

**THE IMPACT OF UNTREATED
PSYCHOSIS IN LOW AND MIDDLE
INCOME (LAMI) COUNTRIES AND
A PARADIGM
FOR EARLY INTERVENTION**

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‘Worldwide, schizophrenia is the eighth largest cause of disability and the illness may shorten life expectancy by 10 years. The direct effects of schizophrenia are comparable to those of many infectious and chronic physical illnesses that receive more funding for both treatment and research. Cost-effective treatment is now available for schizophrenia. A public health initiative to subsidise antipsychotic medication for the critical first 2 years of psychotic illness could greatly improve outcome for psychotic illness worldwide.

Patients with psychosis in low-income and lower-middle income countries may be among the most disadvantaged people on earth and providing them with access to basic treatment would be a cost-effective public health measure.’

Large M. Farooq S; Nielsen O (2008). Duration of Untreated Psychosis in Low and Middle income economies: The relationship between GDP and DUP. *British Journal of Psychiatry*, 2008. 193; 272-278.

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ABSTRACT

This thesis is based on 13 papers published in peer reviewed journals. These include studies on epidemiology and treatment of major psychotic disorders, and metanalysis of studies on Duration of Untreated Psychosis (DUP) and its relationship with the Gross Domestic Product and the outcome in Low and Middle Income (LAMI) countries. Based on this research that highlighted the extent and impact of untreated psychosis, a series of papers presented a novel approach for early intervention in psychosis in LAMI countries. The final paper presents the randomised controlled trial evaluating this approach.

Seven publications on puerperal psychosis, homicide by patients suffering from Schizophrenia, and the impact of cannabis use on symptomatology and course of schizophrenia highlighted significant gaps in the care of schizophrenia in developing countries. Only 12 patients (24%), charged with homicide had received some form of treatment before the index crime, despite the fact that duration of illness was more than 5 years in most cases. In a clinical sample of 35 patients suffering from acute episode of Puerperal psychosis the mean time between the onset of symptoms and receiving psychiatric care was almost a month. Two third of mothers suffering from Puerperal psychosis could not breast feed, most showing almost total lack of concern for the baby and also other behavior which could result in harm to baby. The publications on Puerperal psychosis argued that prevention of the disorder should be feasible in developing countries in view of high incidence of the disorder following an identifiable life event (childbirth) and the fact that most of the risk factors could be screened in the antenatal period.

A paper published in British Journal of Psychiatry estimated the Duration of Untreated Psychosis (DUP) and its impact on the outcome of psychosis. Based on metanalysis of 98 studies (23 from LAMI countries and 75 were from high-income countries) the DUP of LAMI countries (125 weeks) was twice as long as the DUP in high-income countries (63 weeks, $p=0.012$). The relationship between DUP and the gross domestic product (GDP) purchasing power parity was also examined using the data from International Monetary

Fund (IMF) and the World Bank. There was a strong negative correlation between DUP and GDP ppp, indicating that for every thousand dollars of additional GDP (purchasing power parity), mean DUP was reduced by 8 weeks and median DUP was reduced by 5 weeks.

A study published in Schizophrenia Research examined the association between DUP and at least one of the following outcome measures; psychotic symptoms, cognitive function, social disability or mortality. Patients with a longer DUP had a smaller reduction in symptom scores after treatment when compared to patients with shorter DUP. The pooled estimate indicated that longer DUP was negatively associated with the degree of reduction in symptom scores (random effects Meta analysis; $r=-0.290$, 95% CI= -0.483 to -0.069 , $z=-2.559$, $P < 0.011$) and longer DUP was associated with greater level of disability (fixed effects Meta analysis; $r=0.195$, 95% CI= 0.126 to 0.262 , $z=5.498$, $p<0.000$; heterogeneity Q-value 1.245, $p=NS$, $I^2=0.00$).

These studies clearly established the case for Early Intervention in psychosis. However, an entirely different approach was needed for this in resource poor settings. This approach is described in three papers. This approach termed as ‘Supervised Treatment of Outpatient Schizophrenia’ (STOPS) was evaluated in a Randomized Controlled Trial. The paper describing this RCT which provided proof of the concept will soon be published by British Journal of Psychiatry. In this RCT, fifty five patients were recruited in each arm. Ninety five (86.36%) patients completed the study; 49 in STOPS and 46 in Treatment As Usual (TAU) group. At one year follow up, 37 (67.3%) patients in STOPS group had complete adherence with medication compared to 25 (45.5%) in the TAU group ($P<.02$). The patients in STOPS group also showed more improvement in symptoms ($P=0.003$) and functioning ($P<0.011$).

Appendix A, 1 – 13: FULL TEXT PUBLISHED STUDIES

1. Farooq S (1996). Clinical Features of Puerperal Psychoses. J Coll Physicians Surg Pak. Vol. 6 (3) 148-150.
2. Farooq S (1997). The Impact of Psychiatric disorders during pregnancy and puerperium on the child- A review of the literature. J Coll Physicians Surg Pak. Vol. 9, 331-333.
3. Farooq S (1991). Puerperal Psychiatric Disorders- who cares. Journal of Pakistan Medical Association (J.P.M.A). Nov. 267-268.
4. Farooq S (2004). Postnatal psychiatric disorders need public health action (Editorial).J Coll Physicians Surg Pak. Apr; 14(4):197-8.
5. Farooq S, Deeba F, Ashfaque M, Iqbal M (2003). Mentally-ill patients charged with homicide. J Coll Physicians Surg Pak; 13(4):223-5
6. Rehman IU, Farooq S.(2007a). Cannabis abuse in patients with schizophrenia: pattern and effects on symptomatology. J Coll Physicians Surg Pak. Mar;17(3):158-61.
7. Rehman IU, Farooq S.(2007b). Schizophrenia and comorbid self reported cannabis abuse: impact on course, functioning and services use. J Pak Med Assoc. 57(2):60-4.
8. Large M. Farooq S; Nielssen O (2008). Duration of Untreated Psychosis in Low and Middle income economies: The relationship between GDP and DUP. British Journal of Psychiatry, 193; 272-278.
9. Farooq S; Large M. Nielssen O, Waheed W. (2009). The relationship between the Duration of Untreated Psychosis and outcome in low and middle income countries: Schizophrenia Research. 109, 15–23.
10. Farooq S (2008). Public Health Intervention for Schizophrenia in Developing Countries – From DOTS to STOPS.JPPS (Journal of Pakistan Psychiatric Society).5(2) 1-2.

11. Farooq S (2006). Free pharmacological treatment for schizophrenia in developing countries – case for a public health intervention. *JPPS (Journal of Pakistan Psychiatric Society)*. 3(1), 1-2.
12. Patel V, Farooq S, Thara R(2007). What is the best approach to treating schizophrenia in developing countries? *PLoS Med Jun;4(6):e159*.
13. Farooq F, Nazar Z, Irfan M, Akhte J, Gul E, Irfan U and Naeem F. Schizophrenia treatment adherence in resource poor setting: Randomised Controlled Trial of Supervised Treatment in Outpatients for Schizophrenia (STOPS). *British Journal of Psychiatry*. 2011, 199:467-472.

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My wife Safia and son, Furqan deserve my special gratitude for being patient with my monosyllable responses to their most pressing and important queries whilst I worked on my computer!

LIST OF JOURNALS WITH THE IMPACT FACTORS IN WHICH PAPERS ARE PUBLISHED.

Name of Journal	ISSN Number	Impact Factor	Indexation	Website Address
PLoS Medicine	1549-1277	13.8	Medline and others.	www.plos.org
British Journal of Psychiatry	1472-1465	5.8	Medline and others	www.rcpsych.ac.uk/publications/journals/
Schizophrenia Research	0920-9964	4.45	Medline and others	www.sciencedirect.com/science/journal/09209964
JCPSP(Journal of Physicians and Surgeons Pakistan)	1002-386X	0.55	Medline and others	www.cpsp.edu.pk/index
JPMA(Journal of Pakistan Medical Association)	0030-9982	Not Available	Medline and others	www.jpma.org.pk
JPPS (Journal of Pakistan Psychiatric Society	1726-8710	Not Available	WHO Index Medicus. (IMEMR).Directory of open Access	www.jpps.com.pk

LIST OF COMMONLY USED ABBREVIATIONS

DALYS:	Disability Adjusted Life Years (DALYS)
DUP:	Duration of Untreated Psychosis
GDP:	Gross Domestic Product (GDP)
GDPppp:	Gross Domestic Product purchasing power parity
LAMI:	Low And Middle Income Countries
LRH:	Lady Reading Hospital LRH
NCD:	Non-Communicable Diseases (NCD)
PP:	Puerperal Psychosis
RDC:	Research Diagnostic Criteria
STOPS:	Supervised Treatment in Outpatients for Schizophrenia
WHO:	World Health Organization. WHO
YLD:	Years of Life with Disability
YLL:	Years of Life Lost (due to premature mortality)

SECTION - 1

Chapter 1:

An overview of the thesis

This thesis is based on my published work over more than a decade. The thesis covers 13 publications on related themes of epidemiology, services and a model for early intervention in Psychosis in a typical Low and Middle Income (LAMI) country setting. The publications arising from this research are given in tables 1 and 2. The format of this thesis will, therefore differ essentially in presentation and style from the thesis written generally.

I will only describe essentials of methodologies and major findings of the studies in the main body of thesis. All studies are given as appendix 1 in full text. In the first set of studies, which are based in a mental health services at Peshawar, different aspects of presentation, epidemiology and services for Psychosis are investigated. A list of the papers based on this work is given in table 1.

The second set of studies consists of the Systematic reviews and meta analysis of all the published research from LAMIC countries on Duration of Untreated Psychosis (DUP), its relationship with Gross Domestic Product (GDP) and the outcome of Psychosis. This is followed by a section which describes studies that advocates a new treatment paradigm for Early Intervention for Psychosis in developing countries based on this published research. A list of the papers based on this work is given in table 2. Finally a paper published by British journal of Psychiatry describes the evaluation of this approach in a randomised controlled trial.

The final chapter integrates the data presented in the thesis and describes how the publications presented in this thesis present a coherent body of the knowledge and the way in which this is translated into a complex intervention. In the following sections, I have described only essential findings of these studies which relate to this thesis. The details are available in appendix 1, in which full text studies are given. The tables and diagrams are

also not given in the main body of thesis and are referred to the original studies given in appendix 1.

TABLE: 1. First set of studies on epidemiology, course and preventable aspects of Psychosis in LAMI countries

1. Rehman IU, Farooq S. (2007,a) Cannabis abuse in patients with schizophrenia: pattern and effects on symptomatology. J Coll Physicians Surg Pak. Mar;17(3):158-61.
2. Rehman IU, Farooq S.(2007b). Schizophrenia and comorbid self reported cannabis abuse: impact on course, functioning and services use. J Pak Med Assoc. 2007 Feb; 57(2):60-4.
3. Farooq S, Deeba F, Ashfaque M, Iqbal M (2003). Mentally-ill patients charged with homicide. J Coll Physicians Surg Pak; 13(4):223-5
4. Farooq S (2004). Postnatal psychiatric disorders need public health action (Editorial).J Coll Physicians Surg Pak. Apr; 14(4):197-8.
5. Farooq S (1997). The Impact of Psychiatric disorders during pregnancy and puerperium of the child- A review of the literature. J Coll Physicians Surg Pak. Vol. 9, 331-333.
6. Farooq S (1996). Clinical Features of Puerperal Psychoses. J Coll Physicians Surg Pak. Vol. 6 (3) 148-150.
7. Farooq S (1991). Puerperal Psychiatric Disorders- who cares. (Editorial). Journal of Pakistan Medical Association (J.P.M.A). Nov. 267-268.

TABLE: 2. Second set of studies on epidemiology, course and preventable aspects of Psychosis in LAMI countries

8. Farooq S; Large M. Nielssen O, Waheed W. (2009). The relationship between the Duration of Untreated Psychosis and outcome in low and middle income countries: Schizophrenia Research. Schizophrenia Research. 109 (2009) 15–23.
9. Farooq S (2008). Public Health Intervention for Schizophrenia in Developing Countries – From DOTS to STOPS. JPPS (Journal of Pakistan Psychiatric Society).5(2) 1-2.
10. Farooq S (2006). Free pharmacological treatment for schizophrenia in developing countries – case for a public health intervention. JPPS (Journal of Pakistan Psychiatric Society). 3(1), 1-2.
11. Large M. Farooq S; Nielssen O (2008) Duration of Untreated Psychosis in Low and Middle income economies: The relationship between GDP and DUP. British Journal of Psychiatry,2008. 193; 272-278.
12. Patel V, Farooq S, Thara R(2007). What is the best approach to treating schizophrenia in developing countries? PLoS Med Jun;4(6):e159.
13. Farooq S. Nazar Z, Akhter J et al. Supervised Treatment in Outpatients for Schizophrenia (STOPS): Randomized Controlled Trial of an innovative approach for the treatment of Schizophrenia in developing countries. British Journal of Psychiatry. 2011, 199:467-472.

Chapter 2:

Setting the scene: mental health services and care for psychosis in developing countries

STATE OF CARE AND RESEARCH FOR SEVERE MENTAL ILLNESS IN LOW AND MIDDLE INCOME COUNTRIES

- A total of more than 85% of the global population lives in 153 Low- and middle-income (LAMI) countries.
- Most developing nations have more than one third of their population below 45 years of age- the age group at highest risk of developing Schizophrenia. Around 41.7 million people with schizophrenia are in need of care in LMICs.
- Almost a third of countries do not have a public budget specified for mental health. About a quarter of low-income countries do not provide even basic antidepressant medicines in primary-care settings
- A very limited amount (6%) of internationally accessible mental health literature emanates from low- and middle-income countries
- Families take care of persons with severe mental disorders and often there is little the relatives can do other than to restrain them. One study from Africa found ‘The average time spent in chains of the 109 “mental cases”, who had been chained at some point during their lives, was 2.7 years (SD = 3.9) and the average time being restrained in some other way for the 119 of them who had experienced this, was 3.9 years (SD = 5.1).

2.1.1 Low and Middle Income (LAMI) Countries

More than 85% of the global population lives in 153 Low- and middle-income (LAMI) countries. Nine of 11 countries with a population of at least 100 million belong to the LAMI categories. These countries are distributed in all parts of the world: all of Africa, much of Asia, South and Central America and Eastern Europe. (Patel et al 2007). Health systems in these countries have mostly been geared towards coping with disorders causing high mortality. However, during the last two decades the significant burden of disease caused by Non Communicable Diseases (NCD) has been realized mainly as a result of landmark Global Burden of Disease report (Lopez and Murray, 1996). This section will briefly overview the current status of burden of disease caused by neuropsychiatric disorders and existing mental health services. The contribution of mental health research in these countries will also be highlighted.

2.2 The Burden of Disease caused by Neuropsychiatric Disorders in LAMI countries

Non-Communicable Diseases (NCD) have become the dominant cause of disability in all developing countries. Psychiatric disorders represent a significant proportion of the burden of disease amongst the NCD. The Global Burden of Disease report has revealed the scale of the contribution of mental disorders, by use of a measure of disease burden that takes into account the disability, called Disability Adjusted Life Years (DALYS). DALYs for a specific cause are calculated as the sum of the Years of Life Lost (YLL) due to premature mortality from that cause, and the years of healthy life lost as a result of disability (YLD). The YLL are essentially calculated as the number of cause-specific deaths multiplied by a loss of function specifying the years lost as a function of the age at which death occurs (For detailed calculations and formula see Mathers et al, 2006) . Although the size of the burden of disease caused by these disorders varies between these countries according to income level, the report showed that neuropsychiatric conditions account for up to a quarter of all Disability-Adjusted Life-Years (Lopez and Murray, 2006)

The neuropsychiatric conditions that contribute the most disability adjusted life-years are unipolar and bipolar affective disorders, substance-use and alcohol-use disorders, schizophrenia, and dementia. As most mental disorders begin in childhood or young adulthood and most severe mental disorders begin in the younger age group, the attributable burden of disease for adults in the age group of 15–44 is much higher. Table 3 shows that one of the leading causes of disease burden in this age group is mental and behavioural disorders. It is obvious that overall Schizophrenia is 8th amongst leading causes of disability both in male and females. However, gender wise distribution is different. In females Schizophrenia ranks as 5th and in males it ranks as 8th. This is due to the fact that in males road traffic accidents, substance abuse and violence are responsible for greater burden of disease and hence precede Schizophrenia in the table. The neuropsychiatric conditions contribute the most to overall burden, more than either cardiovascular disease or cancer during the most productive years of life.

TABLE: 3. Burden of mental disorders in young adults

Both sexes, 15–44 year old	Total (%)	Males, 15–44 year old	Total (%)	Females, 15–44 year old	Total (%)
HIV/AIDS	13.0	HIV/AIDS	12.1	HIV/AIDS	13.9
Unipolar depressive disorders	8.6	Road traffic accidents	7.7	Unipolar depressive disorders	10.6
Road traffic accidents	4.9	Unipolar depressive disorders	6.7	Tuberculosis	3.2
Tuberculosis	3.9	Alcohol use disorders	5.1	Iron deficiency anaemia	3.2
Alcohol use disorders	3.0	Tuberculosis	4.5	Schizophrenia	2.8
Self-inflicted injuries	2.7	Violence	3.7	Obstructed labour	2.7
Iron deficiency anaemia	2.6	Self-inflicted injuries	3.0	Bipolar affective disorder	2.5
Schizophrenia	2.6	Schizophrenia	2.5	Abortion	2.5
Bipolar affective disorder	2.5	Bipolar affective disorder	2.4	Self-inflicted injuries	2.4
Violence	2.3	Iron-deficiency anaemia	2.1	Maternal sepsis	2.1

2.3 Mental Health Services in LAMI countries

Despite these startling figures mental health remains a low priority in most LAMI countries. Almost a third of countries (31%) do not have a public budget specified for mental health. Of the 101 countries which have a specified mental health budget, 21 (with more than 1 billion people), spend less than 1% of their total health budget on mental health. This is particularly the case in Africa and Southeast Asia where most countries devote less than 1% of their small health budgets for mental health services. Comparing gross domestic product (GDP) per head with the proportion of the total health budget allocated to mental health, Prince et al 2007 et al demonstrated that mental health in low-income countries faces a double disadvantage: the poorest countries spend the smallest proportion of their already scarce resources on mental health.

2.4 The Myth of Community Psychiatry in LAMI countries

The integration of mental health in primary health care has been a mantra for several decades and WHO advocated the Community Psychiatry as the only viable option for developing countries since the early 70s. In fact, this has been the widely accepted model for provision of the services in these countries. A rather romantic notion of the Community Mental Health existed in these countries that led to a myth that patients with mental disorders are being provided care in the community and somehow stigma was less prevalent in traditional societies. The Author of this thesis challenged the concept more than a decade ago arguing that Community Psychiatry is a misnomer and may be misleading when applied in the context of developing countries. The term neither fulfils the criteria of a public health approach as envisaged in 'Community Medicine' nor that of community mental health services in any form (Farooq and Minhas, 2001). This has been confirmed by the recent literature on mental health in developing countries (WHO 2001). Community Psychiatry does not represent more than an isolated existence of a

mental health centre here and there in the community. The recent research shows that even such a loosely defined community mental health service does not exist in many countries. If community-based mental health care is defined broadly, as “any type of care, supervision and rehabilitation of patients with mental illness outside the hospital by health and social workers based in the community”, then only about half the countries in Africa, the eastern Mediterranean, and southeast Asia provide such care (WHO, 2005). About a quarter of low-income countries do not provide even basic antidepressant medicines in primary-care settings (Saxena et al 2007).

2.5 The role of mental health research in developing countries.

Health research plays a major role in providing solutions for health problems. Inadequate health research from these countries contributes significantly to the vicious cycle that leads to lack of investment in mental health systems. Lack of evidence for the cost effectiveness of mental health interventions in developing countries has been cited as one of the major reasons by development agencies for reluctance to invest in mental health services in developing countries (Saraceno et al, 2006). A very limited amount (6%) of internationally accessible mental health literature emanates from low- and middle-income countries (Saxena et al, 2006). Fewer than 1% of more than 11501 trials world wide for the treatment and prevention of major psychiatric disorders were from low-income countries. Although this has improved to some extent in the last decade (Large et al, 2008), the lack of evidence and reliable information is one of the key factors contributing to the dismal state of mental health services in these countries.

2.6 The burden of disease caused by Psychosis in developing countries.

In this thesis the term ‘psychoses’ will be used instead of a specific diagnostic category such as Schizophrenia in line with the literature on the Duration of Untreated Psychosis and its consequences, the main theme of the thesis. The literature on Duration of Untreated Psychosis (DUP) has used the term ‘psychoses’ without any attempt to delineate the diagnostic categories within this broad group.

In practice, however this almost always implies Schizophrenia, the most common disorder in this category of psychotic disorders.

This is especially valuable in context of developing countries, as focusing on a broad category of psychosis helps to identify a group of disorders which represents most severe form of mental illness.

The median incidence of schizophrenia is around 1.5 per 10,000 inhabitants (McGrath et al, 2004) and the lifetime morbid risk of developing schizophrenia is near 0.7% (Saha et al, 2005). Despite this low incidence it is estimated that around 41.7 million people with schizophrenia are in need of care in LMI countries. This is mainly because of the age structure of these countries. Most developing nations have more than one third of their population below 45 years of age, the age group of maximum risk for developing most psychotic disorders including Schizophrenia. Not surprisingly, Schizophrenia is amongst the top ten causes of the years lived with a disability in developing countries in this age group (Mathers et al 2006).

The mental health services in these countries are woefully inadequate as described above. With less than one qualified mental health professional for half to one million people and about 1% of health budget dedicated for mental health, most people with schizophrenia in LAMI countries probably receive little or no formal care. Consequently, there is a high prevalence of untreated schizophrenia in the form of undetected as well as inadequately and partially treated cases.

Family is the sole care provider in almost all the cases. The family not only has to cope with large economic and social burden due to largely untreated psychosis but also the effects of stigma in closely knit societies. A study from China, reported that more than half the family members of people with schizophrenia said that the effect of stigma on them and their family was such that they had decided to conceal the mental illness in their family (Philips et al, 2002). Poverty and social exclusion have been well known as risk factors for mental illness. Between 40 and 50% of mental health care costs are borne out of pocket in LAMIC (WHO, 2005). The disabling effects of mental disorders and social isolation due to stigma leads to the vicious cycle of inability to work, increasing burden on the family and poverty.

The care for psychosis in these settings is vividly illustrated in the recent report by Vivo, an international Organisation working in conflict zones. In a survey of a representative sample of 612 households in Hargeisa Somaliland, authors noted that ‘Like in many other African countries, the families take care of persons with severe mental disorders and often there is little the relatives can do other than to restrain them in order to avoid harm being done to others or themselves.

Of the 169 persons with severe current mental problems 109 had to be chained at some point during their lives and 113 had to be restrained in some other way by their family (mostly because of aggressive behaviour). At the time of the interview 48 were kept in chains and 85 were restrained in other ways. The average time spent in chains of the 109 “mental cases”, who had been chained at some point during their lives, was 2.7 years (SD = 3.9) and the average time being restrained in some other way for the 119 of them who had experienced this, was 3.9 years (SD = 5.1).’ (Odenwald et al, 2007).

Chapter: 3

The setting: Lady Reading Hospital (LRH), Peshawar.

- The Psychiatry department Post Graduate Medical Institute, Lady Reading Hospital (LRH) Peshawar; Pakistan: A tertiary care teaching facility with 14 in patient beds, daily clinics with average attendance at outpatients of 40. Three consultant psychiatrists, 2 psychologists, 2 social workers and 4 psychiatric nurses comprise the multidisciplinary team.
- The average length of stay for in-patients is less than two weeks and is limited mostly to most acutely ill patients. The services are heavily dependent upon the support provided by the family.
- Peshawar district has population has over 2.5 Millions but patients present from as far as Afghanistan and the actual population from which patients can present to hospital may well be over 20 Millions.
- The Lady Reading Hospital is frontline hospital treating all war traumas resulting from suicide and other bombing at public places during the so called war on terror.

Peshawar is the capital of the Khyber-Pakhtunkhwa province (previously known as NWFP, North West Frontier Province) and the administrative centre for the Federally Administered Tribal Areas of Pakistan, a semiautonomous region bordering with Afghanistan. Located about 40 Km from the historic Khyber Pass, Peshawar is now officially recognised as being one of the Oldest Living Cities in Asia. Peshawar district covers a large area extending over 50 Kilometers and has population over 2.5 Millions and is served by three main teaching hospitals.

Lady Reading Hospital (LRH) Peshawar, was established in 1924. The hospital is named after Lady Reading, the spouse of Viceroy of British India and is the biggest health facility in the entire Khyber-Pakhtunkhwa province. The hospital is one of the two campuses of the only postgraduate medical institute serving the province. The hospital does not serve a specific catchment area. Being the biggest health facility in the region patients present to the Lady Reading Hospital not only from the province but also adjoining Afghanistan and sometimes as far as from central Asian states.

A report in The Daily Telegraph on 19 Nov 2009 succinctly put the past and present of the hospital as follows 'Lady Reading Hospital, or LRH as it is known among the 2.5 million residents of Peshawar, was founded in 1924 when Lord Reading was viceroy of India and is now one of Pakistan's largest teaching hospitals. On a visit to the area, his wife fell off a horse and suffered an injury, only to find that proper treatment was unavailable locally. In England, she collected donations from British philanthropists and set up a hospital that ultimately took her name. But the romance of its beginnings has vanished under the carnage witnessed in Peshawar and the surrounding North West Frontier Province (NWFP) where Taliban bombings and military offensives have been concentrated. "We have dealt with 49 blasts... 2,200 injured and 576 bodies in bombings," said Dr Ataullah Arif, the surgeon in charge of the emergency ward. Tactics are changing. Bombings of crowded markets are

beginning to maximise civilian casualties The 1,543 beds are woefully inadequate and the hospital is intending to overcome dire shortages by building a 500-bed emergency ward. There are fears that a suicide bomber could strike the hospital, a soft target (<http://www.telegraph.co.uk/expat/expatnews/6604667/Peshawar-hospital-in-war-time-crisis.html>). Last assessed 4th July 2010).

Although war is not a new phenomenon for the inhabitants of Peshawar being located strategically on a route for all invaders of the Indo-Pak subcontinent, the last decade has witnessed the worst violence after the so called war on terror.

The war to fight the Taliban insurgency has resulted in a dramatic increase in both physical and psychological trauma. More than 20 thousand people were killed and over 3 million were displaced during recent military operations, bomb blasts at public places and suicide bombings during Taliban insurgency (http://en.wikipedia.org/wiki/War_in_North-West_Pakistan). The hospital has also been battling with the consequences of the conflict going on in the region for the last three decades since early eighties when Soviets invaded Afghanistan.

The Psychiatry department at LRH provided in patients and community services mostly to the Peshawar district. Initially the department had 14 inpatient beds which were increased to 36 beds in 2006. A multidisciplinary team based at the department provides modern psychiatric treatment. The multidisciplinary team consisted of three consultant psychiatrists, 2 psychologists, 2 social workers and 4 psychiatric nurses besides auxiliary staff. The services are heavily dependent upon the support provided by the family. The average attendance at daily outpatient clinics is around 40 patients. The average length of stay in the in patients is less than two weeks and is limited mostly to most acutely ill patients usually suffering from Psychotic disorders. This is due to the fact that the department serves large populations and there are limited inpatient psychiatric facilities. The family provides support and care in community and is able to provide care for acutely ill patients. It is difficult to compare this length of stay with UK due to entirely different nature of two types of services. However, this appears to be considerably

shorter than average stay in developed countries like the United Kingdom. The department is recognized by The College of Physicians and Surgeons, Pakistan for the postgraduate training in Psychiatry and is widely recognized in the country as centre of excellence for training and research even during the worst violence.

SECTION: 2

THE CASE FOR A PUBLIC HEALTH ACTION ON EARLY INTERVENTION: GATHERING THE EVIDENCE

Chapter 4

Publication on epidemiology and course of psychosis in LAMI Countries.

- Puerperal Psychosis has a rather predictable onset (something of a rarity in psychiatric disorders), and is precipitated by well established risk factors thus *making* prevention possible and feasible.
- High fertility rates, infections and other complications of delivery result in high incidence and prevalence of psychosis following childbirth in LAMI countries,
- In a clinical sample of 35 women suffering from acute episode of Puerperal psychosis the mean time between the onset of symptoms and the admission was 27 days. Two third of mothers could not breast feed, most showing almost total lack of concern for the baby and also other behavior which could result in harm to baby.
- Only 12 patients (24%), charged with homicide had received some form of treatment before the index crime, despite the fact that duration of illness was one year in 96% of cases. In this study 38 patients (76%) were involved in a single murder, while 12 patients (24%) were charged with double/multiple murders. Out of 64 victims of the patients, 49 were close relatives.

This phase of my work starts with descriptive studies on the clinical features of puerperal psychosis, followed by an important paper on homicide by patients suffering from Schizophrenia and finally, two publications on the effect of cannabis on symptomatology and course of Schizophrenia. These papers highlighted important aspects of psychotic disorders as these present in developing countries, state of care for those suffering from severe mental illness and the need for a public health action in the form of early intervention.

The details of my initial publications on different aspects of the epidemiology of Psychosis which formed the basis of my later work are presented in following three major areas:

1. **The publications highlighting the distinct epidemiological features of the Puerperal Psychosis (PP).** This highlighted the potential for preventative public health action in view of specific epidemiological features of these disorders and the impact on mother and baby.
2. **An original study on homicide by patients suffering from psychotic disorders.** This study identified that only 12% of patients had any psychiatric treatment before being charged with homicide despite the fact that they had an average duration of illness of more than a year.
3. **Two original studies on the effects of cannabis on symptomatology, course, functioning and service use in patients suffering from schizophrenia.** These helped to elucidate the extent of cannabis abuse and its effects on the course of illness as a preventable factor in the course of a psychotic illness.

In this section, I will present only the salient findings of my studies, with a brief background and discussion of relevant results. The details of all the publications are available in full text as appendix A 1-6.

4.1 Puerperal Psychosis (PP) - A preventable presentation of Psychosis

Background

Most psychiatric disorders are not preventable. This is mainly due to the fact that many risk factors for psychiatric disorders, e.g., stressful life events are not predictable. Other risk factors such as genetic predisposition cannot be readily identified until the disorders manifest. Moreover, the manpower and financial resources required for early diagnosis and intervention are not readily available in Low and middle Income (LAMI) Countries. Postnatal psychiatric disorders on the other hand appear to have a rather predictable onset (something of a rarity in psychiatric disorders), are amenable to easier screening and are precipitated by well established risk factors. These characteristics of postnatal psychiatric disorders can help to initiate a public health strategy in psychiatry.

My work on Psychosis started in 1989, when I completed a dissertation on Puerperal Psychosis. This is 153 pages dissertation submitted to the College of Physicians and Surgeons, Pakistan in 1990 as requirement for the Fellowship of the College. Initially, I was fascinated by symptomatology and presentation of the Puerperal psychosis. However, as the work progressed, I realized the plight of patients and families and the potential for a public health action in this field. The salient findings from these publications are described below.

Paper 1. Clinical Features of Puerperal Psychosis.

(Please see full text article as Annex A1).

Puerperal Psychosis (PP) is a relatively rare disorder and occurs following .2% of all childbirths (Kendell et al, 1987). But, in developing countries like Pakistan which have high fatality rate and multiple pregnancies, PP is not a rare disorder (Farooq, 2004). The identified high risk factors of PP are perinatal death, a previous history of manic depressive illness, previous episode of PP, twin birth and Caesarean Section.

For mothers with previous history of Bipolar Affective Disorder, the risk of psychosis following childbirth is increased 100 fold to one in five (Kendell et al, 1987;Kendell et al, 1981; Pfuhlmann et al, 2002). Most Post Partum Psychotic Disorders are Bipolar in nature. The potential for prevention of these types of disorders was demonstrated by a Randomised Controlled Trial of Lithium Therapy started in the last trimester of pregnancy. Stewart et al (1991) demonstrated that prophylactic use of Lithium initiated either at 34 weeks of pregnancy or within 24 hours of delivery, was associated with lower risk of relapse in patients with a previous history of Bipolar Affective Disorder.

Most literature on PP is from developed nations. I aimed to investigate the clinical features, social determinants and diagnostic breakdown of those suffering from PP in a developing country setting.

Methodology

All patients referred to a Tertiary Care Teaching Hospital in Peshawar over a 15 month period with psychotic symptoms after the delivery were assessed, between November 1988 and January 1990. The patients were assessed with the help of an interview based on Present State Examination. The Puerperal Psychosis was defined as onset of psychotic symptoms within 90 days of childbirth. The onset for the purpose of this study was defined as “the moment when the patient had important symptoms which interfered markedly with her daily activities or abnormality in her behaviour was noted”. The definition of psychosis for the purpose of this study was adopted from DSM III. Patients were assessed with the help of research diagnostic criteria. The diagnosis was made according to Research Diagnostic Criteria (RDC) (Spitzer et al, 1978).

The data on presenting clinical features, help seeking before the contact with psychiatric services, contacts with spiritual healers and effects on the newborn was collected with the help of an instrument constructed for this purpose.

Salient Results

- The mean age of 35 women comprising the sample was 24.2 years (SD 7.08 years). Thirty (30) mothers were primiparae.
- The average time between the delivery and onset of symptoms was 14.34 days (SD 14.59). 80% of patients had onset of symptoms within 3 weeks of delivery and all of them had onset within 2 months.
- The average delay between the onset of symptoms and the admission was 27 days. 15 (42.86) patients had some form of treatment from spiritual healers before admission, which in the majority was the first psychiatric contact.
- Schizophrenia was most common diagnosis (28.57%), followed by Schizoaffective disorders (22.86%). Table 1 in Appendix A-1 shows the details of diagnostic breakdown.
- Two third of mothers could not breast feed, most showing almost total lack of concern for the baby.
- In four cases (11.74%) mother's mental state resulted in some harm to the baby e.g. repeated bathing for the baby due to obsessive concerns about the cleanliness. In seven cases (20%) baby featured in paranoid and nihilistic delusions of the mother. However, none of the mothers expressed any infanticidal thoughts or inflicted any deliberate harm to the newborn.

Discussion

The age of onset of the disorder and the proportion of primiparae mothers in this sample were markedly lower than generally reported. However, both of these were comparable to other studies from developing countries (Maknjoula, 1982). This was understandable in view of younger age at marriage (80% married before 18 years of age in this sample) and the subsequent high fertility. The clinical features of PP were found to be broadly similar to that reported in the literature.

The diagnostic breakdown however revealed some differences. There was low prevalence of affective disorders, particularly that of mania, in sharp contrast to

most of the studies from western countries. There was high proportion of organic psychosis, i.e., 17%. Some of the differences could be explained by the differences in the use of different diagnostic criteria and the diagnostic practices which vary across countries. However, the diagnostic criteria were broadly similar to those reported from other developing countries. For example, most studies from developing countries report a high proportion of organic psychosis (Maknjoula, 1982). This is understandable in view of the high prevalence of complications of postpartum period, i.e., infections, anaemia and various deficiency states.

In agreement with other studies from developing countries (Makanjoula et al, 1982; Shoeb et al, 1990; Ifabumuyi O I, and Akindele MO et al 1985), about half of the patients contacted a spiritual healer before admission, which in the majority of cases was the first point of contact. This seems to be the most important factor for considerable delay (27 days on average) between the onset of symptoms and admission to a Hospital, which may have contributed to the significant physical morbidity and result changes in the clinical picture found in this population.

Paper: 2. The Impact of Psychiatric disorders during pregnancy and puerperium on the child- A review of the literature. (Please see full text article as Annex A2).

This Review Article investigated the impact of psychiatric disorders during pregnancy and in postpartum period on the child. Building on studies which had shown that antenatal stress or anxiety are linked with prematurity or low birth weight, this review article highlighted the impact of postnatal depression and PP on the emotional, psychological and physical health of the infants.

The prospective cohort studies showed that the children of postnatally depressed mothers may show cognitive deficit defects at 4 years of age, difficulties in adjustment and raised level of disturbances leading to difficulties in progress at school. I am not aware of studies or duration of untreated psychosis in puerperal psychosis. I researched literature but could not find studies addressing this specifically in puerperal psychosis. This would be shorter, as women are receiving regular health care in puerperium.

In contrast to the postpartum depression, the effect of postpartum psychosis on the child have not been well studied mainly due to the fact that PP is an uncommon disorder in developed nations, where most of the research on the subject has been done. However, I argued that the children of the mother's suffering from PP may be exposed to similar cognitive, emotional and behavioural disturbances as has been the case for postnatal depression because Postnatal Depression is a much less severe disorder than the PP.

The review article highlighted the fact that the incidence and prevalence of PP may be higher in developing countries due to the following reasons:

- 1 High fertility rate in developing countries resulting in high risk of developing PP after each childbirth.
- 2 The risk for postnatal psychiatric disorder is highest in primiparae and increases with every subsequent delivery. Mothers who develop PP after first delivery have a 1 in 5 risk of developing a similar illness during subsequent childbirth. This means that the risk of relapses after each childbirth actually multiplied.
- 3 Certain causes of PP i.e., infection, anaemia and deficiency states giving rise to Organic Psychosis following childbirth are much more prevalent in developing countries compared to the developed countries. This leads to higher incidence of PP in these countries.

This extensive review of published literature highlighted the fact that even with limited healthcare facilities available in many developing countries; women had the best chance of being cared for by health professionals in pregnancy. This is mainly due to the fact that women during pregnancy and postpartum period are more likely to receive better care from health providers and families during antenatal and postnatal period, compared to any other time in their life, in resource poor settings. The peak incidence of puerperal psychosis is within the first two weeks after delivery. During this period they are more in contact with health services or other sources of help, compared to another period. If health visitors are sensitized and trained to detect postnatal psychiatric disorders, the likelihood of detection and treatment of psychiatric disorders is greatly increased.. It is therefore possible to

focus on the mental health of the mother during the routine antenatal and postnatal care. The potential cases of PP could be identified through a number of well known risk factors and both primary and secondary prevention is therefore possible.

Paper 3: Puerperal Psychiatric Disorders- who cares?

Paper 4: Postnatal psychiatric disorders need public health action.

(Please see full text article as Annex A3 and A4).

Based on the evidence from literature and my original work, I advocated a public health approach for early detection and prevention of Puerperal Psychosis in LAMI countries. My extensive writings and advocacy in the field prompted two invited editorials.

Even based on an incidence of approximately 1 in 500 deliveries, very high fertility rates in many developing countries result in higher prevalence of PP in these countries. The literature reviews highlighted the fact that newborn babies in developing countries may be at risk as a result of malnutrition and gastroenteritis due to lack of maternal care after the onset of postpartum psychotic disorders, something of a rarity in developed nations.

For example, Makanjoula in his study in the Nigerian population found that 7 babies died and another 7 became severely ill as a result of malnutrition and gastroenteritis due to lack of maternal care after the onset of postpartum psychotic disorders. Therefore, this posed a greater risk than the infanticide which has been reported in up to 4% of the cases of PP in western studies.

Based on the characteristics of PP highlighted above, I argued that these disorders need an urgent public health action. This action should be based on following:

- 1 Research on the interventions for postnatal psychiatric disorders which could be cost effective in developing country settings.
- 2 Training for health professionals involved in routine neonatal care for early detection, treatment and prevention of postnatal psychiatric disorders. The

high risk factors for postnatal depression and PP must be included in the routine antenatal screening of the expectant mothers.

- 3 Creating awareness in the public about these disorders on mother and child.

These actions require collaborative efforts between health professionals involved in psychiatric, obstetric and childcare, along with health planners and public health experts. ‘After all, we need a generation of young infants and children which is not only physically healthy but emotionally and intellectually sound as well, brought up by mothers who are free of stigma of mental illness’; concluded one of the articles.

4.2 Psychosis and Homicide

Paper: 5. Mentally ill patients charged with homicide

(Please see full text article as Annex A5)

Background

Continuing with my work on the epidemiology of Psychosis and its impacts, I explored a rather neglected area of research in developing countries i.e. homicide by mentally ill patients. This work was result of my involvement with the Standing Medical Board of the provincial government which is an expert body comprising of psychiatrist and other health professionals to give opinions about the patients with history of mental illness and charged with serious criminal offences. Soon after joining the Board, I was struck by rather long periods of illness in these patients before they committed the index offence which prompted me to examine the relationship between homicide and mental illness in detail.

Most of the research on the association between offending behaviour and mental disorder comes from developed nations. The findings from this research are not applicable to many low and middle income countries. Forensic Psychiatric Services are almost non existent in the majority of these countries. This study investigated the characteristics of patients charged with homicide and referred for psychiatric assessment with a suspicion of mental illness.

Methodology

The notes of all patients who were charged with murder and referred to the Standing Medical Board of the Mental Hospital between 1988 and 1998 were reviewed. The Standing Medical Board comprises of at least 2 qualified Psychiatrists who provided their opinion offering an assessment and after a period of observation of the patients referred for the purpose of assessment. All case notes were systematically reviewed and the details on the following key variables were extracted with the help of an instrument.

- The demographic details of the patient
- Opinion of the Board regarding the diagnosis, fitness to stand trial and mental state.
- The events related to and leading to the homicide
- The details of the victim and their relationship with the patient
- Past psychiatric history and any treatment received before the index offence

Salient Results

Following are salient findings of the study (Table III, IV, V: Appendix A5).

- Fifty patients charged with homicide during this period were assessed. Schizophrenia was the most common diagnosis found in 36 (72%) of patients. Other diagnoses included Bipolar Affective Disorder, Epilepsy, and Delusional Disorder.
- Out of fifty patients only 2 patients (4%) had duration of illness of less than 1 year.
- Almost half (46%) had a chronic illness with duration of illness ranging between one year and twenty years.

- Only 12 patients (24%) had received some form of treatment before the index crime.
- 38 patients (76%) were involved in a single murder, while 12 patients (24%) were involved in double/multiple murders.
- Out of 64 victims of the patients, 49 were close relatives.

Discussion

This was the first study on the relationship between homicide and mental illness in Pakistan and added valuable data to the scarce literature on the subject in developing countries. Predominantly male and young population (mean age 32.40) charged with homicide found in the study was in general agreement with other studies. Similarly, high proportion of those suffering from Schizophrenia (72%) was also in general agreement with the literature.

With the exception of two patients, the duration of illness in the sample was more than 1 year. Despite the fact that these patients had a long duration of illness, only 24% had had any contact with psychiatric services or professionals, which was broadly defined for the purpose of this study to be any contact with a mental health professional in 6 months before the index crime. It could be argued that at least some of these homicides could have been prevented with the provision of proper psychiatric services, as it has been shown that violence and crime can be prevented by improving the response to the patients who start to relapse.

The findings of the study that the majority of the victims were either relatives or well known to the patients, was also in broad agreement with the literature. This was in line with the findings reported by Taylor and Gunn (1999). This study also showed that the public perception of violence by mentally ill patients was highly distorted, as the victims were most likely to be relatives and acquaintances, rather than public at large.

This study was based on the case notes and therefore suffered from limitations of retrospective studies. However, it is worth mentioning that the Mental Hospital at Peshawar was the only Hospital providing Forensic Psychiatric Services for the

whole of the region. It is therefore, unlikely we may have missed patients suffering from severe mental illness and charged with homicide and study sample could be considered representative of the population. It is however, possible that due to inadequate Forensic Psychiatric services, the sample comprised of only those suffering from most severe form of psychiatric disorders.

In common with the research on Puerperal Psychosis this study again highlighted two most important aspects of the Psychosis in LAMI settings. These are, the long duration of untreated illness and its impact on the nearest family members. In case of PP this had serious impact on the newborn and the spouse, while this study showed that the spouses and the close family members risked their lives while providing care of those suffering from Psychotic disorders.

4.2 Salient findings of Studies on Cannabis abuse in patients suffering from Schizophrenia:

CANNABIS ABUSE IN PATIENTS WITH SCHIZOPHRENIA EFFECTS ON SYMPTOMATOLOGY, COURSE, FUNCTIONING AND SERVICES USE.

- The National Survey on Drug Abuse in Pakistan showed 3.01 million people to be suffering from chronic drug abuse in Pakistan, rising at a rate of nearly 7% annually; Cannabis being the most common substance being used.
- About two-thirds of patients (76) met the criteria for Cannabinoid dependence syndrome which meant that cannabis was not being used occasionally or only for recreational use.
- The use of cannabis was associated with more florid positive psychotic symptoms such as excitement, grandiosity, poor impulse control, uncooperativeness, anger , and difficulty in delaying gratification .
- The patients with co morbid cannabis abuse had significantly more relapses, spent longer time in hospital and had significantly poor compliance with treatment compared to control group.
- The early intervention programmes should target the Cannabis abuse as both cannabis abuse and psychosis occur in young populations during the most productive years of the life.

Paper: 6. Cannabis abuse in patients with schizophrenia: pattern and effects on symptomatology.

Paper: 7. Schizophrenia and co-morbid self reported cannabis abuse: impact on course, functioning and services use.

(Please see full text publications as Annex A6 & A7).

The research so far had focused on important but narrowly defined areas. Widely prevalent cannabis abuse and its detrimental effects on the course of Schizophrenia presented an area in which the preventative efforts could have much wider application. This led to the research on the effects of cannabis abuse on the symptomatology, presentation and service use in patients suffering from Schizophrenia.

Background

Many studies have shown that the rate of substance use in subjects with severe mental illness is high; estimates of recent or current abuse for community samples range from 20% to 40%. (Meuser et al, 1990). Patients with comorbid mental illness and substance abuse disorders have been a cause for concern because even low levels of substance abuse or dependence represent a risk factor for serious complications, including suicide, poor compliance with treatment, more inpatient stays, violence, and a poor overall prognosis (Smith and Hucker, 1994)

This comorbidity is associated with poor prognosis and heavy use of expensive inpatient care through recurrent "revolving door" admissions (Haywood, 1995). One survey in UK observed that inpatient admission rates among comorbid patients that were almost double those of patients with psychosis alone (Menzes, 1996) This high prevalence, the problems of clinical management and continued rises in the general rate of drug misuse make comorbidity a major public health issue (Lehman, 1995). Number of studies also found that cannabis abuse might be an important factor in aggression and offending among severely mentally ill individuals. (Scot et al., 1998;

Menezes et al., 1996; Drake et al, 1989,) particularly in terms of aggression and hostility.

Cannabis is a one of the most common drug of abuse in many developing countries including, Pakistan. The National Survey on Drug Abuse in 1993 revealed 3.01 million suffering from chronic drug abuse in Pakistan, rising at a rate of nearly 7% annually. Among young people, cannabis is reported to be the most common drug used, followed by heroin and alcohol. Nearly 72% of the drug abusers were under 35 years of age, with the highest proportion in the range of 26-30 (Narcotics Control Division, 1993).

In a hospital based study, in patients admitted between 1996-2001, it was found that cannabis was the most frequently used drug of abuse (Dogar et al, 2005).

Continuing to explore the epidemiological evidence for factors which could be amenable to preventive efforts, the author published research which helped to elucidate the effects of cannabis use on symptomatology, functioning and service use in patients suffering from schizophrenia in a developing country setting (Rahman and Farooq, 2007 a, b).

Methodology (Please see full text publications as Annex A6 & A7)

A case control design was used for studying the effects of cannabis abuse on the course, symptomatology and outcome of those suffering from Schizophrenia and cannabis dependence. In these studies, patients meeting the International Classification of Disease (ICD)-10 Criteria for schizophrenia (W.H.O. 1993) and admitted to the Psychiatry Department Lady Reading Hospital Peshawar, Pakistan were included. Fifty patients with a diagnosis of Schizophrenia and self reported misuse of cannabis in the last year were selected as cases for study. Patients suffering from Schizophrenia without comorbid cannabis use (n=50) were selected as control group. Patients with co-morbid cannabis misuse were interviewed using section 12 of Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (World Health Organisation 1994). Section 12 of SCAN measures the amount of illicit drugs used and social, legal, physical, and other problems related to these drugs

All the questions of interview were translated into Pushto which is the local language by a bilingual expert and retranslated by another expert who was blind to the first translation. All the patients were also administered PANSS (Positive and Negative Syndrome Scale) to assess severity of schizophrenic symptoms. Social functioning was assessed with the help of Global Assessment of Functioning (GAF) scale. The effect of cannabis on service use was estimated by recording contacts with primary care staff, out-patient services, general hospitals, emergency departments, police services within the past year in both groups. Numbers of psychiatric admissions, days spent in hospital and compliance were also assessed. Compliance was assessed using a 4-point scale that was developed by Barrowclough et al (1999) which defined compliance as the extent to which a person's behavior coincides with the medical advice given. The definition of non-compliance included premature termination of therapy and incomplete implementation of instructions.

Main Results of the studies (Please see full text publications as Annex A6 & A7)

Following are the salient findings of these studies:

- About two-thirds of patients (76%) in the cannabis group met the criteria for Cannabinoid dependence syndrome which meant that cannabis was not being used occasionally or only for recreational use.
- The use of cannabis was associated with more florid positive psychotic symptoms as measured by the PANSS. The patients using cannabis had higher scores on excitement (2.82 v 1.80 $P < .005$, CI 0.40- 1.63), grandiosity (1.74 v 1.12, $p < .005$, CI 0.21-1.03), hostility (3.86 v 2.30, $p > .005$, CI 0.83- 2.29), poor impulse control (3.76 v 1.94 $p < .005$ CI 1.15 -2.49), uncooperativeness (3.86 v 1.90, $p < .005$, CI 1.34- 2.58), anger (4.06 v 2.26, $p < .005$, CI 1.11- 2.49) and difficulty in delaying gratification (3.64 v 1.64, $p < .005$, CI 1.37-2.63) (Table III: Appendix A6 : Comparison of PANSS cluster score between cases and control).

- Patients suffering from schizophrenia and co morbid cannabis use were younger on index admission than non user (25.82 years vs. 30.57 years, $p=0.001$ 95% CI of mean difference -7.54 to -1.96).
- The patients with co morbid cannabis abuse had more relapses as compared to those who were not using the substance (2.46 vs. 1.22 Mean difference 1.24 $p<0.011$ and 95 % CI of difference 0.21 to 2.19). Overall compliance with medication was significantly poorer in patients using cannabis than patients who were not using cannabis ($P<.085$) (Table: 4; Appendix A 7: Comparison of drug adherence in last month between cases and control.).
- Those using Cannabis were also more likely to be admitted to hospitals (number of admission 1.04 vs. 0.52 $p<0.05$; 95 % CI of difference .03- 1.04). They also spent more days in hospitals (19.7 vs. 7.22 $p<0.047$; 95 % CI of difference .18 - 23.58) and have greater number of contacts with police (1.70 vs. 0.20 $p<0.000$; 95 % CI of difference .96- 2.04). (Table 3; Appendix A7: Comparison of service use (Number of admission and days spent in hospital, visits to private clinics and contact with police).
- The age at onset of illness was earlier in those with comorbid cannabis abuse (21.43 years vs. 25.39 years, $p=0.005$). The duration of illness at the time of admission was shorter for cases as compared to controls, probably reflecting presentation with more florid symptoms which necessitated earlier admission.

Discussion and implications for the Early Intervention in Psychosis

These publications support now the well established findings (Gupta et al 1996, Johns 2001) that those suffering from Schizophrenia and co morbid Cannabis abuse have poorer outcomes. Patients using cannabis were more likely to suffer from relapses, had significantly higher number of admissions to hospitals and stayed in the hospital for significantly longer period as compared to the controls. They also had poor compliance with treatment.

It was found that cannabis was associated with excitement, hostility, uncooperativeness, anger, poor impulse, and difficulty in delaying gratification. The constellation of these symptoms in PANNS has been found to be associated with a

high risk profile requiring institutional care (Kay et al 1987). These findings are consistent with the W.H.O 10 country study on schizophrenia which found that the use of cannabis during the follow-up predicted more psychotic symptoms and periods of hospitalizations (Jablensky et al, 1992).

These findings are very significant keeping in mind that cannabis users also had younger age at admission. Considering that Psychosis mainly affects young populations during the most productive years of their lives, it is crucial that early intervention programmes target the Cannabis abuse as one of the main targets. The cannabis abuse was also found to be associated with poor compliance. It was not possible to decide the direction of causation in this study but it was likely that cannabis abuse hindered the compliance with treatment regimen. These findings helped us to develop the educational interventions as will be explained later in the thesis.

These studies suffer from the methodological limitations associated with retrospective research design with possibilities of significant confounding factors and recall bias in relatively small sample size. However, the research highlighted the significant adverse effects which use of cannabis could have on the presentation, course and compliance with treatment which is now consistent with overall evidence from literature. Considering that each relapse in developing country settings adds further burden for the family, perpetuates stigma and the vicious cycle of poverty and social exclusion, it is crucial that these factors are addressed in a public health programme. The programmes for the treatment and rehabilitation for those suffering from Schizophrenia will need to incorporate the interventions to prevent and reduce cannabis abuse.

4.4 Summary of the Publications 1995-2007

In summary, my early scholarly work started with a study of Puerperal psychosis. This highlighted the fact that Puerperal psychosis is not a rare disorder due to very high fertility rates in most developing countries and long delays occur when mothers present with psychosis after childbirth despite the florid and serious nature of these disorders. In view of serious effects these disorders have on mother and baby, the early intervention in Puerperal psychosis must be a priority. This is feasible due to fact that this form of severe mental illness occurs following an identifiable life event (childbirth) and the risk factors can be screened in the antenatal period.

The research on the homicide by mentally ill patients showed that only 24% of patients reported any contact with psychiatric services or professionals, despite the fact they had very long duration of illness and some of the patients were charged with double or multiple murders.

Two further publications highlighted the adverse effects of cannabis use on course, functioning and service use in patients suffering from schizophrenia in a developing country setting, which could be amenable to preventive efforts in an early intervention programme.

This work made me deeply aware of the devastating effects of untreated psychosis in resource poor settings. Interestingly, this was the time when the effects of the long periods of untreated psychosis before the first presentation to psychiatric services were emerging in literature. This work naturally led to my next research focus, the Duration of Untreated Psychosis, its relationship with economic factors and the effects of long DUP on the outcome of psychosis.

Chapter 5

The case for a Public Health action for early intervention – publications on Duration of Untreated Psychosis.

- The public health consequences of long Duration of Untreated Psychosis (DUP) include increased co-morbid substance abuse, suicide, increased treatment resistance, impairment in cognitive and neuropsychological functions, offending behavior, vocational failure and overall poor outcome.
- DUP is a potentially modifiable prognostic factor.
- Employing the most comprehensive search strategy used to date for identifying studies both for developing and developed countries, the Duration of Untreated Psychosis (DUP) was estimated. The relationship between DUP, Gross Domestic Product (purchasing power parity, GDP_{PPP}) and the outcome of psychosis was also investigated.
- The systematic review and meta analysis examined 408 papers in full text and finally included 136 papers which included an operational definition of DUP
- The average mean DUP from LAMI countries was 134.2 weeks which was significantly longer than the average DUP reported from High Income countries i.e. of 65.5 weeks .
- There was a strong negative correlation between DUP and GDP _{PPP}, indicating that for every thousand dollars of additional GDP _{PPP}, mean DUP was reduced by 8 weeks and median DUP was reduced by 5 weeks.
- Longer DUP was associated with at least one measure of a poor outcome. Longer DUP was significantly associated with smaller reduction in symptoms after treatment, a greater level of disability and perhaps increased mortality.

Background

My work over a decade, in daily clinical practice as well as in research publications, illustrated the devastating consequences of untreated psychosis in developing country setting. During this decade the literature revealed the effects of untreated psychosis in the initial years of illness. The concept that there is a critical period in illness where effective interventions can prevent much of the disability later in the course of illness is now well established and manifested in Early Intervention Services in developed countries. I decided to investigate the evidence on Duration of Untreated Psychosis in LAMI countries.

The onset of schizophrenia typically occurs in late adolescence or early adulthood. Manifestations of the disorder and symptoms develop gradually over a period of weeks or even months. The disorder is preceded by less specific prodromal symptoms. Because many of these prodromal phenomena extensively overlap with the normal behaviors of persons in the age group at risk, it is difficult to diagnose the disorder for long period of time before the help is sought. The Duration of Untreated Psychosis (DUP) denotes the time from manifestation of the first psychotic symptom to onset of antipsychotic treatment. Structured assessment of DUP can be done by different diagnostic tools developed for this purpose (Lieberman & Fenton, 2007). Studies, mostly from developed nations have revealed that individuals suffering the first episode of psychosis experience an alarming delay between the onset of psychotic symptoms and the initiation of treatment, typically durations of untreated psychosis that averages 1–2 years

The enormous public health consequences of long duration of untreated psychosis are now well documented (Lieberman & Fenton, 2007). These include increased co-morbid substance abuse, suicide, increased treatment resistance, impairment in cognitive and neuropsychological functions, offending behavior, vocational failure and overall poor outcome.

Long DUP in the first episode of psychosis (FEP) is associated with worse short and long-term prognosis (Marshall et al, 2005; Perkins et al, 2007), an increased risk

of suicidal behaviour (Altamura et al 2003; Melle et al. 2006) and possibly serious violence (Milton. Jet al,2001.; Verma, 2005; Large 2007).

Given its relationship with outcome, DUP assumes significant public health importance as it is a potentially modifiable prognostic factor. It also has implications for understanding the pathophysiology of schizophrenia. Almost all the evidence about the delay in initiating the treatment has been limited to well established health systems in North America and Europe. The actual period of DUP and its effect on the prognosis of psychotic illness in low- and middle-income (LAMI) countries is not known. The long DUP may have more severe consequences in lower-income countries because people who are mentally ill may have limited food, shelter and medical care. In view of the provisions for the mental health care which have been highlighted in the first section of this thesis, the possibility was that the DUP was associated with economic factors. The treatment costs in many LAMI countries are born by patients or families by out of pocket expenses. In these circumstances disorder causing mortality and physical morbidity such as infections take priority over the psychiatric disorders in which the patients and families may suffer in silence over many years before seeking any treatment.

My publications in this area addressed following questions:

- What is the mean and median DUP for LAMI countries? (The median is more important for measurement of DUP as there is robust evidence in literature that mean DUP is skewed by few patients with very long DUP in many studies).
- What is the relationship between DUP and the income as measured by GDP, ppp (Gross Domestic Product, purchasing power parity)?
- What is relationship between mean and median DUP, diagnostic category, age and different categories of countries according to income level?
- What is the relationship between DUP and the outcome of Psychosis?

5.1 Duration of Untreated Psychosis in developing countries: The relationship between GDP and DUP (For full text article see appendix: A. 8)

This paper aimed to systematically review the studies reporting Duration of Untreated Psychosis in order to calculate an average value for DUP for both lower and higher income economies. The World Bank classification of Low-Income (LI), Lower-Middle-Income (LMI) and Upper-Middle-Income (UMI), referred to together as Low and Middle Income (LAMI) economies (also referred to as developing economies) was used for the purpose of this paper. The World Bank term of High-Income (HI) is used to refer to developed economies (World Bank 2006). This study investigated the relationship between DUP and the estimates of Gross Domestic Product purchasing power parity (GDP ppp) published by the International Monetary Fund for 2005. (International Monetary Fund 2005); which is first of its kind

The a-priori hypotheses for the study was that (i) the DUP of patients in LAMI economies would be longer than the DUP of HI economies and (ii) there would be a negative association between GDP ppp and DUP. The null hypothesis was that the mean DUP of studies of DUP from LAMI and HI regions would not differ significantly.

Method

Search Strategy (Please see diagram 1, Appendix A:11 Flow chart of searches for DUP studies from LAMI and High income regions)

Because of the difficulty in finding data on mental health care in developing countries four separate search strategies were employed. Firstly, We searched the electronic data-bases [Medline], [Embase], [Psychlit] and [PsychINFO] from Jan 1975 to Jan 2007 with the search terms ‘duration of untreated psychosis’, ‘delay in treatment’, ‘treatment delay’ or ‘initiation of treatment’ cross referenced with the terms ‘psychosis’, ‘psychotic disorders’, ‘schizophrenia’, ‘schizoaffective’ or

‘schizophreniform’ and ‘first-episode psychosis’. This yielded 280 publications about DUP or first episode psychosis from developed countries but only eight studies reporting DUP from developing countries.

Second we used electronic searches of the text, including letters and conference proceedings of six leading Psychiatric journals with the terms 'Duration of Untreated Psychosis' OR 'DUP' ; Schizophrenia Research, Schizophrenia Bulletin, British Journal of Psychiatry Supplement, Acta Psychiatrica Scandinavica, Journal of Clinical Psychiatry, and International Clinical Psychopharmacology. These journals were chosen because they were identified as having previously published the conference abstracts from international schizophrenia conferences in a PubMed search of the title and abstracts using the terms ‘Schizophrenia’ and ‘Conference’ . This resulted in the location of two more studies.

Third we located one further study by searching the first 40 Google hits using the names of 152 LAMI economies combined with “duration untreated psychosis”.

Fourth we examined every abstract from a search of [PubMed] from Jan 1975 to Jan 2007 using the term “schizophrenia” and the names of 152 LAMI economies. Publications on the topics of movement disorder in untreated patients, gender differences in the age of onset of schizophrenia and studies of epidemiology of schizophrenia in any developing country were examined in full text. Finally, we contacted the authors of 12 recent publications about aspects of schizophrenia in developing countries to see if they had unpublished DUP data and hand searched the references list of all articles for further studies that reported DUP, without finding additional studies.

All the articles identified by [Medline], [Embase], [Psychlit] and [PsychINFO] searches and the full text searches of the 6 journals were examined in full text. Seven differences in the articles selected that were due to the selection of different papers from multiple publications of the DUP of the same subjects were resolved by a joint examination of the publications.

These searches were cross checked during the subsequent searches of PubMed and Google on two occasions three months apart. One additional articles from a HI economy was found in the second set of searches.

Inclusion and exclusion Criteria.

We included studies with non-overlapping samples of the DUP or a close approximation of DUP. Hence articles that provided the age of onset of psychotic symptoms and the age of presentation to treatment, mental health services or researchers, to at least one decimal point were also included. We excluded samples that mixed subjects from different economies and samples with measures of DUP other than the mean or median or from which mean DUP could not be calculated. No additional quality assessment was made if the paper provided met the inclusion criteria. However, all but two studies used a recognised diagnostic system or a structured interview. A number of papers reported samples of male and female patients, samples with different diagnostic characteristics or samples collected at different times or locations. All such samples were included.

Data Extraction

The following data was extracted from all of the samples:

1. Country of origin of the subjects
2. Number of subjects in the sample
3. The end point of DUP (initiation of treatment, contact with mental health services or contact with researchers)
4. Mean age of contact or treatment
5. Mean and/or Median DUP in weeks
6. Whether the study included patients with affective psychosis.
7. Percentage of subjects with a diagnosis of schizophrenia or schizophreniform psychosis
8. Percentage of male subjects

The data was independently extracted by two researchers. Three differences in the DUP data collection were in the HI sample and also three in the LAMI samples. These were unambiguously resolved by further examination.

Definition of DUP

The most widely accepted definition of DUP is the period between the onset of definite psychotic symptoms such as hallucinations and delusional beliefs and adequate treatment (Norman, and Malla, 2001). However, because there were so few studies from the developing world, we accepted the broader definition of DUP in studies from developing countries which included contact with mental health services or researchers, as these patients, particularly those who did not have contact with services did not always get antipsychotic treatment.

We also report on a subset of studies of patients with schizophrenia and other related psychosis all of whom had contact with mental health services and thus fit a narrower definition of DUP used in some studies of DUP from HI regions.

Income data

The LAMI country classification is based on national GDP in US dollars which may not reflect actual ability to purchase all the goods and services available in developing countries in local currency. Therefore, in addition to using the LAMI groupings, the relationship between GDP ppp and DUP was examined, because it takes into account the cost of living in local currency terms.

Statistical Methods

The Mean DUP and Median DUP for the 38 samples from LAMI groups were compared with the 115 samples from HI countries. Neither the Mean or Median DUP values were normally distributed within either the LAMI and HI groups of studies (LAMI, skew of mean 2.6, skew of median 2.4; HI, skew of mean 2.2, skew of median 2.6). This skew was a result of minority of samples from both LAMI and HI economies having a very long mean and median long DUP. Hence a Mann-Whitney test was used to compare both the DUP of LAMI and HI groups.

The number of male patients and the number of patients with schizophrenia in LAMI and HI regions were calculated from the percentage of cases in each study and a two-tailed chi-square was used to compare these variables. The age at presentation and age of onset were compared using a students two tailed t-test. A bonferroni correction for four comparisons was used as age at presentation is not

independent of age of onset or DUP. Mean, and Mean and Median DUP were not considered to be independent observations. A p-value of $0.05/4=0.0125$ was regarded as significant.

Multiple linear regression was used to examine the possible associations between the dependant variable of DUP and LAMI status and the co-variables of age, gender, the proportion of schizophrenic patient and the year of publication of the study. For this analysis DUP was Log_{10} transformed resulting in normally distributed DUP values (skew=0.841). LAMI status was used as an omnibus categorical variable in this post-hoc comparison because DUP ppp in some of the wealthiest countries was observed to be long. This suggests that there may be a non-linear relationship between DUP ppp and GDP ppp if all economies are examined. In this multivariate analysis the samples were given a weighting according to the number of subjects on the assumption that larger samples would have a more accurate estimation of mean DUP.

A linear regression model was also used to examine the relationship between GDP ppp and DUP within LAMI regions after an apparently linear relationship between these two variables was observed in scattergram. In this analysis the DUP values were not Log_{10} transformed in order to quantify the relationship between GDP ppp and DUP. However four samples of patients who never received treatment and who on average had been psychotic for nine years or more were excluded.

The statistical analysis was performed using SPSS, version 15.0.

Results

(Diagram 1, Appendix A: 8. Flow chart of searches for DUP studies from LAMI and High income regions)

In total 408 papers in full text were examined and 136 papers were found which included a measure of DUP. Twenty eight papers were excluded as the samples overlapped with those of other publications. Ten studies were excluded for following reasons; two studies from developed countries that were performed in the 1960s, four other studies of patients who became unwell prior to the advent of

antipsychotic medication, two studies that reported DUP in terms of fixed time intervals and two studies reporting single samples with subjects from regions of differing economic development.

In all 98 studies met the inclusion criteria, of which 23 were from developing countries and 75 were from developed countries (Table DS1 and DS 2; Appendix A 8). The earliest study from a developing country was published in 1995. The 23 studies from developing countries included 21 samples in which DUP was reported directly and 17 samples in which Mean DUP could be calculated. All but three studies were published in full text in peer-reviewed journals. Five authors were contacted for further details and two authors kindly provided more complete accounts of their research published in abstract form (El-Adl, et al, 2006; Ranjbar et al, 2006). Twenty three samples from LAMI countries specifically reported the mean DUP, rather than the interval between the onset of psychosis and contact with researchers) of patients with a schizophrenia related psychosis (excluding affective psychosis) and met a narrower definition of DUP. (The characteristics of studies from LAMI countries are highlighted in table 1)

All the studies from HI countries were in full text in peer-reviewed journals and all but eight studies were published after 1990. The studies from developed countries included 115 samples, 109 of which reported DUP directly and in a further 6 samples from which Mean DUP could be calculated.

Mean and Median DUP (Appendix A 8:Table 1 Duration of untreated psychosis, diagnostic and demographic variables in the LAMI groups and Table DS3).

Thirty seven of 38 samples from LAMI economies reported mean DUP and had an average mean DUP of 134.2 weeks. This was significantly longer than the average DUP reported in 107 of 115 samples from HI economies that reported mean DUP and had a mean DUP of 65.5 weeks (Table 2). The average value of Median DUP was also more than twice as long in the 16 samples from developing countries (45.9 weeks) than the 74 samples from developed countries (18.5 weeks) although this apparently large difference did not reach statistical significance.

Mean age at presentation but not age of onset was higher in studies from LAMI regions than HI regions. Studies from LAMI regions had fewer male subjects and fewer people diagnosed with schizophrenia.

Stepwise multiple linear regression that was weighted by the number of subjects in each sample found that the longer DUP found in LAMI groups was independent of the proportion of schizophrenic subjects, and the mean age of onset. The proportion of males in the samples or the year the research was published was not significantly associated with the Log_{10} of mean DUP. (Tables DS 3, DS 4 and DS 5; Appendix A 8).

Given that there were significant diagnostic differences between the groups, and as it is known that patients with affective psychosis have a shorter DUP, we also controlled for the effects of diagnosis by focusing on the studies that only reported schizophrenia related disorders. In sub-sample of studies we excluded samples of patients who only had contact with researchers and may never have received treatment. The Mean DUP of these 23 studies of DUP in schizophrenia related psychosis from LAMI economies that met a narrower definition of DUP was 90.5 weeks (median 83, 95% CI of mean 52.0-118 weeks), was significantly longer than the mean DUP of 72.7 weeks (median 55, 95% CI of the mean 47.3-71.0) in the 79 samples of patients with schizophrenia related psychosis from HI countries (Mann-Whitney $U=1187$, two tailed $P=0.026$). This suggests that the findings of the study, that patients from a LAMI region have a longer DUP which is independent of the diagnosis and was not a result of including a cohort of untreated patients in the LAMI.

Relationship between GDP ppp and Mean and Median DUP

In a final analysis we examined the relationship between GDP ppp and Mean and Median DUP in LAMI economies. Overall there was a strong negative correlation between DUP and GDP ppp, indicating that for every thousand dollars of additional GDP ppp, Mean DUP was reduced by 8 weeks (table four) and Median DUP was reduced by 5 weeks (Table DS 5; Appendix A 11). An analysis of the mean DUP in 23 samples that met narrower definitions of DUP (patients with schizophrenia related psychosis, all of whom were seen by mental health services) suggested that

DUP fell by 7 weeks for each additional one thousand dollars of GDP ppp (Appendix A 8: Table 1 Duration of untreated psychosis, diagnostic and demographic variables in the LAMI groups).

Discussion

Our principal hypothesis, that DUP would be longer in studies conducted in LAMI regions was confirmed. However, this finding may require qualification in future studies as we found that the small number of studies from UMI regions actually had a shorter DUP than those conducted in HI economies. We also found a linear relationship between GDP ppp and DUP suggesting that the observed relationship between LAMI economies and DUP may be causal.

GDP has not been previously reported to be an association of long DUP, and the treatment delay in HI economies is usually attributed to lack of insight on the part of the patient, lack of understanding in families and the gradual onset of psychosis in some patients. The reasons for longer DUP in LAMI economies need further investigation, but are likely to include the lack of services in many areas as well as the relative cost of treatment.

The cost of treatment is frequently reported as important factor in the lack of treatment in Low Income countries (El Adl et al, 2005; Ran, et al,2003 ; Ran, et al 2001; Selten et al., 2005) and Low Middle Income countries (Tang et al, 2007, McCreadie et al, 1994; Grover et al, 2005). For example, in a region of Nigeria the only available antipsychotic for those suffering from psychosis was a low dose of chlorpromazine for a few weeks per year, provided by a charity (McCreadie et al, 1994).

Even if the patient's family in this context is able to purchase further doses of antipsychotic medication, it may be at the expense of other forms of essential medical care or even food. In India the direct cost of treating schizophrenia is a quarter of the average family income in US dollars (Grover et al, 2005). Hence it is not surprising that mean DUP declined with even modest increases of mean GDP ppp.

This study has only highlighted the initial delay in seeking treatment. The overall treatment gap may be much greater as there are number of studies in developing countries which describe large number of patients who never receive any treatment (Ran, et al 2001; McCreadie et al, 2005; McCreadie and Ohaeri, 1994).

5.2 The relationship between the duration of untreated psychosis and outcome in low and middle income countries: Systematic review with meta analysis.

Background:

After establishing the long delay during the initial episode of Psychosis when patients do not receive any treatment, we decided to investigate the relationship between DUP and outcome of psychosis. Despite less developed health care services, endemic infectious disease, high rates of malnutrition and a shorter life expectancy, several large and well conducted studies have reported that that schizophrenia has a better prognosis in Low and Middle Income (LAMI) countries (World Health Organization, 1973 and 1979; Jablensky et al. 1992; Hopper et al, 2007). However, a recent systematic review by Cohen et al found no evidence for better prognosis for psychotic illness and suggested that methodological issues may have contributed to the findings of a better prognosis of psychotic illness in some LAMI countries (Cohen et al 2008).

Cohen et al (2008) suggested that the proportion of patients lost to follow up may have biased some studies in the direction of finding a better prognosis and they raised excess mortality as an indicator of a poorer prognosis. Mortality may have been given insufficient consideration in some outcome studies as high rates of mortality, mainly from untreated medical illness and malnutrition is regularly reported in studies of psychosis from LAMI countries (Cohen et al 2008, Dube et al, 1984; Mojtabai et al, 2001, Ran, et al 2007; Kurihara, 2006). Furthermore mortality has been found to be associated with lack of psychiatric treatment in two studies. A large prospective study from rural China found that a long duration of untreated psychosis (DUP) and the lack of continued treatment were associated with increased mortality as well as much worse prognosis (Ran et al 2007) while an earlier study from the Indonesian island of Bali found that a DUP of more than a year's duration

was associated with a seven fold increase in mortality in the subsequent decade (Kurihara , 2006)

The adverse effects of long DUP on prognosis have been established in high income (HI) countries by two systematic reviews (Marshall, 2005; Perkins, 2005). There have been relatively few studies examining the association between outcome and DUP in LAMI countries, and it is not known if long DUP is also associated with a poor prognosis outside of HI countries. A finding that longer DUP is not associated with worse prognosis in LAMI countries would support the hypothesis that patients with psychosis in LAMI regions do have a better prognosis.

The aim of this systematic review is to examine the relationship between DUP and measures of outcome in psychotic illness in LAMI countries.

Method

Search Strategies (Fig. 1. Flow chart of searches for DUP studies from LAMI and HI regions; Appendix A 9)

A wide search strategy was undertaken in an attempt to locate all the studies that were available (Fig 1). Firstly, we searched the electronic databases Medline, Embase, Psychlit and PsychINFO from January 1975 to March 2008 using the search terms ‘duration of untreated psychosis’, ‘delay in treatment’, ‘treatment delay’ or ‘initiation of treatment’ cross referenced with the terms ‘psychosis’, ‘psychotic disorders’, ‘schizophrenia’, ‘schizoaffective’ or ‘schizophreniform’ and ‘first-episode psychosis’.

This method yielded more than 300 publications about DUP from developed countries but only eight studies conducted in countries defined as low-income (LI), lower-middle-income (LMI) or upper-middle income (UMI) using the International Monetary Fund’s LAMI classification (World Bank, 2007).

A second search was carried out in Pubmed to identify psychiatric journals that had published the abstracts of international schizophrenia conferences. Based on this identification we electronically searched the text of six leading psychiatric journals. In full text searches of the websites of Schizophrenia Research, Schizophrenia

Bulletin, British Journal of Psychiatry Supplement, Acta Psychiatrica Scandinavica, Journal of Clinical Psychiatry and International Clinical Psychopharmacology, using the terms 'duration of untreated psychosis' or 'DUP', two further studies of DUP from LAMI countries were located.

Third, the first 40 results were examined when combining the names of 152 LAMI countries with “duration untreated psychosis” using the search engine Google, which located one further DUP study from a LAMI country.

Fourth, 12 studies from LAMI regions were found searching PubMed [from January 1975 to January 2007] by sequentially entering the names of 152 LAMI countries and “schizophrenia” and examining all the abstracts. Publications on movement disorder, gender differences or the epidemiology of schizophrenia were examined in full text.

Fifth, the references of DUP studies were hand searched and twelve authors of recent publications about aspects of First episode psychosis (FEP) in LAMI countries for unpublished DUP data were contacted. No further studies were found by these methods.

Finally, we examined all the abstracts in electronic databases that specialize in journals from developing economies that are not indexed on Medline. The terms “schizophrenia” and “psychosis” were used to examine [ExtraMed] for its duration, from 1992 to 2000 and [LILACS] was searched from 1982 to 2008.

Using these methods a total 23 studies were located from LAMI countries that reported DUP or the interval between the onset of psychosis and the initiation of treatment or contact with services. Eleven of these studies met the inclusion criteria for this study as they also; (i) reported an association between DUP and at least one outcome measure, defined as level of symptoms, cognitive function, disability, quality of life or mortality from any cause (ii) used clinician-rated instruments and (iii) included subjects who met the criteria for the diagnosis of a psychotic disorder according to either the DSM or ICD classification systems.

There are no widely agreed-on quality criteria for studies of DUP as all studies of DUP are naturalistic and subjects cannot be randomized to long and short DUP. Thus no specific criteria were used to assess quality of the included studies in the review. However quality was assessed using the following criteria proposed by Marshall et al, 2005 (table 2. Assessment of the studies' quality using Marshall et al.'s (2005) criteria. Appendix A: 9); restricting the population to those with schizophrenia on the basis of standardized diagnostic criteria, assessment of outcome blind to DUP status, a follow-up rate of at least 80%, and use of a standardized method to determine DUP. The quality of studies as assessed by these criteria is reported in table 2. However, due to the small number of studies and the fact that none of the studies met all these criteria we did not apply such quality criteria to exclude any studies.

Data Extraction and Analysis

Using a pilot tested form, the country of origin of the subjects, gender, number of subjects, end point of DUP (initiation of treatment, contact with mental health services or contact with researchers), mean age at contact or initiation of treatment, details of outcome measures reported and percentage of subjects with a diagnosis of schizophrenia or schizophreniform psychosis were recorded. SF and a coauthor (ML) independently extracted the data and minor differences were unambiguously resolved.

Meta analysis was used to pool the reported associations between DUP and (i) positive symptoms at presentation (ii) negative symptoms at presentation, (iii) reduction in total symptom scores after treatment and (iv) measures of disability.

Comprehensive Meta-Analysis, version 2.2.046 was used for the Meta analysis using the same computational options as Revman (Borenstein, 2005). The studies employed different measures of outcome over varying periods of time. Heterogeneity was assessed with Q-value and I^2 for each analysis although in case of small number of studies, between study variance cannot be estimated with precision (Cooper, 1994). A fixed model is reported for outcome measures other

than the degree of improvement in total symptoms score after treatment which exhibited significant heterogeneity and had included the largest number of studies.

Results

Characteristics of studies

Eleven studies conducted in LAMI countries reported an association between DUP and at least one of the outcome measures (Ran, 2007. Kurihara,2006 and Table 1 DUP, diagnostic and demographic variables in the LAMI groups.; Appendix A 9).

The methods and the quality aspects of the studies are reported in tables 1 and 2 (Appendix A: 9). All the studies were prospective in the sense that the DUP was measured at the time of presentation except one study that reported mortality may have been retrospective with respect to the outcome measure (Kurihara, 2006). Only one study had a small sample size of 50 or less (Galinska et al; 2005), and only one study had a dropout rate of more than 20% (Alptekin et al, 2005). All studies reported diagnoses using DSM or ICD diagnostic classifications, in six studies supported by a recognized diagnostic interview. All the studies used corroborative sources of information to assess DUP but none used a purpose designed structured interview and only one study included a measure of inter-rater agreement about DUP (Apiquián-Guitart et al, 2006). All together the studies reported on 1538 subjects in total, of whom 88% met the criteria for a diagnosis of schizophrenia (Table 3; DUP, diagnostic and demographic variables in the LAMI groups. Appendix A9).

The data was reported in a variety of formats including odds ratios (Lieberman, 2003), relative risk (Kurihara, 2006), chi-square statistics for dichotomized groups (Apiquian, 2003; . Patel et al, 2001), means and standard deviations in long and short DUP groups (Oosthuizen et al, 2005; Galinska et al, 2005; Uçok et al, 200627), or as a correlation coefficient (Alptekin et al , 2005; Apiquián-Guitart et al 2006; Apiquian, 2002; Ayres , 2007; Oosthuizen et al,2005; Ran, 2001). As correlation was the most frequently reported measure, meta analysis results are reported in this format. Of the five studies that reported comparisons of symptoms at baseline and after treatment only one study (Lieberman , 2003) used an ANCOVA

to take account of the possibility of the effects of regression to the mean (Vickers et al, 2001).

Association between DUP and symptoms prior to treatment (Figure. 2. Meta analysis of the association between DUP and reduction in total symptoms. Appendix A9)

Four studies reported that patients with a longer DUP had lower positive symptom scores at presentation (Apíquián-Guitart et al 2006; Galinska et al, 2005, Oosthuizen et al, 2005; Uçok et al, 2006). A meta-analysis of these studies found a modest but significant negative correlation between DUP and the positive symptoms on presentation (fixed effects meta analysis; $r = -0.152$, 95% CI=-0.280 to -.02, $z=-2.248$, $p<0.025$; heterogeneity Q-value 1.25, $P = NS$, $I^2 = 0.00$, figure 2.) indicating that patients with a long DUP may have had less severe symptoms such as hallucinations, delusions and thought disorder at the time of presentation.

Three (Galinska et al, 2005; Oosthuizen et al, 2005; Uçok et al, 2006) studies provided data on the relationship between long DUP and negative symptoms. The extent of negative symptoms at presentation was not associated with longer DUP (fixed effects meta analysis; $r = 0.057$, 95% CI=-0.0101 to 0.211, $z=0.705$, $p<0.048$; heterogeneity Q-value 1.01, $P = NS$, $I^2 = 0.00$) (Fig. 3. Meta analysis of the association between DUP and disability. Appendix A: 9)

Association between reduction in total symptom scores and DUP after treatment (Fig. 4. Meta analysis of the association between DUP and positive symptoms at presentation. Appendix A9).

Five studies measured the reduction in symptoms after a period of treatment using change in the BPRS scores (Uçok et al, 2006; Lieberman et al, 2003) or change in total PANNS (Apíquián-Guitart et al, 2006; Oosthuizen et al, 2005; Thirthalli et al, 2005). All five studies found that longer DUP was significantly associated with smaller reduction in symptoms after treatment but associations between DUP had statistically significant heterogeneity (Q-value 25.2, $P = 0.000$, $I^2 = 84.01$). Hence a random effects model was used. In all five studies longer DUP was associated with a less complete response to treatment (random effects meta analysis; $r = -0.290$, 95%

CI=-0.483 to -0.069, $z = -2.559$, $p < 0.011$, figure 4.). This analysis suggests that the detrimental effect of DUP in LAMI countries may be similar to that reported in developed countries.

Association between DUP and disability after treatment (Figure. 5. Meta analysis of the association between DUP and negative symptoms at presentation. Appendix A9)

A study from Turkey found that DUP was significantly associated with social disability as measured by the brief disability questionnaire (Alptekin et al, 2005) and a study from rural China reported that 35% of patients with a DUP of less than a year had a complete remission, in contrast to only 7% with a DUP of greater than a year (Ran et al , 2001). The results of these two large studies were similar to smaller studies from Mexico that reported patients with a DUP of less than 27 months were significantly more likely to make a good social and occupational recovery (Apiquián-Guitart et al, 2006), and southern India that found a trend towards an improved social and occupational outcome in patients with a shorter DUP (Tirupati et al, 2004) . When these somewhat diverse studies were pooled a highly significant association between longer DUP and a greater level of disability was found (fixed effects meta analysis; $r = 0.195$, 95% CI=0.126 to 0.262, $z=5.498$, $p < 0.000$; heterogeneity Q-value 1.245, $P = NS$, $I^2 = 0.00$ figure 5).

Cognitive functions:

Studies from Brazil (Ayres et al, 2007) and Poland (Galinska et al 2005) examined the effects of DUP on cognitive function. Neither study found a significant association between DUP and cognitive abilities at the time of presentation. There was lack of sufficient data to undertake a Meta analysis.

Mortality

Kurihara et al (2006) reported on the mortality of 59 consecutive First Episode Psychosis patients from Bali (Indonesia) followed up to eleven years. They found that patients with DUP longer than one year had 6.7 times the mortality of those with DUP of less than 12 months. Ran et al (2007) also found that the mortality of

long DUP patients was significantly higher than those who received treatment, although long DUP also predicted a failure to receive adequate treatment of any kind after presentation. Only a small proportion of patients received ongoing treatment and no association between DUP and mortality was reported.

Discussion

In this review, nine of eleven studies reported that a longer DUP was associated with at least one measure of a poor outcome. Hence it appears that DUP has similar adverse effects in LAMI and high-income countries. Long DUP probably accounts for as many as a third of patients who do not achieve remission in HI countries (Marshall et al, 2005). The same may be true for patients with psychosis in LAMI countries.

Only one study examined the relationship between DUP and mortality (Kurihara et al., 2006), while a second found that the risk of death of patients who had received even minimal treatment was significantly lower than those who received no treatment (Ran et al, 2007). The reason for the high mortality in the studies from China and Bali was untreated medical illness. This suggests that the disability arising from untreated mental illness may negatively affect the patient's ability to seek medical care and to provide themselves with adequate food and shelter.

The only two studies of cognitive function and DUP had significant methodological limitations, the most obvious being that they examined cognitive function soon after presentation and not after a period of treatment. Thus, no firm conclusions can be drawn about the effect of DUP on cognitive function in LAMI countries, although the reported findings are consistent with the conclusions of systematic review of nine studies in high-income countries, which also found no relationship between measures of cognitive function and DUP (Perkins et al, 2005).

The finding of lower positive symptoms scores in patients with longer DUP suggests that less severely unwell patients may wait longer for treatment than those with more obvious positive symptoms in LAMI countries.

A long DUP in high-income countries has been attributed to the gradual onset of the illness, the lack of understanding of the reason for the morbid change by the patient's family, the patient's own lack of insight and the effect of some mental health laws (Large et al., 2008c). In many LAMI countries the reasons for long DUP include the absence of mental health services and the cost of treatment (Large et al., 2008). DUP has now a well established association with poor outcome of psychosis but methodologically sound studies in LAMI countries are still sparse. There is urgent need to conduct methodologically sound studies particularly those, which try to establish the effect of treatment in relation to outcome and DUP in a LAMI country. Putative protective factors, including family support, that may sometimes be responsible for better course of schizophrenia should also be investigated as it appears that these factors, if any, have limited protective influence during the long period of untreated illness.

Conclusions

Lack of treatment for psychotic illness early in the course appears to be associated with relatively poor outcomes, irrespective of the income or cultural status of the setting. It is time that early intervention services for psychosis are planned for LAMI countries as they have been in HI countries. The findings of this review, and the related study (Large et al., 2008) support the recommendation to supply subsidized antipsychotic medication for at least the first two years of psychotic illness as a way of reducing DUP in developing countries (Patel et al., 2007). Providing very low or no cost psychiatric care in the same setting as other forms of primary health care has been effective in reducing DUP in Zambia (Mbewe et al., 2006) and may be a model that could be adopted elsewhere to reduce DUP.

SECTION: 3

A PARADIGM FOR EARLY INTERVENTION IN PSYCHOSIS IN LOW AND MIDDLE INCOME COUNTRIES

Chapter: 6

Publication on advocating a new paradigm for early intervention in psychosis in LAMI Countries

1. Patients suffering from schizophrenia should be provided free supply of all essential medication at least during initial two years in the First Episode Psychosis, the critical period in the course of schizophrenia. This should be in a public health programme which ensures treatment is provided following a standardised treatment protocol under the close supervision of a family relative or health worker.
2. Supervised Treatment in Outpatients for Schizophrenia (STOPS), which consists of a programme for ensuring free access to antipsychotic medication and training a close relative for regular supervision and administration of the treatment, could be used for this purpose.
3. The early intervention programme should include screening for puerperal psychosis in the antenatal period, which will be able to identify and prevent a significant proportion of potential cases of psychosis.
4. The use of cannabis must be a major target for early intervention programme during the initial two years to prevent relapse and deterioration in symptoms and functioning.

6.1 Development of theoretical framework: An overview of my publications

Before presenting the model, which I advocated in my publications for early intervention in psychosis, it would be helpful to present an overview of the major findings of the studies so far. These studies helped to address following important gaps in the knowledge:

- The treatment for Psychotic disorders in developing countries is at best patchy and limited to acute episodes. This was associated with serious consequences, as was evident in studies of Puerperal psychosis and those involved in homicide with severe mental illness.
- The Duration of Untreated Psychosis (DUP), quantified on the basis of 127 studies both in developed and developing countries, is almost twice long in developing countries compared to the developed countries.
- Within the LAMI group of countries, an additional \$1000 per capita GDP (purchasing power parity) was associated with a decline in mean DUP of six weeks. Hence, there seems to be a possibility of an association between endemic poverty, delayed treatment or lack of treatment, poor outcome after treatment and increased mortality from psychotic illness in LAMI countries. This established, for the first time, an economic case for early intervention.
- Considering that DUP is the strongest predictor of the long term outcome of Schizophrenia, findings of these publications challenge the received wisdom in the literature that the disorder has better prognosis in developing countries.

6.2 The theoretical framework for Early Intervention in Psychosis

I developed and presented an innovative model for Early Intervention (EIP) for Psychosis in a series of papers. This model is based on the research presented in the

previous pages, experience of providing psychiatric services over a decade in resource poor setting and interactions with other disciplines in Medicine who faced similar problems.

The previous sections dealt mostly with publications based on empirical data. The present chapter will present the rationale, concept and the possible model for implementation of an early intervention in LAMI countries, as I elaborated this in a series of papers published since 2005. Unlike the previous sections these studies are not discussed separately for a better understanding of the concept, (The references to my publications are in italics to differentiate these from other references).

I proposed that the model of early intervention for psychosis in these countries should be based on the following principles:

- The large populations in many developing countries have much higher prevalence of chronic mental disorders (Patel et al, 2007). The age structure of LAMI countries (in Pakistan, for example 42% of population is below 45 years of age) means that the number of those suffering from first episode psychosis will be much higher than those in the industrialized (Farooq et al, 2008). This is due to the fact that psychotic disorders predominantly affect the younger population (Shiers and Lester, 2004). Therefore, Early Intervention in Psychosis (EIP) will be a cost effective public health intervention.
- In absence of formal social care networks and almost total nonexistent rehabilitation services, it is even more important to intervene early. Much of the disability associated with Schizophrenia is accumulated in first two years in the course of illness, termed as “critical period” (Harrison et al, 2001). Interventions later in the course of illness may fail to achieve the functional and symptomatic recovery leading to the deficit state which has provided headlines for the present state of care for Schizophrenia in LAMI countries (Farooq, 2008).
- The early intervention model in these countries would differ substantially from those developed in High Income countries. Such a programme of EIP

will need to modeled on a public health model with emphasis on continuity of care and reducing the health inequalities associated with access to and uptake of mental health treatments.

- There may be a plausible set of causal links between endemic poverty, lack of treatment, poor outcome after treatment and increased mortality from psychotic illness in LAMI countries as was evidenced by our study of DUP and its relationship with GDP (Large et al, 2008).
- In many developing countries public health programmes ensure free access to the treatment for infectious disorders causing high mortality, such as HIV and TB as well as for non communicable disorders. In Diabetes Mellitus, for example, at least 67 states around the world including many in developing countries are providing state subsidies for Insulin in order to improve the adherence and continuity of treatment. The direct effects of schizophrenia are comparable to those of many infectious and chronic physical illnesses (Farooq et al, 2008; Farooq, 2006). Hence such programme should provide all essential antipsychotic medication free of cost (Farooq, 2006; Farooq et al, 2008).
- Such programmes should be incorporated with other physical disorders in view of the overwhelming evidence that in developing countries the predominant care should be provided in primary care and the fact that lack of care and continuity is common with other Non communicable Diseases, NCD (Patel et al, 2007).
- Active case finding will not be feasible for a low incidence disorder like schizophrenia in LAMI countries as this would prove too laborious and expensive Therefore the programme should initially care for those presenting at health facilities with First Episode Psychosis. The access to free antipsychotic medication as a part of public health intervention in a well defined catchment area will lead to heightened awareness and early help seeking, thus identifying all the probable cases (Farooq, 2008).

- The EIP intervention should focus on maintaining adherence with treatment and continuity of care during the initial critical period of illness. About 59% of patients may fail to adhere to their treatment in case of schizophrenia (Wieden et al, 2004). The medication status is the strongest predictor of relapse; discontinuation of medication increases the relapse risk five folds (Robinson et al, 1999). Even a gap as small as 1-10 days in medication over one year period has been found to be significantly associated with increased risk of hospitalization with an odds ratio of 1.98 (95% CI = 1.27-3.25) (Weiden and Olfson, 1995). Considering that non adherence may be responsible for approximately 40% of re-hospitalization cost and is also associated with significant increase in other types of service costs (Knap et al, 2004), providing access to medication and ensuring compliance with treatment may be most cost effective measure, especially early in the course of illness (Farooq,2008).

6.3 Early Intervention for Psychosis in Developing Countries – Learning From Tuberculosis?

I advocated that a public Health Programme based on principles of DOTS (Directly Observed Therapy, Short-course), which is a well recognised strategy to control Tuberculosis, is adopted for Early Intervention in Psychosis (EIP). Despite the differences in the nature of two illnesses the core problems in management of both the disorders is the lack of adherence and continuity of the treatment which results in a spiraling costs associated with endemic poverty, a vicious cycle of chronicity and increasingly poor response to the well established treatments (Farooq et al, 2008; Patel et al 2007). An intervention based on principles of DOTS strategy will help to overcome these problems in management of Schizophrenia in the first episode.

What is DOTS?

DOTS stands for "Directly Observed Therapy, Short-course" and is the cornerstone in World Health Organization (WHO) strategy for global TB eradication programme. The DOTS strategy focuses on five main points of action. These include government commitment to control TB, diagnosis based on sputum-smear

microscopy tests done on patients who actively report TB symptoms, direct observation short-course chemotherapy treatments, a definite supply of drugs, and standardized reporting and recording of cases and treatment outcomes. (For full details please see WHO, 1999). In DOTS programme once a patient with infectious T.B is identified, a named supervisor watches and records patient swallowing the correct dosage of anti T.B treatment for six to eight months. Various forms of supervision and educational interventions for the relatives are described. In many developing countries the role of DOTS supervisor is assigned to a family or a community member who regularly administers the drugs under close monitoring by a health worker. There is a clear line of accountability between the T.B control staff and person administering DOTS (WHO, 1999).

The remarkable improvement in tuberculosis control in many developing countries is attributed to this strategy (Squire and Tang, 2004). In China, for example, a survey of 375599 individuals selected from 31 mainland provinces showed a reduction of 48% in smear positive cases in the areas in which DOTS was implemented compared to only 16% in the districts without the programme⁴ China Tuberculosis Control Collaboration, 2004. The World Bank considers DOTS to be one of the most cost effective health interventions. DOTS is more cost effective than self-administered treatment (Moore RD, 1996; Floyd K, 1997)

From DOTS to STOPS

Our team based in Peshawar incorporated these principles of DOTS in an approach termed as STOPS. Supervised Treatment in Outpatients for Schizophrenia (STOPS) was developed after focus group discussions with staff involved in implementation of DOTS programme in tuberculosis. Similar focus groups were held with patients suffering from schizophrenia and their families (Farooq, et al 2008; Patel et al, 2007). The focus group discussions with patients and their relatives revealed that the primary concerns of the family and patients related to perception of the illness, the treatment and its stigma. The relatives also used number of coercive methods in treatment, including violence in dealing with these patients. The pattern of care was episodic. Therefore, we incorporated these concerns in the educational package, in

addition to administering and supervising medication, which are usual components of a traditional DOTS programme.

Supervised Treatment in Outpatients for Schizophrenia (STOPS) consists of the following essential components.

A. Free access to antipsychotic medication during the First Episode Psychosis. The patient is provided free medication as part of the programme one month at a time.

B. A close relative termed as Key Care Supervisor (KCS) is trained in regular supervision and administration of the treatment. The KCS is a family member living with the patients for at least six months and nominated by the patient. The educational package developed as a result of focus group discussions and experience in pilot programme, as mentioned above, focuses on the following two areas.

a) **The nature of illness, the possible causes and consequences of untreated illness.** The local explanatory models for the illness are incorporated in the training. The use of traditional healers is not discouraged. The relatives are encouraged to discuss this with the treating psychiatrist during follow up visits and not to discontinue the treatment. The family member is asked to contact the treatment centre when the traditional healer advice them to discontinue the treatment.

b) **Training in administration and supervision of treatment.** Detailed education is provided on the type of medications used, how to administer these each day and the method of recording the correct dose. Steps involved in collecting the tablets from the treatment centre, storage at home, administering the tablets and the actual ingestion by the patient and how to confirm this are demonstrated. The relatives are provided a treatment card in which they are asked to put a tick in each box for patient taking the dose of medication. Different coloured cards and symbols are utilized for recording

this, as the majority of the population is not educated. These cards are checked at the next delivery of medication. The emphasis is on how to supervise medication without antagonizing or using any coercive methods. In case of depot injections, education about the possibility of acute EPS and how to seek help for these is also given.

- C. A standardized system of recording cases and their progress in treatment using simple measures which could be used in routine clinical care.

A strategy for communicable illness for a non communicable disorder?

The major challenge we faced in adopting a strategy devised essentially for an infections disorder like TB for a non communicable disease like Schizophrenia, is the time course of the illness. Unlike tuberculosis, treatment for schizophrenia may be needed for the lifetime of the patient and “cure” would not be achieved in the strictest sense. Neither health systems in most low income countries nor care givers can be expected to provide a lifelong commitment required for a STOPS programme Farooq, (2008).

To overcome these problems, I suggested that those suffering from schizophrenia in the developing world should be treated in a public health programme utilizing STOPS model for at least initial two years during the course of illness (Farooq, 2008; Patel, 2006). The rationale for the two years period is based on the following crucial pieces of evidence.

The ‘Critical Period’. Initial two years in the course of Schizophrenia have been described as a ‘critical period’. The treatment status during this period is the strongest predictor of long term outcome and disability (Harisson et al, 2001).

Interventions for Non adherence: The evidence from systematic review of interventions to address non adherence in Schizophrenia suggest that clinical

interventions targeting non adherence should continue for at least 18 months (Zygmunt et al, 2002).

6.4 A Paradigm for Early Intervention in Developing Countries

Based on the principles and evidence presented above a paradigm for early intervention in developing countries could be summarized as below.

1. All patients presenting with a psychotic disorder in developing countries must be supplied all essential medication to treat the illness free of cost as part of a public health programme for at least initial two years, the critical period in the course of illness. This programme will not aim at active case detection.
2. A standardized system of recording cases and their progress in treatment using simple measures is used to supervise treatment during this period. Supervised Treatment in Outpatients for Schizophrenia (STOPS,) is an intervention which our team developed to train a close relative for regular supervision and administration of the treatment, can provide such mechanism for providing supervised treatment during this critical period.
3. The early intervention programme should include screening for puerperal psychosis in the antenatal period, which will be able to identify and prevent a significant proportion of potential cases of psychosis. This will also help to integrate the early intervention programmes with other public health programmes such as mother and child health.
4. The use of cannabis must be a major target for early intervention programme during the initial two years to prevent relapse and deterioration in symptoms and functioning.

My publications (*Farooq, 2008; Patel, 2007*) stressed that the following three tasks need urgent action to implement early intervention programme in developing countries:

- a) A global fund to generate the resources for providing free access to antipsychotic drugs should to be created.

- b) Simple, brief and cost effective strategies for enhancing medication adherence which can be used by the caregivers in the developing countries need to be developed.
- c) Small scale programmes based on the DOTS model should be developed locally in developing countries before we can expect the governments to support the same. Insulin Demonstration Projects which have been initiated to improve the access to the Insulin by the IDF Task Force can provide good models for this (International Diabetes Federation, 2004b).

Chapter: 7

The proof of the concept – a randomized controlled trial of STOPS.

Considering that Schizophrenia has incidence of about 15 per 100000 populations in a year, the recruitment of a sample with adequate power to test the effectiveness of STOPS in the First Episode Psychosis would require many years. Therefore, we decided to evaluate the approach in patients with previous history of Psychosis presenting to the Lady Reading Hospital, Peshawar. The trial was registered at ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT00392249) and initiated in 2006..

This Randomized Controlled Trial aimed at testing the effectiveness of Supervised Treatment in Outpatients for Schizophrenia (STOPS). The primary outcome was to compare the effectiveness of STOPS in improving the adherence with a regimen of standard doses of antipsychotic medication in patients suffering from Schizophrenia and Schizoaffective disorders compared to Treatment As Usual (TAU). The study design was a two-arm prospective randomized controlled trial over one year period, with masking of assessors to the status of the intervention.

Methods

The study protocol was approved by the Research Ethics Committee of the Post Graduate Medical Institute, Lady Reading Hospital Peshawar, Pakistan. After a complete description of the study to each subject and the caregivers, written informed consent was obtained. As significant proportion of the patient population was illiterate, special care was taken to explain the procedures in Pushto, the language spoken by this population. No monetary incentives were provided to the participants in the trial.

Study settings and participants

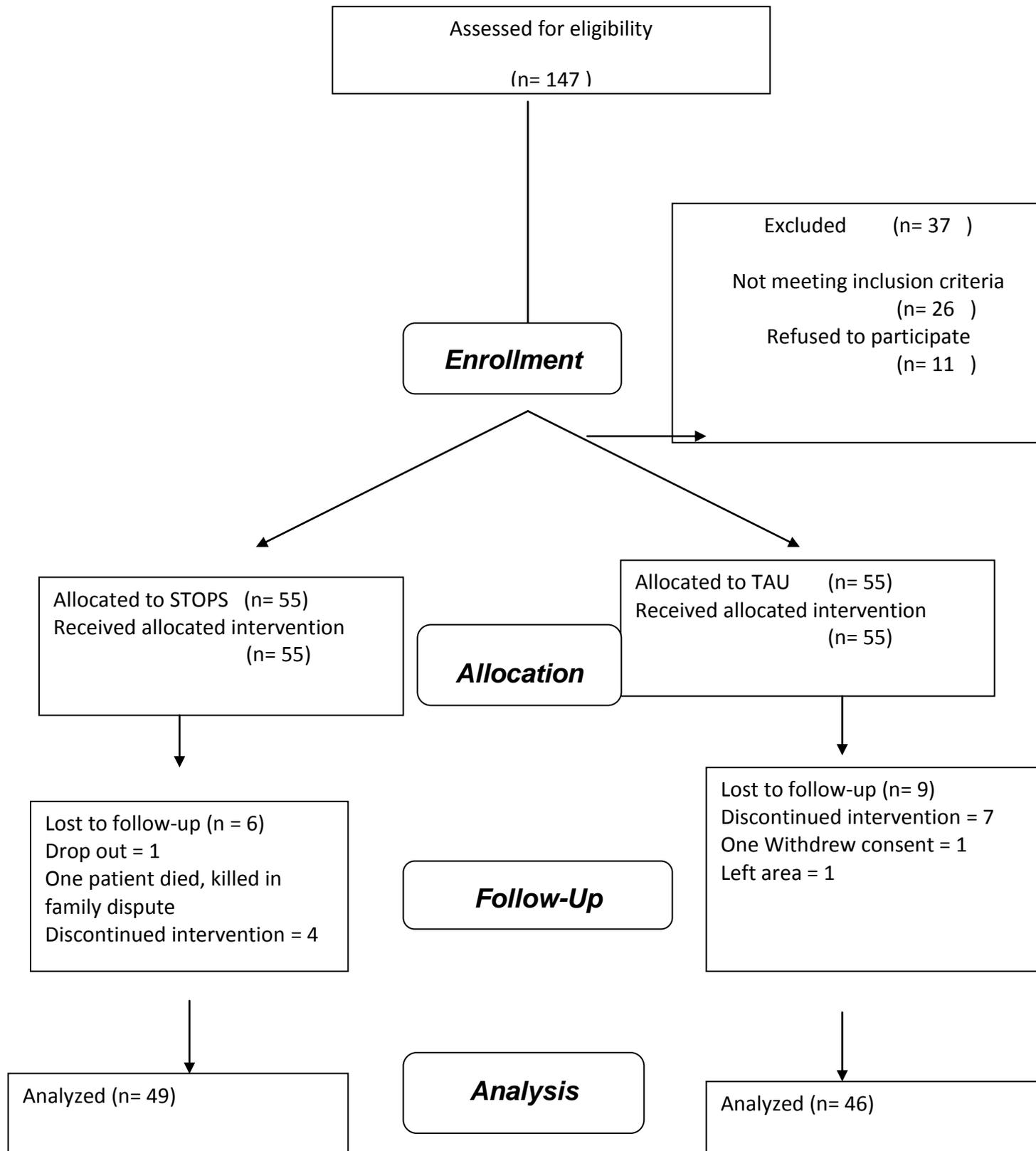
The study was conducted at Psychiatry Department of Lady Reading Hospital Peshawar. This is one of the two major tertiary care mental health centers which serve a large population in North West Frontier Pakistan and adjoining Afghanistan. For the purpose of this study we recruited patients only from the district Peshawar which has population of about two millions. The inclusion criteria were (1) Age - 17 to 60 years (2) Diagnosis of schizophrenia or schizoaffective disorder based on the ICD-10 criteria and (3) Residence in Peshawar district. The exclusion criteria were evidence of organic disorder, mental retardation and severe drug dependence requiring inpatient treatment and/or detoxification. We started recruitment to the study in November 2006 and the final follow up of the participants was carried out in January 2009.

Based on the literature an average rate of adherence to the medication over one year period for those suffering from Schizophrenia was 50 % (Babiker et al, 1986, Weiden et al, 1995). We expected the rate of medication adherence to be 75% in the intervention group. Thus a sample size of 45 patients per group would have 80% power to detect a 25% difference in the rate of adherence to medication between the two study groups with a one-sided significance of 5%. To control for non-compliance and losses to follow-up 55 patients were recruited in each group.

Randomisation

Patients who met inclusion criteria and no exclusion criteria were randomly assigned to each treatment group using a randomization scheme on 1:1 basis. The randomization was done using computer generated numbers. The random allocation of the patients for each group was enclosed in series of opaque envelopes which were sealed and numbered sequentially. These allocations were placed away from the site of assessment. After assessment and satisfying the inclusion criteria, the independent staff in the administration office was asked to open the sealed envelope and reveal the treatment arm for each patient.

Diagram :1
The CONSORT Flowchart. RCT STOPS vs TAU



Eligible patients were identified from the outpatients presenting at Psychiatry department of the LRH. They were first screened by the trained psychiatrists working in the outpatients and subsequently assessed by one of three consultant psychiatrists (SF, ZN, JA) to satisfy the ICD-10 criteria for the diagnosis of Schizophrenia and Schizoaffective disorders¹⁵ (World Health Organization, 1992). After identifying eligible patients through interview and reviews of previous notes therapists were asked to approve their recruitment into the study.

Intervention and control groups

The salient features of the two interventions are highlighted in table 1. Psychiatrists for the Treatment As Usual (TAU), the Control Group were told to provide treatments as they would normally practice in routine outpatient settings. This included prescribing evidence based pharmacological treatments, outpatient attendance in the Psychiatry department as deemed appropriate by the consultant and brief counseling about the treatment and outcome of the disorder. Patients who could not afford to buy the medication, had the option to seek the free drug treatment from the Social Welfare department of the hospital, which provided treatment for the patients from Zakat Fund (a fund established to provide the essential medicine for poor patients from a charity funding based on Muslim Law).

The patients in Supervised Treatment in Out Patients for Schizophrenia (STOPS) received the usual care. In addition, a Key Care Supervisor (KCS) who was a close relative in most cases was trained in regular supervision and administration of the treatment. Key Care Supervisor was defined as any family member living with the patient for at least six months and providing support for the treatment as identified by the patient. Specific education was provided to the key care supervisor about the nature of the illness, misconceptions about the treatment, relationship between the supernatural and biological causes of illness and importance of continuing the medication and basic skills in how to administer and supervise medication. The medications required were provided one month at a time.

The intervention was first implemented in a pilot project over one and half years (Farooq et al, 2008, 2005). Therefore trainers and assessors were adequately trained and experienced in providing the intervention.

The doses in each group were titrated according to the clinical needs of the patient. All patients received atypical antipsychotics with the exception of those who were already on typical antipsychotics and have been stable on these. Treatment teams for both STOP and TAU patients consisted of two consultant psychiatrists, three postgraduate trainees with minimum of two years training in Psychiatry, two qualified psychiatric nurses and a master's level social worker (Table.1).

Measurements

The baseline assessment included a clinical interview to satisfy the ICD-10 criteria for the diagnosis of Schizophrenia and Schizoaffective disorders, demographic data and illness history, Global Assessment of Functioning (GAF) ratings (American Psychiatric Association, 2000), and Positive and Negative Syndrome Scale for Schizophrenia (PANSS)) (Kay et al, 1987). The follow up assessments at 3 months, 6 months and at the end of one year included; Global Assessment of Functioning Scale rating, Positive and Negative Syndrome Scale and medication adherence using a scale devised for this purpose.

Adherence with treatment regimen was measured at interview by using a questionnaire with a 5-point scale (1 = always and 5 = never) adopted from Herz et al (2000). The scale has been used in the pilot project by the research workers who achieved high degree of reliability in ratings (Patel et al, 2007; Farooq et al, 2008). The assessments for the adherence to treatment were done quarterly from the baseline with the help of information provided by patients and relatives. The information was supplemented by the tablet counts from previous prescriptions where available. Complete adherence with medication was defined as patient always taking medication as prescribed without any break during the assessment period.

The non adherence was defined as missing drugs completely for more than a week at a time. If the patient took some medication but not on everyday of the week this was defined as partial adherence.

All assessments were carried out by doctors with at least two years training in Psychiatry. The same team of psychiatrists carried out all the follow up assessments. The follow up assessments were done by the researchers who were blind as to the patient group assignment and were instructed not to inquire about a patient's treatment during interviews. To ensure this, the administration of STOPS was kept completely separate from the research team assessing the compliance and administering the questionnaires for the trial and they were not associated with clinical care of the patients in the trial. The patients and relatives were briefed not to discuss their treatment with the assessors. All the patients remained in the study whether or not they were compliant with treatment, needed hospitalization or relapsed. Attempts to maintain contact were made by telephone and/or home visits if patients did not appear for clinic visits at follow up assessments.

Statistical analyses

Data was analyzed in accordance with the CONSORT guidelines wherein the between group comparisons were done by using intention to treat analysis. SPSS version 16 was used for the analysis. Descriptive statistics were obtained on patient baseline characteristics and the primary outcome measure as a categorical variable. Chi-squared tests for difference in proportions were used to compare the distribution of baseline variables and compliance scores between the two study groups (95% CI's and p-values). The number of patients in partial adherence group were small in follow up assessments. Therefore we combined the partial and non adherence together for the purpose of this analysis. This is also in line with the measurement of compliance, as described originally by Herz et al (2000).

Parametric variables were then assessed for simple group differences with t-test. A Repeated Measure ANCOVA was used to measure the differences between the two groups at four time points. Baseline scores were used as Covariates to take into account the initial differences. Kolmogorov-Smirnov test was used to assess normality. The number of patients needed to be treated with STOPS to prevent one adverse outcome such as one patient not adhering to treatment in one year was calculated.

Results

The details of recruitment and follow up are shown in diagram 1.

Fifty five patients were recruited in each arm. Ninety five (86.36%) patients completed the study; 49 in STOPS and 46 TAU group. The mean age of patients in STOPS group was 29 (SD= 8.1) which did not differ significantly from the TAU group (mean 30 SD = 8.5 $P < .699$). The baseline sociodemographic and clinical variables were not significantly different in two groups (Table 2). Similarly the relationship with the primary care giver as defined by the patients did not differ significantly between the two groups. Both groups had long duration of illness (73.6 months. SD=59 in STOPS Vs 83.8 months in TAU; SD=91 $P < .485$). No statistically significant difference was found between two groups in PANNS and GAF ratings at baseline.

We compared the two groups at four time points to see if the dosage of antipsychotic drugs were different in two groups at any stage. The doses of all antipsychotics were converted into the equivalent doses of Chlorpromazine (British National Formulary, 2009). There were no statically significant difference between the two groups ($P=0.136$) in the dosages of antipsychotic received. The number of patients on depot medication was also not different between two groups.

The medication adherence, symptoms and functioning outcomes (table 3 & 4, fig 1& 2)

Two groups showed statistically significant difference in the primary outcome measure at 3 months ($P < .05$) and at the end of one year ($P < .02$), but not at six months follow up ($P < .23$).

In Intention To Treat analysis at one year follow up 37 (67.3%) patients in STOPS group had complete adherence with medication compared to 25 (45.5%) in the TAU group ($P < .02$). The odds for the STOPS group to adhere to medication is 2.46 (confidence interval = 1.1376 - 3485). The Number Needed to Treat to achieve one positive outcome is 5.

The patients in STOPS group showed more improvement in symptoms and functioning as measured by PANSS and GAF respectively in Intention To Treat Analysis. The total score on PANSS ($P < 0.003$), positive symptoms subscale ratings ($P < 0.011$) and the General psychopathology subscales ($P < 0.007$) were all lower in patients in STOPS group compared to the TAU group. However, for PANSS Negative symptoms subscale the difference between the two groups was not statically significant ($P < 0.149$). The patients in STOPS group also had better functioning as compared to TAU group and the scores on GAF scale was significantly better in the STOPS group ($P < 0.008$).

Table 1. Comparison of the Supervised Treatment in Outpatients for Schizophrenia (STOPS) versus Treatment As usual (TAU)

	STOPS	TAU
Setting	Community	Community
Therapist's Contact with patient/family	Patients and an indentified family member (Key Care Supervisor)	Patient, family optional.(any family member)
Access to medication	Supplied free by the programme	Had the option of availing free drugs provided by social service, may be out of pocket,
Supervision for medication	Medicine administered under supervision of KCS	None.
Patient and family education	One session at the start to educate KCS to administer and supervise the drugs	No specific session, some education may be provided by therapist
Frequency	Once a month to collect the dugs	Variable as deemed necessary by therapist
Service provided by	Psychiatrist, Social worker, Psychiatric Nurses	Psychiatrist, Social worker, Psychiatric Nurses

Table 2. The differences between STOPS and TAU groups at the baseline. All figures are number (%).

	STOPS	TAU	P ¹
Gender			
Male	47(85.5%)	47(85.5%)	1.000
Female	8(14.5%)	8(14.5%)	
Marital status			
Married	30(54.5%)	31(56.4%)	0.999
Unmarried	22(40.0%)	21(38.2%)	
Divorced (widow/widower)	3(5.4%)	3(5.4%)	
Employment status			
Unemployed	40(72.7%)	41(74.5%)	0.480
Employed-	8(14.6%)	12 (21.9)	
Retired	1(1.8%)	0(0%)	
Student	6(10.9%)	2(3.6%)	

Education			
No education	23(41.9%)	21(38.1%)	0.520
5 to 9 years	18(32.7%)	14(25.5%)	
10 years or more	14(25.4)	20(29.3%)	
Relationship with caregivers			
Mother	6(10.9%)	4(7.3%)	
Father	11(20.2%)	16(29.1%)	
Children	1(1.8%)	4(7.3%)	0.286
Spouse	2(3.6%)	5(9.1%)	
Brother	19(34.5%)	16(29.1%)	
Sister	3(5.5%)	4(7.3%)	
Other	13(23.6%)	6(10.9%)	
Course			
Continuous	41(74.5)	35(63.6)	0.216
Episodic	14(24.5)	20(36.4)	
Cannabis use			
Current	6(10.9%)	10(18.2%)	
Past	4(7.3%)	2(3.6%)	0.425

Never	45(81.8%)	43(78.2%)	
Diagnoses			
Schizophrenia	45(81.8)	45(81.8)	1.000
Schizoaffective disorder	10(18.2%)	10(18.2%)	

1. P values using a X^2 test.

Table 3: Differences in medication adherence between the STOPS and TAU groups at three time points. All figures are number (%).

Compliance	STOPS	TAU	P*
<u>3 Months</u>			
Complete	38(69.1)	28(50.9)	0.05
Partial or none	17(30.1%)	27(49.1)	
<u>6 months</u>			
Complete	40(72.7%)	34(61.8)	0.23
Partial or none	15(27.3%)	21(38.2)	
<u>12 months</u>			
Complete	37(67.3%)	25(45.5)	0.02
Partial or none	18(32.7%)	30(54.5)	

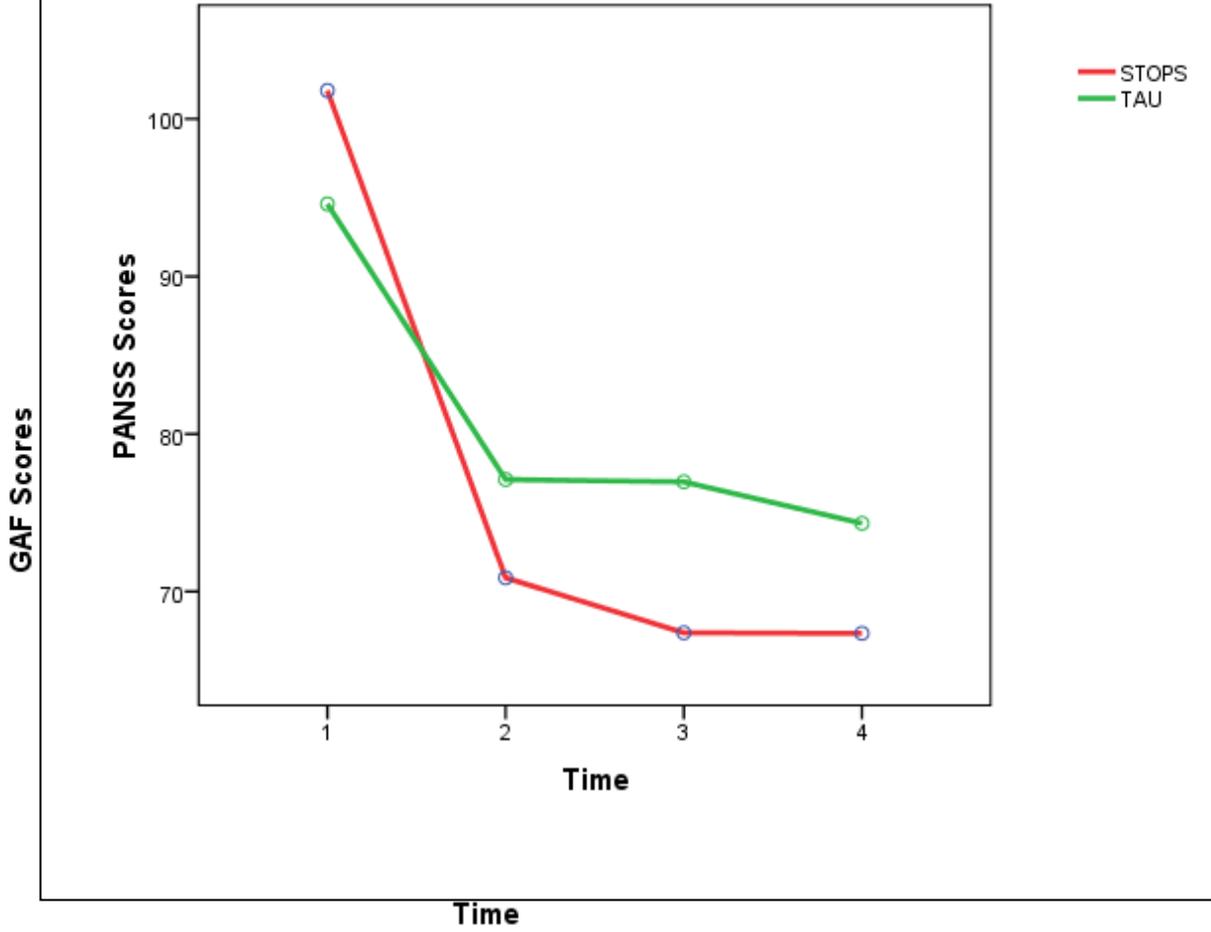
□ P values using X² test

Table 4. The comparison of STOPS and TAU groups for measures of psychopathology. All values are Mean (SD) Number. Higher scores represent more psychopathology on PANSS, but not on GAF where reverse is the case. Analyses were carried out using Repeated Measure ANCOVA (to compare within subject and between the subject differences), with baseline values used as Covariates.

	STOPS Mean (SD) Number	TAU Mean (SD) Number	P Values for between subject differences
PANSS total scores			
Baseline	101.80(21.0)55	94.6(19.4)55	0.003
Time 1	70.87(23.18)55	77.11(21.29)55	
Time 2	67.38(23.9)55	76.96(20.8)55	
Time 3	67.35(24.66)55	74.33(21.58)55	
Positive symptoms			
Baseline	21.6(6.7)53	21.5(6.3)53	0.003
Time 1	12.6(7.2)53	16.6(6.5)53	
Time 2	12.4(7.0)53	16.6(6.7)53	
Time 3	13.6(6.9)53	15.3(5.5)53	
Negative symptoms			
Baseline	21.3(6.1)53	19.4(6.3)53	0.149
Time 1	17.4(6.0)53	17.1(7.6)53	
Time 2	16.3(6.1)53	17.2(7.2)53	
Time 3	16.2(6.8)53	17.1(7.6)53	

General symptoms			
Baseline	47.9(10.6) ⁵³	44.4(8.9) ⁵³	0.007
Time 1	33.7(10.0) ⁵³	36.6(10.5) ⁵³	
Time 2	31.4(10.9) ⁵³	35.2(10.2) ⁵³	
Time 3	30.3(10.3) ⁵³	33.8(8.8) ⁵³	
GAF Scores			
Baseline	42.56(13.54) ⁵³	45.95(11.92) ⁵³	0.008
Time 1	55.18(14.5) ⁵³	52.13(15.8) ⁵³	
Time 2	58.71(15.81) ⁵³	52.67(16.08) ⁵³	
Time 3	62.0(16.70) ⁵³	56.05(18.12) ⁵³	

Figure 1. Differences in PANSS Scores between the two groups at 4 time points



Discussion

To best of our knowledge this is the first study which has attempted to test the effectiveness of a model based on principles of DOTS in a non infectious disease. Results showed that Supervised Treatment in Outpatients for Schizophrenia (STOPS) which used an educational intervention for relatives to administer and supervise the medication and understand the nature of illness and treatment resulted in significant improvement in adherence with medication, the primary outcome measure. The Number Needed to Treat (NNT= 5) shows that intervention used in this trial could be highly effective in improving the adherence with the treatment in a developing country setting.

The timeline of the improvement as depicted in Fig 1&2 shows an interesting time effect. The improvement in symptoms and functioning preceded the improvement in drug adherence between two groups. This probably shows the strong effect of psychoeducational intervention involving the family as the family interventions and management of illness has been shown to reduce symptoms and improve functioning (Mari et al, 2009).

The trial was not designed nor did it have enough statistical power to assess the effects of treatment on other outcome measures. However, the improvement in total PANNS, positive symptoms subscale and GAF scores reflected the improvement in the compliance. Interestingly, the score on negative subscale of PANNS did not differ significantly between the two groups.

This may be due to fact that negative symptoms are difficult to treat, as both groups had a mean duration of illness of more than five years and a deficit state may already have developed. The improvements in the functioning as manifested by highly significant difference ($P < .008$) between the two groups is encouraging showing that maintaining regular treatment and engaging the family can have significant impact even in a population with chronic mental illness.

The information on the effectiveness of strategies for extending care to people with severe mental illness in LAMI countries is scarcely available (Jacob et al, 2001). The essential ingredients of the strategy used in this study i.e. monitoring the drug

compliance by observing and recording the correct medication by a guardian assigned to the patient has been shown to be effective in a retrospective case control study in Rural China (Qui et al, 1994). Broadly similar approaches have been shown to be cost effective and significantly reduced the disability, psychotic symptoms and caregiver's burden in India (Murthy et al, 200; Chatterjee et al, 2003). However, these studies employed family or social interventions typically comprising at least one session of 1-2 hours every two or four weeks over study period which are more akin to assertive outreach programmes employed in developed country settings (Chatterjee et al, 2003). These approaches may be difficult to apply in routine clinical practice in LAMI countries. The STOPS approach, in contrast, used a brief intervention focusing on family and patient education without directly addressing family dynamics or expressed emotion. The better adherence to the treatment in this cohort is consistent with the evidence from systematic review of interventions to improve medication adherence in schizophrenia which showed that relatively brief interventions (both in terms of duration and frequency) which targeted the behaviors related to medication adherence were more effective than longer interventions with broader focus on psycho education (Weiden et al, 1995).

It can be argued that provision of free drugs could have contributed to the better outcome for STOPS group. DOTS is a complex intervention and free access to medication is an essential component of DOTS programme as applied in TB control (World Health Organisation, 2007).

The patients in TAU group had the option of availing free drugs from the social welfare department. Providing free medication as part of the trial would have grossly distorted the Treatment As Usual in these settings. Moreover the recent evidence suggests that even if drugs were free, non-adherence persists. One recent study showed that even among patients who have health plans with no cost sharing for medication, rates of non-adherence were nearly 40%. (Doshi et al, 2009).

Possible limitations in evaluating the results of this study should be recognized. We selected standard outpatient care for comparison as in these settings outpatient care is most often the only type of mental health care available. It could be argued that enhanced care associated with regular assessment of compliance and follow up visits

in RCT was not the typical ‘treatment as usual’. It is possible that patients in TAU received more support for their treatment from the social services department of the hospital, being a focus of attention in a research study. It is also well known that the measures which rely on subjective reports of pill taking to measure adherence in Schizophrenia tend to overestimate adherence and reduce the likelihood of detecting intervention effects (Weiden et al, 1995, Fenton et al, 1997). These limitations should however minimize the difference between two groups. Blindness of research interviewers to treatment group could not be completely assured since the study was not placebo controlled, with the possibility that research interviewers favored STOPS group. The contamination of treatments was also a possibility, i.e., the treatment team providing TAU would act more like the team providing the experimental intervention over time.

Implications for service provision and research – A public health approach for Early Intervention in Schizophrenia in LAMIC?

The interventions for providing care for Schizophrenia in LAMI countries should primarily target the families as more than 90% of people with schizophrenia live with their families in these countries who manage most aspects of patients' lives (Mari et al, 2009).

This study provides preliminary evidence that a package of care based on an educational intervention for the families, and supervision and easy access to medication as envisaged in DOTS strategy based on a simple treatment regimen can be used to scale up the services for Schizophrenia in LAMI countries.

Improvement in treatment adherence in this cohort is more significant considering that impairment in behavioural and cognitive domains resulting from chronic Schizophrenia directly affect compliance with treatment regimen. It should be noted that we used a minimal exclusion criteria, including patients with substance abuse to reflect the population of individuals with schizophrenia being treated in the community. This shows that an approach based on DOTS can also be used for providing care for other Non Communicable Disorders. The details of how the DOTS can be implemented for the Non Communicable Disorders have been

described (Patel et al, 2007). Adopting DOTS model for providing care for NCD will also help to bring the infectious and non communicable disorders together in public health systems, a major challenge in many developing countries.

A simple, standardised system of diagnosis and treatment based on passive case findings and a brief educational intervention as used in this study could feasibly be rolled out in a public health system. The active case finding will be too laborious and expensive for a low prevalence disorder like Schizophrenia. The improved access to treatment as a public health intervention will also lead to better awareness and early help seeking for the cases which at present represent the large untreated prevalence. This may help to reduce very long Duration of Untreated Psychosis (DUP) in LAMI countries. The present study sample consisted of patients with relatively chronic course of illness as recruiting a first episode sample would have taken much longer period and was not feasible within the resources. The approach suggested in this trial now needs to be evaluated in First Episode Psychosis as effective intervention during this period is likely to achieve maximum long term gains in the entire course of illness. The cost effectiveness of the approach also needs to be tested in future studies.

Chapter 8

Integration and knowledge translation: development and evaluation of a complex intervention

In this chapter, I will explain how my work and publications resulted in producing coherent body of knowledge which is one of the requirements of the thesis. This will also present a summary of the publications.

The systematic identification of evidence and its integration which resulted in the development of coherent body of knowledge in my work and publications can best be understood by a framework described by Campbell et al (2000). This frame work describes the development and evaluation of complex intervention, and is illustrated in diagram 1. This frame work describes five stages in the development and evaluation of a complex intervention as following:

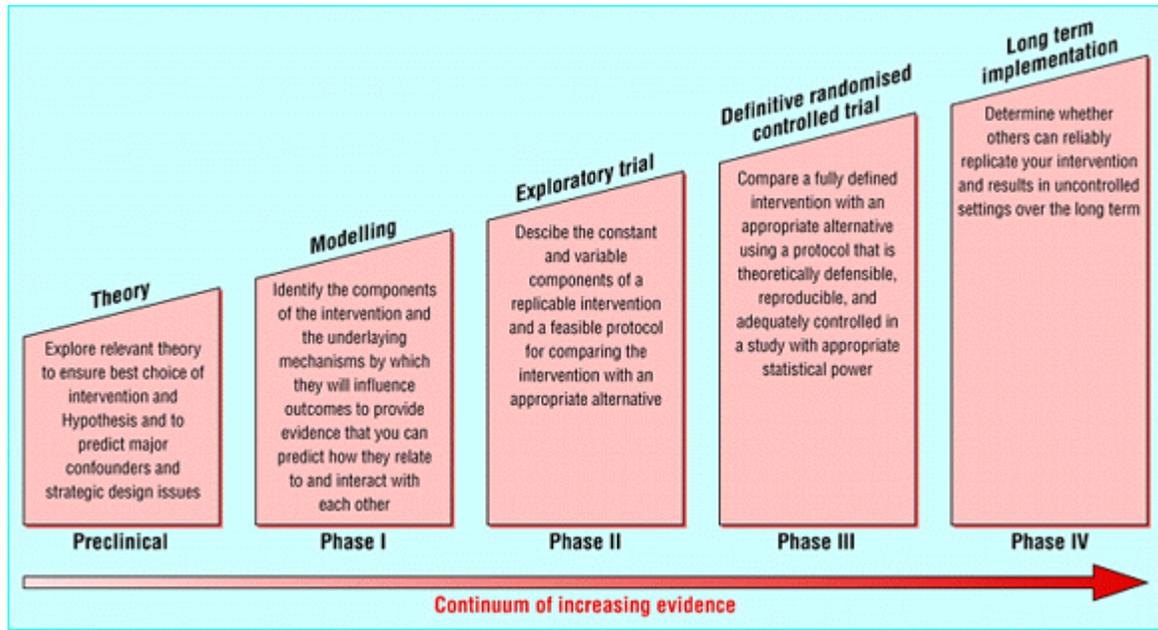
Step 1: Preclinical: Exploring relevant theory

Phase I: Modeling

Phase II: Pilot Study and Explanatory stage

Phase III: Definitive Randomised Controlled Trial

Phase IV: Long term implementation



Campbell, M. et al. BMJ 2000;321:694-696

Using this frame work which is illustrated in above diagram, my research and publications described in previous pages, can be summarized as following:

Step 1: Preclinical: Exploring relevant theory (Section 2; Chapter 4)

This stage involves exploring the relevant theory to ensure best choice of intervention. The hypothesis is identified, major confounders are predicted and strategic design issues are explored. As defined by Campbell et al (2000), the existing evidence and any theoretical basis for the intervention are explored in order to describe the components of the intervention, during this stage. My work on puerperal psychosis, homicide by patients suffering from Schizophrenia, and the impact of cannabis use on symptomatology and course of schizophrenia identified a number of components in the care of schizophrenia in developing countries which could be amenable to a public health intervention. These highlighted gaps in the knowledge and practice which could be incorporated in such an intervention.

Phase 1: Modeling (Chapters 5 & 6)

During this phase, the components of intervention and underlying mechanisms by which these will influence the outcome are identified. Directly Observed Therapy (DOTS), as practiced in tuberculosis provided a model for Schizophrenia which could be used for ensuring compliance and continuity of care. We had extensive liaison with professionals involved in implementation of DOTS in Tuberculosis and assessed the acceptability and feasibility of modeling an intervention which could also be used for a Non Communicable Disorder, like Schizophrenia. The knowledge translation at this stage helped to design the pilot study.

Phase 2: Pilot Study and Explanatory stage (Chapter 6)

This phase consists of constant and variable components of a replicable intervention. During this phase a feasible protocol for comparing intervention with an appropriate alternative is also developed (Campbell et al, 2000). The pilot project (Farooq, 2008) helped us to evaluate various components of intervention in an uncontrolled study. This feasibility of the definitive trial was also tested in this phase. The work on determining the length of DUP in developing countries, its relationship with GDP and outcome of Schizophrenia (Farooq et al, 2009; Large et al, 2008) helped us to identify the barriers in providing early and effective treatment for First Episode Psychosis which could be addressed and incorporated in the intervention as well in the definitive trial. This also established economic case for such an intervention. The gains which could be achieved by providing treatment during the critical period of illness helped us to formulate the intervention in a time limited period, as is the case in an infectious disorder of Tuberculosis.

Phase 3: Definitive Randomised Controlled Trial (Chapter 7)

During this phase, fully developed intervention is compared with an appropriate alternative using a protocol that is theoretically defensible, reproducible and adequately controlled in a study with adequate statistical power. After developing the intervention, I developed a protocol to compare STOPS against Treatment As Usual (TAU).

The protocol of the trial was registered with the Clinical Trials.Gov, the FDA and NIH registry for RCTs. The trial was statistically powered to show difference against the TAU for adherence with treatment over one year follow up period, the primary outcome of the study. The final trial was implemented in a typical developing country setting, as the intervention is primarily aimed for the populations in Low and Middle Income countries.

Phase IV: Long term implementation

This phase consists of determining whether others can reliably reproduce the intervention and results of the RCT in an uncontrolled setting over the long term. The results of the RCT which showed statically significant difference for the primary outcome measure and other clinical variables have produced convincing evidence for this phase. I have presented the results of the trial evaluating STOPS in the number of scientific forums and the paper describing this study has been accepted by British Journal of Psychiatry for publication. I am advocating the implementation of the intervention at community level and actively pursuing the intervention as a feasible form of early intervention in a developing country setting. At the same time, I am planning for an Early Intervention Service based on this model in three districts in Pakistan. This will provide valuable data as well as provide access to medication and services during critical stage of illness.

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CLINICAL FEATURES OF PUERPERAL PSYCHOSIS

Saeed Farooq

ABSTRACT: Thirty-five cases of psychotic disorders arising within 90 days of delivery were studied prospectively. Compared to most reports from the developed world, younger age at onset, a lower proportion of primigravidae, preponderance of catatonic states and high physical co-morbidity were found.

KEY WORDS: Puerperal psychosis, Diagnostic breakdown

INTRODUCTION

Puerperal psychotic (PP) has been recognized since the time of Hippocrates. However, since the Kraepelinian view of the puerperium as a non-specific stressor predominated, it is no longer recognized as a specific entity¹. The nosological status of PP is still a matter of great controversy². Studies attempting to find a specific hormonal basis for PP have so far been inconclusive^{3,4}. Similarly, controlled follow up of matched groups of women with PP and similar illnesses unrelated to childbirth did not show any significant difference between the two groups⁵. Puerperal psychoses is, therefore, not recognized as a distinct entity both in I.C.D-10 or D.S.M. IV^{6,7}. It is mainly defined on the basis of clinical and epidemiological studies⁸. In the majority of studies, PP is defined as psychotic disorders (affective, schizophrenic or organic) arising within 90 days of childbirth⁹. Brockington et al¹⁰, however, recommend that the period to define puerperal psychoses should be limited to two weeks after childbirth.

Lability of mood, insomnia, visual hallucinations, mutism, prominent delusions in depressed mood, rambling and distractibility have been noted by most of the authors as predominant clinical features. Manic symptoms are more common as is confusion. Mixed affective symptoms are also frequently present in the early stages^{11,12}. This may partially be responsible for varying proportions of different diagnostic categories comprising PP in different studies, although recent prospective studies based mainly on Research Diagnostic Criteria have shown a preponderance of affective disorders especially mania¹³.

Most studies on clinical categorization and phenomenology of PP come from Western countries. There is a relative lack of systematic research efforts to study the phenomenon in developing countries, though a high fertility rate in these settings (47/1000 in Pakistan, for example) provides better opportunities to study a relatively uncommon disorder like PP. The only well documented prospective study from Nigeria¹⁴ shows preponderance of schizophrenia, while in other retrospective studies organic and affective disorders prevail^{15,16}. Neonatal deaths caused by lack of maternal care and breast-

feeding but not due to infanticide by the mother, highlight another contrast in these two settings¹⁷.

This paper describes clinical features and diagnostic breakdown of patients treated for PP in a psychiatric unit of a teaching hospital which provides acute psychiatric services to a population of over a million.

PATIENTS AND METHODS

All the patients referred to the Hayat Shaheed Teaching Hospital, Peshawar over a 15-months period (November 1988 to January 1990), suffering from a psychotic disorder with onset of symptoms within 90 days of childbirth, were included in the study. (Onset for this study was defined as 'the moment when the patient had 'important symptoms which interfered markedly with her daily activities or abnormality in her behaviour was noted'). As we discussed earlier, PP is not a well defined diagnostic category in the present classification systems. For the purpose of the present study puerperal psychoses was defined as any psychotic disorder arising within 90 days of childbirth. The definition of 'psychoses' for this purpose was adopted from D.S.M-III¹⁸. The patients were assessed by an interview based on the Present State Examination¹⁹, either immediately or within 48 hours of admission. Specific drug or E.C.T. were withheld during this period, and if necessary longer, for a proper assessment of mental state. Research Diagnostic Criteria (RDC)²⁰ were used for diagnosis of functional psychosis. Delirium, a disorder not operationally defined in RDC, was diagnosed in the presence of a demonstrable physical disease, the characteristic signs and symptoms of an organic psychosis and response to the treatment of the underlying condition.

In addition to the usual clinical and social data, information was collected about the influence of spiritual healers on the patient's health-seeking behaviour and any effect of the illness on breastfeeding by the mother.

RESULTS

The mean age of 35 women comprising the sample was 24.2 years (S.D.=7.08 years) and they constituted 6.3% of total female admissions during this period. Thirteen mothers were primiparous. The diagnostic breakdown is shown in Table I.

The average time between the delivery and onset of symptoms was 14.34 days (S.D. = 14.59); 80% of patients had onset

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TABLE I Diagnostic breakdown (n=35)

Diagnosis	No.	%
Schizophrenia	10	28.57
Shizo-affective disorder	8	22.86
Delirium	6	17.14
Major depressive disorder (MDD)	5	14.29
Unspecified functional psychoses (UFP)	5	14.29
Manic disorder	1	2.86

of symptoms within three weeks of delivery and all of them within two months.

Other salient clinical features are shown in Table II. Not illustrated in this table is the mother's attitude towards the newborn baby. In four cases (11.74%), the mother's mental state resulted in some harm to the baby, e.g. repeated bathing of the newborn due to obsessive concern about its cleanliness. In seven cases (20%), the baby featured in the paranoid and nihilistic delusions of the mother. About two thirds of the mothers could not breastfeed, most showing almost total lack of concern for maternal care. None of the mothers, however, expressed any infanticidal thoughts or inflicted any serious harm.

The average delay between the onset of symptoms and admission was 27 days (range 2-120 days). Fifteen (42.86%) patients had some treatment from spiritual healers before admission which in the majority was the first psychiatric contact. (Not included here are the patients whose families may have practiced traditional methods of healing which may be so for all cases in the sample).

DISCUSSION

The age at onset of the disorder and proportion of primiparous mothers in this sample appear to be significantly lower than generally reported^{1,2} though both are comparable to other studies from developing countries³. Apparent reluctance to admit a younger primiparous mother as compared to a multi-gravida because of social norms has been offered as an explanation⁴. However, a more readily understandable and plausible explanation is the younger age at marriage (80% married before 15 in this sample) and subsequent high fertility.

With few exceptions, the clinical features of the disorder appear to be broadly similar to those reported in the literature. The frequency of characteristic symptoms such as labili-

ty of mood, confusion, agitation, perplexity and delusions in depressed mood did not differ much from that reported in other studies^{5,6}. Similarly, in close agreement with other studies, about 80% of patients had onset of symptoms within the first three weeks of delivery. The high prevalence of physical problems in this sample is understandable in the setting of poor obstetric facilities available for the majority of the population and considerable delay (on the average 27 days) between the onset of symptoms and contact with psychiatric services. An excess of catatonic states (mutism/ stupor in 50% of patients, distributed uniformly across all diagnostic categories) can be partly explained by a common occurrence of such presentations in developing countries⁷. It is interesting to note that this finding is comparable to the findings of Reiman et al⁸. They found a high prevalence of 'motility disturbance' in a 19th century sample of patients suffering from PP, while comparing the clinical features of PP patients in the 19th and 20th century populations.

Risk for babies of psychotic mothers during the puerperium has been reported variously in Western studies. Davidson and Robertson reported infanticide in up to 4% of cases⁹. In this study two thirds of mothers were not able to breastfeed their babies, showing a total lack of concern for the baby. This can actually be more dangerous in these conditions than apparent infanticidal threats or behaviour as reported in previous studies from Western countries. The lack of evidence of the latter, however, should be interpreted cautiously in view of the small size of the sample and the rarity of the phenomenon itself.

The low prevalence of affective disorders, particularly that of mania, is in sharp contrast to most (but not all) of the studies from Western countries^{10,11}. One plausible explanation may be that the small sample in this study is not totally representative, especially when we consider the fact that organic psychoses was a major diagnostic category (i.e. 17%) in the present population. However, the major reason seems to be different diagnostic practices and the fact that the majority of studies on this subject are retrospective. For example, in two studies using the same diagnostic criteria (i.e. RDC), the diagnosis of manic disorder varies from 12%¹² to 43%¹³. This is a wide variation considering the fact that mania is a relatively uncommon condition. The situation is aptly summarized by Smith¹⁴ as "psychiatrists today are unwilling to diagnose schizophrenia in the puerperium. This unwillingness has become so marked in the U.S.A. that Kadramas and his col-

TABLE II Salient clinical features in PP sample and their distribution across different diagnostic categories

Clinical features	Number (percentage) of patients in each diagnostic category (n=35)						Total
	Schizophrenia	SA (Dep) ¹	MDD ²	Delirium	UFP ³	Manic disorder	
Mutism / stupor	6 (17.14)	5 (14.28)	3 (8.57)	3 (8.57)	2 (5.71)	--	19 (54.28)
Affect							
Labile	4 (11.11)	--	--	2 (5.71)	2 (5.71)	--	8 (22.86)
Depressed	5 (14.28)	8 (22.86)	5 (14.28)	3 (8.57)	3 (8.57)	--	24 (68.57)
Elated	--	--	--	--	1 (2.86)	1 (2.86)	2 (5.71)
Visual hallucinations	4 (11.11)	3 (8.57)	1 (2.86)	2 (5.71)	2 (5.71)	1 (2.86)	13 (37.14)
Delusions (nihilistic and paranoid)	6 (17.14)	5 (14.28)	4 (11.11)	5 (14.28)	2 (5.71)	1 (2.86)	23 (65.71)
Perplexity / confusion	3 (8.57)	4 (11.11)	2 (5.71)	6 (17.14)	2 (5.71)	--	17 (48.57)
Physical problems							
Pyrexia	3 (8.57)	2 (5.71)	--	6 (17.14)	1 (2.86)	--	12 (34.28)
Anaemia ⁴	10 (28.57)	7 (20)	5 (14.28)	4 (11.11)	3 (8.57)	1 (2.86)	30 (85.71)

1. SA (Dep) = Schizo-affective (depressed) 2. MDD = Major depressive disorder 3. UFP = Unspecified functional psychoses 4. Haemoglobin below 12gm %

leagues²³ classified psychoses in the puerperium as mania, even though a large proportion of patients had Schneiderian symptoms²⁴. It is interesting to note, however, that these findings are consistent with studies from other developing countries^{1,7}. It will be interesting to see whether this difference in diagnostic categories persists if larger samples are studied prospectively.

In agreement with other studies from developing countries, about half the patients contacted a spiritual healer before admission, which in the majority of cases was the first point of contact for any help. This seems to be the most important factor for considerable delay (27 days on an average) between the onset of symptoms and admission to hospital which may have contributed to the significant physical morbidity and resulting changes in the clinical picture found in this population.

Some of the difference found in this and other studies in developing countries from those observed in the developed world can mostly be explained by the factors already mentioned. However, the possibility of different pathoplastic factors affecting this population cannot be entirely excluded. An important etiological factor might be anaemia due to folate or vitamin B12 deficiency. Ahmed and Ashfaq²⁵ showed that 57% of their sample from the North West Frontier Province (NWFP) suffered from severe anaemia during pregnancy, a significant proportion being afflicted with megaloblastic anaemia. The latter has been shown to be an important etiological factor in depression, paranoid or organic states²⁶. Prospective studies incorporating proper control groups are needed not only to clarify these differences but also to investigate the other aspects of the disorder in these environments.

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THE IMPACT OF PSYCHIATRIC DISORDERS DURING PREGNANCY AND PUERPERIUM ON THE CHILD

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ABSTRACT: Impact of psychiatric disorders during pregnancy and puerperium is reviewed in this article with special reference to the literature from developing countries. It is recommended that the objectives of programmes for reproductive health should not be limited to improve the physical aspect of health. The mental health of mother and the baby should be taken into consideration as well.

KEY WORDS: Puerperal Disorders Depression

INTRODUCTION

The impact of psychiatric disorders during pregnancy and puerperium on the emotional and physical health of the child has been neglected area in almost all the initiatives on the reproductive health in Pakistan. Several independent studies have shown that antenatal stress or anxiety is linked with prematurity or low birth-weight. Similarly, many studies have shown that postnatal depression, can adversely affect the child's emotional and behavioural development. Puerperal psychoses can have similar effects and in addition can result in infanticidal threats or attempts. Limited evidences from studies in developing countries have shown that the effects of these disorders are much more serious both on the physical and emotional health of the baby. Unfortunately, the health professionals involved in the antenatal and postnatal care of the mother are inadequately trained to diagnose and treat psychiatric disorders associated with pregnancy.

A recent World Bank report portrays a grim picture of the health of women in Pakistan¹. According to the report, the health of Pakistani women is among the lowest in the world and worst in the South East Asian region. Almost all the initiatives on reproductive health in our country have been focused on physical health and nutritional problems of mother and child while the mental health has altogether been neglected. There is now increasing evidence that these two aspects are inseparable. The maternal mental health has direct bearing on the her physical health, both during antenatal and postnatal periods. Most importantly, it affects the baby in very crucial stages of development. In this article, the literature regarding the impact of the poor mental health of the mother both in antenatal and postnatal periods on the newborn is reviewed.

The effects of antenatal mental illness on the baby

It has long been known that the behaviour of adult offspring can be altered by prenatal stress in the mother in studies conducted in monkeys and rodents². There is now rapidly accumulating evidence in human being as well that antenatal maternal psychological problems are linked with complications of pregnancy. In several independent studies it has been shown that antenatal stress or anxiety are linked with prematurity or low birth-weight^{3,4}. The best evidence comes from Lou et al⁵. They followed 3021 women through their pregnancy and obtained information through questionnaires about the stresses they had experienced. They then compared the 70 most stressed women with 50 control from the same sample. They found that both antenatal stress and smoking contributed, independent of each other, to a lower gestational age, lower birth weight and smaller head circumference when corrected for birth weight. While the impact of antenatal psychiatric disorder on the fetus and the new born is relatively new area of investigation, affected by many confounding variables like genetic factors, parity, nutritional status of the mother etc, the same is not true for the postnatal period which has been studied extensively.

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There have been numerous studies of postpartum depression, its nature, prevalence and risk factors, well reviewed by O'Hara and Swain⁶. The average overall prevalence rate in 59 studies was 13%. Broadly, similar rates have been found in cross-cultural studies reviewed by Kumar⁷, although investigations outside western cultures have relatively been scarce. Keeping in mind the common symptoms of depression like easy irritability, intolerance to noise, increased fatigability, loss of self-esteem, lack of interest and energy etc which may persist for several weeks and months, it is easily understandable that this condition can adversely affect the baby. The impact of such a condition of the mother on the baby has been well summarised by Radke Yarrow et al⁸ as "Depressed parent is the primary environment of the young child.... the behaviours and mental states of depressed person are all potentially interfering with the functions and responsibilities of a care giver and with the development of good affective relationship with the child".

The effects of postnatal depression on the child

This reduced quality of interaction between the mother and

the child has been confirmed by the empirical studies. Stein et al¹³, compared 49 mothers suffering from postnatal depression with similar number of control mothers who had been free of any psychiatric disorders. They found the reduced quality of interaction between the mother and the child compared to controls. Kumar¹⁴ found that the mothers who had suffered from at least one episode of postpartum mental illness describe "an unexpected often catastrophic failure to love one of their babies". These women reported absent affection, sometimes late rejection, neglect or impulse to harm, in relation to their child, immediately or very shortly after birth.

Of more concern is the effect of postnatal depression on the intellectual functions of the child. Cogill et al¹⁵ showed that the children of postnatally depressed mothers may show cognitive defects at four years of age, a finding confirmed recently by Sharp et al¹⁶. This may be further complicated by the difficulty these children may experience in adjustment to the school, as has been shown by Sinclair and Murray¹⁴. In a longitudinal prospective study of five year old children of postnatally depressed women compared with well women they found that the children of women suffering from depression had significantly raised level of disturbances leading to difficulties in adjustment at the school.

The effects of postpartum psychosis on the child

The postpartum psychoses with an incidence of one in 500 deliveries in Western studies is thought to be a relatively uncommon condition. These are actually affective, schizophrenic and organic psychoses precipitated after the child-birth. More than two-third of the patients suffering from a psychotic breakdown in Western studies had an affective disorder i.e. depression with psychotic features or a manic disorder. It can be argued that the children of the mother suffering from puerperal psychoses may be exposed to similar cognitive, emotional and behaviour disturbances as we earlier discussed for the postnatal depression as the latter is much less severe disorder than the former. In addition the infants may be exposed to serious harm from the mother either as a result of psychotic behaviour or lack of maternal care resulting from the mother's mental state. De Silva and Johnston¹⁷ found 3 cases of deliberate injuries and two deaths, in their study being caused by mother's negligence. Although infanticide has been reported in upto 4% cases with puerperal psychoses in one study¹⁸ it is a relatively rare event. The infant is more at risk in other ways, particularly due to total lack of care and inability to breast feed by a psychotic mother as is discussed below.

The incidence and prevalence of postnatal psychiatric disorders in developing countries is much higher than compared to that reported from developed nations for the following reasons:

- I. High fertility rate in developing countries compared to the developed countries. For example, the fertility rate of Pakistani women is nearly 6/1000 with very low contraceptive prevalence rate.
- II. The risk for postnatal psychiatric disorder is highest in primipara and increases with every subsequent delivery. Mothers who develop puerperal psychoses after first delivery have one in five risk of developing similar illness during subsequent childbirths¹⁹.
- III. Certain causes of puerperal psychoses like, infections, anaemia etc giving rise to organic psychoses are much more

prevalent in developing countries compared to the developed countries²⁰.

In view of these factors it can be said that postnatal psychiatric disorders are one of the most common complications of postnatal period in developing countries. Unfortunately, there is inadequate empirical data on the effects of these disorder on the new born in developing countries.

Kumar¹⁴ in a critical review of literature on cross-cultural aspects of postnatal psychiatric disorders commented on surprising similarities of rates of postpartum depression across many cultures. Ghubash and AbouSaleh²¹ in their study in Dubai found that psycho-social correlates of postnatal depression in Arab culture were broadly similar to those found by O'Hara and Swain⁷ in their studies done in western settings. It can, therefore, be concluded that the adverse effects of postnatal depression on children's cognition, emotional development and the behaviour in our culture should be broadly similar to those reported in studies we reviewed earlier.

However, the immediate effects on baby's physical health that are far serious and can be even life threatening. These effects result most commonly from inadequate maternal care, family and marital conflicts associated with mental illness and occasionally from delusions or hallucinations regarding the baby. The most serious aspect of severe postnatal psychiatric disorders in a country like ours is the cessation of breast feeding which can prove more serious than the infanticidal threats or behaviour reported in Western studies. In a study on patients admitted with puerperal psychoses, Farooq²² found that more than two third of mother were unable to breast feed their babies compared to the findings in other studies that almost all the normal mothers would breast feed their babies at least initially. The effects can be devastating. Makanjola²³ in his study in Nigeria found that over half of mother stopped breast feeding permanently. In his study on 57 mothers suffering from puerperal psychoses, he found that 7 children died while seven others became physically ill, mostly due to malnutrition and gastroenteritis, well known complications of bottle-feeding. In another study²⁴ about 12% of mothers suffering from puerperal psychosis admitted in a psychiatric unit inflicted nonfatal harm to the baby. In another 20% of cases baby featured in paranoid and nihilistic delusions of the mother with serious implications for the safety of the baby if the illness is not promptly treated.

Marital conflict can have far more serious and long lasting effects on the baby's physical and emotional health. In Makanjola's study on 57 patients suffering from puerperal psychoses eleven husbands deserted their wives²⁵. In his words "the patient's husbands faced with his psychotic wife is subject to doubts, often reinforced by his family regarding the future sanity of his wife and future of children. Further there are practical problems resulting from his wife's illness, this may lead to desertion". In our setting, this may be further complicated by superstitious believes about possession of the woman by spirits and jinn etc.

Most recently the evidence for lack of proper mental health of mother in Pakistan and its impact on the child physical health has come from a study carried out by CIET International, an international NGO, in collaboration with the UNICEF, UNDP and Government of North West Frontier province (NWFP). In this study, a survey of 4213 households was carried out in 26 representative community clusters selected from North-West Frontier Province. A total of 3640

women were interviewed, respondents reported on 4137 children under three years on whom anthropometric measurements were also obtained⁹.

It was revealed that the mothers who reported a serious quarrel with a family member during the pregnancy were 12% more at risk of having low birth-weight baby. Similarly children of the mothers who did not feel cared for during their last pregnancy were 50% more likely to have low birth weight, 20% more likely to be stunted, 39% more likely to be wasted, 46% more likely to have delay in standing, 28% more likely to have delay in walking.

It was also found that the children who had negative interaction with their mothers also showed delays in motor milestones like sitting, walking and standing etc. Most importantly, these associations of inadequate care for the mother and their impact on the baby were independent of a number of other variables like socioeconomic status, age of mother etc. studied in this survey.

Unfortunately, it appears that there was very little input from mental health professionals in design of this survey. As a result no reliable and validated instrument to measure the variables like stress in pregnancy were used. However, in view of the very large sample size and the fact that the findings of this survey are consistent with the findings of more rigorously conducted studies reviewed earlier, the results of this study are quite significant. In fact the findings of this survey, represent significant advance in addressing psychosocial care in pregnancy, an area almost totally neglected so far in the developing countries.

What needs to be done

Even with limited health care facilities available in many developing countries at present, a woman has the best chance of being cared by a health professional in a pregnancy. It is therefore possible to focus on the mental health of the mother during her routine antenatal and postnatal care. Sclare² highlighted this many decades ago as "It is not enough for antenatal clinic to regard the woman as a stereotyped case of gravid uterus. Taking blood pressure and testing urine for albumin does not constitute the adequate care. These medical procedures when carried out without due attention to the doctor patient relationship, may actually foster the idea that pregnancy is an illness....Again in the puerperium we can't simply regard the doctor's role as being a matter of perinatal switches and prevention of sepsis. The puerperium is a phase of fresh problems and new adjustment."

The potential cases of postnatal depression and puerperal psychoses can be identified through a number of well known high risk factors reviewed by Kendell, and screening through questionnaires such as Edinburgh Postnatal Depression Scale³. Both primary and secondary prevention is therefore possible for these psychiatric illnesses if these disorders are looked for specifically in the antenatal screening. This will not only help to prevent the suffering of the mother and the family but will also help to prevent irreversible damage to the emotional and physical development of the baby at a very crucial stage of development.

CONCLUSION

It is evident from this review that at least about one out of

ten women become depressed and one out of 500 is afflicted with a psychotic disorder after the child birth with very serious adverse effects on the emotional, cognitive and behavioural development of the baby. In a developing country like Pakistan the effects on the physical health of the baby may be more serious. The lack of breast-feeding, amongst many other effects of inadequate maternal care due to these psychiatric disorders, account to a large extent for the adverse effects on the physical health of the baby. This, however, need to be investigated in future research. The women who are at high risk of developing psychiatric disorders during puerperium can be identified through a number of high risk factors and should be specially looked for in the routine antenatal care of the mother. Reproductive health without adequate mental health can be any thing but a productive health.

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PUERPERAL PSYCHIATRIC DISORDERS - WHO CARES?

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"If we come to think of it, every child that is begotten and born, is a seed of change, a danger to its mother, at childbirth great pain and after birth a new responsibility, a new change" (D.H. Lawrence).

Add to this that eighteen times as many women are admitted to mental hospitals in the first month postpartum as in each month of pregnancy¹. One can easily appreciate that the happy event of childbirth is not always a source of unalloyed joy.

The puerperium has been known to be the most vulnerable period in a woman's emotional life since the time of Hippocrates, who described a woman becoming restless and later delirious following the birth of twins². This condition first described in detail as postpartum psychosis, though very obvious due to its dramatic presentation is not much common. Far more common are two other conditions, the maternity blues³ and postnatal depression⁴. Awareness about these conditions and their deleterious effects on mother and baby has developed only over the last three decades. In developing countries, including our own, where mental health is amongst the lowest priorities, the psychiatric aspect of puerperium still remains largely neglected. The price in terms of physical and mental health of the baby and the mother is high and we can no longer afford to neglect it.

Although their specificity to the postpartum period has recently been questioned⁵, the maternity blues are known to occur in more than half of the mothers. Symptoms include crying spells, sadness, lability of mood, irritability, confusion or forgetfulness, insomnia and anxious feelings often related to convictions of maternal incompetence⁶. The symptoms generally peak between the third and seventh postpartum day⁷. The condition is transitory and no treatment other than reassurance and support is required.

The next condition on the spectrum of severity is postnatal depression. Except one recent methodologically sound study⁸, almost all the investigators including those who used strict diagnostic criteria^{9,10}, have found the incidence of this disorder to be 8-15%. We should not have a false sense of security by being under the impression that the better family support will have a protective effect as similar rates of postnatal depression have been found in African population¹¹.

Anxiety often related to the baby's health, irritability, easy fatigability, variable insomnia, suicidal thoughts or fear of harming the baby are common symptoms. In our setting such symptoms may be disguised as excessive concern about a physical illness which may be attributed to affliction with the "Wind" on

not observing postpartum rituals. The patient may not admit depressed mood, though tears and other depressive behaviour may at times be apparent. The family on the other hand may be concerned about her increased irritability and rather casual attitude towards the baby.

The puerperal psychosis is not a specific diagnostic entity in the present classificatory systems. These are thought to be affective, schizophrenic or organic psychosis which simply happen to be precipitated after childbirth. Nevertheless, the term if not the concept is tenacious and carries special meaning for many clinicians. Although the time limit varies, it usually implies a psychotic disorder arising within 90 days of childbirth characterized by insomnia, confusion, perplexity, visual hallucinations, lability of mood, prominent delusions in depressed mood and morbid ideas relating to the baby and unexpected rejection of the newborn¹².

With an incidence of approximately one in 500 deliveries in Western studies this is thought to be an uncommon condition; but this appears to be an underestimate, as organic psychoses occur very commonly in developing countries due to higher incidence of physical complications of puerperium, i.e., upto 37% in one African study¹² compared to almost none in studies from developed countries. Even based on this incidence, high fertility rate of 6.4¹³ in our country means a higher rate for our female population, particularly so when the risk of further puerperal relapses is increased 100-fold after the first one¹⁴.

These psychiatric disorders have serious implications for the relationships of mother with the newborn in particular and for other interpersonal relationships in general, which seems to be the major reason for recent surge in interest in this field. Postnatal depression has been demonstrated to have adverse effects on the intellectual and emotional development of the younger children in many well executed studies^{15,17}. On the other hand infanticide has been reported in upto 4% of cases with puerperal psychosis¹⁸. Makanjola¹⁹, in his study in Nigerian population, found that seven babies died and other seven became severely ill as a result of malnutrition and gastroenteritis due to lack of maternal care after the onset of a postpartum psychotic disorder. Similarly definite loss of sexual relations, and deterioration in her personal appearance, doubts about future sanity of the wife reinforced by the popular notions about mental illness and practical problems in seeking treatment of these disorders can all combine to cause worsening of marital relationships and even worse, desertion¹⁸.

If one out of ten women becomes depressed and

one out of 500 is afflicted with a psychotic disorder following childbirth with such a serious consequence, we have not much reasons for complacency. The treatment and prevention of postnatal psychiatric disorders should therefore, become a major public health concern.

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ORIGINAL ARTICLES

ROLE OF PROSTAGLANDIN SYNTHESIS INHIBITORS IN THE PASSAGE OF URETERIC CALCULUS

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ABSTRACT

Diclofenac sodium, one of the prostaglandin synthesis inhibitors was evaluated in terms of passage or movement of ureteric stones upto the size of 0.5 cm in a series of 80 patients. Forty-six (57.5%) patients passed the stone with a period of 4 weeks. This frequency of stone passage was significantly higher when compared with stone passage of similar size in other series ($P < 0.001$). In 17 (56.6%) out of 30 patients, stone moved from upper and middle ureter to the lower ureter which is also significant from therapeutic point of view. Complete pain relief was achieved in 67 (84%) patients. No side effects of the drug noted in this series. The sequence of events following ureteral obstruction by the stone, based on recent experimental and clinical studies is discussed and possible mechanism of action of diclofenac sodium was highlighted (JPMA 41: 268, 1991).

INTRODUCTION

Renal colic caused by ureteral obstruction by a stone is one of the most common emergency situation in surgical practice in our country requiring urgent and prompt relief. The aims of the treatment in this situation are urgent and complete relief of pain, to prolong the pain free interval between the pain episodes and adopt measures which enhance the passage of stone. The efficacy of prostaglandin synthesis inhibitors like indomethacin and diclofenac sodium has been established in the treatment of renal colic^{1,2}, but their exact role in facilitating the passage of ureteric stones is not yet clear. The purpose of this study is to evaluate the efficacy of diclofenac sodium in the passage of ureteric stones.

MATERIALS AND METHODS

Eighty patients of both sex, above the age of 15 years, having radiopaque ureteral stones with transverse diameter between 0.3-0.5 cm were included in this study.

Excluded from this study were, (a) patients having stones above a ureteral stricture, due to congenital anomalies and stones associated with severe hydronephrosis requiring urgent relief, (b) patients having history of hypersensitivity reaction to drugs, peptic ulcer, asthma, cardiac failure, hepatic failure, renal impairment and blood coagulation disorders, (c) pregnant women and lactating mothers, and (d) patients who experienced nausea or vomiting due to the acute colic.

All patients had complete clinical evaluation, urine examination, complete blood picture, blood urea, serum creatinine and plain X-ray abdomen and pelvis to see the side, site and size of the stone. Renal ultrasonography was done in all cases to see the dilatation of upper urinary tract and intravenous urography only in selected patients. All the patients were given diclofenac sodium tablets in doses of 100 mg each twice daily for two weeks. The patients were followed at 2 and 4 weeks. On each follow-up, patients were asked about the passage of stone and relief of pain as complete, partial or no relief. Plain X-ray abdomen and pelvis was taken in each case to

POSTNATAL PSYCHIATRIC DISORDERS NEED PUBLIC HEALTH ACTION

Saeed Farooq

The recent world health report has proposed public health action for psychiatric disorders which are now amongst the leading causes of burden of disease in developing countries.¹ Most psychiatric disorders, however, are not amenable to well-known measures of primary, secondary and tertiary prevention. This is mainly due to the fact that most of risk factors for psychiatric disorders e.g. stressful life events can't be readily identified or easily predictable to be targeted by public health actions. Moreover, the manpower and financial resources required for early diagnosis and interventions are not readily available. Postnatal psychiatric disorders, on the other hand, appear to have a rather predictable onset (something of rarity in psychiatric disorders), are amenable to easier screening and are precipitated by well-established risk factors. These characteristics of postnatal psychiatric disorders can help us initiate a public health action in psychiatry.

Maternity blues, depression and psychoses are well-recognized psychiatric disorders following childbirth. We will mainly focus on postnatal depression and psychoses here.

Epidemiological studies of puerperal samples have consistently revealed the prevalence of postnatal depression (PND) around 10%. This high prevalence is peaked in the first three months following delivery.^{2,3} The prevalence rates from developing countries are generally reported to be higher. Thus prevalence rates of 15.8% in Arab women⁴, 16% in Zimbabwe⁵, 34.7% in South Africa⁶, and 23% in Goa, India, have been reported.⁷ It is evident from these prevalence figures that postnatal depression is perhaps the commonest complication of puerperium, along with anemia and puerperal infections, in developing countries. Such a high prevalence in itself is a valid reason for giving a high priority to the prevention of these disorders.

There are, however, other more compelling reasons for urgent intervention. Several prospective studies indicate a definite association between PND and impaired cognitive development of infant. The evidence has been well-summarized in a number of reviews.^{8,9} The effects on cognitive development were still obtained when the children were 4-5 years old. Thus follow-up of the Cambridge cohort, which started at 18 months of age found that children of mothers who had PND, were significantly more likely to be rated by their teachers as behaviorally disturbed at 5 years of age when compared with children of mothers who did not have PND.¹⁰ A study from Pakistan reported that maternal depression causes mothers to stop breast-feeding.¹¹ Similarly, Patel *et al* found that postnatal depression was a strong and independent predictor of low birth weight and length and was significantly associated with adverse mental development quotient scores.¹²

A number of high risk factors have been identified for postnatal depression. These risk factors include the following: poverty, problems with in-laws, adverse life events in pregnancy, the birth of a daughter when son was desired, lack of physical support after delivery and marital violence. These have specifically been identified as risk factors from studies conducted in developing countries.^{13,14} Other factors identified by Lee *et al* in their recent prospective study on Chinese population of Hong Kong are: past history of depression, depressive symptoms in third trimester of pregnancy, inadequate social support and poor relationship with mother-in-law. Interestingly, it was found that absence of Chinese tradition of postpartum support custom (Feiyue), comparable to similar postnatal rituals of initial 40 days in our culture, was also associated with high risk for PND, although, the association was not as robust as found for other factors.¹⁵

Despite such a high prevalence and well-known risk factors, PND, is frequently missed in primary care. This is perhaps not surprising in view of the present state of training for health professionals in mental health and their preoccupation with physical health. A simple and brief self-reported measure known as Edinburgh Postnatal Depression Scale has been developed as a screening device. It has been shown to have specificity of 92.5%, a sensitivity of 88% and a positive predictive value of 35.1% for major depression.^{16,17}

The diagnosis of PND, should not be difficult if the condition is kept in mind while examining a postnatal patient who presents with lethargy, different somatic complaints of body aches, headache, easy fatigability, increased irritability, crying spells or a fear of being incompetent mother.

Although puerperal psychosis is not a separate diagnostic category in present psychiatric classification, the concept is helpful in clinical practice. It encompasses the severe mental illnesses in the form of affective, schizophrenic and organic psychoses following childbirth. It is relatively a rare disorder and occurs following 0.2% of live births.¹⁸ But in a developing country like ours, with high fertility rate, even such a low incidence results in a high burden of disease.⁹ The disorder severely disrupts the mother's interaction and increases risk to the physical health of baby, as has been reported.^{19,20} Indeed, Malagasio reported 7 deaths amongst a series of Nigerian women.²¹

This was mainly due to lack of maternal care rather than infanticide threats. Keeping in view that PND is associated with significant impact on baby, it is not difficult to understand that puerperal psychoses, which is much more severe disorder, would have more serious impact on the child.

The identified high risk factors are: being primipara, perinatal death, a previous history of manic-depressive illness or previous episodes of puerperal psychoses. The other obstetric factors related with puerperal psychosis are obstetric complications, twin birth C-section but evidence for these is rather controversial.^{22,23} For mothers, with previous history of

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bipolar affective disorder postpartum psychoses, the risk is increased 100-fold to one in five.^{20,21} Effective treatments are available both for P.N.D. and puerperal psychoses. The pharmacological treatment of P.N.D. are cost-effective and can be instituted by the health workers involved in the routine postnatal care of mothers, after appropriate training.²² The treatment for puerperal psychoses invariably need specialized psychiatric care. Electroconvulsive therapy is rapidly effective and can result in quick recovery, thus preventing the serious disruption in mother-infant relationship. Use of Lithium is generally contraindicated in pregnancy. However, Stewart *et al* demonstrated that prophylactic use of lithium, initiated either at 34 weeks of pregnancy or within 24 hours of delivery, was also associated with lower risk of relapse in patients with previous history of bipolar affective disorders.²⁴ Their sample size was only 21 and the study needs to be replicated with larger sample size.

Postnatal psychiatric disorders have received little attention in public health measures for mother and child health including the present initiative on reproductive health in Pakistan. This is surprising in view of high prevalence of these disorders, their impact on mother, child and family on the whole, well recognize risk factors, which can be used for early detection, and availability of cost-effective treatments. The following areas need urgent attention.

1. Research on the interventions for postnatal psychiatric disorders, which can be cost-effective in our own setting.
2. Training for health professionals involved in routine natal care for early detection, treatment and prevention of postnatal psychiatric disorders. We also need to incorporate the high risk factors for P.N.D. and puerperal psychoses in the routine antenatal screening of the expectant mothers. Culturally appropriate screening instrument, similar to the one that has been developed for depression in general,²³ needs to be developed for postnatal depression in Pakistan. This can help us in building a reliable predictive index for these disorders.
3. Creating awareness in public about the impact of these disorders on mother and child.

These actions require a collaborative effort between health professionals involved in psychiatric, obstetric and childcare, along with health planners and public health experts. After all we need a generation of young infants and children who are not only physically healthy but emotionally and intellectually sound as well, brought up by mothers who are free of stigma of mental illness.

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In only 6% of patients homicide could be attributed to the mental state abnormalities e.g. commanding hallucinations and delusion of nihilism etc. The recent literature appears to confirm that there is little link between psychotic symptoms and aggression.^{11,12} This finding illustrates the difficulties associated with prediction of violence in such patients. It is, however, based on retrospective case accounts and should be interpreted cautiously.

This study showed that most of mentally ill patients charged with homicide had a chronic illness and only 2 patients had been ill for less than one year. It is, therefore, ironic to note that less than one-third of these patients had any contact with psychiatric service or professional, which was broadly defined for the purpose of this study to be any contact with a mental health professional in six months before the index crime. It can be argued that at least some of these homicides could have been prevented with the provision of proper psychiatric services, as it has been shown that violence and crime can be prevented by improving the response to the patients who start to relapse.²

The finding of majority of the victims being closely related or acquaintances of the patient was also in broad agreement with the literature^{10,12} which showed that those involved closely with the patient case were more at risk of the violence. Only 7 victims in this study were strangers, which was in line with the findings reported by Taylor and Gunn.⁶ This also showed that the public perception of violence by mentally ill patients was highly distorted as the victims of violence, if any, by these patients were most likely to be relatives and acquaintances rather than public at large.

This study also highlighted the inadequacies of the legal system dealing with mentally ill patients. In all the cases the patients were referred for the opinion whether they suffered from the mental illness or were fit to stand the trial. On thorough search through the case notes, even of those with long histories of confinement to the mental hospital, we didn't find evidence that the question of defense on the basis of insanity was raised. The opinion of the medical board was also limited to the questions: (a) whether patient was mentally ill, and (b) whether he was fit to stand trial or not. The patients were confined for long periods either in jail or in the mental hospital before any legal proceedings. In one case, a patient was convicted for murder while he was in the mental hospital throughout the proceedings of the case and the defense never raised the question of mental illness in the session court. This defense was raised only in the high court appeal. This stress the need for proper training in forensic psychiatry for both the legal and the health professionals.

CONCLUSION

This study was based on the case notes and, therefore, had the limitations of the retrospective studies. The sample represented a selective group of patients and, therefore, findings could

not be generalized. However, it highlighted the common psychiatric disorders in patients charged with homicide, the characteristics of the offenders and victims and lack of psychiatric services for mentally ill patients charged with a serious crime. Further prospective studies, incorporating proper control are needed to clear this issue further.

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MENTALLY - ILL PATIENTS CHARGED WITH HOMICIDE

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ABSTRACT

Objective: To describe the clinical, social and demographic features of mentally ill patients charged with homicide.

Design: Retrospective study.

Place and Duration of Study: The study was based on the review of case notes of the patients who were charged with homicide and referred to the mental hospital, Peshawar, between 1988 and 1998 for psychiatric evaluation.

Patients and Methods: The case notes of all the patients referred for psychiatric assessment between 1988 and 1998 were retrieved. Fifty cases with complete essential information were selected for the study. The details of patients' demographic, clinical characteristics, diagnosis, events leading to the homicide, opinion of the medical board, details of the victim and possible provoking factors were recorded on a proforma designed for this purpose.

Results: Out of 50 patients referred for psychiatric assessment with homicide, majority (48) were males, while only one was female. The mean age of the sample was 32.4 years and 30 patients (60%) were educated. Schizophrenia was the most frequent diagnosis (72%). Duration of illness in 96% of the patients was more than one year. Only 12 patients had received some form of treatment before the index crime. Thirty-eight (76%) patients were involved in single murder, while 12 patients were involved in multiple homicides. Majority of the victims (39 out of 64) were close relatives of the patients.

Conclusion: Young male patients are mostly referred for psychiatric assessment after homicide. Close relatives are major victims. Lack of adequate psychiatric treatment is one of the contributing factors. Lack of adequate forensic psychiatric services are also highlighted by this study.

KEY WORDS: Forensic psychiatry; Homicide; Psychoses; Psychotic disorders; Schizophrenia.

INTRODUCTION

There is an emerging consensus that an association exists between offending behavior, particularly those involving violence and certain forms of mental disorders.¹⁻³ The degree of this association and its nature remains controversial. It is suggested that individuals with mental disorders may be two or three times more likely to behave violently than controls.⁴ Schizophrenia and substance abuse disorders have been particularly implicated.^{5,6}

However, research has shown that the public perception of violence by people with mental disorders is greatly exaggerated.⁷ Taylor and Gunn (1999) analyzed the data on homicide between 1957 and 1995 and showed that, contrary to common belief, there has been no increase in the homicide rate, since the policy of community care for the mentally ill was adopted in U.K.⁸ Violent patients form a very small sub-section of all those suffering from psychiatric disorders. It has been argued that efforts to improve the overall psychiatric care can help to decrease the risk of violence by the mentally ill.⁹ This is further facilitated by improving risk assessment in patients who can pose threat to self and to others. Extensive research on the characteristics of the violent patients and associated risk factors has resulted in measures to quantify the degree of the risk involved. Steadman *et al.*, for example constructed a clinical

scale for the measurement of risk posed by the violent patients.¹⁰

Most of the research on the subject comes from Western countries. These findings may not be applicable in our society due to sociocultural differences in the patient population, service provisions and the legal system. Forensic psychiatric services are almost non-existent in our country. The present study aims to investigate the characteristics of the patients charged with homicide and referred for psychiatric assessment with a suspicion of mental illness.

METHODOLOGY

The notes of all the patients who were charged with murder and referred to the standing medical board of mental hospital Peshawar, for psychiatric assessment between 1988 and 1998 were retrieved. A qualified psychiatrist supervised the mental hospital during this period. The standing medical board comprised of at least two qualified psychiatrists, who provided their opinion after an assessment and following a period of observation of the patient referred for this purpose wherever needed. All case notes were thoroughly scrutinized for the following essential information: the demographic details of the patient, diagnosis, opinion of the board, the events related to and leading to the alleged homicide, the details of victim, weapons used, past psychiatric history and any treatment received before the index crime. The cases in which any of the above mentioned information was missing were excluded from the study. The diagnosis was based on opinion of the standing medical board. All the information elicited from the notes was recorded on a proforma designed for this study.

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RESULTS

Amongst the 50 patients assessed, 49 were male and only 1 was female. Thirty-five patients (70%) were married while 15 (30%) were unmarried. The mean age of the sample was 32.4 years. The detailed breakdown of the age is given in Table I. Thirty patients (60%) were educated, while 20 (40%) of the patients were illiterate. The details of levels of education are shown in Table II.

Table I: Age distribution of patients.

Age group (yrs)	Numbers	%
10-20	4	8
20-25	20	40
25-35	18	36
35-45	08	16
Total	50	100

Table II: Level of education in the mentally ill patients.

Level of education	Numbers	%
Primary	9	18
Middle	8	16
Matric	15	30
FA/ FSC	2	4
Total	30	60

Table III: Diagnostic breakdown of the mental disorder given by the medical board.

Diagnosis	Numbers	%age
Schizophrenia	36	72
Bipolar affective disorders	03	06
Epilepsy	03	06
Dissociative disorder	02	04
Delusional psychosis	02	04
Others	04	08
Total	50	100

Table IV: Total duration of illness before the index crime.

Total duration of illness (in years)	Frequency	%
< 1 Yrs	02	04
1-5	20	40
6-10	10	20
11-15	7	14
16-20	3	6
20	3	6
Total	50	100

Table V: Relationship of victims to the patient.

Victims	Numbers
Wife	13
Parents	8
Siblings	8
Daughters	5
Other relatives	5
Acquaintances	10
Not related or known to the patient	7
Total	64

Table VI: Provoking factors leading to homicide.

Provoking factors	Frequency	%
Suspicious about wife	7	14
Family enmity	8	16
Mental state abnormalities	3	06
Unprovoked	3	06
Unprovoked/ not known	29	58

Schizophrenia was the most frequent diagnosis made in 36 (72%) patients. The detailed diagnostic breakdown is shown in Table III. Other diagnoses included bipolar affective disorders, epilepsy, delusional disorder and dissociative disorder. Table IV shows the total duration of illness for these patients, which depicts that most of them were chronic patients. Out of 45 patients whose illness was known to their relatives, 29 patients (64%) had not received any psychiatric treatment. Only 12 patients (24%) had received some form of treatment before the index crime.

In 9 patients (18%) substance abuse was also present. The commonest substance of abuse was cannabis which was found in 8 patients (16%) while heroin was abused only in one (2%) patient.

Thirty-eight patients (76%) were involved in single murder while 12 patients (24%) were implicated in double/multiple murders. Amongst the victims 39 were close relatives of the patients i.e. wife, parents, siblings, daughters and other relatives. The details of the victims are shown in Table V.

Table VI shows the possible provoking factors which could be retrieved from the notes. Mental state abnormalities could be implicated in only 3 (6%) of the cases. The suspicion of illicit relationship regarding the wife was reported in 7 (14%) cases while old family enmity was the provoking factor in another 8 (16%) cases.

The medical board decided that 28 patients (56%) were not fit to stand trial. Thirteen patients (26%) were declared fit to stand trial. In 9 patients (18%) no definite opinion was given.

DISCUSSION

Despite extensive literature search in Pakistan, we could not find a local study published on the subject. It is, therefore, not possible to compare our findings with local literature. As the characteristics of the mentally ill offenders and the offences committed by them largely depend upon the general legal system, and forensic psychiatric services operating in a particular country, therefore, only broad comparisons can be made with other studies.

Predominantly male and young population (average age 32.40 years) charged with homicide found in this study is in general agreement with other studies.^{11,12} Thirty patients (60%) in this study were educated. This appears to be a higher level of education when compared to the literacy ratio in the general population in our country. This is an interesting finding and several explanations are possible. It appears unlikely that higher level of education in mentally ill is more associated with violent crime. In the absence of proper forensic psychiatric services which can cater for all the mentally ill patients charged with criminal offences, it is more likely that only those patients who had some education were more likely to find their way through the legal system for psychiatric assessment.

A high proportion of Schizophrenics (72%) in this study is in general agreement with the literature on the subject.^{13,14} However, only one patient was diagnosed to have a personality disorder. This is again an interesting finding as personality disorders have generally been reported to have a robust association with violence.¹⁵ This may be related to reluctance of the psychiatrists to diagnose the personality disorders as shown by Rehrman et al.¹⁶

CANNABIS ABUSE IN PATIENTS WITH SCHIZOPHRENIA: PATTERN AND EFFECTS ON SYMPTOMATOLOGY

Inayat Ur Rehman and Saeed Farooq

ABSTRACT

Objective: To determine the relationship between cannabis abuse and its impact on the short-term outcome and severity of illness.

Design: Case control study.

Place and Duration of Study: This study was conducted at P.G.M.I. Lady Reading Hospital, Peshawar from January to October 2004.

Patients and Methods: ICD-10 criteria were used for diagnosis of schizophrenia. Severity and type of schizophrenic symptoms were assessed with the help of PANSS. Cases were identified as having problem with cannabis use with the help of section 12 of Schedule for Clinical Assessment in Neuropsychiatry (SCAN) W.H.O. 1994. Amount, duration and frequency of cannabis use was also noted.

Results: Patients with cannabis use were younger had shorter duration of illness and earlier age at onset of illness. They exhibited more positive symptoms. A total of 20% cases met ICD-10 criteria of harmful use of cannabinoid, 76% met ICD-10 criteria of cannabinoid dependence syndrome.

Conclusion: Schizophrenic patients with comorbid cannabis abuse exhibited more positive symptoms and violent behavior, and may be more likely to depend on persons with schizophrenia. This has implication for service development to meet the perceived needs of this group.

KEY WORDS: *Schizophrenia. Cannabis. Substance of abuse. Symptoms. Behaviour.*

INTRODUCTION

Cannabis is a major drug of abuse in Pakistan. The National Survey on Drug Abuse in 1993 revealed 3.01 million chronic drug abusers in Pakistan, rising at a rate of nearly 7% annually. Among young people, cannabis is reported to be the most common drug used, followed by heroin and alcohol. Nearly 72% of the drug abusers are under 35 years of age, (the most economically productive age group), with the highest proportion in the range of 26-30 age.¹ In a hospital-based study, conducted at DHQ Hospital, Faisalabad, in patients admitted between 1996-2001, it was found that cannabis was the most frequently used drug of abuse.²

The comorbidity of schizophrenia has attracted considerable attention in recent years.³⁻⁴ It has been shown that the risk of meeting criteria for substance misused disorder was 4.6 times higher in those suffering from schizophrenia than in general population. Schizophrenia was associated with six-fold increase of developing drug misuse disorder and cannabis was the most commonly misused drug.⁵ There are a number of hypotheses about the relationship between cannabis use and schizophrenia. One hypothesis is that heavy cannabis use causes schizophrenia.⁶ Another hypothesis is that cannabis use can precipitate the illness in predisposed people and thus can exacerbate the symptoms in those who have developed the illness.⁷⁻⁸ Some believe that persons with schizophrenia are

more likely to become regular or problematic cannabis user than a person without it.⁹

Although cannabis abuse is highly prevalent in Pakistan, the relationship between cannabis and psychiatric disorders has rarely been investigated. There has been little research on the subject. Haroon *et al.* found in their study that patients who consumed 'Bhang' (a beverage containing cannabis) ingestion exhibited grandiosity, excitement, hostility, uncooperative-ness, disorientation, hallucinatory behavior and unusual thought content.¹⁰

The aim of the present study was to determine the relationship between cannabis abuse and its impact on the short-term outcome and severity of illness in terms of score on the Positive And Negative Syndrome Scale (PANSS).

PATIENTS AND METHODS

The study was conducted at Psychiatry Department, Post-graduate Medical Institute, Lady Reading Hospital, Peshawar from January to December 2004. All the patients aged between 15-60 years who qualified the International Classification of Disease (ICD)-10 research diagnostic criteria for schizophrenia (W.H.O. 1993) were included in the study in a case control design.

Fifty schizophrenic patients who self reportedly used cannabis in the last year were selected as cases and another 50 schizophrenic patients without cannabis use were selected as control group. The patients using other psychoactive drugs along with cannabis were excluded from the study.

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Informed consent was obtained from the patients after explaining the nature and purpose of study in *Pushto*. For the patients who were unable to give informed consent, the same was obtained from a close relative.

Socio-demographic details and information about the age at onset, duration of illness (period from the appearance or detection of psychiatric symptoms to the index admission) was collected from the patients and their informants who have been involved with the patients during their illness.

The information about the amount of cannabis used in the last month was obtained from the patients in terms of frequency and number of cigarettes used on a 1-6 scale.

All the patients were interviewed and administered PANSS (Positive and Negative Syndrome Scale) to assess severity of schizophrenic symptoms. There are 30 items included in the PANSS, 7 constituting positive scale, 7 forming negative scale and the remaining 16 were part of general psychopathology scale. Each item was rated on 7 points representing increasing level of psychopathology. The composite score was achieved by subtracting score on the negative from the positive scale. Patients with positive composite scale valence (i.e., > 0) were classified as "positive subtypes." And those with a negative valence (i.e., < 0) were classified as "negative subtypes." Three supplemental items were used to assess aggression risk. The cluster score (anergia, paranoid belligerence and supplemental) was the sum of the score on the individual item that represented a set of specific psychopathology. Three supplemental items (anger, difficulty in delaying gratification and affective lability) were used to assess aggression risk.

Patients with co-morbid cannabis misuse were interviewed using section 12 of Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (World Health Organization 1994). All the questions of interview were translated into *Pushto* by a bilingual expert and retranslated by another expert who was blind to the first translation.

Their respective score were entered in a computer base version of SCAN and results were obtained by running algorithm to identify patients as having problem use in the past year.

The data was collected and analysed with the help of statistical programme SPSS, version 10. Chi-square test for categorical data and independent t-tests for continuous variable were used to assess the degree of correlation between different

variables. The statistical significance was calculated at $p < 0.05$.

RESULTS

There was no statistically significant difference between cases and controls in terms of marital status, socioeconomic status, living arrangements and employment. However, there was significant difference in the educational status, age on index admission and age at onset of illness between the user and non-user.

There were only 9 cannabis users who continued their

Table I: Comparison of educational status between cases and control.

Level of education	Case	Control	Total
Uneducated	15	15	30
Primary to middle	26	19	45
Secondary to graduation	09	16	25
Total	50	50	100

Pearson chi square Value 17.260; p-value .004.

education beyond primary-middle level against 16 non-users (Table I).

The schizophrenic patients with comorbid cannabis use were younger on index admission than non user (25.82 years v 30.57 years, $p = 0.001$ 95% CI of mean difference -7.54 to -1.96). The age at onset of illness was earlier in cases than controls (21.43 years v 25.39 years, $p = 0.005$) (Table II).

Symptoms were measured and compared using both the individual scale and cluster scores including positive, negative and composite scores.

The patients who had cannabis abuse exhibited more positive symptoms as they scored more on positive score and composite score. They also scored higher on paranoid and supplemental score while the non-users scored more on negative score (Table III).

The patients using cannabis also scored high on different individual items of PANSS. The patients using cannabis had higher scores on excitement (2.82 v 1.80 $P < .005$, CI 0.40-1.63), grandiosity (1.74 v 1.12, $p < .005$, CI 0.21-1.03), hostility (3.86 v 2.30, $p > .005$, CI 0.83- 2.29), poor impulse control (3.76 v 1.94 $p < .005$ CI 1.15 -2.49), uncooperativeness (3.86 v 1.90, $p < .005$, CI 1.34- 2.58), anger (4.06 v 2.26, $p < .005$, CI 1.11- 2.49) and difficulty in delaying

Table II: Comparison of age of patients on index admission and age at onset of illness between cases and control.

	Case Mean (sd)	Control Mean (sd)	Mean difference	P-value	95% CI of mean difference	
Age of patient on index admission (years)	25.82 (5.06)	30.57 (8.55)	-4.75	0.001	-7.54	-1.96
Age of patient at onset of illness (years)	21.43 (4.62)	25.39 (8.47)	-3.96	0.005	-6.66	-1.25

sd: Standard deviation; CI: confidence interval; Numbers in parenthesis are standard deviations.

Table III: Comparison of PANSS cluster score between cases and control.

	Case Mean (sd)	Control Mean (sd)	t	P-value	Mean difference	95% CI of the difference	
PANSS positive score	18.66 (6.91)	15.24 (6.31)	2.583	.011	3.42	0.79	6.05
PANSS negative score	15.26 (7.02)	22.52 (9.02)	-4.490	.000	-7.26	-10.47	-4.05
Composite score	3.80 (12.19)	-7.28 (13.29)	4.344	.000	11.08	6.02	16.14
Anergia	8.10 (3.90)	12.64 (4.90)	-5.126	.000	-4.54	-6.30	-2.78
Paranoid	10.32 (4.31)	7.24 (3.85)	3.769	.000	3.08	1.46	4.70
Supplemental	18.70 (7.62)	11.68 (5.36)	5.328	.000	7.02	4.41	9.63

sd: Standard deviation CI: confidence interval; Numbers in parenthesis are standard deviations.

gratification (3.64 v 1.64, $p < .005$, CI 1.37-2.63). Non users scored more on blunted affect (3.58 v 2.18, $p < .005$, CI -2.06 to -0.74), passive/apathetic withdrawal (3.82 v 2.50, $p < .005$, CI -2.02 to -0.62), lack of spontaneity and flow of conversation (3.56 v 2.12, $p < .005$, CI -2.12 to -0.74), motor retardation (3.54 v 2.12, $p < .005$, CI -2.09 to -0.75), and preoccupation (3.40 v 2.32, $p < .005$, CI -1.66 to -0.42).

Out of 50 patients who were using cannabis, 10 (20%) met ICD-10 criteria of 'Harmful use of Cannabinoid', 38 (76%) met ICD-10 criteria of 'Cannabinoid dependence syndrome' and 2 patients did not meet the criteria.

The mean age on index admission was 28.20 years (SD=7.39). However, the patients who were having Cannabinoid dependence syndrome were younger (25.08 years SD=5.09), as compared to those who had harmful use of Cannabinoid (28.70 years SD=4.64, Mean difference 3.62 years. T-value=2.037, $p=.047$, 95% CI of difference=2.7-7.20).

DISCUSSION

According to ICD-10, the key features of dependence syndrome are a strong desire to take substance, progressive neglect of alternate source of satisfaction, the development of tolerance and a physical withdrawal state. While harmful use is defined as a pattern of psychoactive substance use that is causing damage to health; the damage may be to physical or mental health.

Younger age on index admission and at onset of illness were important finding of this study. These findings are in line with those of Veen¹¹ and Cantwell.¹² Different explanations are possible for these findings. It may be a confounding factor as drug dependence is primarily a young age phenomenon. The possible mechanism which can explain this association is that cannabis use had no influence on age at onset and younger patient were more likely to use this substance before the first psychotic episode because the use was age related. The second possibility is that cannabis abuse precipitated the onset of schizophrenia at an early age in people who were vulnerable or predisposed to develop the illness.

It was found that cannabis was associated with excitement, hostility, uncooperativeness, anger, poor impulse, and difficulty in delaying gratification. It showed that those who abused cannabis were more likely to present with acute onset of florid symptoms characterized by paranoid ideation, irritability and uncontrolled behavior, a finding supported by W.H.O 10 country study on schizophrenia. There it was found that the use of cannabis during the follow-up predicted more psychotic symptoms and periods of hospitalizations.⁸ However, it was difficult to delineate the effect of multiple drugs use as there were overlaps between cannabis and cocaine. The present study excluded the use of other drug along with cannabis.

Scot *et al.*¹³ also concluded that cannabis abuse might be an important factor in aggression and offending among severely mentally ill individuals. These findings also support those of Menezes *et al.*¹⁴ and reinforce the finding of Drake¹⁵ particularly in terms of aggression and hostility. However, Zisook *et al.*¹⁶ and Cantwell¹² reported less adverse consequences suggesting less adverse impact of cannabis on symptoms. This may also explain another finding of this study. In the present study, it was found that cannabis abuse is associated with younger age at onset of illness and younger

age on admission, compared to the control group. It appears that cannabis abuse not only precipitated the onset of illness at younger age in vulnerable adults but also resulted in admission at an earlier age due to florid symptoms. These findings are also supported by those of Veen¹¹ and Cantwell.¹² High score on individual symptoms of excitement, hostility, poor impulse control, uncooperativeness, anger and difficulty in delaying gratification pointed toward a specific pattern of clinical presentation. PANSS suggests that a patient with peak rating on these individual symptoms may be regarded as one with high danger profile who (if rating is at least 4) probably requires institutional care and (if rating are least 6) perhaps would need direct individual supervision.¹⁷ In this study, the profile was accompanied by high rating on cluster score of paranoid belligerence. The risk of aggression was punctuated by paranoid projection. High score on supplemental cluster score also depicted the high aggression of patients with comorbid substance abuse. It was also found that the cannabis use aggravated the severity of positive symptoms (hallucinatory behavior, excitement, grandiosity and hostility) and symptoms of general psychopathology (poor impulse control, uncooperativeness) and supplemental items (anger and difficulty in delaying gratification) related to uncontrolled violent and impulsive behavior. This is in agreement with Caspari who found similar results in a case control study. They showed that cannabis users scored more on psychopathological syndromes "thought disturbance" and "hostility".¹⁸

The finding that two-thirds of patients (76%) met the criteria for Cannabinoid dependence syndrome means that cannabis is not used occasionally or only for recreational use. This combined with the finding that the users had significantly earlier age of onset than the non-users, is in line with the finding in the literature.^{11,12} that cannabis plays an important role in the precipitating schizophrenia at an earlier age. The finding has an important implication for the treatment of schizophrenia. Patients suffering from schizophrenia with comorbid cannabis use may pose high risk of violence and agitation. Intervention aimed at preventing cannabis use in these patients may also be helpful in preventing aggression and promote therapeutic relationship in schizophrenic patients. The association between cannabis and violence in this study does not amount to a causal relationship, given the possible effect of intervening confounding variable such as age, gender, personality and social factors. There is urgent need to conduct studies with larger sample size while controlling for age and social factors.

CONCLUSION

The evidence is more consistent with the hypotheses that cannabis use may precipitate psychosis among vulnerable individuals at a younger age and schizophrenic patients with co-morbid cannabis use exhibited more positive symptoms, violent behavior, and may be more likely to lead to dependence in persons with schizophrenia.

The explanation for this association remains unclear. Since early onset is associated with a poorer prognosis of the disorder, the relationship between cannabis use and the risk of developing an early onset type of schizophrenia is an important focus for future research.

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Schizophrenia and Comorbid self reported Cannabis Abuse: impact on course, functioning and services use

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Abstract

Objective: To examine the impact of cannabis abuse on the short term outcome in terms of relapses, use of services, compliance and functioning in patients with schizophrenia.

Methods: A case control study was conducted in the Department of Psychiatry PGMI Lady Reading Hospital, Peshawar from January 2004 to October 2004. Fifty schizophrenic patients with co-morbid misuse of cannabis were selected. Fifty schizophrenic patients who were not using cannabis were selected as control group for the study. Data regarding socio-demographic detail, relapse, compliance to drugs and service utilization was collected with the help of a Performa. Problem cannabis use in the past year and social assessment of functioning were assessed with the help of Schedule for Clinical assessment in Neuropsychiatry (SCAN) and Global Assessment of Functioning (GAF) scale respectively.

Results: Schizophrenic patients with cannabis use were younger on admission and had younger age at onset of illness. They had more number of relapses and more contacts with psychiatric services including the police. Patients with comorbid cannabis use had poor drug compliance and their relapses were preceded by poor drug compliance. Cases and control did not differ significantly on score of Global assessment of functioning.

Conclusion: Comorbidity of cannabis seems to have adverse effects on almost all domains of the illness including course, service use and drug compliance (JPMA 57:60;2007).

Introduction

Problems of substance abuse produce dramatic costs to all societies in terms of productivity, family and social disorder, and of course excessive utilization of health care.

The comorbidity of mental illness and substance abuse has been the focus of attention in recent years. Many studies have shown that the rate of substance use in subjects with severe mental illness is high; estimates of recent or current abuse for community samples range from 20% to 40%.¹ These rates are higher than those for the general population², and patients with comorbid mental illness and substance abuse disorders have been a cause for concern because even low levels of substance abuse or dependence represent a risk factor for serious complications, including suicide, poor compliance with treatment, more inpatient stays, violence, and a poor overall prognosis.³

Evidence from the United States suggests that half of all patients with schizophrenia also have a substance misuse disorder.² This comorbidity is associated with poor prognosis and heavy use of expensive inpatient care through recurrent "revolving door" admissions.⁴ The phenomenon has also been recognised in the United Kingdom. One survey observed inpatient admission rates among comorbid patients that were almost double those of patients with psychosis alone.⁵ This high prevalence, the problems of clinical management,⁶ and continued rises in the general rate of

drug misuse make comorbidity a major public health issue. Extensive manual and electronic literature search didn't reveal research pertaining to the subject however studies have shown that after bhang (a beverage containing cannabis) ingestion, patients have exhibited grandiosity, excitement, hostility, uncooperativeness, disorientation, hallucinatory behavior and unusual thought content which understandably leads to more use of mental health services.⁷

The present study is aimed to examine the relationship between cannabis abuse and its impact on the short term outcome in terms of relapses, use of services, compliance and functioning in patients from schizophrenia. We also assessed the amount, frequency and duration of cannabis use in schizophrenic patients.

Methods

This case control study was conducted at department of psychiatry PGMI Lady Reading Hospital, Peshawar from January 2004 to October 2004. All patients aged between 15-60 years with a diagnosis of schizophrenia (after discussion with a senior investigator) based on the ICD-10 research diagnostic criteria (W.H.O. 1993) and meeting the following inclusion and exclusion criteria were approached for informed consent:

Inclusion criteria

1. Patients who self reportedly used cannabis in the last year.
2. Patients aged between 15-60 years.

Exclusion criteria

1. Patients using other psychoactive drugs along with cannabis.
2. Patients who were grossly uncooperative for a meaningful complete intake interview (e.g., mentally subnormal, in acute intoxication or withdrawal, mute, with severe formal thought disorder preventing meaningful communication)

Fifty schizophrenic patients with self reported comorbid misuse of cannabis in the last year were selected as cases for study. Fifty schizophrenic patients who reportedly were not using cannabis were selected as control group. Information about the following variables was obtained by interview with the patients and their relatives, using a structured Performa: Socioeconomic details, age at onset, duration of illness and duration of untreated psychosis (defined as the period between the onset of psychotic symptoms and initiation of treatment). Relapse was defined as contact with psychiatrist over a one year period with clear evidence for decline in functioning from the previous level after improvement in treatment of index episode or exacerbation in psychotic symptoms requiring change or increase in the treatment. The number of relapses and their precipitants was recorded over the last two years.

Service use was estimated by recording contacts with primary care staff, out-patient services, general hospitals, emergency departments, police services within the past year. Numbers of psychiatric admissions and days spent in hospital over the preceding 2 years were also recorded.

Compliance was defined as the extent to which a person's behavior coincides with the medical advice given. The definition of non-compliance included premature termination of therapy and incomplete implementation of instructions. The patients were asked to rate their current and past compliance using 4-point scale that was developed for another study.⁸

Patients were asked whether they had taken their medication at least 90% of the time, between 50% and 90% of the time, between 10% and 50% of the time, or less than 10% of the time during last one month.

The information about the amount of cannabis used in the last month was obtained from the patients in terms of frequency and number of cigarettes used on a 1-6 scale.

Schizophrenic patients with comorbid cannabis misuse were interviewed using section 12 of Schedules for

Clinical Assessment in Neuropsychiatry (SCAN) (World Health Organization 1994). All the questions of interview were translated into Pushto by a bilingual expert and retranslated by another expert who was blind to the first translation.

Social functioning was assessed with the help of Global Assessment of Functioning (GAF) scale. The scale considers psychological, social and occupational functioning on a hypothetical continuum of mental health illness. It did not include impairment in functioning due to physical or environmental limitation. Rating was for the current period of admission. It consisted of range of codes from 100 to 0 in descending order.

The data was collected and analysed with the help of statistical programme SPSS, version 10. Chi-square test for categorical data and independent t-tests for continuous variable were used to assess the degree of association between different variables. The statistical significance was calculated at $P < 0.05$.

Results

Socio-Demographic

The cases and controls did not differ significantly in terms of dwelling, marital status, socioeconomic condition, living arrangement and employment except age on index admission and age at onset of illness and years of education. Comparison of cases and control's age at the time of index admission, at onset of illness and the total duration of illness are given in Table 1.

The cannabis users were younger on index admission than non users (25.82 years v 30.57 years), $p=0.001$ 95% CI of mean difference -7.54 to -1.96. The age at onset of illness was earlier in cases than controls (21.43 years v 25.39 years, $p=0.005$). The duration of illness at the time of admission was shorter for cases as compared to controls

Table 1. Comparison of age on admission, at onset of illness and duration of illness.

	Case n=50 Mean (sd)	Control n=50 Mean (sd)	Mean dif- ference	p-value	95% CI of mean difference	
Age of patient on index admission (years)	25.82 (5.06)	30.57 (8.55)	-4.75	0.001	-7.54	-1.96
Age of patient at onset of illness (years)	21.43 (4.62)	25.39 (8.47)	-3.96	0.005	-6.66	-1.25
Duration of illness (months) till index admission	52.56 (45.68)	64.25 (56.48)	-11.69	0.258	-32.08	8.71

sd: Standard deviation CI: confidence interval
Numbers in parenthesis are Standard deviations

time of admission was shorter for cases as compared to controls (52.56 months v 64.25 months) (p=0.258).

The patients in cannabis abuse group had significantly less numbers of years of education compared to control group (Table 2).

Pearson $\chi^2 = 17.260$ $df=5$ $p=0.004$.

Table 2. Comparison of education between cases and controls.

	Case	Control	Total
Uneducated	15	15	30
Primary- middle	26	19	45
Secondary- graduation	09	16	25
Total	50	50	100

Pearson chi square Value 17.260 p-value.004

Relapses

Sixty two patients had one or more relapse during their course of illness. The patients using cannabis had more relapses as compared to schizophrenic patients who were not using cannabis. (2.46 v 1.22 Mean difference 1.24 p=0.011 and 95 % CI of difference 0.21 to 2.19). When the cases were further subdivided on the basis of severity of cannabis use according to SCAN algorithm (see below) it was found that the two groups differed significantly in the number of relapses in the last 2 years (1.00 vs 2.95 mean difference of -1.95 p=0.002 & 95% CI of mean difference - 3.16 to -0.73).

Out of 38 patients, who had no relapses, 15 patients 39.5% (8 cases and 7 controls) had their first episode of illness on index admission while 23 patients 60.5% (10 cases and 13 controls) did not show any improvement in their illness and had continuous course.

Among those patients who had a continuous course the total duration of illness was shorter for cases as compared to controls (53.80 months vs 77.77 months) (p=0.274).

All schizophrenic patients irrespective of cannabis use started their treatment approximately within one year of onset of illness (12.86 months for cases 11.86 months for control). The mean period of untreated psychosis was much longer in this population of continuing illness, with cases having received their first psychiatric treatment after 31.90 months as compared to 15.23 for controls (p=0.141).

Out of 62 patients who relapsed in the past, 32 cases and 30 controls had their past relapses preceded by poor compliance. Cases had a larger number of past relapses preceded by poor compliance as compared to controls (2.78 v 1.40 p=0.02 mean difference=1.38 95% CI of 0.5-2.26). Out of 32 cases, who relapsed, 27 (84.4%) patients have

current episode preceded by poor compliance as opposed to 21 controls out of 30 (70%). Pearson's $\chi^2=62.00$ $p=.000$

Service Use

Cases were more likely to be admitted to hospitals (number of admission 1.04 vs 0.52 p=0.05). They also spent more days in hospitals (19.7 v 7.22 p=0.047). Cases had greater number of contacts with police (1.70 v 0.20 p=0.000).

Controls made more contacts with private psychiatric clinics than cases (7.00 v 3.96 p=0.002) Cases were no more likely than controls to made use of emergency services and Out door patient department. Table 3.

Table 3. Comparison of services use (Number of admission and days spent in hospital, visits to private clinics and contact with police).

	Case	Control	Mean difference	p-value	95% CI of mean difference	
	Mean (sd)	Mean (sd)				
Number of Admission In Hospital	1.04 (1.63)	0.52 (0.86)	0.48	0.05	.03	1.04
Number of days spent in Hosp.	19.10 (36.91)	7.22 (19.37)	11.88	0.047	0.18	23.58
Number of visits to Private Psych clinics	3.96 (6.07)	7.00 (6.81)	-3.81	0.02	-5.60	-0.48
Number of contact with police.	1.70 (1.89)	0.20 (0.40)	1.50	0.001	0.96	2.04

sd: Standard deviation CI: confidence interval Numbers in parenthesis are Standard deviations

Table 4. Comparison of drug adherence in last month between cases and control.

	Drug adherence in the last month				Total
	90 % of the time	50-90 % of the time	10-50 % of the time	less than 10 % of the time	
Case % (n)	19.5%(8)	7.3%(3)	19.5%(8)	53.7%(22)	100%(41)
Control % (n)	41.9%(18)	9.3%(4)	7.0%(3)	41.9%(18)	100%(43)
Total % (n)	31.0%(26)	8.3%(7)	13.1%(11)	47.6%(40)	100%(84)

Pearson's $\chi^2 = 6.618$ $df=3$ $p=0.085$

For drug adherence in the last month, data was analysed for 84 patients (41 cases and 43 controls). Data for 16 patients was missing as they were either drug naïve or had first episode of illness on their index admission. The compliance with medication was significantly poorer in patients using cannabis than patients who were not using cannabis (Table 4).

Global Assessment of functioning: Cases and controls did not differ significantly on score of Global assessment of functioning. (28.70 v 27.08).

Discussion

Socio-demographic

In this study it was found that cases were of younger age on index admission and had younger age at onset of illness. These findings supported the finding of Veen et al⁹, Cantwell et al¹⁰ and Bersani et al.¹¹ This could be a chance association and with the understanding that cannabis has no influence on risk or age at onset and that younger patients are more likely to use this substance before the first psychotic episode. A second possibility is that cannabis hastens the onset of psychosis in subjects who are predisposed to develop the illness.

Third, it is possible that cannabis makes manifest schizophrenia in young subjects who are genetically at risk for developing the disorder.

This study has shown that cases had less number of education years as compared to controls. A number of prospective longitudinal studies have indicated that early cannabis use may significantly increase risks of subsequent poor school performance and, in particular, early school leaving¹² possible underlying mechanism proposed for such association can be "amotivational syndrome" or that cannabis use causes cognitive impairments or the link arises because of the social context in which cannabis is used. However there appears to be little empirical support for these hypotheses.

Relapses

The study also found that users have more relapses since their illness started. This finding is consistent with that of Gupta et al.¹³ Johns¹⁴; Tomassan and Vaglum,¹⁵ that cannabis use generally provoke relapses. This finding is very significant keeping in mind that cannabis users also had younger age at admission. They probably are more likely to relapse in future.

It is a well known finding in the literature that the prognosis in schizophrenia tends to become poor with each relapse. The increased relapses in patient with dual diagnosis cannot be wholly ascribed to cannabis use only as it might be mediated through poor or non compliance.

Cases' relapses were significantly more likely to be preceded by poor drug compliance than controls. Although this does not prove any causal link, the association points towards the possibility that increased number of relapses might be mediated through non compliance rather than cannabis use. Another possibility is that cases were of younger age and that being young and male are also known as risk factors for noncompliance.¹⁶

It was seen that 38 patients did not have any relapse in their course of illness. This suggests that these patients

either did not have any improvement in their symptoms or presented in early course of their illness.

Services use

Cases were more likely to be admitted to hospitals and for long periods as compared to controls. Linszen¹⁷, Menezes⁵ and Caspari¹⁸ also had similar results. Frequent admissions were more likely due to relapses. In this study cases made more contacts with police. Cantwell also found increase service use (contact with police, psychiatrist).¹⁰ This reflected on the greater reporting of crimes against the participants due to violent behavior, and police contact for other reasons, (possession, wandering, handing over to police by family members because of behavioral disturbance). Increase contact with private psychiatric clinics by the schizophrenic without comorbid cannabis abuse is understandable because of their uncomplicated presentation.

Global Assessment of functioning

Schizophrenic patients with comorbid substance abuse were no more likely to show any difference in assessment of social functioning as compared to those without it, though both groups showed decline on the scale 28.70 v 27.08 $p=0.566$. This lack of difference in the two groups seems to be due to the intrinsic quality of the scale itself, as the measure declines for users because of their violent behaviour and for non users by decreasing the ability to maintain their personal hygiene or their impairment in communication.

Limitations of the study

This study was conducted in a hospital based population with a small sample size. Both groups were not controlled for age and patients' allocation to the groups was not randomized. Further studies are needed with validated instruments and larger and representative sample while controlling for age.

Conclusion

Comorbidity of cannabis seems to have adverse effects on almost all domains of the illness including course, service use and drug compliance.

The youngest cannabis users are most at risk perhaps because, their cannabis use becomes longstanding. This should encourage policy and law makers to concentrate their effort on delaying the onset of cannabis use. At the same time, further research is needed on the long-term impact of frequent cannabis use that begins at an early age and on the possible mechanisms by which cannabis use can lead to psychosis.

During assessment of schizophrenia cannabis abuse needs to be evaluated. Patients and their relatives need to be educated about the impact of cannabis and its adverse

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Review article

Relationship between gross domestic product and duration of untreated psychosis in low- and middle-income countries

Matthew Large, Saeed Farooq, Olav Nielssen and Tim Slade

Background

The duration of untreated psychosis (DUP), the period between the first onset of psychotic symptoms and treatment, has an important influence on the outcome of schizophrenia.

Aims

To compare the published studies of DUP in low- and middle-income (LAMI) countries with the DUP of high-income countries, and examine a possible association between DUP and per capita income.

Method

We used six search strategies to locate studies of the DUP from LAMI countries published between January 1975 and January 2008. We then examined the relationship between DUP and measures of economic activity, which was assessed using the LAMI classification of

countries and gross domestic product (GDP) purchasing power parity.

Results

The average mean DUP in studies from LAMI countries was 125.0 weeks compared with 63.4 weeks in studies from high-income countries ($P=0.012$). Within the studies from LAMI countries, mean DUP fell by 6 weeks for every \$1000 of GDP purchasing power parity.

Conclusions

There appears to be an inverse relationship between income and DUP in LAMI countries. The cost of treatment is an impediment to care and subsidised antipsychotic medication would improve the access to treatment and the outcome of psychotic illness in LAMI countries.

Declaration of interest

None.

The 2001 World Health Report estimated that only a quarter of all patients with active psychosis were receiving treatment.¹ An area of particular concern is the delay in initiating treatment during the critical first episode of psychosis, which is measured as the duration of untreated psychosis (DUP). Long DUP in first-episode psychosis is associated with worse short- and long-term prognosis,^{2,3} an increased risk of suicidal behaviour^{4–6} and possibly serious violence.^{7–10}

Increasing awareness of the adverse consequences of prolonged DUP in high-income countries has led to calls for a public health approach to early psychosis¹¹ and the introduction of early intervention services. The effect of DUP on the prognosis of psychotic illness in low- and middle-income (LAMI) countries is not known, as there are very few relevant studies. However, long DUP may have more severe consequences in lower-income countries because people who are mentally ill may have increased difficulty obtaining food, shelter and medical care.^{12,13}

The aim of this study was to conduct a systematic review of reports of DUP in LAMI and high-income countries. We used the World Bank classification of 'low-income', 'lower-middle-income' and 'upper-middle-income' economies, referred to together as LAMI countries in this paper, and 'high-income' economies (referred to as countries here).¹⁴ We also examined the relationship between DUP and the gross domestic product (GDP) purchasing power parity.¹⁵

The *a priori* hypotheses were that (a) DUP would be longer in LAMI countries than high-income countries and (b) DUP would be inversely proportional to per capita income.

Method**Search strategy**

In view of the difficulty locating studies of DUP from LAMI countries we employed six search strategies. First, we searched the electronic databases Medline, EMBASE, PsychLit and

PsycINFO from January 1975 to January 2007 using the search terms 'duration of untreated psychosis', 'delay in treatment', 'treatment delay' or 'initiation of treatment' cross-referenced with the terms 'psychosis', 'psychotic disorders', 'schizophrenia', 'schizo-affective' or 'schizophreniform' and 'first-episode psychosis'. This yielded 312 publications about DUP from high-income countries and 8 studies from LAMI countries.

Second, we electronically searched the text of six leading psychiatric journals (*Schizophrenia Research*, *Schizophrenia Bulletin*, *British Journal of Psychiatry*, *Acta Psychiatrica Scandinavica*, *Journal of Clinical Psychiatry* and *International Clinical Psychopharmacology*) that were identified as having published the abstracts of international schizophrenia conference proceedings. Two further studies were located from full text searches using the terms 'duration of untreated psychosis' or 'DUP' on the journals' websites.

Third, we examined the first 40 results when combining the names of 152 LAMI countries with 'duration untreated psychosis' using the search engine Google, which located one further DUP study from a LAMI country.

Fourth, 12 studies from LAMI regions were found using PubMed (from January 1975 to January 2008) by sequentially entering the names of 152 LAMI countries and 'schizophrenia', and examining all the abstracts. Publications on movement disorder, gender differences or the epidemiology of schizophrenia were examined in full text.

No further studies were found when hand-searching the references of DUP studies or by contacting 12 authors of recent publications (about aspects of first-episode psychosis in LAMI countries) for unpublished DUP data.

Finally, no additional articles were found by an examination of all the abstracts in electronic databases that specialise in journals from LAMI countries that are not indexed on Medline. The terms 'schizophrenia' and 'psychosis' were used to search ExtraMED from 1992 to 2000 and LILACS from 1982 to 2008.

All the articles identified by Medline, EMBASE, PsychLit and PsycINFO searches in addition to the articles found from the searches of the six journals were examined in full text by M.L. and O.N. Thirteen differences in the selection of articles were found to be due to instances of the selection of different papers from multiple publications about the same sample and these were resolved by a joint examination of the publications. These searches were cross-checked during the subsequent searches of PubMed and Google by M.L. on two further occasions 3 months apart. One additional article (from a high-income country) was found in the second set of searches (Fig. 1).

Inclusion and exclusion criteria

We included studies with non-overlapping samples of DUP that reported mean DUP or median DUP, or the mean age at onset of psychotic symptoms and the mean age at presentation to one or more decimal points from which mean DUP could be calculated. We excluded samples that included individuals from both LAMI and high-income countries.

No additional assessment of the quality of the data was attempted if the paper met the inclusion criteria, although all

but two of the studies from LAMI countries used a recognised diagnostic system.

Forty-four papers reported more than one sample of DUP. All of the samples from different regions or different time frames were used (6 papers), but if a sample was reported in two publications it was only included once. The other reasons for papers reporting more than one sample was to compare participants by gender (17 papers) or diagnosis (13 papers), or more rarely by characteristics such as drug misuse, particular symptom clusters, or the number of subsequent relapses. Papers that dichotomised individuals simply on the basis of the DUP were included as a single sample.

The following data were collected from all of the samples:

- country of origin of participants
- number of people in the sample
- the endpoint of DUP (initiation of treatment, contact with mental health services or contact with researchers)
- mean age at contact or treatment, or mean age at onset of psychosis
- mean DUP and/or median DUP in weeks

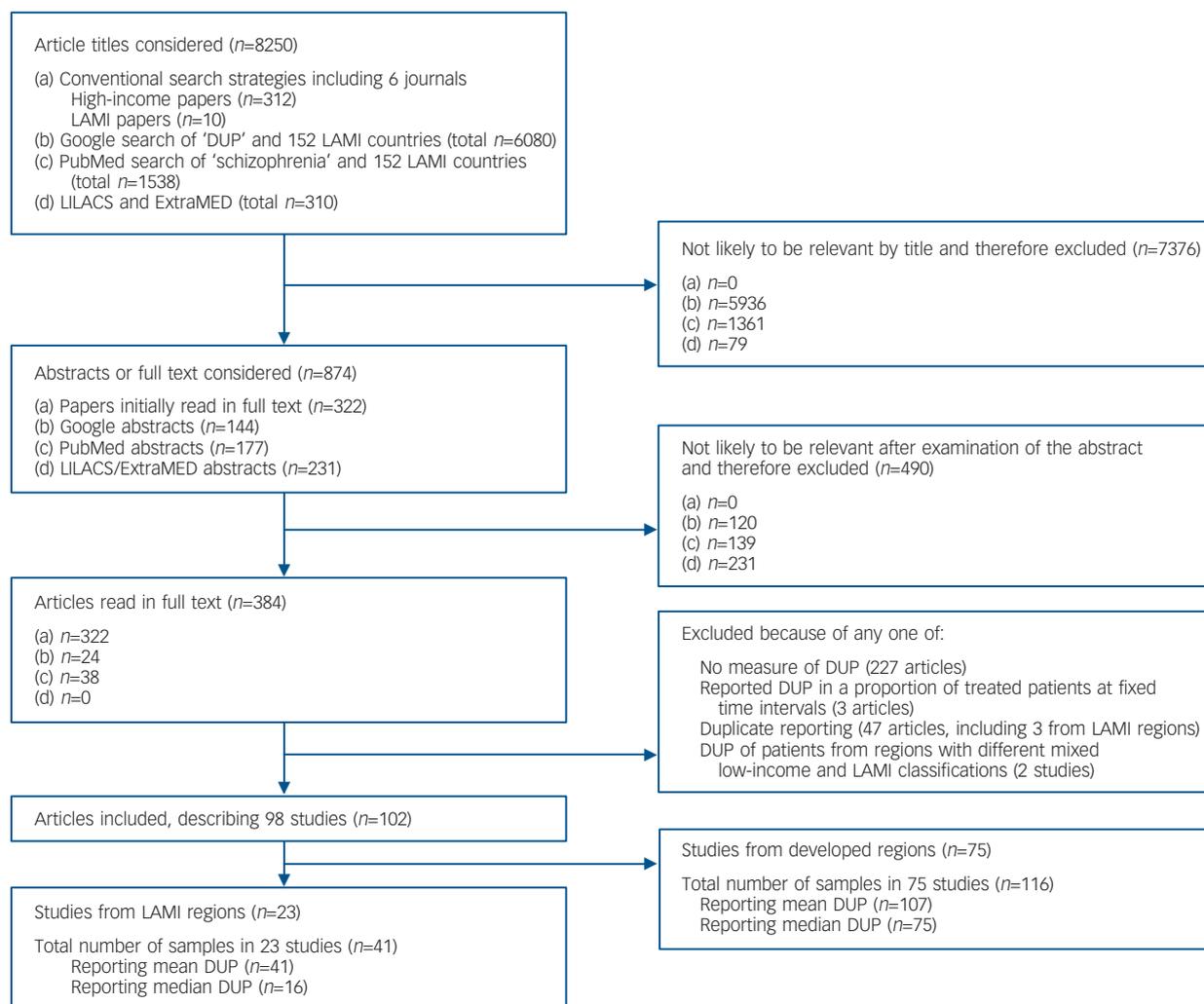


Fig. 1 Flow chart of searches for DUP studies from LAMI and high-income regions.

DUP, duration of untreated psychosis; LAMI, low- and middle-income. (a) Conventional search strategies including of Medline, EMBASE, PsychLit and PsycINFO from January 1975 to January 2007, and the text of *Schizophrenia Research*, *Schizophrenia Bulletin*, *British Journal of Psychiatry* supplements, *Acta Psychiatrica Scandinavica*, *Journal of Clinical Psychiatry* and *International Clinical Psychopharmacology*; (b) Google searches of the first 40 results found after sequentially entering all the names of 152 LAMI countries combined with 'duration untreated psychosis'; (c) PubMed search from January 1975 to January 2008 by sequentially entering the names of 152 LAMI countries and 'schizophrenia', and examining all the abstracts. Publications on movement disorder, gender differences and the epidemiology of schizophrenia were examined in full text; (d) LILACS was searched from 1982 to 2008 and ExtraMED was searched from 1992 to 2000. Hand-searches were performed but found no additional studies for high-income or LAMI regions.

- (f) inclusion of patients with affective psychosis and the proportion with schizophrenia-related psychosis
- (g) proportion of participants with a diagnosis of schizophrenia or schizophreniform psychosis
- (h) proportion of male participants
- (i) year of publication.

Data extraction

The data from studies from LAMI countries were independently extracted by M.L. and S.F. and from high-income countries by M.L. and O.N. Three differences in the DUP data collection in both the LAMI and high-income samples were unambiguously resolved by further examination. A check of the reliability of the rating of the inclusion of patients with schizophrenia-related psychosis was performed and was found to have a kappa of 1, as no differences were found. A final masked check of the electronic record of all the data points was conducted by M.L. 6 months after the initial data extraction. This found five minor errors in age at onset and gender that were probably owing to errors in transcription.

Definitions of psychotic illness

All but five studies used a recognised diagnostic system but there were differences in the way psychotic disorders were classified and reported. Some publications only reported the numbers of patients with the diagnoses schizophrenia, bipolar disorder and psychotic depression, whereas other studies reported the proportion of people with other schizophrenia-related psychoses such as delusional disorder and psychosis not otherwise specified. All the studies stated whether they included patients with affective psychosis, but the proportion of people who were diagnosed with schizophrenia was not available for every sample. As patients with affective psychosis are known to have a shorter DUP than those with schizophrenia-related psychosis (defined as any functional psychosis other than bipolar disorder and psychotic depression) the characteristics of samples of patients with schizophrenia-related psychosis was also analysed. Schizoaffective disorder was included in our definition of schizophrenia-related psychosis.

Definition of duration of untreated psychosis

Duration of untreated psychosis has been defined as the period between the onset of definite psychotic symptoms and the beginning of adequate treatment.¹⁶ We included all the definitions of what is considered to be the end of DUP, including the initiation of treatment, the end of adequate treatment and contact with mental health services. Contact with researchers was also accepted as an endpoint of DUP in studies from LAMI countries as there were so few studies. The inclusion of individuals who only had contact with researchers rather than mental health services would be likely to increase the estimates of mean DUP for LAMI countries given the greater likelihood of undetected DUP being prolonged. Conversely, inclusion of individuals with affective psychosis would be expected to decrease mean DUP. In an effort to counter these potential confounders, we examined a subset of studies of patients in LAMI countries with schizophrenia-related psychoses, who were recruited as a result of contact with mental health services and had at least some treatment, to allow a comparison with similar studies conducted in high-income countries.

Income data

The LAMI country classification is based on per capita GDP in international dollars. However, comparing income between countries in terms of official exchange rates may not reflect the local cost of goods and services. Therefore we also examined the relationship between DUP and GDP purchasing power parity.

Statistical methods

Consideration was given to the use of meta-regression in order to take the degree of variability of the studies into account. However, meta-analysis requires a measure of the variability of the mean such as the standard deviation. After emailing the authors of studies from LAMI countries who did not report the standard deviation of the mean DUP, only 32 of the 41 data points had a standard deviation. Moreover, the average mean DUP of studies from LAMI regions that did not report the standard deviation was 88 weeks and was significantly shorter than the average mean of 138 weeks of studies for which a standard deviation was available. Hence, the exclusion of these studies would have biased our study in favour of finding a prolonged DUP in studies from LAMI countries. Instead, the samples were weighted for regression analysis by the number of participants, as larger samples would be expected to have a more accurate figure for mean DUP.

The degree of variation between mean DUP values was also considered, as mean and median DUP values were significantly skewed. In order to avoid statistical findings that were unduly influenced by samples with a very long DUP, the DUP values were \log_{10} transformed for both the univariate comparisons of the DUP in LAMI and high-income regions, and a multiple linear regression analysis of factors associated with the mean DUP. The distributions of mean DUP values were not significantly skewed after \log_{10} transformation.

Chi-squared tests were used to compare the proportions of male participants, the number of participants with a schizophrenia-related psychosis and the number of participants diagnosed with schizophrenia in LAMI *v.* high-income groups. The age at onset was calculated by subtracting DUP from age at presentation and was used in preference to age at presentation because it is independent of DUP. Ages were compared using a two-tailed Student's *t*-test.

A multiple linear regression model was used to examine the associations between the dependent variable of \log_{10} DUP and high-income *v.* LAMI status and the covariables of age, gender and the inclusion of patients diagnosed with affective psychosis.

A linear regression model using untransformed data was used to examine the relationship between DUP and GDP purchasing power parity within LAMI regions after a scattergram showed an apparently linear relationship between these two variables. Four studies of patients who came into contact with researchers but did not necessarily receive treatment were excluded from this analysis because their DUP was much longer (mean DUP > 5 years) than in other samples. The remaining samples were not significantly skewed.

All statistical tests were two-tailed and results were regarded as statistically significant at or below the 5% probability level. The statistical analysis was performed using SPSS for Windows, version 15.0.

Results

Results of the searches

We examined 384 papers in full text and found 134 papers that included a measure of DUP from high-income countries and 26 from LAMI countries (Fig. 1). Forty-seven papers from high-income

countries were excluded as the samples appeared to overlap with those of other publications. We excluded two studies from high-income countries that were performed in the 1960s, four other studies of patients who became unwell prior to the advent of antipsychotic medication, three studies that reported DUP in terms of fixed time intervals and two studies reporting single samples with a combination of individuals from LAMI and high-income countries.

There were 98 studies that met the inclusion criteria, of which 23 (26 papers) were from LAMI countries^{17–42} (see online Table DS1) and 75 were from high-income countries (Table DS2). The earliest study from a LAMI country was published in 1995. The 23 studies from LAMI countries included 24 samples in which DUP was reported directly and 17 samples in which mean DUP could be calculated; hence, in total there were 41 samples of DUP for patients from LAMI countries. All but 3 studies were published in full text in peer-reviewed journals. We contacted 13 authors to clarify some data points and 2 authors provided some additional information about their research that had been published in abstract form.^{21,38} Twenty-seven samples from LAMI countries reported the interval between the onset of psychosis and contact with services in patients with schizophrenia-related psychosis.

All the studies from high-income countries appeared in full text in peer-reviewed journals and all but eight studies were published after 1990. Mean DUP was reported directly for 88 samples, and in a further 19 samples mean DUP could be calculated by subtracting the mean age at onset from the mean age at presentation.

Results of the study

The weighted mean, average mean DUP and the median mean DUP were significantly longer in studies from LAMI countries

than in studies from high-income countries. The average median DUP was longer in studies from LAMI countries than from high-income countries but the apparently large difference did not reach statistical significance, probably because of the small number of samples from LAMI regions and because of relatively large within-group variability in median DUP (Table 1).

The longer average mean DUP in studies from LAMI countries was a result of a prolonged DUP in low-income and lower-middle-income countries, as the average mean DUP in the studies from upper-middle-income countries was shorter than that of high-income countries (Table 1). Mean age at onset and mean age at presentation were higher in samples from LAMI countries than high-income countries. Studies from LAMI countries had fewer male participants but slightly more participants diagnosed with a schizophrenia-related psychosis. In the LAMI group, more patients who were diagnosed with a schizophrenia-related psychosis were considered to have a diagnosis of schizophrenia or schizophreniform disorder.

We examined a subset of studies of individuals with schizophrenia-related psychosis who had received some treatment. The mean DUP in the samples from LAMI countries (85.2 weeks, s.d.=38.3, 95% CI 70.0–100.3, $n=27$) was significantly longer than the mean DUP in samples from high-income countries (70.5 weeks, s.d.=55.3, 95% CI 57.8–83.1, $n=76$, unpaired t -test. LAMI *v.* high-income d.f.=101, $t=2.05$, two-tailed $P=0.04$, using \log_{10} transformed mean DUP values). This confirmed that the difference between the mean DUP of LAMI countries and high-income countries was not due to the proportion of participants with affective psychoses in high-income countries or the proportion of participants who did not receive treatment in LAMI countries.

Table 1 Duration of untreated psychosis, diagnostic and demographic variables in the LAMI groups

	LAMI subgroups			LAMI	High-income	LAMI <i>v.</i> high-income		
	Low-income	Lower-middle income	Upper-middle income			d.f.	Statistic	<i>P</i>
Samples, <i>n</i>	14	17	10	41	116			
Samples with mean DUP, <i>n</i>	14	17	10	41	107			
Samples with median DUP, <i>n</i>	2	8	6	16	75			
Samples with patients with schizophrenia-related psychosis, <i>n</i>	13	13	6	32	81			
Patients, <i>n</i>	981	1731	638	3350	10459			
Average mean DUP weighted for sample size, weeks	171.1	173.7	50.3	146.9	61.5			
Average of mean DUP, ^a weeks (median, s.d., 95% CI)	160.2 (108.4, 153.6, 71.4–248.8)	141.3 (64.8, 230.9, 22.6–260.0)	47.8 (48.3, 14.6, 37.3–58.3)	125.0 (70.8, 176.3, 69.2–180.5)	63.4 (52.0, 53.3, 53.2–73.6)	146	$t=2.56$	0.012
Average of median DUP, ^a weeks (median, s.d., 95% CI)	132.0 (132, 181, 0–1758)	17.4 (10, 19.0, 1.5–33.3)	21.2 (21.3, 6.9, 14.0–28.5)	33.2 (15.5, 62.1, 0–66.3)	18.6 (13.1, 15.0, 15.1–22.0)	89	$t=0.77$	0.44
Age at onset of psychosis: mean (s.d., 95% CI)	25.7 (4.2, 23.3–28.1)	28.2 (7.1, 24.6–32.0)	27.3 (1.8, 26.0–28.6)	27.3 (5.2, 25.5–28.8)	24.9 (3.9, 24.2–25.7)	155	$t=2.83$	0.005
Age at presentation: mean (s.d., 95% CI)	28.8 (5.8, 25.4–32.1)	30.8 (6.6, 27.4–34.2)	28.2 (1.8, 26.9–29.5)	29.5 (5.5, 27.7–31.2)	26.1 (4.1, 25.4–26.9)	155	$t=4.08$	<0.001
Male patients, <i>n</i> (% in income group)	574 (58.5)	901 (52.0)	355 (55.6)	1830 (54.6)	6409 (61.3)	1	$\chi^2=46.6$	<0.001
Patients with schizophrenia-related psychosis, ^b <i>n</i> (% in income group)	936 (94.4)	1587 (91.7)	607 (95.1)	3130 (93.4)	9245 (88.4)	1	$\chi^2=69.3$	<0.001
Patients diagnosed with schizophrenia, ^b <i>n</i> (% in income group)	936 (94.4)	1528 (88.3)	561 (87.9)	3025 (90.3)	7473 (71.4)	1	$\chi^2=494.5$	<0.001

DUP, duration of untreated psychosis; LAMI, low- and middle-income.

a. Mean and median DUP values were \log_{10} transformed for t -tests but untransformed means and s.d. are tabulated.

b. Contains some estimates as the proportion of patients with schizophrenia or schizophrenia-related psychosis was not always reported. If a value for either schizophrenia-related psychosis or schizophrenia was not reported, the other was used; if both values were missing (5 samples) the proportion of patients with schizophrenia in income group was used.

The univariate finding of a longer mean DUP was confirmed with a multiple linear regression (using \log_{10} mean DUP as the dependent variable and weighted for the number of people in each sample) that found that the association between longer DUP and samples from LAMI countries was independent of inclusion of samples with patients whose diagnosis was affective psychosis. The proportion of males in the samples and age at onset were not significantly associated with \log_{10} mean DUP (model summary: $r=0.462$, $r^2=0.214$, standard error of the estimate=2.92) (Table DS3).

Relationship between gross domestic product and mean duration of untreated psychosis

We examined the hypothesised relationship between GDP purchasing power parity and mean DUP in LAMI countries using linear regression. For every \$1000 of additional per capita GDP purchasing power parity, mean DUP fell by 6 weeks (model summary: $r=0.497$, $r^2=0.247$, standard error of the estimate=296.3) (Table DS4). An analysis of the mean DUP in the samples of patients with schizophrenia-related psychosis suggested a fall of 9 weeks of DUP per \$1000 of per capita GDP purchasing power parity (model summary: $r=0.644$, $r^2=0.415$, standard error of the estimate=268.1) (Table DS5). No significant relationship between median DUP and GDP was found, possibly because so few studies from low-income and lower-middle-income countries reported a figure for median DUP ($n=10$; Table 1).

A surprising finding was that mean DUP rose by 3 weeks per \$1000 of GDP purchasing power parity in studies from high-income countries ($r=0.243$, $r^2=0.059$, d.f.=106, GDP purchasing power parity coefficients: $B=0.003$, s.e.=0.001, $t=2.567$, $P=0.012$). This rise was associated with studies from regions with mental health laws that required the patient to be assessed as dangerous before they could receive involuntary treatment.⁴³ Mean DUP was not associated with GDP purchasing power parity in high-income countries when the presence of this form of mental health law was included in the model.

Discussion

A limitation of this study was that despite a comprehensive search, we were able to obtain DUP data for only 18 of 152 LAMI countries. Lack of data is likely to be a limitation in any study of mental healthcare in LAMI countries⁴⁴ and probably reflects the poor state of mental health services. Health administrators in many countries may not even be aware of the extent of the unmet need for treatment of psychosis.

Long DUP in LAMI countries may be associated with low income

The hypothesis that DUP is longer in LAMI countries was confirmed. We also found a linear relationship between GDP purchasing power parity and DUP in LAMI countries and this raises the possibility of a causal relationship between low income and treatment delay. However, this finding is qualified as the DUP in the small number of studies from upper-middle-income countries was shorter than the average mean DUP of high-income countries.

Long DUP in high-income countries is usually attributed to lack of insight on the part of the patient, the gradual onset of psychosis in some patients and the families' lack of understanding of the need for treatment. The reasons for longer DUP in LAMI countries warrants further investigation, but is likely to include the lack of services in many areas as well as the cost of treatment.

The cost of treatment is frequently reported as a barrier to care in low-income^{21,36,37,39} and lower-middle-income^{40,45,46} countries. For example, in a region of Nigeria the only available anti-psychotic was a low dose of chlorpromazine for a few weeks per year provided by a charity.⁴⁵ In India, the direct cost of treating schizophrenia is a quarter of the average family income in dollars.⁴⁶ Even if the patient's family were able to purchase some antipsychotic medication it could be at the expense of other forms of essential medical care or even food. Hence, it is not surprising that mean DUP declined with even modest increases in income.

Better prognosis in LAMI countries with long DUP?

The relationship of DUP to outcome in LAMI countries has not been extensively investigated. Although it is widely believed that the prognosis of schizophrenia is better in LAMI countries,⁴⁷ we found a number of studies reporting a worse outcome in these regions. For example, both treated and untreated patients from Morocco were less likely to be employed than a similar sample from the USA,⁴⁸ and in rural China where very few patients received adequate treatment, untreated patients were found to have marked social and occupational disability and a fourfold increase in mortality.^{36,37,49} Another study from the Indonesian Island of Bali reported an association between long DUP and increased mortality in the decade after contact with services.²⁸ In Bali and in rural China the excess mortality was not from suicide, but from a lack of physical care.^{28,49} Our finding of a very long DUP in low-income and lower-middle-income countries, and other studies that found large numbers of patients who had never received treatment, raises the possibility that a subset of patients with long DUP in some outcome studies either died or were lost to follow-up for other reasons.

Subsidised psychiatric treatment may shorten DUP

This study has highlighted the initial delay in receiving treatment in LAMI countries. The overall treatment gap may be greater, as there are studies from LAMI countries that describe large numbers of patients who never receive any treatment.^{32,36,37,45}

Worldwide, schizophrenia is the eighth largest cause of disability and the illness may shorten life expectancy by 10 years.⁵⁰ The direct effects of schizophrenia are comparable to those of many infectious and chronic physical illnesses that receive more funding for both treatment and research. Cost-effective treatment is now available for schizophrenia. A public health initiative to subsidise antipsychotic medication for the critical first 2 years of psychotic illness could greatly improve outcome for psychotic illness worldwide.⁵¹ Combining subsidised mental health services with other forms of primary healthcare, as reported from Zambia, a low-income country where the DUP was comparatively short,³¹ could also significantly reduce the delay in treatment and improve the prognosis of mental illness in poorer countries.

Patients with psychosis in low-income and lower-middle-income countries may be among the most disadvantaged people on earth and providing them with access to basic treatment would be a cost-effective public health measure.

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psychiatry in pictures

Untitled pictures (date unknown) by Denis Reed (1917–1979)



Denis Reed was a patient in Glenside Psychiatric Hospital in Bristol during the 1950s and 1960s. These two images portray everyday life in the hospital from the patients' perspective. A sensitive and skilled artist, Reed evokes the atmosphere and activities of the institution. His sketchy, transparent style is reminiscent of Toulouse-Lautrec.

Glenside was originally the Bristol Lunatic Asylum, which had opened in 1861 to take patients from the lunatic wards of St Peter's Hospital. By 1910 it was enlarged to accommodate the increasing numbers of patients being admitted. During the First World War it became a military hospital and provided 1460 beds for war casualties. Sir Stanley Spencer drew on his experience as an orderly there to create the paintings that now adorn the Sandham Memorial Chapel. Although a second mental hospital, Barrow Hospital, was opened in 1939, Bristol Mental Hospital became overcrowded during the Second World War and remained so in post-War years, with a high proportion of long-stay patients. In 1959, following the Mental Health Act, Bristol Mental Hospital was renamed Glenside Hospital. Glenside Museum is situated in the former Chapel at Glenside. It was set up by Dr Donal Early. Together with the collection of paintings by Denis Reed, it houses a permanent exhibition of hospital life between 1940 and 1980. For further information see www.glensidemuseum.org.uk

Researched by Christopher Ramsey & Peter Carpenter, Bristol.

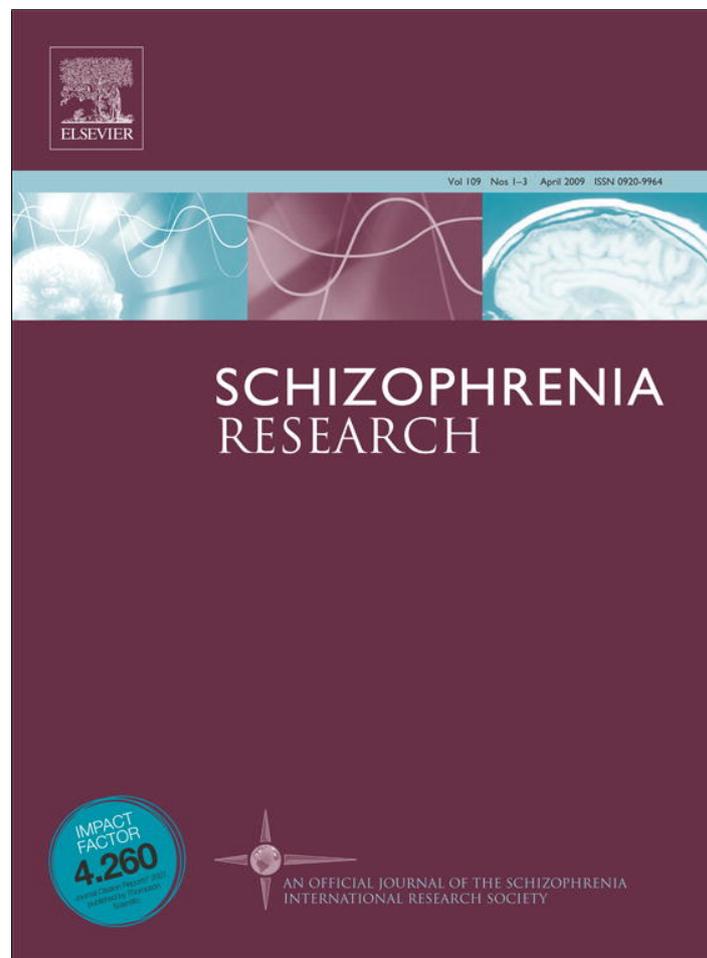
Edited by Allan Beveridge.

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The relationship between the duration of untreated psychosis and outcome in low-and-middle income countries: A systematic review and meta analysis

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ABSTRACT

Background: The duration of untreated psychosis (DUP) is defined as the period between the onset of symptoms of psychosis and the start of antipsychotic treatment. Delay in the initiation of treatment, resulting in a long DUP, is associated with a poor prognosis in high-income (HI) countries. It is not known if longer DUP is associated with poor outcomes in Low and Middle Income (LAMI) countries, where schizophrenia might have a more benign course.

Methods: A systematic review and meta-analysis of studies from LAMI countries that reported an association between DUP and response to treatment, measures of disability and mortality. The association between DUP, symptoms and cognitive function at presentation were also examined.

Findings: Meta analysis of five studies that reported the association between DUP and the reduction in total symptoms scores after treatment found a significant negative correlation between DUP and improvement in symptoms after treatment ($r = -0.290$, 95% CI = -0.483 to -0.069 , $z = -2.559$, $p < 0.011$). Prolonged DUP was also associated with increased levels of disability. One study reported that longer DUP was associated with a higher mortality in the following decade.

Conclusions: Delay in the initial initiation of treatment for psychosis is associated with a poorer response to treatment and increased levels of disability in LAMI countries.

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1. Introduction

Several large and well conducted studies have reported that schizophrenia has a better prognosis in Low and Middle Income (LAMI) countries (World Health Organization, 1973; World Health Organization, 1979; Jablensky et al., 1992; Hopper et al., 2007). However the hypothesis that psychotic disorders have a more benign course in low and middle income (LAMI) countries is not universally accepted, in part because lower income countries are more likely to have poorly developed health care services, endemic infectious disease, high rates of malnutrition and a shorter life expectancy. In a recent review of longitudinal

studies of outcome, Cohen et al. (2008) concluded that it was time to re-examine the presumed wisdom that schizophrenia carried a better prognosis in low- and middle-income countries.

Cohen et al. (2008) suggested that methodological issues, including the proportion of patients lost to follow up, might have biased some studies of the outcome of psychosis in the direction of improved prognosis. Cohen et al. (2008) noted that increased mortality from untreated medical illness and malnutrition are reported in studies of psychosis from LAMI countries (for example Dube et al., 1984; Mojtabai et al., 2001). There are two more recent studies reporting an association between a lack of psychiatric treatment and increased mortality. Kurihara et al. (2006) reported that a prolonged duration of untreated psychosis (DUP) was associated with a seven fold increase in mortality for patients with schizophrenia on the

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Indonesian island of Bali and Ran et al. (2007) found that a long DUP and the lack of continued treatment were associated with increased mortality and a poor prognosis in a large prospective study from rural China.

The ten-country study of schizophrenia reported that about 80% of patients in both the developed and developing countries had been unwell for less than six months at the time of enrollment to the study (Jablensky et al., 1992). However, recent systematic review of relationship between DUP and gross domestic product purchasing power parity (GDP ppp) found

that on average the DUP of LAMI countries (125 weeks) was twice as long as the DUP in high-income countries (63 weeks, $p = 0.012$, Large et al., 2008). Moreover within the LAMI group of countries, DUP declined by six weeks for every additional \$1000 per capita GDP ppp.

Hence the hypothesis that low per capita income is associated with worse outcome in psychotic illness stems from the finding that DUP is inversely proportional to GDP ppp and long DUP might be associated with poorer outcomes possibly including increased mortality in LAMI countries (Large et al., 2008).

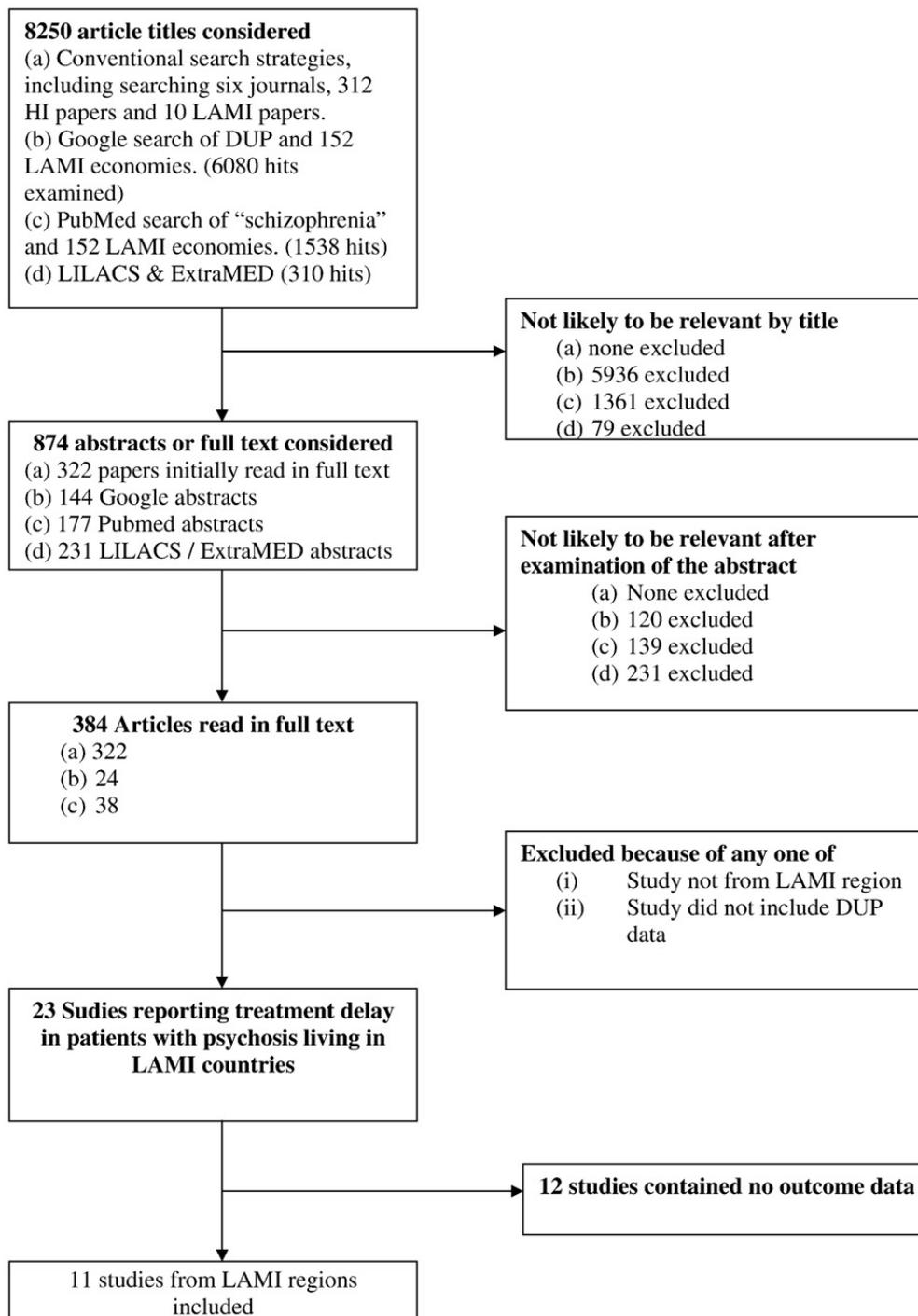


Fig. 1. Flow chart of searches for DUP studies from LAMI and HI regions.

An association between DUP and outcome has been extensively studied in high income (HI) countries. Two recent systematic reviews concluded that there was a consistent association between long DUP and persistent symptoms, poor overall functioning, and lower quality of life (Marshall et al., 2005; Perkins et al., 2005). There are a small number of studies of the association between DUP and various outcome measures from LAMI countries, but it is not known if long DUP is also associated with a poor prognosis in these regions. A finding that longer DUP was not associated with a poor prognosis in LAMI countries would support the hypothesis that schizophrenia had a better prognosis in those countries.

We report a systematic review and meta-analysis of the relationship between DUP and measures of outcome in LAMI countries.

2. Methods

2.1. Search strategies

A wide search strategy was undertaken in an attempt to locate all the available studies (Fig. 1). Firstly, we searched the electronic databases Medline, Embase, Psychlit and PsychINFO from January 1975 to March 2008 using the search terms 'duration of untreated psychosis', 'delay in treatment', 'treatment delay' or 'initiation of treatment' cross referenced with the terms 'psychosis', 'psychotic disorders', 'schizophrenia', 'schizoaffective' or 'schizophreniform' and 'first-episode psychosis'. This method yielded more than 300 publications about DUP from developed countries but only eight studies conducted in LAMI countries defined as (LI), lower-middle-income (LMI) of upper-middle income (UMI) using the World Bank and International Monetary Fund's LAMI classification (World Bank, 2005).

Second, the journals Schizophrenia Research, Schizophrenia Bulletin, British Journal of Psychiatry Supplement, Acta Psychiatrica Scandinavica, Journal of Clinical Psychiatry and International Clinical Psychopharmacology were searched in full text because these journals had published the abstracts of international schizophrenia conferences. Two additional studies were located using the terms 'duration of untreated psychosis' OR 'DUP'.

Third, we examined the first 40 results after combining the names of 152 LAMI countries with "duration untreated psychosis" using the search engine Google. This located one further study of DUP from a LAMI country.

Fourth, 12 studies reporting DUP from LAMI regions were found by examining the abstract of every article located using the names of 152 LAMI countries AND "schizophrenia" in PubMed [January 1975 to January 2007]. Publications on movement disorder, gender differences or the epidemiology of schizophrenia were examined in full text.

Fifth, we hand searched the references of DUP studies and contacted the authors of twelve recent studies of first episode psychosis (FEP) in LAMI countries, which located no further relevant studies.

Finally, no studies were found by examining all the abstracts located using the terms "schizophrenia" and "psychosis" in searches of ExtraMed [1992 to 2000] and LILACS [1982 to 2008]. LILACS and ExtraMed index journals from developing regions that are not found on Medline.

2.2. Inclusion criteria

Using these methods a total of 23 studies were located from LAMI countries that reported DUP or the interval between the onset of psychosis and the initiation of treatment or contact with services (Large et al., 2008). Twelve of the 23 studies did not contain outcome data, but eleven studies met our inclusion criteria, as they reported an association between DUP and at least one of the following:

- (i) (a) the degree of symptomatic improvement attributed to antipsychotic treatment measured using recognized instruments
- (b) disability, using the results of disability scales, social and occupational functioning or global outcome
- (c) mortality
- (d) measures of symptoms or cognitive function at presentation
- (ii) used clinician-rated instruments and
- (iii) reported subjects who met the criteria for the diagnosis of a psychotic disorder according to either the DSM or ICD classification systems.

There are no widely accepted criteria for assessing the quality of studies of DUP. All studies of DUP are naturalistic and it is not possible to randomize subjects to long or short DUP. The quality of the studies was assessed and is reported using the criteria proposed by Marshall et al. (2005, Table 2): restriction of the population to those with schizophrenia using accepted diagnostic criteria, assessment of outcome blind to DUP status, a follow-up rate of at least 80%, and use of a standardized method to measure DUP. However, as there were so few studies and none of the studies met all of these criteria, we did not exclude any of the studies on quality grounds.

2.3. Data extraction and analysis

The following data were collected: the country of origin of the subjects, the proportion of males, number of subjects, mean age at contact or initiation of treatment, details of outcome measures reported and percentage of subjects with a diagnosis of schizophrenia or schizophreniform psychosis. Details of outcome measures are provided in Table 1.

SF and ML independently extracted the data and minor differences were resolved after independent re-examination by both authors.

Meta analysis was used to calculate a pooled estimate of the associations between DUP and the outcome measures of (i) reduction in total symptom scores from base line (ii) levels of disability, measured either by the use of established disability scores or by measures of global function and occupational outcome after treatment.

The associations between DUP and cognitive function, positive symptoms and negative symptoms assessed prior to treatment were also examined. While these measures are not measures of treatment outcome, they are of interest in LAMI countries because a significant proportion of patients with psychosis never receive treatment.

Comprehensive Meta-Analysis (CMA), version 2.2 was used for the analysis. CMA employs the same algorithms that are used by the Cochrane collaborators to assess effect size

Table 1

DUP, diagnostic and demographic variables in the LAMI groups.

Reference	Site, World Bank income status	Diagnostic criteria	Definition of DUP	Study analysis time points	Outcome variable	Definition of remission or outcome	Results
Alptekin et al. (2005)	Multi-center study, Turkey. UMI	DSM IV Schizophrenia	Duration between the appearance of the first identifiable psychotic symptom to the beginning of antipsychotic treatment	Baseline and three monthly for one year	BPRS BDQ	No or Minimal disability as defined by a BDQ score <7	DUP was a moderate predictor of disability at one year.
Apiquian et al. (2002, 2006)	Mexico City, Mexico. UMI	DSM III-R (SCAN) for affective and non-affective psychosis	Duration of psychotic illness until at least four weeks of the equivalent of 5 mg of Haloperidol.	Baseline and at 12 months.	PANSS PAS	None	DUP negatively correlated with positive symptoms and positively correlated with the PAS general subscale. No relationship with DUP was found.
Ayres et al. (2007)	Sao Paulo. UMI Brazil	DSM IV patients with functional psychosis, 98 schizophrenia spectrum, 71 affective psychosis (SCID)	Onset of psychosis to contact with mental health authorities	Baseline	PANSS Tests of memory and verbal fluency	None	No relationship with DUP was found.
Galinska et al. (2005)	Bialystok, Poland. UMI	ICD 10 and DSM IV Schizophrenia	The period between the onset of delusions or hallucinations and antipsychotic treatment	Baseline	WCST WAIS-R GAF PANSS	Correlations with Cognitive measures, PANSS and GAF	No relationship with DUP found
Kurihara et al. (2006)	Bali, Indonesia. LMI	DSM III Schizophrenia	Duration between meeting criteria for schizophrenia and initial treatment	Eleven years	Measures of Mortality	Survival	Patients with a DUP of longer than 12 months had 6.7 times the mortality of those with a DUP of less than 12 months.
Lieberman et al. (2003)	Beijing, China. LMI	DSM IV Schizophrenia	Duration between the first psychotic symptom and entry into drug trial for first episode patients	Twelve weeks and 52 weeks	BPRS SANS CGI GAF	Remission defined as 50% reduction in BPRS and BPRS<3 on 5 psychosis items of BPRS	Patients with longer DUP had higher BPRS scores at 12 weeks. Every year of DUP reduced the likelihood of remission by 15% at 52 weeks.
Oosthuizen et al. (2005)	Cape Town, South Africa. UMI.	DSM IV Schizophrenia, schizophreniform or schizoaffective disorder (SCAN)	Duration between overt hallucinations and delusions and the initiation of antipsychotics. DUP was not reliably established in seven subjects and two subjects with very long DUP were excluded. Non Parametric measures of correlation were used.	Baseline, 12, 18, 21 and 24 months.	PANSS	Correlations with PANNS Scores,	At 21 months and 24 months DUP positively correlated with negative symptom scores
Ran et al. (2001, 2003, 2007)	Xinjin count, China LMI	ICD 10 Schizophrenia (PPHS)	No operational definition of DUP, included patients who had received traditional treatments.	Cross sectional	PSE SDSS PSS	The presence of current or marked and current Symptoms	DUP negatively correlated with level of remission.
Thirthalli et al. (2005)	Bangalore, India. LI	ICD-10 Schizophrenia	Duration between the onset of any psychotic symptoms and presentation for treatment	Four weeks	PANSS	Percentage improvement in PANNS Score	DUP negatively correlated with change in PANNS at 4 weeks.
Tirupati et al. (2004)	Chennai, India. LI	ICD 9 schizophrenia (PPHS)	Duration between definite psychosis measured by care givers and initiation of treatment	Base line and one year	PSE PPHS	Good or Poor outcome in clinical, social and occupational functioning	DUP less than 5 years or less were more likely to have a good clinical and social outcome.
Uçok et al. (2006)	Istanbul, Turkey, UMI	DSM-IV for schizophrenia (SCID)	"The period between the first positive symptom of psychosis estimated by a senior psychiatrist and all sources of information and initial hospitalisation.	Initially and at 6 months	BPRS SAPS SANS PAS	Percentage decrease in BPRS.	Long or short DUP status was not a significant variable predicting outcome in multiple linear regression analysis.

PANSS = Positive and negative symptom scale, BPRS = Brief psychiatric rating scale, PSE = present state examination, SAPS = Scale for Assessment of Positive Symptoms, SANS = Scale for Assessment of Negative Symptoms, SDSS = Social disability screening schedule, PPHS = psychiatric and personal history schedule, BDQ = Brief disability questionnaire, CGI = Global Clinical Impression, GAF = Global assessment of functioning, SCAN = Schedule for clinical assessment in neuropsychiatry, SCID = Structured Clinical Interview for DSM-IV, SCAN = Schedule for clinical assessment in neuropsychiatry, PSE = present state examination LI = low income, LMI = lower middle income, UMI = upper middle income.

Table 2
Assessment of the studies' quality using Marshall et al.'s (2005) criteria.

Study	N	Drop out rate %	Blind rating used for any measure	Measure of inter-rater agreement	ANCOVA used in analysis
Thirhalli et al. (2005)	76	17	Yes	No	No
Tirupati et al. (2004)	75	19	No	No	No
Alptekin et al. (2005)	382	56	No	No	No
Apiquian et al. (2002, 2006)	63	10	Yes	No	No
Ayres et al. (2007)	179	5.5	No	No	Yes
Galinska et al. (2005)	30	Unknown	No	No	No
Kurihara et al. (2006)	59	0	No	No	Nr
Lieberman et al. (2003)	171	5.2	Yes	No	Yes
Oosthuizen et al. (2005)	57	15.7	No	Yes	No
Ran et al. (2001, 2003)	510	2	No	Yes	No
Uçok et al. (2006)	79	0	No	Yes	No

NR = not relevant.

and study weight, the latter by the inverse variance method (Borenstein et al., 2005).

The studies employed different measures of outcome over varying periods of time. Raw data and the results of univariate associations between DUP and outcome and symptoms were used in the meta analysis. Hence, no correction was made for possible confounding variables such as the length of DUP and possible association between DUP and gender (Large and Nielsens 2008a).

Heterogeneity was assessed with *Q*-value and *I*² for each analysis. The between study variance cannot be estimated with precision in meta analysis of a small number of studies (Cooper and Hedges, 1994). A fixed model is reported for meta analysis of four or fewer samples. The choice of random effects model in the analysis of the degree of reduction in total symptoms scores from baseline after treatment, reported in five studies, was made on the basis of a finding of statistically significant between-study heterogeneity.

3. Results

3.1. Characteristics of studies

Eleven studies conducted in LAMI countries reported an association between DUP and at least one of the following: the degree of reduction in total symptoms scores, measures of disability, the level of positive or negative symptoms, cognitive impairment or mortality (Table 1).

The methods and the quality aspects of the studies are shown in Tables 1 and 2. All the studies were prospective in the sense that the DUP was measured at the time of presentation. One study had a sample size of less than 50 (Galinska et al., 2005), and one study had a dropout rate of more than 20% (Alptekin et al., 2005). All studies reported diagnoses using

DSM or ICD diagnostic criteria, confirmed by a recognized diagnostic interview in six of the studies. All the studies used corroborative information to measure DUP but none of the studies used a purpose designed structured interview to assess the length of DUP. One study included a measure of inter-rater agreement about DUP (Apiquian et al., 2002). The studies reported a total of 1538 subjects of whom 88% were diagnosed with schizophrenia (Table 3).

The association between DUP and measures of symptoms, disability and mortality was reported in variety of formats including odds ratios (Lieberman et al., 2003), relative risk (Kurihara et al., 2006), chi-square statistics for dichotomized groups (Apiquian et al., 2002; Tirupati et al., 2004), means and standard deviations in long and short DUP groups (Galinska et al., 2005; Oosthuizen et al., 2005; Uçok et al., 2006), or as a correlation coefficient (Alptekin et al., 2005; Apiquian et al., 2002; Ayres et al., 2007; Oosthuizen et al., 2005; Ran et al., 2003, 2007; Thirhalli et al., 2005). The most frequently reported measure of the associations with DUP was a correlation. Hence the results of the meta analysis are reported in this format. Of the five studies that reported reduction in symptoms from baseline after treatment only one study (Lieberman et al., 2003) used an ANCOVA to take account of the possibility of the effects of regression to the mean (Vickers and Altman, 2001).

3.2. Association between reduction in total symptom scores and DUP after treatment

Five studies reported the extent of the reduction in symptoms from baseline at presentation after a period of treatment using established instruments (BPRS in Lieberman et al., 2003, Uçok et al., 2006; PANSS in Apiquian-Guitart et al., 2006; Oosthuizen et al., 2005; Thirhalli et al., 2005). All five studies reported that patients with a longer DUP had a smaller reduction in symptom scores after treatment when compared to patients with shorter DUP who had greater reductions in symptom scores. The five studies had a statistically heterogeneous effect sizes (*Q*-value 25.2, *p* = 0.000, *I*² = 84.01). Hence a random effects model was used. The pooled estimate indicated that longer DUP was negatively associated the degree of reduction in symptom scores (random effects meta analysis; *r* = -0.290, 95% CI = -0.483 to -0.069, *z* = -2.559, *p* < 0.011, Fig. 2).

Table 3
DUP, diagnostic and demographic variables in the LAMI groups.

	LAMI country group			Total
	LI	LMI	UMI*	
No. of samples	4	5	6	14
No. of subjects	626†	389	523	1538
mean age of onset (weighted)	29.8#	28.9	25.6	28.2
Percentage with male gender	54.4	49.0	55.9	55.6
Percentage with schizophrenia	92.8	69.4	95.5	87.85

†Only 354 of 510 subjects in Ran et al. (2001, 2003) ever received treatment.
*Uçok et al. (2006) not included as the same subjects were included in Alptekin et al. (2005).

Age in study by Tirupati [14] taken from McCreedy [25].

LI = low income. LMI = low middle income. UMI = upper middle income.

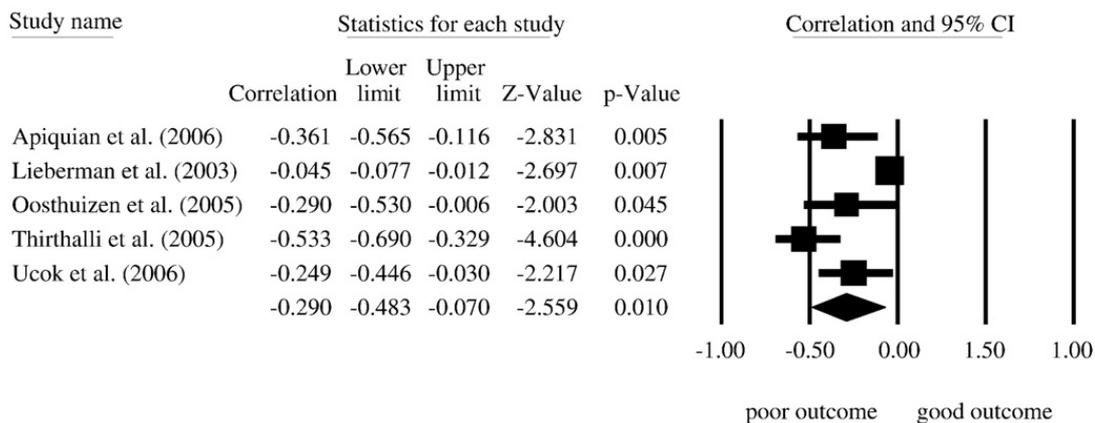


Fig. 2. Meta analysis of the association between DUP and reduction in total symptoms. Correlations inverted such that a relationship between longer DUP and a poorer outcome are expressed as a positive value, and are represented by studies on the right.

3.3. Association between DUP and disability after treatment

A study from Turkey found that DUP was significantly associated with social disability as measured by the brief disability questionnaire (Alptekin et al., 2005) and a study from rural China reported that 35% of patients with a DUP of less than a year had a complete symptomatic and social remission, in while 7% with a DUP of greater than a year (Ran et al., 2003). The results of these two large studies were similar to two smaller studies. A study from Mexico reported that patients with a DUP of less than 27 months were significantly more likely to make a good social and occupational recovery (Apiquián-Guitart et al., 2006) and study from southern India that found a trend towards an improved social and occupational outcome in patients with a shorter DUP (Tirupati et al., 2004). A pooled estimate of these diverse outcome measures found a significant association between longer DUP and a greater level of disability (fixed effects meta analysis; $r = 0.195$, 95% CI = 0.126 to 0.262, $z = 5.498$, $p < 0.000$; heterogeneity Q-value 1.245, $p = NS$, $I^2 = 0.00$ Fig. 3).

3.4. Association between DUP, symptoms and cognitive function at baseline

Four studies reported the association between DUP and positive symptom scores at baseline (Apiquián-Guitart et al., 2006; Galinska et al., 2005; Oosthuizen et al., 2005; Uçok et al.,

2006). Meta-analysis of these studies found a negative association between DUP and the positive symptoms (fixed effects meta analysis; $r = -0.152$, 95% CI = -0.280 to -0.02 , $z = -2.248$, $p < 0.025$; heterogeneity Q-value 1.25, $p = NS$, $I^2 = 0.00$, Fig. 4).

Three studies reported the association between long DUP and negative symptoms (Galinska et al., 2005; Oosthuizen et al., 2005; Uçok et al., 2006). Longer DUP was not associated with the extent of negative symptoms at baseline (fixed effects meta analysis; $r = 0.057$, 95% CI = -0.0101 to 0.211 , $z = 0.705$, $p < 0.048$; heterogeneity Q-value 1.01, $p = NS$, $I^2 = 0.00$ Fig. 5).

Studies from Brazil (Ayres et al., 2007) and Poland (Galinska et al., 2005) examined the effects of DUP on cognitive function at baseline. Neither study found an association between DUP and cognitive abilities. There was insufficient data for a meta analysis of cognitive function.

3.5. Mortality

Kurihara et al. (2006) reported on the mortality of 59 consecutive first episode psychosis patients in Bali who were followed up after eleven years. Patients with a DUP of longer than one year had 6.7 times the mortality of those with DUP of less than 12 months. Ran et al. (2007) also found that the mortality of patients with a long DUP was significantly higher than those who received treatment earlier, although long DUP was also associated with inadequate later treatment. Only a small proportion of patients received ongoing treatment and

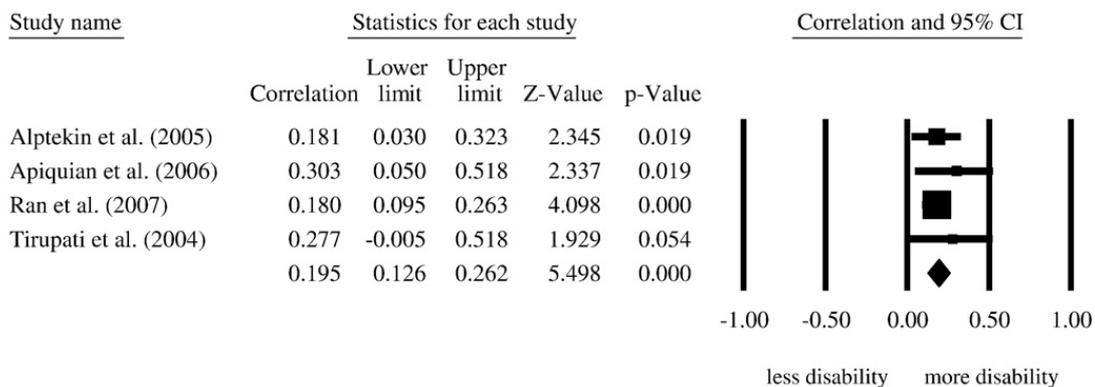


Fig. 3. Meta analysis of the association between DUP and disability.

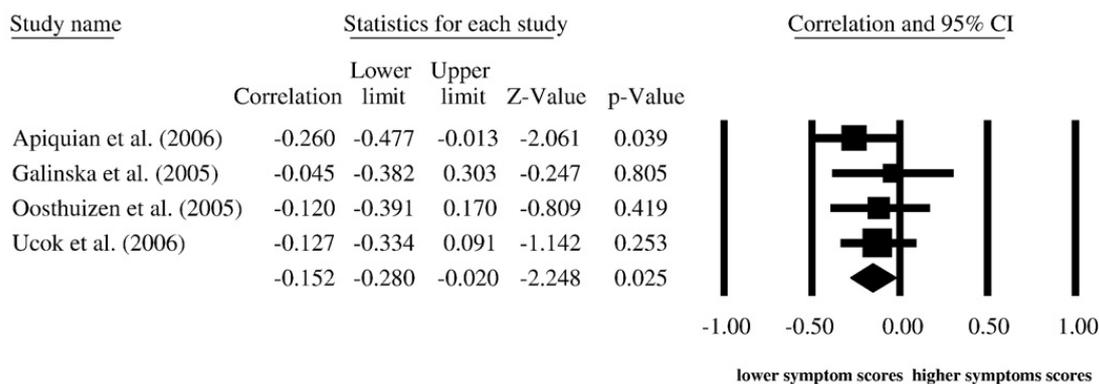


Fig. 4. Meta analysis of the association between DUP and positive symptoms at presentation.

a definite association between DUP and mortality could not be inferred.

4. Discussion

The main finding of this study is that, after controlling for symptoms at baseline by measuring the degree of reduction in symptoms score after treatment, a longer period of DUP was associated with a poorer response to treatment in all of the five relevant studies from LAMI regions and by meta analysis. Hence there appears to be a similar association between long DUP and a poor response to treatment in LAMI countries to that found in HI countries.

We also found evidence of an association between long DUP and subsequent disability, although the available data did not allow us to control for levels of disability at the time of presentation. Hence, we could not exclude a possibility that both the poor prognosis and the long DUP might have been due to a higher level of disability in the pre-morbid period.

The findings of a negative correlation between positive symptoms and DUP and the absence of an association between DUP and negative symptoms are of interest, but should be interpreted cautiously. Positive symptoms might hasten treatment and negative symptoms might delay the treatment of some individuals.

The main limitation of this study is the small number of relevant studies from LAMI countries, which is likely to be common to other reviews of other reviews of psychiatric research in LAMI countries (Patel and Sumathipala, 2001). A consequence of the lack of data was that we elected not to exclude studies according to strict quality criteria, in keeping with other reviews of research in LAMI regions (see Mirza and Jenkins, 2004). The studies were all relatively recent and employed adequate methodology, but none of the studies employed optimal methods. Perhaps the most significant limitation was that none of the studies used a semi-structured interview to measure DUP. Although the use of semi structured instruments do not contribute to the between study heterogeneity of mean DUP in reported studies (Large et al., 2008b) the main independent variable (DUP) may not have been accurately recorded in all cases.

With these limitations, the main implication of this study is that long DUP has a similar effect in LAMI countries as it has in HI countries. Studies in HI countries have not yet conclusively

established that prolonged DUP is the cause of a poor outcome found to be associated with prolonged treatment delay. However, if it is accepted that long DUP is a cause of poor outcome in HI countries, this study suggests it is likely to have similar adverse effects in LAMI countries.

Based on the studies included in this review it is not possible to rule out the possibility that factors such as an insidious onset contributed both to poor outcome and a longer DUP. Conversely, patients with mild forms of illness might have delayed treatment in countries where there is little available care, lessening the observed association between DUP and outcome. Outliers with an extremely long DUP that skew the distribution of DUP might be more common in studies from LAMI countries. However, the studies included in this review used appropriate methods such as non-parametric statistics and log transformation in order to minimize the potential for results that were unduly influenced by a minority of subjects with long DUP (Large et al., 2008b). Furthermore, in HI countries the association between DUP and outcome appears to be independent of the degree of skew in DUP distributions and other variables (Marshall et al., 2005; Perkins et al., 2005). This is probably the case in LAMI countries as well.

One study examined the relationship between DUP and subsequent mortality (Kurihara et al., 2006), while a second found that the risk of death of patients who had received even minimal treatment was significantly lower than those who received no treatment (Ran et al., 2007). The main reason for the premature death of subjects in the studies from China and Bali was untreated medical illness. Hence the beneficial effects of psychiatric treatment could be even greater in LAMI countries than in HI regions because untreated patients may have difficulty obtaining life saving medical care in LAMI countries.

Our findings are consistent with the conclusions reached by Cohen et al. in a comprehensive review of evidence on outcome of schizophrenia in developing countries i.e. lack of proper biomedical treatment is associated with relatively poor outcomes in schizophrenia irrespective of the income or cultural status of the setting. This is more evident in present review as we studied outcome in relation to well defined income categories instead of a broad category of 'developing countries'. Despite considerable heterogeneity within the LAMI group of countries the outcome seems to be universally poor when DUP is long.

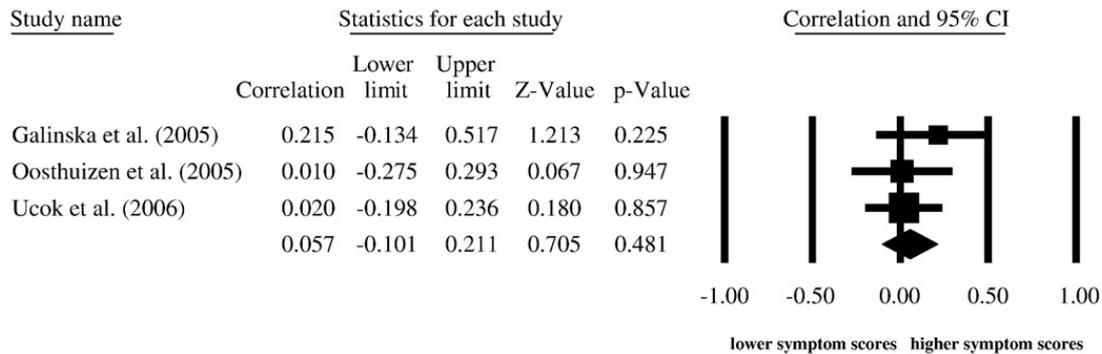


Fig. 5. Meta analysis of the association between DUP and negative symptoms at presentation.

A long DUP in high-income countries has been attributed to the gradual onset of the illness, the lack of understanding of the reason for the morbid change by the patient's family, the patient's own lack of insight and the effect of some mental health laws (Large et al., 2008c). In many LAMI countries the reasons for long DUP include the absence of mental health services and the cost of treatment (Large et al., 2008).

DUP has now a well established association with poor outcome of psychosis but methodologically sound studies in LAMI countries are still sparse. There is urgent need to conduct methodologically sound studies particularly those, which try to establish the effect of treatment in relation to outcome and DUP in a LAMI country. Putative protective factors, including family support, that may sometimes be responsible for better course of schizophrenia should also be investigated as it appears that these factors, if any, have limited protective influence during the long period of untreated illness.

5. Conclusions

Lack of treatment for psychotic illness early in the course appears to be associated with relatively poor outcomes, irrespective of the income or cultural status of the setting. It is time that early intervention services for psychosis are planned for LAMI countries as they have been in HI countries. The findings of this review, and the related study (Large et al., 2008) support the recommendation to supply subsidized antipsychotic medication for at least the first two years of psychotic illness as a way of reducing DUP in developing countries (Patel et al., 2007). Providing very low or no cost psychiatric care in the same setting as other forms of primary health care has been effective in reducing DUP in Zambia (Mbewe et al., 2006) and may be a model that could be adopted elsewhere to reduce DUP.

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None.

Contributors

Saeed Farooq conceived and wrote initial protocol for review. Saeed Farooq and Waqas Waheed devised search strategy. Saeed Farooq and Mathew Large searched the references, selected studies and extracted the data. Mathew Large and Olav Nielssen analyzed the data. Saeed Farooq, Mathew Large and Waqas Waheed wrote the final draft.

Conflict of interest

None to be declared.

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FROM DOTS TO STOPS — PUBLIC HEALTH INTERVENTION FOR SCHIZOPHRENIA IN LOW AND MIDDLE INCOME COUNTRIES

Saeed Farooq, Zahid Nazar, Javaid Akhtar, Muhammad Irfan, Sher Naeem

ABSTRACT

Case management and early intervention strategies are well established for schizophrenia in the industrialized countries, majority of those with schizophrenia in low and middle income countries (LAMICs) do not have access to primary or secondary care psychiatric services. This results in an unacceptably high untreated and partially treated prevalence of the disorder. One of the fundamental problems in achieving and maintaining symptomatic recovery in schizophrenia is the lack of adherence to drug treatment. A number of programmes in LAMICs have shown that providing essential antipsychotic drugs under the supervision of a guardian, usually a relative, results in a significant reduction in the disability, psychotic symptoms and caregiver's burden. This article proposes a model of public health intervention based on the principles of DOTS (Directly Observed Treatment, Short course) which has been shown to be effective in overcoming non-adherence and maintaining long term treatment for Tuberculosis. We discuss the rationale for translating an intervention from a communicable disease to a non communicable chronic disorder based on preliminary analysis of data from our recent study and discuss how this can be implemented.

Keywords: Schizophrenia, Public health, Adherence, Intervention, Effectiveness.

THE CHALLENGE

It is ironic that while the early intervention for psychosis is a major priority in high income countries, the mental health professionals in the LAMICs face an entirely different challenge; to provide some treatment for those suffering from psychosis.

More than half of these countries have either no or less than 1% of health budget for mental health and the treatment gap for psychiatric disorders is close to 90%. Most individuals are, therefore left to cope with severe mental illness on their own¹. Consequently, there is high

untreated prevalence of schizophrenia in the form of undetected as well as inadequately and partially treated cases. While it may be difficult to reach for the undetected cases, the present level of untreated cases in patients who have had some contact with mental health services represents a catastrophic failure of mental health policy and services in these countries. In this article, we will argue that a public health intervention based on the principles of DOTS could be an effective strategy for coping with schizophrenia in these countries.

WHAT IS DOTS?

A single case of tuberculosis can spread the disease to 10-15 persons on average². DOTS (Directly Observed Treatment, Short course) was devised as a response to the public health challenge of non-adherence and maintaining long term treatment for tuberculosis.

DOTS has the following essential components. (For the discussion of all the five components of DOTS and its implementation see WHO, 1999)².

- (a) A regular uninterrupted supply of all essential Anti TB drugs backed by governments' commitment to sustained TB control activities.
- (b) Standardized treatment regimen of six to eight months chemotherapy under supervision. In many LAMICs the role of DOTS supervisor is assigned

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to a family or a community member who regularly administers the drugs under close monitoring by a health worker.

The World Bank considers DOTS to be one of the most cost effective health interventions. DOTS are more cost effective than self-administered treatment^{3, 4}.

Supervised treatment for schizophrenia in community - What is the theoretical rationale?

We believe that there is urgent need for a public health intervention based on the principle of DOTS in developing countries in view of the following:

1. The longer duration of untreated schizophrenia is associated with very serious Public health consequences.

The enormous public health consequences of long duration of untreated psychosis is well documented in context of literature on duration of untreated psychosis⁵. These include increased co-morbid substance abuse, suicide, increased treatment resistance, impairment in cognitive and neuropsychological functions, offending behavior, vocational failure and overall poor outcome. The medication status is also the strongest predictor of relapse; discontinuation of medication increases the relapse risk five folds⁶.

2. The cost effective interventions for schizophrenia are available.

Out of 20 recommendations for optimal treatment suggested by Schizophrenia Patient Outcome Research Team (PORT), 14 relate to pharmacological interventions. These were also rated to be highest on the ease for implementation⁷. These can be implemented in LAMICs provided essential drugs are made available. It has been argued that such an optimal treatment can at least avert 22% of burden of schizophrenia in developed countries⁸. In LAMICs where the treatment gap is very wide a much greater burden of illness could be averted by optimal pharmacological treatment.

3. Patients suffering from Schizophrenia need supervision and it is possible.

About 59% of patients may fail to adhere to their treatment in case of schizophrenia⁹ which unlike TB, is also complicated by impaired insight and cognitive functioning. Supervision by the family members is therefore of critical importance if the therapy is to succeed.

One of the essential ingredients of DOTS i.e. monitoring the drug compliance by observing and recording the correct medication has also been described in a number of interventions aimed at improving treatment adherence in the treatment of schizophrenia¹⁰⁻¹². A re-

view of interventions to improve medication adherence in schizophrenia found that relatively brief interventions (both in terms of duration and frequency) which targeted the behaviors related to medication adherence were more effective than longer interventions with broader focus on psycho education¹³.

4. We owe it to the family.

In LAMICs the family has largely 'subsidized' the treatment of schizophrenia for the society and the state at large by providing the social, psychological, residential and occupational support which constitute the major proportion of the cost of treatment for this disorder. Provision of free drugs to these patients as a part of DOTS programme would only help to share this burden in a small but very significant way.

5. A strategy for communicable illness for a non communicable disorder?

It could be argued that a strategy adopted for an infectious disorder is unlikely to succeed for a non communicable disease, which runs a much longer course. It must, however be realized that the core problems in both the disorders is the lack of adherence and continuity of the treatment which results in a spiraling costs and a vicious cycle of chronicity and increasingly poor response to the well established treatments. Providing free access to the treatment and supervision by the family member should significantly reduce these problems.

From DOTS to STOPS (Supervised Treatment in Out Patients for Schizophrenia)?

Based on the rationale described above we started a small pilot project which incorporates the principles of DOTS. This is termed as Supervised Treatment in Out Patients for Schizophrenia (STOPS). This is a programme which aims to stop preventable relapses in schizophrenia through:

- a. Provision of free psychotropic medication.
- b. Training relatives in supervision of administration of medication to improve patient adherence with the drugs as well as training relatives in the identification of early signs of a relapse.

EVALUATION OF STOPS - A PILOT PROJECT

We started a pilot project based on principles of STOPS in Lady Reading Hospital, Peshawar. The patients suffering from Schizophrenia and schizoaffective disorder were recruited and we trained the on of the close relatives, termed Key Care Giver to supervise the medication adherence. We assessed the outcome with Global assessment of Functioning¹⁴ and compliance with

the help of a structured questionnaire at baseline and follow up appointments. Ninety two patients were enrolled in this pilot project. As this was a pilot project we recruited all the patients irrespective of duration of illness. The mean duration of illness in these patients was 56.40 years (SD=60.69).

We developed a standard regimen for treating schizophrenia which was administered by under the close supervision of a relative. The patients were required to collect the medication monthly when treatment adherence and improvement was also assessed.

At one year follow up the mean GAF for the group was 61.43 (SD = 23.76) compared to 41.46 (SD = 28.84) at baseline. 70.7% had complete compliance with the treatment compared to 42.3% at baseline (Further details available from authors on request). The most encouraging aspect was that a number of patients started working early in the programme after some improvement thus actively supporting their families, instead of being burdens on them.

The average drugs cost per month for a case of schizophrenia with was RS.127 (1 US Dollar= Rs.86) with conventional anti-psychotics. For those patients receiving atypical anti-psychotics using the most economical local brand of Risperidone available in Pakistan the same cost was about three times this figure. Considering that in schizophrenia there are no additional costs of laboratory investigations and radiography used for T.B control activities, this compares quite favorably with six to eight months treatment of Tuberculosis in DOTS programme which ranges from Rs.1350 to 3130, depending upon the type and combination of drugs used. Encouraged by this success we commenced a Randomized Controlled Trial to evaluate the effectiveness of STOPS versus Treatment As Usual (TAU). The trial is registered at Trails.Gov, the one of the registers for RCTs and further details are available at www.clinicaltrials.gov.

CONCLUSIONS AND FUTURE DIRECTIONS

It is suggested that those suffering from schizophrenia in the LAMICs could at least be supplied pharmacotherapy for two years under close supervision, if not for the whole duration of illness. This will help to overcome the non adherence for a period of illness which has been shown to be the strongest predictor of long term outcome and disability¹⁵.

Three tasks need urgent action:

- a) A global fund to generate the resources for providing free access to antipsychotic drugs should be created.

- b) Simple, brief and cost effective strategies for enhancing medication adherence which can be used by the caregivers in the LAMICs need to be developed.
- c) Small scale programmes based on the DOTS model should be developed locally in LAMICs in collaboration with international organizations before we can expect the governments to support the same. Insulin Demonstration Projects which has been initiated to improve the access to the Insulin by the IDF Task Force can provide good models for this¹⁶.

Free access to the treatment has been provided not only for disorders like TB but also for many non communicable disorders in other disciplines. In Diabetes Mellitus, for example, at least 67 states around the world including many in LAMICs are providing state subsidies for the Insulin¹⁷. A community based intervention based on the principles of DOTS for a relatively low prevalence disorder like Schizophrenia could also help to put the mental health strongly on the agenda of public health. Unlike non-multi drug resistant tuberculosis, treatment for schizophrenia would be needed for much longer period and “cure” would not be achieved in the strictest sense. Nor is there incentive to address the schizophrenia because a sufferer is not infectious to those around him or her. However, maintaining regular treatment in up to 2/3rd of cases for the critical two years period would not be a mean achievement. The improved access to treatment as a public health intervention will also lead to better awareness and early help seeking for the cases which at present represent the large untreated prevalence. Most importantly, perhaps it can also help to reduce the stigma for the disorder as effectively as the advent and effective implementation of anti tuberculosis treatment did for tuberculosis.

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NEVER TREATED SCHIZOPHRENIA IN DEVELOPING COUNTRIES

Saeed Farooq

One of the most significant recent developments in treatment of schizophrenia has been the early intervention for psychosis. Unacceptably long duration of untreated psychosis (DUP) has been considered as a major challenge for psychiatric services. The studies from developing countries report a DUP almost twice as long as that in developed countries; thus necessitating an action for early intervention¹. An even more alarming trend reported in many studies is large number of cases which remain untreated for many years, often in inhuman condition. Malik and Bokharey² reported what they described as 'human zoo' for a group of patients which according to authors provided 'cure' for patients suffering from schizophrenia "chained to the trees in the open spaces around the shrine— through the chilly winter nights and the blazing heat of summers for days, months and at times for years".

Souza et al³ identified 49 patients only in two months period in Darfur region of Sudan by active case findings. Some patients were in such dramatic situations as being chained to their beds. Srinivasan et al⁴ describe a cohort of 72 never-treated chronic schizophrenia patients in Chennai, India. Similar untreated cohorts are reported from China and number of other developing countries.

Almost all these studies report serious effects in term of psychological, physical and social outcomes. A common problem is high mortality. In rural China where very few patients received adequate treatment, untreated patients were found to have marked social and occupational disability and a fourfold increase in mortality^{5,6}. The high mortality reported in these studies is not due to suicide, the commonest cause of higher mortality in schizophrenia but due to malnutrition, infectious disease and other physical causes.

Ironically, number of these studies have focused on these patients as 'interesting' cases, in which details and manifestations of a chronic mental illness are examined in microscopic details without much attention to

the challenges these cases pose for the service provision. Few isolated programmes have tried to address the need for provision of some treatment for these patients². However there is need for more systematic and coherent approach in addressing the large gap in treatment these populations pose.

Lack of treatment for many years in patients suffering from Schizophrenia is related to many factors and there is little evidence for effective interventions to address this issue. Srinivasan et al⁴ found that unemployed status of male patients, living in a joint family setting and families initially unaware of the psychiatric nature of the problem were the factors that related to failure to seek treatment. Patient's sex, age, education, marital status, economic status, age at onset and duration of illness, degree of disability and clinical symptoms (except self-neglect) were not related to taking treatment.

Cost of treatment is an important barrier. Medicines account for 20–60% of health spending in developing and transitional countries,⁷ compared with 18% in countries of the Organisation for Economic Co-operation and Development⁸. Up to 90% of the population in developing countries purchase medicines through out-of-pocket payments,³ making medicines the largest family expenditure item after food. People with severe mental illness who have increased difficulty obtaining food, shelter and medical care⁹. are most vulnerable to these effects.

There is urgent need to devise effective public health interventions to improve the access to the pharmacological treatment for those suffering from Schizophrenia in developing countries. Isolated programmes in many countries have shown that it is possible to provide standardized regimen of antipsychotic treatment. However these programmes have rarely been replicated outside model programmes. An article in this issue¹⁰ describes such an approach. It is interesting to note that the approach described in this article is based on principles of DOTS, an intervention originally proposed for Tuberculosis. Although TB has nothing in common with schizophrenia two disorders share some rather interesting historic facts. Tuberculosis is perhaps the only physical disorder which needed treatment in institutions like schizophrenia. The stigma associated with TB has

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been bad as we have today for Schizophrenia. However, implementation of an effective treatment at public health level changed the situation dramatically for Tuberculosis. The success story of Tuberculosis demonstrates that an effective interventions applied optimally at the public health level is the most effective way of reducing the stigma. Interestingly, since DOTS like treatment approach was suggested for Schizophrenia, it has been advocated for other Non Communicable Disease as well to overcome the problem of poor access to the treatment. At present it seems that any intervention for psychosis is the early intervention for this serious disorder in Low and Middle Income Countries (LAMIC). It is now time that early intervention for psychosis is considered as major public health priority in developing countries.

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What Is the Best Approach to Treating Schizophrenia in Developing Countries?

Vikram Patel, Saeed Farooq, R. Thara

Background to the debate: Schizophrenia affects an estimated 25 million people in low- and middle-income countries, with an average lifetime risk of about 1%. The illness is associated with excess mortality from a variety of causes. A 2001 Institute of Medicine report on mental illness in developing countries found that in 1990, over two-thirds of people with schizophrenia in these countries were not receiving any treatment (<http://www.nap.edu/catalog/10111.html>). The report found no evidence that the proportion of treated people in the developing world had increased since 1990. There is now a debate among mental health professionals in low-income countries over how best to improve patient care. In this article, three psychiatrists give their different viewpoints on the current status of treatment efforts for schizophrenia in the developing world and the measures that can be taken to increase the proportion of patients receiving treatment.

Vikram Patel's Viewpoint: Non-Specialist Community Health Workers Should Play a Key Role in Delivering Care

Although schizophrenia is relatively rare, it is also arguably the most severe mental disorder. In many individuals, the disorder runs a chronic and relapsing course, leading to progressively worsening disability, loss of livelihoods and social networks, and increased risk of discrimination and human rights abuse. To consider what might be the best approach for treating schizophrenia in low- and middle-income countries (LAMIC), we must first address three questions: What is the burden of this disorder? What are the resources available for care? And what is the evidence base for the treatment of this disorder in LAMIC?

Assuming that the point prevalence of schizophrenia in LAMIC is the median figure reported in a recent systematic review—4.6 per 1,000 population [1]—and that the population of LAMIC is 5.3 billion [2], then about 25 million people with schizophrenia live in LAMIC. The health systems of LAMIC are woefully unprepared to address the myriad health and social needs of people with schizophrenia; in most parts of LAMIC, there is less than one qualified mental health professional for half a million to a million people [3] (which will include about 2,500 to 5,000 people with schizophrenia). Therefore most people with schizophrenia in LAMIC probably receive little or no formal care.

What impact does this lack of care have on patients' lives? A recent household study from Mozambique reported that up to half of the patients with psychotic disorders were reported by key informants in their households to be currently in poor

health [4]. Traditional medicine was by far the most common type of health care accessed. Lack of services contributes to delayed treatment, which in turn leads to poorer long-term outcomes [5], higher direct and indirect costs of treatment with antipsychotic drugs [6], and increasing mortality [7–9].

Thus, the lack of evidence-based care, exacerbated by rapid changes in social and economic conditions in less developed countries that compromise the ability of informal systems to care for people with schizophrenia [9], represents a looming mental health crisis in these countries. Despite these scarce resources, there is now growing evidence that antipsychotic drugs and community-based, family-focused interventions are effective treatments in LAMIC [10]. The latter help reduce stigma, improve adherence to medication, and strengthen social integration.

How can these treatments be delivered in low-resource settings? The most appropriate model of care is a community-based program that is affordable, feasible, acceptable, and evidence based. Who are the key health professionals needed to deliver such a model? Given the scarce specialist resources in LAMIC, the lion's share of the service delivery would need to be the responsibility of non-specialist health workers. Indeed, the front line of the community mental health-care system need not even be represented by health workers at all, but may be made up of people who live in the community and are trained to provide a range of family- and community-based interventions.

Such care models are now being implemented by a number of community-based organizations such as Basic Needs (a mental health non-governmental organization operating in a number of developing countries and based in the United

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Abbreviations: DOTS, directly observed therapy, short-course; LAMIC, low- and middle-income countries; TB, tuberculosis

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Kingdom), and have been shown in quasi-experimental designs to be superior to simple outpatient care on clinical and functional outcomes [11]. These programs still require a health practitioner—who could be an appropriately trained physician or nurse practitioner—with sufficient skills in diagnosis and drug treatment. The role of specialists may need to be carefully redefined; where available, outreach services provided by specialists in collaboration with local non-governmental organizations are a clinically effective and cost-effective approach that produces significant improvements in functioning and decreased burden on the family [12]. In many places, however, the most feasible role for specialists might be to design programs, build capacity of non-specialist health workers, and supervise the quality of care delivered.

The first step in a population-based model must be to improve awareness about the disorder and the service. The community mental health worker needs to establish close networks with members of grass-root, health service, and social welfare organizations. Next, the community mental health worker must identify probable cases of schizophrenia, preferably as early as possible after the onset of the disorder. The ideal model for case identification is likely to be through the use of key informants (individuals who are familiar with the health status of members of the community they live in), a cost-effective method for identifying mental disorders in LAMIC [13]. Then the skilled health practitioner should make the diagnosis and initiate drug treatment. Health practitioners must also play close attention to the physical health needs of their patients, given that physical health problems are common in people with schizophrenia and are often neglected, contributing to higher mortality [14]. Health practitioners should also have access to an inpatient unit for the short-term care of patients who are acutely disturbed.

After this predominantly clinical phase, the focus of care shifts back to the community, involving three strategies: (1) Strengthening opportunities for paid employment; (2) building individual and family capacity to cope with the disorder (e.g., to support medication adherence); and (3) ensuring that the costs of long-term care are at least partly borne by an equitable financing system, such as a voucher system, insurance plan, or fixed monthly payments. The role of the community worker may extend to care for people with other severe neuropsychiatric disorders, such as mental retardation and epilepsy, which share many characteristics with schizophrenia (e.g., chronicity, disability, stigma, and loss of livelihood), and are also more likely to occur together. Community-based residential care will still be needed for the few individuals who are severely disabled and cannot continue to live either independently or with their families.

The model that I have outlined is not a pipe dream. It is an affordable prescription for a commitment to ensure that people with schizophrenia receive the basic minimum package of evidence-based care in LAMIC, care that meets their human rights.

Saeed Farooq's Viewpoint: Directly Observed Therapy (DOTS) Is an Approach Worth Testing

In developing countries, treatment for schizophrenia is limited mostly to acute episodes and seldom involves primary care physicians. Developing countries typically

spend less than 1% of their health budget on mental health [15], and one of the consequences of this under-spending is a high prevalence of untreated schizophrenia in the form of undetected as well as inadequately and partially treated cases. In Bihar, one poor state in India, there are more people suffering from schizophrenia than in the whole of North America [16]. The high prevalence in developing countries is partly explained by the predominantly younger population of the developing world (schizophrenia is a disease of young adults).

One approach to tackling the burden of untreated schizophrenia in low-income countries that may prove effective is directly observed therapy. This approach is the cornerstone of current global efforts to tackle tuberculosis (TB). Successful TB treatment, and the prevention of multi-drug resistant TB, requires long-term therapy and high adherence rates. The internationally recommended TB strategy known as DOTS (Directly Observed Therapy, Short-Course) [17] has two essential components: (1) a regular uninterrupted supply of a standardized treatment regimen of six to eight months chemotherapy, and (2) its administration under the supervision of a health worker or trained close relative who watches and records the patient swallowing the correct dose of drugs. A discussion of all five components of DOTS and its implementation is found in [17].

The DOTS strategy has led to remarkable improvements in TB control in many developing countries [18,19]. The World Bank considers DOTS to be one of the most cost-effective health interventions, more cost-effective than self-administered treatment [20,21]. I would argue that the principles underlying the DOTS strategy could form the basis for an effective public health intervention to cope with the burden of schizophrenia in developing countries.

Providing a regular supply of antipsychotic medication and supervising its administration may be one mechanism for addressing the enormous public health burden of long-term untreated psychosis in developing countries. This burden includes increased co-morbid substance abuse, suicide, treatment resistance, impaired cognitive and neuropsychological function, offending behavior, vocational failure, and overall poor outcome [22]. In addition, the strongest predictor of relapse is discontinuation of medication, which increases the relapse risk 5-fold [23]. Even a very short break from taking medication (just one to ten days over a one-year period) is significantly associated with increased risk of hospitalization (odds ratio 1.98, 95% confidence interval 1.27–3.25) [24].

Long-term antipsychotic medication for treating schizophrenia in developing countries is a cost-effective intervention. Out of 20 recommendations for optimal treatment suggested by the Schizophrenia Patient Outcome Research Team, a research team funded by the US National Institute of Mental Health, 14 were related to pharmacological interventions [25]. These interventions were also rated highest on ease of implementation and can be implemented in developing countries, provided access to the drugs is ensured through a programme akin to DOTS. The cost of antipsychotic medication, including recent atypical drugs, is surprisingly very low in many developing countries [16].

We surely owe it to the families of patients with schizophrenia in poor countries to provide free drugs. The families have largely subsidized schizophrenia treatment

for society and the state at large by providing the social, psychological, residential, and occupational support that constitutes the major proportion of the cost of treatment for this disorder. Provision of free drugs to these patients as a part of “DOTS-type” programme would help to share this burden in a small but very significant way.

Drug treatment for schizophrenia is likely to be more effective if its administration is supervised. Such a system of supervision is feasible in low-income settings in view of the family’s integral involvement in the patient’s care. About 60% of patients with schizophrenia may fail to adhere to their treatment [26], in part because the disease itself leads to impaired insight and cognitive functioning. Approaches that are broadly similar to DOTS, entrusting the monitoring of drug compliance to a relative, have been found to be effective in improving treatment adherence for schizophrenia in developing countries [27,28,11].

I suggest that patients with schizophrenia in the developing world be supplied free access to drugs for two years under close supervision. This will help to overcome non-adherence during the period of the illness (i.e., the first two years) that has been shown to be the strongest predictor of long-term outcome and disability [29]. Indeed, a recent systematic review of interventions to address non-adherence in people with schizophrenia also recommended that clinical interventions targeting non-adherence should continue for at least 18 months [30]. In our pilot project, we found that a supervised treatment approach was associated with greater adherence rates. Encouraged by this finding, we have started a randomized controlled trial of “Supervised Treatment of Outpatient Schizophrenia (STOPS)” to evaluate its effectiveness versus usual care (further details available from author on request and at <http://www.clinicaltrials.gov/ct/show/NCT00392249?order=1>).

Would direct observation of schizophrenia treatment be overly coercive? In view of the wide treatment gap, there will always be a large population of those with schizophrenia who will be willing to take treatment under supervision, and they must be provided with effective interventions. Moreover, in view of the present poor state of mental health legislation in many developing countries, patients with untreated schizophrenia are likely to suffer from much greater human rights abuses than those who are treated.

Effective treatments for schizophrenia have neither been applied optimally nor advocated as public health interventions in developing countries. A public health intervention for schizophrenia modeled on DOTS may lead to greater awareness of the benefits of treatment and may encourage untreated patients to seek help earlier in the course of their illness. Promoting awareness of the benefits of treatments may help to reduce the stigma of schizophrenia, just as the advent and effective implementation of anti-tuberculosis treatment did for TB. A community intervention for schizophrenia based on the principles of DOTS could also help to put mental health strongly on the public health agenda.

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R. Thara’s Viewpoint: We Must Tackle Stigma by Offering Proven Treatments

The incidence and prevalence of schizophrenia does not vary widely enough across the world to merit markedly different local treatment approaches or programmes [1,31]. However, the reality is that there are widespread differences in the treatment that people with schizophrenia receive in different parts of the world. Understanding the reasons for these differences is the key to improving the care of people with schizophrenia in developing countries, including India, where I work.

An important reason underscoring these differences is that many developing countries have far too few mental health professionals [3], reflecting the very low priority accorded to mental health by many governments. In many low-income countries, there is an urgent need to improve and expand mental health services.

Community care in India is almost synonymous with family care. There are no organized community-based programmes for people with chronic mental illness. The commonest site of treatment is the mental hospital, many of which are large and isolated, with little contact with the community they serve. Efforts are under way to improve the conditions of many of these hospitals. While the number of general hospital psychiatry beds has increased in the last decade, the total number is still grossly inadequate. Most private psychiatrists are located in urban areas. There are very few non-governmental organizations, and these are largely concentrated in the southern part of the country.

India’s National Mental Health Programme did envisage the diffusion of mental health skills to primary health-care centres at the village and district levels, and the integration of mental health with primary care. However, poor monitoring and lack of coordination with the local state governments meant that such diffusion and integration efforts were not implemented, with the exception of a few sporadic programmes.

In India, people with chronic mental illness do not generally receive any welfare benefits, except for some minor benefits in just a few areas. Medical insurance seldom covers treatment of mental disorders. The result is that families have to bear the entire costs of the treatment and ongoing care of these patients. A heavy financial, physical, and emotional burden is therefore imposed upon family members. Indeed, over 90% of patients with schizophrenia live at home with their families [32]. Such family involvement is not merely a result of close kinship ties, but is also due to inadequate treatment facilities. Religious and traditional modes of intervention are still widely practiced, especially in rural areas, where mental health services are almost non-existent. Families are equal partners in all stages of intervention, be it choice of a drug, detection of side effects, or early symptoms of relapse, ensuring compliance with medication and supporting the affected family member through life events such as jobs or marriages.

Stigma, and the presence of competing and conflicting explanatory models of mental illness (often based on “magico-religious” beliefs), have also contributed to the non-use of existing treatment facilities. A study that we conducted at the Schizophrenia Research Foundation in Chennai found that women with schizophrenia were more stigmatized than

men with schizophrenia, and that female caregivers were more sensitive to stigma than male caregivers. Being single or divorced compounded the problem of stigma even further [33]. Stigma is an all-encompassing phenomenon and a profound barrier to effective help seeking.

In terms of the availability of medication for treating schizophrenia in India, both first and second generation antipsychotics (risperidone, olanzapine, clozapine, quetiapine, and sulpiride) are available at fairly low prices. Both groups of drugs are being used as first-line medication. In my clinical experience I have found that Indian patients require a much lower dosage of medicines than patients in the West, in both the acute and maintenance phases of treatment. However, more research is needed to document whether there are indeed different dosage requirements in Indian patients and, if there are, to critically address the actual reasons for this difference. Unfortunately, a large proportion of patients in both rural and urban settings remain untreated [34,35]. Even when patients are prescribed medication, non-compliance during the symptomatic phase is common in India. In our study of patients attending an urban outpatient care center, we noted that when the patients were acutely ill and refused to take medication, in half the cases the families administered medication to them without the patients' knowledge, under the supervision of the psychiatrist [32].

Given all of these different factors affecting the current management of schizophrenia, what can be done to improve such care? Ensuring that patients receive effective treatments promises to be the best antidote to stigma. When patients' conditions improve, especially in the restoration of their social functioning, the community's explanatory model of schizophrenia often shifts from a magico-religious to a medico-social viewpoint. The National Mental Health Programme will have to be scaled up to ensure that mental health care reaches the masses. At the same time, the government should plan and implement awareness programmes for schizophrenia all over the country, as it did for leprosy and tuberculosis.

Efforts will simultaneously have to be made to prevent Indian psychiatrists from going abroad, since their numbers have dwindled rapidly in the last few years. More psychiatry tuition in the undergraduate medical curriculum is also critical. Unless all these measures are implemented urgently and in a comprehensive manner, mental health care will continue to languish in the backyards of the health-care system. ■

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Schizophrenia medication adherence in a resource-poor setting: randomised controlled trial of supervised treatment in out-patients for schizophrenia (STOPS)

Saeed Farooq, Zahid Nazar, Muhammad Irfan, Javed Akhter, Ejaz Gul, Uma Irfan and Farooq Naeem

Background

Most people with schizophrenia in low- and middle-income (LAMI) countries receive minimal formal care, and there are high rates of non-adherence to medication.

Aims

To evaluate the effectiveness of an intervention that involves a family member in supervising medication administration – supervised treatment in out-patients for schizophrenia (STOPS) – in improving treatment adherence and clinical outcomes.

Method

Individuals ($n=110$) with schizophrenia or schizoaffective disorders were allocated to STOPS or to treatment as usual (TAU) and followed up for 1 year. The primary outcome was

adherence to the treatment regimen. Positive and Negative Syndrome Scale for Schizophrenia and Global Assessment of Functioning scores were also assessed.

Results

Participants in the STOPS group had better adherence (complete adherence: 37 (67.3%) in STOPS v. 25 (45.5%) in TAU; $P<0.02$) and significant improvement in symptoms and functioning.

Conclusions

STOPS may be useful in enhancing adherence to treatment for schizophrenia in LAMI countries.

Declaration of interest

None.

Maintaining long-term treatment in non-communicable diseases is a major public health challenge faced by many low- and middle-income (LAMI) countries, where these disorders are likely to account for more than 40% of the burden of disease by 2040.¹ The situation is particularly alarming for chronic mental disorders. In LAMI countries only 13% of people with bipolar disorders receive treatment compared with 51% and 77% of those with asthma and diabetes.² With less than one qualified mental health professional for half to one million people and about 1% of the health budget dedicated to mental health,³ most people with schizophrenia in LAMI countries probably receive little or no formal care. One manifestation of this is a very long duration of untreated psychosis (DUP) in the first episode in LAMI countries: 125 weeks compared with 62.5 weeks reported in high-income countries.⁴ This poses a major public health problem considering that around 41.7 million people with schizophrenia may need care in LAMI countries.⁵

Poverty is a major barrier to adherence to treatment in schizophrenia in these countries.⁵ It is estimated that rates of adherence to treatment 1 year after discharge from hospital are only around 50%.^{6,7} The actual rate of non-adherence may be even higher, as these estimates do not account for individuals who refuse treatment or drop-out of follow-up studies⁸ and are based on studies from health systems where drug treatment is at least partially subsidised. Moreover, there is little evidence to suggest that newer antipsychotics are associated with better rates of adherence compared with first-generation antipsychotics.⁹ The result is high relapse rates, spiralling costs and perpetuation of stigma.

We suggested that a framework based on the principles of DOTS (directly observed therapy, short course), devised originally for tuberculosis, could be used to overcome the public health challenge of non-adherence and maintaining long-term treatment in people with schizophrenia in resource-poor settings.^{10,11} The

strategy promoted by the World Health Organization as DOTS has been the cornerstone of a policy package to provide the complete course of treatment in tuberculosis, which is crucial to avert the emerging challenge of highly dangerous multiple-drug-resistant tuberculosis arising from partially treated cases.¹² We argued that the essential ingredients of the DOTS approach – registration and recording of individuals, free access to essential medication, and monitoring drug adherence by observing and recording the correct medication – could be used to treat schizophrenia in LAMI countries.

These principles of DOTS were incorporated in an intervention entitled STOPS^{9,10} (supervised treatment in out-patients for schizophrenia). The intervention was developed after focus group discussions with staff involved in implementation of DOTS in the local tuberculosis control programme in order to learn about the principles of DOTS that could be incorporated into the care of those with schizophrenia. Focus group discussions were also conducted with people with schizophrenia and their families. This revealed that the primary concerns for family members centred on misconceptions about treatment, stigma and supernatural beliefs about the illness. Therefore, we incorporated psychoeducation in the intervention to address these concerns, in addition to techniques for administering and supervising the medication.

The rationale and details of the approach are fully described elsewhere.^{9,10} Briefly, STOPS comprises the following components.

- Registration and recording of all people presenting with a diagnosis of schizophrenia/schizoaffective disorder from a geographically defined catchment area.
- Training a key care supervisor, identified by the patient and usually a close relative, in administering and supervising the medication. The key care supervisor took responsibility for

collecting the medicine from the health facility, administering the correct dosage of all the medication and recording adherence with treatment.

- (c) Uninterrupted drug supplies to provide drug treatment following a simple standardised treatment protocol. The treatment protocol was adapted from the American Psychiatric Association guidelines for treatment of schizophrenia.¹³ The sequence of treatment was simplified to reflect the services and resources available in a LAMI country setting. Medicines were provided every month at the health facility. Both the patient and the carer reported on adherence with treatment.
- (d) Standardised monitoring of therapy and outcome. This consists of adherence with the medication and assessment of functioning using the Global Assessment of Functioning (GAF) scale.¹⁴

The present study describes a randomised controlled trial (RCT) aimed at testing the effectiveness of STOPS. The primary outcome was to compare the effectiveness of STOPS in improving adherence with a regimen of standard doses of antipsychotic medication in participants with schizophrenia and schizoaffective disorders compared with treatment as usual (TAU). The study design was a two-arm prospective RCT over a 1-year period, with masking of assessors to the status of the intervention. The trial is registered at ClinicalTrials.gov (NCT00392249).

Method

The study protocol was approved by the Research Ethics Committee of the Postgraduate Medical Institute, Lady Reading Hospital, Peshawar, Pakistan. After a complete description of the study was given to the participant and the caregiver, written informed consent was obtained from both. Since a significant proportion of the patient population was illiterate, special care was taken to explain the procedures in Pushto, the language spoken by this population. No monetary incentives were provided to the participants in the trial.

Study settings and participants

The study was conducted at Psychiatry Department of Lady Reading Hospital, Peshawar. This is one of the two major tertiary care mental health centres that serve a large population in Khyber Pukhtunkhwa province (previously known as North West Frontier Province) of Pakistan and adjoining areas of Afghanistan. For the purpose of this study we only recruited people from the Peshawar district, which has a population of about two million. The inclusion criteria were: (a) aged 17 to 60 years; (b) a diagnosis of schizophrenia or schizoaffective disorder based on the ICD-10 Research Diagnostic Criteria (RDC);¹⁵ and (c) residence in Peshawar district. The exclusion criteria were evidence of organic disorder, ICD-10 'mental retardation', and severe drug dependence requiring in-patient treatment and/or detoxification. Recruitment to the study started in November 2006 and the final follow-up of participants was carried out in January 2009.

Based on the literature, an average rate of adherence to medication at 1 year for those with schizophrenia is 50%.^{6,7} We expected the rate of medication adherence to be 75% in the intervention group. Thus, a sample size of 45 participants per group would have 80% power to detect a 25% difference in the rate of adherence to medication between the two study groups with a one-sided significance of 5%. To control for non-adherence and losses to follow-up 55 people were recruited in each group.

Procedures

Eligible individuals were identified from the out-patients presenting to the psychiatry department at Lady Reading Hospital.

They were first screened by trained psychiatrists working in the out-patients department and subsequently assessed by one of three consultant psychiatrists (S.F., Z.N., J.A.) to satisfy the ICD-10 criteria for the diagnosis of schizophrenia and schizoaffective disorders.¹⁵ After identifying eligible individuals through interview and reviews of previous notes, therapists were asked to approve their recruitment into the study. Individuals who met inclusion criteria were randomly assigned to each treatment group. The random allocations of patients to each group were enclosed in opaque envelopes which were sealed and numbered sequentially. These allocations were placed away from the site of assessment. After assessment and satisfying the inclusion criteria, the staff which were not part of the study were asked to open the sealed envelope and reveal the treatment arm for each patient.

STOPS and control groups

The salient features of the two interventions are shown in the Appendix. Psychiatrists for the TAU (control) group were asked to provide treatments as they would normally deliver in routine out-patient settings. This included prescribing evidence-based pharmacological treatments, out-patient attendance in the psychiatry department as deemed appropriate by the consultant and brief counselling about the treatment and outcome. Participants who could not afford to buy medication had the option to seek free drug treatment from the social welfare department of the hospital, which provided treatment for the participants from the Zakat Fund (a fund established to provide essential medicine for patients who are poor from a charity funding based on Muslim law). The participants in the STOPS arm received the usual care and in addition they each had a key care supervisor, defined as any family member living with the individual for at least 6 months and providing support for the treatment as identified by the participant. Specific education was provided to the key care supervisor about the nature of the illness, misconceptions about treatment, the relationship between supernatural and biological causes of illness and the importance of continuing the medication, as well as basic skills in how to administer and supervise the medication. It was emphasised that participants should not be antagonised and violence should never be used in case of refusal to accept the treatment. Steps involved in collecting medicine from the treatment centre, storage at home, administering tablets and their ingestion by the participant and how to confirm this were demonstrated. The medications required were provided 1 month at a time. The intervention was first implemented in a pilot project over 1.5 years⁹ and therefore trainers and assessors were adequately trained and experienced in providing the intervention.

Doses in each group were titrated according to the clinical needs of the individual. All participants received atypical antipsychotics with the exception of those who were already on typical antipsychotics and were stable on these. Treatment teams for both STOPS and TAU participants consisted of two consultant psychiatrists, three postgraduate trainees with a minimum of 2 years training in psychiatry, two qualified psychiatric nurses and a master's level social worker.

Measurements

The baseline assessment included a clinical interview to satisfy the ICD-10 RDC criteria for diagnosis of schizophrenia and schizoaffective disorders, demographic data and illness history, GAF ratings¹⁴ and the Positive and Negative Syndrome Scale (PANSS) for Schizophrenia.¹⁶ The follow-up assessments at 3 months, 6 months and at the end of 1 year included: GAF ratings, PANSS and medication adherence using a scale devised for this purpose.

Adherence with medication was measured at interview using a questionnaire with a 5-point scale (where 1 is always and 5 is never) adapted from Herz *et al.*¹⁷ The scale was used in the pilot project by the research workers with a high degree of reliability.⁹ The assessments for adherence to treatment were done quarterly from baseline with the help of information provided by participants and relatives. The information was supplemented by the tablet counts from previous prescriptions where available. Complete adherence with medication was defined as participants always taking medication as prescribed without any break during the assessment period. Non-adherence was defined as missing drugs completely for more than a week at a time. If a participant took some medication but not on every day of the week, this was defined as partial adherence.

All assessments were carried out by doctors with at least 2 years' training in psychiatry. The same team of psychiatrists carried out all the follow-up assessments. The follow-up assessments were done by researchers who were masked to participant group assignment and instructed not to enquire about a participant's treatment during interviews. To ensure this, the administration of STOPS was kept completely separate from the research team assessing adherence and administering questionnaires for the trial and they were not associated with clinical care of the participants in the trial. The participants and relatives were briefed not to discuss their treatment with the assessors. All the participants remained in the study whether or not they were adherent with treatment, needed hospitalisation or relapsed. Attempts to maintain contact were made by telephone and/or home visits if participants did not appear for clinic visits at follow-up assessments.

Statistical analyses

Data were analysed in accordance with the CONSORT guidelines wherein the between-group comparisons were done using an intention-to-treat analysis.¹⁸ The intention-to-treat analysis was performed with the last observation carried forward. SPSS Version 16 for Windows was used for the analysis. Descriptive statistics were obtained on participants' baseline characteristics and the primary outcome measure was analysed as a categorical variable. Chi-squared tests were used to compare the distribution of baseline variables and adherence scores between the two study groups (95% CIs and *P*-values). The number of participants who had partially adhered to treatment was small in the follow-up assessments. Therefore, we combined the results for those with partial and non-adherence together for the purpose of this analysis. This is also in line with the measurement of adherence, as described originally by Herz *et al.*¹⁷ Parametric variables were then assessed for simple group differences using the *t*-test. A repeated-measures ANCOVA was used to measure the differences between the two groups at four time points (within- and between-group analyses). Baseline scores were used as covariates to take into account the initial differences. The Kolmogorov–Smirnov test was used to assess normality. The number of participants needed to be treated with STOPS to prevent one adverse outcome such as one participant not adhering to treatment in 1 year was calculated.

Results

The details of recruitment and follow-up are shown in Fig. 1. Fifty-five individuals were recruited in each arm and 95 (86.4%) participants completed the study; 49 in STOPS and 46 in the TAU group. The mean age of participants in the STOPS group was 29 years (s.d.=8.1), which did not differ significantly from the TAU group (mean age 30 years (s.d.=8.5), *P*=0.699). The

baseline sociodemographic and clinical variables were not significantly different in the two groups (Table 1). Similarly the relationship with the primary caregiver as defined by the participants did not differ significantly between the two groups. Those in the STOPS group had mean durations of illness of 73.6 months, compared with 83.8 months in the TAU group (*P*=0.485). No statistically significant difference was found between the two groups for PANSS and GAF ratings at baseline.

We compared the two groups at four time points to see whether the mean dosage of antipsychotic drugs was different in the two groups at any stage. The doses of all antipsychotics were converted to chlorpromazine equivalents.¹⁹ The differences were not significant for the time effect (Wilks' lambda 0.94, *F*(3,93)=1.89, *P*=0.136), and between-participant effect (*F*=0.24, d.f. = 1, *P*=0.878). The number of participants on depot medication also did not differ between the two groups.

Medication adherence, symptoms and functioning outcomes

The two groups showed a statistically significant difference in the primary outcome measure at the end of 1 year. In the intention-to-treat analysis at 1-year follow-up 37 participants (67%) in the STOPS group had complete adherence with medication compared with 25 (45%) in the TAU group (*P*<0.02) (Table 2). Using relative risks, it is estimated that participants in the STOPS group were 1.59 times more likely to adhere to medication than those in the TAU group (95% CI 1.03–2.53). The number needed to treat to achieve one positive outcome is five for STOPS.

The participants in the STOPS group showed significantly more improvement in symptoms and functioning, as measured by PANSS and GAF in the intention-to-treat analysis. Differences between the STOPS and TAU groups over time were measured using analysis of covariance, with baseline scores being used as covariates to account for the initial differences. Statistically

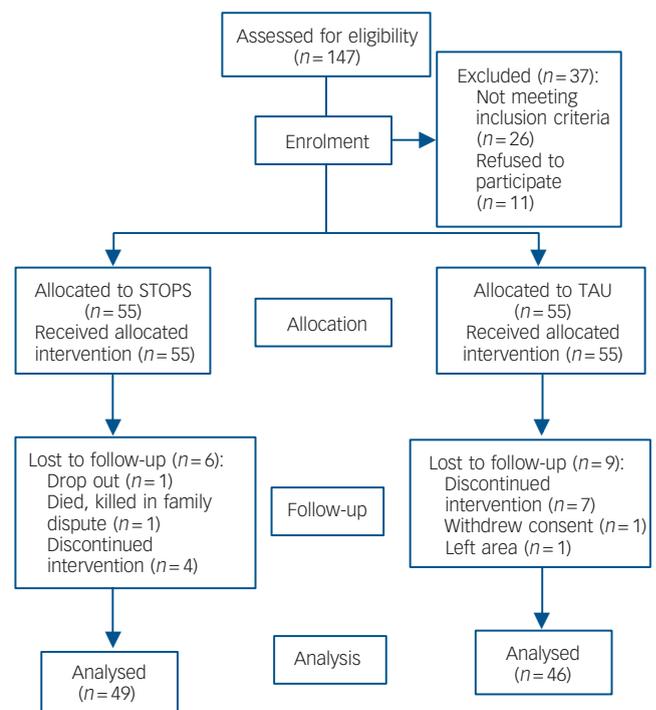


Fig. 1 The CONSORT flow chart for the randomised controlled trial of supervised treatment in out-patients for schizophrenia (STOPS) v. treatment as usual (TAU).

Table 1 Differences between the supervised treatment in out-patients for schizophrenia (STOPS) and treatment as usual (TAU) groups at baseline

	STOPS, n (%)	TAU, n (%)	P ^a
Gender			1.000
Male	47 (85.5)	47 (85.5)	
Female	8 (14.5)	8 (14.5)	
Marital status			0.999
Married	30 (54.5)	31 (56.4)	
Unmarried	22 (40.0)	21 (38.2)	
Divorced, widow/widower	3 (5.4)	3 (5.4)	
Employment status			0.480
Unemployed	40 (72.7)	41 (74.5)	
Employed	8 (14.6)	12 (21.9)	
Retired	1 (1.8)	0 (0)	
Student	6 (10.9)	2 (3.6)	
Education			0.520
No education	23 (41.9)	21 (38.1)	
5–9 years	18 (32.7)	14 (25.5)	
10 years or more	14 (25.4)	20 (29.3)	
Relationship with caregivers			0.286
Mother	6 (10.9)	4 (7.3)	
Father	11 (20.2)	16 (29.1)	
Child	1 (1.8)	4 (7.3)	
Spouse	2 (3.6)	5 (9.1)	
Brother	19 (34.5)	16 (29.1)	
Sister	3 (5.5)	4 (7.3)	
Other	13 (23.6)	6 (10.9)	
Course			0.216
Continuous	41 (74.5)	35 (63.6)	
Episodic	14 (24.5)	20 (36.4)	
Cannabis use			0.425
Current	6 (10.9)	10 (18.2)	
Past	4 (7.3)	2 (3.6)	
Never	45 (81.8)	43 (78.2)	
Diagnosis			1.000
Schizophrenia	45 (81.8)	45 (81.8)	
Schizoaffective disorder	10 (18.2)	10 (18.2)	

a. χ^2 -test.

significant differences existed for PANSS total scores, (time effect: Wilks' lambda 0.90, $F(3,105) = 3.54$, $P = 0.017$ and between-participant effect: $F = 9.0$, d.f. = 1, $P = 0.003$) and PANSS positive symptoms (time effect: Wilks' lambda 0.91, $F(3,102) = 3.31$, $P = 0.011$ and between-participant effect: $F = 5.9$, d.f. = 1, $P = 0.003$) in favour of STOPS. However, for PANSS negative symptoms neither time effect (Wilks' lambda 0.94, $F(3,102) = 1.2$, $P = 0.303$) nor between-participant effect ($F = 2.11$, d.f. = 1, $P = 0.149$) was significant. The GAF scores significantly improved over time in the STOPS group compared with the TAU group (time effect: Wilks' lambda 0.90, $F(3,106)$ d.f. = 3.66, $P = 0.036$ and for between-participant effect: $F = 7.3$, d.f. = 1, $P = 0.008$). Table 3 shows the descriptive statistics.

Discussion

Main findings

To our knowledge this is the first study that has attempted to test the effectiveness of a model based on the principles of DOTS in a non-infectious disease. A framework based on the DOTS strategy has been suggested to overcome the problems of non-adherence and continuity of care for non-communicable disorders in LAMI countries^{10,20} and has also been used for the delivery and monitoring of antiretroviral therapy for HIV/AIDS in resource-poor countries.²⁰ However, the effectiveness of the approach has not been tested in an RCT.

Table 2 Differences in medication adherence in the supervised treatment in out-patients for schizophrenia (STOPS) and treatment as usual (TAU) groups at three time points

Adherence	STOPS, n (%)	TAU, n (%)	P ^a
3 months			0.05
Complete	38 (69.1)	28 (50.9)	
Partial or none	17 (30.1)	27 (49.1)	
6 months			0.23
Complete	40 (72.7)	34 (61.8)	
Partial or none	15 (27.3)	21 (38.2)	
12 months			0.02
Complete	37 (67.3)	25 (45.5)	
Partial or none	18 (32.7)	30 (54.5)	

a. χ^2 -test.

We found that STOPS, which used an educational intervention for carers to administer and supervise the medication provided free of cost as part of a treatment programme, resulted in a significant improvement in adherence with medication. The trial did not have the statistical power to assess the effects of this experimental intervention on symptoms and functioning but the participants in the STOPS group showed a significant improvement in symptoms and functioning compared with TAU. The mean duration of illness in the two groups was more than 6 years. The improvement in symptoms and functioning in the STOPS group shows that maintaining regular treatment and engaging the family can have a significant impact even in a population with

Table 3 Comparison of the supervised treatment in out-patients for schizophrenia (STOPS) and the treatment as usual (TAU) groups for measures of psychopathology^a

	STOPS (n = 55) mean (s.d.)	TAU (n = 55) mean (s.d.)	P
Positive and Negative Syndrome Scale total scores			0.003
Baseline	101.80 (21.0)	94.6 (19.4)	
3 months	70.87 (23.18)	77.11 (21.29)	
6 months	67.38 (23.9)	76.96 (20.8)	
12 months	67.35 (24.66)	74.33 (21.58)	
Positive symptoms			0.003
Baseline	21.6 (6.7)	21.5 (6.3)	
3 months	12.6 (7.2)	16.6 (6.5)	
6 months	12.4 (7.0)	16.6 (6.7)	
12 months	13.6 (6.9)	15.3 (5.5)	
Negative symptoms			0.149
Baseline	21.3 (6.1)	19.4 (6.3)	
3 months	17.4 (6.0)	17.1 (7.6)	
6 months	16.3 (6.1)	17.2 (7.2)	
12 months	16.2 (6.8)	17.1 (7.6)	
General symptoms			0.007
Baseline	47.9 (10.6)	44.4 (8.9)	
3 months	33.7 (10.0)	36.6 (10.5)	
6 months	31.4 (10.9)	35.2 (10.2)	
12 months	30.3 (10.3)	33.8 (8.8)	
Global Assessment of Functioning scores			0.008
Baseline	42.56 (13.54)	45.95 (11.92)	
3 months	55.18 (14.5)	52.13 (15.8)	
6 months	58.71 (15.81)	52.67 (16.08)	
12 months	62.0 (16.70)	56.05 (18.12)	

a. Higher scores represent more psychopathology on the Positive and Negative Syndrome Scales, but not on the Global Assessment of Functioning scale where the reverse is the case. Analyses were carried out using repeated-measures ANCOVA (to compare within-participant and between-participant differences), with baseline values used as covariates.

chronic mental illness. This is consistent with other studies that reported similar improvement in symptoms and functioning at 9 months after discharge in participants receiving family education,²¹ and at 12- and 18-months follow-up in participants receiving a family-based intervention.²²

There is little available information on the effectiveness of strategies for extending care to people with severe mental illness in LAMI countries.²³ The essential components of STOPS (i.e. monitoring drug adherence by observation and recording of the correct medication by a guardian assigned to the patient) has been shown to be effective in a retrospective case-control study in rural China.²⁴ Broadly similar approaches have been shown to be cost-effective and significantly reduced disability and psychotic symptoms.^{25,26} However, these studies employed family or social interventions typically comprising at least one session of 1–2 h every 2 or 4 weeks over the study period, which is more akin to an assertive outreach programme and may be difficult to apply in LAMI countries. The STOPS approach, in contrast, used a brief intervention of initially one session, which was reinforced on subsequent visits, without directly addressing family dynamics or expressed emotion. The better adherence to treatment and improvement in symptoms in this cohort is consistent with the evidence from a systematic review of interventions to improve medication adherence in schizophrenia that showed that relatively brief interventions (both in terms of duration and frequency) that targeted the behaviours related to medication adherence were more effective than longer interventions with a broader focus on psychoeducation.⁷

Most of the key care supervisors were first-degree relatives. Spouses were involved only in 3.6% and 9.1% of STOPS and TAU groups respectively, despite the fact that more than half of the participants in both groups were married. This reflects the routine involvement of the extended family in the care of those with a severe mental illness. Involvement of family members as treatment supervisors to improve treatment adherence could have adverse consequences for the family members and possibly for patients in the form of coercion to take treatment. The latter was specifically addressed during the pilot phase and the development of the intervention.^{9,10} Psychoeducational programmes are generally found to decrease the family burden and improve aspects of family functioning such as problem-solving, communication and interpersonal relationships.^{21,26} These aspects of care were, however, not evaluated in this RCT and will need to be addressed in future studies.

Limitations

It can be argued that the provision of free drugs could have contributed to the better outcome in the STOPS group. The average cost of medication for a month using atypical drugs is about 900 rupees (£1 is equivalent to approximately 136 rupees), which can be quite costly for patients and families from lower socioeconomic backgrounds presenting in a public hospital such as Lady Reading Hospital. The DOTS is a complex intervention and free access to medication is an essential component of the DOTS programme as applied in tuberculosis control.¹² The participants in the TAU group had the option of accessing free drugs from the social welfare department. Providing free medication as part of the trial would have grossly distorted the TAU condition in these settings. The evidence, however, suggests that even if drugs were free, non-adherence persists. One recent study showed that even among people who have health plans with no cost-sharing for medication, rates of non-adherence were nearly 40%.²⁷

Other limitations in evaluating the results of this study should also be recognised. We selected standard out-patient care for

comparison, which is most often the only type of mental healthcare available in these settings. Treatment as usual is criticised as a comparator in evaluation of complex interventions as the healthcare system in which the treatment programme is embedded is known to have important consequences for outcome.²⁸ The drug supply for the TAU group could vary in supply and quality, being dependent upon local pharmacies. It can be argued that the participants in the STOPS group had increased contact with the team to collect medication, which could have contributed to better adherence. However, this should be balanced against the fact that participants in the TAU group received more support for their treatment from the research and social services department of the hospital, being a focus of attention in a research study. Enhanced care associated with regular assessment of adherence and follow-up visits in this RCT was not typical 'treatment as usual'. It is also well known that the measures that rely on subjective reports of pill taking to measure adherence in schizophrenia tend to overestimate adherence and reduces the likelihood of detecting intervention effects.⁸ These limitations should, however, minimise the difference between the two groups. The masking of research interviewers to the treatment group could not be completely assured since the study was not placebo-controlled, with the possibility that research interviewers favoured the STOPS group. The contamination of treatments was also possible, i.e. the treatment team providing TAU would act more like the team providing the experimental intervention over time.

Implications for service provision and research

Interventions for people with schizophrenia in LAMI countries should primarily involve the families as more than 90% of patients in these countries live within a family unit.⁵ This study provides preliminary evidence that a package of care based on a brief educational intervention for the families, and supervision and easy access to medication as envisaged in the DOTS strategy using a simple treatment regimen can be used to improve services for people with schizophrenia in LAMI countries. Adopting a model of care devised essentially to treat an infectious disorder like tuberculosis for a chronic illness that may run a lifelong course will require certain modifications. Neither health systems in most LAMI countries nor caregivers can be expected to provide the lifelong commitment required for a STOPS programme. However, the initial 2 years in the course of schizophrenia have been described as the 'critical period'. The treatment status during this period is the strongest predictor of long-term outcome and disability.²⁹ Even a gap as small as 1–10 days in medication adherence over a 1-year period has been found to be significantly associated with an increased risk of hospitalisation with an odds ratio of 1.98.³⁰ Based on this evidence and recommendations from a systematic review of interventions to address non-adherence in schizophrenia that clinical interventions targeting non-adherence should continue for at least 18 months,⁸ we suggest an approach for early intervention for psychosis in LAMI countries. It is proposed that people with schizophrenia should be provided with an uninterrupted drug supply based on a public health programme like STOPS for an initial 2-year period.

The present study sample consisted of participants with a relatively chronic course of illness as recruiting a first-episode sample would have taken much longer and was not feasible within our resources. The approach suggested in this trial now needs to be evaluated in first-episode psychosis, as effective intervention during this period is likely to achieve maximum long-term gains during the entire course of the illness. The effectiveness of this approach in non-specialist health settings in view of the shortage

of psychiatrists in LAMI countries, and the cost-effectiveness of STOPS, will also need to be evaluated.

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Appendix

Comparison of supervised treatment in out-patients for schizophrenia (STOPS) with treatment as usual (TAU)

	STOPS	TAU
Setting	Community	Community
Therapist's contact with patient/family	Participants and an identified family member (key care supervisor)	Participant, family member (any family member)
Access to medication	Supplied free by the programme	Had the option of obtaining free drugs provided by social service, may be out of pocket
Supervision for medication	Medicine administered under supervision of key care supervisor	None
Participant and family education	One session at the start to educate the key care supervisor to administer and supervise the drugs	No specific session, some education may be provided by therapist
Frequency	Once a month to collect the drugs	Variable as deemed necessary by therapist
Service provided by	Psychiatrist, social worker, psychiatric nurses	Psychiatrist, social worker, psychiatric nurses

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Data supplement

Table DS1 Studies of DUP from low- and middle-income (LAMI) economies classified using World Bank criteria

Study	Country	Main outcome studied	Included affective psychosis	Onset of DUP	End of DUP	Diagnostic system	Number of samples	Mean DUP of all patients in the study
Upper-middle-income economy								
Alpteken <i>et al</i> , 2005 ¹⁷	Turkey	Outcome DUP	No	Psychotic symptoms	Antipsychotic treatment	DSM-IV	2	48.4
Apiquian <i>et al</i> , 2002 ¹⁸	Mexico	Outcome DUP	Yes	Psychotic symptoms	Contact with services	SCAN	2	54.3
Fresán <i>et al</i> , 2003 ²²	Mexico	Premorbid functioning	Yes	Psychotic symptoms	Antipsychotic treatment	SCAN/DSM	2	60.0
Gill <i>et al</i> , 2005 ²⁵	Malaysia	Descriptive DUP	Yes	Psychotic symptoms	Hospital admission	SIPS	1	47.7
Galińska <i>et al</i> , 2005 ²⁴	Poland	Cognitive function	No	Psychotic symptoms	Antipsychotic treatment	PANNS	1	31.3
Oosthuizen <i>et al</i> , 2005 ³⁵	South Africa	Outcome DUP	No	Psychotic symptoms	Antipsychotic treatment	DSM-IV	2	32.7
Lower-middle-income economy								
Ayres <i>et al</i> , 2007 ¹⁹	Brazil	Cognitive function	Yes	Psychotic symptoms	Contact with services	DSM-IV	3	37.7
El-Adl <i>et al</i> , 2007 ²¹	Egypt	Pathways to care DUP	Yes	Psychotic symptoms	Contact with services	ICD-10	2	30.1
Gorwood <i>et al</i> , 2008 ²⁶	Reunion Island ^a	Gender and onset	No	Criteria for schizophrenia	Contact with services	DSM-III-R	2	51.6
Kurihara <i>et al</i> , 2002 ^{28,29}	Indonesia	Mortality DUP	No	Psychotic symptoms	Hospital admission	DSM-III	1	124.8
Lieberman <i>et al</i> , 2003 ³⁰	China	Drug trial	No	Psychosis symptoms	Antipsychotic treatment	SCID/DSM	1	79.1
Ran <i>et al</i> , 2001 ^{36,37}	China	Outcome of psychosis	No	Psychosis symptoms	Contact with researchers	PSE	3 ^b	236
Ranjbar <i>et al</i> , 2006 ³⁸	Iran	Pathways to care DUP	Yes	Psychotic symptoms	Hospital admission	DSM-IV	2	45.5
Selten <i>et al</i> , 2005 ³⁹	Suriname	Incidence	No	Psychosis symptoms	Contact with services	IRAOS	1	88.1
Tang <i>et al</i> , 2007 ⁴⁰	China	Pathways to care DUP	No	Psychosis symptoms	Hospital admission	ICD-10	2	116.5
Low-income economy								
Calvo de Padilla <i>et al</i> , 2006 ²⁰	Argentina ^c	Temperament	No	Psychotic symptoms	Contact with researchers	SCAN	1	468
Gangadhar <i>et al</i> , 2002 ²³	India	Gender and onset	No	Psychotic symptoms	Contact with services	–	4	98.8
Gureje & Bamidele, 1998 ²⁷	Nigeria	Gender and onset	No	Nuclear symptoms	Contact with services	RDC	2	152.4
Mbewe <i>et al</i> , 2006 ³¹	Zambia	Descriptive DUP	Yes	Psychotic symptoms	Hospital Admission	DSM-IV	1	48.1
McCreadie <i>et al</i> , 2005 ³² ; Tirupati <i>et al</i> ⁴²	India	Movement disorder	No	Psychotic symptoms	Contact with researchers	DSM-IV	1	556
Murthy <i>et al</i> , 1998 ³³	India	Gender and onset	No	Psychotic symptoms	Contact with services	DSM-IV	2	85.8
Naqvi <i>et al</i> , 2005 ³⁴	Pakistan	Gender and onset	No	Psychotic symptoms	Contact with services	–	2	110.2
Thirithalli <i>et al</i> , 2005 ⁴¹	India	Outcome DUP	No	Psychosis symptoms	Contact with services	ICD-10	1	97.2

DUP, duration of untreated psychosis; IROAS, Instrument for the Retrospective Assessment of the Onset of Schizophrenia; PANNS, Positive and Negative Syndrome Scale; PSE, Present State Examination. RDC, Research Diagnostic Criteria; SCAN, Schedule for Clinical Assessment in Neuropsychiatry; SCID, Structured Clinical Interview for DSM-IV; SIPS, Structured Interview for Prodromal Symptoms.

a. Overseas department of France.
b. One sample of intermittently treated patients was excluded, those with contact with traditional healers only regarded as untreated.
c. Classified as low-income as the study was conducted in a remote indigenous community.

Table DS2 Studies from high-income countries used as a control group

Study ^a	Country in which the study was conducted	Includes affective psychosis	No. samples used ^b	DUP weighted mean of all included participants in samples used, ^c weeks
Addington <i>et al.</i> , ¹ 2004	Canada	No	1	84.2
Altamura <i>et al.</i> , ² 2003	Italy	No	2	52
Altamura <i>et al.</i> , ³ 2001	Italy	No	2	83.4
Archie <i>et al.</i> , ⁴ 2005	Canada	Yes	1	91
Ballageer <i>et al.</i> , ⁵ 2005	Canada	No	2	69.6
Barnes <i>et al.</i> , ⁶ 2000	UK	No	1	59
Beiser <i>et al.</i> , ⁷ 1993	Canada	Yes	6	33.4
Birchwood <i>et al.</i> , ⁸ 1992	UK	No	1	30.3
Black <i>et al.</i> , ⁹ 2001	Canada	No	1	75.5
Carbone <i>et al.</i> , ¹⁰ 1999	Australia	Yes	2	29.1
Carlsson <i>et al.</i> , ¹¹ 2006	Sweden	No	2	55.6
Caton <i>et al.</i> , ¹² 2006	USA	No	2	51.3
Chen <i>et al.</i> , ¹³ 2005	Hong Kong ^d	No	1	73.3
Chong <i>et al.</i> , ¹⁴ 2005	Singapore	No	1	137.6
Chow <i>et al.</i> , ¹⁵ 2005	Hong Kong ^d	Yes	1	34.3
Clarke <i>et al.</i> , ¹⁶ 2006	Ireland	No	1	76.5
Cohen <i>et al.</i> , ¹⁷ 2000	Canada	No	2	91.2
Compton <i>et al.</i> , ¹⁸ 2006	USA	No	1	65.3
Cougnard <i>et al.</i> , ¹⁹ 2004	France	yes	1	187.2
Craig <i>et al.</i> , ²⁰ 2000	USA	No	3	MNR
Crespo-Facorro <i>et al.</i> , ²¹ 2007	Spain	No	1	61.5
de Hann <i>et al.</i> , ²² 2003	The Netherlands	No	1	37
Drake <i>et al.</i> , ²³ 2000	UK	No	1	38
Fannon <i>et al.</i> , ²⁴ 2000	UK	No	1	28.1
Friis <i>et al.</i> , ²⁵ 2004	Norway	No	1	MNR
Fuchs <i>et al.</i> , ²⁶ 2004	Germany	No	1	71
Gunduz-Bruce <i>et al.</i> , ²⁷ 2005	USA	No	2	69.5
Haas <i>et al.</i> , ²⁸ 1992	USA	No	3	98.8
Hafner <i>et al.</i> , ²⁹ 1993	Germany	No	1	109.2
Haley <i>et al.</i> , ³⁰ 2003	UK	No	1	53.2
Harrigan <i>et al.</i> , ³¹ 2003	Australia	Yes	2	26.4
Harris <i>et al.</i> , ³² 2005	Australia	Yes	3	42.6
Hides <i>et al.</i> , ³³ 2006	Australia	Yes	1	16.7
Ho <i>et al.</i> , ³⁴ 2000	USA	No	1	74
Kalla <i>et al.</i> , ³⁵ 2002	Finland and Spain	No	2	28.1
Kampman <i>et al.</i> , ³⁶ 2004	Finland	Yes	1	40
Keshavan <i>et al.</i> , ³⁷ 2003	USA	Yes	1	95.7
Kinoshita <i>et al.</i> , ³⁸ 2005	Japan	No	1	42.6
Lambert <i>et al.</i> , ³⁹ 2005	Australia	Yes	1	12.2
Larsen <i>et al.</i> , ⁴⁰ 2001	Norway	No	1	114.2
Linzen <i>et al.</i> , ⁴¹ 2001	Netherlands	No	1	23.22
Loebel <i>et al.</i> , ⁴² 1992	USA	No	2	51.9
Loranger, ⁴³ 1984	USA	No	2	88.4
Madsen <i>et al.</i> , ⁴⁴ 1999	Denmark	No	2	36.7
Mauri <i>et al.</i> , ⁴⁵ 2006	Italy	No	1	72.3
Melle <i>et al.</i> , ⁴⁶ 2005	Norway and Denmark	No	2	49.1
Meng <i>et al.</i> , ⁴⁷ 2006	Germany	Yes	1	30.5
Milton <i>et al.</i> , ⁴⁸ 2001	UK	Yes	2	MNR
Møller, ⁴⁹ 2001	Norway	No	1	38.4
Morgan <i>et al.</i> , ⁵⁰ 2006	UK	Yes	1	58
Moscarelli <i>et al.</i> , ⁵¹ 1991	Italy	No	1	81.7
Pek <i>et al.</i> , ⁵² 2006	Singapore	Yes	2	70.1
Peralta <i>et al.</i> , ⁵³ 2005	Spain	No	1	169.4
Perkins <i>et al.</i> , ⁵⁴ 2004	USA	No	3	67.9
Petersen <i>et al.</i> , ⁵⁵ 2005	Denmark	No	2	MNR

(continued)

Table DS2 (continued)

Study ^a	Country in which the study was conducted	Includes affective psychosis	No. samples used ^a	DUP weighted mean of all included participants in samples used, ^b weeks
Preston <i>et al.</i> , ⁵⁶ 2003	Australia	Yes	2	30.5
Reilly <i>et al.</i> , ⁵⁷ 2006	USA	No	1	52
Röpcke & Eggers, ⁵⁸ 2005	Germany	No	1	40.8
Rosen & Garety, ⁵⁹ 2005	UK	No	4	18.4
Rowlands, ⁶⁰ 2001	UK	No	1	54.6
Sannomiya <i>et al.</i> , ⁶¹ 2003	Japan	No	1	41.1
Seikkula <i>et al.</i> , ⁶² 2006	Finland	No	2	16
Singh <i>et al.</i> , ⁶³ 2005	UK	Yes	2	15.4
Skeate <i>et al.</i> , ⁶⁴ 2002	UK	No	1	42.1
Stratowski <i>et al.</i> , ⁶⁵ 1995	USA	Yes	3	187.7
Szymanski <i>et al.</i> , ⁶⁶ 1996	USA	No	1	166
Turner <i>et al.</i> , ⁶⁷ 2006	New Zealand	Yes	1	28.14
Turner <i>et al.</i> , ⁶⁸ 2006	UK	No	1	47.3
Verdoux <i>et al.</i> , ⁶⁹ 2001	France	Yes	1	97.6
Wade <i>et al.</i> , ⁷⁰ 2006	Australia	Yes	3	24.4
Wang <i>et al.</i> , ⁷¹ 2005	Japan	No	2	129.7
Wunderink <i>et al.</i> , ⁷² 2006	The Netherlands	No	1	46.3
Yamazawa <i>et al.</i> , ⁷³ 2004	Japan	No	2	58.91
Yap <i>et al.</i> , ⁷⁴ 2001	Singapore	No	1	23.7
Yung <i>et al.</i> , ⁷⁵ 2003	Australia	Yes	1	67

DUP, duration of untreated psychosis; MNR, mean DUP not reported.
a. Reference numbers refer to list in this supplement, not to the list in the main paper.
b. Samples that were reported in other included studies were omitted.
c. Weighted mean calculated by dividing the sum of products of the number of participants and the mean DUP of each sample by the total number of included participants.
d. Special administrative region of China.

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Table DS3 Multiple linear regression of factors associated with \log_{10} mean DUP, weighted for the number of participants in each sample

	Unstandardised		Standardised		P
	B	s.e.	Beta	t	
Constant	2.127	0.220		9.648	<0.001
Study from a LAMI economy	0.237	0.063	0.295	3.749	<0.001
Samples of schizophrenia-related psychosis	0.238	0.061	0.298	3.922	<0.001
Proportion of male participants	-0.001	0.001	-0.091	-1.186	0.237
Mean age at onset of psychosis	-0.011	0.008	-0.112	-1.416	0.159

DUP, duration of untreated psychosis; LAMI, low- and middle-income.
ANOVA regression: sum of squares=332.6, d.f.=4, mean square=83.17, $F=9.72$, $P\leq 0.001$; ANOVA residual: sum of squares=1223, d.f.=143, mean square 8.56.

Table DS4 Relationship between GDP purchasing power parity and mean DUP of all samples that had contact with services from LAMI countries^a

	Unstandardised		Standardised		P
	B	s.e.	Beta	t	
Constant	114.2	12.7		8.99	<0.0001
GDP purchasing power parity	-0.006	0.002	-0.497	-3.337	0.002

DUP, duration of untreated psychosis; GDP, gross domestic product; LAMI, low- and middle-income.
ANOVA regression: sum of squares=977 170, d.f.=1, mean square=977170, $F=11.13$, $P=0.002$; ANOVA residual: sum of squares=2 984 387, d.f.=34, mean square=87 776.
a. Samples of patients who had not received treatment (contact with researchers only) omitted. Dependent variable mean DUP. Linear regression weighted by sample size.

Table DS5 Relationship between GDP purchasing power parity and mean DUP of samples of patients with schizophrenia-related psychosis from LAMI countries^a

	Unstandardised		Standardised		P
	B	s.e.	Beta	t	
Constant	135.5	13.66		9.92	<0.001
GDP purchasing power parity	-0.009	0.002	-0.644	-4.212	0.001

DUP, duration of untreated psychosis; GDP, gross domestic product; LAMI, low- and middle-income.
ANOVA regression: sum of squares=1 274 546, d.f.=1, mean square=1 274 546, $F=17.74$, $P\leq 0.0001$; ANOVA residual: sum of squares=1 796 477, d.f.=25, mean square=71 859.
a. Samples of patients who had not received treatment (contact with researchers only) omitted. Dependent variable Mean DUP. Linear regression weighted by sample size.

