ABSTRACT: An editorial posited that low- and middle-income countries (LMICs) take longer to access schizophrenia treatment innovations, but this lag may be an advantage in that it allows them to have better evidence to inform clinical and policy decisions. We sought to determine whether LMIC policymakers do in fact use the best available evidence to make decisions regarding access to atypical antipsychotics, the latest innovation in schizophrenia therapeutics. Since there were no relevant policy analyses, we approached the issue by assessing the quality of the scientific evidence available to policymakers and examining in detail the experience of Chile, a middle-income country. We found that there is minimal LMIC-specific scientific evidence to inform policy analyses. Moreover, the modest body of cost-effectiveness evidence is undermined by the source of its effectiveness estimates. Only two of the four cost-effectiveness studies accounted for antipsychotics’ side-effects, and only one included the long-term effects of metabolically active antipsychotics. LMICs that are able to manufacture or import cheaper generic atypical drugs have readily embraced them. Chile’s experience indicates that an LMIC that implemented policies when evidence from higher-income countries strongly favored atypical drugs responded to new evidence to the contrary, but
not forcefully enough to counter pressure from advocates or market forces. It appears, then, that most LMIC policymakers were not aware that the modest body of LMIC-relevant cost-effectiveness evidence did not favor atypicals, or if they were aware, their decisions were not influenced by this evidence. We conclude with a discussion of the implications of this finding.

In an editorial published in the *British Journal of Psychiatry* (2006), the authors wrote:

Rich countries develop and evaluate the new drugs, and these same nations are the first focus of the initial decades of marketing. As the battle of the companies is fought out in high-income countries, clouds of dust from marketing obscure the view. Unless effects are dramatic, it takes decades for the dust to settle. . . . During this period many in the lower-income countries have to observe the battle from afar and they are forced to use older drugs. . . . Evidence-based practice is the judicious use of the best available evidence in patient care or policy making . . ., by the time drugs are widely accessible in lower-income nations, the “best available evidence” may well be better in these poor countries than was the case when the drugs were first marketed in rich nations. [1]

Do low- and middle-income countries (LMICs) in fact use the best available evidence on antipsychotic drugs, the mainstay of treatment regimens for schizophrenia? Because most people receiving treatment for schizophrenia are likely to be cared for in publicly funded settings, the main consumers of the said evidence are policymakers concerned with decisions on whether and how the beneficiary population will have access to different antipsychotic drugs. In this article, the experience of high-income countries (HICs) with antipsychotic drugs is reviewed, along with a description of the impact of schizophrenia in LMICs and the resources available to meet the need. In an attempt to answer the question, available evidence is examined, in particular the experience of Chile, a middle-income Latin American country.

Antipsychotic Drugs for the Care of Schizophrenia: Experience of High-Income Countries

Chlorpromazine, the first phenothiazine medication available for the specific treatment of psychotic symptoms, was released to the market in 1953. Between 1953 and 1955, use of chlorpromazine spread rapidly around the world. Although it was not approved by the U.S. Food and Drug Administration (FDA) until 1957, clinicians in the United States began using chlorpromazine in 1954. Its rapid adoption had a profound impact on the U.S. mental health care system, driving the shift from institutional and largely custodial care to community-based and treatment-oriented care. Use of chlorpromazine declined in the United States and other HICs in the late 1950s and early 1960s, when newer and more potent antipsychotic drugs became available. Although all these antipsychotic drugs,
herein referred to as *conventional* antipsychotics, have the same mechanism of action, their side-effect profiles differ. Chlorpromazine and other low-potency conventional drugs carry a higher risk for weight gain and other metabolic side-effects [2]. Conventional drugs of higher potency, such as perphenazine and haloperidol, carry a lower risk for metabolic effects, but have a higher risk for a cluster of neurological effects such as extrapyramidal side-effects (EPS) characterized by abnormal involuntary movements. Although most of these side-effects occur acutely and may be effectively managed with dose reduction or addition of anticholinergic drugs, a minority of patients develop tardive dyskinesia and other chronic and hard-to-treat neurological conditions [3]. Both types of conventional drugs, as well as anticholinergic drugs that may need to be coprescribed with higher-potency conventional drugs, have long been available in LMICs as inexpensive generic formulations [4, 5].

Clozapine was the first antipsychotic of the newer class of antipsychotic drugs, herein referred to as atypical antipsychotics. Although briefly available in HICs in the 1970s, its full-fledged entry in the United States and other HICs occurred several years later once regulators found a way to bring it to market in a manner that minimized its rare but potentially lethal hematological risks [6]. Clozapine gained restricted entry in the U.S. market in 1989 after the FDA approved its use for people with treatment-resistant schizophrenia who submitted to a strict hematological monitoring system [6]. Clozapine’s superior effectiveness prodded the pharmaceutical industry to develop safer atypicals. Following the release of risperidone in 1994, several atypicals were developed and rapidly brought to market. The enthusiastic embrace of atypicals in the United States and other HICs led to a sharp drop in the use of conventional antipsychotics, a shift that transformed the routine care of schizophrenia [7–10]. Claims of greater efficacy and safety for atypical agents channeled through promotional and academic vehicles, and government decision to include atypicals in publicly funded drug formularies, their high prices notwithstanding, played a significant role in this phenomenon [11–14]. In 2005 and 2006, results of two publicly funded trials conducted in the United States and the United Kingdom were published. They showed that with the exception of clozapine, atypicals were no more effective than conventional drugs [15–17], nor were they cost-effective [18, 19], stunning stakeholders and leading to widespread soul-searching [14, 20–22]. A parallel development was the accumulation of evidence linking atypical drugs with metabolic side-effects [23–28]. It is now widely accepted that clozapine, olanzapine, risperidone, and quetiapine—all of them marketed in the 1990s and thus already available as generic formulations or close to patent expiry in HICs—carry a substantial risk of metabolic side-effects that sharply increase users’ risk for diabetes and cardiovascular disease [29, 30]. This radical reassessment of the effectiveness and safety of atypical drugs was reflected in the main U.S. and U.K. clinical practice guidelines, the later versions of which walked back earlier recommendations to use atypicals as first-line antipsychotics [31–34].
Significance of Schizophrenia in LMICs

Epidemiology and Cost of Schizophrenia

Schizophrenia affects 0.5–1 percent of the LMIC population. The majority of the estimated 25–42 million cases are concentrated in Asia and Africa [35, 36]. Schizophrenia is among the top ten causes of years lost to disability (YLD) in LMICs, accounting for 2.1 percent of total YLD [37]. Further, the disease burden attributable to schizophrenia in LMICs is projected to increase by 50 percent by 2020, an increase that is comparable to that of malaria or malnutrition [38]. Evidence from HICs demonstrates that the illness is associated with premature mortality due to suicide and poorly treated chronic medical conditions [39–41]. Not surprisingly, the economic burden of schizophrenia is significant. Cost-of-illness studies have assessed direct costs associated with care-related activities and indirect costs associated with lost productivity, premature mortality, and negative effects on family members. In HICs, studies have shown that indirect costs are high as or higher than direct costs of treatment. Several cost-of-illness studies have been conducted in LMICs. A World Health Organization (WHO) sponsored study conducted in Nigeria found that schizophrenia had the highest cost per treated case among all the mental disorders included in the study [42]. Another study, conducted in India, found that schizophrenia is associated with high direct and indirect costs [43].

Meeting the Treatment Need

Resources for the treatment of the large contingent of people with schizophrenia living in LMICs are vastly inadequate, and thus the treatment gap is large [44]. Advances in the treatment and outcome of schizophrenia notwithstanding, the treatment gap has remained essentially unchanged in LMICs. An Institute of Medicine report on mental illness in developing countries found that the proportion of people with schizophrenia who were not receiving any form of treatment had not changed between 1990 and 2000 [38]. By 2004, only 50 percent of the WHO countries in Africa, 72 percent in the Americas, and 55 percent in Asia had mental health policies, that is, specific goals, priorities, and directions outlined by the government for improving mental health [45, 46]. Most of the LMICs with existing mental health policies spend less than 1 percent of their total health budget on mental health [46]. As a result of insufficient governmental support for mental health services, many LMICs have high levels of out-of-pocket mental health expenditures [46]. Because so many people with schizophrenia living in LMICs are responsible for all the expenditures associated with the care of their illness, the cost of psychotropic drugs plays an outsized role in determining initiation and persistence of antipsychotic treatment. About 12 percent of the daily minimum wage of a worker in Africa is required to purchase essential antipsychotic drugs [47]. Inadequacy of the mental health workforce add another layer of complexity. Of great relevance to the care of
schizophrenia, many LMICs have fewer than one psychiatrist per 100,000 people [48]. Furthermore, most LMICs lack the infrastructure necessary to screen and monitor side-effects of antipsychotic drugs [46].

The inability of many LMICs to adequately meet the treatment needs of people with schizophrenia has consequences. Duration of untreated psychosis is strongly correlated with poorer outcomes [43, 49, 50]. Moreover, treatment delays and substandard care are associated not only with higher indirect costs but also with higher direct costs for those who eventually access treatment [43, 51]. Although how best to deliver care is the subject of an animated debate among mental health professionals in LMICs, there is broad consensus that antipsychotic drugs are the mainstay of the treatment of schizophrenia [36].

Do LMICs Use the Best Evidence?

The optimal method for evaluating whether LMIC policymakers use the best available evidence to make decisions regarding access to atypical antipsychotics entails a systematic review of official documents containing policy analyses focused on whether these drugs should be made available, at what maximum cost, and for what slice of the beneficiary population. We were unable to find any such documentation. As an alternative approach, we assessed the quality of the scientific evidence available to LMIC policymakers, investigated the reality on the ground (atypical utilization, costs, and drivers of variation), and conducted a detailed examination of Chile’s experience. To ensure that our review of the evidence available to policymakers was exhaustive and that our description of the reality on the ground was comprehensive, we undertook systematic literature reviews. We searched the databases of MEDLINE, CINAHL, Cochrane Library, and the WHO/PAHO—sponsored Library Online Catalog & Institutional Memory Database, restricting our search to studies published in English or Spanish between 1980 and August 2011. We also performed hand searches of the retrieved reference lists. While all searches included the keywords “atypical or second-generation antipsychotic” [or generic name of drug] to identify candidate studies, we combined these primary keywords with different keywords depending on the body of evidence in which we were interested (“developing or low income or middle income or LMIC” [or names of LMICs] for evidence on availability of atypicals in LMICs, along with “efficacy” or “safety,” for randomized control trial (RCT) evidence on efficacy and safety; and “cost effectiveness,” “cost utility,” “economic,” “cost,” “value,” or “policy analysis,” for cost-effectiveness evidence regardless of country).

**Scientific Evidence on the Value of Atypical Antipsychotics**

Policymakers are constantly setting health care priorities and making resource allocation decisions. A critical input to their decision-making is knowledge of the public health significance of disorders affecting the population. As critical, however,
is knowledge of whether available interventions are effective and safe enough, and in environments where the need is high and public resources are scarce, so is knowledge of the costs of interventions. Knowledge of the value (or outcomes and costs) of interventions would allow policymakers to have a better appreciation of the expected health returns of funding allocations, and thus allocative efficiency would be maximized [52].

Cost-effectiveness analyses (CEAs) provide a tool for describing the value of interventions. On the cost side, CEAs only include direct costs associated with the treatment, but studies vary in the kinds of costs they attribute to the intervention [18, 19, 53]. Because antipsychotic drugs have multiple effects, ranging from improved symptoms to safety effects such as weight gain and tardive dyskinesia, antipsychotic CEAs may assess effectiveness at multiple outcome domains [54]. Unlike traditional CEAs, cost-utility analyses (CUAs) combine all effectiveness domains into a composite outcome measure. Examples of such effectiveness metrics are quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs). While QALYs are estimated as the preference-weighted sum of key outcome measures and represent a positive outcome, DALYs are years lost to premature death or disability and represent a negative outcome. Studies employing DALYs as their effectiveness metric require information on the epidemiology and natural history of the disorder as well as the predicted effect of the intervention on time spent in different states of ill-health. Through its Choosing Interventions That Are Cost Effective (CHOICE) program, WHO has employed this methodology in several studies [56]. Although cost-effectiveness research in schizophrenia is fraught with methodological complications, and the quality of extant research is variable [54, 56], there is a clear need for knowledge of the most efficient way to avert the burden associated with this illness [53, 55].

Regardless of the method used to represent treatment outcomes, CEAs require evidence of effectiveness and safety. For scientific and credibility reasons [51, 57], “best evidence” originates from studies conducted in LMICs. However, the body of evidence is not well developed and is geographically concentrated, a phenomenon that affects mental health research in general [58]. More than sixty trials including eight single- and double-blind RCTs have been conducted in India to assess the efficacy and safety of conventional and atypical antipsychotics [59]. The RCT findings include negative results for studies comparing conventional versus atypical antipsychotics: centbutindol, a conventional antipsychotic, was as effective as risperidone [60], and haloperidol was as effective as risperidone [61]. Another study in China, a 52-week-long RCT of clozapine versus chlorpromazine among first-episode patients, showed that although clozapine-treated subjects exhibited faster and more sustained remission, the clozapine advantage had dissipated by the end of the study [62]. Consistent with evidence from HICs, LMIC studies have found that neurological side-effects are more common with higher-potency conventional antipsychotic drugs, whereas weight gain is more common with the atypical antipsychotics clozapine, olanzapine, and risperidone [59].
Regarding cost-effectiveness evidence, because assumptions for CUA effectiveness metrics may not be generalizable across cultures [54], and because cost structures are so different for HICs and LMICs, here, too, “best evidence” would originate from LMICs [63].

We found only four studies that compared the value of atypical and conventional drugs in LMICs; all of them used a combination of locally gathered cost data and efficacy evidence derived from meta-analyses of HIC trials (Table 1). Two cost-effectiveness studies conducted under the auspices of the CHOICE program used a combination of local demographic, epidemiological, treatment coverage, resource utilization, and cost information to contextualize subregional effectiveness findings [42, 53]. Only half of these studies included side-effects in the estimation of the effectiveness metric or in their cost calculations. A DALY-based study conducted in Thailand included EPS as well as current and estimated morbidity and mortality effects of weight gain in the calculation of the disability weight [5]. On the cost side, authors accounted for the costs of preventing clozapine’s hematological risks and treating EPS [5]. A QALY-based study conducted in Brazil using local cost data and HIC effectiveness evidence accounted for side-effects in the computation of both effectiveness and costs [64]. While the two WHO-sponsored studies concluded that conventional were more cost-effective than atypicals, the other DALY-based study arrived at the opposite conclusion, and the QALY-based studies concluded that atypicals were more cost-effective, and the other had mixed results, as shown in Table 1.

Reality on the Ground: LMICs and Atypical Antipsychotics

Availability of antipsychotic medications is limited in many LMICs. A study, sponsored by WHO, of thirty-three countries found that by 2009, almost all of them included at least one psychotropic drug on their essential medicines list, yet in only 38 percent of them were psychotropic drugs available at all primary health centers [47, 65]. Even in countries with national health care systems such as Ghana, where psychotropic drugs are supposed to be free, availability of antipsychotics can be erratic or limited [66].

There is a wide variation in utilization of atypical antipsychotics across LMICs. Important drivers of this variation are policies regarding both the target population for publicly financed atypical drugs and the manufacturing and importation of generic formulations.

By 2003, while some LMICs had regulations restricting the use of atypical antipsychotics to patients who had not responded to treatment with conventional drugs [68], most countries had moved toward adopting them as first-line treatment for schizophrenia [67].

Cheaper generic atypical formulations have become more widely available in LMICs, especially in India and China—the largest exporters of pharmaceuticals to other LMICs—where atypicals are considered first-line treatment. In China in the 1990s, clozapine was the most widely used antipsychotic for schizophrenia [62].
<table>
<thead>
<tr>
<th>First author (ref)</th>
<th>Year</th>
<th>Effectiveness metric</th>
<th>WHO-sponsored</th>
<th>Source*</th>
<th>Accounts for side-effects</th>
<th>Accounts for side-effects</th>
<th>Cost</th>
<th>Effectiveness accounts for side-effects</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chisholm [53]</td>
<td>2008</td>
<td>DALY</td>
<td>Yes</td>
<td>Meta-analysis [77]</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
<td>Conventionals &gt; Atypicals</td>
</tr>
<tr>
<td>Lindner [66]</td>
<td>2009</td>
<td>QALY</td>
<td>No</td>
<td>Cochrane Review [98]</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td>Clozapine &gt; Risperidone (in severe patients) Haloperidol &amp; Risperidone &gt; Olanzapine</td>
</tr>
</tbody>
</table>

*Note: *Cochrane Database reviews and other meta-analyses summaries of findings from *efficacy* studies conducted in HICs.*
A study conducted in India in 2005 found that a majority of patients with schizophrenia were treated with atypical antipsychotics, a finding attributed to the negligible cost difference between atypical and conventional antipsychotics [43]. Another study confirmed this finding: while 56 percent of Indian patients were on risperidone and 21 percent on olanzapine, only 16 percent were on conventional antipsychotics [68]. In countries where generics are not available yet, prices are much higher. This is exemplified by a 2000 study in Nigeria that found a 27-fold difference in per-person costs between ambulatory treatment with atypical versus conventional drugs (US$2,387 vs. US$88) [69].

The greater availability of generic antipsychotic formulations in LMICs is partly the result of legal loopholes in the process patent, where only the product is patented but not the manufacturing process [1]. However, essential medicines are at risk of becoming less affordable in LMICs as a result of international trade agreements such as the Trade-Related Aspects of Intellectual Property Rights (TRIPS) [70]. The TRIPS agreement requires patent protection for all processes, and more recently of products also, for a minimum of twenty years, thus curtailing local manufacturing and accessibility of low-cost generic medicines in LMICs [70]. Low-cost generics continue to be available in LMICs, however, because compulsory licensing enables governments to license the use of a product to third parties without the consent of the patent holder, and parallel importation allows the importation of patented product marketed in another country without the patent-holder’s consent [70]. Additionally, the TRIPS Agreement does not prevent generic substitution, a process that can be facilitated by compulsory licensing, legislation on patentability by governments, and the use of exceptions to exclusive rights [70]. As in HICs [14], pharmaceutical marketing strategies also affect utilization of atypicals within and across LMICs. A study on the relationship between industry and physicians reported that a multinational pharmaceutical company had provided various financial incentives and perks to Pakistani doctors just as the company was launching a psychotropic drug [71].

**Chile’s Experience**

For three decades, starting in 1952, Chile’s publicly funded national health care system was the main provider of health care services, which wealthier Chileans supplemented with private health care services. In the early 1980s, the military dictatorship (1973–1990) introduced legislation to promote the privatization of the health care market as part of several radical reforms of the health care system [72, 73]. The advent of democracy in 1990 did not fundamentally change the health care system, and it remained a public-private system financed by workers’ and pensioners’ compulsory contributions of a fixed percentage of their income. Because younger and more affluent Chileans tend to allocate their contributions to private insurers, the public health care system loses a large source of funding, yet it is responsible for the care of those with the most need, including the majority of those with schizophrenia.
In 1993, the first democratic government implemented a national mental health plan which left schizophrenia out of its six priority areas but did include the rehabilitation and social reintegration of people with mental disability [74]. During the 1990s, relatives of people with schizophrenia and other mental illnesses became increasingly vocal about the poor quality of public mental health care. For many of these advocates, poor quality was epitomized by the limited availability of antipsychotic medications in the public sector. Their frustration with the narrow selection—chlorpromazine, haloperidol, and depot fluphenazine—was compounded by frequent shortages which caused treatment interruptions and anecdotally reported clinical decompensation events. Thus, a centerpiece of the advocacy movement was a call for expanding the public formulary to include atypical antipsychotics. Advocates had become acquainted with clozapine and other atypicals through their relatives' participation in industry-funded trials occasionally conducted by the public mental health system.

The Chilean government started developing the second National Mental Health Plan in 1999 after both epidemiological evidence [75] and a burden of disease study conducted for priority-setting purposes focused attention on the significance of mental health problems in the country [74]. This time, schizophrenia was included among the priority areas. To fast-track its implementation, the Ministry of Health launched in 2000 the Programa Nacional de Antipsicoticos Atipicos (Atypical Antipsychotic National Program). Its mission was to provide clozapine and other atypicals to people with schizophrenia who had not responded to maximal treatment with conventional antipsychotics. In 2001, the Ministry of Health developed clinical guidelines for the treatment of schizophrenia. With regard to antipsychotic choice, the guideline recommended that non-clozapine atypical antipsychotics be used as second-line treatment and clozapine as third-line treatment for people with treatment-resistant illness only.

For costing purposes, developers of the second National Mental Health Plan estimated average utilization of various psychosocial and pharmacological interventions for the six mental health priorities. For patients with schizophrenia, it was estimated that less than 10 percent would need atypical drugs, with approximately 5 percent needing clozapine, 2.5 percent needing risperidone, and 1 percent needing olanzapine [74]. Only four years later, the Ministry of Health estimated that almost every person with a first episode of schizophrenia would be treated with atypical drugs; the proportions of clozapine and olanzapine use were roughly unchanged, but the proportion of risperidone use grew larger by 39-fold.

In 2004, a program of therapeutic health guarantees became law in Chile. According to this law, both the public health care system and the private health insurance industry must offer an explicit set of guarantees in terms of access, quality, opportunity, and financial coverage for fifty-six priority diseases; schizophrenia has been among them since 2005 [76]. The guarantees are clearly specified for each disease, including populations entitled to receive them, level of care, types of interventions, maximum waiting time, minimum qualifications of providers,
and ceilings for co-payments. Clinical guidelines were developed or revised to guide their correct implementation. The 2005 revised version of the guideline for schizophrenia contained different recommendations depending on the stage of the illness. While for people with first onset schizophrenia, risperidone was recommended as first-line, non-clozapine atypicals as second- and third-line, conventional drugs as fourth-line, and clozapine as fifth-line treatment, the guidelines stated that people with more advanced illness should be treated with conventional or atypical antipsychotics selected according to the patient’s history and preferences. That same year, approximately 36 percent of all public patients with schizophrenia were treated with clozapine, 35 percent with risperidone, 1 percent with olanzapine, and the balance with conventional antipsychotics.

The dramatic shift in antipsychotic utilization patterns in the Chilean public sector was driven by several factors, but three appear to have played the largest role. First, the Atypical Antipsychotic National Program was extremely successful. Starting in 2001, centralized medication purchasing allowed the government to import clozapine from China at increasingly favorable prices, as evidenced by the large drop in clozapine’s average annual-per-person costs between 2000 and 2001 (from US$1,247 to US$170). This figure included the costs of the drug, routine blood monitoring to prevent serious hematological conditions, and the treatment of those conditions. The clozapine savings were mainly invested in the purchase of risperidone, the annual-per-person cost of which was lower to the government in 2002 than that of clozapine (US$77 on average). Second, because of the emphasis placed on evidence-based medicine at the Ministry of Health, findings from studies and meta-analyses conducted at HICs in the late 1990s and early 2000s, as well as recommendations from the 2002 National Institute of Clinical Excellence (NICE) in the United Kingdom, convinced many policymakers that the benefits of atypical drugs justified their higher acquisition costs [77–79]. Last, the pharmaceutical industry conducted a powerful marketing campaign that promoted the benefits of atypical antipsychotics among potential prescribers, which in addition to detailing included gifts and invitations to scientific congresses around the country and abroad.

In 2009, the Ministry of Health issued another revision of the clinical guideline for the treatment of first-episode schizophrenia. The guideline developers did an exhaustive review of the evidence on effectiveness and safety of antipsychotics, frequently citing the review performed by the revised 2009 NICE guidelines, which no longer recommended atypical drugs as first-line treatment. It is interesting, however, that the cited studies did not include a WHO-sponsored CEA of schizophrenia interventions in Chile and other LMICs, co-authored by two Chilean researchers and published in 2008, which concluded that the most cost-effective interventions were those using conventional antipsychotics [53]. Notably, except for an isolated typo, the guidelines no longer call for the use of atypicals as first-line treatment, instead stating that choice of antipsychotic should be guided by the patient’s history and preferences (www.redsalud.gov.cl/archivos/guiasges/EsquizofreniaR_Mayo10.pdf).
Currently, several pharmaceutical companies sell atypical antipsychotics in the Chilean market (risperidone, olanzapine, quetiapine, and aripiprazole), and several of them participate annually in tenders called by the Ministry of Health for centralized purchasing. As a result, acquisition costs of atypical drugs have been much lower in Chile than in other countries; however, those costs are still higher than the acquisition costs of conventional drugs. Current spending on atypical antipsychotics is estimated to represent 69 percent of total drug spending for people with schizophrenia in the public system, and 6 percent of all spending, including inpatient services [80].

Discussion

We set out to answer the question of whether policymakers in LMICs do in fact use the best available evidence to make decisions regarding access to atypical antipsychotics. The best way to answer this question would entail a systematic review of these countries’ policy analyses and decisions on whether, at what maximum cost, and for what slice of the beneficiary population atypical drugs should become available. Since this information is not available, we attempted to answer the question by assessing the quality of the scientific evidence available to policymakers, investigating atypical utilization, costs, and drivers of variation in these domains, and conducting a detailed examination of the experience of Chile. We believe that the answer to the question is a qualified no.

We determined that there is minimal LMIC-specific scientific evidence to inform policy analyses. Further, the modest body of cost-effectiveness evidence is undermined by the source of its effectiveness estimates, a body of HIC efficacy research that has come under fire for prematurely concluding that non-clozapine atypicals had better outcomes than conventional drugs. Only two of the four cost-effectiveness studies accounted for the side-effects of the antipsychotics in their effectiveness and cost calculations, and only one of them included the long-term effects of metabolically active antipsychotics. The latter is an important methodological issue. The downstream medical consequences of weight gain and other metabolic side-effects—mainly diabetes and cardiovascular disorders—may take months or years to develop or be detected [28, 81, 82]. However, they are sure to put further service use and cost demands on countries with limited or nonexistent slack capacity. We further determined that LMICs that have found a way to manufacture or import cheaper generic atypical drugs have readily embraced them, as evidenced by high rates of utilization even for clozapine, a drug that is underused in HICs [8, 83]. Although such highly favorable pricing may have led policymakers to cast aside the available cost-effectiveness evidence, given that it was based on different pricing, it is not clear whether the new evidence on atypical antipsychotic drugs’ effectiveness and other sources of costs associated with their use has entered the decision-making regarding atypical drug manufacturing and importation.

Chile’s experience indicates that an LMIC implementing policies at the time
when evidence from HICs strongly favored atypical drugs did respond to new evidence to the contrary, but not forcefully enough to counter pressure from advocates or market forces acting upon psychiatrists who have been shown to be slow to absorb the new evidence in HICs [84, 85].

**Conclusion**

It is unclear whether LMIC policymakers reviewed the then-available scientific evidence prior to making decisions regarding access to atypical drugs by the beneficiary population. Regardless, it appears that most policymakers were not aware that the modest body of LMIC-relevant cost-effectiveness evidence did not favor atypicals, or if they were aware, that their decisions were not influenced by this evidence. Cost appears to have been a critical driver of atypical availability, suggesting that policymakers in many LMICs assumed that if atypicals were affordable, they would be a better clinical option than conventional drugs. In addition, as suggested by the Chilean experience, policymakers are influenced by pressure from advocacy groups.

It is a well-established truism that health policy decisions are influenced not just by scientific evidence, but by the advocacy of multiple stakeholders and also by larger societal dynamics [86]. Some have argued that human rights and social justice should be taken into consideration in addition to science in making policy decisions. At a minimum however, policymaking should be informed by scientific evidence, particularly when resources are scarce and the need and opportunity costs are high [87]. Further, when the evidence is modest or flawed, policymakers should not discard the evidence but rather use reasonable approaches to build on it and thus make decisions that are most conducive to meeting the health needs of the greatest number at the lowest cost.

It is critical to implement initiatives to reduce the HIC-LMIC gap in mental health research and thus generate policy-relevant evidence that is specific to the reality if not of particular countries, at the very least of LMIC regions. Investing in the training of clinical and services researchers and ensuring availability of non-industry funding are key initiatives [88, 89]. However, because in many LMICs antipsychotics of any class are still a luxury, it is critical for the world community to focus on ways to narrow the schizophrenia treatment gap so that more people living in LMICs can finally access a basic package of treatments for schizophrenia [35, 36].

**References**


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