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First-Episode Psychosis: An Overview of Research in Iran

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In the last two decades, the importance of developing strategies that reduce the burden of new onset psychosis on affected persons, their families, and the community has been recognized. This article reviews the literature on First-episode psychosis (FEP) in Iran. In the last decade, several studies on FEP have been published in Tehran concerning Duration of untreated psychosis (DUP), pathways to care, diagnostic stability, outcome predictors, treatment, aftercare services, psychosocial interventions, and Neurological soft signs (NSSs). However, the samples in most studies were small, and most participants were recruited from inpatient wards. Therefore, caution must be exercised when generalizing the results to patients with FEP in the community, particularly in other parts of the country. We conclude that it is necessary to conduct follow-up research with sufficiently large samples from the community to support the previously published longitudinal studies on FEP, as well as to help to inform the development of specialized FEP and early intervention services.

Keywords: Early psychosis • First-Episode Psychosis • Iran

Introduction

First-episode psychosis (FEP), the first presentation of psychotic symptoms or signs, usually occurs in adolescents or young adults [1,2]. The effect of FEP on the patients, their families, and the community can be immense. Patients often become confused, frightened, depressed, socially isolated, and overwhelmed by the disruption to their lives and goals [3,4]. In the last two decades, attention is being paid on developing strategies that reduce the individual, social, and economic burden of new onset psychosis on affected persons, their families, and the community. A study from Nottingham, England estimated the incidence rate of FEP to be at least 1.36 per 100,000 people (0.74 per 100,000 men and 1.99 per 100,000 women) [5]. However, in Melbourne, Australia, the age-specific treated incidence of FEP in 15–29-year-old persons was reported to be much higher (16.7 per 10,000 person-years in males, and 8.1 per 10,000 person-years in females) [6]. Susser and Wanderling (1994) reported that the incidence of non-affective acute remitting psychosis in developing countries is ten times higher than that in industrialized countries [7]. The incidence of schizophrenia differs between various populations around the world, and the distribution is asymmetric, with a median of 15.2 (7.7-43.0) per 100,000 people [8]. These distributions are also significantly influenced by sex, urbanicity, and migrant status [8]. However, to date, there is no information about the incidence of FEP in Iran.

We believe that it is necessary to conduct studies regarding FEP in developing countries, especially those with a relatively young population, such as Iran. This article reviews the literature on FEP in Iran as compared to other parts of the world. Several aspects of FEP have been studied in Iran including Duration of untreated psychosis (DUP); pathways to care; short-term diagnostic stability; outcome predictors; treatment; specialized

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care in the acute and continuation phases for patients and their families; and Neurological soft signs (NSSs).

Duration of Untreated Psychosis

Duration of untreated psychosis (DUP), which refers to the time interval between the onset of psychosis and the beginning of treatment, is often broad. At the same time, there is substantial evidence that longer DUP leads to poorer outcomes (9,10).

Sharifi et al (2008) studied DUP among a group of patients with FEP at Roozbeh Hospital in Tehran (11). The median and mean DUP were 11 weeks and 52.3 weeks, respectively. DUP in this sample was not long compared to DUP reported in several other studies (9,10,12), possibly because of the predominance of acute psychosis in the sample. In another study from Iran, 42.7% of those interviewed sought treatment within 1 month of the onset of psychotic symptoms (13). Most clinical benefits appear within the first six months of treatment (14). Unfortunately, the time between the first symptom and the decision to contact a professional is often very long. Public campaigns that provide information about warning symptoms may be helpful for decreasing the time taken to seek treatment (15). However, Malla et al. (2005) suggest that efforts to shorten the delay between the onset of symptoms and treatment must consider the several factors associated with seeking help other than public awareness. These factors include referral patterns and the time taken to engage patients in treatment after they are referred to a specialized service. Different intervention strategies may be required to resolve issues with each of these factors (16). In addition, there is growing evidence that untreated psychosis is "toxic" in that neurological damage may progress if psychosis is left untreated. The concept of a "critical period" in the development and course of psychosis is a strong argument in favor of early intervention and supports the importance of reducing the DUP. Interventions for psychosis are usually "blind to the phase and age of illness" (17). Given the importance of adherence to treatment for future prognosis, a

specialized approach to starting patients on antipsychotic medication may be desirable to ensure continued engagement in treatment. Most FEP patients are reluctant to voluntarily adhere to treatment, and are admitted to the hospital involuntarily (18,19).

Pathways to Care

Studies of pathways to care for patients with FEP show the complexities of the mental healthcare system, which are not easy for patients and their families to discuss (20,21). Only a small proportion of patients seek out treatment for psychotic symptoms (21). Obtaining information concerning patients' help-seeking behavior and their pathways to care is crucial before any modification to service delivery can be made (15). Studies that examined pathways to mental health care identified that the most common route to mental health services was via general practitioners, and general practitioners increasingly play the role of gatekeepers to these services (22-24). On the other hand, in a study from Germany, only 29% of the patients made any contact with a general practitioner before admission to the hospital, and only 18% had their first contact after FEP with a general practitioner (15). Moreover, a survey conducted in a district of inner-city London revealed that half of the identified patients were brought to the hospital by police (25). In contrast, a study from Tehran showed that following the onset of psychosis, the majority of patients were first seen by a psychiatrist (n=23, 25.3%), a traditional healer (n=21, 23.1%), or a general practitioner (n=16, 17.6%) (11). Referral to a mental hospital was mostly made by the family (n=30, 33.1%), health professionals (n=29, 31.9%), or the legal system (n=15, 19%) (11).

Outcome Predictors

Several demographic and clinical variables may accurately predict treatment outcome in FEP (26). In a naturalistic study, Tabatabaee et al. (2008) investigated 163 FEP patients admitted to a hospital in order to explore acute treatment response and its predictors (27). They reported a higher treatment response

rate as compared to several other studies conducted in western countries. Patients showed a response rate of 91.5% for positive symptoms, 71.4% for negative symptoms, and 67.5% for functioning, whereas the response rate in other studies of FEP have been between 46% and 96% (28,29). Patients who had a negative family history and more severe negative symptoms prior to treatment were more likely to show improvement in negative symptoms. This may be because there is less room to improve when negative symptoms are initially less severe. Conversely, previous studies have shown that the intensity of negative symptoms at admission was a predictor of poor response to treatment (30). In line with previous studies, acute onset, lower pre-treatment functioning, and higher premorbid functioning were associated with a better functional response (31-34). Tabatabaee et al. (2008) did not find any association between treatment response and symptom dimension.

In another study conducted as a part of the Roozbeh First-episode program (RooF), Mahmoodi-Gharaei et al. (2010) investigated the associations between premorbid adjustment, symptom profile, and quality of life in a sample of patients with FEP (35). Poor premorbid adjustment was significantly associated with more severe negative symptoms in late adolescence, as measured by the Positive and negative syndrome scale (PANSS). Additionally, peer relationships and sociability were positively associated with scores on the negative subscale of the PANSS. This study failed to find any significant differences between affective and non-affective FEP in terms of premorbid functioning (35). These results were consistent with some previous studies (36-38).

Diagnostic Stability and Course

Robins and Guze (1970) suggested five validating criteria, including diagnostic stability, to verify diagnosis of psychiatric disorders (39). Diagnosis may change over time due to various factors, such as the emergence of new information, reinterpretation of previously gathered data, unreliability of measurement, or evolution of the illness (40,41). It is clear

that diagnosis will be difficult at the time of FEP because the course of the illness is not well known, making a definitive diagnosis conceptually and clinically premature. A study was conducted at Roozbeh Hospital in Tehran to verify the stability of a diagnosis of psychosis one year after FEP (42). According to both the DSM-IV and ICD-10 classification systems, diagnoses of bipolar disorder and schizophrenia were highly stable (100%). Additionally, all patients diagnosed according to the ICD-10 criteria as "Acute and transient psychotic disorders" or according to the DSM-IV criteria as "brief psychotic disorder" received the same diagnosis in a follow-up assessment. The DSM-IV "schizophreniform disorder" had the lowest prospective consistency (50%) (42). This finding could reflect the infrequency of relapse in acute brief psychoses, especially in developing countries. In contrast, Singh et al. (2004) showed that the ICD–10 criteria classify a diagnostically unstable group of disorders, including "good-outcome schizophrenia", "affective psychosis" and a group of non-schizophrenic, non-affective psychoses with an acute onset and benign 3-year course (5). Diagnostic stability was not related to any particular subgroup of ICD–10 ATPDs.

Alaghband-Rad et al. (2006) investigated the concept of Non-affective acute remitting psychosis (NARP) in a group of patients with FEP in Tehran (43). Susser and Wanderling (1994) defined NARP as a psychotic illness with acute onset (developed within one week), short duration (remission within six months), and the absence of prominent mood symptoms (7). Alaghband-Rad et al. (2006) found that out of the 49 patients who completed the 24-month follow-up, 15 (30.6%) had NARP, which accounted for 60% of the diagnosed non-affective psychoses. Ten patients with NARP continued to be relapse-free, four showed a very short-lived relapse, and only one had a chronic illness. During the follow-up, patients with NARP received medication for fewer months than did patients with other non-affective psychoses (43). The investigators concluded that there is a high rate of NARP among patients with FEP, and

the favorable course of treatment is similar to that reported in studies in developing countries where the incidence of NARP was higher (7). Susser et al. (1998) and Mojtabai et al. (2000) reported that in developing countries, between 21% and 25% of patients referred to a health center with non-affective psychoses were diagnosed with NARP (34,44). Nevertheless, stability of diagnoses in adolescent patients with FEP may be different from those in adult patients, especially considering the preponderance of mood disorders in the former group (45).

Treatment

Studies show that Low Dose atypical Antipsychotics (LDA) are as effective as higher doses and have fewer adverse effects. McEvoy et al. (1991) showed that patients with FEP are both more responsive and more sensitive to a particular dose of typical antipsychotics than patients with chronic schizophrenia (46). The results also demonstrated that among antipsychotic-naïve patients with FEP, the mean dose of haloperidol that elicited extrapyramidal symptoms was half that of patients with prior antipsychotic exposure (2.1 vs. 4.3 mg/day), and the higher dose did not improve the speed or magnitude of drug response (46). The results from subsequent studies with atypical antipsychotics confirmed that lower doses of atypical antipsychotics were sufficient to achieve a therapeutic response for most patients with FEP (47-51). The effectiveness of using LDA compared with Treatment as usual (TAU) was examined as part of RooF (52). Totally, 73 hospitalized patients with FEP aged 15–60 years were recruited and randomly assigned to the LDA or TAU group, 65 subjects completed the study. There were no significant differences between the two groups at discharge with regard to symptom severity and extrapyramidal side effects. Risperidone equivalent mean dose was 3.4 mg/day in the LDA group, and 4.9 mg in the TAU group. In the latter group, most patients received atypical antipsychotics and a minority received typical antipsychotics with haloperidol equivalent mean dose of 10.1 mg.

Duration of hospitalized treatment was longer in the LAD group compared with the TAU group (43.0 vs. 31.1 days).

These results suggest that although prescribing low dose atypical antipsychotics may be as effective as routine practice in treating hospitalized patients with FEP, potential adverse consequences, such as longer hospitalization for patients and the consequences for the healthcare system, should be examined in future studies (52). In addition, another study conducted in Tabriz, Iran, reported a significant relationship between the incidence of adverse extrapyramidal side effects and the dosage of risperidone (53).

Several studies have shown that antipsychotics work fast (54,55). Derks et al. (2010) showed that response measures taken after two weeks were associated with remission within one year in a sample of patients with FEP (56). Nevertheless, the ability to predict remission improved when 4- and 6-week measures of response were included (56). Furthermore, in general practice, there is a tendency to reserve Long-acting antipsychotic injection (LAI) drugs for patients who have already experienced significant adverse effects because of non-adherence. However, non-adherence is a big problem in patients with FEP. Many patients have not fully acknowledged the reality of their illness, and since remission of symptoms is common after treatment in the acute phase of a first episode, there is often a false belief that continued medication is not needed (57). McEvoy et al. (2007) reported an overall medication discontinuation rate of 70% (58). It is noteworthy that more than half of the discontinuations reported in this study occurred against the advice of the treating physicians.

However, two studies investigate the use of LAI drugs in patients with FEP. Emsley et al. (2008) studied 60 patients with FEP who were eligible for risperidone LAI. Only 9 (15%) refused this treatment (59). Follow-ups with the patients occurred for up to 2 years; 72% completed the full 2-year follow-up period. In the second study, Weiden et al. reported that 83% of eligible patients consented to

participate, and 73% of those who were randomly assigned to receive LAIs accepted them (60). In a follow-up after 12 weeks, medication adherence was found to be significantly better in the group receiving injections. These studies suggest that the use of LAI medication in FEP is feasible and may have advantages over other treatments. Undoubtedly, further research is warranted. A critical question that needs to be addressed is whether using LAIs raises the risk of experiencing extrapyramidal side effects, such as tardive dyskinesia. Another important question related to medication use in FEP is how long a patient should continue taking antipsychotic drugs following FEP remission. Further studies are necessary to identify what factors predict which patients in FEP remission are likely to relapse when medication is discontinued. To conclude, more data are needed to develop a broader understanding of LAIs (57).

Aftercare Services and Psychosocial Interventions

Two critical aims of FEP programs are to prevent psychotic relapse and promote recovery (61). Moreover, Linszen et al. (1998) suggested that there are four reasons for adding psychosocial interventions to a regimen of antipsychotic medication: problems with adherence (mainly due to unpleasant side effects); persistence of negative symptoms, inadequate social recovery or treatment resistance; deinstitutionalization, with emphasis on the family's role in recovery; and presence of high "expressed emotion" (62). In particular, psychosocial interventions help patients improve the quality of their lives and regain their psychological well-being and ability to participate in social and occupational events. Key elements of psychosocial intervention include psycho-education and family engagement.

As a part of RooF, patients and their families received two main services—home care and telephone follow-up—and then, the effectiveness of these services was evaluated (63). Totally, 48 patients with FEP admitted to Roozbeh Hospital were randomly assigned to home care (n=15), telephone follow-up (n=9)

or treatment-as-usual (n=24). Patients in the home care group received monthly home visits from trained general practitioners and social workers. Patients in the telephone follow-up group had monthly outpatient visits with telephone prompts to encourage attendance. As part of both services, patients received family psycho-education, either in their homes or at the outpatient clinic. Patients were followed up for 12 months and data on re-hospitalization, relapse, symptoms, functioning, quality of life, and service satisfaction were compared. The results showed that no patient in the home care group experienced a relapse, which was significantly less than patients in the telephone follow-up and treatment-as-usual groups, where 4 (44%) and 6 patients (25%) experienced a relapse, respectively. The re-admission rate was zero for patients in the home care group, as compared to 22.9% of patients in the telephone follow-up group and 13.9% of patients in treatment-as-usual group. Other outcome measures were comparable across groups. However, this study showed that the development of specialized early psychosis services in a developing country is practical, and home care may be more effective compared to less intensive care (63).

The results of a large randomized trial conducted by Peterson et al. (2005) were largely in favor of an integrated treatment. This treatment was based on the assertive community treatment model and was enhanced by specialized protocols for social skills training and family involvement regarding adherence to treatment, psychopathology, comorbid dependence, user satisfaction, social outcomes, and use of health services. The response outcomes from the first year with regard to positive and negative symptoms persisted in the second year, indicating robustness (64). In contrast, the effectiveness of an integrated program was compared to treatment-as-usual in a group of inpatient adolescents with FEP in a randomized trial as part of the RooF program (65). The integrated program consisted of a standard pharmacological treatment, family psycho-education, and telephone follow-up for regular visits. The

results showed no significant difference between the two groups after two years (65). However, these results should be interpreted with caution because of the small sample size.

A high rate of distress and burden among families of patients with FEP reveals the need for family intervention. Mottaghipour et al. (2008a) showed that 49% of family members of patients with FEP had psychiatric morbidity at the onset of the disorder that decreased to 29% six months later (66). Scores on the Negative scale of Experience of caregiving inventory (ECI) decreased significantly after family education, and families' psychological well being was significantly associated with their experience of caregiving (66). Therefore, training health professionals to conduct family psycho-education is an important component of any specialized FEP program. As part of RooF, Mottaghipour et al. (2010) studied how effectively trained health professionals conducted family education sessions (67). The overall rate of adherence to protocol in leading the four sessions of family psycho-education was satisfactory (72%). However, there was less adherence to protocol in family psycho-education sessions carried out at home compared to the group sessions performed at the hospital (67).

Neurological Soft Signs

Neurological soft signs (NSSs) are objective, non-localizable, minor signs that are considered to be indicative of damage in the connection between cortical and subcortical areas or between different cortical regions (68,69). In a study at Roozbeh Hospital, the prevalence of NSSs in patients with FEP, their first degree relatives, and a group of healthy control subjects, was evaluated (70). The study showed that patients with FEP had significantly more NSSs than the first-degree relatives and the control group. In addition, the patients had significantly higher scores than controls on the "sequencing of complex motor acts," "motor coordination," and "sensory integration" subscales of the Neurological evaluation scale (NES). Finally, the patients showed significantly higher scores on "motor coordination" and "eye movements" NES

subscales than their relatives. In line with previous studies, the authors concluded that NSSs may be part of a neural dysfunction that triggers psychosis, rather than being the consequence of a neurodegenerative process caused by the disorder (71).

In another study, Abedi Sohroforouzani et al. (2008) studied the associations between NSSs and manic and psychotic symptomatology, and treatment response in patients with first episode mania. They reported that there was no significant correlation between NSSs and the severity of manic symptoms in patients with first episode mania. Furthermore, whenever the severity of baseline NSSs was high, the reduction in negative psychotic symptomatology decreased over the course of acute treatment. There was no significant correlation between NSS severity and changes in the severity of manic symptoms over the course of treatment, but the study showed a negative association between pre-treatment scores on the "motor sequencing" subscale of the NES and the reduction in manic symptoms over the course of acute treatment (72). They concluded that there might be a neurodevelopmental basis for psychotic mania like schizophrenia.

In the third study, Shadloo et al. (2008) studied the association between NSSs and symptom profile in a group of patients with FEP (73). They found no correlation between NSSs (measured by the NES) and symptom severity (measured by the PANSS). This finding is in line with one study (74), but contrary to others (75-78). However, for the subscales, PANSS negative symptoms were highly correlated with primitive reflexes (73), consistent with previous studies (79,80).

Conclusion

Research on FEP in Iran has increased in the last decade. There are preliminary findings on FEP in terms of DUP, pathways to care, diagnostic stability, outcome predictors, treatment, aftercare services, psychosocial interventions, and NSSs. However, a majority of published studies on FEP from Iran are the

results of a specialized program for patients with FEP, entitled the Roozbeh First-episode psychosis program (RooF). In other words, most of the published studies were conducted in Roozbeh Hospital, a referral teaching mental hospital without a well-defined referral policy and catchment area, located in Tehran, the capital city of Iran. In addition, caution must be exercised when generalizing the results to patients with FEP in the community and other parts of the country because the samples in the published studies were small, and most participants were recruited from the inpatient wards. Another limitation of the published studies is the short duration of follow-ups. Thus, it is necessary to support the longitudinal studies on FEP with studies that involve longer follow-up periods.

Our country is currently facing several challenges in terms of mental health service development. Although there is a partially developed community mental health program in rural areas of Iran, community-based mental health care has not been fully established in urban areas (81). In addition, primary health care does not entirely cover the urban population, and there is no defined referral system in cities. Mental health services are inadequate and not integrated with primary health care. Furthermore, with some exceptions in a few centers in Tehran, there is no continuously active aftercare program for patients with severe mental illnesses. Such conditions prevent patients with FEP from taking part in an early intervention program. However, the results from RooF in Iran have clarified the strengths and weaknesses of similar experiences in other parts of the country. Mottaghipour et al. (2008b) developed a checklist that would be helpful for future research in terms of developing better trials, especially for studying FEP (82). Unfortunately, negligence of priority of mental health care in health policy making, absence of required infrastructures in different parts of the health care system, lack of continuous funding, and unavailability of community psychiatry training in residency curriculums are restricting the development and expansion of early intervention programs for patients with FEP in Iran.

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