

Review article

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

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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

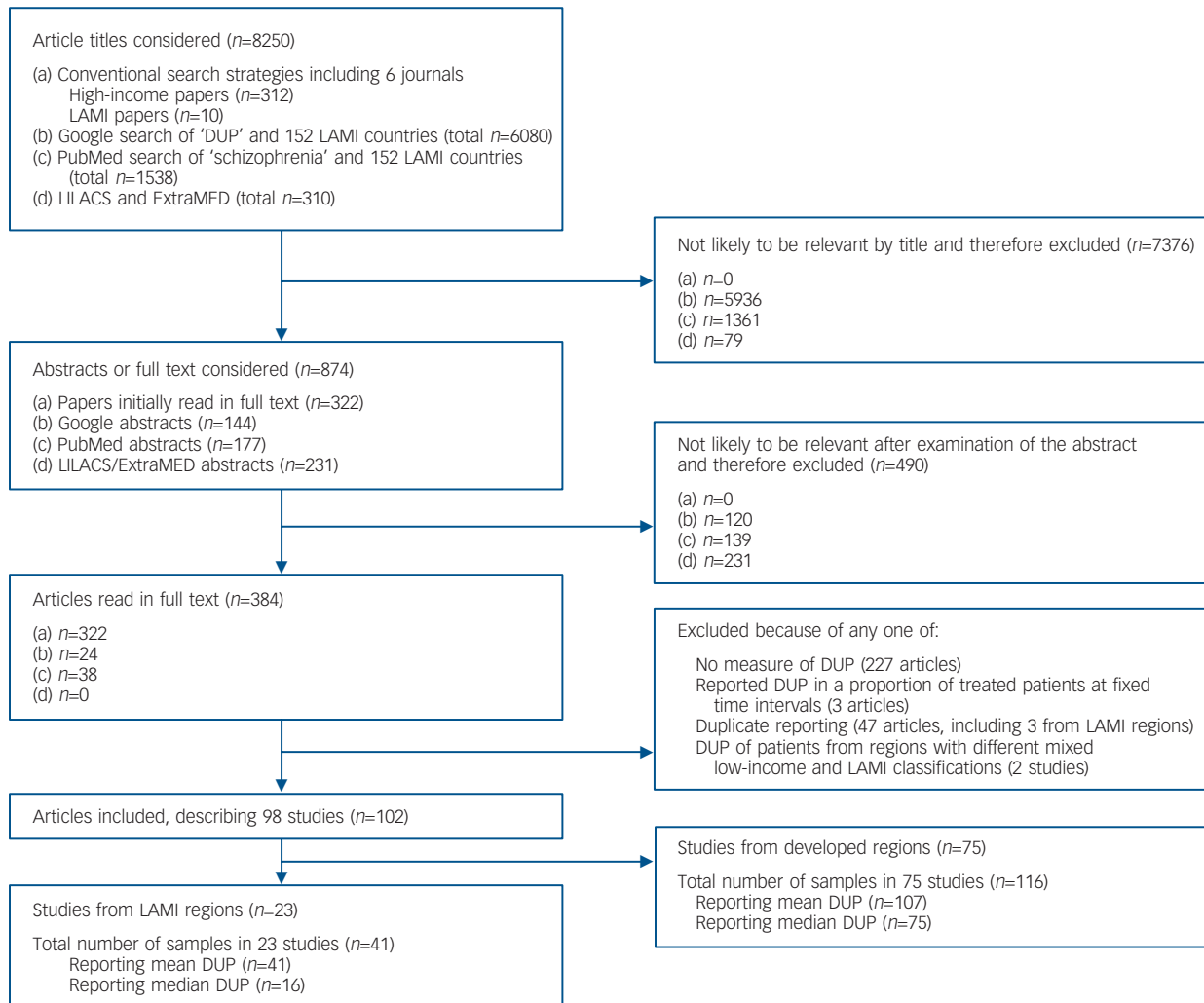


Fig. 1 Flow chart of searches for DUP studies from LAMI and high-income regions.

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 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 v. high-income		d.f.	Statistic	P
	Low-income	Lower-middle income	Upper-middle income	LAMI	High-income			
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

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