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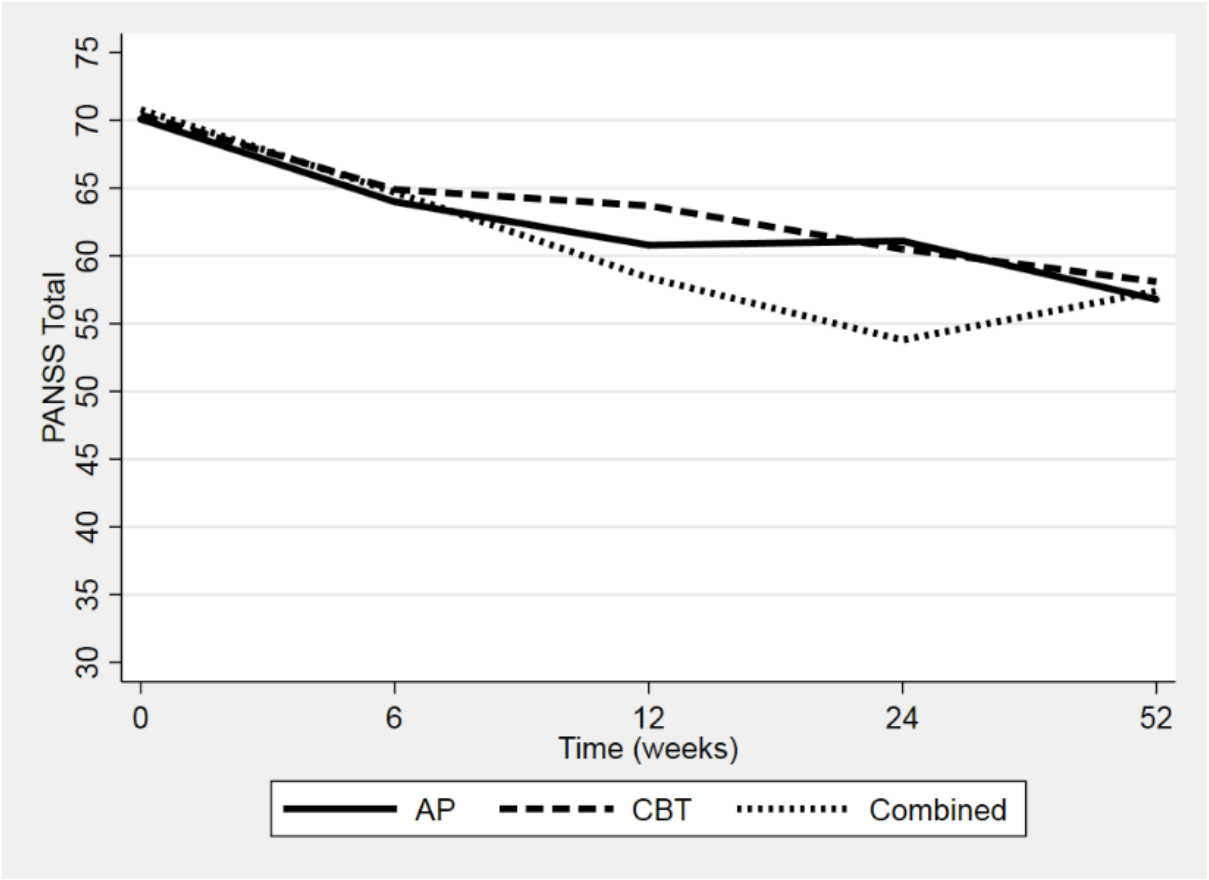
Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Morrison AP, Law H, Carter L, et al. Antipsychotic drugs versus cognitive behavioural therapy versus a combination of both in people with psychosis: a randomised controlled pilot and feasibility study. *Lancet Psychiatry* 2018; published online March 28. http://dx.doi.org/10.1016/S2215-0366(18)30096-8.

Web Appendix



Referrals and randomisations by participating clinical team

	Number of referrals	**Number randomised**
Salford Early Intervention Team (EIT)	55	29
Bolton EIT	40	19
Trafford EIT	18	13
Manchester North EIT	6	3
Oldham EIT	5	4
Cromwell Community Mental Health Team (CMHT)	4	2
Manchester Central Crisis Resolution Team	2	0
Manchester South EIT	2	1
Wigan EIT	2	2
Manchester Central West CMHT	1	1
Greater Manchester Child and Adolescent Services (CAMHS)	1	0
Ramsgate CMHT	1	1
Bolton Assessment Team	1	0
Manchester Central East CMHT	0	0
Manchester Crisis Resolution Team	0	0
Trafford Crisis Resolution Team	0	0
Salford Crisis Resolution Team	0	0
Prescott House CMHT	0	0
Wigan Assessment Team	0	0
Wigan Crisis Resolution Team	0	0
Wigan CMHT	0	0
Wigan CAMHS	0	0
TOTAL	**138**	**75**

Antipsychotic details for participants in the antipsychotic monotherapy arm and combined treatment arms

Primary antipsychotic*	Number of participants	Mean modal dose (mg per day for oral drugs)	Max dose used (mg per day for oral drugs)
Aripiprazole	14	10.6	20
Olanzapine	10	8	10
Quetiapine	10	270	700
Risperidone	2	2.5	3
Promazine	1	50	100
Haloperidol decanoate	1	50mg intramuscular injection every 2 weeks	75mg intramuscular injection every 2 weeks

* Primary antipsychotic = antipsychotic prescribed to each participant for longest duration during the study. (38/49[78%) participants in these two arms received a regular antipsychotic.

PANSS Outcomes analysed without age as a covariate. Mean (SD), number of observations. Effect is common to all follow-up times (ITT).

Variable	Time	Antipsychotics (N = 24)	CBT (N = 26)	Combination (N = 25)	Effect (SE); (95%CI); P-value		
					CBT vs. AP	CBT vs. combined	AP vs. combined
PANSS total	0	70.13 (10.11), 24	70.35 (8.03), 26	70.76 (8.46), 25	-1.05 (2.46); (-5.88, 3.78); 0.669	-5.09 (2.47); (-9.94, -0.24); 0.040	-4.04 (2.51); (-8.96, 0.88); 0.108
	6	64.05 (11.39), 22	64.85 (7.85), 20	64.7 (9.74), 20			
	12	60.81 (16.52), 21	63.74 (7.73), 23	58.4 (14.51), 20			
	24	61.09 (14.44), 22	60.5 (8.74), 22	53.77 (12.54), 22			
	52	56.77 (14.1), 22	58.14 (11.68), 21	57.4 (13.58), 20			
PANSS Positive	0	23.04 (4.6), 24	23.15 (4.63), 26	21.92 (3.63), 25	-1.15 (1.15); (-3.41, 1.11); 0.317	-1.81 (1.15); (-4.06, 0.44); 0.116	-0.66 (1.17); (-2.95, 1.63); 0.574
	6	19.36 (5.44), 22	21 (4.38), 20	20.1 (4.41), 20			
	12	19.19 (7.72), 21	21 (4.72), 23	17.4 (5.65), 20			
	24	17.81 (6.85), 21	18.18 (4.81), 22	15.23 (5.31), 22			
	52	18.18 (6.52), 22	17.9 (5.92), 21	16.8 (6.05), 20			
PANSS Negative	0	16.17 (5.72), 24	15.5 (4.1), 26	15.24 (5.17), 25	-1.23 (0.80); (-2.79, 0.33); 0.123	-2.13 (0.80); (-3.70, -0.57); 0.008	-0.91 (0.80); (-2.48, 0.67); 0.259
	6	14.64 (5.06), 22	15.05 (3.52), 20	13.9 (4.85), 20			
	12	14 (4.32), 21	14.83 (3.1), 23	13 (5.23), 20			
	24	14.14 (5.47), 22	14.91 (4.72), 22	12.41 (4.6), 22			
	52	12.73 (4.58), 22	14.62 (4.52), 21	12.8 (3.68), 20			
PANSS Disorganised	0	16.25 (2.59), 24	17.15 (3.65), 26	17.8 (4.27), 25	-0.15 (0.80); (-1.71, 1.42); 0.855	-0.65 (0.80); (-2.21, 0.92); 0.416	-0.50 (0.83); (-2.12, 1.12); 0.544
	6	15.77 (3.18), 22	16.8 (2.91), 20	17.5 (4.01), 20			
	12	15.19 (4.96), 21	16.39 (3.37), 23	16.25 (4.1), 20			
	24	15.1 (3.86), 21	15.5 (3.53), 22	14.5 (3.78), 22			
	52	14.82 (3.67), 22	15.67 (3.73), 21	15.8 (4.25), 20			
PANSS Excitement	0	18.25 (4.35), 24	17.85 (3.86), 26	17.4 (4.14), 25	-0.44 (0.76); (-1.93, 1.06); 0.566	-0.66 (0.76); (-2.15, 0.83); 0.388	-0.22 (0.77); (-1.73, 1.29); 0.774
	6	15.95 (4.09), 22	15.9 (3.93), 20	15.75 (4.05), 20			
	12	15.52 (4.77), 21	15.52 (3.16), 23	14.35 (4.97), 20			
	24	14.77 (3.37), 22	14.45 (3.4), 22	12.86 (4.36), 22			
	52	13.41 (4.07), 22	13.62 (2.89), 21	13.8 (4.26), 20			
PANSS Emotional Distress	0	25.46 (5), 24	25.31 (3.83), 26	26.28 3.47), 25	0.01 (1.11); (-2.16, 2.19); 0.990	-1.84 (1.11); (-4.03, 0.34); 0.098	-1.86 (1.13); (-4.07, 0.35); 0.100
	6	22.55 (5.21), 22	21.5 (4.27), 20	23.1 (3.93), 20			
	12	21.38 (6.91), 21	22.48 (4.31), 23	19.6 (5.74), 20			

	24	21.55 (5.75), 22	20.95 (3.7), 22	17.5 (5.49), 22			
	52	19.86 (6.12), 22	19.1 (5.49), 21	20.1 (5.08), 20			

Hospital admissions on an as treated basis

	Antipsychotics (N = 21)	CBT (N =20)	Combination (N =21)	Neither (N=13)
Voluntary admission				
Total number of admissions	0	2	3	0
Number (%) of participants admitted	0	1 (5%)	2 (10%)	0
Mean (SD) days in hospital	0	35 (21.2)	67 (88.4)	0
Compulsory admission				
Total number of admissions	0	2	1	0
Number (%) participants admitted	0	2 (10%)	1 (5%)	0
Mean (SD) days in hospital	0	65.5 (54.45)	18	0

Additional details regarding serious adverse events

The 9 participants were randomised to the following treatment arms: antipsychotics n=1, cognitive behavioural therapy n=4, combined n=4. In terms of the interventions these 9 participants actually received, one received neither intervention, 2 received cognitive behavioural therapy, and 6 received the combined treatment. The additional 10 potential SAEs included two admissions related to physical health (one participant in the combined as-treated group experienced seizures which led to a head injury and admission to medical ward, one participant who received neither intervention from the trial was admitted to a medical ward due to pneumonia); and one admission following an overdose (participant was in the combined as-treated group). There was also one event involving aggression to others whilst in hospital (participant was in the combined as-treated group), four attempted overdoses of five or less paracetamol or eight sleeping tablets (these four events related to three participants, one in the combined as-treated group and two in the cognitive behavioural therapy as-treated group), one report of self-harm in the form of superficial cutting (combined as-treated group) and one A&E attendance following reports of suicidal thoughts and self-harm by punching objects (combined as-treated group).

These SAEs were reviewed by the chair of the independent trial steering committee, resulting in six reports being sent to the Research Ethics Committee. These related to 5 different participants: two in the cognitive behavioural therapy as-treated group (events were section 3 hospitalisation and overdose of 3 paracetamol tablets); and 4 in the combined as-treated group (events were superficial cutting; physical health hospital admission following seizures and head injury; informal admission due to risk to self and one hospital admission following an overdose). Only one SAE was considered related to the trial (the overdose of 3 paracetamol tablets in the cognitive behavioural therapy participant).

Considerations for a definitive efficacy and effectiveness trial

Given that the safety and feasibility of such a trial has been demonstrated, a large, efficacy and effectiveness randomised controlled trial is now required to answer the questions regarding the relative clinical and cost-effectiveness of CBT and antipsychotics in a head-to-head comparison. This trial demonstrated that the randomised participants were almost exclusively experiencing a first episode of psychosis, so a definitive trial should target this population specifically and recruit via early intervention services, which seemed to support treatment choice and view the question of which treatments are required with greater equipoise than the more generic community mental health teams. It does not appear feasible to conduct such a trial in people with multiple episode psychotic disorders in generic community mental health teams (mostly because potential participants are already prescribed antipsychotics). Given the possibility of non-adherence and variation in the quality of antipsychotic treatment between clinical teams, for example in terms of dose, duration of treatment before switching, and information given, it may be worth an efficacy and effectiveness trial employing research psychiatrists to help standardise the quality of antipsychotic treatment; however, this may jeopardise support from clinical teams and local Consultant Psychiatrists. It may also be worth considering the introduction of: a diagnostic interview to allow accurate reporting of diagnoses; a measure of substance misuse to allow characterisation of the population; and a placebo condition to facilitate meaningful comparisons of response rates (although this could raise ethical issues). On the basis of our data, it would seem reasonable to suggest that an efficacy and effectiveness trial should evaluate the following hypotheses: i) CBT will be equivalent to antipsychotics on efficacy; ii) CBT will be superior to antipsychotics on side effects; iii) the combined intervention will be superior in efficacy to both monotherapies. Further consideration, including consultation of stakeholders such as service users and clinicians, is required to inform the selection of the most appropriate outcome measure an efficacy and effectiveness trial (for example, symptom change, quality of life or subjective recovery).