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Safety and acceptability of clozapine and risperidone in progressive multiple sclerosis: a phase I, randomised, blinded, placebo-controlled trial

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ABSTRACT

Objective Because clozapine and risperidone have been shown to reduce neuroinflammation in humans and mice, the Clozapine and Risperidone in Progressive Multiple Sclerosis (CRISP) trial was conducted to determine whether clozapine and risperidone are suitable for progressive multiple sclerosis (pMS).

Methods The CRISP trial (ACTRN12616000178448) was a blinded, randomised, placebo-controlled trial with three parallel arms (n=12/arm). Participants with pMS were randomised to clozapine (100–150 mg/day), risperidone (2.0–3.5 mg/day) or placebo for 6 months. The primary outcome measures were safety (adverse events (AEs)/serious adverse events (SAE)) and acceptability (Treatment Satisfaction Questionnaire for Medication-9).

Results An interim analysis (n=9) revealed significant differences in the time-on-trial between treatment groups and placebo (p=0.030 and 0.025, clozapine and risperidone, respectively) with all participants receiving clozapine being withdrawn during the titration period (mean dose=35±15 mg/day). Participants receiving clozapine or risperidone reported a significantly higher rate of AEs than placebo (p=0.00001) but not SAEs. Specifically, low doses of clozapine appeared to cause an acute and dose-related intoxicant effect in patients with pMS who had fairly severe chronic spastic ataxic gait and worsening over all mobility, which resolved on drug cessation.

Interpretation The CRISP trial results suggest that patients with pMS may experience increased sensitivity to clozapine and risperidone and indicate that the dose and/or titration schedule developed for schizophrenia may not be suitable for pMS. While these findings do not negate the potential of these drugs to reduce multiple sclerosis-associated neuroinflammation, they highlight the need for further research to understand the pharmacodynamic profile and effect of clozapine and risperidone in patients with pMS.

Trial registration number ACTRN12616000178448.

INTRODUCTION

Clozapine and risperidone are atypical antipsychotic agents originally developed in 1959 and 1992, respectively, and are used to treat several neurological disorders, including schizophrenia.[1] Both are potent antagonists of a wide range of neuroreceptors, including dopamine and serotonin receptors,[1 2] and recent studies indicate that these agents have anti-inflammatory actions on microglia.[3 4] Given the known role for neuroinflammation in schizophrenia,[5–7] it is now believed that this class of agents may provide superior benefits during schizophrenia due to their immune-modulatory activity in the central nervous system (CNS).[5 6 8–10]

Previous work has shown that clozapine and risperidone reduce disease severity and improve disease resolution in mouse models of multiple sclerosis (MS) including experimental autoimmune encephalomyelitis, a model of immune-mediated demyelination that recapitulates aspects of relapsing-remitting MS, and cuprizone intoxication, a model of non-immune demyelination, which models aspects of progressive multiple sclerosis (pMS).[11–13] Protection correlates with reduced CNS inflammation and enhanced functional recovery, and can be achieved at doses that do not promote weight gain, a dose-dependent side effect of both clozapine and risperidone.[12 13] Together, this preclinical work suggests that clozapine and risperidone, which readily pass through an intact blood–brain barrier and reduce neuroinflammation in mice and humans,[1] may be useful to treat the chronic neuroinflammation and demyelination associated with pMS in contrast to current disease-modifying treatments which target peripheral immune responses but not those restricted to the CNS compartment.[14–16]

To this end, the Clozapine and Risperidone in Progressive Multiple Sclerosis (CRISP) trial was designed to investigate the suitability of clozapine and risperidone treatment for people

with pMS. Although there have been several case reports describing the successful use of risperidone or clozapine in patients with MS to treat psychosis,[17 18] this was the first trial of clozapine or risperidone in humans to treat MS itself. The primary aim of this study was to determine if doses of 100–150 mg of clozapine and 2.0–3.5 mg of risperidone are safe and well tolerated in patients with pMS.

METHODS

Study design and participants

The CRISP study was a blinded, placebo-controlled trial of clozapine and risperidone treatment in patients with pMS conducted at Wellington Regional Hospital in Wellington, New Zealand. Initially, the trial planned to recruit thirty-six participants (n=12/group) to receive clozapine, risperidone, or placebo for 6 months. An interim analysis was performed after the first block of nine participants, and here we report the results from that interim analysis. Participants were identified and recruited from the neurology ward, neurology outpatient clinics, community MS support group meetings, and after a review of existing databases. We recruited nine participants that fulfilled the inclusion criteria of a diagnosis of pMS with the continuous worsening of neurological impairment over at least 6 months, aged 18–70 years, and an Expanded Disability Status Scale (EDSS) of 3.5–7.0. Full inclusion criteria can be found in the online supplementary information.

Participants were excluded if they were or had a current diagnosis of RRMS; pregnant or lactating; unable to undergo regular blood tests or MRI scans; contraindications to clozapine or risperidone; known hypersensitivity to clozapine, risperidone or to any of the excipients thereof; past intolerance to clozapine or risperidone; concomitant use of medications known to affect clozapine treatment; concomitant disease likely to interfere with the trial medication; serious medical comorbid illness or any other disease or condition which, in the opinion of the investigator, means that it would not be in the patient's best interests to participate in the study. The full exclusion criteria can be found in the online supplementary information.

Standard protocol approvals, registrations and patient consents

The trial was registered (11 February 2016) in the Australian New Zealand Clinical Trials Registry. All participants provided written informed consent prior to screening. Additionally, all methods were performed in accordance with the relevant guidelines and regulations (online supplementary trial protocol).

Randomisation and blinding

Permuted-block randomisation using a block size of nine with no stratification was generated using the statistical software R to allocate a study medication to each participant study number. The treating neurologist, assessing neurologist, research nurse and the participants were blinded as to the treatment allocation. For the interim analysis, the databases were locked after review by the trial site staff and independent trial monitor. The trial statistician then analysed the primary and secondary outcome measures from the interim data.

Procedures

Participants provided written consent and then were screened. Baseline measurements were collected, including EDSS, MSFC, FSS, electrocardiogram and blood tests, and if eligible, participants were enrolled and randomised into the study. Participants received clozapine suspension (50 mg/mL), risperidone tablets (0.5, 2.0 and 3.0 mg tablets) or placebo suspension (matched to clozapine suspension); study medications were provided by Douglas Pharmaceuticals (Auckland, New Zealand). The study medication was titrated slowly over a 2-week period starting at 5 mg/day (clozapine) and 0.5 mg/day risperidone until participants reached 100 mg/day clozapine and 2 mg/day risperidone (online supplementary table S4). After 2.5 months, the dose of study medication was increased over a 2-week period up to 150.0 and 3.5 mg/day of clozapine and risperidone, respectively (online supplementary table S4). Participants were monitored in Wellington Hospital for 4 hours after each of the first five doses to assess body temperature, blood pressure lying, heart rate and AEs as per recommended guidelines for clozapine treatment.[19 20] After 6 months, participants were titrated off the study medication over a 2-week period and had their final end of study visit 4 weeks later.

Outcomes

Participants visited Wellington Hospital or were contacted by the research nurse by phone on alternate weeks to assess AEs and monitor compliance. Additionally, the treating neurologists assessed adverse and SAEs during the visits at baseline and 3 and 6 months and throughout the trial as required.[21 22] Full blood counts (FBCs) were assessed at baseline, weekly for the first 18 weeks and every 4 weeks thereafter until week 26 (6-month visit). A final FBC was taken at week 32 (end of study). Alanine aminotransferase, alkaline phosphatase, gamma glutamyltransferase, total bilirubin, serum albumin, total serum protein, serum creatinine, creatine phosphokinase, glycosylated haemoglobin and prolactin were assessed at baseline and at 3 and 6 months. C reactive protein and troponin T were assessed at baseline, weekly for the first 4 weeks, and at 3 and 6 months. The full schedule of haematological parameters can be found in online supplementary table S5. MRI was assessed at baseline and 6 months by Pacific Radiology (Wellington, New Zealand), and an echocardiogram was performed at baseline by Wakefield Cardiology (Wellington). At baseline and at 3 and 6 months, the EDSS, MSFC, FSS and TSQM-9[23] (3 and 6 months only) were administered by separate, blinded assessors.

Statistical analyses

The statistical analyses were designed and conducted by DS. For the primary outcome measures, the rates of AE/SAEs were compared between groups using the number of events per patient-week using OpenEpi software and Fisher's exact tests. The total time in the study between the three groups was compared using Kaplan-Meier analysis (survival analysis) and the log-rank test. Finally, the TSQM-9 at 3 months was compared between groups using a Kruskal-Wallis test. For secondary analyses, to determine if there was any difference between the participants who withdrew or were withdrawn from the study and those who did not withdraw/were not withdrawn, baseline data on all participants including clinical parameters (EDSS, age and haematological parameters) were compared by Wilcoxon tests.

Post hoc analyses to assess differences in clinical parameters and leucocyte populations between treatment groups at baseline were also analysed using Kruskal-Wallis (for three groups) or Wilcoxon (for two groups) so that we did not have to assume the parameters were normally distributed. Post hoc analyses are indicated in the table legends and were performed using GraphPad Prism (La Jolla, California, USA) software V.7.

RESULTS

Between 8 April 2016 and 8 September 2017, 55 people were identified through visits to the Neurology Clinics at Wellington Hospital, hospital databases, regional MS societies and volunteer recruitment adverts. Of these, 12 were screened at Wellington Hospital for eligibility, and 9 were enrolled into the CRISP trial and randomly allocated to a treatment arm (figure 1). There were no significant differences in the baseline clinical parameters between the treatment groups (table 1), although a significant elevation in WBC and neutrophils (clozapine, p<0.001) and WBC (risperidone, p<0.01) compared with placebo was found (online supplementary table S1).

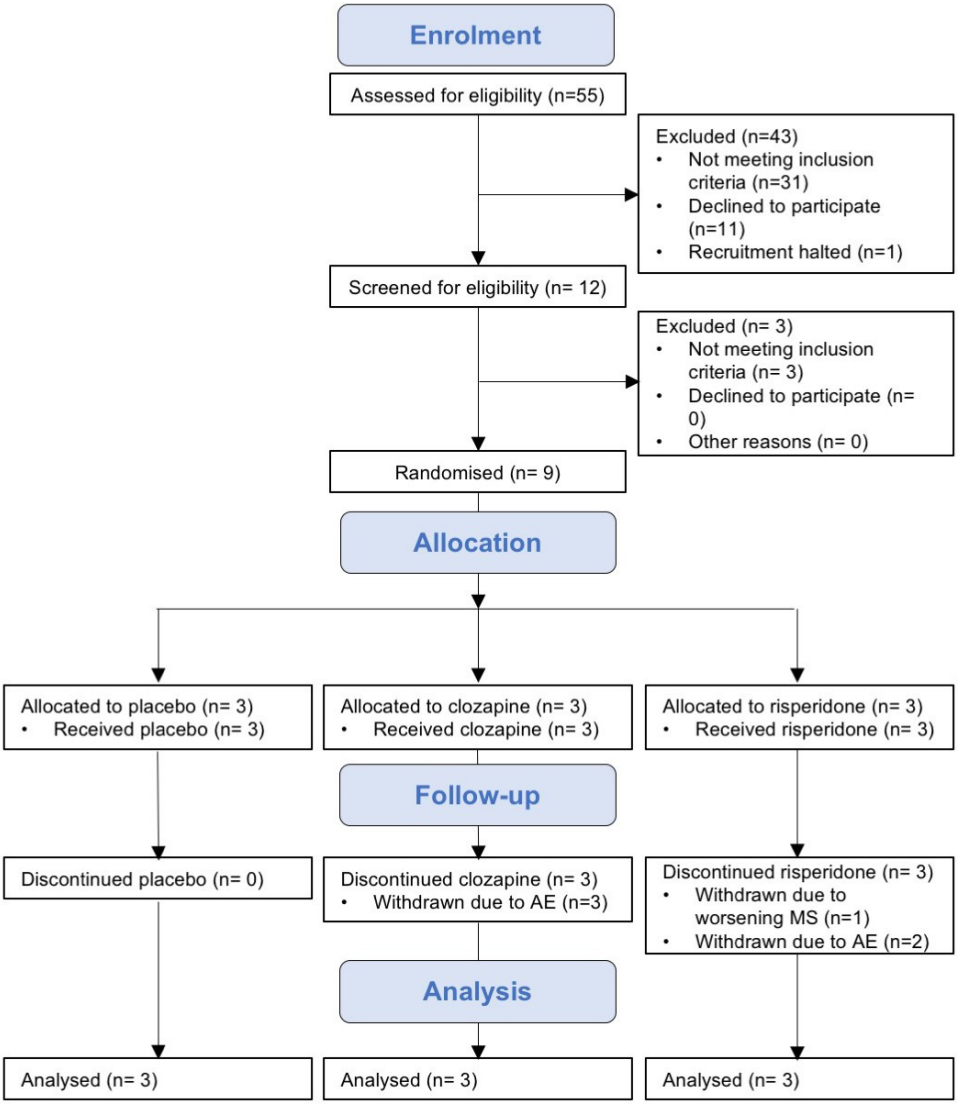

Figure 1 Consolidated Standards of Reporting Trials diagram for the Clozapine and Risperidone in Progressive Multiple Sclerosis trial. AE, adverse event; MS, multiple sclerosis.

Table 1 Baseline clinical characteristics

	Placebo (n=3)	Clozapine (n=3)	Risperidone (n=3)
% Female (n)	67 (2)	67 (2)	100 (3)
Age (years)	58 (12)	57 (6)	57 (9)
Bodyweight (kg)	75.8 (21.6)	89.4 (10.9)	86.3 (26.6)
BMI (kg/m^2)	28.4 (3.7)	30.8 (2.4)	33.6 (7.9)
EDSS (±SD)	6.3 (0.3)	6.2 (0.6)	6.2 (0.6)
FSS (±SD)	6.4 (0.4)	4.2 (1.5)	6.3 (0.8)
MSFC (±SD)	−1.41 (1.2)	−0.91 (0.2)	−0.76 (1.1)
hsCRP (±SD)	3 (0)	4 (1)	5.7 (2.3)
TropT (±SD)	11.3 (4.7)	7.3 (4.0)	5.3 (0.6)
Prolactin (±SD)	194 (78)	203 (87)	200 (88)

BMI, body mass index; EDSS, Expanded Disability Status Scale; FSS, fatigue severity scale; hsCRP, high-sensitivity C reactive protein; MSFC, Multiple Sclerosis Functional Composite; TropT, troponin-T.

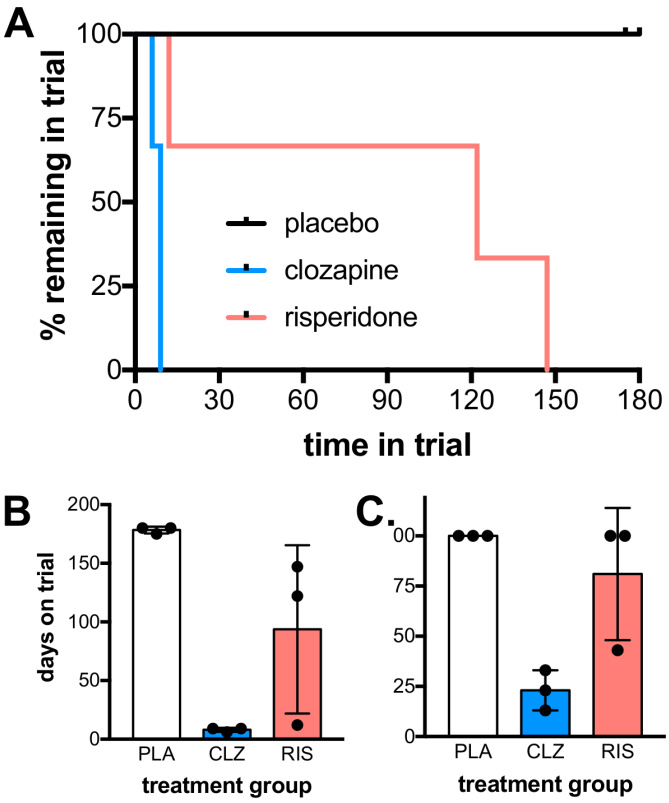

Figure 2 Time on trial was significantly reduced in active treatment arms. (A) A Kaplan-Meier plot for the time to withdrawal for each treatment group. CLZ versus PLA (log rank, p=0.030). RIS versus PLA (p=0.025). (B) Time in days on trial. (C) Percentage (%) of final dose at end of study (PLA) or on day of withdrawal (mean CLZ=35 mg/day, mean RIS=2.8 mg/day). CLZ, clozapine; PLA, placebo; RIS, risperidone.

Three participants (33%) completed the trial as per protocol, while six participants (67%) were withdrawn from the trial; four of whom were withdrawn within the first 2 weeks. Due to the high number of participants withdrawn from the trial, after completion of enrolment of the first block of nine participants, recruitment was halted for an interim analysis to assess safety (number and rate of adverse event (AE)/serious adverse event (SAE)) and acceptability (Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9)). We used number of the days on trial to compare the total time in the study between each treatment and placebo. The participants who completed the trial (ie, not withdrawn) were entered as censored observations in the Kaplan-Meier analysis (figure 2A). We found a significant difference in the time on trial between the groups (p=0.03, P vs C; and p=0.025, P vs R) with a mean time of 8±1 days for participants receiving clozapine and 94±41 days for risperidone compared with 178±3 days for placebo (figure 2B). Because the doses of the study medications were titrated during the first 2 weeks when four participants were withdrawn, we compared the per cent of the final study medication dose (figure 2C), which indicated that participants in the clozapine group received 23%±10% of the final dose or 35±15 mg/day, while those in the risperidone group received 81%±33% or 2.8±1.2 mg/day. A comparison of selected baseline parameters between those withdrawn (n=6) and those who completed the trial (n=3) revealed a higher white blood cell (WBC) count in those withdrawn (p=0.048 by Wilcoxon test) but no other significant differences (online supplementary table S2).

The rate of all AEs was significantly higher (p=0.00001 by Fisher's exact test) in both clozapine and risperidone groups (37.5 and 11.0/100 person-days, respectively) compared with placebo (2.43/100 person-days, table 2). The most common AEs (≥3 occurrences) assigned a possible, probable or likely treatment association were drowsiness, dry mouth, dry eyes, muscle weakness, falls and increased prolactin (online supplementary table S3). Only three SAEs occurred over the whole course of the trial, and no significant differences were found in the rate between treatment groups. One participant receiving risperidone was hospitalised due to rapidly progressing MS. The other two SAEs resulted from a participant in the placebo group who broke her right wrist and left clavicle in a motor vehicle accident (table 2).

For those participants who completed at least 3 months of treatment (n=3, placebo, and n=2, risperidone), no difference in treatment acceptability was found in any of the three domains (efficacy, convenience and global satisfaction) assessed by the TSQM-9 (table 3). Additionally, after 3 months of treatment, there were no significant changes from baseline parameters, including bodyweight, body mass index, Expanded Disability Status Scale (EDSS), Functional System Score (FSS), Multiple Sclerosis Functional Composite (MSFC), WBC, neutrophils, TropT, and CRP except for an elevation in serum prolactin in the risperidone group as expected (table 4; online supplementary figure S1).[24]

Table 2 All adverse events and SAEs

	Placebo (n=3)	Clozapine (n=3)	Risperidone (n=3)
CNS			
Sedation/drowsiness	0	3	0
Headache	0	0	1
Parkinsonism	0	0	1
Balance problems	1	0	0
Vertigo/dizziness	1	0	0
Gastrointestinal			
Dry mouth	0	2	3
Hypersalivation	0	0	1
Constipation	1	0	0
Nausea	1	0	0
Neuromuscular			
Rapid progression of weakness	0	0	1*
Muscle weakness	0	3	2
Leg dragging	1	0	0
Other			
Dry eyes	0	0	3
Rash	0	0	1
Fall	0	1	13
Increased prolactin	0	0	2
Pain or aches	2	0	1
Itchiness	1	0	0
Can't stand smell of meat	1	0	0
Sore throat	1	0	0
Fatigue	0	0	1
Vivid dreams	0	0	1
Urinary tract infection	1	0	0
Broken wrist, broken clavicle (motor vehicle accident)	2*	0	0
Total	13	9	31
Number of person-days	535	24	281
Normalised (per 100 person-days)	2.43	37.5	11
P value†		0.00001	0.00001

*SAE.
†Calculated by Fisher's exact test compared with placebo.
SAE, serious adverse event.

DISCUSSION

This study is the first report of the use of clozapine and risperidone to treat pMS and revealed an unexpected sensitivity in this population to clozapine and, to a lesser extent, risperidone. Specifically, all participants receiving active treatment were withdrawn from the study with the clozapine-treated group averaging only 8 days while the risperidone-treated participants remained in the trial for an average of ninety-four days. In comparison, all participants in the placebo group completed the trial as per protocol. The decreased time in trial was associated with an increased rate of AE but not SAE with the key AE being dry mouth, drowsiness, dry eyes, muscle weakness, and falls. This increased sensitivity to clozapine as well as risperidone in people with pMS is particularly unexpected given that the doses administered were exceptionally low for clozapine (35 mg/day at study termination) and moderate to low for risperidone (2.8 mg/day).[21 25–27]

When initiating atypical anti-psychotic treatment, a slow titration is recommended over a 2 week period until the therapeutic dose is reached.[19 28] For schizophrenia, this dose is 350–400 mg/day for clozapine and 2–6 mg/day for risperidone.[25 26] The titration allows a slow tolerisation to the drug and reduces side effects.[1] For clozapine, a dose of 12.5 mg/day is recommended for the first dose when used for schizophrenia or Parkinson's disease.[19] In contrast, the starting clozapine dose in the CRISP trial was 5 mg/day allowing a very slow and conservative titration up to the target dose (100 mg/day) for the first 3 months. Despite the low dose, AEs occurred by day 3, equating to 15 mg/day, and participants were withdrawn at a mean dose of 35 mg/day. While 7.1% to 15.6% of patients may be withdrawn from clozapine due to AEs,[21] this is the first report of a categorical sensitivity to clozapine at extremely low doses by a cohort of individuals.

During clozapine titration, a common AE is orthostatic hypotension, and this hypotension occurs even at a dose of 12.5 mg/day.[29] Although we did not test specifically for orthostatic hypotension due to the progressive MS disability, no effect on blood pressure was detected at any time during the 4 hour monitoring period post-doses one and two of clozapine (online supplementary figure S2). In addition to the initial orthostatic hypotension, the most common AE occurring in more than one in ten patients administered clozapine are weight gain, drowsiness, sedation, dizziness, tachycardia, constipation, and hypersalivation.[25 29] For the CRISP participants, all three patients allocated to clozapine developed a similar syndrome with lower limb weakness alone in one, lower limb weakness and poor balance in the second, and drowsiness followed by poor balance in the third. In the first two, it began at day five (35 mg) and worsened over 4 days (35–50 mg) until they could no longer walk. The third noted drowsiness after the third dose (15 mg) and unsteadiness the following day after 20 mg. Medication was stopped. She was worse the following day with a fizzy feeling in her fingers, an exacerbation of a pre-existing symptom, but recovered a day later. Rechallenge with a lower dose produced identical symptoms. In all three cases, the symptoms wore off within 48 hours and resembled an intoxication. Their EDSS scores at study entry were 6.5, 6.5, and 5.5, respectively. These observations suggest that patients with advanced MS with cerebellar and pyramidal tract

Table 3 Treatment Satisfaction Questionnaire for Medication-9 at 3 months

	Efficacy	Convenience	Global satisfaction
Placebo (n=3)			
Mean (SD)	66.7 (17)	77.8 (25)	71.4 (25)
Median (min–max)	66.7 (50.0–83.3)	83.3 (50.0–100.0)	57.1 (57.1–100.0)
Risperidone (n=2)			
Mean (SD)	58.4 (4)	94.5 (8)	42.9 (20)
Median (min–max)	58.4 (55.6–61.1)	94.5 (88.9–100.0)	42.9 (28.6–57.1)
P value*	0.564	0.374	0.197

*Calculated by Kruskal-Wallis test to compare means between groups.

dysfunction may be unusually susceptible to intoxication by clozapine.

Galletly reported five patients with schizophrenia, one of whom also had muscular dystrophy, who reported an unpleasant sensation of weakness and reduced muscle tone during treatment with doses of clozapine between 100 and 500 mg/day.[30] The patients complained of a feeling of weakness, difficulty walking and one also of imbalance more severe at night. There was no objective weakness or gait disturbance. Objective sedation and subjective asthenia, a sense of fatigue, are reported in about 30% of patients treated with clozapine.[31] Galletly commented on the difficulty distinguishing the effects of these entities.[30] Clozapine is a dibenzodiazepine reported to have muscle relaxant properties in animal studies.[32] Galletly proposed that the patient experiences resulted from muscle relaxation and hypotonia, rather than from sedation.[30] Our patients all had high EDSS, and quite a severe degree of spasticity and lower limb ataxia. They developed intolerable symptoms of weakness, and varying degrees of imbalance, and sedation similar to those reported by Galletly, although at a much lower dose. We suggest that the most likely cause of our patients' adverse reactions were because they were much more susceptible to the central effects of clozapine, likely including those on muscle tone.

Table 4 Changes to clinical parameters after risperidone treatment—3 months

Parameter: mean (SD)	Time (months)	Placebo (n=3)	Risperidone (n=2)
Bodyweight (kg)	0	75.9 (21)	71.2 (6)
	3	75.8 (21)	69.5 (3)
BMI	0	28.4 (4)	29.3 (4)
	3	28.4 (4)	28.6 (3)
EDSS	0	6.3 (0.3)	6.0 (0.7)
	3	6.2 (0.3)	6.3 (1.0)
FSS	0	6.4 (0.4)	6.1 (1.0)
	3	6.1 (0.2)	5.6 (1.0)
MSFC	0	−1.4 (1.2)	−1.1 (1.2)
	3	−1.1 (0.4)	−1.3 (1.1)
WBC	0	5.9 (1.1)	7.5 (1.3)
	3	5.7 (0.9)	6.9 (0.1)
Neutrophils	0	3.7 (0.3)	4.7 (1.4)
	3	3.6 (0.2)	4.5 (1.1)
TropT	0	11.3 (4.7)	5.5 (0.7)
	3	13.0 (5.3)	5.0 (0.0)
CRP	0	3.0 (0.1)	5.0 (2.8)
	3	3.0 (0.1)	4.5 (2.1)
Prolactin (ng/mL)	0	194 (78)	216 (117)
	3	271 (154)	4207 (1854)

BMI, body mass index; CRP, C reactive protein; EDSS, Expanded Disability Status Scale; FSS, Functional System Score; MSFC, Multiple Sclerosis Functional Composite; TropT, troponin-T; WBC, white blood cell.

Although two participants experienced few AEs during the risperidone titration period, one participant experienced rashes after the first dose, treatment was halted, and then rechallenged 1 week later. However, the participant was unable to tolerate risperidone and was withdrawn. Adverse cutaneous reactions occur in 2%–5% of individuals treated with psychiatric medications including atypical antipsychotics and predominantly occur within the first 2 weeks.[33 34] Exanthematous rashes have been associated with risperidone and resolve after discontinuing treatment.[35]

Other AE experienced by the risperidone-treated group included dry mouth, dry eyes, muscle weakness, falls and increased prolactin. Whereas dry eyes and dry mouth are common (1%–10%) AEs, muscle weakness is far less common (0.1%–1%). Risperidone is associated with elevated serum prolactin and by 3 months, the risperidone group had elevated levels of prolactin as expected.[24] While there were a high number of falls in the risperidone-treated group, most (12 of the 13) occurred in one participant, whose MS was deteriorating relatively rapidly over months and who was barely able to walk at the time of recruitment. These falls were not initially classified as having a possible association with risperidone treatment. Interestingly, one side effect that was not observed in the risperidone group was weight

gain, which has been reported in one study to occur in 58.4% of patients after 3 months (>7% gain).[26 36]

In conclusion, we report an increased sensitivity to clozapine and risperidone in a pMS cohort. Furthermore, the sensitivity is striking in that (1) it occurred at very low doses for clozapine and (2) the adverse reaction pattern was different from expected with no occurrence of hypotension or weight gain and increased reports of muscle weakness and falls. However, despite having statistically significant findings, this study has limitations that need to be considered, the most important of which is the very low number of participants in each treatment group. Although possible that our findings are within the expected AE pattern, the categorical early withdrawal of *all* participants from the active arms provides strength to our conclusions.[21] An additional limitation is that with the unexpected withdrawal of 44% of the participants within the first 2 weeks, no samples were collected to confirm the serum levels of the study medication in these subjects. Finally, because this study was not powered to assess efficacy, the potential of these two atypical antipsychotics to treat the neuroinflammation associated with pMS, was not evaluated. However, current studies are underway to assess the safety and tolerability of quetiapine (300 mg daily), a clozapine analogue, as a remyelinating therapy in MS.[37 38] Given the results of our trial using low doses of clozapine, our findings suggest that it may not be appropriate to administer either clozapine or risperidone in the same manner during pMS as during schizophrenia or the other neurological disorders for which they are indicated.

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Contributors The authors contributed to the study as follows: study design: ACL, DA, DS, BC; data collection: DA, LG, DB, IM, TG, PJ, EW, DS, SL; data analysis and interpretation: ACL, DA; statistical analysis: DS; independent trial monitoring: ML; writing: ACL; editing: DA, DS, BC; ACL, DA, LG, ML, and DB had full access to the data, reviewed manuscript drafts, and approved the final manuscript. ACL had final responsibility for the decision to submit for publication.

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Competing interests ACL and BC have a patent for the use of clozapine and risperidone during MS. ACL is a founding scientist and shareholder in ReKover Therapeutics, which has no relationship to the Clozapine and Risperidone in Progressive Multiple Sclerosis study. In addition, BC has a patent PCT/US2011/042244 issued.

Patient consent for publication Not required.

Ethics approval The Clozapine and Risperidone in Progressive Multiple Sclerosis study was approved by the New Zealand Central Health and Disability Ethics Committee (15/CEN/216) and the Standing Committee on Therapeutic Trials (15/SCOTT/177).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. Deidentified data collected during this study and presented in this manuscript are available from the corresponding author on request from individuals affiliated with research or health care institutions.

REFERENCES

1 Kapur S, Remington G. Atypical antipsychotics: new directions and new challenges in the treatment of schizophrenia. *Annu Rev Med* 2001;52:503–17.
2 Roth BL, Sheffler D, Potkin SG. Atypical antipsychotic drug actions: unitary or multiple mechanisms for 'atypicality'? *Clin Neurosci Res* 2003;3:108–17.
3 Hou Y, Wu CF, Yang JY, *et al*. Effects of clozapine, olanzapine and haloperidol on nitric oxide production by lipopolysaccharide-activated N9 cells. *Prog Neuropsychopharmacol Biol Psychiatry* 2006;30:1523–8.
4 Kato T, Monji A, Hashioka S, *et al*. Risperidone significantly inhibits interferon-gamma-induced microglial activation in vitro. *Schizophr Res* 2007;92:108–15.
5 Kim Y-K, Myint A-M, Lee B-H, *et al*. Th1, Th2 and Th3 cytokine alteration in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2004;28:1129–34.
6 Kim Y-K, Suh I-B, Kim H, *et al*. The plasma levels of interleukin-12 in schizophrenia, major depression, and bipolar mania: effects of psychotropic drugs. *Mol Psychiatry* 2002;7:1107–14.
7 Kirkpatrick B, Miller BJ. Inflammation and schizophrenia. *Schizophr Bull* 2013;39:1174–9.
8 Al-Amin MM, Nasir Uddin MM, Mahmud Reza H. Effects of antipsychotics on the inflammatory response system of patients with schizophrenia in peripheral blood mononuclear cell cultures. *Clin Psychopharmacol Neurosci* 2013;11:144–51.
9 Maes M, Bocchio Chiavetto L, Bignotti S, *et al*. Increased serum interleukin-8 and interleukin-10 in schizophrenic patients resistant to treatment with neuroleptics and the stimulatory effects of clozapine on serum leukemia inhibitory factor receptor. *Schizophr Res* 2002;54:281–91.
10 Cazzullo CL, Sacchetti E, Galluzzo A, *et al*. Cytokine profiles in schizophrenic patients treated with risperidone: a 3-month follow-up study. *Prog Neuropsychopharmacol Biol Psychiatry* 2002;26:33–9.
11 O'Sullivan D, Green L, Stone S, *et al*. Treatment with the antipsychotic agent, risperidone, reduces disease severity in experimental autoimmune encephalomyelitis. *PLoS One* 2014;9:e104430.
12 Green LK, Zareie P, Templeton N, *et al*. Enhanced disease reduction using clozapine, an atypical antipsychotic agent, and glatiramer acetate combination therapy in experimental autoimmune encephalomyelitis. *Mult Scler J Exp Transl Clin* 2017;3:205521731769872.
13 Templeton N, Kivell B, McCaughey-Chapman A, *et al*. Clozapine administration enhanced functional recovery after cuprizone demyelination. *PLoS One* 2019;14:e0216113.

14 Bar-Or A. The immunology of multiple sclerosis. *Semin Neurol* 2008;28:029–45.
15 Lassmann H, van Horssen J, Mahad D. Progressive multiple sclerosis: pathology and pathogenesis. *Nat Rev Neurol* 2012;8:647–56.
16 Weiner HL. A shift from adaptive to innate immunity: a potential mechanism of disease progression in multiple sclerosis. *J Neurol* 2008;255(Suppl 1):3–11.
17 Hussain A, Belderbos S. Risperidone depot in the treatment of psychosis associated with multiple sclerosis -- a case report. *J Psychopharmacol* 2008;22:925–6.
18 Davids E, Hartwig U, Gastpar M. Antipsychotic treatment of psychosis associated with multiple sclerosis. *Prog Neuropsychopharmacol Biol Psychiatry* 2004;28:743–4.
19 Adult clozapine titration chart, 2012. Available: http://www.safetyandquality.gov.au/wp-content/uploads/2013/01/National-Adult-Clozapine-Titration-Chart.pdf
20 Medsafe. *Clozapine close monitoring required. prescriber update ed*, 2015: 18–21.
21 Medsafe. *New Zealand data sheet: Clozaril® (clozapine)*, 2011.
22 Freudenreich O, McEvoy J. Marder S, ed. *Guidelines for prescribing clozapine in schizophrenia [Internet]*, 2020. http://www.uptodate.com/contents/guidelines-for-prescribing-clozapine-in-schizophrenia
23 Bharmal M, Payne K, Atkinson MJ, *et al*. Validation of an abbreviated treatment satisfaction questionnaire for medication (TSQM-9) among patients on antihypertensive medications. *Health Qual Life Outcomes* 2009;7:36.
24 Bostwick JR, Guthrie SK, Ellingrod VL. Antipsychotic-induced hyperprolactinemia. *Pharmacotherapy* 2009;29:64–73.
25 Nielsen J, Damkier P, Lublin H, *et al*. Optimizing clozapine treatment. *Acta Psychiatr Scand* 2011;123:411–22.
26 Pajonk F-G. Risperidone in acute and long-term therapy of schizophrenia--a clinical profile. *Prog Neuropsychopharmacol Biol Psychiatry* 2004;28:15–23.
27 Medsafe. *DP-risperidone*, 2005.
28 Williams R. Optimal dosing with risperidone: updated recommendations. *J Clin Psychiatry* 2001;62:282–9.
29 Young CR, Bowers MB, Mazure CM. Management of the adverse effects of clozapine. *Schizophr Bull* 1998;24:381–90.
30 Galletly C. Subjective muscle weakness and hypotonia during clozapine treatment. *Ann Clin Psychiatry* 1996;8:189–92.
31 Gerlach J, Peacock L. Motor and mental side effects of clozapine. *J Clin Psychiatry* 1994;55(Suppl B):107–9.
32 Stille G, Lauener H, Eichenberger E. The pharmacology of 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo(b,e)(1,4)diazepine (clozapine). *Farmaco Prat* 1971;26:603–25.
33 MacMorran WS, Krahn LE. Adverse cutaneous reactions to psychotropic drugs. *Psychosomatics* 1997;38:413–22.
34 Bliss SA, Warnock JK. Psychiatric medications: adverse cutaneous drug reactions. *Clin Dermatol* 2013;31:101–9.
35 Chae B-J, Kang B-J. Rash and desquamation associated with risperidone oral solution. *Prim Care Companion J Clin Psychiatry* 2008;10:414–5.
36 Maayan L, Correll CU. Management of antipsychotic-related weight gain. *Expert Rev Neurother* 2010;10:1175–200.
37 Harlow DE, Honce JM, Miravalle AA. Remyelination therapy in multiple sclerosis. *Front Neurol* 2015;6:257.
38 Metz L. *Safety and tolerability of quetiapine in multiple sclerosis*. Bethesda, MD: National Library of Medicine (US), 2000. https://clinicaltrials.gov/ct2/show/NCT02087631