Comparison of clinical outcomes following 2 years of treatment of first-episode psychosis in urban early intervention services in Canada and India

Ashok Malla*, Srividya N. Iyer*, Thara Rangaswamy, Padmavati Ramachandran, Greeshma Mohan, Aarati Taksal, Howard C. Margolese, Norbert Schmitz and Ridha Joober

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*First and second listed authors have made equal contributions to this study and the report

Word count: Abstract 247; Main text 4009.

Conflict of interest:

None: TR, PR, GM, AT, NS

AM served as a research consultant to and gave lectures at conferences supported by Lundbeck and Otsuka and was on an advisory board meeting for the same two companies for which he received honoraria.

SI reports grant and salary award from Canadian Institutes for Health Research, and Fonds de recherche du Que´bec–Sante´, outside the submitted work.

HCM reports grants from Acadia, Amgen, SyneuRx international; grants, honoraria and non-financial support from Janssen, Lundbeck, Otsuka; honoraria and non-financial support from Pfizer; honoraria from Sunovion, Purdue, HLS therapeutics, Mylan, Shire within the last 3 years, unrelated to the submitted work.

RJ served as speaker and member of advisory board committees for Pfizer, Janssen, BMS, Sunovian, Myelin, Otsuka, Lundbeck, shire and Perdue. He also received grants from Janssen, BMS, Otsuka, Lundbeck, Astra Zeneca and HLS, within the last 3 years, unrelated to the submitted work.

Funding: This Research was funded by an R-01 Grant from NIH 5R01MH093303-05. The funding source had no further role in study design, data collection and analysis, writing of the report, and in the decision to submit the report for publication.

Acknowledgements: We would like to thank Megan Pope, Heleen Loohuis, Nicole Pawliuk, Kevin MacDonald, Emily Schorr, Helen Martin, and service providers, clients and families at PEPP, SCARF, and PEPP-MUHC.

Author Contribution:

Study design and protocol: A Malla, SN Iyer, R Thara, R Padmavati, R Joober, N Schmitz

Implementation and Data acquisition: SN Iyer, G Mohan, A Malla, R Padmavati, R Joober, HC Margolese

Data analysis: A Taksal

Statistical input and interpretation: N Schmitz, A Malla, SN Iyer, R Thara, R Padmavati, R Joober.

First draft of the manuscript: A Malla, A Taksal, SN Iyer

All authors contributed to several drafts and have approved the final manuscript.

Data Availability: All data were available to the principal as well as co-investigators.

ORCID Id: Ashok K. Malla: http://orcid.org/0000-0002 -5863-4191

Abstract

Background: Purported superior outcomes for treatment of psychosis in low-middle income (LMIC) compared to high income (HIC) countries have not been examined in an early intervention service (EIS) context.

Aims: To compare two-year clinical outcomes in first-episode psychosis (FEP) treated in EIS in Chennai (LMIC) and Montréal (HIC) using a similar EIS treatment protocol and to identify factors associated with any outcome differences.

Method: FEP patients, treated in EISs in Chennai (N=168) and Montréal (N=165), were compared on change in level of symptoms and rate and length of positive and negative symptom remission over a two-year period. Repeated-measures analysis of variance, and logistic and linear regression analyses were conducted.

Results: Four patients died in Chennai compared to none in Montréal. Family support was higher for Chennai patients ($F=14.05, df=1, p<0.001, \eta p^2=0.061$) and increased over time at both sites ($F=7.0, df=1.915, p<0.001, \eta p^2=0.03$). Negative symptom outcomes were significantly better in Chennai for level of symptoms (time X site interaction $F=7.36, df=1.49, p=0.002, \eta p^2=0.03$), length of remission (mean 16.1 vs 9.78 months, $t=-7.35, df=331, p<0.001$, Cohen's $d=0.80$) and the proportion of patients in remission (81.5% vs 60.3%, $\chi^2=16.12, df=1, p<0.001$). The site differences in outcome remained robust after adjusting for inter-site differences in other characteristics. Early remission and family support facilitated

better outcome on negative symptoms. No significant differences were observed in positive symptom outcomes.

Conclusions: FEP patients treated in EIS in LMIC contexts are likely to show better outcome on negative symptoms compared to those in HIC contexts. Early remission and family support may benefit patients across both contexts.

Keywords: First-episode psychosis; early intervention service; clinical outcomes; high-income low-income country comparison; family support.

Introduction:

Early Intervention Services (EIS) have been shown to improve outcomes in first-episode psychosis (FEP) (1). Key components of EIS generally include case management, low-dose second-generation antipsychotics and family intervention(2). However, most of the evidence for superior effectiveness of EIS comes from high-income countries (HICs).

Past reports of better outcomes in psychotic disorders in low-and-middle-income countries (LMICs) compared to HICs (3-6) have been criticized (7) on the grounds that they did not take into account mortality using standard mortality ratios, the underreporting of suicides in LMICs, the lack of representative samples and inadequately measured outcomes. Despite these criticisms, this observation may hold true for India (4) for patients who actually receive adequate treatment.

Whether the differences in outcomes reported in the past between India and HICs would persist, if similar EIS principles and treatment components were applied in both settings, has never been examined. Hypotheses focused around culture (8) have been proposed to explain any differences in outcome. However, what might facilitate better outcomes within a culture remains unexplored. The impact of overall social support on outcome has been well documented (9). A greater role of families, as a specific and deeper form of social support, in India might be one important facilitator, given the context of a family structure in which the individual remains integrated with and supported by the family amidst a general lack of state support (10).

We have previously confirmed differences in clinical and functional outcomes in a pilot study (11) using relatively small FEP samples in Montreal (Canada) and Chennai (India). Based on these findings, we conducted a larger study across the two sites, comparing multiple outcomes that were established a priori and included clinical, functional and subjective domains. Here we report only on clinical outcomes (symptoms). We hypothesized that (a) following application of key components of EIS, clinical outcomes would be better for patients in Chennai compared to those in Montréal; and (b) that such differences would be explained by differences in previously known predictors of outcomes, especially family support.

2. Methods

2.1 Research and treatment context

This longitudinal, two-year prospective outcomes study was conducted between 2012 and 2018 in Montréal (population 3.2M), Canada and Chennai (population 6M), India. Within Montréal's McGill University network, the Prevention and Early Intervention Program for Psychoses (PEPP) is comprised of a larger service situated at the Douglas Institute (since 2003) and a smaller service at the McGill University Health Centre (12). The former serves a defined catchment area (total population 300,000) in South-west Montréal, with a significant proportion from minority ethnic groups (30%) and the latter mostly central Montréal (no defined catchment area) with a sizable student population. The two services are attached to a psychiatric and a general hospital, respectively, with designated in-patient beds and operate largely as outpatient, community programs.

Chennai, a large metropolis in South India, has a population of 6 million, has a predominantly Tamil-speaking population with literacy rates of 90%. It hosts SCARF, a non-governmental organization (NGO) and a WHO research centre. Not being a catchment area-based service, SCARF accepts patients from all sources and all parts of Chennai. Its capacity for EIS was built collaboratively between 2006 and 2008 and adapted to sensitivities of the Indian cultural context and resource constraints, prior to the pilot project (2008-2010). It does not have an emergency psychiatric service but has access to beds when needed. We acknowledge that neither Chennai nor Montréal can be considered as representing the entire world of urban India or urban Canada, respectively.

Both PEPP and SCARF followed EIS protocols for treatment of FEP, i.e., second-generation antipsychotic medications in lowest effective doses, case management, family psycho-education and individual family intervention, cognitive-behavior therapy when indicated and an overall recovery orientation (11). Services, including medication, were available to patients free of charge at both sites. All study procedures complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008; and were approved by the Institutional Review Board at SCARF, Chennai; and the Research Ethics Board at McGill University, Montréal.

2.2 Participants

Inclusion criteria: A FEP defined as meeting DSM-IV(13) criteria for a primary DSM-IV (13) diagnosis of either schizophrenia-spectrum psychotic disorder or

affective psychosis irrespective of the time since onset of psychosis, and not having received antipsychotic medication for more than 30 days since the onset of psychosis; age 16-35 years; and ability to communicate fluently in Tamil or English in Chennai, and French or English in Montréal.

Exclusion criteria: IQ below 70; psychosis secondary to a central nervous system disorder (e.g., epilepsy) or a medical condition; and a primary diagnosis of substance dependence. Patients who met the inclusion criteria but had a co-morbid diagnosis of substance abuse were included.

Admission criteria for the EISs were the same as study entry criteria, except for the Montreal network also admitting 14- to 16-year-olds.

Sample size calculation: For clinical outcomes, using pilot data (11) on symptom assessments, we assumed a difference of 15% in reduction of positive and negative symptoms between the two samples. We found that a total sample of 200 would allow us to detect a significant time-by-site interaction with 90% power at type I error = 0.05. Conservatively factoring in attrition rates of 15% at SCARF and 24% at PEPP, we had estimated that a sample of 150 would be required at each site to observe significant differences in outcome. Figure 1 (supplementary material) provides details of patient recruitment. All consecutive patients (248 in Montreal; 244 in Chennai) entering the treatment programs were assessed for inclusion in the study. Those meeting the inclusion-exclusion criteria were approached for participation in the study. The final sample comprised of 333 individuals with previously untreated first episode

psychosis (N=168 Chennai; N=165 Montreal). Informed consent was obtained from all participants. Participants were offered a 24-month treatment program.

2.3 Assessments

2.3.1 Socio-demographic and clinical information: Diagnosis was established through the Structured Clinical Interview for DSM-IV (SCID)(14). Socio-demographic information, age at onset for psychosis and duration of untreated psychosis (DUP) were obtained through administering the Circumstances of Onset and Relapse Schedule (CORS)(15). DUP was defined as the number of weeks between the onset of psychosis and the initiation of antipsychotic medication. The use of the CORS in cross-cultural research and inter-rater reliability between raters at the two sites were established on 10 randomly selected cases (ICC 0.89-0.97) (11).

2.3.2 Symptom assessments: The Scale for Assessment of Positive Symptoms (SAPS)(16) and the Scale for Assessment of Negative Symptoms (SANS)(17) were used to rate symptoms at baseline, and at Months 2, 3, 6, 12, 18, and 24. Positive and negative symptom severity were based on total SAPS and SANS scores respectively. The latter excluded scores on the items of "Inappropriate affect", "Poverty of Content of Speech" and the items for the "Attention" subscale, as these have been shown to not be part of the negative symptoms domain. (18).

2.3.3 Medication: All patients were prescribed a second-generation antipsychotic medication, with the specific choice based on clinical

consideration and availability. Prescription of other psychotropic medications was based on clinical need. Adherence to medication was recorded monthly based on information obtained from patients and/or their family members. Participants were regarded as adherent in a given month if they took the antipsychotic medication 76-100% of the time in that month. This method has been validated and used in other studies (19, 20). Percentage of adherence was calculated by dividing the number of months that the participant was adherent by the number of months for which they were prescribed antipsychotic medication, multiplied by 100.

2.3.4 Remission: The Remission in Schizophrenia Working Group's consensus criteria(21) were used to define remission. Participants were in positive and negative remission if they scored 2 or less on each global subscale of 'hallucinations, delusions, bizarre behavior and formal thought disorder' on the SAPS and 'flat affect, alogia, avolition and apathy; and anhedonia' of the SANS, respectively. Remission status was based on the symptom severity criterion every month. The total duration of positive, negative and total remission during the two-year period was calculated for each participant based on repeated symptom ratings at baseline, months 2, 3, 6, 12, 18 and 24. The cumulative length of symptom remission has been reported to be a strong predictor of functional (occupational and social) outcomes (22). For missing data, ratings at each time point were carried forward for the next period for up to a maximum of six months. Clinical outcome was assessed using three variables—change in symptom severity over 24 months, duration of remission,

and remission status at month 24. Early remission was defined as meeting remission criteria by Month 3.

2.3.5 Family support: Family support and the quality of family relationships were based on ratings on the following two questions, derived from Wisconsin Quality of Life Index -Provider Version(23): "During the past four weeks, this person has received _____ support" (Likert-type scale with 1 being infrequent; 2 moderate and 3 good); and "How would you describe the quality of this person's relationship with his/her family in the last 4 weeks?", assessed on a Likert-type scale from 0 "None" to 5 "Excellent". This was evaluated at Months 3, 12, and 24. This measure was chosen for its simplicity and its limited potential for cultural bias. This assessment was made about the patient by the service provider (typically case manager) based on observation and enquiry. The score on the support received was multiplied by the score on the quality of relationship to obtain a weighted score (range 0-15) as a measure of overall family support. Higher scores indicate higher levels of family support.

Training and inter-rater reliability across sites: Staff at both sites were rigorously trained during the pilot phase and the current study. Inter-rater reliability was established using four videotaped interviews of FEP patients (two from each site), which were rated on the SAPS and SANS by all raters. The Cronbach's alpha for global subscale scores on SAPS ranged from 0.93-0.99, and from 0.86-0.97 for SANS. This compares with pilot phase IRRs of 0.82-0.87 on the PANSS (11).

2.4 Data analyses

Data analyses were carried out using SPSS v22 (24). The two samples were compared using inferential statistics like independent samples t-tests for continuous variables and chi-square for categorical variables. Repeated-measures analysis of variance (R-MANOVA) was used to examine the effect of time and site on symptom severity, controlling for baseline severity of each symptom domain. Any emerging site differences were adjusted for the influence of family support at 3 months. Sensitivity analyses were repeated to account for missing subjects with no data on family support.

Linear and logistic regressions were conducted to determine predictors of length and status of remission, respectively. Based on the hypotheses of the present study, the variables were selected based on differences between the sites: gender (male/female); presence of comorbid substance abuse and dependence disorder (Yes/No); diagnosis (schizophrenia spectrum disorders/ affective psychosis); age at onset of psychosis; baseline SAPS/SANS scores; 'early remission status' (Yes/No); level of family support; and site (Chennai vs Montréal). We also controlled for baseline remission status. Effect sizes were computed using Cohen's d and partial eta squared (ηp^2), and interpreted according to the following guidelines: Small: Cohen's d=0.2 and ηp^2=0.01; Medium: Cohen's d=0.5 and ηp^2=0.06; Large: Cohen's d=0.8 and ηp^2=0.14 (25, 26). All multivariate analyses were carried out on patients who completed the study (Fig 1, Suppl).

3. Results

3.1 Baseline sociodemographic and clinical characteristics (Table 1)

Participants at both sites were in their mid-twenties, although significantly younger and more often male and single in Montréal than those in Chennai. Most patients in Montréal and almost everyone in Chennai lived with their families. For occupational status, a substantial proportion of women in Chennai described their full-time role as homemakers.

Most patients had a primary diagnosis of schizophrenia-spectrum disorder, albeit significantly more in Chennai. A significantly higher proportion had a concurrent substance abuse disorder (mostly cannabis) in Montréal. Age at onset was significantly lower in Montréal, while there was no difference in DUP between the two sites. At baseline, patients in Montreal showed significantly higher level of positive symptoms while no differences were observed on severity of negative symptoms.

A comparison of patients included in the study and those who declined to participate (N=35) in Montreal revealed no significant differences on demographic and clinical characteristics, except for a lower median DUP among non-participants (4 weeks) vs participants (11.57 weeks). In Chennai, only 6 patients declined participation. In Montréal 31 (18.8%) patients did not complete the study compared to 2 (1.2%) in Chennai. A comparison of completers in Montréal with non-completers did not reveal any differences on any demographic or clinical characteristics except that the proportion with family contact was higher among the completers than non-completers (50% vs 29.3%, χ^2=4.10,df=1, p=0.043).

Medication: Upon entry to the program, all patients (N=166) at Chennai and most participants in Montreal [141/156 (90%)] were prescribed and agreed to take antipsychotic medication. The daily dose of antipsychotic (CPZ equivalents) (27, 28) at the start of treatment was higher in Montréal (Mean=202.59 mg, SD=146.44), compared to Chennai (Mean=168.11mg, SD 78.04) (t=2.671, df=186.401, p <0.01). There were no significant differences in the use of other psychotropic medications. Olanzapine and Aripiprazole were the most common antipsychotic medication used in Chennai (N=111; 63.4%) and Montréal (N= 65, 38%), respectively.

----Insert Table 1 about here---

3.2 Outcomes:

3.2.1 Mortality: Four patients (2.38%), all women (age 27-34), died at the Chennai site, all within 3 months of entry to the program, compared to none in Montréal over the entire two-year period. One patient died from recurrence of remitted thyroid cancer and the other three from suicide.

3.2.2. Family Support (Supp. Table S1): Family support was higher in Chennai than in Montreal at Month 3 (Mean 9.39, SD 4.25 vs 8.31, SD 3.91), month 12 (Mean 10.64, SD 3.72 vs 8.49 SD 4.07) and 24 (Mean 10.6, SD 3.41 vs 8.79, SD 3.46). There was an effect of time (F =7.007, df=1.915, p<0.001, ηp^2=0.03) and site (F=14.05,df=1, p<0.001, ηp^2=0.06) but no time x site interaction (F= 2.56, df=1.915,p =0.08, ηp^2=0.01). Family support increased over time at both sites.

3.2.3. Decrease in positive and negative symptom severity (See Table 2):

Results of R-MANOVA showed that for both positive and negative symptoms, there were significant main and interaction effects of time and site (Table 2). Participants at both sites improved significantly over the 24 months. However, the improvement was greater in Montreal for positive symptoms (ηp^2=0.18) and in Chennai for negative symptoms (ηp^2 =0.08). This analysis controlled for baseline symptoms. The time*site interactions reported in table 2, were adjusted for the effect of family support at month 3; the latter being the main variable of interest that might account for site differences. Following this adjustment, the interaction remained significant for negative symptoms (F=3.95 (1.49), p<.03, ηp^2=0.20) and for positive symptoms (F=54.33(1.51), p<.001, ηp^2 =0.21). These results suggest that the greater reduction of negative and positive symptoms in Chennai and Montreal, respectively, is independent of family support. In the case of negative symptoms, it may be enhanced by the latter.

-Insert Table 2 about here---

3.3 Length of remission:

Over the 24-month period, the average length of positive symptom remission was similar in Montreal (Mean 15.53, SD 7.46 months) and Chennai (Mean 15.65, SD 7.93 months) (t= -0.13, df=331, p=0.89, Cohen's d=-0.01). On the other hand, compared to Montreal, patients in Chennai were in negative

symptom remission for a significantly longer period (Mean 16.10, SD 7.56 months vs Mean 9.78, SD 8.13) (t= -7.35, df=331, p<0.001, Cohen's d=-0.80).

3.3.1 Is the greater length of negative symptom remission in Chennai independent of other confounders? (See Table 3):

Multiple linear regression analysis was conducted only to establish if any of the differences between the two samples (Table 1) contributed to the difference in length of negative symptoms, independent of site. The results of the linear regression (N=236) indicated that attaining early negative symptom remission, and site (Chennai) significantly predicted a longer duration of negative symptom remission, and accounted for 45% of variance in outcome.

To further explore the relationship between family support and length of negative symptom remission, bivariate correlations with family support at each site revealed modest correlation at Months 3 and 12 in Chennai (r=0.31) and only at Month 12 in Montréal (r=0.26).

3.4. Remission status at 24 months: The percentage of patients in positive, and negative symptom remission increased over the two-year period at both sites. The percentage of patients in positive symptom remission at Month 24 was comparable between Montreal and Chennai (82.6% and 83.3%, respectively; χ^2= 0.33, df=1, p=0.86), while only 60.3% of participants in Montreal were in negative symptom remission compared to 81.5% in Chennai (χ^2= 16.12, df=1, p<0.001).

3.4.1 Are site differences in negative symptoms remission status at month 24 explained by differences on other patient characteristics between the two samples? (Table 3):

As there was no difference in rate of positive symptom remission between the two site, binary logistic regression analyses were used to examine this question for negative symptom remission status only. This analysis (N=216) revealed that only early remission (higher rate in Chennai) of negative symptoms was an independent predictor of remission status at 24 months. Neither site nor family support accounted for this difference.

3.5 Early Remission and impact on differences in outcome:

'Early remission' (by month 3) appears to be strongly and consistently associated with better outcome for length of negative symptom remission as well as remission status at 24 months, independent of site. In Chennai 141 (84%) patients were in negative symptom remission at 3 months compared to 65 (39%) in Montréal (χ^2 69.98, $p<0.001$). Therefore, we conducted a logistic regression with early negative symptoms remission as the dependent variable and characteristics generally associated with better outcome on negative symptoms as independent variables (Table 4). Our results show that early negative symptom remission was independently associated with shorter DUP and site (Chennai) and only marginally by not having comorbid substance abuse. Given that there was no difference in DUP across the two sites, it can be concluded that the difference in the rate of early remission of negative symptoms is associated with site alone.

----Insert Table 3, 4 about here---

Discussion:

We had hypothesized that clinical outcomes would be better in Chennai than in Montréal. This was confirmed for negative but not for positive symptoms. Positive symptoms respond well to antipsychotic medication, especially in an EIS environment, as indicated by previous reports of high rates of remission (80-85%) (15). This appears to be the case in both settings. Indeed, the higher magnitude of improvement in positive symptoms in Montréal could very likely be the result of regression to the mean.

Better negative symptom outcomes reported in EIS compared to regular care are likely related to the integration of several psychosocial interventions with medication (29). Our results show that in addition to site (Chennai) the better outcomes on negative symptoms are associated with greater family support at 3 months in the case of reduction in symptoms over time and by higher rates of early negative symptom remission (within three months) in the case of length of remission. On the other hand, status of being in remission at 24 months is associated mostly with higher rate of early remission in Chennai. Achieving early remission of negative symptoms seems to be a key ingredient to better outcome on negative symptoms. Our examination of the predictors of early remission suggests that this is driven largely by site and DUP, latter being the same across the two sites. These results further confirm our first hypothesis of better outcome in the EIS in Chennai compared to the one in Montréal but only for negative symptoms.

We also demonstrated that family support early on (at 3 months), higher in Chennai, further enhances better negative symptoms outcome independent of site. Family support, however, increases with time at both sites and may contribute to better outcomes in Montréal as well, if increased sufficiently and early enough.

Our results suggest there may indeed be something other than, or in addition to, family support that influences both early remission as well as its sustenance in Chennai. Our family support measure may not have captured nuances of family involvement. There may be other unexplored contextual aspects of family involvement or some other patient or service characteristics that explain inter-site differences in negative symptom outcome. Other inter-site differences may pertain to trust from patients and families in treatment providers and attributions of relative responsibility for care to patients, families and the state (30, 31).

Our model explained considerable proportion of variance (45%) in length of negative symptom remission and suggests that characteristics that differentiate the EIS in Chennai from that in Montréal make up the 'site' variable and could be influencing the outcome. However, there are likely to be other unexplored variables that contribute to this difference. A substantial amount of unexplained variance may be attributable to individual variations across patients related to genetic or other neurobiological or environmental factors not accounted for in this model (e.g. social deprivation, history of trauma)(32, 33).

Better outcome for negative symptoms in Chennai is unlikely to be related to differences in baseline symptom levels as these were controlled for in our analyses. Variation in the rating of negative symptoms across the two sites is also unlikely to explain this difference, given a high level of inter-rater reliability on measurement of negative symptoms across the two sites. While comorbid substance abuse diagnosis did not contribute significantly to any of the regression models, we did not measure continuous use of cannabis over time. Very low rates of drug use in Chennai have also been reported in previous studies (34, 35).

Strengths

Our study has several strengths. The samples of essentially untreated FEP patients at both sites were very well characterized, met the same inclusion and exclusion criteria, and received treatment in an EIS with components of treatment that were similar within respective cultural and economic contexts. Considerable time and resources had been used in building capacity at the Chennai site during the pilot phase. Rigorous training of staff and regular evaluation of inter-rater reliability were conducted across the two sites.

Limitations

Differences in service structures may have resulted in patients in Montreal being more representative of a catchment area sample compared to Chennai. In Chennai, a large metropolitan area in a LMIC, patients and families may have come from a much larger and wider-spread population base. Patient

characteristics varied across the two sites and may reflect true differences in the epidemiology of psychotic disorders in India and Canada (e.g., difference in sex distribution, age at onset and substance abuse) or sampling bias (severity of symptoms). However, these confounders did not explain the site differences in our multivariate analyses. Our controlling for all baseline differences between the two samples is likely to have minimized but not eliminated bias, which must be acknowledged in interpreting differences.

Implications

Our findings suggest that an EIS with essential elements of integrated care, including case management, contextualized to local circumstances of a LMIC urban environment can produce clinical outcomes that are even better than those in an urban setting in an HIC. The differences in outcome in FEP across the two very diverse economic and cultural environments are not attributable to differences in some known predictors of outcome that may apply across disparate environments. Clinicians may need to pay particular attention to achieving early remission of symptoms through addressing factors associated with it, while also being vigilant about risk of suicide, especially for women in India. Increasing family support and reducing treatment delay may lead to both early remission and improvements in longer-term outcome, across geographies. Improving family support early in the treatment of young people with FEP may be necessary in Western settings like Montréal, where family involvement may not occur as naturally as in LMIC settings like Chennai. There may indeed be a dose-response relationship between family support and outcome and family support may need to be sustained over the entire period of treatment.

Table 1: Socio-demographic and clinical characteristics at entry for treatment

Variable	Montreal Mean (SD) N[a] (%)	Chennai Mean (SD) N[a] (%)	Statistical Test	p-value
Age at entry (years)	24.20 (5.3)	26.60 (5.24)	t(331) = 4.15	<0.001
Gender N (%)				
Men	110 (66.7)	82 (48.8)		
Women	54 (32.7)	86 (51.2)	$\chi^2(2) = 12.37$	0.002
Transgender	1 (0.6)	0		
Total	**165**	**168**		
Education (years)	12.24 (2.63)	11.75 (3.9)	t (293.938) = 1.34	0.182
Education				
Less than High School	44 (27.2)	47 (28)	$\chi^2(1) = 0.03$	0.868
High school or more	118 (72.8)	121 (72)		
Total	**162**	**168**		
Occupation Status				
Student	40 (29.0)	24 (14.4)		
Paid employment	35 (25.3)	25 (15.0)	$\chi^2(3) = 30.0$	<0.001
Homemaker	7 (5.1)	40 (24.0)		
Unemployed	56 (40.6)	78 (46.7)		
Total	**138**	**167**		
Marital Status				
Single	149 (90.9)	95 (56.5)		
Married/ Common Law relationship	13 (7.9)	62 (36.9)	$\chi^2(2) = 50.51$	<0.001
Separated/ divorced / widowed	2 (1.2)	11 (6.5)		
Total	**164**	**168**		
Living Situation				
Alone	16 (10.0)	2 (1.4)		
With family	125 (78.1)	140 (96.6)	$\chi^2(3) = 22.95$	<0.001
With friend / room-mate	16 (10.0)	2 (1.4)		
In residence, group home or homeless	3 (1.9)	1 (0.7)		
Total	**160**	**145**		
SCID Diagnosis Type				
Schizophrenia-spectrum Disorders	109 (67.3)	150 (90.4)	$\chi^2(1) = 26.29$	<0.001
Affective psychosis	53 (32.7)	16 (9.6)		
Total	**162**	**166**		
Substance Abuse or Dependence (SCID) Yes	54 (37.8)	17 (10.2)	$\chi^2(1) = 32.9$	<0.001
No	89 (62.2)	149 (89.8)		
Total	**143**	**166**		
Age at onset of current psychotic episode (years)	23.41 (5.67)	25.81 (5.22)	t(318) = 3.94	<0.001
DUP (weeks) to presenting episode [$](analysis on log of mean)	40.79(88.46) Median =9.9 (0 – 684.3)	32.82 (61.09) Median =11.8 (0.29 -518.71)	[$]t(270.4) = 0.42	0.674

SAPS	34.53 (14.91)	19.90 (9.92	t(259.558)= 10.192	<0.001
SANS	22.5 (12.47)	21.62 (15.72)	t(259.18)= 0.549	0.583

(p< 0.05 are significant; a: the sample sizes vary because of missing data; SAPS: Scale for Assessment of Positive Symptoms; SANS: Scale for Assessment of Negative Symptoms)

Table 2: Repeated measures analysis of variance for change in symptom severity over time

Measure	Site	Assessment point			Time			Site			Time*Site		
		Baseline Mean (SD)	Month 12 Mean (SD)	Month 24 Mean (SD)	F (df)	p	np^2	F (df)	p	np^2	F (df)	p	np^2
SAPS	Montreal (N=114)	35.1 (14.51)	6.69 (11.57)	5.96 (9.86)	583.937 (1.634)	<0.001	0.69	60.442 (1)	<0.001	0.187	44.061 (1.634)	<0.001	0.144
	Chennai (N=150)	19.95 (9.91)	4.04 (7.59)	3.12 (6.45)									
SANS	Montreal (N=120)	23.17 (12.86)	12.27 (11.64)	11.18 (11.73)	154.955 (1.491)	<0.001	0.404	20.697 (1)	<0.001	0.083	7.363 (1.491)	0.002	0.031
	Chennai (N=111)	22.04 (16.05)	4.18 (8.79)	4.60 (10.56)									

($p < 0.05$ are significant; SAPS: Scale for Assessment of Positive Symptoms; SANS: Scale for Assessment of Negative Symptoms; np^2: partial eta square (Effect size)

Table 3: Regression analyses for negative remission

Predictors for linear regression	**Length of remission (N=236)**			**Predictors for logistic regression**	**Remission status at M24 (N=216)**			
	B	**SE**	**p value**		**OR**	**95% C.I. for OR**		**P-value**
						Lower	Upper	
Gender	0.38	0.85	0.652	Gender (Ref: Female)	1.14	0.56	2.33	0.704
Substance Abuse/Dependence at Baseline	0.27	1.04	0.795	Substance Abuse/Dependence at Baseline (Ref: No)	1.45	0.64	3.26	0.368
Age at onset of psychosis	-0.01	0.07	0.881	Age at onset of psychosis	1.00	0.94	1.06	0.916
Diagnosis	1.00	1.01	0.322	Diagnosis (Ref: Affective Psychosis)	1.24	0.55	2.81	0.602
Baseline Negative Remission	-2.01	1.07	0.063	Negative Remission status at Baseline (Ref: No)	0.47	0.16	1.37	0.172
Early Negative Remission	**-9.04**	**1.03**	**<0.001**	Early Negative Remission (Ref: No)	**0.38**	0.17	0.82	**0.014**
Family support at Month 3	0.13	0.09	0.177	Family support at Month 3	0.95	0.87	1.03	0.248
Site	**2.79**	**1.04**	**0.008**	Site (Ref: Chennai)	1.48	0.66	3.32	0.335
Constant	22.74	3.96	<0.001	Constant	0.63			0.683
Adjusted R^2	0.45							

Table 4: Logistic regression analysis to examine predictors of early negative remission

Predictors	Early negative remission status			
	OR	95% C.I. for OR		p value
		Lower	Upper	
Gender	2.26	1.16	4.38	0.016
Substance Abuse/Dependence at Baseline	0.62	0.28	1.37	0.246
Age at onset of psychosis	1.00	0.94	1.07	0.793
Duration of untreated psychosis (DUP; analysis on log)	2.38	1.41	4.00	**0.001**
Diagnosis	0.75	0.33	1.70	0.495
Early Adherence Percentage	0.99	0.98	1.00	0.534
Site	8.86	4.16	18.86	**<0.001**
Constant	0.09			0.052

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Author Details

(corresponding author) Ashok Malla: MBBS, MRC Psych, FRCPC, Professor, Department of Psychiatry, McGill University, Montreal, Quebec, Canada; Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), Douglas Mental Health University Institute, Wilson Pavilion, 6875 boulevard LaSalle, Montreal, Quebec H4H 1R3, Canada
ashok.malla@mcgill.ca

Srividya Narayanan Iyer: PhD, Assistant Professor, Department of Psychiatry, McGill University, Montreal, Quebec, Canada.

Thara Rangaswamy: MD, PhD, Vice Chairperson, Schizophrenia Research Foundation (SCARF), Chennai, Tamil Nadu, India.

Padmavati Ramachandran: MD, Director, Schizophrenia Research Foundation (SCARF), Chennai, Tamil Nadu, India.

Greeshma Mohan: MA, Project Coordinator, Schizophrenia Research Foundation (SCARF), Chennai, Tamil Nadu, India.

Aarati Taksal: PhD, Research Assistant, Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), Douglas Mental Health University Institute, Montreal, Quebec, Canada.

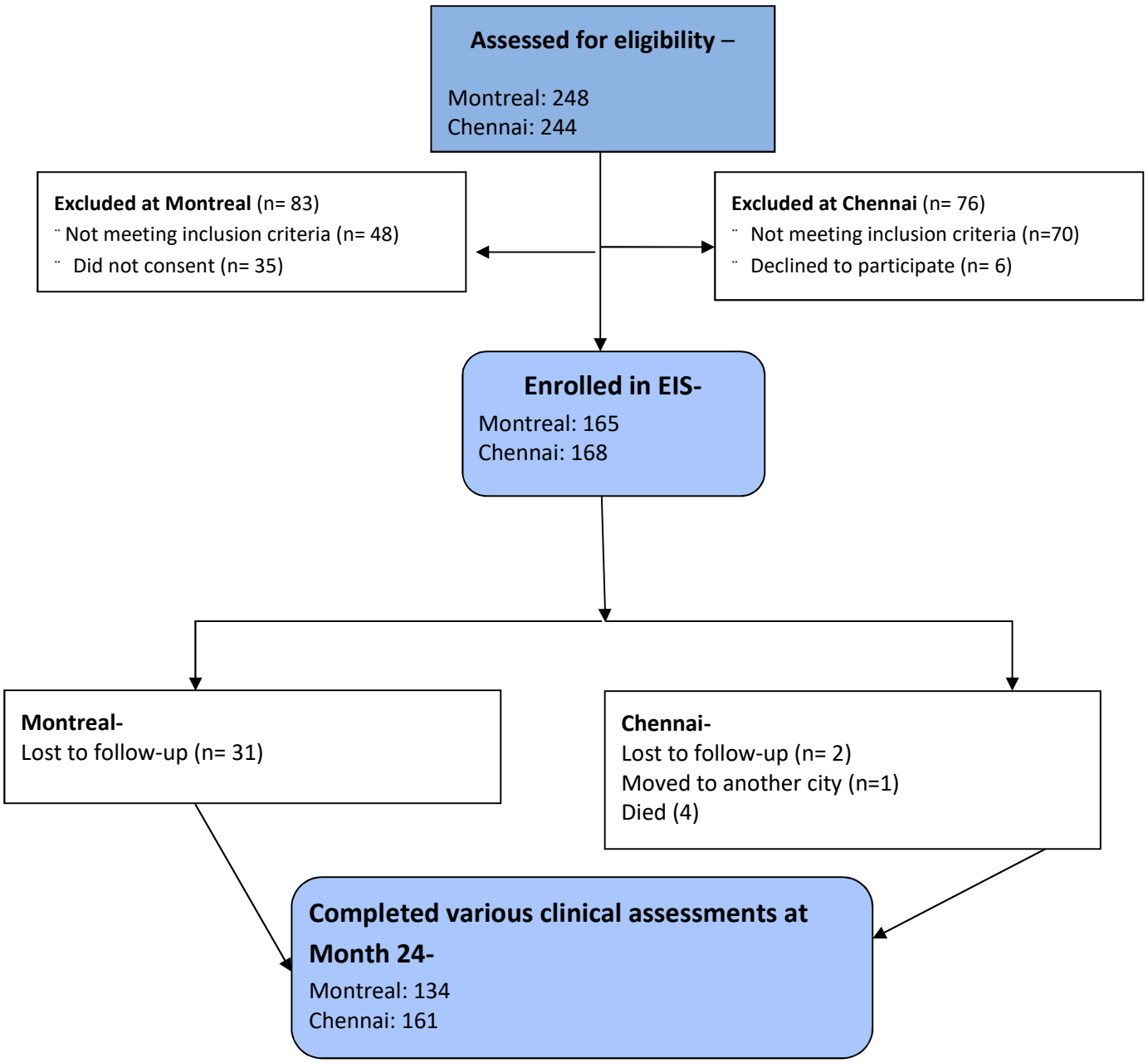
Howard C. Margolese: MD, CM, MSc, FRCPC, Associate Professor, Department of Psychiatry, McGill University, Montreal, Quebec, Canada.

Norbert Schmitz: PhD, Professor, Department of Psychiatry, McGill University, Montreal, Quebec, Canada.

Ridha Joober: MD, PhD, Professor, Department of Psychiatry, McGill University, Montreal, Quebec, Canada.

Supplementary Material

Supplementary Fig 1: Flowchart of sample recruitment at both sites



Supplementary Table S1: change in family support over time based on RMANOVA

Measure	Site	Assessment point			Time			Site			Time*Site		
		Month 3 Mean (SD)	Month 12 Mean (SD)	Month 24 Mean (SD)	F (df)	p	np^2	F (df)	p	np^2	F (df)	p	np^2
Family Support	Montreal (N=86)	8.31 (3.91)	8.49 (4.07)	8.79 (3.46)	7.007 (1.915)	<0.001	0.031	14.053 (1)	<0.001	0.061	2.562 (1.915)	0.081	0.012
	Chennai (N=133)	9.39 (4.25)	10.64 (3.72)	10.6 (3.41)									

($p < 0.05$ are significant; np^2: partial eta square)