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Letter to the Editor

An investigation into the relationship between clozapine treatment and cognitive performance in patients with treatment resistant schizophrenia

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Dear Editor

Cognitive deficits reduce the quality of life of people with treatment-refractory schizophrenia (TRS), and the anti-cholinergic effects of medications can exacerbate such deficits.

Clozapine is the medication of choice for TRS (Land et al., 2017; Siskind et al., 2016). The effect of clozapine on cognition is uncertain. Clozapine has anti-cholinergic activity at the M1, M3 and M5 receptors, however its primary metabolite nor-clozapine is a partial-agonist at these sites. Therefore, clozapine and nor-clozapine can have opposing effects on cholinergic neuro-transmission and cognition. Clozapine metabolism also varies significantly between patients, with clozapine/nor-clozapine ratios ranging from 0.7 to 5. It has been reported that the clozapine/nor-clozapine ratio may more accurately reflect anticholinergic burden than clozapine dose or levels alone.

A small number of studies with limited participants have examined clozapine/nor-clozapine ratios and cognitive performance, reporting higher clozapine/nor-clozapine ratios were associated with impaired cognitive performance in patients with schizophrenia (Molins et al., 2017; Rajji et al., 2015; Rajji et al., 2010). We hypothesised that higher clozapine/nor-clozapine ratios would be associated with poorer cognitive function. We investigated the relationship between cognitive performance and clozapine/nor-clozapine ratios in patients receiving clozapine for TRS.

Ethical approval (HREC/17/QPAH/763) was obtained to use retrospectively collected routine clinical data from patients attending a community clozapine clinic between September 2015 and June 2017. Inclusion criteria included: patients open to the rehabilitation service of Metro South Addiction and Mental Health Service, age > 18, DSM-V diagnosis of schizophrenia or schizoaffective disorder, >18 weeks of clozapine treatment, stable dosage for 4 weeks, night-time only clozapine, stable illness without admission in 3 months, and a cognitive assessment completed within four weeks of a clozapine/nor-clozapine level. Cognitive tests included California Verbal Learning test: Short delay free recall and Long delay free recall, Trail Making Test A and B, Controlled Oral Word Association Test: semantic and phonemic fluency, and Symbol Digit Modalities Test.

We collated clinical parameters including age, sex, clozapine dose, clozapine/nor-clozapine ratios, smoking status, education status and other medications. Anticholinergic burden of co-prescribed medications was estimated using the Anticholinergic Cognitive Burden Scale (ACB). The ACB threshold reported to be associated with impaired cognition is 3 (Boustani et al., 2008). Correlations between cognitive tests and clozapine/nor-clozapine ratios were examined using Spearman correlations with alpha corrected for number of tests being. We also examined correlations between the ACB and cognitive tests.

Participants were stratified by smoking status, education (less than high school or high school and greater.) ACB (score of 3, or >3) and age (> or < to the mean age, 38.8 years). Sensitivity analyses by these stratification groups were conducted for correlations between clozapine/nor-clozapine level and cognitive tests.

Baseline characteristics of the 32 patients meeting the inclusion criteria are provided in Supplementary Table 1. With a corrected alpha set at 0.0055, the only significant correlation between the cognitive tests and the clozapine/nor-clozapine ratio was for poorer performance on the Symbol Digit Modalities Test (correlation coefficient = −0.501, p = 0.005) (Table 1). There were no significant correlations between the ACB and the cognitive tests. There were no significant correlations on the stratified tests of clozapine/nor-clozapine ratio and cognition.

Significant correlation was found between higher clozapine/nor-clozapine ratios and impaired cognition. Specifically, higher clozapine/nor-clozapine ratios were associated with the completion of fewer symbols in the allotted time on the Symbol Digit Modalities Test, demonstrating slower processing speeds.

Higher clozapine/nor-clozapine ratios are associated with greater cholinergic antagonism. The cholinergic nervous system mediates cognitive function and has a role in modulating attention and encoding memory. The cholinergic system may be altered in patients with schizophrenia, predisposing them to deficits in memory and learning. It is also known that the anticholinergic effects of medication can impair cognition. The anticholinergic effects of clozapine have been difficult to quantify because of the opposing effects of clozapine and nor-clozapine on cholinergic transmission. The clozapine/nor-clozapine ratio may accurately reflect the anticholinergic burden in patients taking clozapine as the anticholinergic effects of clozapine and pro-cholinergic effects of nor-clozapine are considered.

Our results are in keeping with the findings of Rajji et al. (2015) who reported that higher clozapine/nor-clozapine ratios were associated with poorer working memory (Rajji et al., 2015). Similarly, Molins et al. (2017) reported that higher clozapine/nor-clozapine ratios were associated with impaired executive function (Molins et al., 2017).

We saw no impact of the ACB on cognition. However, no participants had an ACB <3.

Clozapine is metabolised to nor-clozapine through the cytochrome P450 1A2 system in the liver, with a small contribution of Cytochrome P450 3A4. Theoretically inducers of cytochrome P450 1A2 or 3A4 may

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Table 1
Correlations between clozapine/nor-clozapine ratios and cognitive tests.

Cognitive domain	N	Correlation Coefficient	2 tailed p-value
Phonemic fluency	30	0.121	0.523
Semantic fluency	30	−0.034	0.86
Trail making test A	32	0.395	0.025*
Trial making test B	26	0.322	0.108
Digit symbol coding	30	−0.501	0.005**
CVLT trial 1	31	−0.162	0.383
CVLT total	31	−0.072	0.699
Short delay free recall	25	−0.182	0.385
Long delay free recall	31	−0.325	0.074

** ≤0.01.
* ≤0.05.

reduce the clozapine/nor-clozapine ratio leading to a reduction in anticholinergic burden and improved cognitive function. Conversely, co-administration of hepatic inhibitors including some SSRIs may increase cognitive dysfunction. Smoking induces cytochrome P450 1A2 leading to lower clozapine/nor-clozapine ratio (van der Weide et al., 2003). There are a limited number of pharmacological inducers of cytochrome P450 1A2. These include omeprazole, carbamazepine and rifampicin. Omeprazole, the most promising of these agents, has been shown to lower clozapine levels in non-smokers, though nor-clozapine levels were not reported (Mookhoek and Loonen, 2004). Carbamazepine may increase neutropenia when co-administered with clozapine. Rifampicin, an antibiotic, may induce antimicrobial resistance.

Medications such as fluvoxamine, paroxetine and fluoxetine, amiodarone, ciprofloxacin, inhibit the metabolism of clozapine to nor-clozapine, potentially increasing the clozapine/nor-clozapine ratios and increasing the risk of cognitive impairment.

This study has a number of limitations. Our numbers were small, and as such the analyses may have been underpowered. As this data is retrospective, we can only demonstrate correlation, not causation. However, the results are consistent with the hypothesis that the anticholinergic burden associated with higher clozapine/nor-clozapine ratios may contribute to impaired cognitive performance in patients with TRS, notably in slower processing speeds.

Research is required to determine whether it is possible to intervene pharmacologically, with agents such as omeprazole, to reduce clozapine/nor-clozapine ratios and potentially improve cognition. In the absence of this information, caution and is advised when co-prescribing drugs which may increase the clozapine/nor-clozapine ratio and exacerbate cognitive deficits in patients taking clozapine.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.11.030.

Conflict of interest
The authors declare no conflict of interest.

CRediT authorship contribution statement

P.A. McArdle: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **V. De Mel:** Conceptualization, Data curation, Formal analysis, Writing - review & editing. **V. DeMonte:** Writing - review & editing. **K. Winckel:** Writing - review & editing. **V. Gore-Jones:** Writing - review & editing. **S. Foley:** Writing - review & editing. **N. Korman:** Writing - review & editing. **S. Parker:** Writing - review & editing. **F. Dark:** Writing - review & editing. **D. Siskind:** Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing.

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