rTMS for clozapine refractory schizophrenia: a systematic review and pairwise meta-analysis [Letter]

Dan Siskind, Faraz Honarparvar, Alkomiet Hasan, Elias Wagner, Surabhi Sinha, Stacy Orr, Steve Kisely

Angaben zur Veröffentlichung / Publication details:

Siskind, Dan, Faraz Honarparvar, Alkomiet Hasan, Elias Wagner, Surabhi Sinha, Stacy Orr, and Steve Kisely. 2019. "rTMS for clozapine refractory schizophrenia: a systematic review and pairwise meta-analysis [Letter]." *Schizophrenia Research* 211: 113–14. https://doi.org/10.1016/j.schres.2019.07.004.

Letter to the Editor

rTMS for clozapine refractory schizophrenia – A systematic review and pairwise meta-analysis

Keywords:
Schizophrenia
Treatment-refractory schizophrenia
Clozapine
rTMS
Transcranial magnetic stimulation

Dear Editor,

Only 40% of people with treatment refractory schizophrenia will respond to clozapine (Siskind et al., 2017), even though is the most effective antipsychotic for this population (Land et al., 2017; Siskind et al., 2016).

There is limited evidence for pharmacological augmentation of clozapine (Siskind et al., 2018; Wagner et al., 2019a). By contrast, non-pharmacological strategies such as repetitive transcranial magnetic stimulation (rTMS), defined as repetitive application of magnetic pulses through the scalp targeting the prefrontal or temporal cortex, may hold promise. Among people with schizophrenia on any antipsychotic, rTMS can reduce both auditory hallucinations and negative symptoms, with a substantial heterogeneity across trials (Kennedy et al., 2018). A recent sub-analysis of rTMS for people with predominant negative symptoms of schizophrenia on clozapine found reductions in total and positive psychotic symptoms (Wagner et al., 2019b).

We therefore undertook a systematic review and pairwise meta-analysis of rTMS studies for clozapine refractory schizophrenia as there has been none to date.

This study was registered with PROSPERO (CRD42018036210), and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (Moher et al., 2009). We searched Pubmed, PsycInfo, Embase and the Cochrane Schizophrenia Group's Trials Register from inception to 1 May 2019. Pubmed search terms are provided in Supplementary Table 1. We included any randomised controlled trial of rTMS vs sham treatment (irrespective whether predominant negative symptoms or persistent hallucinations were the primary outcome) in people with clozapine refractory schizophrenia.

Two authors (DS and FH) reviewed articles at title/abstract, then full text level. The following data were extracted by FH and validated by DS: total, positive and negative symptoms of schizophrenia; country; diagnostic tool; definition of inadequate clozapine response; placement of rTMS electrode; dose of rTMS; duration; type of sham; completion rates; age and gender. Risk of bias was assessed using the Cochrane Collaboration guidelines (Higgins and Green, 2011).

We used RevMan version 5.3 to perform pairwise meta-analyses on endpoint data with total psychotic symptoms as the primary outcome and secondary outcomes of positive and negative symptoms and auditory hallucinations. Heterogeneity was assessed using the I^2 statistic. Random effects model was used for all the analyses. If more than 10 meta-analyses were found, publication bias would be tested using funnel plot asymmetry (Sterne et al., 2011).

Sensitivity analyses were conducted on location of electrode placement and study duration. A meta-analysis of adverse events was undertaken.

We identified 88 unique articles, of which 24 were included at full-text review. Three studies met inclusion criteria and had usable data for meta-analysis (de Jesus et al., 2011; Rosa et al., 2007; Wagner et al., 2019b) (Supplementary Fig. 1 PRISMA Diagram).

Studies published between 2007 and 2019 were conducted in two countries, Brazil and Germany (Supplementary Table 2). Treatment duration ranged from 10 to 28 days. The three included studies had data on 54 participants (26 rTMS/28 sham). All studies had a low risk of bias (Supplementary Table 3). All studies provided definitions of inadequate response to clozapine, however only one study (Wagner et al., 2019b) met TRIPP symptom criteria (Howes et al., 2016). Two studies reported electrode placement over the left temporoparietal cortex (between sites T3 and P3, persistent auditory hallucinations) (de Jesus et al., 2011; Rosa et al., 2007), while one used the left dorsolateral prefrontal cortex (predominant negative symptoms) (Wagner et al., 2019b). Sham stimulus was coil tilted at 45° in two studies (de Jesus et al., 2011; Wagner et al., 2019b), and sham coil in the other study (Rosa et al., 2007).

There was no significant difference between rTMS and sham for total, positive nor negative symptoms (Supplementary Fig. 2). Heterogeneity ($I^2 = 0\%$) was low for all analyses. Meta-analysis was performed across all three trials irrespective of the stimulation location to test whether there is an overall effect of rTMS in clozapine-resistant schizophrenia patients.

Although two studies reported data on auditory hallucinations, it was not in a format amenable to meta-analysis. Both studies reported no significant difference in auditory hallucinations between the rTMS and sham groups at study endpoint (de Jesus et al., 2011; Rosa et al., 2007).

Sensitivity analysis by location of electrode placement did not affect the results. Four patients in the rTMS group, and none in the sham group reported headaches, however this did not reach statistical significance in meta-analysis. Rates of dropout between the groups were not statistically significantly different.

There were insufficient studies to assess publication bias.

This is the first pairwise meta-analysis of published data on rTMS for clozapine-refractory schizophrenia. We found no benefit of rTMS for total, positive or negative psychotic symptoms of clozapine refractory schizophrenia when analysing all three trials. The only adverse event consistently reported was headaches in the rTMS group, but there was no statistically significantly difference between the two groups.

Our results are in contrast to a recent meta-analysis of rTMS for people with schizophrenia, that was not limited to people on clozapine and that suggested that rTMS reduced both negative symptoms and auditory hallucinations (Kennedy et al., 2018). While we were not able to conduct a meta-analysis on auditory hallucinations, neither of the included studies with auditory hallucinations as an outcome showed significant results. It is therefore possible that the ultra-refractory nature of people poorly responsive to clozapine may confer additional resistance to rTMS.

This meta-analysis is small, with data for only 54 participants from 3 studies, so the results must be reviewed with caution. Additionally, the location of the rTMS electrode varied between study, with two using the left temporoparietal cortex and one left dorsolateral prefrontal cortex. The type of sham stimulus also varied. In contrast to pharmacological treatment where studies with similar endpoints can be merged, rTMS studies with different stimulation targets may not be able to be compared. In our meta-analysis, we combined low-frequency (left temporoparietal cortex) and high frequency (left dorsolateral prefrontal cortex) rTMS data to evaluate the overall efficacy of augmentation with rTMS for inadequate response to clozapine treatment. Sham conditions varied across the included studies. Given sham conditions can impact the outcome of rTMS trials (Dollfus et al., 2015), this is a potential limitation. Although the definitions of inadequate clozapine response were broadly similar, it is possible that variations may have impacted the results.

There remains a need for effective pharmacological and non-pharmacological interventions for people with clozapine refractory schizophrenia. Further studies are required to validate the efficacy for rTMS for people with clozapine refractory schizophrenia, particularly given the heterogeneity of design among existing studies. However, until further studies are undertaken, it may not be appropriate to routinely add rTMS to our treatment armoury for people with schizophrenia with inadequate response to clozapine treatment.

Contributors

DS, FH, AH, EW, SO, SS and SK developed the search strategy. SO and SS piloted the search strategy. DS and FH conducted the search and extracted the data. DS analysed the data and wrote the first draft of the manuscript. All authors contributed to the revision of the manuscript.

Declaration of Competing Interest

DS, FH, EW, SO SS, and SK have no interests to declare. AH has been invited to scientific meetings by Lundbeck, Janssen-Cilag, and Pfizer, and he received paid speakerships from Desitin, Janssen-Cilag, Otsuka and Lundbeck. He was member of Roche, Otsuka, Lundbeck and Janssen-Cilag advisory boards.

Acknowledgements

DS is supported in part by an NHMRC ECF APP1111136.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.07.004.

References

Dollfus, S., Lecardeur, L., Morello, R., Etard, O., 2015. Placebo response in repetitive transcranial magnetic stimulation trials of treatment of auditory hallucinations in schizophrenia: a meta-analysis. Schizophr. Bull. 42 (2), 301–308.

Higgins, J.P., Green, S., 2011. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons.

Howes, O.D., McCutcheon, R., Agid, O., De Bartolomeis, A., Van Beveren, N.J., Birnbaum, M.L., Bloomfield, M.A., Bressan, R.A., Buchanan, R.W., Carpenter, W.T., 2016. Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. Am. J. Psychiatr. 174 (3), 216–229.

de Jesus, D.R., Gil, A., Barbosa, L., Lobato, M.I., da Silva Magalhães, P.V., de Souza Favalli, G.P., Marcolin, M.A., Daskalakis, Z.J., da Silva Belmonte-de-Abreu, P.J.P.R., 2011. A pilot double-blind sham-controlled trial of repetitive transcranial magnetic stimulation for patients with refractory schizophrenia treated with clozapine. 188 (2), 203–207.

Kennedy, N.I., Lee, W.H., S, F., 2018. Efficacy of non-invasive brain stimulation on the symptom dimensions of schizophrenia: a meta-analysis of randomized controlled trials. Eur. Psychiatry 48, 69–77.

Land, R., Siskind, D., McArdle, P., Kisely, S., Winckel, K., Hollingworth, S.A., 2017. The impact of clozapine on hospital use: a systematic review and meta-analysis. Acta Psychiatr. Scand. 135, 296–309.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. 151 (4), 264–269.

Rosa, M.O., Gattaz, W.F., Rosa, M.A., Rumi, D.O., Tavares, H., Myczkowski, M., Sartorelli, M.C., Rigonatti, S.P., Elkis, H., Cabral, S.B., 2007. Effects of repetitive transcranial magnetic stimulation on auditory hallucinations refractory to clozapine. 68 (10), 1528–1532.

Siskind, D., McCartney, L., Goldschlager, R., Kisely, S.J., 2016. Clozapine v. first-and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. 209 (5), 385–392.

Siskind, D., Siskind, V., Kisely, S., 2017. Clozapine Response Rates Among People With Treatment-Resistant Schizophrenia: Data From a Systematic Review and Meta-analysis. SAGE Publications Sage CA, Los Angeles, CA.

Siskind, D.J., Lee, M., Ravindran, A., Zhang, Q., Ma, E., Motamarri, B., Kisely, S.J.A., Psychiatry, N.Z.J.o., 2018. Augmentation strategies for clozapine refractory schizophrenia: a systematic review and meta-analysis. 52 (8), 751–767.

Sterne, J.A., Sutton, A.J., Ioannidis, J.P., Terrin, N., Jones, D.R., Lau, J., Carpenter, J., Rücker, G., Harbord, R.M., Schmid, C.H., 2011. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. Bmj 343, d4002.

Wagner, E., Löhrs, L., Siskind, D., Honer, W.G., Falkai, P., Hasan, A.J.J.o.P., 2019a. Clozapine augmentation strategies–a systematic meta-review of available evidence. Treatment Options for Clozapine Resistance (0269881118822171).

Wagner, E., Wobrock, T., Kunze, B., Langguth, B., Landgrebe, M., Eichhammer, P., Frank, E., Cordes, J., Wölwer, W., Winterer, G., Gaebel, W., Hajak, G., Ohmann, C., Verde, P., Rietschel, M., Ahmed, R., Honer, W.G., Siskind, D., Malchow, B., Strube, W., Schneider-Axmann, T., Falkai, P., Hasan, A., 2019b. Efficacy of high-frequency repetitive transcranial magnetic stimulation in schizophrenia patients with treatment-resistant negative symptoms treated with clozapine. Schizophr. Res. https://doi.org/10.1016/j.schres.2019.01.021 (in press).

Dan Siskind
University of Queensland School of Medicine, Brisbane, Australia
Metro South Addiction and Mental Health Service, Brisbane, Australia
Corresponding author at: University of Queensland School of Medicine, Brisbane, Australia.
E-mail address: d.siskind@uq.edu.au

Faraz Honarparvar
University of Queensland School of Medicine, Brisbane, Australia

Alkomiet Hasan
Department of Psychiatry and Psychotherapy, University Hospital, LMU, Munich, Germany

Elias Wagner
Department of Psychiatry and Psychotherapy, University Hospital, LMU, Munich, Germany

Surabhi Sinha
University of Queensland School of Medicine, Brisbane, Australia

Stacy Orr
University of Queensland School of Medicine, Brisbane, Australia

Steve Kisely
University of Queensland School of Medicine, Brisbane, Australia
Metro South Addiction and Mental Health Service, Brisbane, Australia

25 June 2019