

# THE LANCET Psychiatry

## **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, Pyle M, Gumley A, et al. Cognitive behavioural therapy in clozapine-resistant schizophrenia (FOCUS): an assessor-blinded, randomised controlled trial. *Lancet Psychiatry* 2018; published online July 9. [http://dx.doi.org/10.1016/S2215-0366\(18\)30184-6](http://dx.doi.org/10.1016/S2215-0366(18)30184-6).

## Reasons for ineligibility

	n
<b>After patients identified</b>	<b>N=79</b>
No current positive symptoms of psychosis or problems	21 (26.6%)
Dose of clozapine below 400mg and not limited due to side effects	16 (20.3%)
Lacking capacity to consent	9 (11.4%)
Current CBT or CBT in past year	8 (10.1%)
Never taken clozapine	7 (8.9%)
Diagnosis not schizophrenia spectrum	7 (8.9%)
Discontinued clozapine > 2 years ago	6 (7.6%)
Moved out of area	2 (2.5%)
Diagnosis of a developmental disability	1 (1.3%)
Not English speaking	1 (1.3%)
Deceased before consented	1 (1.3%)
<b>After patients found to be eligible</b>	<b>N=47</b>
Below threshold on the Positive and Negative Syndrome Scale	40 (85.1%)
Diagnosis not schizophrenia spectrum	2 (4.3%)
Lacking capacity to consent	2 (4.3%)
Dose of clozapine below 400mg and not limited due to side effects	1 (2.1%)
No current positive symptoms of psychosis or problems	1 (2.1%)
Unable to complete the baseline assessment	1 (2.1%)

# Number of sessions attended for those randomised to CBT

	CBT N=242
0	12 (5.0%)
1-5	17 (7.0%)
6-10	20 (8.3%)
11-20	48 (19.8%)
21-30	124 (51.2%)
>31	21 (8.7%)
Median (25th, 75th centile); n	23 (13, 28); 242

### PANSS outcome by symptom severity based on inclusion criteria

	CBT N = 242	TAU N = 245
PANSS total		
Delusions < 4	73.5 (11.7); 34	75.9 (13.2); 38
Delusions ≥ 4	84.3 (13.4); 208	84.7 (13.7); 207
Hallucinatory behaviour < 4	80.6 (12.0); 53	81.0 (10.7); 42
Hallucinatory behaviour ≥ 4	83.4 (14.1); 189	83.8 (14.6); 203
Grandiosity < 5	81.4 (13.2); 207	82.1 (13.8); 208
Grandiosity ≥ 5	90.7 (13.9); 35	90.4 (13.1); 37
Suspiciousness persecution < 5	77.3 (11.8); 119	78.0 (13.5); 113
Suspiciousness persecution ≥ 5	88.0 (13.3); 123	87.9 (12.8); 132
PANSS positive		
Delusions < 4	17.6 (4.1); 34	18.4 (3.0); 38
Delusions ≥ 4	25.9 (5.3); 208	26.4 (5.2); 207
Hallucinatory behaviour < 4	23.3 (4.4); 53	23.0 (3.7); 42
Hallucinatory behaviour ≥ 4	25.1 (6.2); 189	25.6 (6.0); 203
Grandiosity < 5	23.6 (5.5); 207	24.1 (5.1); 208
Grandiosity ≥ 5	31.1 (4.0); 35	31.4 (4.9); 37
Suspiciousness persecution < 5	21.5 (5.2); 119	21.8 (4.8); 113
Suspiciousness persecution ≥ 5	27.8 (4.7); 123	28.1 (4.8); 132
PANSS negative		
Delusions < 4	19.6 (5.4); 34	20.4 (7.7); 38
Delusions ≥ 4	19.3 (6.2); 208	19.2 (6.1); 207
Hallucinatory behaviour < 4	19.3 (6.4); 53	19.2 (5.8); 42
Hallucinatory behaviour ≥ 4	19.3 (6.0); 189	19.5 (6.5); 203
Grandiosity < 5	19.8 (6.1); 207	19.6 (6.4); 208
Grandiosity ≥ 5	16.7 (4.9); 35	18.4 (5.9); 37
Suspiciousness persecution < 5	18.2 (5.4); 119	18.5 (6.9); 113

Suspiciousness persecution $\geq 5$	20.4 (6.5); 123	20.2 (5.8); 132
PANSS disorganised		
Delusions $< 4$	21.9 (6.5); 34	23.3 (7.4); 38
Delusions $\geq 4$	25.2 (6.4); 208	25.1 (6.4); 207
Hallucinatory behaviour $< 4$	25.3 (6.2); 53	24.8 (6.2); 42
Hallucinatory behaviour $\geq 4$	24.6 (6.6); 189	24.8 (6.6); 203
Grandiosity $< 5$	24.0 (6.1); 207	24.3 (6.4); 208
Grandiosity $\geq 5$	29.1 (7.5); 35	27.7 (6.7); 37
Suspiciousness persecution $< 5$	24.2 (6.5); 119	23.9 (7.2); 113
Suspiciousness persecution $\geq 5$	25.3 (6.5); 123	25.6 (5.8); 132
PANSS excitement		
Delusions $< 4$	15.2 (3.7); 34	15.9 (3.9); 38
Delusions $\geq 4$	18.5 (4.4); 208	18.3 (4.3); 207
Hallucinatory behaviour $< 4$	18.4 (4.4); 53	18.2 (3.7); 42
Hallucinatory behaviour $\geq 4$	17.9 (4.5); 189	17.8 (4.5); 203
Grandiosity $< 5$	17.4 (4.2); 207	17.4 (4.3); 208
Grandiosity $\geq 5$	21.4 (4.5); 35	20.8 (3.3); 37
Suspiciousness persecution $< 5$	16.6 (3.9); 119	16.6 (4.0); 113
Suspiciousness persecution $\geq 5$	19.4 (4.6); 123	19.0 (4.3); 132
PANSS emotional distress		
Delusions $< 4$	23.6 (5.2); 34	24.8 (5.2); 38
Delusions $\geq 4$	27.6 (5.5); 208	27.9 (5.5); 207
Hallucinatory behaviour $< 4$	25.9 (5.1); 53	27.2 (4.6); 42
Hallucinatory behaviour $\geq 4$	27.3 (5.8); 189	27.5 (5.7); 203
Grandiosity $< 5$	27.0 (5.7); 207	27.5 (5.5); 208
Grandiosity $\geq 5$	27.0 (5.0); 35	27.2 (6.0); 37
Suspiciousness persecution $< 5$	23.8 (4.6); 119	24.8 (4.9); 113
Suspiciousness persecution $\geq 5$	30.2 (4.7); 123	29.7 (5.1); 132

**PANSS outcomes using multiple imputation**

	<b>MD</b>	<b>95% CI</b>	<b>p-value</b>
PANSS total			
9 months	-2.50	(-4.98, -0.02)	0.048
21 months	-0.63	(-3.22, 1.96)	0.63
PANSS positive			
9 months	-1.64	(-2.65, -0.63)	0.002
21 months	-0.74	(-1.80, 0.33)	0.17
PANSS negative			
9 months	-0.43	(-1.44, 0.59)	0.41
21 months	0.28	(-0.77, 1.32)	0.60
PANSS disorganised			
9 months	0.05	(-0.88, 0.98)	0.92
21 months	0.22	(-0.75, 1.19)	0.66
PANSS excitement			
9 months	-1.14	(-1.84, -0.44)	0.001
21 months	-0.51	(-1.25, 0.23)	0.18
PANSS emotional distress			
9 months	-1.04	(-2.02, -0.05)	0.040
21 months	-0.10	(-1.14, 0.94)	0.85

**PANSS outcomes after removing participants who discontinued clozapine due to side effects**

	<b>CBT (N=242)</b>	<b>TAU (N=245)</b>	<b>Mean difference</b>	<b>95% CI</b>	<b>P Value</b>
<b>PANSS total</b>					
Baseline	82.8 (14.0); 226	82.8 (13.7); 222			
9 months	75.6 (15.5); 204	77.1 (14.0); 203	-1.84	(-4.27 to 0.58)	0.14
21 months	73.1 (16.8); 195	73.8 (14.8); 196	-1.05	(-3.53 to 1.43)	0.41
<b>PANSS positive</b>					
Baseline	24.7 (6.0); 226	24.9 (5.7); 222			
9 months	21.8 (6.6); 204	23.2 (6.1); 204	-1.25	(-2.25 to -0.25)	0.014
21 months	21.2 (6.9); 195	22.3 (6.1); 196	-0.94	(-1.96 to 0.08)	0.071
<b>PANSS negative</b>					
Baseline	19.3 (6.2); 226	19.4 (6.3); 222			
9 months	18.2 (7.0); 206	18.8 (6.7); 205	-0.63	(-1.63 to 0.38)	0.22
21 months	17.7 (6.7); 197	17.6 (6.1); 196	0.03	(-1.00 to 1.06)	0.95
<b>PANSS disorganised</b>					
Baseline	24.8 (6.6); 226	24.7 (6.5); 222			
9 months	23.4 (6.5); 204	23.0 (5.9); 204	0.16	(-0.77 to 1.09)	0.74
21 months	22.9 (6.7); 196	22.4 (6.3); 196	0.21	(-0.74 to 1.16)	0.67
<b>PANSS excitement</b>					
Baseline	17.9 (4.4); 226	17.8 (4.3); 222			
9 months	16.2 (4.1); 206	17.2 (4.1); 206	-1.07	(-1.77 to -0.37)	0.003
21 months	15.4 (4.0); 196	15.9 (3.9); 196	-0.65	(-1.37 to 0.06)	0.074
<b>PANSS emotional distress</b>					

Baseline	27.1 (5.7); 226	27.3 (5.5); 222			
9 months	24.2 (6.2); 206	25.1 (6.2); 206	-0.82	(-1.78 to 0.14)	0.095
21 months	23.3 (6.5); 196	23.9 (6.0); 196	-0.40	(-1.38 to 0.59)	0.43



**CACE analysis estimates for PANSS outcomes using a minimum of 6 sessions of CBT attendance**

	<b>Mean difference</b>	<b>95% CI</b>	<b>p-value</b>
<b>9 months PANSS</b>			
PANSS total	-2.50	(-5.10 to 0.11)	0.060
PANSS positive	-0.52	(-1.60 to 0.56)	0.35
PANSS negative	-1.67	(-2.68 to -0.67)	0.001
PANSS disorganised	-0.00	(-0.97 to 0.97)	0.99
PANSS excitement	-1.28	(-2.05 to -0.50)	0.001
PANSS emotional distress	-1.17	(-2.21 to -0.13)	0.028
<b>21 months PANSS</b>			
PANSS total	-0.87	(-3.69 to 1.96)	0.55
PANSS positive	0.36	(-0.76 to 1.48)	0.53
PANSS negative	-0.95	(-2.10 to 0.19)	0.10
PANSS disorganised	0.17	(-0.87 to 1.22)	0.74
PANSS excitement	-0.56	(-1.32 to 0.20)	0.15
PANSS emotional distress	-0.33	(-1.47 to 0.80)	0.57

### Potential unwanted effects of trial participation

Forms returned	313 of 487 = 64.2%	
Forms returned by group	CBT 146 of 242 (60.3%)	TAU 167 of 245 (68.1%)
Participants endorsing at least one item 3 or 4	CBT n=40/146 (27.3%)	TAU n=42/167 (25.1%)

Total counts for all participant responses (i.e. TAU and CBT plus TAU)

Item*	0 Not at all	1 Very little	2 A little	3 Quite a lot	4 Very much	Responses n=313	Missing
Q1	114	43	79	54	21	311	2
Q2	243	45	17	3	3	311	2
Q3	165	66	65	12	2	310	3
Q4	221	49	34	8	1	313	-
Q5	225	45	33	6	2	311	2
Q6	256	36	15	2	1	310	3
Q7	190	58	45	11	7	311	2
Q8	147	62	65	24	14	312	1
Q9	262	31	14	5	-	312	1
Q10	211	59	34	8	1	313	-
Q11	219	61	22	10	1	313	-
Q12	280	19	11	3	-	313	-
Q13	279	21	8	3	2	313	-
Q14	253	39	16	1	1	310	3
Q15	289	15	5	2	-	311	2
Q16	259	33	13	5	-	310	3
Q17	283	17	6	2	1	309	4
Q18	263	21	7	6	6	303	10
Q19	155	59	64	21	4	303	10
Q20	282	12	7	1	-	302	11
Q21	229	43	19	9	3	303	10
Q22	273	17	8	5	-	303	10
Q23	228	39	25	8	1	301	12
Q24	196	43	43	16	4	302	11
Q25	286	7	2	2	1	298	15
Q26	237	38	22	3	2	302	11
Q27	171	42	61	15	7	296	17

\* For item description see subsequent tables

# CBT plus TAU Group Responses

Taking part -	0	1	2	3	4	Resp. n=146	M
1 hasn't helped me with my problems	58	16	38	24	9	145	1
2 made my problems worse	117	17	7	2	1	144	2
3 made me feel more anxious	82	26	31	6	-	145	1
4 took up too much time	105	24	13	4	-	146	-
5 led to my mood becoming very low	103	22	15	3	2	145	1
6 made me feel more angry and irritable	121	13	9	2	-	145	1
7 I didn't feel ready to talk about my problems	91	24	19	6	6	146	-
8 made me think too much about bad things that have happened in the past	71	25	29	11	9	145	1
9 meant I stopped looking after myself properly	121	15	7	2	-	145	1
10 made me feel more suspicious	100	31	11	4	-	146	-
11 required too much energy or motivation	100	33	7	5	1	146	-
12 increased my thoughts of killing myself	132	8	6	-	-	146	-
13 I didn't feel listened to or believed by FOCUS staff	131	10	3	2	-	146	-
14 made my voices or visions worse	121	15	6	1	1	144	2
15 was making me fall out with my family or friends	137	6	1	1	-	145	1
16 was having a bad effect on my self-esteem	120	16	4	4	-	144	2
17 was making me want to harm myself	136	8	-	1	-	145	1
18 I didn't like or feel I could trust the FOCUS team members	127	6	5	2	2	142	4
19 I felt embarrassed talking about my problems with people I had not met before	77	24	31	8	2	142	4
20 made me have thoughts of harming other people	137	2	2	-	-	141	5
21 was making me feel hopeless about the future	102	25	8	5	2	142	4
22 meant I had to increase my medication in order to cope	131	5	3	3	-	142	4
23 involved too much hard work.	108	17	14	2	1	142	4
24 made me worry that people would think badly of me because of my diagnosis	98	16	18	8	1	141	5
25 made me fall out with my doctor or care team	133	5	1	1	1	141	5
26 made me worry about losing control of my mind	107	21	10	2	2	142	4
27 My problems have improved to the point I no longer feel I need help	73	17	35	12	3	140	6

## TAU Group Responses

Taking part -	0	1	2	3	4	Resp. n=167	M
1 hasn't helped me with my problems	56	27	41	30	12	166	1
2 made my problems worse	126	28	10	1	2	167	-
3 made me feel more anxious	83	40	34	6	2	165	2
4 took up too much time	116	25	21	4	1	167	-
5 led to my mood becoming very low	122	23	18	3	-	166	1
6 made me feel more angry and irritable	135	23	6	-	1	165	2
7 I didn't feel ready to talk about my problems	99	34	26	5	1	165	2
8 made me think too much about bad things that have happened in the past	76	37	36	13	5	167	-
9 meant I stopped looking after myself properly	141	16	7	3	-	167	-
10 made me feel more suspicious	111	28	23	4	1	167	-
11 required too much energy or motivation	119	28	15	5	-	167	-
12 increased my thoughts of killing myself	148	11	5	3	-	167	-
13 I didn't feel listened to or believed by FOCUS staff	148	11	5	1	2	167	-
14 made my voices or visions worse	132	24	10	-	-	166	1
15 was making me fall out with my family or friends	152	9	4	1	-	166	1
16 was having a bad effect on my self-esteem	139	17	9	1	-	166	1
17 was making me want to harm myself	147	9	6	1	1	164	3
18 I didn't like or feel I could trust the FOCUS team members	136	15	2	4	4	161	6
19 I felt embarrassed talking about my problems with people I had not met before	78	35	33	13	2	161	6
20 made me have thoughts of harming other people	145	10	5	1	-	161	6
21 was making me feel hopeless about the future	127	18	11	4	1	161	6
22 meant I had to increase my medication in order to cope	142	12	5	2	-	161	6
23 involved too much hard work.	120	22	11	6	-	159	8
24 made me worry that people would think badly of me because of my diagnosis	98	27	25	8	3	161	6
25 made me fall out with my doctor or care team	153	2	1	1	-	157	10
26 made me worry about losing control of my mind	130	17	12	1	-	160	7
27 My problems have improved to the point I no longer feel I need help	98	25	26	3	4	156	11

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