A rural lifestyle and lack of stigma might help Indians recover faster from schizophrenia.

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DEVELOPING COUNTRIES

# The outcomes paradox

*Schizophrenia patients in developing countries seem to fare better than their Western counterparts. Researchers are keen to find out why.*

BY T. V. PADMA

The pattern for most diseases is clear: the richer and more developed the country, the better the patient outcome. Schizophrenia appears to be different.

This paradox first came to light 40 years ago. Studies from Mauritius and Sri Lanka appeared to show better outcomes than developed countries: patients experienced fewer delusions and hallucinations, less disorganized speech, and improved social functioning. But these studies lacked standardized diagnostic criteria and assessment methods, and had varying attrition rates.

In the late 1960s, in an effort to standardize research methods, the World Health Organization (WHO) launched the first of the following three landmark international studies: the International Pilot Study of Schizophrenia (IPSS); the Determinants of Outcomes of Severe Mental Disorders (DOSMeD); and the International Study of Schizophrenia (ISoS).

The IPSS enrolled a total of 1,202 patients in nine countries: three developing countries (Colombia, India and Nigeria) and six developed ones (Denmark, Taiwan, the United Kingdom, the United States, the Soviet Union and Czechoslovakia). The patients' outcomes were assessed by using three indicators — the percentage of time with psychosis symptoms, the type of remission after each episode, and the degree of social impairment — and were classified on a scale of one (best) to seven (worst). At the five-year follow-up, India had the most success, with 42% of cases reporting 'best' outcomes, followed by Nigeria with 33% of cases. By contrast, the developed countries had poor showings: 'best' outcomes were seen in only 17% of cases in the United States, and in fewer than 10% in the other developed nations.

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Beginning in the early 1980s, the DOSMeD study examined schizophrenia incidence, prevalence and outcomes in 12 centres across 10 countries (the IPSS countries plus Ireland). Its 1,379 patients were assigned to 1 of 9 categories, ranging from a single episode of psychotic illness followed by complete remission, to continuing illness. The study found that developing countries had higher rates of complete recovery: an average of 37% compared with 15.5% in developed countries. The rates of chronic illness, however, were similar: 11.1% in developing and 17.4% in developed countries. Patients in developing countries experienced longer periods of unimpaired social functioning, even though far fewer of them were on continuous antipsychotic medication. The researchers concluded that "a strong case can be made for a real pervasive influence of a powerful factor which can be referred to as 'culture' in the context of gene–environment interactions that influence a disease. The contribution of the present study is not in providing the answer but in clearly demonstrating the existence of the question."

The ISoS study returned to the IPSS and DOSMeD patients after 15 and 25 years, and included two other groups, to test whether the better outcomes observed in the previous studies continued in the long term. It traced about 75% of the patients, finding that about half had favourable outcomes, but there was wide variation across different centres. The study concluded that socio-cultural conditions can modify the long-term disease course, and that early intervention programmes with social and pharmacological treatments could have longer-term benefits.

## VARIABLE RESULTS

These WHO studies were far from perfect, however. The IPSS studies looked only at patients in psychiatric facilities, and so may not represent the wider population. The DOSMeD study, in contrast, actively sought out patients not in such facilities. All the studies experienced high attrition rates from participants in developing countries, for reasons ranging from premature death to losing track of patients. Unfortunately, these drop-outs biased the results, as it was generally the 'worst' patients who dropped out. Patient selection and assessment of social functioning also varied. But despite these reservations, the idea that culture affects schizophrenia outcomes — and that developing countries perform better because of their culture — persisted.

In 2009, psychiatrist Parmanand Kulhara of the Postgraduate Institute of Medical

Education and Research in Chandigarh, India, reviewed 58 schizophrenia studies to compare outcomes from developed and developing nations[1]. With a few exceptions, he found that developing countries have a larger proportion of patients (50–60%) with good outcomes than developed countries in follow-up examinations after two and five years. These differences persisted beyond 15 years, but to a lesser extent. "Despite the controversies surrounding the favourable outcome hypothesis, we believe that the evidence arising from various studies cannot be simply dismissed," his review concluded.

Nevertheless, some scientists remain sceptical. One of these is Vikram Patel, a public-health psychiatrist at the London School of Hygiene and Tropical Medicine. To look for trends within and between countries, Patel and his colleagues analysed[2] data from 23 longitudinal schizophrenia studies covering 11 low- and middle-income countries. They found inconsistent results based on different time frames that make direct comparisons difficult. For example, the proportion of people with chronic schizophrenia ranged from 4.5% over five years in India to 51.7% over 12 years in China. The disease pattern varied over time with patients shifting between best, worst and intermediate categories several times over the years. Disability and social outcomes also varied, being good in India and Indonesia, but poor in Brazil, China and Ethiopia. Patients in India fared better than in those countries, but good outcomes could not be generalized to other developing countries. Patel's analysis concluded that it was "time to re-examine presumed wisdom about schizophrenia outcomes in low- and middle-income countries".

## CULTURAL CONTEXT

Even if the schizophrenia paradox is confined to India, the explanation is no clearer. "Patients seem to be doing better in poorer countries, despite limited resources such as health facilities and health infrastructure, and treatment facilities," Kulhara says. This could be due to a different socio-cultural milieu in developing countries with a greater dependence on family members for care and support, and to better social support and social networking. However, Kulhara adds, "these variables have not received the research attention that they deserve."

Other scientists are also trying to figure out the nature and role of cultural factors. "In the past three decades, the field has embraced the notion of 'cultural differences' as the reason for better outcomes in developing countries," says Naren Rao, a neuroscientist at the Indian Institute of Science in Bangalore, India. "However, the nature of the cultural factors is not exactly known and culture remains a black box." Even Kulhara, who has concluded that the difference in outcomes is real, notes in his review that "culture should not be used as a synonym for unexplained variance".

In trying to pin down these cultural factors, Rao points to studies showing that schizophrenia patients in India face fewer critical or hostile remarks than their equivalents in other countries — and says this may "contribute to the reason for better outcomes". But an attentive family can cut both ways: in some cases, extended families provide additional care, but in others they prevent patients from seeking treatment for fear of stigma.

Some researchers attribute the improved outcomes to the less rigid nature of rural life in developing countries. Although people with schizophrenia in remote locations have less access to treatment, they tend to enjoy better social inclusion. Patel speculates that the disorganized rural labour markets offer more opportunities, such as field work for people with disabilities, which helps them integrate and overcome their illness. But he cautions against drawing too sweeping a conclusion. "When it comes to a complex disorder like schizophrenia," he says, "it is difficult to generalize even for just India, let alone for all developing countries."

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Scientists are also examining the potential role of the widespread practice of yoga in India in the good outcomes for those with schizophrenia. Several studies from India over the past decade[3] have reported that yoga has beneficial effects on schizophrenia, both with regard to 'positive' (psychotic) symptoms and 'negative' symptoms (such as lack of motivation or enjoyment), for which there are few effective treatments (see 'Negative feedback', page S10). Researchers have previously reported that both physical exercise and psychotherapy (including 'mindfulness' techniques such as meditation) can ease the symptoms of schizophrenia. "Since yoga involves both exercise and mindfulness, it seemed reasonable that it could be helpful too," says Holger Cramer, a psychologist at the University of Duisburg-Essen in Germany.

Even so, the power of yoga remains questionable. Cramer recently led a review[4] of five trials, including two from India, on the role of yoga in schizophrenia. He found no evidence that yoga has any effect on schizophrenia symptoms. Any positive effects seen in individual trials "could easily be just a statistical artefact", he says.

## RE-EXAMINING ASSUMPTIONS

This string of negative results makes any explanation for the Indian schizophrenia paradox even more obscure. Some scientists are therefore taking a step back, to examine factors that influence outcomes in a particular setting. For example, two crucial indicators of improved social outcomes are employment and marriage. Marriage rates are higher for people with schizophrenia in India than in the United Kingdom, says Patel. But he argues that this should be juxtaposed against the fact that marriage rates in India are higher in general, partly due to family pressures for arranged marriages. "There are other linked factors, such as the huge numbers of untreated persons, human-rights abuses and high death rates" that such analyses ignore, says Thara Rangaswamy, director of the Schizophrenia Research Foundation in Chennai, India, a WHO collaborating centre for mental-health research and training. Rangaswamy has worked with Patel's team in multicentre studies.

One of the more ambitious attempts to find out whether there really are differences in outcomes between locations is the three-year Intrepid study, in which Patel is involved. Its pilot phase, which takes place in India, Nigeria, and Trinidad and Tobago, runs until the end of 2014.

There is little directly comparable research on psychoses in low- and middle-income countries, partly as a result of logistical and methodological challenges, explains Craig Morgan, a psychologist at King's College London who works on the Intrepid project. The pilot phase of Intrepid, Morgan says, is one of the first systematic attempts to develop and test robust psychoses research methods in diverse settings. This will lay the groundwork for a second phase aimed at studying actual causes and outcomes in large samples in each of the sites.

But conducting such research in countries with limited resources poses several challenges: recruiting representative groups of people with psychoses and population-based comparison groups; training staff and ensuring reliable assessments; and enabling cross-cultural comparison of assessments. Finding out whether there are indeed differences in symptoms, risk factors and outcomes in diverse settings "is important because differences provide a window into understanding the disorders more fully," says Morgan. Rather than draw comparisons, researchers now want to untangle the factors that drive the onset and outcomes of schizophrenia — and they can then discover whether the paradox persists. ■

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