Early intervention in psychosis

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EARLY INTERVENTION IN PSYCHOSIS

A data-driven
population health approach
to reduce
the duration of untreated psychosis

Maria Ferrara

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**A data-driven population health approach
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Early Intervention in Psychosis

A data-driven population health approach
to reduce the duration of untreated psychosis

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If not us, then who?

If not now, then when?

Rep. John Lewis, 1941

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CHAPTER 1

INTRODUCTION

First episode psychosis (definition, direct and indirect cost, prognosis).

Psychosis refers to the presence of perceptual abnormalities (e.g. hallucinations), cognitive distortions, thought content disorders, dysregulated affect, and bizarre behavior. Psychosis can occur as one of the features of an endogenous primary psychotic disorders (affective and non-affective disorders), or represent the manifestation of an organic disease (e.g. organ dysfunction, brain tumor, metabolic disorders (American Psychiatric Association. & American Psychiatric Association. Task Force on DSM-IV., 2000).

Primary psychotic disorders emerge in late adolescence-early adulthood, with a peak of incidence of 22 and 25 years, for men and women, respectively. Primary psychotic disorders include schizophrenia spectrum disorders and affective disorders (bipolar disorders).

The most recent report on Disability Adjusted Life Years (DALY), a measure of overall disease burden (the sum of years lived with disability and years of early death), showed that neuropsychiatric disorders are the main cause of DALY for 10-24 olds(Gore et al., 2011). According to the WHO multinational study, 70% of male and 60% of female will manifest psychosis by age 25. Lifetime prevalence of schizophrenia worldwide is 4.0/1000 (D. Bhugra, 2005). In USA, 100,000 new cases of psychosis/schizophrenia are diagnosed per year. In Europe, the incidence of all psychotic disorders is 26.6/100,000 person-years, varying considerably from 6.3/100,000 person-years (95%CI 4.5-8.8) to 90 (88.3-91.8). The incidence is higher for non-affective disorders, such as schizophrenia spectrum disorders: 18.7/100,000 person-years, compared to that of affective psychotic disorders: 4.6/100,000 person-years(Jongsma et al., 2018).

Schizophrenia is also responsible for a high economic burden. In 2013, in the U.S., it has been estimated that the cost of people affected by schizophrenia, compared to individuals without schizophrenia, was 155.7 billion \$ which included excess direct health care costs (i.e. hospitalization), direct non-health care costs (law enforcement, homeless centers) and indirect costs (productivity loss from unemployment, and caregiving)(Cloutier et al., 2016). This burden on the individual, the caregivers, and the high cost for society make psychosis a public health problem (Kelly K. Anderson, 2019; Christensen et al., 2020).

Many possible etiologies of primary psychotic disorders have been proposed, from paternal age (Frans, MacCabe, & Reichenberg, 2015), genetic predisposition, antenatal and perinatal/obstetric complications (Cannon et al., 2002), childhood trauma (Varese et al., 2012) social factors (e.g. urbanicity (Vassos, Pedersen, Murray, Collier, & Lewis, 2012) (Castillejos, Martin-Perez, & Moreno-Kustner, 2018)); migration (Bourque, van der Ven, & Malla, 2011), (Cantor-Graae, Zolkowska, & McNeil, 2005; Castillejos et al., 2018)), and high potency cannabis use (Gibbs et al., 2015; Marconi, Di Forti, Lewis, Murray, & Vassos, 2016)). However, we are still far from defining a cause-effect model for psychosis.

The field has been moving pretty slow. During the last five decades, recovery from schizophrenia remained low (median, 13.5%), without significantly improving (Jaaskelainen et al., 2013). Furthermore, individuals with schizophrenia die on average 15 to 20 years prematurely (Wildgust, Hodgson, & Beary, 2010), with an increasing mortality gap, due to poor lifestyle, side effects or inappropriate use of medications, comorbid substances abuse, lack or poor access to physical health care, social isolation, absent employment or supportive welfare, and therefore lack of means to access care (Jaaskelainen et al., 2013).

Despite this gloomy pessimism of Kraepelinian memory, in the past 20 years, the scientific community and mental health providers have embraced a radical shift in the approach to psychosis, by implementing early interventions services (EIS), with the ambition not only to improve prognosis but also to prevent psychosis (McGorry, Purcell, Goldstone, & Amminger, 2011).

Conceptualization of EIS for psychosis is based on two fundamental notions. First, compelling evidences show that duration of untreated psychosis is strongly correlated with both short and long term outcomes: specifically, worse positive and negative symptoms at clinical presentation, poorer rates of remission, and more severe cognitive impairment (Melle et al., 2004). This association has been consistent across many healthcare systems and many methods of measuring DUP (Penttila et al., 2010; Penttila, Jaaskelainen, Hirvonen, Isohanni, & Miettunen, 2014). Thus, reducing DUP has become a public health priority. A multitude of evidences show that, by reducing DUP, the social consequences of psychosis, social isolation, unemployment, homelessness, deliberate self-harm, and violence toward others are reduced (Challis, Nielssen, Harris, & Large, 2013; M. Large, Nielssen, Slade, & Harris, 2008; M. M. Large, 2014; M. M. Large & Nielssen, 2011; Marshall et al., 2014). Second, the two to the five years following psychotic symptom onset, biological, social and psychological factors are most

plastic (Max Birchwood & Fiorillo, 2000). This so-called “critical period”, as first coined by McGlashan, is not usually followed by a progressive decline, but by a “plateau” in symptoms and functioning, with a more stable remission or chronicity (McGlashan, 1988, 1999; Srihari et al., 2009; Thara, 2004). This speaks about the importance of intervening as early as possible, when the disease is more malleable, in order to change its trajectory (Max Birchwood & Fiorillo, 2000). The EIS paradigm has brought two conceptually overlapping approaches to improve the lives of those affected and their family members: early detection and first episode services.

Early Detection (ED) seeks to reduce delays to care, while the provision of packages of empirically based interventions by specialty teams, or First-Episode Services (FES), has emerged as a best practice (Correll et al., 2018; Srihari, 2018).

Strategies to reduce DUP

Early detection actions. What works? And for whom?

Reducing DUP has become a mental health policy priority (L. Dixon, 2017; Malla & McGorry, 2019).

Many strategies have been adopted to reduce DUP, which included initiatives to detect subjects experiencing symptoms of full blown psychosis or at risk for psychosis earlier in the course of the illness, and to encourage prompt referral to specialized services (FES).

Many barriers to early detections have been identified. These barriers include patients’ and families’ awareness of the illness, symptoms severity and urgency of presentation, difficulties in formulating a correct diagnosis by healthcare providers or reluctance to label a highly-stigmatized disease like psychosis. Moreover, early detection should immediately be followed by prompt referral to FES, which can be delayed due to patient’s lack of insight, socioeconomic or cultural barriers to access care, and hesitance to refer a client to an external referral when a therapeutic alliance has been already built.

One of the first targeted audience by ED efforts was the lay population, because of the observation, in Australia, that lack of knowledge about mental illness and about the availability of mental health services could represent a barrier for accessing treatment. Therefore, an annual week-long conference about schizophrenia and other severe mental

illnesses was organized since 1989 in the city of Stavanger (Norway), with the goal to raise the general level of awareness about psychosis, covering an area of 370,000 people. In Melbourne, Australia, in order to accelerate the referral to specialized first-episode services, a FES was established in 1992, with a dedicated ED team. This team consisted of mental health clinician, available 24h, in charge of evaluate potential FEP cases in a short time, and initiate the appropriate treatment. Since then, clinicians and researchers have been trying to address one or more than one of these challenges across different health care systems, using a variety of research design, with non-homogeneous results (Oliver et al., 2018).

Scandinavia, TIPS

After more than 20 years, the early treatment and intervention in psychosis (TIPS) project represents the most prominent early detection effort conducted so far. The TIPS study included a prospective clinical trial designed to test wherever the timing of intervention in FEP could change the course of the disorder.

The project was conducted in three FEP centers: Rogaland County, Norway that served as experimental site, Ulleval sector, Oslo, Norway and Riskilde County, Denmark that were the control sites. All three sites were offering the same pharmacological and psychosocial treatment protocol, but they differed for the ED intervention aimed to reduce DUP.

The experimental site, Rogaland County, established a comprehensive, multi-target information, education and service delivery system to change DUP. It began in 1997 and was fully funded until 2000. It consisted in ED teams and an education program, targeting the general population, health professionals and school.

The ED team encouraged low threshold for referrals (that could also be self-referrals), accompanied by the offer of a rapid and comprehensive care. Specifically, two detection teams were integrated into the ordinary outpatient units. Potential cases were met at different locations (including home visits), in the context of a proactive outreach attitude. Eligibility was assessed within 24 hours, and the treatment would start in a week (or immediately, if urgent).

The TIPS education program was aimed at: 1) Inform the population about psychiatric disorders and early signs of severe mental illness; 2) Change the help seeking behavior trying to focus on positive outcomes; 3) Reducing stigma; 4) Provide analogies between mental illness and physical illness to foster the attitude usually shown towards the latter. General

population was reached through brochures sent to household, mass media, postcards, car stickers, distributed to cinemas, restaurant, and public gathering places. Free lectures were also offered, and the presence of the ED team at public events was also assured. Health practitioners, especially primary health care workers, were educated about recognizing early signs of psychosis, and access to care. School were also part of the ED efforts, through specific visits and educational material provided to administration, principals, but also teachers and students.

The TIPS project was first funded from January 1st 1997 to December 31st 2000, reducing DUP from 26 to 5 weeks (as detailed in **Chapter 2**) then after a stop of one year during which the results obtained vanished, the ED campaign was funded again.

The TIPS main results can be summarized as it follows:

- TIPS proved that a massive ED campaign can reduce duration of untreated psychosis (Larsen et al., 2001).
- At presentation, subjects coming from the ED- sites showed lower severity of negative and positive symptoms, and suicidal behavior (Melle et al., 2006) compared to subjects coming from the No-ED sites(Melle et al., 2004).
- At 2 and 5 years follow up, subjects coming from ED area had fewer negative, cognitive, and depressive symptoms(Larsen et al., 2011).
- Subjects coming from the early detection area, at 10 year follow up, showed higher rates of recovery, a higher proportion lived independently, and had full time work, compared to no – ED area (Hegelstad et al., 2012).

Australia, the EPPIC

In Australia, an early detection campaign commenced on June 1996 and stopped on May 31st 1997, in a catchment area of 300,0000, comparable to a control area where the campaign was not implemented. Both areas were similar in terms of demographic of the population, and comparable in terms of high socio economic disadvantage, ethnic diversity, and gender. In both areas, an active outreach team was making assessment at home, and was in charge of a rapid referral to CSC services. Secondary schools, where potential FEP could be identified, were the main target of the educational piece of the campaign. Actions were also taken to improve recognition of psychotic disorders, and the target were general practitioners, school teachers and youth workers through tailored newsletter, workshop, and advertisement visits.

A total of 98 subjects were enrolled in the program, 58 belonging to the intervention area. Despite researchers acknowledged that a reduction in median DUP was not observed between the two areas, a difference in the distribution of DUP was indeed observed. Specifically, the intervention group had more cases with a DUP of more than 3 years, while the campaign did not have an effect on shorter DUP. Moreover, when 9 outliers were removed from the analysis, mean DUP in the intervention area halved (91.7 days vs 189.7 days). Those findings highlighted that while the campaign could have in fact reduced DUP, it might also have attracted subjects with a longer DUP (McGorry, Edwards, Mihalopoulos, Harrigan, & Jackson, 1996).

Canada, the PEPP study

The PEPP study was conducted within the catchment area of the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), which serves approximately 300,000 people in southwest Montreal (Malla et al., 2014). The quasi-experimental designs compared the effect of the ED campaign with an historical control group. The study consisted of three phases.

Phase 1 was 3 years long pre-intervention phase from January 2003 to December 2005, where a standard information campaign was used to inform primary care and mental health services in the catchment area about the service offered. This phase was also used to collect information out potential referrals for the following phase.

Phase 2 was 6 months intervention phase where targeted early detection campaign was carried out in health facilities (primary care, mental health services, acute care hospitals, school health and counselling centers, community health and social service clinics, clergy services. Educational sessions (academic detailing) were performed at each site, during which pre PEPP study was explained, and the rationale of FEP services.

Phase 3 was 3-year period, until May 2009, during which booster sessions were also provided every 6 months. This phase was used to evaluate the persistence of campaign' effect after the completion of the intervention phase.

This study failed to reduce total DUP, or the referral portion of DUP. Interestingly, the referral time to FEP services remained shorter for those coming from emergency department services, and the campaign was unable to increase the referrals from community-based services. The hypothesis is that community services struggled to identify cases of psychosis

or failed to incorporate this knowledge in the daily practice. The numbers of referrals from community services in fact increased over time, but they were found not eligible for the program. It is also possible that the potential cases identified by community services were promptly directed to emergency services, where immediate service is provided, and a previously scheduled appointment is not required.

Singapore, EPIP

The early psychosis Intervention Programme (EPIP), was a nationwide program initiated in April 2001 in Singapore. The main aim was to raise awareness of psychosis among the general public, and health care workers in primary health care sector, being those the main providers of health care (2500 general practitioners). The campaign directed at the general public included the use of mass media, public forums, involvement of local celebrities, postcards, art exhibitions, and hotline for public inquiry. Health care professionals were engaged through bi-monthly newsletters, regular workshops, and phone consultations. In the first two years, EPIP was able to reduce DUP from a historical median of 12 months to 4 months. Moreover, pathways to care was positively affected by the ED campaign, with a dramatic increase of referrals from families, and a substantial reduction of referrals by the police (Verma, Poon, Subramaniam, Abdin, & Chong, 2012).

UK, Birmingham, the YouthSpace

A quasi-experimental prospective study was conducted in South Birmingham from July 2011 to December 2013, targeting two components of delay to specialized service for psychosis: referrals from within mental health services, and help seeking behaviors. North Birmingham served as control area. In order to improve FEP early detection and expedite referrals, a youth mental health pathway was introduced: this new youth team, embedded within two community mental health teams, provided rapid engagement, proactive assessment for young people aged 15-25, and direct referral to FEP service (bypassing usual pathways involving regular mental health services). A “family-focused” public health campaign with the strapline “Don’t turn your back on the symptoms of psychosis” was also initiated. This media and local campaign targeted young individuals with FEP and their caregivers, raising

awareness on the early symptoms of psychosis, and providing education on how to reach available services in the area.

In the post-intervention period, DUP was reduced in the intervention area (median 39 days vs 71 in the control area); investigators found that the introduction of the new pathway may have played a role in the reduction in DUP (Connor, Birchwood, et al., 2016).

Do ED campaigns work? The challenge of interpreting DUP results

A meta-analysis conducted by Oliver D. and colleagues reported a non-significant effect of ED campaigns to reduce DUP (Oliver et al., 2018). One of the limitation in drawing definitive conclusions about the variance observed in the effectiveness of programs designed to reduce DUP was the heterogeneous definition of DUP. The definition of DUP onset explained a substantial proportion of variation between the studies: when studies used structured definition of psychosis (onset of frank positive psychotic symptoms or by using the Positive and Negative Syndrome Scale [PANSS]) there was an association with a greater decrease in DUP compared to other onset definitions (nonspecific psychotic symptoms). Moreover, the definition of the “first” episode of psychosis varies between studies, making comparison difficult (Breitborde, Srihari, & Woods, 2009). Both the start point “psychosis onset” of DUP and the end point of DUP “treatment onset” can differ across studies, making it very difficult to operationalize DUP (Norman and Malla, 2001, Norman et al., 2005, Perkins et al., 2005, Singh, 2007, Breitborde et al., 2009, Farooq et al., 2009, Dell'Osso et al., 2013).

A recent review reported that the most commonly used instrument to date the onset of DUP was the Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS)(Register-Brown & Hong, 2014). Other groups preferred scales designed to measure the severity of psychotic illness, like the PANSS. However, the most common way of determining DUP onset was through clinical interviews. Moreover, investigators did not find an instrument that had a higher inter-rater reliability compared to the others.

The endpoint of DUP might also fall into one of six categories: i) first psychiatric hospitalization, ii) first antipsychotic treatment, iii) first adequate treatment (for a certain number of weeks with/without a certain % of adherence); iv) enrollment in study; v) first treatment for psychotic symptoms, vi) undefined (Register-Brown & Hong, 2014).

In a systematic review, authors pointed out the major challenges in analyzing and therefore interpreting results about DUP. The distribution of DUP is skewed; median is not representative of the whole sample; and DUP length differ between affective and not affective psychosis (shorter for the former)(M. Large et al., 2008).

A method to analyze the effect of early detection campaign across the whole distribution of DUP was needed, along with the ability to identify threshold after which ED affect outcomes. Guloksuz et al. applied quantile regression to interrogate the effect of ED across the full range of DUP (Guloksuz et al., 2016). In this first study, quantile regression was applied to study the effectiveness of an ED strategy across different levels of DUP. Specifically, in contrast to ordinary least-square regression, QR regression was able to find that higher education level was correlated with lower levels of extreme DUP during the early but not the late epoch of the campaign. Meaning that, as the service became better known to referrals, the effect of greater educational attainment on improved access was likely muted.

Chapter 2 describes the application of quantile regression analysis to the seminal early detection campaign, the Scandinavian TIPS study. The goal is to investigate the differential impact of the TIPS early detection initiative across the DUP distribution. Moreover, secondary analysis aims to explore possible predictors of DUP and moderators of the effect of the TIPS campaign. This study attempts to answer to the question: what works for whom in terms of early detection for psychosis. The findings will help the refinement of extant early detection initiatives across different countries and health systems. For example, the identification of gender as a possible moderator of the effectiveness of the ED campaign might contribute the support of a gender-sensitive messaging, in the context of ED initiatives. As already shown in several studies, gender is a critical determinant of health, including mental health. Psychosis does not represent an exception to this finding. In fact, schizophrenia presents differently in both genders, and might need gender-sensitive approaches for early interventions. Initiatives to improve access to care and quality of care for women with FEP will be discussed in details in **Chapter 6**.

The TIPS' early intervention initiative included not only early detection outreach efforts in the community but also low threshold first episode psychosis teams employed within the catchment area. The implementation of such services varies across countries and health care systems. It can be centralized, with a stand-alone specialized FEP team for a catchment area, or "disperse" with mini-specialized teams distributed within the extant

community mental health services. **Chapter 3** describes in details the first initiative still operating in Italy for the implementation of FEP services in an entire region, Regione Emilia Romagna, a catchment area of 705,393 inhabitants, overseen by the Department of Mental Health in Modena. In particular, **Chapter 3** focuses on the implementation of FEP in Modena province. Chapter 7, on the other hand, offers a glimpse of the current status of first antipsychotic prescription practice in the Hunan Province of China, investigating practice in inpatient units where the majority of care is provided to FEP.

Implementation of early intervention for psychosis

Brief review of EIS implementation in Italy.

The still running Italian National Health Service (Sistema Sanitario Nazionale, SSN) was established in 1978, with the Law 1978/833, which incorporated the reform of mental health care in Italy, the so-called Law 180. The Law 180, or Basaglia Law, was named after the psychiatrist who passionately fought for it during the tumultuous and considered by many “revolutionary Italian seventies” (divorce and abortion became also legalized during this period), and it outlined four specific objectives: 1) Gradual closure of all psychiatric hospitals (stop admissions), 2) establishment of psychiatric units, in the context of general hospitals, with a maximum of 15 beds each, 3) setting up community-based mental health centers (CMHCs), 4) providing psychiatric care over geographically defined catchment areas, 5) introduction of more restrictive criteria and procedures for compulsory admission. This transition from psychiatric asylums to community mental health centers was not uniform across the Country (Piccinelli, Bortolaso, Bolla, & Cioffi, 2016). Its full realization still carries many disparities especially between Northern and Southern Regions, with the former more efficient, as a reflection of an historical and longstanding challenge for the South to receive and/or utilize resources (Daniele & Malanima, 2007).

The development and implementation of Specialized services for first Episode Psychosis in Italy, started in 2005 with the innovative “Programma2000” in Milan, Northern

Italy, carries the inequalities between Regions outlined above. According to the most current published report, 44 Early Intervention in Psychosis centers are operating within the public mental health care network in Italy (A. Cocchi, Meneghelli, A., Preti, A., Cavicchini, A., Collavo, M., Macchi, S. , 2011; Ghio et al., 2012) (Addington et al., 2020). However, such services are not homogeneously distributed in the Country: 79% are present in northern and central Italy, and 22% in Southern Italy (A. Cocchi, Cavicchini, et al., 2015). Mental health service in Italy is completely provided by the Public Health Care, taxed funded (single payer), which allocates resources to the Region, and then to local districts. Private practitioners could also provide mental health care (psychotherapy and pharmacological consultation); however, given the intensity of care required for severe mental health conditions, the provision of care for psychosis is completely absorbed by the public sector, and primary care physicians are instructed to refer to local CMHCs (Lasalvia et al., 2014). A different combination of specialized care to FEP and subject at clinical high risk for psychosis is therefore delivered across Regions and local districts.

The first National Italian Guidelines for Early Intervention in Schizophrenia were published in 2008 (De Masi et al., 2008), and soon afterward the first randomized controlled trial (GET-UP PIANO (Ruggeri et al., 2015)) for first episode psychosis targeting a cohort of 10 million inhabitants was launched. In the following years, many Regions funded the implementation of local services for first episode psychosis. Within those regions, in 2012, Region Emilia Romagna, in northern Italy, funded an early intervention initiative to cover all its nine provinces. This has been led by the Department of Mental Health and Substance Abuse in Modena (Modena DSM), and represents the first attempt to provide first episode services across an entire Region. **Chapter 3** describes its rationale in details. Before this report, only sparse treated incidence reports referring to single CMHCs, or provinces were reported. For example, Bianchini et al reported the results of the project “SMILE” (Service for Monitoring and early Intervention against psychological and mental suffering in young people) (Bianchini et al., 2015; A. Cocchi, Balbi, et al., 2015; Pollice et al., 2007). This service was established in November 2005 under the auspices of the Department of Mental Health, University of L’Aquila, Italy with the goal to target severe anxiety and mood disorder in people aged 16 to 30, and to detect schizophrenia as well as other SMI early in the course of illness. The results of the first year of implementation showed that 35% of referrals had a diagnosis of schizophrenia, bipolar disorder, and incipient risk for psychosis. They increased the

referrals by 64% compared to the previous year by putting a lot of efforts in liaison activities with primary care physicians and university hospital psychiatrist (Pollice et al., 2007). Incidence data were not reported.

In November 2005, the Italian Center on Control of Maladies, a department operating under the Ministry of Health, financed a project aimed at evaluating the feasibility of a protocol of intervention based on the early intervention in psychosis (EIS) model within the Italian public mental health-care network. The study, carried out between March 2007 and December 2009, involved five EIS centres operating in Milan (Programma 2000), Rome (area D), Grosseto, Salerno (Nocera) and Catanzaro (Soverato). During the first trial period lasting 12 months, a total of 67 patients, of which 43 FEP and 24 Ultra High-Risk patients were enrolled (A. Cocchi, Balbi, et al., 2015).

The Psychosis Incident Cohort Outcome Study (PICOS) was a multisite naturalistic research study aimed to examine contributors to clinical and social outcomes in a cohort of FEP patients in contact with public mental health services in the Veneto Region (North Eastern Italy). During the indexed period (January 1st 2005 to December 31st 2007), 555 subjects were identified as potential eligible cases. Of those, 397 were assessed. Despite a throughout retrospective examination of EMRs showed that some sites did not refer all eligible patients, an estimated treated incidence rate of psychosis in the Region was reported as 18.8/100 000 a year (Lasalvia et al., 2012).

In Palermo, Southern Italy, 204 FEP participants, aged 18-65, were identified over a 3-year period. The crude incidence of all psychoses was 15.9 (95% CI 13.7-18.1). The risk of schizophrenia was higher in males compared to females and in migrants compared to native Italians (adjusted IRR= 4.02, 95% CI 2.39-6.75 (Mulè et al., 2017)). The higher rate of psychosis in migrants compared to natives was also reported by Tarricone et al. in the context of the Bologna first episode psychosis study, which included 187 patients, aged 18-64, who made contact with the Bologna West psychiatric services, between 2002 and 2010 (Tarricone et al., 2016). This study also reported an incidence of 16.4 per 100,000 for psychotic disorders diagnosed according to ICD 10 criteria, 7.3 per 100,000 for schizophrenia, 1.7 per 100,000 for affective psychoses, and 11.3 per 100,000 for other non-affective psychoses.

Preti and Miotto reported on first admission rates to Italian psychiatric wards of patients affected by schizophrenia, affective psychoses and other non-affective psychoses according to data published by the Italian National Institute for Statistics (ISTAT) in the health-

care statistics yearbooks(Preti & Miotto, 2000). Rates of schizophrenia ranged from 6 to 8.8 per 100,000 persons per year, rates of other non-affective psychoses ranged from 5.7 to 7.8 per 100,000 persons per year, and rates of affective psychoses from 3.3 to 8 per 100,000 persons per year. The above studies did not involve interviews to confirm diagnosis. More recently, reported the incidence data of the three participating sites from Italy were reported, as part of the EU-GEI study, a multicenter incidence and case-sibling control study of genetic and environmental determinants of psychotic disorders: specifically, the already mentioned Palermo city, part of Veneto region, and Bologna municipality(Jongsma et al., 2018). Service delivery and FEP service implementation was outside the goal of this study.

In a survey conducted during six conference between October 2012 and December 2013, several authors have warned of the difficulties of implementing and disseminating evidence-based interventions in Italy (Casacchia & Roncone, 2014). The most recent report about the implementation of EIP service in Italy reported that despite of the traditional focus of regional health care services on care provided through community mental health centres, there is evidences of limited development and implementation of EIP services in Italy (Csillag et al., 2017).

In this regard, **Chapter 3** describes the first report, in Italy, of 1) a treatment Program dedicated to first episode psychosis (FEP) and CHR which involves an entire region in Italy, Regione Emilia Romagna 2) its implementation in the province of Modena, within the context of a real-world public mental health services.

USA, the STEP-ED study. A population health approach to reduce duration of untreated psychosis

As the final report of the World Health Organization's Commission on Social Determinants of Health stated, "health is neither created nor maintained solely within the health sector"(World Health Organization Commission on Social Determinants of Health, 2008). Severe mental health disorders, especially psychosis, does not represent the exception. In order to reduce DUP and build effective EIS, we must take into account the social determinants of health, and the health disparities that can affect health outcomes. Psychosis can be framed as a public health problem (Malla & McGorry, 2019), therefore a public or

population health approach has to be employed. Population health (PH) is the goal of “achieving measurable improvements in the health of a defined population”(Kindig, Asada, & Booske, 2008). These determinants can have differential impacts on different subgroups, contributing to health disparities. For example, minority racial status and residence in a high crime neighborhood can lead to aversive pathways to care (e.g. via the criminal justice system), that if not addressed can contribute to poor engagement with FES and poorer outcomes.

FEP services can thus shape population outcomes, for example by reducing patients’ interactions with the criminal justice system. **Chapter 5** shows the results of the first RCT demonstrating a reduction up to 10 years of criminal justice convictions in a FEP population, compared to usual treatment in the community.

Gender is also a determinant of health, including mental health, thus FES need to tailor their outreach efforts and tailor the care delivered in order to improve FES for women. **Chapter 6** reviews the socio-demographic characteristics that limit the women’s access to FES care, including age, clinical presentation, and caregiving burden. Moreover, women have a gender-unique risk factors for psychosis onset and relapse, such as pregnancy, and female-specific adjunctive risk for breast and cervical cancer due to a reduce access to preventative services

As the interactions between social determinants and access to FES care are better understood, they can be leveraged as targets for specific interventions. The viewpoint in **Chapter 6** outlines possible strategies to reduce the inequalities in FES care based on gender. This is an example of FES service that embraces a population health framework. This approach provides FES the opportunity to step out of the clinic and engage in a fruitful conversation with local stakeholders, as many determinants (e.g. food insecurity, transportation, health insurance) are not within the capabilities of health clinic, including mental health facilities. Therefore, the outcome of FES should be determined by the “social valuation” of local stakeholders. This also means that the population health outcomes might vary from site to site in order to reflect local needs.

The population health framework acquires a very important role when we think about a young person manifesting the first signs of a severe mental illness like psychosis and his/her pathway to specialized care. The local actors play a detrimental role in shaping his/her experience of the illness and can impact the disease’s outcomes. This young person might

interact with different actors belonging to the local community and health care facilities: for example, the help-seeking individual could access the emergency services, or interact with the police because of disorganized and dangerous behavior (one of the phenotypes of an acute psychotic episode) therefore, it is necessary to expand the network of care beyond traditional clinical settings to include all who might be expected to facilitate pathways to and through FES. The goal is to facilitate access to FES and reduce the duration of untreated psychosis.

We can identify two sides of delay determining the duration of untreated psychosis: the 'demand' side (illness identification, attempts to access healthcare) and 'supply' side (diagnosis of psychosis, initiation of treatment and referral to a FES) of DUP (Srihari et al., 2014). On the demand side of DUP can be included all the actors, events and opportunities that emerge in the window of time that begins with the onset of frank psychosis and ends with contact at a healthcare provider or facility with the ability to initiate treatment and referral to best practice care. The supply side begins with such contact and ends with entry into best practice care or FES. Both delays in the *demand* and *supply* sides are implicated in prolonged DUP, need to be addressed, and show varying relative contributions across settings.

A FES that takes a Population Health approach to ED will need to decide on a target region and then consider how to intervene on these variables to shorten DUP. One way to begin is to consider who the relevant actors may be in the local network and in which measure they are contributing to delays. For example, long delays on the *demand side* may suggest that FEP individuals and their families are waiting too long to seek care. This may reflect a low degree of awareness in the community of the common signs and symptoms of psychosis. Information campaigns, such as those tested by the TIPS investigators (using media), were partly directed at this possibility (J. O. Johannessen et al., 2001). Such delays however, could also be due to the relative inaccessibility, or unattractiveness, of available care. Quick, flexible responses to requests for help, the ability to conduct assessments in familiar (homes, college campuses) or acute care (emergency rooms, inpatient units) settings and the lowering of structural barriers to care access (e.g. insurance coverage, age restrictions, transportation costs) are a few among many interventions that can have an impact. Furthermore, the initial actions undertaken by patients, caregivers, and the network of community resources (including non-health care providers, e.g. police, school) play a pivotal role in shaping the pathway to FES. In

a domino-like effect, the first help-seeking event defines the personal experience of the distressed patient within the healthcare system. While it has the potential to create a new supporting net for the help-seeker, the first such help-seeking event could also alter the outcomes of a potentially disabling illness like psychosis, during what has been defined as “the critical period” for changing its prognosis (M. Birchwood, Todd, & Jackson, 1998). In the exploratory study discussed in **Chapter 4**, we analyzed the first help-seeking attempts of individuals admitted to a specialty team-based psychosis service to investigate whether those seeking help before psychosis onset differed from those who sought help after psychosis onset in terms of sociodemographic and clinical characteristics, overall functioning, and occurrence of adverse events during their pathways to specialized care.

Aims of this thesis

Using data from different sources, an historical northern European cohort, an ongoing early detection campaign in New Haven (CT) USA, and a community-based department of mental health in Italy, this project aims to cover three unexplored areas regarding strategies to reduce duration of untreated psychosis (DUP), the interval between the first onset of psychosis, and the initiation of appropriate clinical treatment.

This project covers three distinct but intertwined unexplored aspects of research in this area, and provides some insight into the future direction for the field within a population health framework.

Chapter 2 shows how quantile regression was applied to analyze the differential impact of the seminal ED campaign (TIPS) across the DUP distribution. We hypothesized that the effectiveness of TIPS' ED campaign would vary across different quantiles of DUP. The secondary aim was to explore if this differential impact across DUP quantiles was moderated by demographic, clinical, premorbid and social factors.

Chapter 3 outlines the implementation of the first FEP service in Modena, Northern Italy, representing the country's first effort to provide consistent and comprehensive early intervention services across an entire region. We hypothesized that main source of referrals would be general practitioners, given the longstanding educational and coordinated efforts in providing them with diagnostic instruments to assess young people suffering from psychosis.

The exploratory study described in **Chapter 4** analyzed the first help-seeking attempts of individuals admitted to a specialty team-based psychosis service (STEP) to investigate whether those seeking help before psychosis onset differed from those who sought help after psychosis onset in terms of sociodemographic and clinical characteristics, overall functioning, and occurrence of adverse events during their pathways to specialized care.

Chapters 5 and 6 provide some insights into FES outcomes within a population health framework. **Chapter 5** reports the secondary analysis of a pragmatic randomized clinical trial of a FES vs usual treatment for criminal justice outcomes. **Chapter 6** outlines challenges and

possible solutions to tailor FES services around women's gender-specific care needs. **Chapter 7** audits prescription practice in FEP in eight inpatient units in Hunan Province, China.

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CHAPTER 2

PARSING THE IMPACT OF EARLY DETECTION ON DURATION OF UNTREATED PSYCHOSIS (DUP): APPLYING QUANTILE REGRESSION TO DATA FROM THE SCANDINAVIAN TIPS STUDY

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Abstract

Background

Prolonged duration of untreated psychosis (DUP) is associated with poor outcomes. The TIPS study halved DUP with an early detection (ED) campaign; however, conventional statistical analyses, focused on mean estimates, failed to reveal the effects of ED across the full DUP distribution, restricting inferences about ED's effectiveness. Utilizing a novel quantile regression based analysis, we examined the differential impact of ED across DUP. Secondary analysis explored possible predictors of DUP, and moderators of the effect of the campaign.

Methods

The TIPS ED campaign was conducted in two health care sectors in Norway, with two equivalent health care sectors serving as controls. Quantile regression analysis was performed to analyze ED campaign's effect.

Results

281 patients with first episode psychosis were recruited, including 141 from the ED area. ED had no effect on the first quartile (Q1) of DUP, whereas a significant reduction in Q2 (11 weeks), and Q3 (41 weeks) of DUP was observed. The effect of ED was significantly stronger on reducing Q3 than Q1 or Q2, suggesting that the campaign was more effective in longer DUP samples. Male gender and single status predicted longer DUP in Q3: by 38 and 27 weeks, respectively. Single status, but not gender, emerged as a significant moderator of ED campaign effect.

Conclusions

Quantile regression provided in depth information about the non-uniformity, and moderators, of TIPS's ED effort across the full distribution of DUP, demonstrating the value of this analytic approach to re-examine prior, and plan analyses for future, early detection efforts.

Keywords: Psychosis; Early Detection; Schizophrenia; Early Intervention; Untreated Psychosis.

1. Introduction

The duration of untreated psychosis (DUP) refers to the period of time between the emergence of psychotic symptoms and initiation of appropriate clinical treatment (J. O. Johannessen et al., 2001; Melle et al., 2004). Prolonged DUP is consistently associated with poorer outcomes, including: more severe general, positive and negative symptoms at clinical presentation; reduced likelihood of remission; poorer social functioning; and global outcome (Penttilä et al., 2014). This observational evidence has prompted several tests of strategies to reduce DUP (Lloyd-Evans et al., 2011; Srihari et al., 2014), and early detection (ED) has emerged as a key priority for mental health services (L. B. Dixon, Goldman, Srihari, & Kane, 2018).

The Treatment and Intervention in Psychosis (TIPS) study was designed to test an approach to DUP reduction, and to study the effects of this reduction on the course and outcome of psychotic disorders (Hegelstad et al., 2012). The TIPS ED intervention included an intensive information campaign integrated with early detection teams that provided community-based assessment to enable rapid access to care, across two healthcare sectors in Norway. TIPS ED was able to halve DUP compared to two control sites (in Norway and Denmark) that provided equivalent care but without the ED intervention (median, 5 weeks [range, 0-1196 weeks] vs. 16 weeks [range, 0-966 weeks]) (Larsen et al., 2001; Melle et al., 2004). This study also demonstrated a prognostic link between the timing of care and outcomes: at 10 year follow up, a significantly higher percentage of patients from ED sites had recovered i.e. achieved defined standards of symptom remission and social and role functioning (Hegelstad et al., 2012; Joa et al., 2007; Larsen et al., 2011; Melle et al., 2006; Ten Velden Hegelstad et al., 2013).

These results imply that early detection can confer a significant and lasting advantage for patients with psychotic disorders. However, the differential effectiveness of ED campaigns in reducing delay across the spectrum of DUP has not yet been examined. This leaves open the question of ‘what works for whom’ in terms of shortening a prognostically important variable. Also, separate from its potential impact on treatment outcome, the time between onset of frank psychosis and entry into stable clinical care can be a period of ‘destructive chaos’(McGlashan, 1999) with significant distress in the young person and family, elevated risk for impulsive self-harm and aggression, and potentially catastrophic social losses, including incarceration, and the loss of employment, college placement or relationships. Understanding better which subgroups benefit from ED is necessary to refine such efforts, and further minimize suffering and disability.

Previously, we demonstrated that quantile regression (QR) can both manage skewed distributions and allow analysis for meaningful heterogeneity in DUP(Guloksuz et al., 2016). Unlike ordinary least-squares regression, which focuses on the conditional mean response, QR can estimate the heterogeneous effects of predictors (e.g., age, sex, education, or ED) across different quantiles of outcome (DUP), rather than presuming a uniform mean effect. Furthermore, unlike linear regression that relies on a normality assumption, QR can provide more accurate estimates in samples with extreme outliers, as is common in DUP distributions.

The current study aims to leverage quantile regression to analyze the impact of a seminal ED campaign, across the DUP distribution. Data is drawn from the first experimental approach to demonstrate DUP reduction: the Scandinavian Treatment and Intervention in Psychosis (TIPS) study (Melle et al., 2004). We hypothesized that the effectiveness of TIPS’

ED campaign would vary across different quantiles of DUP. The secondary aim of this analysis is to explore if this differential impact across DUP quantiles is moderated by demographic, clinical, premorbid and social factors.

2. Method

2.1. Design of The Treatment and Intervention in Psychosis (TIPS) Study

The TIPS study was a prospective clinical trial which included three first-episode psychosis centers across four Scandinavian healthcare sectors: Rogaland County, Norway, Ulleval sector, Oslo, Norway and Roskilde county, Denmark (Joa et al., 2008). The Rogaland sector was the experimental site, having developed an early detection (ED) system to reduce DUP in a catchment area of 370,000 inhabitants. The TIPS project established a comprehensive, multi-level, information, education and service delivery system which began on January 1st, 1997 and ended on December 31, 2000. Ulleval and Roskilde were the control sectors, with a combined total of 295,000 inhabitants. Here, ED campaign was not implemented, and they relied on usual detection and referral systems for first episode cases. The populations of the health care sectors showed comparable characteristics regarding age and sex distribution, main income levels and unemployment rates. Participants from the ED area were less likely to be immigrants from a non-western country (4% vs 12%), to be educated beyond high school (21% vs 31%), and live in urban areas (84 vs 96%)(Melle et al., 2004). The incidence of schizophrenia for Rogaland county was estimated to be 5.5/100,000 in 1982-1983(Jan Olav Johannessen, 1985). As expected, since the campaign promoted a lower threshold for help seeking, the number of persons undergoing screening was higher in the ED area, but those who were eligible for the study were fewer (186 [50/100,000] vs 194

[66/100,000] in the No-ED area). Incidence varied across the years and within the two areas: this may have been due to natural variation in the base rate of relatively rare disorders, or the higher degree of urbanization in the No-ED area compared to the ED area(Melle et al., 2004).

The ED intervention consisted of messaging about recognition and treatment for psychotic symptoms that targeted the general population via newspaper advertisements, and schools and general practitioners via outreach. Specialized low threshold early detection teams could be activated by a single phone call from potential patients, families, or friends. These teams responded with rapid assessments in community settings, and facilitated transfer to specialized treatment teams. Inclusion criteria and assessments are detailed elsewhere(Melle et al., 2008).

2.2. Definition of Duration of Untreated Psychosis

DUP was determined at study entry from all available information, including semi-structured interviews with patients and relatives, and medical records. DUP was defined as the time, in weeks, from psychosis onset to the start of adequate treatment. Onset of psychosis was equated with the first appearance of positive psychotic symptoms, defined as the first week with symptoms corresponding to a Positive and Negative Syndrome Scale (PANSS) score of 4 or more on at least one of the positive subscale items 1 (delusions), 3 (hallucinatory behavior), 5 (grandiosity), or 6 (suspiciousness/persecution) or general subscale item 9 (unusual thought content). Adequate treatment was defined as a structured course of antipsychotic medications or hospitalization in highly staffed psychiatric wards organized to manage disturbing psychotic symptoms(Melle et al., 2004). A few non-

hospitalized patients enrolled in outpatient psychotherapy that was structured and directed towards psychosis, but declined antipsychotic medication. For these patients, the initiation of such psychotherapy was coded as the start of adequate treatment (Simonsen et al., 2010). For the rare cases with prior brief and self-remitting psychotic episodes, the lengths of these episodes were included in the DUP estimate.

2.3. Statistical analysis

Demographic, social and clinical characteristics of enrolled patients were compared across ED and no-ED areas. Quantile Regression (QR) was used to model the relationship between various independent variables and conditional quantiles of response. The impact of ED was examined across the full range of DUP, and particular effects on Q1, Q2 and Q3 are presented. We further examined the statistical significance of the heterogeneity of ED's effect on DUP using the Wald test (Koenker & Bassett, 1978), which provides a χ^2 statistic with degrees of freedom, and p values for tests of differences. We conducted secondary analyses to evaluate baseline predictors of DUP quartiles, as well as moderators of ED effects across quartiles using interaction terms in the QR model. Sociodemographic terms included: age, gender, marital status (single vs. other, including: separated/divorced/living with partner/married), family contacts (from 1=never, to 5=daily) (Simonsen et al., 2007), and objective financial adequacy as measured by the Lehman Quality of Life Interview (L-QoLI) (Melle et al., 2005). Clinical variables included: presence of core schizophrenia-spectrum diagnoses and premorbid functioning, measured with the Premorbid Adjustment Scale (PAS). PAS scores were divided into two domains: Academic and Social, each categorized as good, intermediate or poor (initial level) and whether the course was stable or deteriorating (change) (Larsen et al., 2004). Also, global psychopathology was assessed

with the PANSS total score and subscales (positive symptoms, negative symptoms, general symptoms), and overall functioning was evaluated with the Global Assessment of Functioning (GAF) scale, that provided GAF symptom and GAF function scores(Joa et al., 2008; Pedersen & Karterud, 2012).

SAS 9.4 (Cary, NC) was used for all statistical analyses(SAS Institute., 2017). The statistical significance level was set at $p < 0.05$, two-sided.

3. Results

3.1. Baseline characteristic of the sample

Altogether, 281 patients were included, 141 belonging to the early detection (ED) area. Compared to residents of no-ED areas, ED exposed samples were younger (mean age 26 vs. 31; $P < 0.0001$). The two groups showed no difference with respect to affective vs. non-affective psychosis diagnoses; however, participants coming from the ED area presented with significantly lower psychopathological symptom severity and better global functioning(Melle et al., 2004), as detailed in Table 1 and previously reported(Melle et al., 2004).

Table 1

Differences of baseline characteristics between participants coming from the Early Detection (ED) and the No-ED area.

	No-ED (n=140)	ED (n=141)	p value
Age at study entrance, Mean(SD)	31.1(10.5)	26.2(7.6)	<.0001
Gender, male	79(56.4%)	87(61.7%)	0.37
Marital status, single ^a	88(62.9%)	109(77.3%)	0.008
DUP weeks, median [IQ]	16 [3,66]	5 [2,26]	
mean (SD)	56.5(118.3)	41.6(122.8)	0.30
Diagnostic distribution			0.15
Schizophrenia	41(29.3%)	39(27.7%)	
Schizophreniform disorder	30(21.4%)	31(22.0%)	
Schizoaffective disorder	12(8.6%)	22(15.6%)	
Affective psychosis	21(15.0%)	19(13.5%)	
Delusional disorder	9(6.4%)	6(4.3%)	
Brief Psychotic Episode	6(4.3%)	13(9.2%)	
Psychosis NOS	21(15.0%)	11(7.8%)	
Narrow schizophrenia spectrum diagnosis	83(59.3%)	92(65.2%)	0.30
GAF_function, mean (SD)	28.76(9.72)	33.63(10.01)	<.0001
GAF_symptom, mean (SD)	27.13(6.88)	30.96(6.36)	<.0001
PANSS score, mean (SD)			
PANSS_total_score	76.80(19.68)	64.28(13.46)	<.0001
PANSS_negative scale	16.64(7.47)	13.86(5.70)	0.0005
PANSS_positive scale	21.66(5.64)	18.81(4.93)	<.0001
PANSS_general scale	38.42(10.38)	31.57(7.64)	<.0001
PAS score, mean (SD)			
PAS social level change	0.78 (1.30)	0.89(1.57)	0.54
PAS academic level change	0.52(1.29)	0.65(1.22)	0.40
PAS_social_cluster			0.82
missing	4(.%)	4(.%)	.
Good Stable	61(44.9%)	64(46.7%)	.
Intermediate Stable	26(19.1%)	23(16.8%)	.

3.2. Differential impact of ED campaign on DUP

Figures 1A and 1B display the differential impact of ED campaign between ED and No-ED samples across the entire distribution of DUP. In the No-ED sample, Q1=3 weeks, Q2(median)=16 weeks and Q3=66 weeks. Within the ED sample, Q1=1.5 weeks,

Q2(median)=5 weeks and Q3=26 weeks. The widths of the 95% confidence interval bands differ across quantiles, illustrating the advantage of QR in revealing the heterogeneous effects on different quantiles in contrast to traditional analyses that assume homogenous effect across the entire distribution of the outcome. In addition, Figure 1B shows that the upper band of 95% CI at Q2 and Q3 are away from 0 effect, respectively -4.6 weeks for Q2, and -10.4 weeks for Q3.

As outlined in Table 2, QR analysis revealed that ED had no discernible effect on DUP in the first quartile (Q1), but engendered a significant reduction in the second quartile (Q2 or median: 11 weeks reduction, 95% CI -17.4 to -4.6, $P=.0008$), and the third quartile (Q3: 41 weeks reduction, 95% CI -71.6 to -10.4, $P=.009$). Moreover, the effect of ED was significantly stronger in Q3 vs. Q1 ($P=.009$), Q3 vs Q2 ($P=0.03$) and Q2 vs. Q1 ($P=.006$), suggesting that the effect of ED was stronger for longer DUPs.

Table 2
Differential effect of early detection (ED) campaign on quartiles of the Duration of Untreated Psychosis (DUP) (in weeks) in the whole sample.

Quartile	Duration of Untreated Psychosis (weeks)		P value (compared to Q1)	P value (compared to Q2- median)
	ED-No-ED: Difference (95% CI)	P value		
Q1 (25%)	-1.5 (-3.7, 0.7)	0.18	-	-
Q2-Median (50%)	-11.0 (-17.4, -4.6)	0.0008	0.0006	-
Q3 (75%)	-41.0 (-71.6, -10.4)	0.009	0.009	0.03

Q1, 2, 3=Quartiles of Duration of Untreated Psychosis (DUP).

Table 3
Results of predictors of Duration of Untreated Psychosis (DUP) quartiles in the whole sample. Male and single status are associated with both lower median and Q3 of duration of untreated psychosis (DUP). Comparisons of the different effect of the predictor within quartiles are also reported.

	DUP Quartile	DUP Difference weeks (95% CI)	P value	P value (compared to Q1)	P value (compared to Q2)
Gender, (Male < Female)	Q1 (25%)	-2 (-3.5, -0.5)	0.009	-	-
	Median (50%)	-7 (-13.2, -0.79)	0.03	0.07	-
	Q3 (75%)	-38.0 (-68.0, -8.0)	0.01	0.02	0.02
Marital status*, (Single < Nonsingle)	Q1 (25%)	-1 (-2.3, 0.3)	0.12	-	-
	Median (50%)	-4.9 (-11.2, 1.4)	0.13	0.18	-
	Q3 (75%)	-27.0 (-53.7, -0.3)	0.048	0.05	0.06

* Non-single group includes married, separated, divorced, widowed.

3.3. Predictors of DUP

We evaluated potential associations between baseline characteristics and DUP quartiles. Male gender was associated with longer DUP (Table S1), and in the higher quartiles: males endured a DUP that was 7 weeks longer in Q2 (95% CI -13.2 to -0.79, $P=.03$) and 38 weeks longer in Q3 (95% CI -68 to -8, $P=.01$) (Table 3). Also, single participants had a DUP 27 weeks longer in Q3 (96% CI -53.7 to 0.3, $P=.04$).

We also explored associations between clinical variables and DUP quartiles (supplemental material, Table S2): higher initial PAS academic level scores (or worse premorbid academic functioning) or having a narrow schizophrenia spectrum diagnosis was associated with longer DUP across all quartiles; higher scores in PANNS total and general symptoms subscales at clinical presentation (or higher symptom severity) was associated with a slightly longer DUP across the upper quartiles. Higher baseline GAF symptom and function scores were associated with longer DUP in the lower and median quartiles.

3.4. Moderators of ED effect on DUP

Moderation effects of gender on ED efficacy were evaluated after controlling for age and marital status. After splitting the sample by gender, a statistically significant reduction of DUP was observed only for male participants in Q3 (-48.1, 96% CI -90.5 to -5.6, $P=.03$) in the ED vs. no-ED areas (Table 4). The distribution of DUP is detailed in Table S3. A large difference of 43.3 weeks in the reduction of DUP in Q3 between males and females did not reach the conventional threshold for statistical significance.

Moderation effects of marital status on ED efficacy were evaluated after controlling for age and gender. After splitting the sample by marital status, a statistically significant reduction of DUP was observed only for singles in Q3 (difference at Q3=-48.2 weeks; 95% CI -79.7 to -16.7, $P=.003$) (Table 4). The distribution of DUP is detailed in Table S3. The difference of the effect of ED among singles in Q3 differed statistically from the effect among non-single (difference in DUP effect=-50.3 weeks; 95% CI -93.3 to -7.3, $P=.02$). Thus, singlehood was a significant moderator of ED's impact on the longest extreme of the DUP distribution.

DUP Quartile	ED campaign effect among males	ED campaign effect among females	Difference
Q1 (25%)	-4 (-8.5, 0.5) $P=0.08$	0 (-1.9, 1.9) $P=1.00$	-4.0 (-8, 0.9) $P=0.11$
Median (50%)	-17.1 (-35.4, 1.2) $P=0.07$	-5.1 (-13.5, 3.26) $P=0.23$	-12.0 (-32.0, 8.0) $P=0.24$
Q3 (75%)	-48.1 (-90.5, -5.6) $P=0.03$	-4.8 (-30.4, 20.9) $P=0.71$	-43.3 (-92.8, 6.23) $P=0.09$
DUP Quartile	ED campaign effect among single	ED campaign effect among non-single ^c	Difference
Q1 (25%)	-3.6 (-8.2, 1.0) $P=0.12$	-1.0 (-3.2, 1.2) $P=0.37$	-2.6 (-7.6, 2.5) $P=0.32$
Median (50%)	-14.3 (-30.5, 1.8) $P=0.08$	-1.0 (-8.7, 6.7) $P=0.80$	-13.3 (-31.1, 4.5) $P=0.14$
Q3 (75%)	-48.2 (-79.7, -16.7) $P=0.003$	2.1 (-27.2, 31.3) $P=0.89$	-50.3 (-93.3, -7.3) $P=0.02$

^a adjusted for age and marital status.
^b adjusted for age and gender.
^c Non-single group includes married, separated, divorced, widowed. DUP is measured in weeks.

Additional exploratory analyses were performed to detect other clinical and social moderators of the effect of the ED campaign across quartiles of DUP, after controlling for age, gender and single status (Table 5). Higher objective financial adequacy was associated with longer DUP in the lowest quartile of the ED cohort (2 weeks increase, $P=.04$), but had no impact in other quartiles. The effect of ED in Q1 of DUP was greater with increasing

episodes of arrest by police. Each adjunctive episode of arrest was associated with more DUP reduction only in Q1 (12.3 weeks, $P=.047$). A more severe clinical presentation, being diagnosed with a narrow schizophrenia spectrum diagnosis, and premorbid functioning (both social and academic) were not moderators of ED across the DUP quartiles. Number of family contacts also did not moderate ED effects across DUP quartiles.

Table 5
Exploring other possible clinical and environmental moderators of the ED campaign effect (reduction of DUP), across DUP quartiles, after controlling for age, gender and single status. The effect modification is presented here with its 95% confidence interval as extent of increase (positive values) or decrease (negative values) in DUP (measured in weeks) in the ED cohort, per every unit increase in moderator.

Moderators	Effect modification at Q1 (95% CI)	P value	Effect modification at Q2 (95% CI)	P value	Effect modification at Q3 (95% CI)	P value
Narrow schizophrenia spectrum diagnosis (Yes vs. No)	-1.0 (-6.3, 4.3)	0.71	-11.3 (-27.5, 5.0)	0.17	-23.4 (-75.2, 28.3)	0.37
PAS social level childhood	-0.2 (-2.4, 1.9)	0.84	3.7 (-4.9, 12.2)	0.40	-3.0 (-39.4, 33.3)	0.87
PAS academic level childhood	-1.0 (-2.5, 0.5)	0.19	-2.7 (-8.6, 3.3)	0.38	-8.7 (-29.0, 11.7)	0.40
PAS academic level change	-1.9 (-4.3, 0.5)	0.12	-3.8 (-12.8, 5.1)	0.40	-7.0 (-42.1, 28.0)	0.69
GAF_symptom	-0.8 (-2.5, 0.9)	0.33	-0.5 (-5.7, 4.7)	0.84	4.5 (-10.2, 19.1)	0.55
GAF_function	-0.2 (-0.5, 0.1)	0.18	-0.5 (-1.6, 0.6)	0.38	-0.7 (-3.7, 2.3)	0.67
Number of family contacts	-0.2 (-0.4, 0.1)	0.18	-0.3 (-0.9, 0.4)	0.46	-0.3 (-2.6, 2.1)	0.83
Objective financial adequacy	1.0 (-0.8, 2.8)	0.27	3.1 (-2.0, 8.2)	0.23	6.3 (-14.9, 27.5)	0.56
Episodes of arrest by police	2.0 (0.1, 3.8)	0.04	2.2 (-2.6, 7.0)	0.36	5.3 (-15.5, 26.1)	0.62
	-12.3 (-24.4, 0.1)	0.047	-6.7 (-15.7, 2.3)	0.14	-53 (-187.1, 81.1)	0.44

Note: DUP = Duration of Untreated Psychosis. Q 1,2,3 = DUP quartiles 1, 2, 3. PANNS = The Positive and Negative Syndrome Scale. CI= Confidence Interval.

4. Discussion

This is the first study to interrogate the differential impact of an early detection intervention across a full DUP distribution. As hypothesized, we were able to show that TIPS' successful ED campaign did not have a uniform effect. DUP reduction appeared to follow a graded response: not observed in those with short DUP, with significant effects of increasing magnitude in the second (11 weeks reduction) and third quartiles (41 weeks reduction). TIPS' previously reported success in reducing DUP thus appears largely due to effects in the longer tail of the DUP distribution. Hence, a vulnerable subgroup i.e., those suffering the greatest delays in accessing care for the distressing and potentially life-disrupting symptoms of psychosis, benefited the most from this ED effort. This is a reassuring inference about the potential public health impact of such campaigns. Also, the use of Quantile Regression (QR), to parse the impact of early detection, offers additional useful insights (outlined below) and should be considered in the design of future campaigns.

The distribution of DUP in the whole sample showed significant sociodemographic differences: TIPS recruited men, and singles (across genders) with significantly longer DUP in the upper tail of the distribution (Q3). When dividing the sample by gender, DUP was found to be significantly reduced by ED only in men in Q3 (by 48.1 weeks). However, gender was not found to be a significant moderator of EDs greater impact on longer DUPs. These results add to the mixed findings about the role of gender in affecting the length of DUP (Cascio, Cella, Preti, Meneghelli, & Cocchi, 2012). However, the lack of statistically significant DUP reduction in women merits further consideration: it is possible that the messaging and media channels used by the TIPS campaign were more accessible to men than women, or that the campaign reached the targeted female audience, but stigma or other barriers to accessing treatment were differentially greater for women. Qualitative studies have suggested obstacles unique to women seeking FEP treatment: e.g. the threat of loss of child custody, and gender stereotypes (e.g. being labelled as “overdramatic”) (Chernomas et al., 2017; Diaz-Caneja & Johnson, 2004; Hagen & Nixon, 2011). While these and other gender specific factors are expected to vary across cultures and regions, such interrogations of prior DUP data across the distribution can inform ED campaigns and FEP services e.g., to reinforce the value of their parenting role, target psychosis onset that could emerge in the context of childbirth, and to offer multi-disciplinary services that can meet many needs at one site (Chernomas et al., 2017).

A more reassuring interpretation of the gender disparity disfavoring women in ED effectiveness is a possible floor effect. Men in the ED area showed similar (median) or even longer (Q1 and Q3) DUP compared to women in the No-ED area, suggesting the need to focus on barriers specific to men. While the data on greater reduction of DUP in men

suggests that these barriers are modifiable to a significant degree, there is clearly more ground to cover to catch up with female enrollees in first episode care. Overall, these data support tailoring of ED campaigns toward assessing and responding to the specific needs of each gender.

Marital status played an important role in the effect of ED. Single patients tended to have longer DUPs and also benefited the most in terms of size of DUP reduction in the longest quartile. Singlehood also positively moderated DUP reduction in this quartile, adding a new and unexpected finding to a recent meta-analysis on factors influencing the effect of DUP reduction interventions (Oliver et al., 2018). More frequent family contacts were observed in participants coming from the ED area, however number of family contacts did not seem to moderate the effect of TIPS ED on DUP quartiles. Factors such as living with someone, and proactive social networks (Peralta, Cuesta, Martinez-Larrea, Serrano, & Langarica, 2005) have been reported, in other samples, to play a significant role in accelerating access to care for a target population that is young and often unmarried. While this makes the longer DUPs in the single sample here unsurprising, the selectively greater impact of TIPS ED on this subgroup is a welcome finding. The moderator analyses did not show significant effects for narrow schizophrenia diagnosis, and other clinical and premorbid variables across the DUP quartiles. However, the exploratory nature of this post-hoc analysis of DUP suggests caution in over-interpreting positive or negative effects.

This analysis demonstrates the utility of quantile regression to reveal meaningful differential effects of an ED campaign across an entire DUP distribution. First, the magnitude of differences in delays to care in the upper vs. lower quartiles of DUP would be recognized by most clinicians and caregivers as important. Second, subsets of participants, because of gender or marital status, appeared to have been less responsive to this campaign, offering a

basis to refine ongoing or future campaigns. Third, the majority of ED efforts have reported a lack of overall change in DUP(Lloyd-Evans et al., 2011). The analysis modeled here might recover more granular information on positive impacts on portions of the DUP distribution across subgroups that may support continuation and refinement of valuable efforts that would otherwise be deemed unsuccessful.

Additionally, such subgrouping can be helpful for future ED campaigns that are able to use social media channels to target messaging in ways that were unavailable during the TIPS study. There is increasing use of the internet and social media(Kemp, 2019), in particular amongst teens(M. Anderson, Jiang, J., 2018), and there is growing evidence that young people affected by psychosis use social media to obtain health information(Birnbaum, Candan, Libby, Pascucci, & Kane, 2016). The ability afforded by these digital media channels to iteratively adapt messaging, and target specific population segments can leverage QR-based identification of subgroups that are differentially responsive to ongoing ED efforts and enable more dynamic, ecologically responsive campaign designs(Srihari et al., 2014).

Our analysis did not find a significant effect of ED campaign in quartile 1 of DUP. Aside from a floor effect, another possibility might have to do with mode of onset: the shortest quartile may have included a greater proportion of individuals with rapidly escalating positive symptoms, that more quickly drew clinical attention regardless of the presence of an ED campaign.

Several cautions must be made in the interpretation of these results. As a post-hoc analysis, the findings are not definitive evidence but present plausible inferences from prior studies or more defensibly, hypotheses that can be built into the design of future studies of early detection(Srihari et al., 2014). Also, the lack of ability to detect a significant effect of ED in the shorter end of the DUP distribution (Q1=2 weeks) may have been related to the

use of weeks rather than days (M. Large et al., 2008) as a unit of measurement in the TIPS study.

4.1. Conclusion

QR revealed that, across the length of DUP, the effect of TIPS' ED intervention varied significantly. It also showed the potential to provide new information about clinical and social moderators across the length of DUP that could become crucial in targeting intervention for reducing the burden of disease in first episode of psychosis. Previous ED campaigns (Malla, Norman, Scholten, Manchanda, & McLean, 2005; McGorry et al., 1996) have not been as successful as TIPS in showing a significant effect across a median DUP on a population level. It is possible however, that a similar analysis across quartiles might reveal impact in some parts of the overall distribution. Conversely, campaigns that show overall success might use this approach to discover underserved subgroups. Further, the use of QR can help assess for moderators of these differential effects, and inform tailoring of future ED efforts.

Contributors

MF, FL, SG, CT, VS designed the analysis. MF and SB managed the literature searches. FL undertook the statistical analyses. MF wrote the first draft of the manuscript. TIPS investigators (SF, WVH, IJ, JOJ, IM, ES) contributed to the interpretation of the results. All authors contributed to, and approved, the final manuscript.

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CHAPTER 3

EARLY INTERVENTION SERVICE FOR FIRST EPISODE PSYCHOSIS IN MODENA, NORTHERN ITALY: THE FIRST HUNDRED CASES

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Abstract

Aim

To report on the development of an Early Intervention Service in Modena, Italy, with information relevant to the first hundred cases.

Methods

The 2-year Service was offered to people aged 18-35 with psychotic manifestations, within two years from psychosis onset/or naïve to antipsychotics, by teams placed within Community Mental Health Centers, according to a "specialist within generalist" model. Treatment included pharmacological consultation, psychoeducation, and social inclusion programs. Health of the Nation Outcome Scale was administered at baseline.

Results

One hundred cases accepted the treatment from March 1st, 2013 to December 31st, 2016. Of these, 71% were male with a median age of 23. 90% were diagnosed with non-affective psychosis, yielding an estimated treated incidence of 19.1/10⁵. General practitioners (GPs) represented the most frequent referrers to the program (38%), followed by referrals from acute general and psychiatric hospital units (22%), and self-referrals (14%). Meaningful clinical improvement was observed, six months after enrollment.

Conclusions

An early intervention service for psychosis was successfully implemented within existing community outpatient services. General practitioners represented the main referrals, providing some validation of the "specialist within generalist" model of care. A promising clinical improvement and trend of reduction in duration of untreated psychosis was found, supporting the variety of early detection efforts in the community. The high median age and lack of information about pathways to care underline possible barriers to access for younger patients. These findings will inform refinement of treatments and service models for the Region.

Key words: Community Mental Health Centers, Early Intervention, First Episode Psychosis, Psychotic Disorders, Service Implementation

Introduction

Psychotic disorders peak in incidence between late adolescence and early adulthood, the crucial period for building social capital and becoming an active citizen (Edwards, Harris, & Bapat, 2005). Inadequately treated distress and dysfunction during the first years after psychosis can thus lead to adverse long-term outcomes (Srihari, Shah, & Keshavan, 2012). Therefore, the implementation of psychiatric care tailored to this young population has been gaining much attention from the scientific community (M. Birchwood et al., 2013; A. Cocchi, Balbi, et al., 2015).

In Italy, psychiatric care is provided by 139 Departments of Mental Health (DMH), each one embedded in a Local Health Trust, which on average covers a catchment area of $\approx$ 270,000 inhabitants. Each of the 20 Italian Regions' administrations is responsible for the allocation of resources to the Local Health Trust, which has full economic accountability in planning, delivering, and managing services. The levels of care within each DMH include community-based mental health centers (CMHCs), inpatient units and rehabilitation facilities (Csillag et al., 2017; de Girolamo & Cozza, 2000). Following the National Plan for Actions in Mental Health (Ministero della Salute, 2013) that listed early intervention for psychosis as its priority target, 45 Early Intervention Services (EIS) for psychosis are currently operating within the public mental health care network. Although CMHCs are the fulcrum of public psychiatric care for adults, and for young adults too, therefore an ideal platform for early psychosis care, EIS are not homogeneously distributed (A. Cocchi, Cavicchini, et al., 2015): 79% are located in Northern and Central Italy, and 21% in Southern Italy. Also, these EIS deliver varied combinations of specialized care to patients at clinical high risk for psychosis, and/or with new onset psychosis (i.e. first-episode services, FES).

Since 2012, the Emilia Romagna region in Northern Italy has funded an early intervention initiative representing the country's first effort to provide consistent and comprehensive EIS across an entire region. Here, we report on the development and implementation of EIS (early detection and first-episode services) by the DMH in Modena, a province in Emilia Romagna.

2. Methods

2.1 Setting

In 1978, national policy reforms established a network of CMHCs to serve as hubs of psychiatric care for geographically-defined catchment areas between 50,000 and 150,000 inhabitants (Ferrannini et al., 2014). Mental health care in the province of Modena is provided by eight CMHCs, covering a catchment area of 2,688 square kilometers, with a population of 703,114 (1.2% of the Italian population) (Istituto Nazionale di Statistica Istat). In 2015, Modena DMH's mental health service staff for adult users consisted of 44 full time equivalent (FTE) mental health employees/100,000 inhabitants over 18 years old. Within those employees, there were 50 FTE psychiatrists working in the CMHCs, making it 8.5 psychiatrists/100,000 inhabitants over 18 years old; each psychiatrist was responsible for a mean caseload of 175 patients. People under the care of the CMHCs had a median age of 51 years, and the mean duration of psychiatric treatment was 6.3 years (SD 6.6).

2.2 Pathways to Care

CMHCs accept referrals from several sources including general hospital and emergency room, primary care, police, social services, and other mental health agencies

(e.g., inpatient units, and drug treatment services). Self-referrals are also possible; however, general practitioners are encouraged to act as a filter to determine the urgency of the consultation and to become engaged early in the patient's pathway to care (Curcetti C., 2005).

The initial assessment for eligibility criteria for EIS might take place either in the inpatient unit before discharge, at the designated CMHC, or at patient's home. This decision is made by the designated psychiatrist based upon collateral information provided by the referrer. Potential first episode psychosis (FEP) patients are given priority regardless of the severity of their clinical presentation, and assessed at CMHC within 48 hours from referral (vs. 15 days in standard care).

The EIS treatment is offered at CMHC to people who meet eligibility criteria (outlined in Figure 1 below). Once identified as FEP, the patient is assigned to a 'mini FES team' (mFES) and offered treatment as described below. If a FEP patient refuses clinical care, the mini team will coordinate with the referral and try to engage the person into treatment, according to the urgency of care needed.

Inclusion criteria:	
•	Presence of psychotic symptoms within two years from onset/or naïve to treatment with antipsychotic medications
•	ICD 9 Diagnosis of affective psychosis (295.34, 296.24, 296.44, 296.14, 296.54, 296.64) and non-affective psychosis (295.0-295.95, 299.9, 297, 298)
•	Age between 18–35 years
•	Resident in Modena Province
•	Fluency in Italian
Exclusion criteria:	
•	severe intellectual disability (IQ less than 50)
•	presence of symptoms of psychosis secondary to a medical condition or substance intoxication

2.3 Organization of First-Episode Services (FES)

FES in Modena DMH is organized as a “specialist within generalist” model (Ghio et al., 2012), meaning that FES are managed by a 'mini FES team' (mFES) that includes a designated psychiatrist and a specialized nurse or psychiatric rehabilitation therapist. The

mFES, usually reserved for long term patients who receive services from different social and health agencies, liaises with several other services available within the CMHC to personalize treatment.

A FES “hybrid” model was adopted for several reasons: i) to avoid the higher cost of staffing separate FES teams since there is comparatively low expected incidence in the Province (Gigantesco, Lega, Picardi, & Group, 2012) compared to other presenting disorders, ii) to keep with the long-term goal of integrating those practices within all CMHC teams, simultaneously educating as many mental health professionals as possible, iii) to enhance liaison with local General practitioners (GPs), facilitating referrals and greater patient engagement with the CMHC. Therefore, the presence of FES within each CMHC reinforces the proactive outreach mission of the service, eases access for local users, and can enhance social inclusion of patients in their own communities.

FES psychiatrists from CMHCs of the Modena province meet once a month with the aim to achieve clarity on assessment, and cohesiveness between CMHCs.

2.4 The Regione Emilia Romagna framework

The Modena FES operates according to recommendations elaborated in March 2013 by the Regional Health Administration and published in 2015 (Gruppo di lavoro Esordi Psicotici, 2016). These include two years of specialized treatment, followed by a transition to care as usual, delivered by the same mini team.

Clinical interventions run by the CMHC mFES include:

- Brief interview for eligibility that is carried out at the first access to mental health care facility by the assigned psychiatrist of the inpatient unit, or by the mFES at CMHC;
- First psychiatrist visit for diagnostic assessment and initial treatment planning;

- Psychiatric consultation: weekly clinical visit for the first 8 weeks, then monthly as in standard care. The assigned psychiatrist from the mFES provides the case formulation and individual psychoeducation, informed by biopsychosocial and stress-vulnerability models of relapse (M. Birchwood et al., 1989; Zubin & Spring, 1977), prescription of antipsychotic medications according to current guidelines (National Institute for Health and Care Excellence), and physical health monitoring based on local adaptation of a monitoring algorithm (Curtis, Newall, & Samaras, 2012; M. Ferrara, Mungai, F., Miselli, M., Shiers, D., Curtis, J., Starace, F., 2015);
- Individual psychotherapy, that can be performed by the mFES psychiatrist or the mFES psychiatric rehabilitation therapist, is based on a cognitive behavior therapy approach (Smith, 2003); it also includes supportive counselling, coping strategies, and stress-reduction techniques;
- Individual family psychoeducational sessions including information about psychosis, crisis prevention plans, problem solving and communication skills training;
- Consultation performed by the nurse, to assess individual needs and goals to promote the inclusion of the patient in the community, and for them to return to the most suitable educational or occupational role.

The rapidity and intensity of consultations, the immediate provision of a mini team, individual psychotherapy and family psychoeducation, are exclusively provided to FEP patients.

2.5 Measures

The diagnostic procedure consists of a comprehensive clinical assessment by the mini team. Clinical variables assessed for include: Duration of Untreated Psychosis (DUP)

and presence of personality disorders and/or substance abuse comorbidity. DUP was defined as the time interval from the first emergence of at least one positive psychotic symptom (hallucinations, delusions, disorganized thoughts, bizarre behavior) to the start of antipsychotic medication for treating psychosis (D. O. Perkins, Gu, Boteva, & Lieberman, 2005), which in most cases coincided with the access to public psychiatric services. Demographics collected in a computerized electronic record included age, gender, educational level, vocational status, proficiency in Italian and place of birth (which defined migrant status).

Clinical outcomes are evaluated using the Health of the Nation Outcome Scale – Mental Health Clustering Tool (HoNOS-MHCT) at baseline, and every 6 months after intake. The HoNOS scale has been widely adopted in early intervention programs in Italy (A. Cocchi, Balbi, et al., 2015; Preti et al., 2012).

2.6 Data extraction and statistical analysis

All users who presented to the eight FES teams in the Modena catchment area from March 1st 2013 to December 31st 2016 were included in the analysis. Data were gathered from the computerized charts program. It was not possible to retrieve information on people eligible for the program but who refused services, or those not offered the program (e.g. because of uncertainty about diagnosis). Moreover, accesses to ER, to private health facilities, or to health agencies outside Modena province were not available.

Descriptive analysis examined incidence rates based on the data extraction as described above.

Kruskal-Wallis test was used to compare mean values of DUP. Wilcoxon Mann-Whitney test

was used to compare continuous variables between two independent groups. Sensitivity to change was measured with the Wilcoxon rank sum test on HoNOS individual and total score from the assessment to the 6-month follow-up(Preti et al., 2012).

After checking for uniformity between single-year incidence rates using Brandt-Snedecor chi square, the annual average incidence rate per 100,000 inhabitant aged 18-35, was calculated with 95% confidence interval(Saracci, 1957). Data were analyzed using SAS Version 9.1. P values less than 0.05 were considered to be statistically significant.

RESULTS

The number of new cases accepting the program (n=100) yielded an estimated treated incidence of 19.1/10⁵. As detailed in Table 1 and 2, the majority were males (n=71, 71%), with a mean age at intake of 25.4 years (SD=5.8).

TABLE 1 Baseline characteristic of first-episode psychosis sample and referrals

	N	%
Age, y: mean (SD), median	25.4 (5.8), 23	25.4
Sex, male	71	71%
Migrant	27	27%
Marital status		
Single	84	84%
Married	9	9%
Divorced	2	2%
Missing	5	5%
Educational level		
Secondary school	47	47%
Diploma (high school)	39	39%
University (bachelor degree, master degree)	4	4%
Elementary school	2	2%
Missing	8	8%
Vocational status		
Unemployed	41	41%
Employed	25	25%
Student	23	23%
Missing	11	11%

Immigrants constituted 27% of the total sample and double the proportion for the province (12.9)(Istituto Nazionale di Statistica Istat). The vast majority (90%) of the sample was diagnosed with schizophrenia spectrum disorders. Within HoNOS subscales, the symptoms subscale score (including delusions and hallucinations) was the highest at baseline.

TABLE 2 Clinical characteristic of Modena user enrolled in a first episode psychosis (FEP) services

Clinical characteristic of FEP sample (n = 100)	N	%
Diagnosis		
Non affective disorders		
Schizophrenia 295.*	49	49%
Delusional disorder 297.*	12	12%
Psychosis NOS 298.*, 299.*	29	29%
Affective disorder		
Bipolar disorder 296.*	10	10%
Comorbidity		
Personality disorder diagnosis	15	15%
Substance use/abuse diagnosis	33	33%
DUP, months: mean (SD), median	8.2 (12.3), 4	
HoNOS total score (items 1-12) mean $\pm$ SD (median)	18.1 $\pm$ 6 (18)	
HoNOS subscales score at baseline mean $\pm$ SD (median)		
Behavioural problems_items 1-3	3.1 $\pm$ 2.1 (3)	
Cognitive/physical impairment_items 4-5	1.7 $\pm$ 1.6 (2)	
Symptoms problems_items 6-8	6.8 $\pm$ 2.4 (7)	
Environmental problems_items 9-12	6.3 $\pm$ 2.7 (7)	

Abbreviations: DUP, duration of untreated psychosis; HoNOS, Health of the Nation Outcome Scale.

TABLE 3 Sources of referral to EIS

Referral to EIS	N	%
Primary care provider n (%)	38	38%
Self-referrals	14	14%
Hospital	13	13%
Other health agencies	11	11%
General health facilities	11	11%
Acute psychiatric service (SPDC, SPOI, RTI)	9	9%
Local police enforcements	2	2%
Health agencies (outside Modena)	1	1%
Social work services	1	1%
Total	100	100%

Abbreviations: EIS, early intervention services; RTI, Residenza a Trattamento Intensivo: intensive residential treatment; SPDC, Servizio Psichiatrico Diagnosi e Cura (Acute inpatient unit, for voluntary and involuntary admission); SPOI, Servizio Psichiatrico Ospedaliero Intensivo (Inpatient Unit, Private Conventionate Hospital, only voluntary admission).

General practitioners (GPs) represented the most frequent referrers to the program (38%), as they were almost double the proportion of referrals from acute general and psychiatric hospital units, as reported in Table 3. Fourteen participants were self-referrals to the program. No differences in baseline HoNOS (total and subscales) scores were found across referrals from hospital (general and psychiatric), GP, and other referrals (Table 4).

TABLE 5 Change in total scores and individual HoNOS between baseline and 6-months assessment

	FEP 6-months patients (N = 74)	
	Mean change in score	Wilcoxon rank test
Behavioural problems	1.78	Z = -5.78, P < 0.0001
1. Aggressive and disruptive behaviour	1.00	Z = -6.17, P < 0.0001
2. Non-accidental injury	0.26	Z = -3.29, P < 0.001
3. Alcohol and (or) drug misuse	0.53	Z = -4.39, P < 0.0001
Impairments problems	0.51	Z = -2.32, P < 0.05
4. Cognitive and (or) scholastic problems	0.55	Z = -3.39, P < 0.001
5. Physical illness or disability problems	-0.04	Z = 0.31, NS
Symptoms problems	2.72	Z = -5.93, P < 0.0001
6. Hallucinations and (or) delusions	1.64	Z = -6.72, P < 0.0001
7. Depressed mood	0.38	Z = -3.01, P < 0.005
8. Emotional problems and other related symptoms	0.70	Z = -4.72, P < 0.0001
Social problems	1.49	Z = -3.68, P < 0.001
9. Problems with relationships	0.59	Z = -5.51, P < 0.0001
10. Activities of daily living and (or) self-care	0.91	Z = -5.75, P < 0.0001
11. Living conditions and (or) family life	0.09	Z = -1.19, NS
12. Occupation and (or) school attendance	-0.11	Z = 0.57, NS
HoNOS total	6.50	Z = -5.99, P < 0.0001

FEP, first episode psychosis; HoNOS, HoNOS, Health of the Nation Outcome Scale.

TABLE 4 Health of the Nation Outcome Scale (HoNOS) (total and subscale) scores at baseline, according to source of referral to FES

Baseline HoNOS score	Referral			P-value*
	Hospital units	General practitioners	Other	
Behavioural problems subscale	3.8	2.5	3.0	0.09
Cognitive/physical impairment subscale	2.1	1.5	1.7	0.54
Symptoms problem subscale	7.4	6.3	6.9	0.10
Environmental problem subscale	7.1	6.8	6.2	0.46
HoNOS total score	20.4	17.0	17.8	0.09

Abbreviation: FES, first-episode services.
*Kruskal-Wallis non-parametric test.

Clinical outcomes after 6 months of treatment were available for 74 patients, of the remainder: five were discharged from the program as their primary diagnosis was revised, ten patients dropped out, and assessments were not collected for 11 patients. The 26 patients excluded from this analysis did not differ from those included with respect to demographic, while their HoNOS total and social problem scores were higher, respectively (20.3 (SD=5.8) vs 17.3 (SD=5.9), $p < 0.05$; and 7.9 (SD=3.1) vs 6.1 (SD=2.7), $p < 0.05$). HoNOS showed a significant reduction in 9 out of 12 of the individual score, as shown in Table 5.

The estimated duration of untreated psychosis (DUP), obtained from 99% of the total sample, was 4 months (median, interquartile range 1-10 months). In the post-hoc analysis, DUP showed a trend reduction over the study time (Table 6).

Discussion

This report establishes the feasibility of a provincial implementation of comprehensive early intervention services in Northern Italy. Modena's Mental Health Department was able to engage 100 patients diagnosed with a first episode of psychosis into care, between 2013 and 2016. Within the catchment area, the annual incidence of first episode psychosis slightly exceeded the expected estimate drawn from published reports (Gigantesco et al., 2012; Lasalvia et al., 2012), suggesting success in enabling access to care.

Several findings are worthy of comment and offer lessons for ongoing implementation efforts. The recruited sample is worthy of comment. First, the rate of affective psychosis was lower than expected. It is possible that the age limit of our program excluded subjects with a delayed onset of bipolar disorder, or that clinical presentation of mood disorders was masked by predominant non-psychotic symptomatology (Phillips &

Kupfer, 2013) complicating the differential diagnosis. Second, the proportion of migrants in our FEP sample was double that in the general population of the

TABLE 6 Comparison of the distribution of duration of untreated psychosis (DUP) from 1 March 2013 to 31 December 2016 for patients enrolled in the early intervention program in Modena

Year	DUP months, mean $\pm$ SD	DUP months, median	P-value*
2013	13.0 $\pm$ 16.8	6	0.15
2014	7.6 $\pm$ 12.9	3	
2015	6.0 $\pm$ 10.9	3	
2016	6.9 $\pm$ 9.0	4	

*Kruskal-Wallis non-parametric test.

catchment area, but consistent with reports from FES in the neighboring provinces of Bologna (Tarricone et al., 2014) and Verona (Lasalvia et al., 2014). While this is reassuring in terms of acceptability of services to immigrant users and their families, this highlights the

necessity to tailor culturally appropriate services for these communities. Third, the high rate of comorbid substance use at intake highlights the need to resource treatments for substance use disorders.

Some remarks can also be made about pathways to care. General practitioners (GPs) represented a high proportion of referrals. This provides some validation of the “specialist within generalist” model of care within each CMHC (Ghio et al., 2012). Also, this results can also be considered one of the accomplishments of the longstanding regional *Leggieri* Project, (named after a local GP) that has facilitated closer collaboration between general practitioners and psychiatrists, through the adoption of a stepped-care model of delivering treatment for a variety of mental illnesses (Curcetti C., 2005).

The proportion of self-referrals (14%) is consistent with a prior Italian FEP sample (Del Vecchio et al., 2015) (17.6%), but lower compared to the neighboring city of Bologna (26.7%) (Tarricone et al., 2016). This evidence signals the need to implement programs which encourage the younger population to have a more active role in help-seeking and treatment decisions. The median age of the sample could also indicate the resistance from the younger population to access directly to CMHCs. Those results outline the risk that this model of delivering FES misses the goal to reach the younger population that needs those services the most (De Girolamo, Dagani, Purcell, Cocchi, & McGorry, 2012). One possible reason is that we excluded, by design, subjects younger than 18 years old. Furthermore, younger patients could be intimidated by walking into a historically stigmatized place (Tanskanen et al., 2011) like the CMHC, where most users are older and long term. There is the need to close the gap between adolescent mental health and adult by promoting smooth access pathways into services, creating joined teams (Behan, Masterson, & Clarke, 2017; Raballo, Poletti, & McGorry, 2017), and offering consultations for first-onset

users in locations different from the CMHC (such as Community Health Centers(Odone, 2016)).

While these should be considered only preliminary results of a two-year program, promising clinical improvements were observed after six months into treatment (as measured by the HONOS scale), especially for those areas more responsive to psychopharmacological treatment: behavioral problems, psychotic and mood symptoms.

Modena DMH did not conduct comprehensive outreach to all possible referral sources. However, since 2013, general practitioners have received specific training about the Program. Moreover, a large community event for raising awareness on the importance of mental health is held annually since 2011. This is hosted with local healthcare organizations, community stakeholders, service users and their families, and includes workshops, seminars on FEP and artistic activities. Therefore, the trend in DUP reduction is a positive signal of the early detection strategies adopted, but what works for whom in terms of DUP reduction should be tested in future studies.

This study has several limitations. The sample size limit inferences about the impact of the EIS on measures of access to care (referral sources, DUP). Additionally, while informative on population needs, the recruited sample may not be representative of other provinces within the region or other regions. However, the minimal cost of included assessments combined with a clearly feasible service implementation offers a blueprint for EIS in other catchments in Italy (e.g. other provincial programs). We acknowledge that the collection of a limited set of variables might be useful in characterizing the sample studied, but this is not the same for correlating the impact of EIS Program on engagement into treatment and on clinical outcomes. Nevertheless, we consider this study an important preliminary set of data that could help foster a conversation between relevant local

stakeholders, family and users' organizations, and mental health professionals. The goal will be to set explicit shared objectives linked to patient-centered outcome measures that can be audited against national or international standards(Srihari, Jani, & Gray, 2016).

Results obtained from this study have led the local team to reconsider practices and plan new ones. The higher than expected treated incidence of first episode psychosis cases in the province raises sustainability challenges, with additions to the already high caseload of the lead psychiatrists working in CMHCs. A strategy that has been considered was to assign new cases to a different psychiatrist within a specialist FES team. The risk of this approach could be a temporary lowering of fidelity to the program and the possibility of some disengagement with local GPs. CMHCs are also promoting a higher level of responsibility to the assigned nurse to act as case manager.

The large coverage offered by socialized mental health care in the Province make our estimate of new cases very close to the real incidence in the catchment area(Ruggeri et al., 2015). However, new studies focusing on the systematic collection of data with emphasis to the local pathways to care of FEP are needed, providing some insight on possible barriers preventing citizens from accessing specialized public health facilities. In order to facilitate greater referrals, it seems also necessary to promote a new culture to destigmatize mental health care, by beginning with educational activities in schools, religious organizations, volunteers' associations, social work services and police corps(Srihari et al., 2016). Social media and marketing campaigns are a youth friendly tool(Birnbaum et al., 2016; Srihari et al., 2014) that could help advertise the value of a free, patient-centered EIS program embedded in the community.

In conclusion, community mental health centers in Modena, funded by Region Emilia Romagna, successfully implemented an early intervention service as shown by reaching a

higher than expected number of new treated cases of first episode of psychosis. The program was successful in implementing active outreach educational activities and providing coordinated specialty care. These findings can set the stage for expanding access to FEP mental health care and offering services that are better tailored to the population in the province; those results provides a template for expanding EIS implementation across Emilia Romagna and other regions in Italy.

Conflict of interest

The authors whose names are listed above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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CHAPTER 4

FIRST HELP-SEEKING ATTEMPT IN PSYCHOSIS ONSET: MEASURES OF DELAY AND AVERSIVE PATHWAYS TO CARE

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Abstract

Purpose Delay in receiving effective treatment for psychosis adversely impacts outcomes. We investigated the timing of the first help-seeking attempt in individuals with recent onset non-affective psychotic disorders by comparing those who sought help during the prodrome to those who sought help after psychosis onset in terms of sociodemographic and clinical characteristics, overall functioning, and occurrence of adverse events during their pathways to care.

Methods Patients were admitted from February 1st, 2014 to January 31st, 2019 to STEP, a first episode psychosis service in New Haven, CT. Psychosis onset date was ascertained using the Structured Interview for Prodromal Syndromes. Key dates before and after onset of psychosis, along with initiators, and adverse events were collected by semi-structured interviews.

Results The sample comprised 168 individuals, 82% had their first help-seeking event after psychosis onset, and did not differ in terms of sociodemographic characteristics from prodrome help-seekers. When the first help-seeking episode started before (i.e. during prodrome) vs after psychosis onset, it was mostly initiated by patients vs family members (Cramer's $V = 0.23$, $p = .031$), and led to a more rapid prescription of an antipsychotic once full-blown psychosis emerged (time to antipsychotic since psychosis onset = 21 vs 56 days, $p = .03$). No difference in adverse events before enrollment into care was detected across groups.

Conclusion Help-seeking during the prodrome is associated with faster initiation of antipsychotic treatment and is more likely to be self-driven when compared to help-seeking after psychosis onset. Early detection efforts that target prodromal samples may leverage reductions in DUP and adverse pathways to care.

Keywords: First Episode Psychosis · Pathways to Care · Help-Seeking Behaviour · Duration of Untreated Psychosis · Early Intervention · Early Detection

Introduction

There is a need to improve the speed and tolerability of pathways to care for individuals with first episode psychosis, in order to then improve associated outcomes. Help-seeking attempts during psychosis, when contact with reality and insight is poor (Belvederi Murri & Amore, 2018), are unfortunately often triggered by aggressive or dangerous behavior towards oneself or others, leading to aversive events along the pathways to care, often involving police, emergency rooms, and involuntary psychiatric hospitalization (Singh & Grange, 2006). Such adverse experiences might reduce trust and adherence to care in subjects, ultimately hampering recovery (K. K. Anderson, Fuhrer, Schmitz, & Malla, 2013; Cairns, Reid, & Murray, 2015; Connor, Greenfield, et al., 2016). Delay to receive effective treatment is associated with poorer short and long-term outcomes (M. Birchwood et al., 1998; Drake et al., 2020; Penttila et al., 2014; Srihari, 2018). Seminal early detection (ED) efforts, such as the Scandinavian TIPS study, demonstrated that halving the duration of untreated psychosis (DUP) produced benefits evident ten years later (M. Ferrara, Guloksuz, et al., 2019; Hegelstad et al., 2012).

In up to 70% of cases, psychosis is preceded by a variably defined prodromal period (Shah et al., 2017) that is itself characterized by subthreshold symptoms of the disorder, and reductions in social, academic, or general functioning. However, recent data from South London (UK) FEP services show that only a minority of individuals with FEP (4.1% of 338) had sought help for pre-onset subthreshold symptoms of psychosis at the prodromal service (Ajnakina et al., 2017), confirming a retrospective study conducted in the USA which showed only 14.5% of a FEP sample had sought professional help during the prodrome (Compton, Goulding, & Walker, 2010). These data highlight the importance of early detection and intervention for optimizing pathways to care in subjects with prodromal symptoms of psychosis (Fusar-Poli, 2017). However, little is known regarding whether and how patient characteristics influence pathways to care in the prodromal and early psychotic phases of schizophrenia (MacDonald, Fainman-Adelman, Anderson, & Iyer, 2018).

Furthermore, the initial actions undertaken by patients, caregivers, and the network of community resources (including non-health care providers, e.g. police, school), by setting in motion the very first help seeking attempt for psychosis, play a pivotal role in shaping the pathway to specialized care. In a domino-like effect, the first help-seeking event defines the personal experience of the distressed patient within the healthcare system. While it has the

potential to create a new supporting net for the help-seeker, the first such help-seeking event could also alter the outcomes of a potentially disabling illness like psychosis, during what has been defined as “the critical period” for changing its prognosis (M. Birchwood et al., 1998).

As a result, the study of the first help-seeking event can reveal how events unfold in the real world in order to foster optimal ED efforts. In order to tailor early interventions and ultimately prevent treatment delays, it is important to understand how individual characteristics and timing of the first instance during which patients or caregivers seek help for psychosis influence participants’ interactions with the healthcare system. A study conducted in Ireland found that, within 142 subjects diagnosed with FEP, only 40% sought help for themselves after the psychotic illness had started and even fewer (25%) sought help during the interval between onset of prodromal symptoms and access to specialized care (O’Callaghan et al., 2010). The authors also reported distinct factors that affected delay across illness phases. During the prodromal phase, but not after psychosis onset, male gender, poorer premorbid adjustment and negative symptoms at admission were associated with delays. During the psychotic phase, family involvement in help-seeking attempts reduced delays. Thus, demographic, socio-economic, and clinical features of help-seekers need to be better characterized to prevent delays to care and improve the choice of provider of such care.

In this exploratory study, we analyzed the first help-seeking attempts of individuals admitted to a specialty team-based psychosis service (FES) to investigate whether those seeking help before psychosis onset (as ascertained by a structured interview) differed from those who sought help after psychosis onset in terms of sociodemographic and clinical characteristics, overall functioning, and occurrence of adverse events during their pathways to specialized care.

Methods

Sampling

Subjects for this analysis were drawn from consecutive admissions to a community health center based first episode psychosis service (Specialized Treatment Early in Psychosis, STEP) over five years (February 1st, 2014, to January 31st, 2019). STEP's broad eligibility criteria include subjects between the ages 16-35 who were within the first three years of psychosis onset, and also met Structured Clinical Interview for DSM-IV TR diagnosis for any non-organic schizophrenia-spectrum or schizoaffective psychosis, including schizophreniform disorders, brief psychotic episode, and psychosis NOS. Services were also restricted to residents in a 10 town catchment contiguous with the clinic in New Haven, Connecticut. The clinic excluded referrals with an established diagnosis of affective psychosis (Bipolar Disorder and Major Depressive Disorder with psychotic features), and psychosis secondary to substance use or a medical illness. For most of this period, STEP hosted an early detection campaign that sought to recruit a representative sample across the catchment area (Srihari et al., 2014). Informed consent was obtained from all participants per procedures of the study protocol approved by the Yale University Institutional Review Board.

Definition of prodrome and psychosis onset

The Structured Interview for Prodromal Syndromes (SIPS), Version 5.3, was administered at enrollment to identify psychosis onset and retrospectively prodrome onset (T. J. Miller et al., 2003).

The SIPS instrument categorizes risk of progression to full blown psychosis with three non-mutually exclusive clinical high risk syndromes: the Brief Intermittent Psychotic Syndrome, Genetic Risk and Deterioration Syndrome, and Attenuated Positive Symptom Syndrome (APS) (Tandy J. Miller et al., 1999). APS is defined as the presence of recent attenuated positive symptoms of sufficient severity and frequency (T. J. Miller et al., 2003). To meet criteria for an attenuated symptom, a patient must receive a rating of level "3", "4", or "5" on scales P1-P5 of the SOPS. A rating in this range indicates a symptom severity that is at a psychosis-risk level of intensity. Also, the symptom must either have begun in the past year or must currently rate at least one scale point higher than it would if rated 12 months ago. It must occur at the current intensity level at an average frequency of at least once per week in the past month. Based on available literature (Schultze-Lutter et al., 2015; Shah et al., 2017), we expected that APS would not be identifiable for a subset of patients.

For this analysis, we have therefore used only cases where an identifiable APS date was present (with a prodrome start date corresponding to the APS syndrome onset date). Despite a lack of consensus on what constitutes the prodromal interval and how to measure it, the APS interval, mainly characterized by subthreshold positive symptoms of psychosis, was selected to date prodrome onset because it was the most reliably identifiable in retrospective interviews of our sample and is also closest to the DSM-5 defined attenuated psychosis syndrome (Salazar de Pablo, Catalan, & Fusar-Poli, 2020; Tsuang et al., 2013).

Psychosis onset was defined as meeting the Presence of Psychotic Syndrome (POPS) criteria or a rating of “6” or higher on scales P1-P5 of the SIPS. Also, one of the above rated symptoms must have occurred over a period of one month for at least one hour per day at a minimum average frequency of four days per week, or the symptom must have been seriously disorganizing or dangerous (T. J. Miller et al., 2003).

Overall impairment in functioning due to mental health factors was assessed with the Global Assessment of Functioning (GAF) scale at admission (American Psychiatric Association. & American Psychiatric Association. Task Force on DSM-IV., 2000). The GAF score reflects the overall impairment in the past 30 days, with a single score ranging from 1 to 100, where a higher score represents better functioning.

Measures of Delay

For this sample of FEP individuals, we were able to retrospectively build a detailed narrative of the continuum between the prodromal period and onset of psychosis. Per inclusion criteria, the progression of symptoms led to psychosis in the whole sample, therefore we considered duration of untreated illness (DUI) as the interval from APS syndrome onset date to the first prescription of antipsychotic medication for psychosis [see Fig. 1] (Murru & Carpiello, 2018). The APS interval was defined as the time from APS onset to psychosis onset (per POPS criteria).

Figure 1. Pathways to care in first episode psychosis. Definitions of measures of delay.

Note: PTC = Pathway to care. APS = Attenuated Positive Symptoms Syndrome. DUI = Duration of untreated illness. APD = antipsychotic drug. STEP = Program for Specialized Treatment Early in Psychosis. DHS_p* = Delay initiating Help-Seeking (patient); DHS_f* = Delay initiating Help-Seeking (Family). DHF = Delay in Help-finding. *can be prior to, or after, Psychosis onset defined as the date on which Presence of Psychotic Syndrome (POPS) criteria within the Structured Interview for Prodromal Syndromes (SIPS) were first met.

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The interval between the onset of psychosis to admission to STEP was defined as DUP-total. It is further divided into the “demand” and “supply” sides of delay to specialized care, DUP-demand, and DUP-supply, respectively (Srihari et al., 2014). DUP-demand, defined as the time interval from psychosis onset to the first prescription of an antipsychotic for psychosis, includes the delays in illness identification, and help-seeking by participants and caregivers. The first prescription of antipsychotic for psychosis is a proxy for accurate identification and initiation of treatment for psychosis by a healthcare provider (and excludes off label prescriptions of antipsychotics, e.g. for sleep disturbances). DUP-supply, the time interval from the first prescription of antipsychotic to admission to STEP, cumulates delays attributable to actors in the healthcare system in enrollment into best practice care (i.e. local FES or STEP) [see Fig. 1] (Srihari et al., 2014). For those instances when an individual was antipsychotic-naïve at STEP admission, DUP-supply was zero, and DUP-total equaled DUP-demand.

Pathways to care (PTC)

The STEP-ED PTC Scale, adapted from the Pathways to Care Interview (PCI) (Judge, Perkins, Nieri, & Penn, 2005; D.O. Perkins, Nieri, Bell, & Lieberman, 1999), assessed help-seeking by guiding interviews of patients and systematic collection of collateral from caregivers and clinical records. This resulted in detailed information about each help-seeking attempt,

including symptomatic or behavioral precipitants, to whom participants turned for help, the outcome of each help-seeking attempt, and perceived barriers to care.

This study focused on the first help-seeking episode (HSE). Details about critical dates when someone (either patient, family, or others) first noticed a change in behavior related to psychosis were also recorded and analyzed. A help-seeking episode begins when someone (patient, family, others) seeks help *for symptoms that are attributable to psychosis (change in thinking, feeling, or behavior)* and ends when either the patient falls out of mental health treatment or enrolls in FES.

The onset of psychosis was defined as the date that POPS criteria were met. All patients were divided into two groups based on whether their first HSE was before (Prodromal-HS) or after (Psychosis-HS) psychosis onset.

As represented in Fig. 1, important measures of delay were derived from the scale. Specifically, within DUP-demand are more granular measures of delays in help-seeking: the time interval between the awareness of psychotic symptoms and initiation of the first HSE by the family (DHSf) or the patient (DHSp). Subsequent to this is the delay in help finding (DHF) or the delay to receipt of the first antipsychotic. In the case of Prodromal-HS, DHF could include a prodromal period when the prescription of an antipsychotic is not indicated.

From the PTC interview, we also selected indicators of aversive pathways to care from the first help-seeking attempt to STEP admission. These indicators included encounters with the police (as initiator of a help-seeking attempt and/or as recipient of a request for intervention by patients or caregivers), and involuntary hospital admissions to inpatient psychiatric units.

We used an adapted version of the Service Utilization and Resources Form (SURF) to retrieve information about the number and duration of hospitalizations in inpatient psychiatric units in the six months preceding admission to STEP (R. Rosenheck et al., 2016; R. A. Rosenheck et al., 2006).

Statistical analysis

In this exploratory study, demographics including age at first HSE, age at POPS, age at enrollment, race, and gender; clinical characteristics including diagnosis, GAF at enrollment,

and sources of delay; socioeconomic variables including employment status, and household income (categorical variable dichotomized at \$40,000) were compared between Prodromal-HS and Psychosis-HS participants. Three participants who did not have complete PTC and SIPS were excluded.

In order to investigate if the start of the first help-seeking episode (HSE) correlated with prolonged delays to entering care, the groups (Prodromal-HS vs Psychosis-HS) were compared across various measures of delay (as detailed above and in Fig. 1).

Finally, Prodromal-HS and Psychosis-HS were compared across measures of adverse events during pathways to care: the total number of contacts with the police, the total number and duration of hospital admissions to psychiatric inpatient units (voluntary and involuntary).

Based on the contact made by the initiator during the first HSE, participants were classified into one of the three following categories: family and community resources (family, friends, school, social welfare agency, consumer's and youth organization), health service providers-potential prescribers (emergency department, hospital, private practice, mental health clinic, adult and child primary care provider), or police.

Demographic and clinical characteristics were compared across three groups using ANOVA or Kruskal-Wallis test depending on normality for continuous variables, and Chi-square test for categorical variables. SAS 9.4 (Cary, NC) was used for all statistical analyses. The statistical significance level was set at $p < 0.05$, two-sided.

Results

Sample characteristics

The sample comprised 168 FEP participants of 202 eligible referrals. Those who were eligible but refused to be admitted to the program ($n=34$) did not differ from the final sample for age and gender distribution.

Table 1 Frequency characteristics of the study population (N=168)

Variable	Total sample	First help-seeking episode before POPS N= 30	First help-seeking episode after POPS N=138	Difference p-value
Gender, M, n (%)	118 (70%)	20 (66.7%)	98 (71.0%)	0.64
Race, n (%)				0.16
Black (e.g. African, African Caribbean)	75 (44.6%)	11 (36.7%)	64 (46.4%)	
White (European)	57 (33.9%)	14 (46.7%)	43 (31.2%)	
Interracial	26 (15.5%)	2 (6.7%)	24 (17.4%)	
Other	10 (6.0%)	3 (10.0%)	7 (5.1%)	
Age at different time points				
Age at admission,				
mean (SD)	22.4 (3.8)	21.7 (3.2)	22.6 (3.9)	0.22
median [range]	21.5 (16.0 – 34.5)	21.3 (16.0 – 27.3)	22.0 (16.0 – 34.5)	0.30
Age at first Help seeking attempt				
mean (SD)	21.8 (3.8)	20.3 (3.3)	22.1 (3.9)	0.02
median [range]	21.0 (14.8 – 33.4)	19.3 (15.1 – 26.6)	21.3 (14.8 – 33.4)	0.02
Age at Psychosis onset (POPS)				
mean (SD)	21.6 (3.8)	21.0 (3.3)	21.8 (3.9)	0.41
median [range]	21.0 (13.7 – 33.1)	20.4 (15.2 – 26.7)	21.0 (13.7 – 33.1)	
Prodromal phase				
CHR with identifiable APS onset date	148 (88.1%)	30 (100.0%)	118 (85.5%)	
CHR without identifiable APS onset date	4 (2.4%)	0 (0.0%)	4 (2.9%)	
No presence of CHR/APS, very acute onset of psychosis	7 (4.2%)	0 (0.0%)	7 (5.1%)	
Undetermined presence/absence of prodrome (unable to determine)	9 (5.4%)	0 (0.0%)	9 (6.5%)	
Living situation in the 6 months before admission				
With family	147 (88.6%)	27 (90.0%)	120 (88.2%)	0.78
With spouse/partner	9 (5.4%)	3 (10.0%)	6 (4.4%)	0.22
In a shelter	7 (4.2%)	5 (3.7%)	2 (6.7%)	0.46
On the street	5 (3.0%)	1 (3.3%)	4 (2.9%)	1.00
Incarcerated	2 (1.2%)	0 (0.0%)	2 (1.5%)	1.00
Household income				
Less than \$40,000	66 (39.3%)	9 (30.0%)	57 (41.3%)	0.23
\$40,000 and above	83 (49.4%)	19 (63.3%)	64 (46.4%)	
Don't know or refused	19 (11.3%)	2 (17.8%)	17 (12.3%)	
GAF at admission				
mean (SD)	31.3 (10.7)	29.1 (11.9)	31.8 (10.4)	0.22
median [range]	31.0 [8.0 – 79.0]	21.0 [20.0 – 63.0]	31.5 [8.0 – 79.0]	0.09

The final sample was predominantly male (118, 70%), racially diverse, and young (mean age at admission was 22.4 ± 3.8) (Table 1). The majority were diagnosed with schizophrenia and significantly impaired in general functioning at admission to STEP (median GAF score was 31.3 ± 10.7). Eighty-two percent of the individuals in this sample ($n=138$) were Psychosis help-seekers (Psychosis-HS): they had their first help-seeking event after psychosis onset. The Prodromal-HS group ($n=30$) was, on average, two years younger (20.3 ± 3.3 vs 22.1 ± 3.0 for Psychosis-HS, $p < .02$).

Delays to Care

The Prodromal-HS and Psychosis-HS groups showed similar durations of APS and untreated illness (DUI) (Table 2). Patients who had first sought help during the prodrome (i.e. Prodromal-HS) took expectedly longer to get prescribed an antipsychotic (median 245 days [range: 5-1400] vs. 1 day [0 – 999], $p < 0.001$ for Psychosis-HS) (Table 2). In contrast, it took significantly less time for Prodromal-HS patient to receive an antipsychotic after psychosis onset (median DUP-demand 21 days [range 0 – 445] vs. 56 days [0 – 1153], ($p = .03$) for Psychosis-HS]. This difference in DUP-demand however, was not present when we excluded nine Prodromal-HS who were already in psychiatric care at the moment of transition to full blown psychosis and thus did not need to subsequently initiate help seeking ($p = 0.21$).

Prodromal-HS subjects did not show a significant reduction in delays to enrollment at STEP once they crossed the threshold for psychosis: median DUP-total 109 (2-1008) days vs 184 (4-1189) days; $p = .30$ (Table 2).

Table 2 Comparison of delays along the pathway to care: first help-seeking attempt before (Prodromal-HS) vs after psychosis onset (Psychosis-HS)

Delays to care, intervals	Prodromal-HS N=30	Psychosis-HS N=138	p-value
APS interval, days			
mean (SD)	581.5(618.7)	530.7 (779.2)	
median [range min max]	363.5 [31.0 - 2571]	197.0 [1.0 – 4567]	0.18
DUI, days			
mean (SD)	653.7 (622.4)	669.2 (808.5)	
median [range]	441.5 [49.0, 2575]	389.0 [2.0, 5104]	0.61
DUP-demand, days			
mean (SD)	72.2(110.6)	166.5(243.1)	
median [range]	21.0 [0.0 - 445.0]	56.0 [0.0 – 1153]	0.03
DUP-total, days			
mean (SD)	242.0 (266.4)	298.3(308.2)	
median [range]	109.0 [2.0 – 1008]	184.0 [4.0 – 1189]	0.29
DUP-supply, days			
mean (SD)	169.8 (255.5)	131.8 (231.0)	
median [range]	25.50 [1.0 - 941.0]	21.0 [0.0 – 1106]	0.65
Delay in help finding (DHF), days,			
mean (SD),	337.8 (348.2)	43.0 (138.7)	<.0001
median [range]	245.0 [5.0 - 1400]	1.00 [0 - 999.0]	
DHSp Patient side delay, days,			0.09
mean (SD)	162.7 (324.1)	291.0 (600.0)	
median [range]	14 [0 – 1093]	75 [0 - 3928]	
N available(%)	N=21(70%)	N=126(91%)	
DHSf Family side delay, days			0.36
mean (SD)	82.9 (120.8)	199.6 (422.9)	
median [range]	14.5 [0 – 266]	31.0 [0 – 2949]	
N available(%)	N=10(33%)	N=95(68%)	

APS = Attenuated Positive Symptoms Syndrome. DUI: duration of untreated illness. DUPd: time interval between psychosis onset (POPS date) to first prescription of antipsychotic. DUPt: time interval between psychosis onset (POPS date) to admission to STEP program. DUPs: time between the first APD prescription to STEP admission. STEP = Program for Specialized Treatment Early in Psychosis. DHF: Delay from the first time someone sought help and first antipsychotic prescription. DHSp = Delay initiating Help-Seeking (patient). DHSf= Delay initiating Help-Seeking (Family). For further details see Figure 1.

Pathways to care

There was a significant association between the timing of the first HSE and type of help-seeking initiator. The first HSE was more likely to be initiated by the patient during APS, but by the family after psychosis onset (chi-square =6.932, p=.032, with a medium Cramer's V effect size =0.23, p=.031) (see Fig. 2).

Figure 2. Initiators of the first help-seeking attempt during prodromal (pre-POPS) vs psychotic (post-POPS) phase.

Table 2 shows patient- and family-side delays (time interval between when the patient or family respectively noticed a change, to the initiation of HSE, see Fig. 1), which were not significantly different between the two groups. Of note, during the prodromal phase, 70% of patients, compared to only 33% of family members acknowledged a change in patient's behavior/thinking before the first HSE. After psychosis onset, 91% of patients and 68% of family members noticed similar changes of psychopathologic origin. Regardless of who first noticed a change (either family, patient, or others), the delay for this initiator to set in motion the first HSE from the moment a change perceived was not different between Prodromal-HS and Psychosis-HS groups ($p=0.06$).

Table 3 reports the frequency of aversive pathways to care, which did not have a significant difference in the two groups. For the whole sample, 23% had at least one encounter with the police and 32% had at least one involuntary admission to the inpatient psychiatric unit before their enrollment to STEP.

Age, gender, and symptom threshold severity (prodrome vs psychosis) did not significantly impact on the type of first responder or contact (either family/community resources, health care providers, or police) (Table 4). The choice made by the HSE initiator for the first contact did not significantly influence the delay to receive the first antipsychotic or enrollment to STEP (DUP-demand n.s. $p=.93$, DUP-total n.s. $p=.14$) (Table 4).

The vast majority of encounters with the police during the first HSE occurred after psychosis onset (17/18, 94%), and involved mainly male patients (15 men vs 3 women).

For the Prodromal-HS group, in most cases the initiator connected with a health care provider (20/30, 66%). In contrast, for Psychosis-HS, the initiator was less likely to reach health care providers first (73/138, 52%), but instead another family or community member was involved in 34% of cases (48/138).

Table 3 Aversive pathways to care

			Prodromal-HS N=30	Psychosis-HS N=138
Contact with the police	Total number of contacts with the police (sum of police as initiator, and police as responder in all help seeking episode in PTC interview)	Subjects who had at least one contact	7 (23%)	32 (23%)
		Total number of contacts	8	42
		Median [range]	1 (1-2)	1 (1-4)
	Hospital admissions across all help seeking episodes	Subjects who had at least one hospital admission	25 (83%)	112 (81%)
Psychiatric Hospital admissions	Involuntary admissions to psychiatric hospital across all help seeking episodes.	Subjects who had at least one event	8 (27%)	47 (34%)
		Total number of involuntary admissions	14	64
		Median [range]	1.5 (1- 3)	1 (1-5)
	Number of nights spent in psychiatric hospital 6 months before admission	N of subjects with events	22 (73%)	101 (74%)
		Total (total number of nights)	349	1803
		Median [range]	14.5 (6-31)	14.0 (1-176)

Table 4 Difference of Patient Characteristics by First Contact of Help-Seeking Attempt Side

First Contact during the First Help-Seeking Attempt					
	Family and Community resources (N = 57)	Health Care providers (N = 93)	Police (N = 18)	Total (N = 168)	p- value
Age, Years					
					0.49
Mean (SD)	22.0 (3.9)	22.7 (3.8)	22.5 (3.4)	22.4 (3.8)	
Median [range]	20.9 (16.0, 33.5)	21.6 (16.0, 34.5)	22.5 (16.0, 28.0)	21.5 (16.0, 34.5)	
Sex, n (%)					
Female	18 (31.6)	29 (31.2)	3 (16.7)	50 (29.8)	0.44
Male	39 (68.4)	64 (68.8)	15 (83.3)	118 (68.4)	
First Help-Seeking Timing, n (%)					
					0.28
Before POPS	9 (15.8)	20 (21.5)	1 (5.6)	30 (17.9)	
After POPS	48 (84.2)	73 (78.5)	17 (94.4)	138 (82.1)	
DUP-demand, days					
					0.93
Mean (SD)	141.1 (204.2)	144.3 (225.1)	204.9 (307.8)	149.7 (227.8)	
Median [range]	49.0 (0, 846)	52.0 (0, 1059)	58.5 (0, 1153)	52.0 (0, 1153.0)	
DUP-total, days					
					0.14
Mean (SD)	227.0 (270.6)	318.9 (307.0)	323.6 (347.5)	288.3 (301.2)	
Median [range]	95.0 (2.0, 1008.0)	207.0 (9.0, 1189.0)	243.0 (17.0, 1159.0)	160.5 (2, 1189)	
DUP-supply, days					
Mean (SD)	86.0 (188.9)	174.7 (261.7)	118.7 (196.2)	138.6 (235.2)	
Median [range]	15.0 (0, 941.0)	27.0 (0, 1106.0)	23.5 (0, 726)	21.0 (0, 1106.0)	

The first contact made by the initiator during the first help seeking attempt was clustered in the following three groups: 1) health providers (potential prescribers): ER, Hospital, Private Practice, Mental health clinic, Adult and child primary care; 2) Police; 3) Family and Community resources: Friend, Family, School Counsellor, Social Welfare Agency, Mental Health consumers' Organization.

Discussion

This is the first study to quantitatively interrogate the comparative impact of help-seeking in the prodromal versus post-psychotic phases of recent onset schizophrenia. Several findings illuminate the similarities and differences in the speed and quality of the ensuing pathways to best practice care. The vast majority of enrollees to our population-based FES reported their first help-seeking episode only after psychosis onset (82%). The two groups who were classified by whether they first sought help during the prodrome (Prodromal-HS) vs after florid psychosis onset (Psychosis-HS) did not differ in terms of demographic (gender, race, age at psychosis onset or admission to care), socioeconomic (accommodation, household income) or functional (GAF) variables at enrollment. When the first HSE was initiated during the prodrome, patients were more likely than family members to initiate help-seeking, while the reverse was true after psychosis onset. Help-seeking during the prodrome was associated with shorter delays to first antipsychotic treatment after psychosis onset (median of 21 vs. 56 days), and this reflected the benefits of being in care during conversion to psychosis (Lucia R. Valmaggia et al., 2015). Such earlier connection to clinical care however did not result in faster referral to the local FES. Other reports have suggested that being in treatment during the prodromal phase might actually prolong DUP (Boonstra et al., 2012), and while our data suggests this is not the case for antipsychotic initiation, it may well delay referral onwards to specialty FES.

In addition to the speed of access to care, our investigation of the quality of these pathways, as measured by the frequency of aversive events, did not reveal significant differences between the two groups. While as many as one in five patients had at least one interaction with the police before enrollment in our FES, reassuringly this rarely resulted in incarceration and might reflect the active role of jail diversion and crisis intervention training for police in our catchment (Pollard et al., 2020). However, the degree of police involvement in intercepting FEP likely varies across regions and patient sub-groups, thus limiting the generalizability of these findings (Dinesh Bhugra, 2000; Broussard, McGriff, Demir Neubert, D'Orio, & Compton, 2010; Compton, Esterberg, Druss, Walker, & Kaslow, 2006). Other regions may have higher rates of inappropriate diversion to the criminal justice system after disruptive psychosis driven behavior, where the comparative benefits of help-seeking during the

prodrome could be greater. Similarly, we did not find a difference in frequency of involuntary hospitalization between the two groups.

The strengths of this approach included the use of the SIPS instrument to explicitly identify and date the onset of both the prodromal phase and the transition to full-blown psychosis. When integrated with the detailed pathways to care interview, this allowed a granular measurement of the pathways that patients and their families undertake as they access care, both in terms of time (delay) and quality (aversive interactions). Both of these elements have prognostic value in terms of predicting responsiveness to care. This approach also provides actionable information for early detection efforts. For example, our data showed that the vast majority of patients did acknowledge a change in their behavior or thinking, yet this awareness was a more reliable trigger for help-seeking during the prodromal phase than after full blown psychosis onset. This may be related to the common loss of insight after psychosis onset, with the family needing to assume the role of initiating efforts to access healthcare. However, family members may wait to seek help until severe symptoms increase the likelihood of aversive events (involuntary hospitalization or entanglement with the criminal justice system) that can reduce engagement into ongoing care (O'Callaghan et al., 2010). Proactive and age-appropriate early detection efforts that target prodromal samples may both reduce DUP and aversive pathways, and better leverage the impact of local FES (L. R. Valmaggia et al., 2015). These findings were derived from a defined catchment in the Greater New Haven region that is highly representative of U.S. demography (Kolko, 2016), and a clinical sample with illness severity and socioeconomic characteristics that are likely representative of the kinds of early psychosis patients who present for care in community settings.

Some differences between the groups may have not been detectable because of the size of the sample, or as noted above, the lower base rate of aversive events such as diversion to jail, in our catchment. However, the methodology described here could guide useful analyses in other systems of care and reveal actionable targets to improve the speed and quality of access to best practice care. The rapid dissemination of Coordinated Specialty Care (CSC) services across the U.S. and increasing availability of similar clinics for recent onset psychotic disorders around the world makes a focus on access to such services a logical next step in service delivery.

The reported analysis did not specifically address the effect of an ongoing early detection campaign (Srihari et al., 2014). Future time trend analyses might reveal which specific aspects of the pathway was impacted by this ongoing campaign, while comparisons with other regions may reveal to what degree the magnitude of the effects seen here were a result of this catchment-wide early detection effort.

Conclusions

Timing of first help-seeking in early psychosis can be crucial in shaping both the duration and experience of pathways to care. Help-seeking during the prodromal state was associated with shorter delays to appropriate antipsychotic treatment, and was more likely to be self-driven. Early detection efforts targeting prodromal samples have the potential to yield greater reductions in DUP and also in the frequency of involuntary hospitalization and inappropriate diversion to criminal justice pathways.

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CHAPTER 5

EARLY INTERVENTION SERVICES ON ADULT JUDICIAL OUTCOMES: ANALYSIS OF A RANDOMIZED CONTROLLED TRIAL OF SPECIALTY TEAM BASED CARE FOR FIRST EPISODE PSYCHOSIS

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Introduction

New onset psychotic disorders can increase entanglements with the criminal justice system(Ford, 2015). The resulting convictions and incarcerations can increase risk for suicide, delay access to care, and irrevocably impair employment and other opportunities for already vulnerable young adults(Ford, 2015). Specialty team-based services for first-episode psychosis (FES) are effective across a range of outcomes(Correll et al., 2018), but little is known about their impact on criminality(Stevens, Agerbo, Dean, Mortensen, & Nordentoft, 2013). We report a secondary analysis, for criminal justice outcomes, of a pragmatic randomized controlled trial of an FES (STEP) vs. usual treatment (UT)(Srihari et al., 2015).

Methods

All participants in the original study(Srihari et al., 2015) gave consent for review of judicial data, per IRB-approved procedures. Randomized treatment allocation occurred between 2006-2012, and publicly available databases (Connecticut Judicial Branch and Criminal/Motor Vehicle Convictions) were queried through December 31, 2016: allowing extended follow up post- (median 6.6 years, range 4.8 -10.6), and pre-enrollment (median 4.2 years, range 1 to 23.4). Juvenile (<18yo) and out of state convictions were unavailable. Number of criminal convictions, crime description, category, type of sentence (jail vs. probation), and offense dates were retrieved for each participant. Judicial categories reflect seriousness: *infractions* designate petty crimes or rule violations; *felonies* typically lead to jail sentences ≥ 1 year, and *misdemeanors* fall between these. We added the category of *violent crime* for offences involving physical contact.

Logistic regression was used to evaluate differences in conviction profiles post-enrollment by randomization group, with adjustment for prior convictions. Time to first crime post enrollment by group was analyzed using the Kaplan-Meier method.

Results

The sample included 117 young (mean age 22.7 years), predominantly male (81.2%), recent onset psychosis patients (median Duration of Untreated Psychosis, DUP: 3 months), who were racially and ethnically diverse. Patients allocated to STEP vs. UT did not differ by age, gender, race, ethnicity, DUP,(Srihari et al., 2015) or prior convictions (Table). A minority (12%) had convictions prior to allocation.

The overall number and seriousness of offences was reassuringly low (Table). Only 13 of 85 (15.3%) total convictions were for violent offenses, 18 (21.2%) for felonies, with a predominance of misdemeanors (n=54). After adjusting for prior convictions, patients allocated to STEP were subsequently less likely to be convicted of any crime (OR 0.19, 95% CI,0.04-0.85; $P = 0.03$), and trended less likely to be sentenced to jail (OR 0.22, 95% CI,0.05 to 1.01; $P = 0.05$). The number of new offenders trended lower in STEP (1.7% vs. 10.5% in UT, $P = 0.06$). Notably, there was a 76% reduction in the risk of committing a first crime for STEP vs. UT (Hazard Ratio 0.24; 95% CI: 0.07-0.86; $P < 0.02$) (Figure). STEP participants also trended toward a lower 5-year first crime rate of 5% (95% CI,0.51% to 10.51%) vs. 17.54% in UT (7.66% to 27.42%). Participants convicted of at least one crime did not differ across STEP vs. UT by age at enrollment, race, gender, or DUP.

Discussion

FES can reduce criminality. The low overall prevalence of convictions in this sample was reassuring, but limited detection of group differences. Nevertheless, allocation to STEP reduced subsequent and first-time convictions, and below levels in a larger European trial(Stevens et al., 2013). Putative mechanisms include STEP's improvement of vocational functioning(Srihari et al., 2015), which is associated with reduced youth criminality(Heller, 2014); and reduction of psychiatric hospitalizations⁴ which disrupt work and school functioning, but may also signal reductions in episodes of behavioral dysregulation, that can result in arrests(Wasser, Pollard, Fisk, & Srihari, 2017). However, these speculations need to be tested against more granular information about the circumstances of each arrest. Such replication, and with a larger sample and more comprehensive (e.g. adding juvenile, jail diversion and department of corrections) databases, is urgently needed to inform service design and policy.

Table. Criminal Justice involvement in a first-episode psychosis sample

Convictions	STEP (n = 60)		Usual Treatment (n = 57)	
	Before enrollment	Post enrollment	Before enrollment	Post enrollment
Any offense	6 (10.0%)	3 (5.0%)	8 (14.0%)	11 (19.3%)
Felony	3 (5.0%)	1 (1.7%)	4 (7.0%)	4 (7.0%)
Misdemeanor	2 (3.3%)	2 (3.3%)	7 (12.3%)	9 (15.8%)
Motor vehicle	2 (3.3%)	(0.0%)	1 (1.8%)	4 (7.0%)
Violation of probation	0 (0%)	1 (1.7%)	0 (0%)	1 (1.8%)
Violent crime	2 (3.3%)	1 (1.7%)	2 (3.5%)	4 (7.0%)
Sentenced to jail	5 (8.3%)	3 (5.0%)	8 (14.0%)	10 (17.5%)
Probation	3 (5.0%)	3 (5.0%)	5 (8.8%)	8 (14.0%)

Figure Legend. Time to first crime post enrollment in STEP vs Usual Treatment (UT)

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CHAPTER 6

EARLY INTERVENTION FOR PSYCHOSIS IN THE UNITED STATES: TAILORING SERVICES TO IMPROVE CARE FOR WOMEN

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Specialty team-based services for first-episode psychosis (FEP) have the potential to transform the course of schizophrenia spectrum disorders(L. B. Dixon et al., 2018). Gender differences in the epidemiology, presentation, and course of schizophrenia have been well described(Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012); however, less is known about possible gender-based disparities in care. We acknowledge that both genders have specific service needs for FEP, and in this this Viewpoint we focus on women with FEP, because they are currently less represented as service recipients, and their service needs are hence at risk for being overlooked.

We briefly consider seven factors that might disadvantage women in terms of both access to and quality of care in first-episode services. We hope that awareness of these specific needs will inform service refinements within an ongoing nationwide rollout of FEP services across the United States(L. B. Dixon et al., 2018).

Factors That Can Affect Access to Care for Women With FEP

Age at onset.

Many first-episode services target transition-age youths or young adults. Although this focus allows programming tailored to the developmental needs of this particular age group, it risks excluding those women who experience psychosis onset later in life(Jongsma et al., 2018) A large-cohort study in Europe (the EUropean network of national schizophrenia networks studying Gene-Environment Interactions, N=2,774) reported both an older median age for women at first contact with FEP services (age 34 vs. age 28 for men) and a second peak in the incidence of psychosis for women in their fifties(Jongsma et al., 2018).

Therefore, there is a dilemma between designing psychosocial interventions to address a coherent set of needs for educational and employment support for younger individuals and serving the needs of women across the lifespan. Options to tackle this challenge include flexibility in setting the maximum age of admission to services. In this regard, the national effort in the United Kingdom to widen inclusion in these services to age 65 may offer some useful lessons for the United States(National Institute for Health Care Excellence, 2016). Preliminary reports suggest a 25% increase in total referrals to services, with those over age 35 representing one-third of the total FEP sample(Jagger et al., 2020). Of note, FEP in those older than 35 years results in higher care complexity, requiring more intensive care

planning, as well as sustained social worker support for child care, navigating involvement with child protective services, and consideration of economic needs(Jagger et al., 2020).

Clinical presentation.

Compared with men, women tend to present with more mood symptoms and may be more likely to receive a misdiagnosis of psychosis due to a primary affective disorder(Ochoa et al., 2012), which is often a criterion for exclusion from first-episode services. Additionally, women tend to have better overall functioning at symptom onset(Ochoa et al., 2012), which may result in an underestimation of their needs that delays entry into FEP services. Gender stereotypes can also impair access, with women's efforts to seek help being mischaracterized as attention seeking. In response to these presentation characteristics, first-episode services may more strongly consider including women with concomitant psychosis and mood symptoms, reevaluating diagnoses, and referring women to other services only after preliminary treatment and several months of careful longitudinal assessment.

Pathways to care.

For both patients and families, urgent help-seeking often includes involuntary admission and involvement with the criminal justice system in the United States, experiences that can jeopardize engagement with services. Paradoxically, women with FEP, who are less likely to display disorganized or threatening behavior due to psychosis(Ochoa et al., 2012), may be less well identified by these referral pathways and may experience longer delays in receiving care. Accordingly, first-episode services should be sensitive to these gender differences and target outpatient health facilities (e.g., primary care and obstetric and gynecologic clinics) where women with under-recognized psychosis may be found.

Gender roles.

Across different societies, women spend more time in informal caregiving for infants and elderly relatives than do men and thus may not adequately prioritize their own need for care. To increase the likelihood that caregiving women will access and accept care, FEP services should integrate their outreach and engagement activities to settings where relevant services (e.g., social services and child care) are co-located and readily available.

Factors Affecting Quality of Specialized Care for Women With FEP

Sexual and reproductive health.

Psychosis usually manifests during the period of greatest fertility for women. Young women carrying the added burden of psychotic symptoms may need more support to manage personal contraception or to negotiate condom use with male sexual partners. First-episode services should routinely provide education to help prevent sexually transmitted diseases and unintended pregnancies. Shared decision making around family planning is also critical when medications with potential teratogenic risks are prescribed. Particular sensitivity to asking patients about any adverse effects of medications and managing the impact of these effects on, for example, gendered societal expectations (e.g., weight gain and hair loss) or on reproductive health (e.g., secondary amenorrhea due to hyperprolactinemia) can ameliorate the often-unpleasant experience of taking antipsychotic medications.

Women have a unique risk for developing psychosis in the peripartum period; pregnant patients or those planning a pregnancy and having a history of psychosis or experiencing a current psychotic episode should receive tailored care. First-episode Services may facilitate ad hoc consultations with other services (e.g., pediatric, primary care, and obstetrics) or more systematic interagency collaborations that make it easier for FEP patients to get best practice reproductive care during the peripartum for themselves and access to pediatric care for their infants.

Preventive medicine.

Compared with women without a severe mental illness, women with schizophrenia are less likely to receive Pap test screening for cervical cancer and are half as likely as the general population to receive mammography screening for breast cancer (Hwong, Wang, Bent, & Mangurian, 2019). Possible explanations for these disparities among women with schizophrenia include lack of awareness of these available health screenings, fewer invitations by primary care physicians to access the screening, fear of the procedures, and economic constraints. First-episode services should consider providing education and care coordination to facilitate appropriate access to preventive measures (e.g., human papillomavirus (HPV) vaccination, breast self-examination, and diagnostic imaging).

Trauma.

Growing evidence has associated exposure to traumatic events in childhood with an increased risk for psychosis. Moreover, intimate partner violence, which victimizes more

women than men, is linked to an increase in psychotic experiences, especially in cases of multiple victimizations. While most controlled trials of psychotherapy for posttraumatic stress disorder have excluded patients with psychotic disorders, first-episode services should consider offering trauma-focused psychological interventions as part of the services provided.

Conclusions

In summary, women with FEP have specific needs that can be proactively addressed to refine the current expansion of first-episode services in the United States. The historical underrepresentation of women in using these services may have diminished the incentive to implement some of the refinements we have suggested here; hence, we are presenting a dual focus on access and care within a comprehensive approach that envisions pathways to *and* through specialty care for women with FEP.

These recommendations may be difficult for U.S.-based first-episode services to implement. In this country, both access pathways and care provision are fragmented across multiple agencies and payment systems, which can impede systematic approaches. We have articulated a population health framework to guide service design (M. Ferrara, Mathis, Cahill, Pollard, & Srihari, 2019). This framework includes a commitment to measure outcomes relevant to all stakeholders and may reduce subgroup disparities that arise from demographic, geographic, and other structural factors. Specific attention to women's voices and needs as part of this focus on population health can both widen and deepen the impact of emerging first-episode services across the United States.

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CHAPTER 7

DRUG-NAÏVE FIRST-EPIISODE SCHIZOPHRENIA SPECTRUM DISORDERS: PHARMACOLOGICAL TREATMENT PRACTICES IN INPATIENT UNITS IN HUNAN PROVINCE, CHINA: TREATMENT PRACTICE IN DRUG-NAIVE PSYCHOSIS

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Abstract

Aim: This study describes antipsychotic prescription patterns for drug-naïve inpatients diagnosed with first-episode schizophrenia-spectrum (FES) disorders, and factors associated with practices deviating from China's current guidelines.

Methods: All inpatients aged 7 to 45 years experiencing a first episode of schizophrenia-spectrum disorder with a duration of untreated illness less than 18 months, and admitted between Aug 1st, 2016 and Aug 1st, 2017 to one of eight psychiatric hospitals in Hunan were included. Demographics, clinical characteristics, and prescriptions at discharge were collected from electronic medical records. Logistic regression and random forest methods were used to model relationships between demographic and clinical factors and deviations from China's guidelines.

Results: Of the 602 inpatients included in the study, 598(99.3%) were prescribed antipsychotics and no patients were discharged on long-acting injectable antipsychotics. Polypharmacy (more than one antipsychotic prescribed) was present in 121 (20.2%) participants. Clozapine was prescribed to 45 (7.5%) patients. Adults receiving polypharmacy were more likely to be prescribed high-dose antipsychotics than those receiving single antipsychotic. Minors under 13 were more likely to receive polypharmacy and unapproved antipsychotics than those over 13.

Conclusions: Our findings suggest that most of the inpatients were prescribed a single antipsychotic at discharge, consistent with China's guidelines. Minors with FES, and patients discharged on polypharmacy and clozapine may require more intense monitoring and management. With the current implementation of China's National Mental Health Working Plan, these results will assist decision-makers in allocating resources and conducting reforms to facilitate best practice treatment for FES.

KEYWORDS

antipsychotic agents, clozapine, first episode schizophrenia, guidelines, polypharmacy

1 | INTRODUCTION

Treatment with antipsychotic medication is a core component of services for first-episode schizophrenia (FES)(L. B. Dixon & Stroup, 2015). Prescribing antipsychotics to this young population is challenging. First, they are experiencing a disorder that may impact their ability to make decisions for their health and wellbeing(Parellada et al., 2009). Second, patients with FES are at increased risk of developing side effects (Buchanan et al., 2010) which can motivate medication discontinuation (Naber & Kasper, 2000). Therefore, the choice of the first psychopharmacological intervention in drug-naïve FES patients is a sensitive task, influencing not only adherence to medications but also the course of illness(Diana O. Perkins et al., 2008).

Currently, FEP treatment in mainland China is provided by psychiatric hospitals, psychiatric departments affiliated with general hospitals, and community mental health centers. National Guidelines recommend early and individualized antipsychotic prescription for FEP patients, combined with family education, psychotherapy, rehabilitation and vocational training(Chinese Society of Psychiatry affiliated with Chinese Medical Association, 2015).

Most studies conducted in Western countries show trends of increasing and predominant use of second-generation antipsychotics (SGAs) as first line choices for FES (Clavenna et al., 2011; Olfson, King, & Schoenbaum, 2015a, 2015b; Schroder et al., 2017). Few studies have explored treatment practice in China since the 2015 guidelines were released, most have focused on tertiary hospitals, and none have specifically addressed FES.

In this study, we will investigate: 1) the current status of prescription practices for drug-naïve patients with FES admitted to psychiatric inpatient units in Hunan, China; and 2) demographic and clinical factors associated with deviations from China's published guidelines.

2 | METHODS

2.1 | Study setting

This study was carried out in Hunan Province, that has 124 hospitals with psychiatric inpatient units (22,492 beds), serving a population of 67.83 million (Hunan Provincial Bureau of Statistics, 2016). In China, mental health care for schizophrenia is mainly provided in psychiatric hospitals, where medications are the primary intervention, with limited resources for community-based care. Moreover, such care is unequally distributed across different levels of hospitals. Tertiary hospitals are the best equipped, and provide advanced medical investigation and treatment to referrals from primary and secondary hospitals (Zhang et al., 2019).

Eight hospitals (3,686 beds in psychiatry units in total; two tertiary and six non-tertiary hospitals) participated in the study through convenient sampling, based on willingness to participate and proximity to the base institution (The Second Xiangya Hospital). It was not possible to collect data from out-patient clinics affiliated to the eight sampling hospitals because medical records were, by default, withheld by the patients.

The data for this study was drawn from a neuroimaging project on neurodevelopment in early schizophrenia (National Natural Science Foundation of China, Grant number: 81561168021) approved by the Ethics Committee of The Second Xiangya Hospital.

2.2 | Data source and study population

Electronic medical records (EMR) were retrospectively examined for all patients who met the following criteria: (i) inpatient admission between 1st August 2016 and 1st August 2017; (ii) age ≤ 45 ; (iii) discharge diagnosis per the 10th International Classification of Diseases (ICD-10) (World Health Organization, 1992) of schizophrenia, schizophreniform disorder, acute and transient psychotic disorder, schizoaffective disorder, or acute schizophrenia-like psychotic disorder; (iv) duration of untreated illness (DUI) ≤ 18 months; (v) naïve for exposure to antipsychotics, antidepressants, mood stabilizers and hypnotics-sedatives. Exclusion criteria were: (i) discharge diagnosis of substance-induced psychosis or mental retardation; (ii) current psychotic disorder due to a general medical condition; (iii) history of head trauma; (iv) hospital discharge without a psychopharmacological prescription.

2.3 | Recommendations in China's Guidelines for Schizophrenia (Chinese Society of Psychiatry affiliated with Chinese Medical Association, 2015)

Second generation antipsychotics (SGAs), except clozapine, are recommended as first-line treatment in first-episode schizophrenia. Clozapine is recommended for treatment-resistant schizophrenia, defined as the persistence of symptoms despite ≥ 2 trials of antipsychotics of adequate dose and duration with documented adherence(Potkin et al., 2020). Antipsychotics recommended for minors (age under 18) refer to those approved by the US Food and Drug Administration (FDA) for treating minors with schizophrenia, summarized in Table S1.

TABLE S1 Approved age range of antipsychotics for schizophrenia in China’s guidelines

Generic Name	Approved Age Range for Schizophrenia by US FDA (Christian et al., 2012)
FGAs	
Chlorpromazine	12 months to 12 years
Perphenazine	≥ 12 years
Sulpiride	NA
SGAs	
Amisulpride	NA
Aripiprazole	≥ 13 years
Clozapine	≥ 18 years
Iloperidone	≥ 12 years
Olanzapine	≥ 13 years
Paliperidone	≥ 12 years
Quetiapine	≥ 13 years
Risperidone	≥ 13 years
Ziprasidone	≥ 18 years

Abbreviations: FGAs, first generation antipsychotics; SGAs, second generation antipsychotics;

NA, not approved for marketing by US FDA(Bethesda, 2006-).

2.4 | Measures and Data collection

Data collected from EMRs included sex, age, ethnicity (Han and non-Han Chinese), residence, diagnosis, tobacco and alcohol consumption, family history of mental illness, insurance (public health insurance only), hospital level (tertiary or non-tertiary), length of stay (LOS), psychopharmacological prescription at discharge (generic name and dosage). DUI was computed as the time interval from the first noticeable thoughts or behavior change related to psychosis to the admission date (Qiu et al., 2019). At discharge, monotherapy was defined as being prescribed one antipsychotic agent; polypharmacy was defined as being prescribed two or more antipsychotics.

For adults (age $\geq$ 18), high-dose use of antipsychotics was evaluated using prescribed daily dose (PDD) and defined daily dose (DDD). PDD was measured as the dose of antipsychotics prescribed at discharge. DDD is defined as “the assumed average maintenance dose per day for a drug used for its main indication in adults”(WHO Collaborating Centre for Drug Statistics Methodology, 2017). A PDD/DDD ratio greater than 1.5 was defined as high-dose monotherapy. The sum of PDD/DDD ratio greater than 1.5 across all antipsychotics was defined as high-dose polypharmacy (Roh, Chang, Yoon, & Kim, 2015).

For minors (age< 18), unapproved antipsychotic use was defined as: either the use of antipsychotics unapproved for marketing by the US FDA (e.g., amisulpride); or antipsychotics unapproved for specific subpopulations (e.g. olanzapine for schizophrenia in 11-year-old minors) (detailed in Table S1).

Three deviations from the guidelines were examined: (i) polypharmacy for all subjects; (ii) high-dose antipsychotics in adults; and (iii) unapproved use of antipsychotics in minors.

2.5 | Statistical analysis

Mean and standard deviations were calculated for continuous variables. Frequencies and percentages were calculated for categorical variables. Logistic regression was conducted to study linear relationships between factors and likelihood of deviations. A random forest model was built to investigate potential non-linear relationships between factors and deviations (detailed in supporting information). Age, sex, ethnicity, insurance, hospital levels, LOS, DUI, diagnosis, cigarette and alcohol consumption, and family history were included as factors in both models. For model interpretation, odds ratio (OR) and 95% confidence interval (CI) were reported for logistic regressions. Gini-based variable importance and predicted partial dependence plots (PDP)(Gareth, Daniela, Trevor, & Robert, 2013; Molnar, 2019) were used to interpret random forests. Statistical significance was set at P value < .05. All analyses were processed in R 3.5.3.

3 | RESULTS

3.1 | Subjects

There were 602 patients eligible for this study. The majority were male (52.8%), adults (74.3%), and were discharged with a diagnosis of schizophrenia (75.9%) (Table 1).

TABLE 1 Demographic and clinical characteristics of the sample

		N	(%)	Mean/median	SD	Range
Age		602	100	25.08/24	9.03	7-45
Adults (age ≥ 18)		447	74.3			
Male		318	52.8			
Han Ethnicity ^a		587	97.5			
Residency in rural areas ^b		390	64.8			
Insurance ^c	Public health insurance	390	64.8			
	No insurance	198	32.9			
Hospitalization in non-tertiary hospitals		270	44.9			
Length of stay (LOS) (weeks)		602	100	4.62/3.6	4.33	0.3-53
Duration of illness (DUI) (months)		602	100	4.07/2	4.73	0.03-18
Discharge diagnosis	Schizophrenia	457	75.9			
	Schizophreniform disorder	40	6.6			
	Acute and transient psychotic disorders	32	5.3			
	Schizoaffective disorder	6	1.0			
	Acute schizophrenia-like psychotic disorder	67	11.1			
	Family history of mental illness ^d	75	12.5			
Cigarette consumption ^e		34	5.6			
Alcohol consumption ^f		11	1.8			

^a Ethnicity data not available for 1 subject.

^b Residency data not available for 26 subjects.

^c Insurance data not available for 14 subjects.

^d Family history data not available for 6 subjects

^e Cigarette consumption data not available for 13 subjects.

^f Alcohol consumption data not available for 13 subjects.

3.2 | Prescription practice

The most commonly prescribed medications at discharge were oral antipsychotics (99.3%), followed by anticholinergics (33.6%), and mood stabilizers (21.9%) (Table 2). Only four patients out of 602 (0.7%) were not prescribed antipsychotics at discharge: two were prescribed mood stabilizers, and the other two were prescribed either hypnotics-sedatives or a combination of hypnotics-sedatives and antidepressants. No subjects were prescribed long-acting injectable antipsychotics.

Within the 598 subjects discharged on antipsychotics, 590 (98.7%) were prescribed at least one SGAs and 24 (4.0%) were prescribed one FGA. Most of the patients (79.8%) were on monotherapy, with the two most commonly prescribed antipsychotics being risperidone (40.5%) and olanzapine (40.5%) (Table 3). Among the 121 (20.2%) patients prescribed polypharmacy, the most frequent combination of antipsychotics was that of risperidone and olanzapine (17.4%).

Among the 45 (7.5%) patients prescribed clozapine at discharge, 35 of them were adults and 43 were diagnosed with schizophrenia. Clozapine prescription was more common in non-tertiary hospitals than tertiary hospitals ($\chi^2= 8.606$, $P=0.003$) (Table S2), and was more frequently prescribed in antipsychotic polypharmacy ($\chi^2= 81.488$, $P<0.001$) than monotherapy. Compared to those without clozapine prescription at discharge, patients prescribed clozapine had longer mean LOS (8.02 vs 4.35 mean LOS in weeks, $P<0.001$).

TABLE 2 Frequency of prescribed medications at discharge (by class of psychotropic)

	N (n=602)	(%)
Antipsychotics	598	99.3
Anticholinergics	202	33.6
Mood stabilizers	132	21.9
Beta blockers	91	15.1
Antidepressants	62	10.3
Hypnotics-sedatives	55	9.1

TABLE 3 Frequency of antipsychotics prescribed at discharge from the inpatient unit

Generic Name	N	(%)
Monotherapy ^a (n=477)		
Olanzapine	193	40.5
Risperidone	193	40.5
Aripiprazole	31	6.5
Quetiapine	19	4.0
Amisulpride	13	2.7
Clozapine	12	2.5
Paliperidone	5	1.0
Chlorpromazine	3	0.6
Perphenazine	2	0.4
Sulpiride	2	0.4
Ziprasidone	2	0.4
Iloperidone	1	0.2
Perospirone	1	0.2
Polypharmacy ^{bc} (n=121)		
Olanzapine + Risperidone	21	17.4
Clozapine + Risperidone	14	11.6
Aripiprazole + Olanzapine	13	10.7
Quetiapine + Risperidone	12	9.9
Aripiprazole + Quetiapine	6	5.0
Chlorpromazine + Risperidone	6	5.0

^aMonotherapy: being prescribed one antipsychotic agent. ^bPolypharmacy: being prescribed two or more antipsychotics. ^cFor polypharmacy, only the six most frequently prescribed patterns of combined antipsychotics were listed (six out of 28).

TABLE S2 Differences of factors in clozapine prescription

	Clozapine (+) (n=45)		Clozapine (-) (n=553)		χ^2/t	P-value
	N	%	N	%		
Adult (age $\geq$ 18)	35	77.8	408	73.8	0.170	0.681
Male	25	55.6	292	52.8	0.040	0.841
Han ethnicity	44	97.8	539	97.5	NA ^a	1.000
Public health insurance	35	77.8	351	63.5	3.220	0.073
Non-tertiary hospitalization	30	66.7	237	42.9	8.606	0.003**
Polypharmacy ^b	33	73.3	88	15.9	81.488	<0.001***
LOS (week) (mean/SD)	8.02/4.93		4.35/4.18		-4.857	<0.001***
DUI (month) (mean/SD)	4.75/4.45		4.01/4.76		-1.069	0.290
Family history (yes)	4	8.9	71	12.8	0.256	0.613
Cigarette consumption (yes)	0	0.0	34	6.1	NA ^c	NA ^c
Alcohol consumption (yes)	0	0.0	11	2.0	NA ^c	NA ^c

Abbreviations: LOS, length of stay; DUI, duration of illness; NA, not applicable.

^a Fisher's exact test was conducted due to not applicable for chi-square test. ^b

Polypharmacy: being prescribed two or more antipsychotics. ^c Statistical tests not applicable. **P<0.01. ***P<0.001.

3.3 | Deviations from China's guidelines

3.3.1 | Deviations from China's guidelines for polypharmacy prescription

Polypharmacy was prescribed to 99 out of 447 (22.1%) adults and 22 out of 155 (14.2%) minors (Table S3). As reported in Table 4, adults (OR= 1.95, 95% CI 1.14-3.34) and patients with longer LOS (OR= 1.09, 95% CI 1.03-1.14) were significantly more likely to

receive polypharmacy. In random forest models (Figure S1), LOS, age, and DUI were the three most important factors predicting polypharmacy prescription.

As shown in Figure 1, the likelihood of being prescribed polypharmacy increased as LOS increased within two months of LOS, but did not increase further with LOS greater than two months. Patients younger than 11 had higher predicted probability of receiving polypharmacy than any other age group. No clear trends could be drawn about the effect of DUI on predicted probability of polypharmacy prescriptions.

TABLE S3 Frequency of prescriptions deviating from guidelines(Chinese Society of Psychiatry affiliated with Chinese Medical Association, 2015).

Type of deviation from guidelines	Adults (n=443)		Minors (n=155)		Total (n=598)	
	N	(%)	N	(%)	N	(%)
Polypharmacy only	45	10.1	9	5.8	54	9.0
High dose antipsychotics only	93	21.0	NA	NA	93	15.6
Unapproved use of antipsychotics only	NA	NA	23	14.8	23	3.8
Polypharmacy and high dose antipsychotics	54	12.2	NA	NA	54	9.0
Polypharmacy and unapproved use of antipsychotics	NA	NA	13	8.4	13	2.2
Total	192	43.3	45	29.0	237	39.6

FIGURE S1 Variable importance plot in predicting polypharmacy^a prescription

Abbreviations: LOS, length of stay; DUI, duration of untreated psychosis. ^a Polypharmacy: being prescribed two or more antipsychotics.

FIGURE 1 Partial dependence plot of predicted probability of receiving polypharmacy based on length of stay (LOS) (1A), age (1B), and duration of untreated illness (DUI) (1C).

TABLE 4 Multinomial logistic regression of different types of deviations from guidelines

Type of deviation	OR	95% CI	P	
Polypharmacy prescriptions (n= 568 ^a)				
Adult	1.95	1.14	3.34	0.015*
Length of stay	1.09	1.03	1.14	0.001**
Diagnosis of acute and transient psychotic disorders	0.19	0.03	1.01	0.051
High dose prescriptions (n= 420 ^b)				
Age	0.96	0.93	0.99	0.008**
Non-tertiary hospitalization	0.38	0.24	0.59	<0.001** *
Polypharmacy	3.56	2.17	5.86	<0.001** *
Unapproved prescriptions in minors (n=149 ^c)				
Age	0.46	0.34	0.63	<0.001** *
Length of stay	1.29	1.09	1.52	0.003**
Polypharmacy	6.22	1.92	20.3	0.002**
1				

Abbreviation: OR: odds ratio.

^a Not included 30 observations with missing values. ^b Not included 22 observations with missing values. ^c Not included 6 observations with missing values. *P<0.05. **P<0.01.

***P<0.001.

3.3.2 | Deviations from China's guidelines for dosage

Among 443 adults, 147 (33.2%) were prescribed high dose antipsychotics (Table S3). As reported in Table 4, subjects with non-tertiary hospitalization (OR=0.38, 95% CI 0.24 - 0.59, compared to tertiary hospitalization) were less likely to be prescribed high-dose antipsychotics. Patients of younger age (OR= 0.96, 95% CI 0.93-0.99) and receiving polypharmacy (OR= 3.56, 95% CI 2.17 - 5.86, compared to monotherapy) were more likely

to receive high-dose antipsychotics. Olanzapine, quetiapine and amisulpride were dosed higher when used as mono- vs. polypharmacy (Table S4). In random forest models (Figure S2), LOS, age and DUI were the three most important factors predicting high-dose use. As shown in Figure 2, the likelihood of receiving high dose antipsychotics increased as LOS increased within nine weeks of LOS and but did not increase further after nine weeks of LOS. Younger patients were more likely to receive high-dose antipsychotics. Patients with shorter DUI (<2months) and longer DUI (>12months) were more likely to receive high-dose antipsychotics.

TABLE S4 Dosage of single antipsychotic in monotherapy^a and polypharmacy^b

	Monotherapy ^a		Polypharmacy ^b		P-value
	Mean	SE	Mean	SE	
Amisulpride	800.0	66.67	542.9	84.11	0.033*
Aripiprazole	24.8	2.98	18.2	1.55	0.061
Chlorpromazine	500.0	0	125.0	21.13	NA ^c
Clozapine	164.3	47.51	73.1	11.55	0.106
Olanzapine	15.9	0.38	11.0	0.81	<0.001***
Paliperidone	8.0	1	9.0	NA ^d	NA ^d
Quetiapine	413.1	58.81	219.0	39.8	0.011*
Risperidone	4.1	0.09	4.3	0.23	0.559
Sulpride	900.0	100	400.1	136.21	NA ^c
Ziprasidone	160.0	NA ^d	100.0	15.49	NA ^d

^a Monotherapy: being prescribed one antipsychotic agent. ^b Polypharmacy: being prescribed two or more antipsychotics. ^c Sample size is not large enough to conduct t-test. ^d Only one observation in the sample. *P< 0.05. ***P< 0.001

FIGURE 2 Partial dependence plot of predicted probability of receiving high dose antipsychotics based on length of stay (LOS) (2A), age (2B), and duration of untreated illness (DUI) (2C) in adults.

FIGURE S2 Variable importance plot in predicting high dose prescription in adults

Abbreviations: LOS, length of stay; DUI, duration of untreated psychosis.

3.3.3 | Deviations from China’s guidelines for unapproved use of antipsychotics

Among 155 minors, 36 (23.2%) received antipsychotics with unapproved use (Table S3): 25% of these were younger than 12. As shown in Table 4, minors with younger age (OR= 0.46, 95% CI 0.34-0.63), longer LOS (OR= 1.29, 95% CI 1.09-1.52) and polypharmacy (OR= 6.22, 95% CI 1.90-20.31, compared to monotherapy) were more likely to be in unapproved use of antipsychotics. In random forest model (Figure S3), age, LOS and DUI were the three most important factors predicting unapproved use. As shown in Figure 3, the predicted probability of unapproved use was higher for minors under 13 than any other ages, minors with longer LOS, and those with shorter DUI (<2 months), respectively.

FIGURE 3 Partial dependence plot of predicted probability of receiving unapproved antipsychotics based on length of stay (LOS) (3A), age (3B), and duration of untreated illness (DUI) (3C) in minors.

FIGURE S3 Variable importance plot in predicting unapproved use of antipsychotics in minors

Abbreviations: LOS, length of stay; DUI, duration of untreated psychosis.

4 | DISCUSSION

This is the first study to explore treatment practices for inpatients with drug-naïve first-episode schizophrenia-spectrum (FES) disorders in China, after the release of the latest national guidelines.

Most patients, at discharge, were prescribed a single antipsychotic, which is consistent with guideline recommendations. None of the patients were prescribed long-acting injectable antipsychotics. One in five patients was prescribed polypharmacy. Among adults, one-fourth were prescribed high-dose antipsychotics. In minors, one-fifth received an unapproved antipsychotic at discharge. Patients with longer length of stay (LOS) had higher likelihood of being prescribed polypharmacy. Within adults, high-dose antipsychotics were more likely to be prescribed to younger adults, and to those receiving polypharmacy (compared to monotherapy). Unapproved antipsychotic prescription in minors was more likely to be directed at those below age 13, and in those with longer LOS.

4.1 | Prescription practice

As expected, the majority of patients were discharged with a prescription for antipsychotics, and most received SGAs, mainly risperidone and olanzapine, which is consistent with practice in the U.S. (Robinson et al., 2015). While there is a lack of robust evidence supporting the preferential use of olanzapine or risperidone versus other SGAs (Komossa et al., 2010; Temmingh, Williams, Siegfried, & Stein, 2018), this may be explained by greater medication availability and prescriber familiarity, as both drugs have been available in China since the late 1990s. However, prescribing olanzapine to first-episode patients as first-line treatment has become controversial (L. B. Dixon & Stroup, 2015). Increasing evidence shows significant severe adverse metabolic effects caused by olanzapine which can increase risks for cardiovascular diseases and diabetes (Correll et al., 2014; L. B. Dixon & Stroup, 2015; Tek et al., 2016). Close monitoring and management of adverse metabolic effects are needed after discharge to reduce long-term risks and to maintain medication adherence (Curtis et al., 2012; M. Ferrara et al., 2015). This would require an increased engagement of community-based mental health care services, currently not available in China.

None of the patients were prescribed long-acting injectable (LAI) antipsychotics at discharge. This may be related to China's guidelines that recommend LAI for patients only with poor medication compliance or multiple relapses, in contrast to evidence showing benefits earlier in the course of treatment (Stahl, 2014). Alternatively, higher costs, reduced availability in non-tertiary hospitals or psychiatrists ambivalent or negative attitudes toward

LAIs may influence patient acceptance of these medications (Liu et al., 2015; Weiden et al., 2015).

In our study, 7.5% FES patients were prescribed clozapine. As the prevalence of treatment-resistant schizophrenia is estimated to be 20% among FES (Demjaha et al., 2017), this suggests clozapine underutilization, consistent with previous studies (Tang et al., 2016; Thien et al., 2018). Additional training on the safe and optimal use of clozapine may be helpful.

4.2 | Deviations from China's guidelines

In our sample, the prevalence of polypharmacy (20.2%) is higher than that in the US (11.0%)(Robinson et al., 2015) and U.K. (7.4%)(Tungaraza et al., 2017). China's guidelines discourage polypharmacy in keeping with the lack of robust evidence for effectiveness over monotherapy(Fleischhacker & Uchida, 2014). Also, prescribing more than one antipsychotic may increase adverse effects and medical costs(Putignano, Clavenna, Reale, & Bonati, 2019). Auditing the most difficult cases in routine workflows may guide quality improvement approaches to promote adherence to current guidelines (Severi et al., 2018).

Both random forest and logistic regression models showed longer LOS was associated with higher likelihood of polypharmacy prescription, which is consistent with a previous study(Saldaña et al., 2014). As LOS has been shown to be influenced by multiple factors including patients' disease severity, prescriptions during hospitalization, and insurance type (Baeza, da Rocha, & Fleck, 2018), more information is needed to explain the relationship between LOS and polypharmacy at discharge.

Among adults, one-third were discharged with high-dose antipsychotics, a known risk factor for side effects(Centorrino et al., 2004), without evidence for improved efficacy(Mace & Taylor, 2015). Lower doses of individual antipsychotics were used within polypharmacy compared to monotherapy, however, patients receiving polypharmacy were more likely to be prescribed high-dose antipsychotics vs. those receiving monotherapy. This can place a greater burden of monitoring and management of side effects upon already under-resourced outpatient services. Compared to hospitalizations in non-tertiary facilities, patients admitted in tertiary hospitals were more likely to receive high-dose antipsychotics.

This finding might reflect the admission or transfer of patients with more severe illnesses to tertiary hospitals.

In minors, the prevalence of unapproved use of antipsychotics (23.2%) is below the lower limit of the range reported in previous studies (36.0% to 93.2%(Putignano et al., 2019)) but still clinically significant. Minors below 13 had higher odds of receiving unapproved prescriptions. This prescription practice could be a consequence of limited studies informing evidence-based treatment of childhood schizophrenia, and limited antipsychotics approved for minors under 13(Christian et al., 2012). Our finding that 25% of 36 minors who were prescribed off label antipsychotics were younger than 12 years old are even more significant if we consider that only chlorpromazine is recommended by FDA for children under 12 years old (Christian et al., 2012). When there is a scarcity of evidence-based recommendations, unapproved use can depend on the attitudes and competence of psychiatrists(Putignano et al., 2019). Moreover, unapproved medications are more likely to be implicated in adverse reactions (Brauner, Johansen, Roesbjerg, & Pagsberg, 2016), and minors have more variable antipsychotic pharmacokinetics(Caccia, 2013). These factors make unapproved prescriptions more problematic. Further research is needed to better guide prescription practices in the youngest patients.

4.3 | Strengths and limitations

Since the vast majority of mental health care in Hunan is provided by inpatient facilities, our study provides a good representation of current practice and highlights specific gaps in guideline implementation. Education, training and research, as well as improved monitoring and management systems after discharge, will be needed to deliver guideline concordant care.

This study combined, for the first time, logistic regression and random forest to model the relationship between factors and deviations from China's guidelines. The two models gave similar prediction trends. In addition to the linear relationships modeled by logistic regression, our further analysis using random forest revealed that length of stay had a significant impact on all three deviations from China's guidelines.

This study had several limitations. The convenience sample may have limited representativeness. However, the sample included the two best-rated tertiary hospitals in

Hunan, which suggests that greater deviations from the guidelines might exist in the out-of-sample hospitals. Data on symptom severity at admission were not collected which makes it difficult to investigate the rationale for prescription practice and deviations from guidelines. Moreover, data on clinical outcomes at discharge were not collected, which limits the interpretation of the results. Also, since the sample was drawn from inpatient psychiatric hospitals, with more acute, aggressive, and rapidly escalating clinical presentations, the findings may not generalize to outpatient facilities. Further investigation of FES care in outpatient services is necessary.

5 | CONCLUSIONS

Our study showed that, at discharge, most of the inpatients diagnosed with first-episode schizophrenia were prescribed antipsychotic monotherapy, in compliance with current guidelines. Our findings suggested potential challenges to optimal prescription practices, especially for minors and treatment-resistant schizophrenia. More research, education, and training is warranted to verify and resolve these challenges. Given the ongoing implementation of China's National Mental Health Working Plan, these results provide a useful representation of current inpatient practice in China, and can inform resource allocation toward optimal treatment of first-episode psychosis.

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CHAPTER 8

DISCUSSION

Discussion

The overall aim of this thesis was to investigate how different strategies, within a population health framework, can shape the course of first episode psychosis, through early detection and early intervention efforts. My research has raised different questions pertaining to this issue, which are summarized below.

Are early detection efforts able to reach all subjects equally or are these more effective in subgroup of patients?

The first two to five years after the first episode of psychosis represent a critical period that can shape the prognosis of a potentially devastating and disabling illness. Thus, early detection and early intervention that aim to reduce the duration of untreated psychosis have become a public health priority. The most successful effort so far has been the one implemented in the Northern Europe, the TIPS Study.

The TIPS Study had demonstrated that it is possible to reduce the duration of untreated psychosis by implementing a massive early detection (ED) effort. In the first two years since its implementation, the DUP was halved (median 5 vs 16 weeks in the control area) in the area reached by the TIPS campaign. The immediate effect of this reduction resulted in a less severe clinical presentation of participants with first episode psychosis at entry to care, including a reduction in suicidality (Melle et al., 2004). The long-lasting effects of the reduction of DUP were observed up to 10 years later: a higher proportion of patients coming from the ED area had achieved symptoms remission (compared to those coming from the control area not exposed to the campaign) (Ten Velden Hegelstad et al., 2013). What remains to be understood is the possibility that the ED effort had a different effect across the DUP distribution. **Chapter 2** described how quantile regression was applied to investigate this potential different effect of the ED campaign. It also explored if this differential impact across DUP quantiles was moderated by demographic, clinical, premorbid and social factors. As hypothesized, the DUP reduction was not observed in

those with short DUP, but the campaign had significant effects in the second and third quartiles of DUP. This aligns with the previous result of the TIPS study that underlined the fact that they were able to attract to care those with longer DUP. With the current study, I demonstrated that those with longer delays were also those who benefited the most by the ED efforts. Our study also found that the TIPS study recruited men, and singles (across genders) with significantly longer DUP in the upper tail of the distribution. However, gender did not seem to be a moderator of ED (M. Ferrara, Guloksuz, et al., 2019). This result provides a further element of discussion to what delineated in **Chapter 6**: women need targeted early identification efforts, and tailored programs to promote access to specialized care for psychosis. Our study also found that single patients tended to have longer DUPs but they were also those who benefited the most from the DUP reduction.

With this current study, I was able to demonstrate that the TIPS ED efforts had a differential effect across the DUP distribution and across other social characteristics. These findings provide useful insights to investigators, clinicians, and stakeholders who want to implement an ED initiative. The message and the outreach activities need to be tailored to meet the different needs according to gender, marital status, living condition, and duration of untreated illness.

Can we implement First Episode Psychosis services within the pre-existent community mental health services in Italy?

In Italy, the provision of Early Interventions for Psychosis varies across the different regions. Since the inception of the early intervention program called Progetto2000 in Milan, it has been shown that the implementation of FES in Italy have been suffering the historical disparities of resources and resources utilization across the country. Accordingly, the majority of FES have been implemented in the northern regions that have a more developed economic asset (A. Cocchi, Meneghelli, A., Preti, A., Cavicchini, A., Collavo, M., Macchi, S. , 2011; Meneghelli, Cocchi, & Preti, 2010). Moreover, a very recent report underlines that even within implemented FES, the provision of services varies across them. Targeted individuals might vary (affective vs non-affective psychosis, FEP only vs FEP and CHR), as well as the type of interventions provided (i.e. individualized psychotherapy only vs a “care package” that include psychotherapy, pharmacotherapy, psychoeducation and supported employment) (Addington et al., 2020).

In 2012, the region Emilia-Romagna in the Northern Italy has formulated regional recommendations for the implementation of FEP services across the region, targeting individuals with first episode psychosis and at risk of developing psychosis (Gruppo di lavoro Esordi Psicotici, 2016). The Department of Mental Health and Substance Abuse in Modena province has been overseeing the implementation of such recommendations in the nine provinces of the region. The recommendations were targeting individuals aged 18-35 years, experiencing a non-organic primary psychotic disorder (affective and non-affective), treated for no more than two years, and resident in the region.

As outlined in **Chapter 3**, the Department of Mental Health and Substance Abuse in Modena was able to implement the program in 2013. The program includes individualized psychotherapy and pharmacotherapy, family psychoeducation, supported employment and education, programs for social inclusions, monitoring of physical health and wellbeing. The program also offers rapid consultation for potential candidates by a close collaboration with primary care physicians, emergency departments, and other services (i.e. social services). From March 1 2013, to December 31 2016, the Modena community mental health services were able to admit into care 100 individuals, observing: 1) a treated incidence higher than what previously published ($19.1/10^5$) (Gigantesco et al., 2012; Lasalvia et al., 2012), 2) a

relative higher proportion of migrants compared to the resident population, 3) a progressive reduction in the duration of untreated psychosis (median 6 months in 2013 vs 4 months in 2016), 4) a pronounced involvement of primary care physicians as main referrers to the program, and 5) clinical improvement after 6 months since admission to care.

This study is the first report establishing the feasibility of the implementation of a regional program in the Modena Province. While confirming the feasibility of such program in the pre-existent community mental health services, it also underscores the higher than expected incidence which demands a stronger attention to resource diversion. It also confirms what others have already reported: a subgroup of the resident population, such as migrants, might need further studies and a targeted approach to interpret these findings and find possible solutions. A population health framework, such as the one implemented at STEP, might offer a smart strategy to approach these real-world challenges (M. Ferrara, Mathis, et al., 2019).

As outlined in **Chapter 7**, there are Countries where a coordinated effort to implement community FES hasn't been implemented as a whole, and most of the FEP care relies on the treatment received in the inpatient units (for those who are admitted). In Hunan Province, most patients, at discharge, were prescribed a single antipsychotic, which is consistent with guideline recommendations. Interestingly, none of the patients were prescribed long-acting injectable antipsychotics. One in five patients was prescribed polypharmacy, especially patients with longer length of stay. In minors, one-fifth received an unapproved antipsychotic at discharge, particularly in those aged 13 and below. As detailed in **Chapter 7**, treatment practices for inpatients with drug-naïve first-episode schizophrenia-spectrum disorders in Hunan Province, China, might differ from the latest national guidelines released in 2015, but these findings can guide changes in processes and practice.

Is the first help seeking attempt for psychosis symptoms pivotal in shaping the pathways to and through care?

The initial actions undertaken by patients, caregivers, and the network of community resources by setting in motion the very first help seeking attempt for psychosis play a pivotal role in shaping the pathway to specialized care. In a domino-like effect, the first help-seeking event defines the personal experience of the distressed patient within the healthcare system. While it has the potential to create a new supporting net for the help-seeker, the first such help-seeking event could also alter the outcomes of a potentially disabling illness like psychosis, during what has been defined as “the critical period” for changing its prognosis (M. Birchwood et al., 1998). As a result, the study of the first help-seeking event can reveal how events unfold in the real world in order to foster optimal ED efforts.

In order to tailor early interventions and ultimately prevent treatment delays, it is important to understand how individual characteristics and timing of the first instance during which patients or caregivers seek help for psychosis influence participants’ interactions with the healthcare system. In the exploratory study detailed in **Chapter 4**, we analyzed the first help-seeking attempts of individuals admitted to a specialty team-based psychosis service (STEP in New Haven, CT). This is the first study to quantitatively interrogate the comparative impact of help-seeking in the prodromal versus post-psychotic phases of recent onset schizophrenia. 82% of 168 enrollees reported their first help-seeking episode only after psychosis onset. Psychosis help-seekers did not differ in terms of demographic (gender, race, age at psychosis onset or admission to care), socioeconomic (accommodation, household income) or functional (GAF) variables at enrollment from prodromal help-seekers. When the first help-seeking episode was initiated during the prodrome, patients were more likely than family members to initiate help-seeking, while the reverse was true after psychosis onset. Help-seeking during the prodrome was associated with shorter delays to first antipsychotic treatment after psychosis onset (median of 21 vs. 56 days), and this reflected the benefits of being in care during conversion to psychosis (Lucia R. Valmaggia et al., 2015). Our investigation of the quality of these pathways, as measured by the frequency of aversive events (involuntary admission to inpatient psychiatric units, interactions with the police), did not reveal significant differences between the two groups. While as many as one in five patients, mostly men, had at least one interaction with the police before enrollment in our FES, reassuringly this rarely

resulted in incarceration and might reflect the active role of jail diversion and crisis intervention training for police in our catchment as outlined in **Chapter 5** (Pollard et al., 2020). However, the degree of police involvement in intercepting FEP likely varies across regions and patient sub-groups, thus limiting the generalizability of these findings (Dinesh Bhugra, 2000; Broussard et al., 2010; Compton et al., 2006). Other regions may have higher rates of inappropriate diversion to the criminal justice system after disruptive psychosis driven behavior, where the comparative benefits of help-seeking during the prodrome could be greater.

The strengths of this study included the use of the Structured Interview for Psychosis-Risk Syndromes (SIPS) instrument to explicitly identify and date the onset of both the prodromal phase and the transition to full-blown psychosis. When integrated with the detailed pathways to care interview, this allowed a granular measurement of the pathways that patients and their families undertake as they access care, both in terms of time (delay) and quality (aversive interactions).

This approach also provides actionable information for early detection efforts. Proactive and age-appropriate early detection efforts that target prodromal samples may both reduce DUP and aversive pathways, and better leverage the impact of local FES (L. R. Valmaggia et al., 2015).

Conclusion and Future Perspectives

In the last 20 years, psychiatry has not progressed at the same speed as other specialties of medicine, such as oncology or infectious disease. Psychosis still represents an insidious and potentially devastating disease: individuals affected by psychosis recover only in 15% of cases and they die 15-20 years earlier than their peers without a severe mental illness.

One of the cultural revolution that happened in the last 20 years was that of early intervention. Substantial data coming from different health system and countries have shown that, by intervening early in the first few critical years since psychosis onset, there is the possibility to improve drastically patients' prognosis.

As outlined in **Chapter 2**, early intervention efforts need to take into account socio-demographic characteristics, such as marital status, living condition, gender, and duration of illness in order to personalize the outreach efforts and make them more effective. Quantile regression has been successfully used in this project to interpret the results of the TIPS early detection efforts and can be used to reexamine prior, and plan analyses for future interventions. Such efforts should also include a detailed analysis of the whole pathway to care, as a key to understand the complexity of the events occurring while psychosis unfolds, which include help-seeking attempts, the interactions with the network of care (health and non-health providers, i.e. school), and possible aversive events.

When a system of care adopts a population health approach to design interventions for first episode psychosis, the benefits are not only limited to the subgroup of individuals with FEP, but they involve the whole population. For example, the enrollment of a patient in FES led to a lower risk of interaction with the criminal justice system, as compared to patient admitted to usual care (see **Chapter 5**). This result translated in better outcomes for the single individual, and for the community as a whole.

There are several subgroups that can be identified through a systematic analysis of real-world data. **Chapter 7**, For example, it is possible that behind the higher incidence of FEP in migrants compared to the proportion of migrants residing in the area, as discussed in **Chapter 3**, there are social determinants that can be tackled with the involvement of key stakeholders. As outlined in **Chapter 6**, women are underrepresented in FES, and thus there

is a risk that their needs are being overlooked. A population health approach can help re-define criteria for accessing FES (for example by expanding the age range), and facilitate women's engagement with FES through the coordination with other services, such as child-care, and social services. FES can also play a key role in helping women receiving the best care: for example, by encouraging women in accessing preventive medicine visits (i.e. breast cancer screening, HPV vaccination).

In conclusion, findings from data-driven early detection and early intervention efforts sustained by a population health approach targeting individuals affected by a first episode of psychosis can inform the implementation of tailored services in our communities and lead future research.

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CHAPTER 9

SUMMARY

Chapter 1 provides an overview on the prevalence and incidence of primary psychotic disorders. It includes the rational of interventions conducted across the world aimed at reducing the duration of untreated psychosis (DUP). Finally, it introduces the concept of population health as a comprehensive approach to design early detection (ED) initiatives for first episode psychosis.

Chapter 2 presents the use of quantile regression analysis for examining the differential impact of the TIPS early detection initiative across DUP. Secondary analysis explored possible predictors of DUP, and moderators of the effect of the TIPS campaign. 281 patients with first episode psychosis were recruited, including 141 from the ED area. ED had no effect on the first quartile (Q1) of DUP, whereas a significant reduction in Q2 (11 weeks), and Q3 (41 weeks) of DUP was observed. The effect of ED was significantly stronger on reducing Q3 than Q1 or Q2, suggesting that the campaign was more effective in longer DUP samples. Male gender and single status predicted longer DUP in Q3: by 38 and 27 weeks, respectively. Single status, but not gender, emerged as a significant moderator of ED campaign effect. This study offers evidence that quantile regression provided in depth information about the non-uniformity, and moderators, of TIPS's ED effort across the full distribution of DUP, demonstrating the value of this analytic approach to reexamine prior, and plan analyses for future, early detection efforts.

Chapter 3 reports on the development of an early intervention service in Modena, Italy, with information relevant to the first four years of implementation. The 2-year service was offered to people aged 18-35 with psychotic manifestations, within 2 years from psychosis onset/or naïve to antipsychotics, by teams placed within community mental health centers, according to a “specialist within generalist” model designed by the Regione Emilia-Romagna. Treatment included pharmacological consultation, psychoeducation and social inclusion programs. One hundred cases accepted the treatment from 1 March 2013 to 31 December 2016. Of these, 71% were male with a median age of 23, yielding an estimated treated incidence of 19.1/105. General practitioners represented the most frequent referrers to the program (38%), followed by referrals from acute general and psychiatric hospital units (22%) and self-referrals (14%). Meaningful clinical improvement was observed, 6 months after enrolment. This study is the first to report outcomes of an early intervention service for psychosis successfully

implemented within existing community outpatient services. The promising clinical improvement and the trend of reduction in duration of untreated psychosis supports the variety of early detection efforts in the community. These findings can inform refinement of treatments and service models for the Region.

Chapter 4 reports on an exploratory study on the timing of the first help-seeking attempt in individuals with recent onset non-affective psychotic disorders. The study compared those who sought help during the prodrome to those who sought help after psychosis onset in terms of sociodemographic and clinical characteristics, overall functioning, and occurrence of adverse events during their pathways to care. Of 168 individuals, 82% had their first help-seeking event after psychosis onset, and did not differ in terms of sociodemographic characteristics from prodrome help-seekers. When the first help-seeking episode started before vs after psychosis onset, it was mostly initiated by patients vs family members and led to a more rapid prescription of an antipsychotic once full-blown psychosis emerged (time to antipsychotic since psychosis onset= 21 vs 56 days, $p=.03$). No difference in aversive events before enrollment into care was detected across groups. These findings can inform early detection efforts: targeting prodromal samples may leverage reductions in DUP and aversive pathways to care.

Chapter 5 presents the secondary analysis of a pragmatic randomized clinical trial of a FES (Specialized Treatment Early in Psychosis [STEP]) vs usual treatment for criminal justice outcomes, as it is well known that new-onset psychotic disorders can interact with the criminal justice system during their pathways to care. This analysis found that FES is associated with reduced criminality. Of 117 patients with recent-onset psychosis, only a minority (14[12.0%]) had convictions prior to allocation. After adjusting for prior convictions, patients allocated to STEP were significantly less likely to be convicted of any crime (odds ratio, 0.19; 95%CI, 0.04-0.85; $P = .03$) and non-significantly less likely to be sentenced to jail (odds ratio, 0.22; 95%CI, 0.05-1.01; $P = .05$). Notably, there was a 76% reduction in the risk of committing a first crime for those assigned to STEP vs usual treatment (hazard ratio, 0.24; 95% CI, 0.07-0.86; $P = .02$). Participants assigned to STEP also had a non-significantly lower 5-year first crime rate (5.00%; 95%CI, -0.51-10.51) compared with those assigned to usual treatment (17.54%; 95% CI, 7.66-27.42). These findings that need to be replicated in larger

samples offer an important insight on the positive social consequences of FES that can inform service design and policy.

Chapter 6 is a viewpoint on the risk of underestimating the gender-specific needs of women in accessing FEP care and receiving the best quality of care in FES. The four factors that could represent barriers in accessing care are: 1) older age at onset, 2) clinical presentation characterized by prominent mood symptoms and overall better functioning, 3) less involvement of emergency departments in pathways to care, 4) gender role and caregiving burden (children and elderly). The three factors that should receive more attention in FES are: 1) sexual and reproductive health, as psychosis manifest during the period of greatest fertility for women, 2) promote access to preventative medicine (i.e. breast cancer screening), 3) offering trauma-focused interventions.

Chapter 7 provides an overview of the findings and discusses them in the light of the evidence of the change in the perspective of care of first episode psychosis. It offers the population health approach as a new framework to design services for first episode psychosis that can benefit not only the single individual but the entire community. It also provided directions for future research.

CHAPTER 10

IMPACT

Impact

Psychotic disorders include schizophrenia(s) and affective psychoses (bipolar and major depressive with psychotic features). The peak age of onset is 22 years for males (McGrath et al., 2004); women have the first peak of incidence around 25 years, and an adjunctive peak in their late fifties (Jongsma et al., 2018). The lifetime risk of psychosis is 3.5% (Perälä et al., 2007), the world prevalence is 1% for schizophrenia (the most severe form of psychosis). Psychosis leads the societal cost and productivity loss per single individual within mental health disorders, and follows autism for non-health care cost per patient (Christensen et al., 2020).

The implementation of Early interventions for psychosis has proven its superior benefit compared with usual care by reducing the duration of untreated psychosis (DUP), and by providing targeted and multi-component interventions(Penttilä et al., 2014). Despite the solid evidence of the effectiveness of EIS in shaping prognosis, the implementation of EIS is sparse and not homogeneous across countries and health systems.

We need a better understanding on what works for whom in terms of early interventions, in order to tailor early detection efforts, optimize treatment and measuring key outcomes.

Relevance

Initiatives to reduce DUP have become of public health imperative(L. Dixon, 2017; Malla & McGorry, 2019). Converging evidence has demonstrated the positive effect of early detection efforts on improving short and long term outcomes for psychosis (up to 10 years later)(Ten Velden Hegelstad et al., 2013).

Given the high societal cost of psychosis(Christensen et al., 2020), it is necessary to define new approaches to translate research finding into real world practice.

This thesis seeks to provide insights on the effect of ED strategies, real world examples of the implementation of such services in community mental health services, and new information on pathways to care of individual with FEP.

The findings add important data to the scientific literature on FEP and strategies to reduce DUP.

This thesis has filled an important gap in the field of FEP: for the first time, it employed quantile regression to derive new information on the results of the TIPS study, it also used quantitative and detailed methods to understand key events along the pathways to care. This thesis offers evidence of the feasibility to implement a local functional FEP service within local community mental health services, underscored the positive effect of FEP service in reducing aversive outcomes (such as interactions with the criminal justice system), and the value of intervening earlier in the course of illness by showing that prodrome help seekers can benefit of a reduced DUP because already connected to the network of care.

Although a lot has been written on efficacy of strategies to reduce DUP, this thesis provides evidence of the importance of implementing such efforts to prevent a potentially disabling and costly disease.

Target groups

Psychoses can have a potential disruptive impact on the life trajectory of a young adult individual, therefore it is imperative to adopt the best strategies to reduce such impact and improve outcomes. The findings of this thesis offer new methods and new perspective useful for the design of FES and for tailoring extant FES to the need of sub-groups of patients.

A wide array of professionals can benefit from the application of the finding of this thesis. Mental health providers working in the field can see the positive result of a feasibility project for the implementation of FES in extant community mental health settings: the positive results obtained in Modena province represented the great opportunity to show that it could be possible to offer the best treatment to all FEP in the catchment area.

Community leaders and service users, such as patients with FEP and their families, can see in this thesis the attempt to offer an optimistic approach to a potentially very disabling disease. While many questions about etiology and biomarkers of psychosis are still unanswered, this thesis provides evidence of the effectiveness of early detection interventions, and new insight on how to build better services tailored around patients' needs.

The population health approach described in this thesis offers a comprehensive framework to involve all the key players in the network of care in building a service for first episode psychosis. This perspective allows to counterbalance the importance which is usually given to medical care over all the other determinants of health and therefore several approaches to care. A key element of this approach is the involvement of stakeholders in the decision-making process, thus obtaining a consensus list of outcomes that respond to all the key players' values.

As outlined in this thesis, criminal justice outcomes for FEP can have not only clinical consequences but also societal consequences (e.g. reduction of crimes and costs related to legal procedures and incarceration). This is just one example of the importance of stepping outside the "comfort" of the clinical zone and move towards a broader population health approach for psychosis. This approach can also be applied to address the many challenges suffered by women with a first episode of psychosis. As outline in this thesis, if you are a woman, gender can represent a barrier preventing access to the best care for FEP. A first episode psychosis service that embraces a population health approach can work closely with health agencies, local communities, and key decision-makers to address these challenges by building an integrated supportive network of care.

Hopefully, a first episode psychosis service that looks at the imminent future should be able to collect data, interpret results, and then transform findings in actionable items that respond to stakeholders' values within a population health framework(Malla & McGorry, 2019; Srihari & Kane, 2019).

Innovation

This thesis is innovative in several specific ways.

First, it showed that, by using a different approach, it is possible to quantify the results of early detection efforts, enabling a tailored planning of initiative to shorten duration of untreated psychosis.

Second, it showed the preliminary results of the implementation in Modena province of the Regione Emilia Romagna (Italy)' First Episode Psychosis Program; the ongoing Regional Program represents the only initiative currently operating in Italy aimed to offer a coordinated specialty care service to subjects diagnosed with first episode psychosis, within the public mental health system of care.

Third, it offers a glimpse on the key importance of the timing of the first help seeking episode in shaping the pathways to care of young individuals suffering from their first psychosis outbreak.

Lastly, it offers two examples of the application of a population health approach to FES: it shows that FES are superior compared to usual care in reducing criminal justice outcomes for subjects with FEP, moreover FES can play a key role in improving access to and quality of care for women with FEP by tailoring the service provided to their gender-specific needs.

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An Italian proverb goes like this: “Quando si chiude una porta, si apre un portone” (lit: When one door shuts, a bigger doorway opens). Honestly, I had never had faith in it, until I was offered a Postdoctoral position at Yale School of Medicine and started working towards this PhD thesis.

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Curriculum vitae

Maria Ferrara was born on December 13th 1982 in Sassuolo, Italy. She received her medical doctor degree from the University of Modena and Reggio Emilia in 2007, and she was awarded for the Best Experimental Graduation Thesis. In 2008, she started her residency in Psychiatry at the same University. During her residency, she won a Scholarship Award to attend the first European Psychiatric Association Summer School in Comorbidity between mental & Physical Disorders. In 2011, she obtained a visiting scholar position at the HIV Neurobehavioral Research Program (HNRC) in San Diego, UCSD, where she designed and conducted a research project on the combination of antipsychotic and antiretroviral therapy. In 2011, she gave input for the institution of the World Psychiatric Association HIV/AIDS Psychiatry Section, of which she served as vice-president until 2019. She obtained a Master in Psychopharmacology Program from the Neuroscience Education Institute, the Master Degree in “Addiction: theory and clinical intervention” at the Beck Institute in Rome, and she was awarded with a fellowship to attend the Neuropsychopharmacology Summer School, held by the European College of NeuroPharmacology (ECNP), in Oxford, UK, in 2013.

Upon the completion of her residency, in 2012, she was involved from the start in the Program for First Episode Psychosis promoted by the local Government of Regione Emilia-Romagna. She soon attained the role of coordinator in the group, and she led the implementation of a first episode psychosis program in the Modena Province.

In 2017, she started to work as a Post-Doctoral Associate at Yale University Department of Psychiatry, at the Program for Specialized Treatment Early in Psychosis (STEP), where she acts now as research coordinator. During her work at STEP, she obtained the Yale certification as assessor and trainer for the Structured Interview for Prodromal Syndromes (SIPS) by Dr. Barbara Walsh, becoming the only Yale certified SIPS trainer in Italy. In 2018, she won a Travel Award to attend the Schizophrenia International Research Society SIRS Conference in Florence, Italy.

In 2018, she started her Ph.D. at the School for Mental Health and Neuroscience in the Department of Psychiatry and Neuropsychology at Maastricht University.

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Freudenreich O., **Ferrara M.** HIV Psychiatry Bibliography, Academy of Psychosomatic Medicine <https://www.clpsychiatry.org/member-resources/clinical-monographs/hiv-biblio/>

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