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Feasibility and Effectiveness of a Multi-Element Psychosocial Intervention for First-Episode Psychosis: Results From the Cluster-Randomized Controlled GET UP PIANO Trial in a Catchment Area of 10 Million Inhabitants

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Integrated multi-element psychosocial interventions have been suggested to improve the outcomes of first-episode psychosis (FEP) patients, but they have been studied primarily in experimental settings and in nonepidemiologically representative samples. Thus, we performed a cluster-randomized controlled trial, comparing an integrated multi-element psychosocial intervention, comprising cognitive behavioral therapy, family intervention, and case management, with treatment as usual (TAU) for FEP patients in 117 community mental health centers (CMHCs) in a large area of northern Italy (10 million inhabitants). The randomized units (clusters) were the CMHCs, and the units of observation the patients (and, when available, their family members). The primary hypotheses were that add-on multicomponent intervention: (1) results in greater improvements in symptoms, as assessed with positive and negative syndrome scale and (2) reduces in-hospital stay, based on days of hospitalization over the 9-month follow-up. Four hundred and forty-four FEP patients received the intervention or TAU and were assessed at baseline and 9 months. Based on the retention rates of patients (and families) in the experimental arm, multi-element psychosocial interventions can be implemented in routine mental health services. Regarding primary outcomes, patients in the experimental arm showed greater reductions in overall symptom severity, while no difference could be found for days of hospitalization. Among the secondary outcomes, greater improvements were detected in the experimental arm for global functioning, emotional well-being, and subjective burden of delusions. No difference could be found for service disengagement and subjective burden of auditory hallucinations. These findings support feasibility and effectiveness of early interventions for psychosis in generalist mental health services.

Key words: schizophrenia/early psychosis/outcome assessment/cognitive behavioral therapy/family intervention

This paper is dedicated to the memory of Professor Angelo Cocchi

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Introduction

Interest in psychosocial interventions to facilitate recovery and reduce long-term disability in patients with first-episode psychosis (FEP) has been growing.[1–3] Clinical guidelines for this population recommend an early and integrated approach, based on psychosocial interventions.[4–9]

The results of multi-element interventions, including early detection strategies; individual, group, and family therapy; case management; and pharmacological treatment, are promising,[10] with symptom reduction, improved quality of life, increased social and cognitive functioning, lower inpatient admission rates, less in-hospital time, improved insight, greater treatment satisfaction, decreased substance abuse, and fewer self-harm episodes.[11–14]

However, most multi-element approaches have been administered to nonepidemiologically representative samples in (quasi-)experimental settings—rarely in epidemiological samples against a control[15]—raising the risk of underestimating the complexities of treating FEP in real-world services.[16–18] In clinical practice, although some countries have recently implemented early psychosis intervention programs, most have not become routine.[19] Few studies have identified barriers that hinder feasibility of these interventions or address patient/family conditions that render them ineffective or inappropriate.

There are 3 models through which early interventions are provided.[20] The *early intervention service* advocated as the standard in the United Kingdom,[21] and also in United States, Australia, New Zealand, and Scandinavia, ensuring provision of a comprehensive package by dedicated and trained staff. It is resource-intensive, can result in the loss of a single entry point into mental health services, and has implications for continuity of care when it ceases.[22–25] The *hub-and-spoke model* comprises a central specialist service ("hub") that supports existing generic teams. The third model involves *generic services adopting the principles of early intervention* for treating patients by educating the entire team. Although inexpensive,[26] particularly for less resourced areas,[27] this model might not ensure specific and optimal treatment for FEP patients.[28]

There are pros and cons to each model[22–28] with no evidence to support the superiority of any delivery; implementation of multi-element FEP-targeted interventions in routine services based on rigorous scientific method is thus necessary.[29]

The GET UP (Genetics, Endophenotypes, Treatment: Understanding early Psychosis) PIANO (Psychosis: early Intervention and Assessment of Needs and Outcome) trial[30] was undertaken to assess the feasibility and effectiveness of multi-element psychosocial intervention for FEP patients and their families in routine MH services, per the third delivery model, vs treatment as usual (TAU) in a large epidemiologically based cohort from community mental health centers (CMHCs). Experimental treatment was an adjunct to TAU, comprising: (1) cognitive behavioral therapy for psychosis (CBTp) to patients; (2) psychosis-focused family intervention (FIp) to families; and (3) case management (CM) to both parties. The intervention was provided by CMHC staff, trained in the previous 6 months and supervised by experts.

The primary hypotheses were that add-on multicomponent intervention: (1) results in greater improvements in symptoms, as assessed with positive and negative syndrome scale (PANSS) and (2) reduces in-hospital stay, based on days of hospitalization over the 9-month follow-up. Secondary hypotheses were that the intervention results in greater improvements in subjective burden of psychotic symptoms (auditory hallucinations and delusions), social functioning and emotional well-being and lower service disengagement rates.

Methods

Study Design

Participation in this cluster-randomized controlled trial[30] was offered to all CMHCs located across 2 northern Italian regions (Veneto and Emilia-Romagna) and the urban areas of Florence, Milan, and Bolzano, covering an area of 9 951 306 inhabitants. Of 126 CMHCs, 117 (92.8%, covering 9 304 093 inhabitants) participated.

The assignment units (clusters) were the CMHCs, and the units of observation and analysis were patients and their families.

Care Context and Participating Sites

MH care in Italy is delivered by the National Health Service through the Departments of Mental Health (DMH). In each catchment area, one or more CMHCs provide outpatient care, daycare, and rehabilitation to nearly 100 000 inhabitants (online supplementary material, part 1). The catchment areas of rural CMHCs usually encompass small towns and villages, and urban CMHCs correspond to one or more neighborhoods.

Randomization

Stratified randomization of CMHCs was performed to balance differences in their characteristics (catchment area size, urban/mixed versus rural context) and account for organizational constraints (affiliation to the same DMH). One CMHC each in the intervention and TAU arms withdrew consent to participate and were excluded (online supplementary material, part 2).

Participants

All CMHCs were asked to refer potential psychosis cases at first contact during the index period to the study team. Based on the WHO 10-country study,[31] the inclusion criteria to ascertain FEP were as follows:

- age 18–54 years,
- residence in catchment areas of CMHCs,
- presence of at least one of the following: hallucinations, delusions, qualitative speech disorder, qualitative psychomotor disorder, bizarre, or grossly inappropriate behavior, or two of the following: loss of interest, initiative, and drive; social withdrawal; episodic severe excitement; purposeless destructiveness; overwhelming fear; or marked self-neglect, per the WHO Screening Schedule for Psychosis,[31]
- first lifetime contact with CMHCs, prompted by these symptoms.

Exclusion criteria were: (1) antipsychotic medication (>3 months) prescribed for an identical or similar mental disorder; (2) mental disorders due to general medical condition; (3) moderate-severe mental retardation per a clinical functional assessment; and (4) psychiatric diagnosis other than International Classification of Diseases (ICD)-10 for psychosis.

All eligible patients, identified as those who reached the clinical stabilization, were invited to provide written informed consent to be assessed and informed of the nature, scope, and possible consequences of the trial and that they could withdraw consent at any time. Patients were asked to give consent for family member assessments; family members who agreed to participate provided written informed consent (online supplementary material, part 3).

The trial received approval by the ethics committees of the coordinating center (Azienda Ospedaliera Universitaria Integrata di Verona) and each participating unit and was registered with ClinicalTrials.gov (NCT01436331).

Diagnostic Ascertainment

Since FEP is generally a phase of high diagnostic instability, the specific ICD-10 codes for psychosis (F1x.4; F1x.5; F1x.7; F20–29; F30.2, F31.2, F31.5, F31.6, F32.3, F33.3) were assigned at 9 months. The best-estimate ICD-10 diagnosis was made by consensus of a panel of clinicians by considering all available information on the time interval from patient's intake needed to apply the Item Group Checklist of the Schedule for Clinical Assessment in Neuropsychiatry.[32]

Treatments

Experimental Intervention. The intervention was provided by CMHC staff, trained in the previous 6 months and supervised by experts. The multi-element psychosocial intervention, adjunctive to TAU, comprised: CBTp to patients[33–36]; FIp[37,38] to families; and CM[39] to both (online supplementary material, part 4).

The intervention began as soon as patients achieved clinical stabilization (condition in which they could collaborate in a brief clinical examination) and core baseline measures were taken.

Treatment as Usual. Control arm CMHCs only provided TAU, which, in Italy, comprises personalized outpatient psychopharmacological treatment and nonspecific supportive clinical management by the CMHC.[40,41] Family interventions consisted of nonspecific informal support sessions.

Therapist Training, Supervision, and Fidelity

Before the trial, ≥2 psychiatrists/psychologists per experimental CMHC received CBTp and FIp training, and ≥1 nurse/educator undertook CM training. At the end of the training, competence was assessed (score 0–50, with minimum 35/50 required to treat patients). Intervention manuals per international standards were given to the professionals as treatment references. During intervention's delivery, professionals were supported by expert psychotherapists assigned to each CMHC; written reports of each session were supervised by external experts who held 1-day meetings every 2 months and were regularly available for consultation to ensure fidelity of the intervention. A random sample of sessions were audio recorded to allow further fidelity measurement by independent raters.[42–44]

Outcome Measures

The *primary outcomes* were assessed by the PANSS[45] for symptoms severity and case records for days of hospitalization. The *secondary outcomes* were assessed by Psychotic Symptom Rating Scale (PSYRATS)[46] for subjective appraisal of psychotic symptoms (auditory hallucinations and delusions); Global Assessment of Functioning (GAF)[47] for social functioning; Hamilton Rating Scale for Depression (HAM-D)[48] for emotional well-being; and Verona Interview for Treatment Termination,[49] case records, and local databases for service disengagement.

Assessment

After clinical stabilization and before treatment, core outcomes (PANSS, PSYRATS, GAF, HAM-D) were measured by 17 independent researchers.

Patients, clinicians, and raters could not be blinded to the trial arm. Every effort was made to preserve the raters' independence; conflicts of interest were monitored.[17]

Psychosocial and pharmacological treatment data, number and days of hospitalizations in the 9-month follow-up were also collected. Service disengagement was assessed by interviewing patients who interrupted contact with services before study termination.

Statistical Analyses

Analyses on patients' outcomes were conducted on an intention-to-treat (ITT) basis. Patients meeting inclusion criteria, clinically stabilized, giving consent to assessment and assessed at baseline were analyzed in their original allocation regardless of the number of sessions attended.

Missing outcome data at follow-up were described in the online supplementary material, part 5 and they were coped by addressing them with nonresponse weights. Specifically, the effect of intervention on outcomes was examined using multilevel mixed-model analysis, which is the appropriate form as reported in the Consolidated Standards f Reporting Trials (CONSORT) guidelines for cluster-randomized trials[50] (outcomes are observed on patients [level 1], who are nested within CMHCs [level 2]). Estimates of the intervention effect at 9-month follow-up on continuous outcomes were obtained with weighted random effects linear regression models ("xtreg" from Stata 11.0) with CMHC as a random effect and the corresponding baseline score (where appropriate) and the treatment assignment as fixed effects. With nonresponse weight method, patients with nonmissing outcome data who "look like" patients with missing outcome data were given greater weight in the analysis. Specifically, weights were constructed to be proportional to the inverse of the predicted probability of having nonmissing outcome data. The predicted probabilities were constructed by estimating a logit model of the probability of having nonmissing outcome data conditional on covariates. The robustness of the results with respect to violation of normality was guaranteed by estimating CIs and *P*-values from 1000 bootstrap samples, using the nonparametric method (Stata 11.0 "bootstrap" command). Data on completers (patients who were assessed at both baseline and follow-up) are reported in the online supplementary material, part 6.

Results

Effectiveness

Overall, 626 FEP patients (364 experimental; 262 TAU) were eligible for the study in the recruitment phase (April 1, 2010 to March 31, 2011) in the catchment area (Figure 1, bottom). A full description of the extent and nature of missing outcome data at the different stages of patients' recruitment is given in the online supplementary material, part 5.

Baseline Data. At baseline, 272 experimental arm and 172 TAU arm patients were assessed (Table 1).

The groups did not differ in any sociodemographic characteristics, except patients in the experimental group, with a lower mean age at first service contact. No other between-group differences were observed in any demographic or diagnostic variable or outcome measure.

Experimental Treatment. Most experimental group patients (n = 208; 76.5%) received ≥10 CBT sessions over the study period (Table 2), 66.3% receiving over 20 sessions.

Twenty-four (8.8%) patients did not receive any CBT session; 220 relatives out of 256 available (85.9%) participated in at least 1 family session. Most relatives (n = 196; 76.6%) received ≥5 FI sessions, 140 of whom (71.4%) received ≥10. All experimental arm patients were assigned to an individual case manager and had regular contacts (21.7 on average). Of 272 patients, 80.1% received at least 1 session of all 3 interventions; 220 (85.9%) family members received at least 1 session; CBTp could not be provided to 2 (0.7%) patients. Thirty (11.0%) patients received CBTp only; out of these, 43.4% cases had no available relatives, 23.3% did not give consent to contact relatives, 16.7% relatives did not give consent for FI, 10.0% relatives dropped out after giving consent but before beginning FI, 3.3% moved, and 3.3% had incompatible working hours with FI appointments. For the delivery of the intervention see online supplementary material, part 7.

Routine Treatment Provision. Experimental arm patients were allowed to receive routine care, based on the staff's clinical judgment. Patients and relatives in the experimental arm received fewer routine psychosocial interventions (Table 3).

Study Retention. Fifty-two (11.7%) patients dropped out: 33 (12.1%) and 19 (11.0%) in the experimental and TAU groups, respectively (not significant). There were no significant differences in demographic variables between completers and noncompleters.

Primary Outcomes. Both groups had similar baseline clinical symptom severity patterns and experienced improvement in clinical measures at the 9-month follow-up (Table 4)—more so for the experimental group in PANSS general psychopathology and PANSS total score, while PANSS negative and positive symptom subscales did not reach statistical significance.

With regard to PANSS items, the experimental group showed greater improvement in some positive ("conceptual disorganization" regression coefficient = −.17, P = 0.050; "hostility" regression coefficient = −.17, P = .032), negative ("social withdrawal" regression coefficient = −0.38, P = .009), and general psychopathology symptoms ("preoccupation" regression coefficient = −.31, P = .042).

Few subjects in both arms underwent hospitalization in the 9 months following clinical stabilization (Table 3). No difference could be found in total number of days of hospitalization.

Secondary Outcomes. Both groups experienced improvement in social functioning and emotional well-being at the 9-month follow-up—more so for the experimental group in HAM-D and GAF scores.

As required by the instrument's manual, PSYRATS was administered to patients scoring ≥3 on PANSS items of hallucinations, delusions, unusual thought content, and suspiciousness. In this subgroup, during the 9-month period, PSYRAT Delusion Scale scores improved more on all items of cognitive interpretation and emotional characteristic factors in the experimental group with respect to the TAU group. No difference could be found

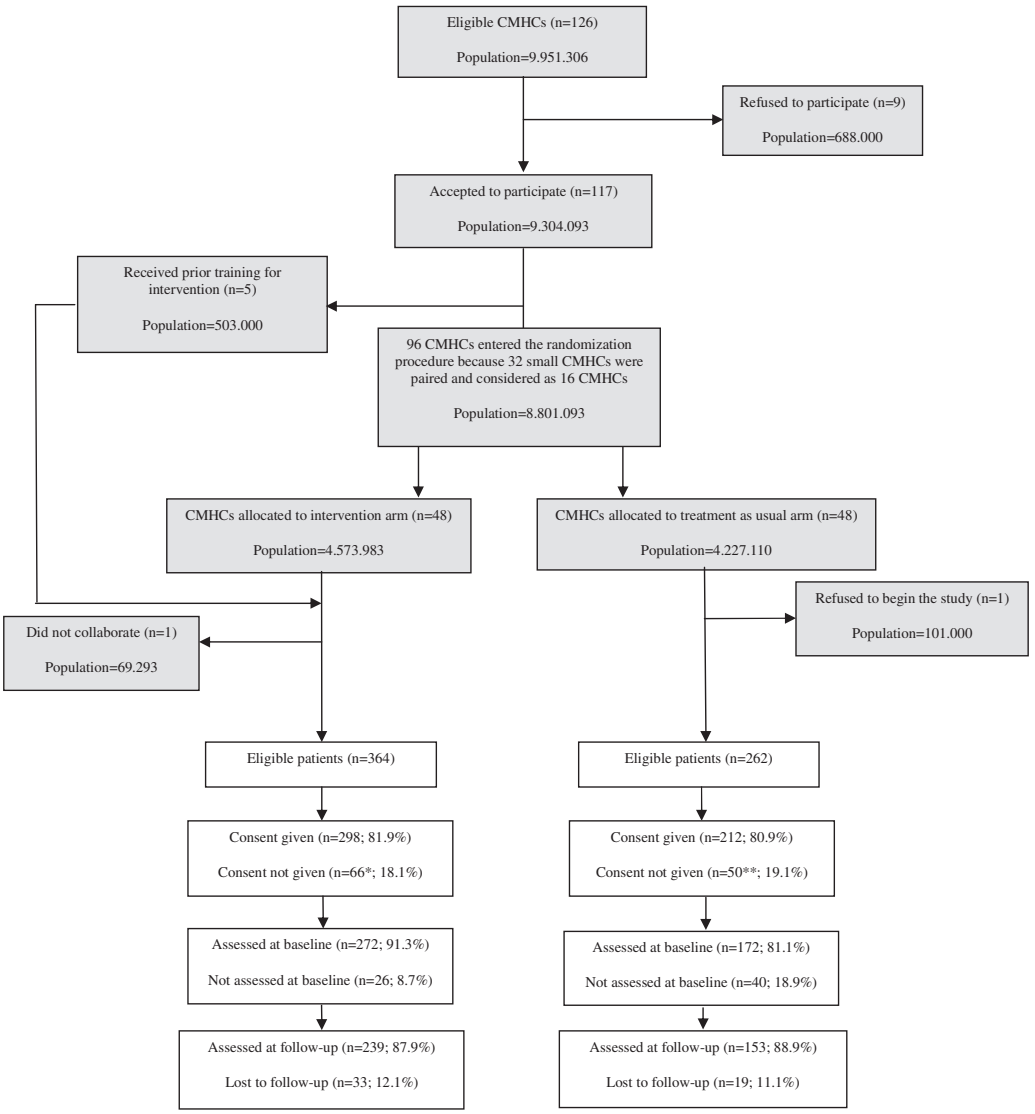

Fig. 1. Trial profile. *18 from leakage study; **45 from leakage study.
Reasons for not being assessed at baseline. Intervention arm: 7 once only contact, 2 few contacts, 15 drop out before assessment, 2 moved; treatment as usual arm: 33 once only contact, 1 few contacts, 5 drop out before assessment, 1 moved. Reasons for not being assessed at follow-up. Intervention arm: 27 drop out, 1 died, 5 no consent to assessment; treatment as usual arm: 13 drop out, 2 died, 4 no consent to assessment.

for PSYRAT Auditory Hallucination Scale, but a tendency toward a greater improvement in the experimental group with respect to the TAU group was described.

No difference could be found for service disengagement rates.

Quantification of Side Effects. Registration of adverse events reported 4 deaths (2 car accidents in the experimental group; 1 organic disease and 1 suicide in the TAU group) and 11 serious neurological side effects (5 in the TAU group and 6 in the experimental group).

Feasibility

Good feasibility of the intervention was indicated by the <10% dropout rate at participating sites in the experimental arm; <10% of professionals in the experimental arm not achieving sufficient competence after an ad hoc training program; >50% of intervention sessions being considered optimal; and <20% of patients and families dropping out prematurely.

Representativeness of Participating CMHCs. In total, 117 of 126 CMHCs participated in the study, and 115 completed it.

Representativeness of Trial Subjects. A leakage study was undertaken at monthly intervals and on study completion in each CMHC to ensure accuracy of the recruitment. Electronic and paper information systems were scrutinized for cases aged 18–54 years with an ICD-10 code of psychosis presenting to CMHCs for the first time during the index

Table 1. Sociodemographics of Patients Assessed at Baseline (After Clinical Stabilization) and Schedules for Clinical Assessment in Neuropsychiatry (SCAN)-Confirmed Diagnosis at 9 Months From Baseline

	Baseline (After Clinical Stabilization)		
	Treatment as Usual Group (n = 172)	Experimental Treatment Group (n = 272)	Test and Significance of Difference
Gender, n (%)			$\chi^2 = 1.77$, $df = 1$, $P = .184$
Male	94 (54.7%)	166 (61.0%)	
Female	78 (45.3%)	106 (39.0%)	
Age at first contact with services, mean (SD)	31.5 (9.2)	29.3 (9.8)	$t = 2.40$, $df = 442$, $P = .017$
Educational level, n (%)	(13 missing)	(9 missing)	$\chi^2 = 1.85$, $df = 1$, $P = .174$
Low (primary–middle school)	68 (42.8%)	95 (36.1%)	
High (secondary school, university)	91 (57.2%)	168 (63.9%)	
Marital status, n (%)	(12 missing)	(12 missing)	$\chi^2 = 4.15$, $df = 2$, $P = .125$
Unmarried	118 (73.8%)	195 (75.0%)	
Married	27 (16.9%)	53 (20.4%)	
Widowed, separated, divorced	15 (9.3%)	12 (4.6%)	
Living condition, n (%)	(14 missing)	(12 missing)	$\chi^2 = 1.51$, $df = 3$, $P = .680$
Alone	9 (5.7%)	14 (5.4%)	
With partner and/or children	39 (24.7%)	60 (23.0%)	
With other relatives	105 (66.5%)	182 (70.0%)	
Other	5 (3.1%)	4 (1.6%)	
Working status, n (%)	(4 missing)	(11 missing)	$\chi^2 = 2.35$, $df = 3$, $P = .502$
Employed	64 (38.1%)	95 (36.4%)	
Unemployed	61 (36.3%)	83 (31.8%)	
Housewife, student, retired	38 (22.6%)	76 (29.1%)	
Other	5 (3.0%)	7 (2.7%)	
Nationality, n (%)			$\chi^2 = 0.38$, $df = 1$, $P = .535$
Italy	149 (86.6%)	241 (88.6%)	
Other[a]	23 (13.4%)	31 (11.4%)	
Diagnosis (SCAN-confirmed at 9 months), n (%)			$\chi^2 = 0.23$, $df = 1$, $P = .632$
Nonaffective psychosis	132 (76.7%)	214 (78.7%)	
Affective psychosis	40 (23.3%)	58 (21.3%)	

Note: [a]Standard care: East Europe (n = 11), Africa (n = 10), South America (n = 1), Asia (n = 0), Other (n = 1); Experimental treatment: East Europe (n = 17), Africa (n = 6), South America (n = 6), Asia (n = 2), Other (n = 0).

period: 18 subjects in the experimental group and 45 in the TAU group were identified as missed cases. This study thus confirmed the satisfactory representativeness of those who sought help in CMHCs of the catchment area.

Therapist Training, Supervision, and Fidelity. Ninety-six of 105 (91.4%) professionals in the experimental arm completed the CBT training; 94.8% achieved the required competence score. Sixty-four of 72 (88.9%) professionals completed the FI training; 96.9% achieved the required competence score. No difference in acquisition of competence by age, years from graduation, years of work, or theoretical orientation was noted. Supervisors rated the professionals' fidelity to the manual (including attitude, therapeutic style, and congruency with CBT requirements) as ranging from medium to high (paper in preparation).

Discussion

Service Models for FEP Patients

The GET UP PIANO trial applied innovative and targeted forms of psychological interventions for FEP psychosis and determined their effectiveness and feasibility in Italian CMHCs. Its principal challenges were to learn how to manage interrelated organizational factors of treatment provision in routine services and to implement effective interventions in routine CMHCs that are tailored to patients and their families. This strategy—a model of generic services adopting the principles of early intervention for FEP patients[26–28]—complements specialized stand-alone services and is a valid alternative in countries in which stand-alone services experience accessibility problems or cannot be implemented. Our novel findings provide robust empirical support of initial reports[51,52] that FEP psychosis units can be embedded in generic mental health services.

A Large Pragmatic Trial

GET UP PIANO is the first FEP patients trial performed in such a large catchment area, corresponding to nearly 10 million inhabitants and encompassing 2 regions (Veneto and Emilia Romagna) and the metropolitan areas of Bolzano, Florence, and Milan. Coverage of this area was ensured by careful monitoring of the 117 CMHCs

Table 2. Treatment Provision in the Experimental Group During the Period Between Baseline (BL) (After Clinical Stabilization) and 9-Month Follow-Up (FU)

	Period Between BL and FU	
	Experimental Treatment Group (n = 272)	Subgroup With 0 Sessions: Reasons, n (%)
		N = 24
CBT sessions, n (%)		No consent to CBT 13 (54.2%)
0	24 (8.8%)[a]	Drop out 4 (16.7%)
1–4	15 (5.5%)	Moved to private care 2 (8.4%)
5–9	25 (9.2%)	Moved 3 (12.5%)
10–19	70 (25.8%)	High-risk pregnancy 1 (4.1%)
20+	138 (50.7%)	Working hours incompatible with appointments 1 (4.1%)
Number of CBT sessions, mean (SD), min–max	17.8 (10.3), 0–44	N = 52
Family intervention sessions, n (%)		No relative available 16 (30.8%)
0	52 (19.2%)[a]	No consent to contact relatives 6 (11.5%)
1–4	24 (8.8%)	No consent to CBT 13 (25.0%)
5–9	56 (20.6%)	No consent to FI (given by relatives) 7 (13.5%)
10–19	120 (44.1%)	Drop out 4 (7.7%)
20+	20 (7.3%)	Moved 3 (5.8%)
		Moved to private care 2 (3.8%)
		Working hours incompatible with appointments 1 (1.9%)
Number of FI sessions, mean (SD), min–max	9.3 (7.0), 0–36	—
Case management contacts, n (%)		—
0	0 (0.0%)	
1–4	96 (35.3%)	
5–9	40 (14.7%)	
10–19	59 (21.7%)	
20+	77 (28.3%)	
Number of CM contacts, mean (SD), min–max	21.7 (24.4), 1–120	—

Note: CBTp was based on models per Fowler et al[33] and Kuipers et al[34] and has demonstrated efficacy[35,36] (expected delivery: ≥10 CBT sessions per patient in 9 months, optimally 20, with weekly sessions in the first 3 months and fortnightly thereafter). Family intervention (FIp) was administered per Leff et al[37] and Kuipers et al[38] (expected delivery: ≥8 FIp sessions per family in 9 months, optimally 10–15: 6 in the first 3 months and at least 1/month thereafter). To improve continuity of care, each patient/family was assigned to a case manager who coordinated all interventions and collaborated with therapists per Burns[39] Case managers made contact with patients immediately after first service contact and facilitated the patient's and family's engagement into treatment, optimally 2–3 times/month. Each CBTp and FIp session and contact with the case manager were recorded using an ad hoc schedule.
[a]22 patients did not have any type of experimental intervention.

throughout the project. Routine cases were examined through ongoing liaisons between research teams at each CMHC. This study addressed a treated incidence sample of psychotic patients who made their first contact with public CMHCs. We know that treated incidence in Italy reflects the "true" incidence because the vast majority of patients suffering from psychosis do contact public mental health services.[53] Previous research has in fact shown that only a negligible fraction of psychotic patients in Italy are treated in private hospitals or practice alone and that it is a standard practice for general practitioners to refer all psychosis cases to public mental health services.[54]

This large epidemiologically based cohort comprised affective and nonaffective psychoses to reduce the probability of selection bias due to diagnostic sampling. Every effort was made to ensure that the experimental and TAU arm samples were representative of routine treatment of FEP patients in the study area CMHCs—eg, by performing a leakage study that assessed missing cases throughout the procedures.

A significant challenge was to measure clinical changes from clinical stabilization rather than the peak of symptom severity, as often done in FEP studies. Consequently, the magnitude of changes from intake to follow-up declined, but the changes in the experimental arm were more likely to be linked to the intervention than to nonspecific factors (including pharmacotherapy).

Feasibility

Over 90% of CMHCs asked to participate in, accepted, and completed the study, demonstrating high representativeness of the services and subjects and confirming that FEP teams can be fostered in generalist CMHCs.

Table 3. Nonspecific Interventions, Admissions, and Service Disengagement During the Period Between Baseline (BL) (After Clinical Stabilization) and 9-Month Follow-Up (FU)

	Period Between BL and FU		
	Treatment as Usual Group (n = 172)	Experimental Treatment Group (n = 272)	Test and Significance of Difference
Nonspecific interventions			
Patients receiving nonspecific interventions, n (%)	66 (49.3%) (38 missing)	68 (27.3%) (23 missing)	$\chi^2 = 18.44$, $df = 1$, $P < .001$
Families receiving nonspecific interventions, n (%)	34 (25.4%) (38 missing)	25 (10.0%) (23 missing)	$\chi^2 = 15.72$, $df = 1$, $P < .001$
Hospital admissions			
At least 1 admission, n (%)	26 (15.8%) (7 missing)	45 (16.9%) (5 missing)	$\chi^2 = 0.09$, $df = 1$, $P = .765$
Number of admissions (for admitted pts), n (%)			
1	18 (69.2%)	31 (68.9%)	$\chi^2 = 0.001$, $df = 1$, $P = .976$
>1	8 (30.8%)	14 (31.1%)	
Mean length of stay (days) (for admitted pts), mean (SD) [range]	23.5 (19.6) [5–75] (2 missing)	20.8 (16.0) [4–82][a] (3 missing)	$t = .61$, $df = 64$, $P = .546$
Service disengagement			
In contact with service at FU n (%)	157 (91.3%)	247 (90.8%)	$\chi^2 = 0.03$, $df = 1$, $P = .866$
Reasons for treatment discontinuation (for disengaged pts), n (%)			
Appropriate termination	4 (26.7%)	4 (16.0%)	na
Drop out	11 (73.3%)	21 (84.0%)	
Dissatisfaction with the care received	0 (0.0%)	1 (4.7%)	
Self-perceived clinical improvement	5 (45.4%)	6 (28.6%)	
Practical constraints	0 (0.0%)	2 (9.5%)	
Other reasons	1 (9.2%)	6 (28.6%)	
No answer	5 (45.4%)	6 (28.6%)	
Months from BL to the last contact (for disengaged pts), mean (SD)	4.6 (2.2) (1 missing)	3.3 (3.1) (1 missing)	$t = 1.38$, $df = 36$, $P = .177$

Note: na, not applicable. Due to the low number of subjects, only descriptives are allowed.
[a]1 outlier (with 1 admission of 244 days) was deleted from the calculation of the days of admission.

Engagement of professionals and their capacity building in specific treatments for early psychosis were high. No difference in acquisition of competence in administering CBTp was observed between ages, years from graduation, years of work, or theoretical orientation.

Further, most CMHC personnel were available to implement the add-on psychosocial interventions. Most patients (and relatives) accepted it, and details on the proportion of subjects included in different treatment intensity intervals were provided. These data will allow to relate "dosage" and outcome, thus providing further knowledge on the ongoing debate as to what the "optimal dose" of psychological intervention is, and clarify the role of individualization and flexibility in routine early interventions.[17,54]

The interventions decreased the need for nonspecific treatments, replaced by multi-experimental treatments, demonstrating the feasibility of the treatment.

Effectiveness

The multi-element intervention produced a greater symptomatic improvement compared with standard care, as reflected by a reduction of overall symptoms level and general psychopathology assessed by the PANSS. This data show that routine CMHC activities in Italy induce substantial improvements, even with ordinary interventions.[40,41] However, positive and negative symptoms showed a trend for improvement with the experimental treatment, which reached statistical significance only for some specific symptoms (such as conceptual disorganization, hostility, social withdrawal, and preoccupation). The lack of significant differences in positive and negative symptoms might also be due to the large improvement occurred in TAU patients. It should be also said that the effect of early intervention on positive and negative symptoms is an inconsistent finding. In fact, our findings parallel those from Lambeth Early Onset[11,55] and Croydon Outreach and Assertive Support Team[56] studies, in which integrated early intervention by specialized services did not produce greater symptomatic improvement, but contrast with those from OPUS[12] and EPPIC (Early Psychosis Prevention and Intervention Centre).[57]

Unfortunately, our study could not find any difference on both number of hospital admissions and on length of

Table 4. Primary and Secondary Outcomes: PANSS, PSYRATS, GAF, and HAMILTON of Intention to Treat Patients Assessed at Baseline (BL) (After Clinical Stabilization) and at 9-Month Follow-Up (FU). Total Number of Days of Hospitalization During the Period Between Baseline (After Clinical Stabilization) and 9-Month Follow-Up, Together With Weighted Regression Coefficients of Experimental Treatment vs Treatment as Usual (95% CI) and Effect Sizes (95% CI)

	Treatment as Usual Group		Experimental Treatment Group		Weighted Regression Coefficient[#] of Experimental Treatment vs Treatment as Usual (95% CI)	*P*-Value	Effect Size[°] (95% CI)
Primary Outcomes	BL (n = 172)	FU (n = 153)	BL (n = 272)	FU (n = 239)			
PANSS total	2.32 (0.68)	1.78 (0.64)	(1 missing) 2.37 (0.67)	(1 missing) 1.67 (0.57)	−0.11 (−0.22 to −0.01)	.044	−0.24 (−0.47 to −0.01)
PANSS positive	2.22 (0.86)	1.52 (0.70)	(2 missing) 2.30 (0.88)	(2 missing) 1.46 (0.57)	−0.07 (−0.18 to 0.04)	.232	−0.15 (−0.36 to 0.07)
PANSS negative	2.56 (1.11)	(4 missing) 2.01 (0.99)	(3 missing) 2.51 (1.14)	(2 missing) 1.87 (0.94)	−0.12 (−0.29 to 0.04)	.149	−0.17 (−0.37 to 0.03)
PANSS general	2.27 (0.67)	1.81 (0.64)	(1 missing) 2.35 (0.65)	(3 missing) 1.68 (0.56)	−0.14 (−0.25 to −0.03)	.015	−0.29 (−0.52 to −0.06)
Hospital admissions Total number of days of hospitalization mean (SD) [median; range]	Period between BL and FU (n = 163) 5.4 (20.2) [0; 0−150]		Period between BL and FU (n = 264) 4.6 (15.2) [0; 0−150][§]		−0.88 (−4.05, 2.29)	.586	−0.08 (−0.33 to 0.18)

	Treatment as Usual Group		Experimental Treatment Group		Weighted Regression Coefficient[#] of Experimental Treatment vs Treatment as Usual (95% CI)	*P*-Value	Effect Size[°] (95% CI)
Secondary Outcomes	BL (n = 172)	FU (n = 153)	BL (n = 272)	FU (n = 239)			
GAF score	(1 missing) 45.69 (12.96)	(1 missing) 60.11 (16.63)	(1 missing) 44.46 (13.81)	63.15 (16.94)	3.98 (1.15 to 6.82)	.006	0.35 (0.06 to 0.64)
HAMILTON score	(2 missing) 16.42 (9.90)	(5 missing) 10.62 (10.17)	(1 missing) 17.29 (8.29)	(3 missing) 8.81 (6.58)	−1.86 (−3.40 to −0.31)	.019	−0.25 (−0.48 to −0.03)
PSYRAT auditory hallucination scale	N = 22[a] 2.03 (1.25)	N = 22 0.51 (1.08)	N = 29[b] 1.67 (1.34)	N = 29 0.41 (0.93)	−0.17 (−0.75 to 0.42)^	.580	−0.23 (−1.13 to 0.66)
PSY AHS distress	2.13 (1.52)	0.76 (1.48)	1.69 (1.57)	0.48 (1.09)	−0.40 (−1.21 to 0.40)^	.328	−0.62 (−1.85 to 0.62)
PSY AHS cognitive	2.38 (1.39)	0.57 (1.08)	1.94 (1.48)	0.42 (0.90)	−0.25 (−0.90 to 0.39)^	.443	−0.35 (−1.29 to 0.60)
PSY AHS physical	1.87 (1.19)	0.45 (0.97)	1.56 (1.27)	0.40 (0.94)	−0.09 (−0.61 to 0.45)^	.772	−0.07 (−0.82 to 0.68)
PSYRAT delusion scale	N = 31[c] 2.78 (1.15)	N = 31 1.59 (1.38)	N = 50[d] 3.12 (0.73)	N = 50 0.76 (1.11)	−0.96 (−1.52 to −0.39)^	.001	−0.82 (−1.29 to −0.35)
PSY DS distress	2.62 (1.38)	1.60 (1.53)	3.05 (0.97)	0.75 (1.12)	−0.93 (−1.59 to −0.28)^	.005	−0.78 (−1.32 to −0.23)
PSY DS cognitive	2.84 (1.14)	1.65 (1.45)	3.15 (0.77)	0.77 (1.12)	−1.01 (−1.56 to −0.46)^	.000	−0.86 (−1.32 to −0.39)

Note: Interrater reliability was determined for the clinical measures before beginning the assessment phase. Each rater independently coded 3 videotaped interviews of psychotic patients. The agreement between raters was 0.86 (95% CI 0.80–0.90) using the intra-class correlation coefficient (ICC) per a linear random effects model. PANSS and PSYRATS were calculated as means of individual item scores. Weights are constructed to be proportional to the inverse of the predicted probability of having nonmissing outcome data. The predicted probabilities are constructed by estimating a logit model of the probability of having nonmissing outcome data conditional on covariates (gender, age of onset, diagnosis). CIs and *P*-values were generated from 1000 bootstrap samples, using the nonparametric method.

[#]Variables PANSS, PSYRAT, GAF and HAMILTON: weighted (not for PSYRAT) random effects linear regression models with CMHC as a random effect and the corresponding baseline score and the treatment assignment as fixed effects. Variable "Total number of days of admission": weighted random effects linear regression models with CMHC as a random effect and the treatment assignment as fixed effect. Estimated ICCs (95% CI) at BL: PANSS TOTAL 0.11 (0.05 to 0.22); PSYRATS AHS 0.22 (0.04 to 0.59); PSYRATS DS 0.03 (0.00 to 0.80); GAF SCORE 0.11 (0.04 to 0.23); HAMILTON 0.09 (0.03 to 0.22); Total number of days of hospitalization 0.10 (0.02 to 0.31).

[°]Effect size = regression coefficient/pooled standard deviation at baseline.

[§]1 outlier (with 1 admission of 244 days) was deleted from the calculation of the days of admission.

^Weights were not applied to PSYRAT scales.

Percentages of patients assessed with PSYRATS: [a]12.8%; [b]10.7%; [c]18.0%; [d]18.4%.

hospital stay, consistently with other studies with similar follow-up period.[12,13]

Regarding secondary outcomes, PSYRATS data—which were collected (as required by the instrument's guidelines) in the patient subgroup with more severe psychotic symptoms—showed a significant reduction in the experimental group for the subjective appraisal of delusions (emotional and cognitive components). This finding is notable because a component of the intervention, CBTp, is expected to specifically impact the subjective appraisal of distorted cognition and abnormal perceptions rather than symptom severity levels (like neuroleptics).[58] Our study demonstrates that multi-element psychosocial intervention has a greater beneficial effect on the amount and duration of preoccupation with delusions and the level and intensity of delusion-linked distress.

Conversely, the intervention did not show significant improvement in subjective appraisal for voices, consistent with other studies.[59] One explanation is that it was not tailored to patients with auditory hallucinations. Focusing on cognitive restructuring and beliefs about the power of voices—not the relationship between the voice and hearer[60,61]—might have resulted in the loss of an essential factor for change. Alternatively, there was insufficient focus on replacing maladaptive coping strategies with more adaptive approaches.[62] These issues will be examined when all CBT session transcripts are analyzed.

Intervention improved global functioning in the experimental arm. The largest proportion of improved functioning due to the intervention was observed in subjects with a GAF score of 30–60, consistent with the literature[12,13,55–57] and likely representing the most specific effect that is expected by these interventions.

The multi-element intervention reduced emotional distress—patients in the experimental group reported greater improvement in depressive symptoms, supporting CBT as the preferred treatment for psychological and emotional dysfunctions following a psychotic episode.[63,64]

Our findings could not provide evidence for lower rates of service disengagement in the experimental treatment group; this is probably due to the short follow-up period and to the fact that community-based mental health service organization in the whole area covered by the GETUP may facilitate continuity of care of people with severe mental disorders.

Strengths and Limitations

The GET UP PIANO trial overcomes the shortcomings of previous studies by providing a randomized controlled design[17]; a large sample size under routine clinical conditions in actual MH services; appropriate inclusion criteria; a detailed and manualized treatment protocol; and careful management of fidelity. The GET UP PIANO trial has some limitations. The training of professionals who administered the intervention was intensive but short; sufficient skills were gathered, but they should not be considered the highest quality. Data on the monitoring of relapses could refer only to admissions as the quality of the information on relapses for outpatients recorded in the case notes on a monthly basis, that we had foreseen in the protocol, was not reliable. Also, the extent of statistically significant differences between groups in the scores of the assessments should be analyzed carefully and translated into clinically meaningful differences. The magnitude of the effect size for total and general psychopathology (−0.24 and −0.29, respectively; negative sign favors treatment group) was small, thus suggesting clinically significant changes in most (about 60%) but not in all patients belonging to the experimental arm.[65] Two recent meta-analyses[66,67] found small effect sizes of the CBTp effect on symptoms, thus suggesting that these ones are not the most adequate and sensitive target when evaluating the effects of CBTp for psychosis. It should however be noted that the ITT approach used in the analyses has probably hampered the magnitude of the effect. In fact, the predefined criterion for an optimal intervention delivery was at least 20 sessions of CBTp for patients and 10 sessions of FIp for relatives, and this has naturalistically been satisfied only by respectively 66.3% of patients and 71.4% of relatives. In a per protocol approach (paper in preparation), we expect that the effect sizes in favor of the subjects who attended optimal doses of the experimental intervention will increase, as it has been proved in other studies. Finally, the pragmatic design has chosen—in order to preserve the representativeness of patients attending generalist mental health services—inclusion criteria among the broadest in the literature.

Due to financial constraints, the follow-up for this trial could not exceed 9 months: this is another significant limitation, as such a short study duration could hamper the possibility to fully exploit the effects of treatment in reducing hospital use—both for admission and total days—and might also be a reason why this study results are not comparable with other first-episode randomized studies with longer follow-up.

Conclusions

Longer follow-up in the GET UP trial is warranted to determine whether experimental patients will experience greater benefit over the long run compared with TAU patients. However, these findings support the feasibility and effectiveness of early interventions for psychosis in generalist mental health services.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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