Supplementary Methods: Participant selection
To be eligible for inclusion into this trial, the subjects must fulfil all of the following criteria:

Inclusion criteria

1. Progressive multiple sclerosis with the continuous worsening of neurological impairment over at least 6 months
2. Aged 18 years to 70 years
3. An EDSS at baseline of 3.5 to 7.0
4. Willing and able to participate in the trial and provide written, informed consent

Exclusion criteria

1. Relapsing-remitting MS
2. Pregnant or lactating women
3. Patients unable to undergo regular blood tests or MRI scans
4. Patients with contraindications to clozapine or risperidone
5. Known hypersensitivity to clozapine, risperidone or to any of the excipients thereof
6. Reported past intolerance to clozapine or risperidone
7. Postural hypotension, defined as a reduction in systolic blood pressure (BP) of 20 mmHg within 2 – 5 minutes of standing up
8. Dysphagia
9. Current diagnosis of substance abuse or history of alcohol or drug abuse in the past 3 months
10. Concomitant disease likely to interfere with the trial medication (e.g. capable of altering absorption, metabolism or elimination of the trial drug)
11. History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy)
12. Impaired bone marrow function
13. Alcoholic and other toxic psychoses, drug intoxication, comatose conditions
14. History of circulatory collapse and/or CNS depression of any cause
15. Moderate or severe renal or cardiac disorders (e.g. myocarditis)
16. Hepatic impairment; active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure
17. Paralytic ileus
18. History of cardiovascular disease
19. Elevated glycosylated haemoglobin levels (HbA1c; $\geq$ 41mmol/mol)
20. Hyperthyroidism
21. Serious medical co-morbid 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
22. A white blood cell (WBC) and differential blood count taken within 10 days of starting treatment shows a WBC count of < 3500/mm^3 and absolute neutrophil count (ANC) of < 2000/mm^3
23. An abnormal platelet count taken within 10 days of starting treatment
24. Concomitant use of medications known to affect clozapine treatment:
    a. Fluvoxamine, ciprofloxacin, or enoxacin
    b. Oral contraceptives
    c. Cimetidine, escitalopram, erythromycin, paroxetine, buproprion, fluoxetine, quinidine, duloxetine, terbinafine, or sertraline
25. Concomitant use of medications known to reduce the effectiveness of clozapine treatment, including phenytoin, carbmazepine, St John's wort, rifampin

26. Patients taking drugs that increase the risk of agranulocytosis, including carbamazepine, phenylbutazone, azapropazone, co-trimoxazole, penicillamine, cytotoxic agents, sulphonamide antibiotics, or chloramphenicol
27. Patients taking medications that prolong the QT interval or inhibit clozapine metabolism, including ziprasidone, iloperidone, chlorpromazine, thioridazine, mesoridazine, droperidol, pimozide, erythromycin, gatifloxacin, moxifloxacin, sparfloxacin, quinidine, procainamide, amiodarone, sotalol, pentamidine, levomethadyl acetate, methadone, halofantrine, mefloquine, dolasetron mesylate, probucol, or tacrolimus.
28. Patients taking other medications that may potentiate the side effects of treatment with atypical antipsychotics, including frusemide or anti-cholinesterase treatment
29. Treatment with cyclophosphamide or mitoxantrone within 12 months; systemic corticosteroid therapy within 30 days; treatment with interferon beta, glatiramer acetate, natalizumab, fingolimod, dimethyl fumerate, plasmapheresis, or intravenous immunoglobulin within 60 days.

Supplementary Table 1: Baseline leukocyte populations

	Placebo (n=3)	**Clozapine (n=3)**	**Risperidone (n=3)**
WBC	5.9 (1.1)	**9.3 (1.4)*** **	**8.7 (2.5)*** **
Neutrophils	3.7 (0.3)	**6.3 (0.9)** **	5.3 (1.4)
Lymphocytes	1.6 (0.7)	2.2 (0.8)	2.7 (1.1)
Monocytes	0.4 (0.2)	0.6 (0.1)	0.6 (0.2)
Eosinophils	0.1 (0.1)	0.2 (0.1)	0.2 (0.1)
Basophils	0.0 (0.1)	0.1 (0.1)	0.1 (0.0)

***p<0.001 by two-way ANOVA with Dunnett's multiple comparison test compared to placebo.

** p<0.01 by two-way ANOVA with Dunnett's multiple comparison test compared to placebo.

La Flamme AC, *et al. BMJ Neurol Open* 2020; 2:e000060. doi: 10.1136/bmjno-2020-000060

Supplementary Table 2: Comparison between those who completed and those withdrawn with respect to age, EDSS and haematological parameters at baseline.

Parameter: mean (SD) median (min, max)	Completed (n=3)	Withdrawn early (n=6)	P value*
Age - years	57.7 (12)	56.0 (5)	
	59 (45, 69)	56.5 (50, 61)	0.905
EDSS	6.3 (0.3)	6.2 (0.5)	
	6.5 (6, 6.5)	6.5 (5.5, 6.5)	0.905
FSS	6.4 (0.4)	5.3 (1.6)	
	6.2 (6.1, 6.9)	5.4 (2.6, 6.8)	0.262
FSS - global	4 (2)	4.8 (2.5)	
	4 (2, 6)	5 (2, 8)	0.714
WBC	5.9 (1.1)	9.1 (1.8)	
	5.3 (5.3, 7.2)	8.6 (6.6, 11.6)	**0.048**
Neutrophils	3.7 (0.3)	5.8 (1.2)	
	3.8 (3.4, 3.9)	5.9 (3.7, 7.2)	0.095
Lymphocytes	1.6 (0.8)	2.5 (0.9)	
	1.5 (1, 2.4)	2.3 (1.5, 4)	0.262
Monocytes	0.4 (0.2)	0.6 (0.1)	
	0.4 (0.3, 0.6)	0.6 (0.5, 0.8)	0.167
RCC	4.8 (0.4)	4.8 (0.2)	
	4.9 (4.3, 5.1)	4.9 (4.6, 5.1)	0.905

platelets	294 (33)	354 (85)	
	278 (272, 332)	345 (249, 483)	0.381
Prolactin – ng/mL	194 (78)	201 (78)	
	195 (115, 271)	197 (107, 299)	0.905

* Calculated by Wilcoxon for difference between groups.

Supplementary Table 3: Adverse and serious adverse events with possible treatment association

	Placebo (n=3)	Clozapine (n=3)	Risperidone (n=3)
CNS			
sedation/drowsiness	0	3	0
parkinsonism	0	0	1
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
Other			
dry eyes	0	0	3
fall	0	1	7

increased prolactin	0	0	2
fatigue	0	0	1
vivid dreams	0	0	1
TOTAL	3	9	22

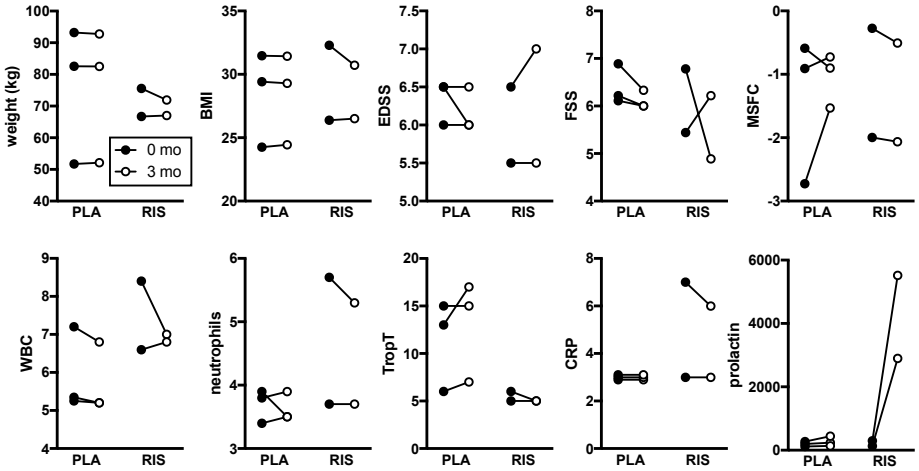
* Serious adverse event

Supplementary Table 4: Schedule of clozapine and risperidone titration in mg/day

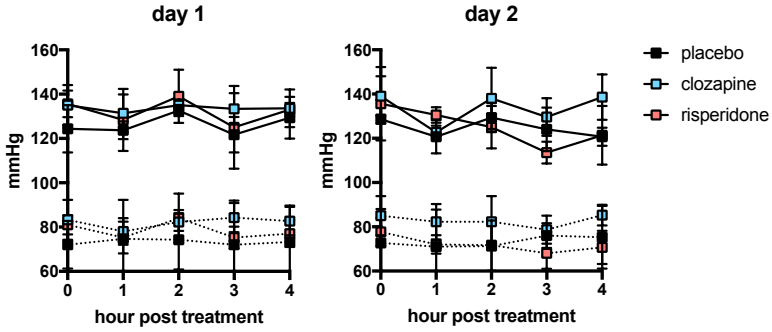
Study Day:		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15 - 91**	**92 - 98**	**99 - 105**	**106 - 180**
		M	**T**	**W**	**Th**	**F**	**Sat**	**Sun**	**M**	**T**	**W**	**Th**	**F**	**Sat**	**Sun**				
Clozapine	**AM**	5	10	15	20	25	25	25	25	25	25	25	25	25	25	25	30	30	30
	PM	-	-	-	-	10	10	10	25	25	45	45	60	60	60	75	90	105	120
	Total:	5	10	15	20	35	35	35	50	50	70	70	85	85	85	100	120	135	150
Risperidone	**AM**	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	-	-	-	-
	PM	-	-	-	-	0.5	0.5	0.5	0.5	1.0	1.0	1.0	1.5	1.5	1.5	2.0	2.5	3.0	3.5
	Total:	0.5	0.5	0.5	0.5	1.0	1.0	1.0	1.0	1.5	1.5	1.5	2.0	2.0	2.0	2.0	2.5	3.0	3.5

Supplementary Table 5: Haematological parameters assessed.

Parameter:	Base-line	Weekly			wk 13	wk 22	wk 26	wk 32
		wk 1-4	wk 5-12	wk 14-18				
FBC	x	x	x	x	x	x	x	x
CRP	x	x			x		x	
TropT	x	x			x		x	
ALT	x				x		x	
GGT	x				x		x	
Total bilirubin	x				x		x	
Serum albumin	x				x		x	
Total serum protein	x				x		x	
Serum creatinine	x				x		x	
Creatine phosphor-kinase	x				x		x	
HbA1c	x				x		x	
Prolactin	x				x		x	



Supplementary Figure 1: Comparison of clinical parameters between placebo (PLA) and risperidone (RIS) participants at baseline (0 mo) and 3 months (3 mo).



Supplementary Figure 2: Clozapine treatment did not cause hypotension in treated pMS patients during dose titration period.