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Psychosocial Intervention With or Without Antipsychotic Medication for First-Episode Psychosis: A Randomized Noninferiority Clinical Trial

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This triple-blind (participants, clinicians, and researchers) randomized controlled noninferiority trial examined whether intensive psychosocial intervention (cognitive-behavioral case management, CBCM) for first-episode psychosis (FEP) in 15–25 year-olds managed in a specialized early intervention for psychosis service was noninferior to usual treatment of antipsychotic medication plus CBCM delivered during the first 6 months of treatment. To maximize safety, participants were required to have low levels of suicidality and aggression, a duration of untreated psychosis (DUP) of less than 6 months, and be living in stable accommodation with social support. The primary outcome was level of functioning as assessed by the Social and Occupational Functioning Scale (SOFAS) at 6 months. Ninety young people were randomized by computer, 46 to placebo, and 44 antipsychotic medication and 33% of those who commenced trial medication completed the entire 6-month trial period. On the SOFAS, both groups improved, and group differences were small and clinically trivial, indicating that treatment with placebo medication was no less effective than conventional antipsychotic treatment (mean difference = −0.2, 2-sided 95% confidence interval = −7.5 to 7.0, $t = 0.060$, $P = .95$). Within the context of a specialized early intervention service, and with a short DUP, the immediate introduction of antipsychotic medication may not be required for all cases of FEP in order to see functional improvement. However, this finding can only be generalized to a very small proportion of FEP cases at this stage, and a larger trial is required to clarify whether antipsychotic-free treatment can be recommended for specific subgroups of those with FEP. Trial Registration: ACTRN12607000608460 (www.anzctr.org.au).

Introduction

Early intervention for psychosis, which involves multicomponent treatment including psychosocial therapies has been shown to produce outcomes superior to those of treatment as usual.[1] The provision of low-dose second-generation antipsychotic medication, for which there is good evidence of efficacy in the treatment of positive psychotic symptoms[2] is usually a central component of treatment. However, these medications can have direct and indirect negative effects,[3] and evidence supporting the efficacy of nonpharmacological interventions for psychosis is increasing.[4,5] For example, Bird et al[6] in a systematic review and meta-analysis found that cognitive behavioral therapy (CBT) and family interventions offered in early intervention services contributed to the improved outcomes produced by these services. Additionally, the clinical staging model of psychiatric disorders,[7] strongly argues for the use of milder and simpler treatments early in the course of illness. If psychosocial interventions are effective early in

the course of psychotic illnesses, this could help improve the risk–benefit balance in early intervention.

Antipsychotic medications are associated with a number of adverse effects, including weight gain, altered glucose metabolism, sexual dysfunction, long-term cardiovascular disease and premature mortality.[8] These concerns are greater for first-episode patients who are younger, usually treatment naïve, and more susceptible to side effects and long-term impacts of medication.[9] Improved efforts at early detection may result in patients presenting at earlier stages and in less acute mental states, raising the possibility of recovery through psychosocial support alone, as is often the case in at-risk mental states.[10] In light of these potential adverse effects of treatment, the point at which antipsychotic treatment is introduced to those in the early illness stages may need to be reconsidered.

In order to determine whether antipsychotic medication is required in FEP, a randomized control trial (RCT) is necessary, in which a subset of patients do not receive medication. It was previously considered that withholding effective treatment from patients with psychosis was unethical. However, long-term follow-up of patients with psychosis who were initially unmedicated has demonstrated that it is not harmful to withhold antipsychotic medication, at least in the short-term.[11,12] Against this, more recently, evidence suggesting that duration of untreated psychosis (DUP) is associated with poorer outcome[13,14] has been a major argument in support of early detection efforts and early intervention programs. However, the specific role of antipsychotic medication in this association has not been established, supporting the need for RCTs.

Psychosocial treatments offer promise as effective treatments for both positive psychotic symptoms and functional impairments, without negative physical health consequences. Meta-analyses have indicated that CBT is beneficial for psychosis.[15–18] CBT strategies delivered within a specialized first-episode psychosis (FEP) service may be effective in delaying and preventing psychotic relapse,[19] as well as managing auditory hallucinations,[20,21] hopelessness,[22] adaptation to illness,[23] treatment adherence,[24] and comorbid substance use.[25] CBT has usually been tested as an additional intervention for people also taking antipsychotic medication. However, 2 recent trials conducted in the United Kingdom[26,27] demonstrated that CBT can be a safe and effective alternative treatment to antipsychotic medication. Another critical consideration in cost-benefit considerations of early administration of antipsychotics is a shift from focusing treatment solely on alleviating positive psychotic symptoms to including improving functional outcomes. Young people, in particular, have reported that psychosocial functional improvement is more important to them than alleviation of positive symptoms.[28,29]

The aim of this trial was to determine whether psychosocial treatment without antipsychotic medication would be noninferior to standard treatment for FEP as assessed by functional outcome. The STAGES Study[30] investigated the effects of randomized withholding of antipsychotic medication up to 6 months, thereby increasing DUP, among treatment-seeking FEP patients. We aimed to investigate the effects on functional outcomes and psychopathology assessed at 6, 12, and 24 months after commencement of the trial, with functioning at 6 months as the primary outcome.

Methods

Study Design and Participants

The study was a 6-month triple-blind noninferiority RCT comparing 2 groups, who both received intensive psychosocial intervention, with one also receiving low-dose antipsychotic medication (medication group), and the other receiving placebo (placebo group). Allocation occurred on 1:1 ratio. It aimed to test whether the antipsychotic medication-free experimental treatment was no less effective than the active control or standard treatment (a noninferiority trial). The primary outcome was the level of functioning measured by the Social and Occupational Functioning Scale (SOFAS[31]), at 6, 12, and 24 months, with the 6-month outcome as the primary prespecified endpoint. A noninferiority margin of 10.5 on the SOFAS was selected, after consultation with clinicians and review of historical SOFAS data from a previous sample at our center, as the smallest value that represents a clinically important effect, as advocated in the literature on noninferiority trials.[32,33] Ethical approval for the study was granted by the Melbourne Health Human Research Ethics Committee (MHREC:2007.616).

Participants were aged 15–25 years, presenting with FEP to a specialist early psychosis service (Early Psychosis Prevention and Intervention Centre, EPPIC). EPPIC is part of Orygen Youth Health, a public youth mental health service that serves a catchment area of approximately 1 million in the Western region of metropolitan Melbourne, Australia. Eligibility was defined as fulfilling criteria for a DSM-IV psychotic disorder, including schizophrenia, schizophreniform disorder, delusional disorder, brief psychotic disorder, major depressive disorder with psychotic symptoms, substance-induced psychotic disorder, or psychosis not otherwise specified (NOS). Potential participants were also required to meet strict inclusion criteria to minimize risk: ability to provide informed consent; comprehension of the English language; DUP of less than 6 months; living in stable accommodation; low risk to self or others (score of <5 on the Brief Psychiatric Rating Scale version 4 [BPRS-4[34]] Suicidality and Hostility subscales); low previous exposure to antipsychotic medication (less than 7 days or lifetime maximum 1750 mg chlorpromazine equivalent).

To further ensure safety, several discontinuation criteria were applied. These were operationally defined as any of the following: increased risk to self or others (score

of ≥5 on the BPRS-4 Suicidality or Hostility subscales, maintained for 1 week); increase in positive psychotic symptom severity (2-point increase on the BPRS-4 subscale of Conceptual Disorganisation, Hallucinations, Unusual Thought Content, or Suspiciousness) maintained for at least 1 week not due to substance use; decrease in overall functioning (20-point drop in SOFAS score from baseline maintained for 1 month); request by the participant for the introduction of antipsychotic medication; failure to satisfactorily recover 3 months after study entry (a score of 5 or more on the BPRS-4 Hallucinations, Suspiciousness, and Unusual Thought Content subscales or a score of 4 or greater on Conceptual Disorganisation); or becoming pregnant. Treating clinicians monitored symptom levels and SOFAS scores at each session. Participants who discontinued study medication continued to receive cognitive behavioral case management (CBCM) and were prescribed medications, including antipsychotics as deemed appropriate by their treating team. They were followed-up according to the study assessment protocol and the treatment they received was recorded. All participants gave written informed consent after having the study fully explained to them, parental consent was also obtained for participants under the age of 18.

Randomization and Masking

A stratified randomization design was used to allocate participants to treatment groups, stratifying for DUP (3 levels: 0–30, 31–90, and >90 days) and gender.[13] Treatment allocation occurred using randomly permuted blocks within each stratum, to ensure approximately equal group sizes. The computerized randomization was set up by an independent person. Clinicians, research staff, and participants remained blinded to treatment allocation throughout the trial. Allocated trial medication (antipsychotic or placebo) was dispensed in identical packaging by the independent trial pharmacist according to the computer-generated randomization list.

Procedures

Functioning was assessed with the SOFAS[31] and the Heinrich Quality of Life Scale (QLS[35]). SOFAS is evaluated on a continuum from grossly impaired functioning, 1–10 (*persistent inability to maintain minimal personal hygiene; unable to function without harming self or others without considerable external support*) to superior functioning, 91–100 (*superior functioning in a wide range of activities*). It is intended to measure aspects of social and occupational functioning that are separate to symptom severity[36] with excellent inter-rater reliability ($ICC_{1,k}$ = .94) between clinician and external rater scores and good convergent validity with patient measures of social adjustment and interpersonal relationships reported. Positive psychotic symptoms were assessed with the BPRS-4.[34] Negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms.[37] Depression was assessed with the Hamilton Rating Scale for Depression[38] and anxiety rated using the Hamilton Rating Scale for Anxiety.[39] Assessments were conducted at baseline, 6 months and at follow-up assessments at 12 and 24 months after study enrollment by research assistants who were trained in the administration of the study assessments. Over the course of the study, there were 6 research assistants who conducted assessments. In addition, case managers assessed positive psychotic symptoms on the BPRS and rated the SOFAS each week in order to ensure that each participant did not meet study discontinuation criteria.

Participants allocated to the medication group received risperidone (1 mg) or paliperidone (3 mg), depending on when they were enrolled in the study. The study commenced recruitment in 2008 using risperidone 1 mg tablets and matched placebo and then paused in August 2009 when this matched active and placebo trial medication became unavailable. It recommenced in June 2012 using paliperidone 3 mg capsules and matched placebo and paused again in March 2013 when the paliperidone and matched placebo was no longer available. The final recruitment phase from September 2013 to December 2016 used 1 mg risperidone and matched placebo manufactured specifically for the study. The total recruitment period was 4 years and 11 months. Dosing was increased by prescription of additional tablets/capsules after medical review appointment with treating psychiatrist. At each phase of the study, placebo group participants received placebo tablets that were identical in appearance, taste, and packaging to the active medication. Other medications, excluding other antipsychotic medication and mood stabilizers, were permitted during the trial. These were recorded. Adverse events were defined as any undesirable medical condition occurring from the time of signing consent (even if no study treatment or pharmaceutical product has been administered) and were recorded using the Udvalg for Kliniske Undersogelses (UKU) side effects rating scale[40] which was administered by trial doctors at weeks 1, 2, 3, 4, 12, 26, 52, and 104.

All participants received CBCM, a comprehensive manualized intervention developed specifically for early psychosis, which has a strong focus on therapeutic engagement. CBCM provides formulation-driven CBT and psychoeducation delivered within a therapeutic case management framework.[41] CBCM incorporates CBT for positive and negative psychotic symptoms, comorbidities, enhancement of coping strategies, and relapse prevention. Typical CBT strategies were employed, including symptom monitoring, activity scheduling, and behavioral experiments. Case managers met with young people weekly, usually at the outpatient clinic, and offered support, problem-solving, links to group programs,

and advocacy in addition to formulation-driven CBT. Therapists were tertiary-trained mental health professionals, mostly clinical psychologists who received both group and individual supervision in CBCM. They completed a psychological interventions checklist after each therapy session to record the interventions used. CBCM was enhanced by close monitoring of mental state and risks, family work and 24-h crisis response and home-visits when required. Participants were also seen regularly by the treating psychiatric registrar and consultant psychiatrist.

Outcomes

The primary hypothesis was that levels of functioning of the placebo group would be no worse, within an a priori specified margin of clinical significance, than the level of functioning of the medication group at the conclusion of the trial (6 months, the primary endpoint), and the 12- and 24-month follow-up assessments. A secondary hypothesis was that symptom levels would be no worse in the placebo group than the medication group at these time points.

Statistical Analysis

The software program "R" was used to perform the statistical analysis.[42] Noninferiority trials are designed to determine whether an experimental intervention is not inferior to a standard treatment.[43] For this, a "zone of indifference" or margin within which the intervention is considered noninferior is defined. Based on consultations with clinical staff and recommendations in the literature on noninferiority designs,[33,44,45] a clinically meaningful noninferiority margin of 10.5 points on the SOFAS, which has a range of 0–100, was selected. The 2-sided 95% confidence interval (CI) for the mean difference between the 2 treatments was used to assess noninferiority. Noninferiority was declared if the CI included zero and if its upper limit was below the prespecified margin. The participants were analyzed according to the group they were originally assigned. For the primary endpoint (6-month SOFAS), 2 approaches were used to deal with missing data. Firstly, *t*-test was employed to compare the 2 groups using participants with nonmissing data at 6 months. Upon checking the reasons for discontinuation, we believe that any possible bias resulting from this observed-case analysis would not be great (see supplementary tables and analyses for further information). Nevertheless, a second approach allowing all participants to be included was used—mixed-effects modeling. This approach could effectively handle missing data in noninferiority trials.[40] For this study, it utilized data at the primary endpoint as well as longitudinal data from earlier time points to estimate the between-group difference at 6 months. As advised by CONSORT,[32] a per protocol analysis (analyzing only those who continued on trial medication for 6 months) was also performed.

The sample size calculation was powered on an analysis which compares the 6-month SOFAS scores of the 2 groups. It was determined that 30 participants per group (60 in total) are required for study to have 80% power to demonstrate that the treatment means are not-inferior and with alpha set at 0.05. Due to strict discontinuation criteria, it was estimated that a proportion of participants would discontinue study medication, therefore a target sample size of 95 participants was set, allowing for an attrition of 37.5%.

For other outcome measures (psychopathological measures, time to discontinuation, and cumulative antipsychotic dose), *t*-test were used, with chi-square test used to compare concomitant medication use.

Results

Figure 1 displays participant flow through the study. EPPIC patients (N = 1279) were screened for eligibility for the study between December 2007 and December 2016, and 90 young people were randomly assigned to receive either placebo or medication. Nine young people did not commence trial medication (5 from the placebo group, 4 from medication) and did not have a baseline assessment, and were thus excluded from analyses.

The medication and placebo groups were similar in age, gender, and diagnoses at baseline (table 1). Table 2 displays measures of psychopathology and functioning at baseline, the end of the 6-month intervention period, and at 12- and 24-month follow-up. At baseline, the 2 groups had similar scores across all measures of functioning and psychopathology. The severity of symptoms according to the BPRS in both groups at baseline (medication group = 57.3, SD = ±9.8, placebo = 58.5, SD = ±8.9) corresponds to markedly ill, with relatively high quality of life scores in both groups (medication group = 71.5, SD = ±20.9, placebo = 70.0, SD = ±21.2).

At 6 months, the 2 groups again displayed similar psychopathology and functioning ratings, both having lower symptoms and higher functioning and QLS scores than at baseline. Observed case analysis of the primary outcome measure of functioning (SOFAS), found no significant difference between the groups (mean difference [medication minus placebo] = −0.2, 2-sided 95% CI = −6.3 to 5.8, t = 0.060, P = 0.95). Mixed-effects modeling analysis gave similar results (95% CI = −4.2 to 3.6). As the upper limit of the CI was below the inferiority margin (10.5), this is evidence that placebo was noninferior to medication at the 6-month assessment.

At 12- and 24-month outcome points, although the differences between the SOFAS ratings for the 2 groups were not significant, noninferiority of the placebo condition could not be confirmed because the CIs included the inferiority margin at each time point (12 months: mean

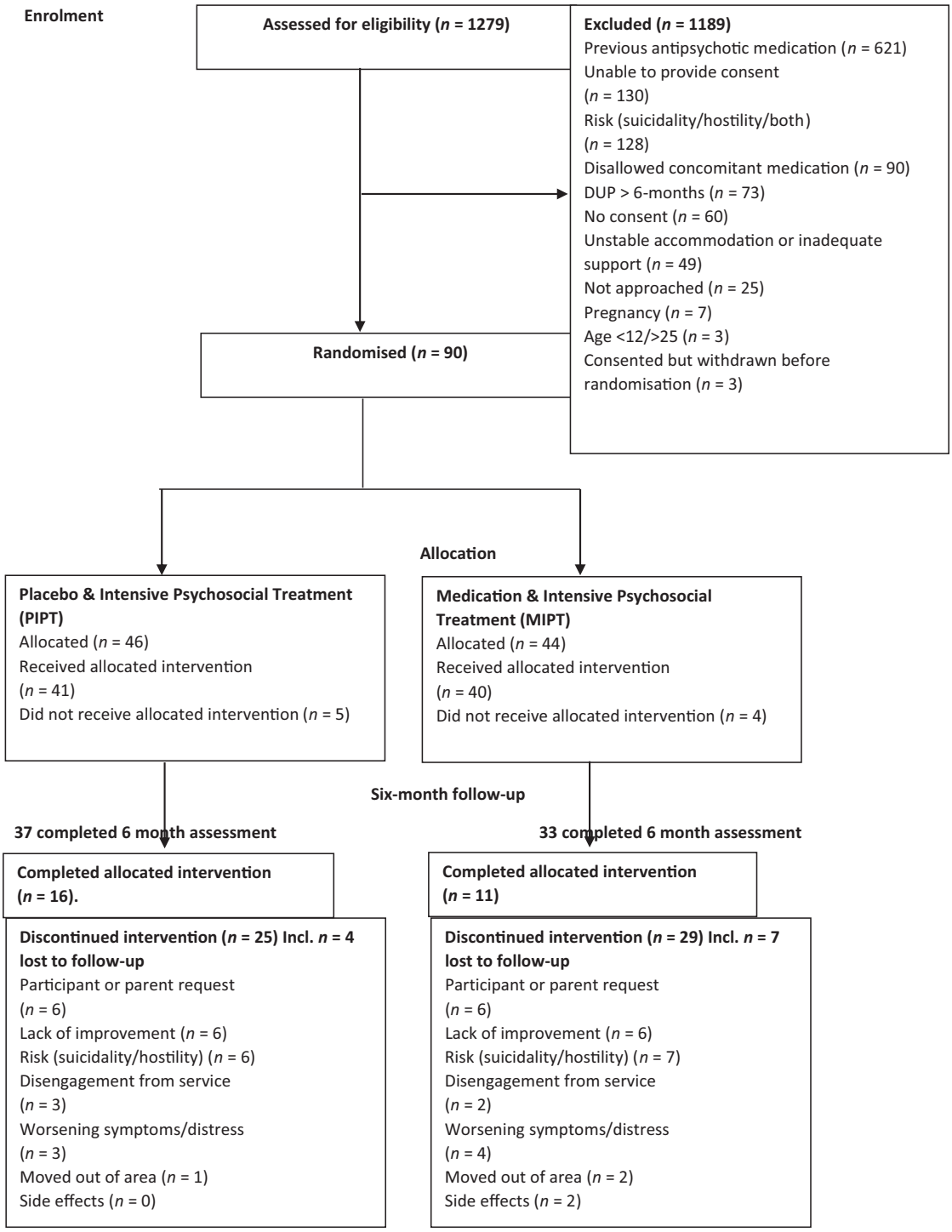

Fig. 1. Participant flow.

difference = 3.5, 2-sided 95% CI = −4.2 to 11.2, $t = 0.905$, $P = .37$; 24 months: mean difference = 4.0, 2-sided 95% CI = −4.3 to 12.4, $t = 0.980$, $P = .33$).

There were no significant differences between the groups at 6 months on any of the measures of psychopathology or the QLS, thus the placebo group did not display any worse symptoms than the group medication after the intervention period. At 12 and 24 months, all comparisons between the groups were nonsignificant, with the exception of the SANS at 12 months. At this assessment, the placebo group had significantly higher negative symptoms than the medication group.

The baseline assessment scores of those who completed the 6-month intervention period on trial medication were compared with those who discontinued and it was found that while there were mostly no significant differences,

Table 1. Demographics and Diagnosis

Variable	Mean (SD)	
	Placebo	Medication
Age	18.2 (2.6)	18.9 (2.9)
	***N* (%)**	
Gender		
Female	23 (56.1)	22 (55.0)
Male	18 (43.9)	18 (45.0)
Diagnosis		
Psychosis NOS	12 (29.3)	8 (20)
Schizophreniform disorder	7 (17.1)	9 (22.5)
Major depression with psychosis	8 (19.5)	8 (20)
Substance-induced psychotic disorder	6 (14.6)	6 (15)
Schizophrenia	7 (17.1)	5 (12.5)
Delusional disorder	1 (2.4)	4 (10)
Living arrangements		
Rented flat/house	4 (9.8)	7 (17.5)
Family home	33 (80.5)	29 (72.5)
Supported residential service	2 (4.9)	0
Boarding house	0	2 (5.0)
Other	2 (4.9)	1 (2.5)
Missing	0	1 (2.5)
Highest education level		
Years 8–9	8 (19.5)	5 (12.5)
Years 10–11	12 (29.3)	13 (32.5)
Years 12–13	2 (4.9)	4 (10.0)
Post high school training or education incomplete	13 (31.7)	9 (22.5)
Post high school training or education complete	6 (14.6)	8 (20.0)
Missing	0	1 (2.5)
Employment status		
Unemployed	7 (17.1)	7 (17.5)
Full-time paid employment	7 (17.1)	3 (7.5)
Part-time/casual paid employment	3 (7.3)	6 (15.0)
Full-time student	21 (51.2)	23 (57.5)
Part-time student	3 (7.3)	0
Missing	0	1 (2.5)

Note: NOS, not otherwise specified.

within the placebo group the noncompleters had higher baseline BPRS psychotic subscale scores, and within the medication group, the noncompleters had higher baseline BPRS total score (supplementary Table 1). There were no significant differences between the 2 groups on primary and secondary outcome variables in per-protocol analyses of those who completed 6 months on trial medication (supplementary table 2) at any assessment. At 6 months, noninferiority of the antipsychotic medication-free intervention was again supported (mean difference = −3.7, 2-sided 95% CI = −7.5 to 7.0, t =0.628, P = .54).

The numbers of participants in each group who completed the 6-month intervention period, and time to discontinuation for those who did not complete the intervention are presented in table 3. The placebo group were on trial medication for longer than those who received antipsychotic medication (P = .04) and had a higher proportion of completers.

Figure 1 presents reasons for discontinuation revealing they were similar for both groups. Medications received by the 2 study groups during the 6-month intervention period are displayed in tables 4 and 5. Doses of trial medication (0.5–4 mg risperidone or 3–9 mg paliperidone) are given in supplementary table 3. Participants who discontinued trial medication were given usual EPPIC treatment including antipsychotic medication and continued CBCM. Seventy-six percent (19/25) of those who discontinued from the placebo group commenced antipsychotic medication after discontinuation of trial medication. Antipsychotic medications were converted to olanzapine equivalent doses and cumulative dose for each participant up to the 6-month end of intervention were calculated (table 4). The medication group had a mean cumulative antipsychotic medication dose more than twice that of the placebo group and this was a significant difference (P < .001). For other psychotropic medications, percentage of each group who had any of each class is given in table 5. The groups did not differ in the proportion receiving adjunctive medications or the number of CBCM and medical review sessions they received during the trial intervention period. Both groups received a mean of 14 CBCM sessions by the 6-month endpoint of the trial. On the psychological interventions checklist, the number of sessions for which therapists recorded delivering CBT interventions were not significantly different between the 2 groups (P = .51): the placebo group had a mean of 8.8 (SD = 6.4) sessions and the medication group had a mean of 7.9 (SD = 6.2) sessions.

Adverse Events

Adverse events recorded during the study are displayed in table 6 and included side effects as measured on the UKU scale (psychic, neurologic, autonomic, and other), abnormal blood results, deterioration of mental state and nonclinically significant abnormalities detected on MRI scan. There were no significant differences between the groups in the number of adverse events reported in each category, or in the percentage of each group who recorded an adverse event.

Discussion

In a noninferiority design, we examined whether intensive psychosocial intervention without antipsychotic medication results in poorer outcome than usual treatment of a combination of antipsychotic medication and psychosocial intervention, in young people with FEP. In the highly selected sample recruited to this study, psychosocial treatment alone was not inferior to psychosocial treatment plus antipsychotic medication at the end of the intervention period, raising the possibility that some young people with early psychosis may not require antipsychotic medications to recover. The study

Table 2. Baseline, Postintervention and 12- and 24-Month Follow-Up Functioning and Psychopathology Scores

		Intervention Period				Follow-Up Period			
		Baseline		6 months		12 months		24 months	
Measure	Group	*N*	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)
SOFAS	Placebo	41	54.4 (13.1)	37	61.7 (16.8)	36	61.3 (16.5)	34	64.1 (13.7)
	Medication	39	53.9 (10.8)	33	61.5 (13.4)	29	64.8 (14.5)	22	68.1 (15.9)
					P = .952		*P* = .369		*P* = .333
BPRS Total	Placebo	41	58.5 (8.9)	35	44.8 (12.4)	35	45.0 (9.7)	33	42.3 (11.3)
	Medication	39	57.3 (9.8)	31	43.4 (14.3)	27	40.6 (10.9)	22	39.9 (10.2)
					P = .658		*P* = .101		*P* = .404
BPRS Psychotic	Placebo	41	15.0 (3.0)	36	7.8 (3.4)	35	8.6 (4.0)	33	7.7 (3.8)
	Medication	39	13.9 (3.6)	33	8.2 (4.8)	28	7.1 (3.2)	22	7.0 (3.3)
					P = .646		*P* = .096		*P* =.444
SANS Total	Placebo	41	27.5 (15.0)	35	20.4 (15.9)	35	21.0 (13.5)	33	17.1 (12.5)
	Medication	39	25.7 (14.6)	30	19.4 (14.2)	25	13.2 (9.5)	22	14.5 (10.6)
					P = .790		*P* = .011		*P* = .405
HAM-Anxiety	PIacebo	41	21.2 (6.9)	35	12.9 (9.8)	33	12.8 (8.1)	33	12.8 (9.2)
	Medication	39	20.2 (6.9)	31	13.8 (10.9)	26	11.3 (8.5)	22	10.6 (9.7)
					P = .746		*P* = .510		*P* = .412
HAM-Depression	PIacebo	41	18.4 (6.1)	35	12.8 (8.0)	33	12.4 (6.8)	33	11.4 (8.3)
	Medication	39	18.3 (5.8)	30	11.5 (8.8)	26	9.5 (7.4)	22	8.8 (7.2)
					P = .540		*P* = .123		*P* = .221
QLS	Placebo	38	70.0 (21.2)	34	77.9 (26.1)	34	80.7 (24.8	30	85.3 (21.3)
	Medication	39	71.5 (20.9)	30	75.2 (24.4)	26	88.2 (23.0)	22	88.6 (22.1)
					P = .662		*P* = .232		*P* = .597

Note: Medication, Medication and Intensive Psychosocial Treatment group; Placebo, Placebo and Intensive Psychosocial Treatment group; SOFAS, Social and Occupational Functioning Assessment Scale; BPRS, Brief Psychiatric Rating Scale; BPRS Psychotic, Psychotic subscale of the BPRS; SANS, Scale for the Assessment of Negative Symptoms; HAM-Anxiety, Hamilton Anxiety Scale; HAMD-Depression, Hamilton Depression Scale; QLS, Quality of Life Scale; *P*, *P* value of *t*-test.

Table 3. Number of Medication Group Vs Placebo Group Who Remained on Trial Medication to 6 Months, and Time on Trial Medication if Discontinued

Completed 26 Weeks				Discontinued		Time to Discontinuation (Weeks)			
Group	No.	%	Chi-square test	No.	%	Mean (SD)	Min	Max	*t*-Test
Placebo	16	39·0	$P = .39$	25	61·0	12·3 (6·0)	2·0	25·9	$P = .044$
Medication	11	27·5		29	72·5	8·9 (6·2)	0·1	21·9	

Table 4. Cumulative Antipsychotic Dose (Olanzapine Equivalent in mg) at 6 Months

Group	Mean	SD	*n*	*P* Value[a]
Placebo	269.8	418.6	41	<.001
Medication	726.0	539.5	40	

[a]*P* value of *t*-test.

Table 5. Percentage of Each Treatment Group Who Received Each Class of Concomitant Medication During the 6-Month Trial Period

Medication Class	Placebo	Medication	*P* Value[a]
Benzodiazepine	22.0	20.0	.83
Antidepressant	56.1	42.5	.22
Mood Stabiliser	4.9	0	.16
Other[b]	17.1	20.0	.74

*P value of chi-square test.
[#]Other psychotropic medications were zopiclone, dexamethasone, benztropine, and clonidine.

also demonstrated that antipsychotic medication-free research can be conducted safely in the acute phase of FEP with the close monitoring available in comprehensive early intervention services.

This study suggests that some young people with early-stage FEP and short DUP can achieve remission of symptoms and improve functioning without antipsychotic medication when they are provided with psychological interventions and comprehensive case management. This challenges the conventional wisdom that antipsychotic medications are indicated for all cases of psychosis to control or abate positive psychotic symptoms. Both groups improved in their functioning over the course of the 6-month intervention period, moving from a level indicating serious functional impairment to a level indicating only "some" functional difficulty. This level (above a score of 60) has been considered by some FEP researchers to indicate "generally functioning well" or to signal recovery.[46] Importantly, both groups had improved on all measures of psychopathology after 6 months, and there were no differences between the groups. There was no discernible advantage to receiving antipsychotic medication from the start of the trial. Given the serious negative physical sequelae of antipsychotic medications for some people,[8] managing FEP through psychosocial interventions could be considered, in the relatively small subgroup of patients where it is safe to do so. This should take place within a closely monitored, stepped care, shared-decision making framework.

The longer-term results are less clear, as although there were almost no significant differences between the groups on measures of psychopathology and functioning at 12 and 24 months, noninferiority of the antipsychotic medication-free intervention was not established. Furthermore, there were trends in the results to favor the group who were allocated to receive antipsychotic medication on symptomatic outcomes. We also observed a significantly higher level of negative symptoms in the group that received placebo at the 12-month assessment only. This may be due to treatment of secondary negative symptoms, due to selective attrition or type I error. However, this is not concordant with a known dominant effect of antipsychotics on positive symptoms and requires further research.

It is important to note that there was a high rate of discontinuation of trial medication. In order for the study to be safe and ethical, strict intake, and discontinuation criteria were applied. Participants discontinued trial medication due to lack of improvement, worsening symptoms, request, or other reasons. It is not unusual for the initially prescribed antipsychotic medication to be changed, indeed studies have reported that around 70% of patients do not remain on the first antipsychotic[47,48] for a variety of reasons, and the decision to try a different antipsychotic led to discontinuation of trial medication in this study. Thus, a significant rate of discontinuation accords with usual clinical practice in the prescription of antipsychotic medication and perhaps could have been predicted. This underscores the challenges in conducting such a trial and the need for a larger participant group to accommodate discontinuations. It is interesting that there were more and earlier discontinuations in the group who were on antipsychotic medication, 2 of whom cited side effects as the reason, and that those who discontinued may have had some worse symptoms at baseline.

The sample recruited in the current study cannot be considered to be representative of the entire FEP population, and the results are not generalizable beyond the relatively small subgroup defined by the inclusion criteria employed to minimize risk. Only 7% of those screened

Table 6. Mean (SD) Number of Adverse Events Reported by Each Treatment Group During the 6-Month Trial Period and Percentage of Each Group Reporting an Adverse Event During the Trial

Adverse Event	Group	Mean	SD	% With AE	*t*-Test *P* Value	Chi-Square Test *P* Value
UKU Psychic	Placebo	1.7	2.5	48.8	.064	.568
	Medication	0.8	1.3	40.0		
UKU Neurologic	Placebo	0.2	0.7	14.6	.367	.532
	Medication	0.4	0.8	22.5		
UKU Autonomic	Placebo	0.5	1.2	22.0	.614	.951
	Medication	0.4	0.7	25.0		
Other	Placebo	1.0	1.4	56.1	.883	.437
	Medication	1.0	1.6	45.0		
Any AE	Placebo	3.4	4.3	75.6	.326	.751
	Medication	2.5	3.2	70.0		
SAE	Placebo	0.2	0.6	17.1	.964	>.999
	Medication	0.2	0.5	17.5		

Note: UKU Psychic, UKU Side Effects Rating Scale Psychic items; UKU Neurologic, UKU Side Effects Rating Scale Neurologic items; UKU Autonomic, UKU Side Effects Rating Scale Autonomic items; Other, UKU Side Effects Rating Scale Other items, abnormal blood results, abnormal MRI findings (nonclinically significant) and overdose; AE, adverse event; SAE, serious adverse event.

for inclusion in the study met the inclusion criteria (including agreeing to consent), however, specific features of this study contributed to this, and thus it is likely that a higher proportion of FEP patients could be considered for a trial of initial medication-free treatment. The current study excluded people with prior exposure to antipsychotic medication of more than a week, those with concomitant medications and other factors indicative of risk. In different circumstances such exclusions may not be required. However, this study has demonstrated that it is feasible and safe to conduct antipsychotic medication-free research in FEP, consistent with Morrison et al.[26] Given the ability to recruit fully informed participants to the trial, it was clearly acceptable to some young people to have treatment that might not include antipsychotic medication while being certain of receiving psychosocial intervention. The placebo condition did not lead to more discontinuations than the medication condition overall, in fact, participants remained on trial medication significantly longer if they were in the placebo group. Importantly, there were not more discontinuations for clinical deterioration (worsening of symptoms) or failure to improve in the placebo group, nor were there more serious adverse events.

Further antipsychotic-free research in FEP should explore predictors of those who do not need medication in the early phase of illness and a more personalized approach to treatment. A larger, representative, possibly "stepped," effectiveness RCT could help identify the optimal thresholds for antipsychotic initiation in those with FEP. Such a trial could include an antipsychotic free period, intensive psychological therapies, exploration of efficacy of novel therapeutic agents, and shared decision making in the timing of initiation of antipsychotic medications.

Limitations

The unrepresentativeness of the sample is an obvious limitation of the study. In addition, only one-third of the combined sample completed the 6-month intervention phase, limiting generalizability further. Reasons for discontinuation were not markedly different between the groups. As the study was examining a treatment strategy that contravened current clinical guidelines, clear informed consent and very low thresholds for discontinuation were rigorously pursued. This, combined with discomfort about taking unknown medication by some participants and their parents, increased the discontinuation rate and reduced the size of the completer groups. While the missing data for the primary outcome of functioning at 6 months was not high, there was a high proportion of missing data for other outcomes, including functioning at 12 and 24 months. In addition, the margin of difference of 10.5 on the SOFAS was determined prior to the commencement of the study and this may have been too large of a "margin of difference," as both groups improved by less than 10 points at the 6-month outcome. Finally, 2 different antipsychotic medications were used during the trial due to availability of matched placebo medication. Although this was not ideal, the study assessed the noninferiority of psychosocial medication-free treatment compared to standard treatment and not the effect of any specific medication, thus using 2 antipsychotics was considered acceptable.

Conclusion

In this RCT examining the need for antipsychotic medication at the first onset of psychosis, we demonstrated that antipsychotic medication-free research can be conducted safely in FEP in the context of a comprehensive early

intervention program, albeit with a highly selected sample. In this sample, the addition of antipsychotic medication to intensive psychosocial intervention did not lead to superior symptomatic or functional outcomes at 6 months, suggesting that antipsychotic medication may not be needed early in the course of illness for all people within the spectrum of psychosis. However, the longer-term outcomes were less clear and the low completion rate renders the conclusions speculative. A larger, adequately powered trial is needed to clarify whether antipsychotic-free treatment can be recommended for specific subgroups of those with FEP.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

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