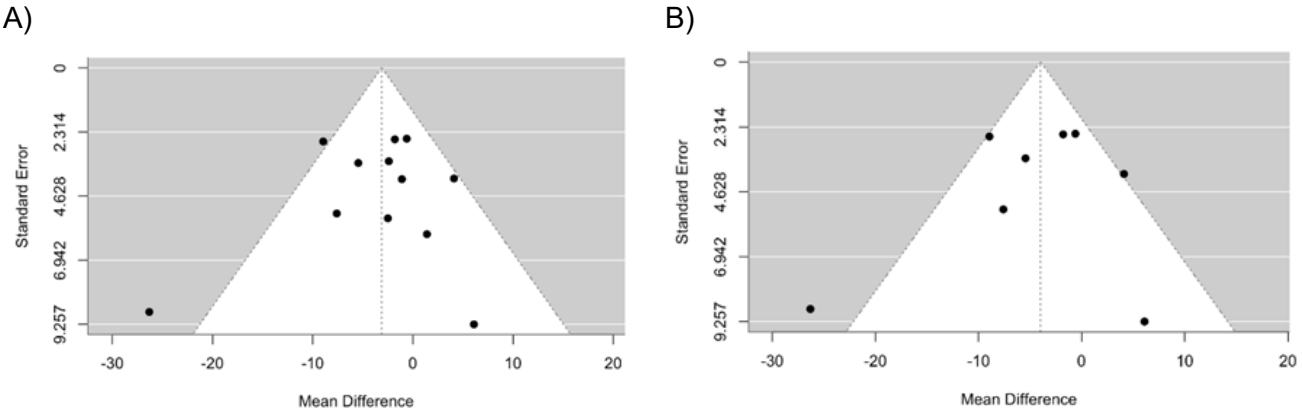
Supplementary Figure S5 Forest plots for the minocycline subgroup adjusted by time of follow-up (in weeks)



Supplementary Figure S6 Funnel plots



A) Whole sample; B) minocycline articles.