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Where Old is Gold Again: Antidepressants in Nepal, 1961-2021

Abstract

The so-called psychopharmaceutical revolution began in the 1950s, with apparently ever better drugs coming to market. Amitriptyline (Elavil), introduced in 1961, was one of the first "antidepressants." Over the next decades, many other antidepressants came out, including fluoxetine (Prozac). In the 2000s, critiques that antidepressants were no better than placebos could not slow down a massive global rise of prescriptions. In 2018, a large meta-analysis of clinical trials argued that antidepressants were indeed better than placebos, but that none of the new drugs was as effective as the old amitriptyline. 1961 is also the birth year of psychiatry in the Himalayan country of Nepal. Since the 1960s, Nepali psychiatrists have been using amitriptyline as their first-line drug. The inclusion of amitriptyline in the first WHO list of *Essential Drugs* (1977) cemented its status. All the "new" psychopharmaceuticals came to Nepal, but they never displaced the "old" amitriptyline. No other drug could beat amitriptyline's affordability, availability, and efficacy for the typical Nepali depression patient: a "somatizer" who suffers from multiple bodily aches, insomnia, and anxiety.

Fieldwork with Nepali psychiatrists reveals the tenacity of local affordances over global changes in evidence and health policy.

In the late 2010s, depression was said to be the world's third-leading problem by years lived with disability (James et al. 2018). The prevalence and chronicity of depression became a problem for sustainable development (Patel et al. 2018). Global mental health advocates argue that much more money should be put into providing therapy for depressed people. Investments in antidepressant medications, in particular, would give a great return on investment: "depressive disorders can be treated with low-cost therapeutics," and this could "avert potential loss of functional status in the work force" (James et al. 2018: 1837). What are these "low-cost therapeutics" and how did they come into use in low-income countries? How did the world's "psycho-pharmaceuticalization" (Rose 2018) play out in marginal places? I reconstruct the history of one of the oldest antidepressants, amitriptyline, in one of the world's poorest countries, Nepal, in the period from 1961 to 2021. The case of amitriptyline in Nepal shows how socioeconomic poverty engenders both typical presentations of mental distress and restricts therapeutic choice. In Nepal, amitriptyline first got widely

available as the leading low-cost treatment of depression because it is affordable, and it remained the leading treatment because it is widely available. Its easy availability and affordability insulated amitriptyline from changes to treatment routines on the global level through the decades to the 2020s. The drug's affordability and availability also protected it against being displaced by all the newer drugs that were heavily promoted by pharmaceutical companies in income-rich countries (Appelbaum 2009; Kitanaka 2011; Dumit 2012; Banerjee 2016). According to the country's psychiatrists, Nepalis express depression through multiple physical complaints because they are poor and lack education. In turn, they cannot afford expensive treatments, or those that are only available in urban centres. The most valuable drug covers both mental and somatic complaints, is available even in remote rural areas, and affordable even for the poorest. On all these points, amitriptyline appears as the overall best choice to the psychiatrists. Amitriptyline is "old," but in a poor country with an extreme geography, it is "gold."

The WHO Report of 2001, the first dedicated to global mental health, glowed with a "new understanding, new hope" of psychopharmaceuticals. The then-latest generation of antidepressants, the selective serotonin reuptake inhibitors (SSRIs) were said to be both highly effective for symptom reduction and highly cost-effective because they "reduced the need for other care and treatment" (WHO 2001: 61). "The best drugs" should be available "whenever possible" (WHO 2001: xi). No one should be "deprived, on economic grounds only, of the benefits of advances in psychopharmacology" (WHO

2001: 61). Also in 2001, Eli Lilly's patent for fluoxetine (Prozac) expired, and inexpensive generic versions became widely available. The only barrier to mending depressive moods now seemed to be the irrational stigmatization of psychopharmaceuticals. A supreme confidence in antidepressants fired up the project of Global Mental Health as it was conceived in Geneva, London, and Boston (AUTHOR 2021).

The "golden era" of the so-called psychopharmacology revolution was in the 1950s and 1960s. Amitriptyline (Elavil), a tricyclic antidepressant (TCA), was one of the earliest of these "wonder" drugs. The psychopharmaceutical revolution came to a crushing end in the 2010s, when all the major patents expired and the industry withdrew from further R&D (Harrington 2019; AUTHOR 2021). But between the 1950s and the 1990s, psychopharmacology appeared to go from strength to strength. Prozac, which was FDA-approved in 1987, looked like the continuation of this revolution. In hindsight, the SSRIs were the last hurrah of this so-called revolution.

Ever since Eli Lilly lost the Prozac patent, fluoxetine never lost its pre-eminence in GMH guidelines. The 2016 *mhGAP Intervention Guide*, which is the WHO training manual for primary healthcare workers in low-income countries, recommends fluoxetine as the "first choice" for treatment and warns against using other drugs: "Avoid amitriptyline if possible" (WHO 2016: 28). For patients with cardiovascular diseases, "Do NOT prescribe amitriptyline" (*ibid.*). For suicidal patients, fluoxetine

should always be preferred to amitriptyline: "Overdose of TCAs such as amitriptyline may be fatal and therefore should be avoided in this group" (ibid.).

Despite the hype around "new" drugs, the old amitriptyline never disappeared completely. Indeed in some places it hung on for long enough to become fashionable again. This is what happened in Nepal, a Himalayan country of 28 million people wedged between India and China. By GDP per capita, Nepal is among the world's poorest countries. Its recent history is marked by great turmoil and traumatic change. There was a general strike and pro-democracy uprisings in 1992; a Maoist insurgency from 1996 onwards; the massacre of King Birendra, Queen Aishwarya and other senior royals in 2001; the abolition of the Monarchy in 2008; and tremendous death and devastation caused by the 2015 Gorkha earthquake. Through all these profound upheavals, the treatment of depression stayed constant: amitriptyline first arrived in Nepal in the early 1960s and remained the most popular drug ever since. No amount of sociopolitical change translated into psychopharmaceutical change because relative poverty remained a constant.

It is not the case that the psychotropics revolution passed by Nepal. All the drugs that came out of Euro-American laboratories since the 1950s are available in the country, and have been so for decades. Indian pharmaceutical companies have been exporting generic versions of all available psychopharmaceuticals to Nepal. The country also has its own pharmaceutical industry, which covers a third of domestic

consumption (Subedi 2009; Brhlikova et al. 2015). Despite several new drugs coming to market, Nepali prescribers stayed loyal to amitriptyline long after the drug was branded as outdated elsewhere. In this article, I reconstruct the history of antidepressants in Nepal to show why this "old" drug remained "gold" in Nepal.

Amitriptyline in Nepal is a case study in the deep history of global mental health. The story of amitriptyline reveals the tenacity of local affordances over global policy changes. I will first discuss the recent revaluation of amitriptyline as the most effective of all antidepressants, despite being long shoved aside by newer antidepressants. I then retrace the history of psychiatric institutions and personnel in Nepal, both governmental and non-governmental, to explain why amitriptyline became so entrenched in the country's clinics. In the final section, I analyze how Nepali psychiatrists compare amitriptyline to other antidepressants, and why they continue to value it as the best overall drug despite its many toxic side effects.

Data for this article come from a combination of expert interviews, field observations, and a review of policy documents. The interviews I cite here were conducted with 15 Kathmandu-based psychiatrists. All my interlocutors were in prominent positions within the field of Nepali psychiatry, including government hospitals and teaching universities. All of them spoke English. Data collection in Nepal took place in 2008 and 2018 within two larger research projects on mental health services and psychopharmaceutical uses in South Asia (AUTHOR 2021). There are just

about 150 psychiatrists practicing in Nepal, the majority of them in Kathmandu Valley, hence the present sample of 15 doctors is fairly representative for how Nepali psychiatrists compare different drugs to each other.

Essentializing antidepressants

In February 2018, Dr. PSY-K, one of Nepal's younger psychiatrists, welcomed me to his cramped office in Kathmandu's Teaching Hospital. He studied medicine from 2003 and finished his MD in psychiatry in 2014. His current research project, a collaboration with a team from Norway, explored connections between genetics, inflammation, and mental disorders. A few days before our meeting, the largest-ever study on the efficacy of antidepressants by Cipriani and colleagues (2018) had been published. Results from the study were widely reported in the media—I kept the front page of *The Times* from my flight to Kathmandu and brought it to the interview. Cipriani told reporters that “antidepressants *do* work” and that this study gave “the final answer to a long-standing controversy about whether antidepressants work for depression” (Cipriani, cited in Therrien 2018). What was only mentioned in passing—if it was mentioned at all—is that the oldest drug in the study came out as the most effective: amitriptyline was far better at treating depression than fluoxetine. “Amitriptyline came out as the most effective antidepressant. Of course! I'm not surprised at all. I use amitriptyline for at least a quarter of all my patients,” Dr. PSY-K said. He was pleased.

Amitriptyline was first on sale, in the US, in 1961. It has almost the same chemical structure as imipramine (Tofranil). Amitriptyline and imipramine were the first compounds to be dubbed "antidepressants" rather than, less specifically, "psychic energizers" (Healy 1997: 76). The idea to study drugs in randomized controlled trials (RCTs), where an active ingredient is compared to a placebo, formed in the same era. The Hamilton rating scale, which tries to gauge the severity of depressive symptoms, was developed in tandem with RCTs, co-producing the "gold standard" for how depression should be diagnosed and treated (Harrington 2019: 231). Amitriptyline is at the beginning of what seemed to be a revolution of constantly improving drugs.

The first psychiatrist to publish on the effects of amitriptyline was Frank Ayd, an American. In an interview with David Healy, Ayd later recounted why amitriptyline became a bestseller for the companies that brought it to market in the 1960s: "Schering marketed as Etrafon in the United States and Merck marketed as Triavil. Well that product turned out to be a huge commercial success. Family doctors loved it because it was sedative, it had some definite antianxiety as well as antidepressant properties" (Ayd, in Healy 2001: 99). Amitriptyline was the first psychopharmaceutical that got established among general physicians, pioneering the marketing trend that the biggest sales come from the most general prescribers (Applbaum 2009: 191).

Corporate spending on advertising the new psychopharmaceuticals first peaked in the early 1960s (Green, Aronson & Haddad 2018). Merck's advertising strategy for

amitriptyline made marketing history: the company bought 50,000 copies of Ayd's book *Recognizing the Depressed Patient* (1961) and gifted them to family doctors around the world. Merck "not only sold amitriptyline, it sold an idea. Amitriptyline became the first of the antidepressants to sell in substantial amounts" (Healy 1997: 76). With this marketing stunt, Merck also established the role of "Key Opinion Leader" (KOL): psychiatrists sponsored by companies to educate nonspecialist physicians about psychopharmaceuticals (Harrington 2019: 278). What was further unusual about amitriptyline was that several different companies were marketing the molecule under different brand names. This is why the drug entered global markets so quickly.

Amitriptyline lost its US patent in 1977, and since then it has been cheaply and widely available in generic form. The patent expired just in time to put amitriptyline on the World Health Organization's first Essential Drugs list, which it published the same year. WHO's essential drug lists have been described as a "peaceful revolution" in global health (Laing et al. 2003). Drugs featured on the WHO list were deemed to give public health providers the best returns on investment. "Essential" are drugs that are most cost-effective. The WHO list, which is now in its 21st edition, defines the minimum of what any healthcare system should provide. The importance of this list for the insertion of certain drugs into the health provisions of low-income countries cannot be exaggerated. It continues to be "a key mechanism by which psychopharmaceuticals get into bodies globally" (Mills 2017: 230). The 1977 edition featured the following

psychotropics: amitriptyline, chlorpromazine, diazepam, fluphenazine decanoate, haloperidol, and lithium carbonate (WHO 1977: 29). Among these, amitriptyline was the only antidepressant. It remained the lists' only antidepressant until fluoxetine entered in 2007. Even the latest edition (WHO 2019) includes only amitriptyline and fluoxetine.

In the 1990s, the SSRIs pushed aside the TCAs in European and North American prescription routines (Harrington 2019: 239). Fluoxetine is the best-known SSRI, but there are many other molecules from this group, such as citalopram (Celexa), escitalopram (Lexapro), sertraline (Zoloft), and paroxetine (Paxil). Amitriptyline is still prescribed for severe depression, especially when patients also experience chronic pain. But the drug's safety profile makes it much riskier than the SSRIs. Serious and fatal outcomes resulting from amitriptyline poisoning or overdosing are worryingly common. Of all the different psychopharmaceuticals in use today, amitriptyline has the highest rate of fatal outcomes: four out of 10 deaths owing to psychopharmaceutical consumption are attributed to amitriptyline (Nelson & Spyker 2017).

In the late 2010s, amitriptyline had a startling tortoise-and-hare moment when it came out as the most effective medication against depression. Cipriani and colleagues' (2018) meta-analysis of 522 clinical trials of 21 different antidepressants is the largest study of its kind to date. After a decade of criticism that antidepressants are "no better than placebos" (Kirsch 2010), the study seemed to exonerate the massive rise of

antidepressant prescriptions over the past decades. As Rose (2018: 213-214) points out, the press coverage left out serious limitations of the Cipriani study. It was not reported that the study only looked at severe depression and not at mild to moderate depression, which makes up the bulk of prescriptions; that the newer trials do not show nearly as significant results as the older, smaller trials; that the drug side effects made many of them intolerable; and that none of the included studies look at long-term effects. What was hardly mentioned by either Cipriani or by the media was the deeply embarrassing fact that the "new" antidepressants were significantly less effective than the "old" amitriptyline. It looked as if, in the antidepressant segment, the golden era of the mid-20th century was the only era of effective novel medicines.

When I interviewed Dr. PSY-K about antidepressant uses in Nepal, it was impossible not to ask about amitriptyline. It continues to be the most easily available and most widely used antidepressant in the country (Harper 2014; Seale-Feldman 2020). Nepali doctors' preference for amitriptyline had long looked like a bad old habit. Doctors in India, just like doctors in Europe and the US, had moved away from amitriptyline since the 1990s because of its dangerous side effects (AUTHOR 2013). Amitriptyline can make people sleepy, agitated, irritable, and delusional. It can increase suicidality and can be used to kill oneself. Coma, seizures, and cardiac arrest can also come from an amitriptyline overdose. The adverse effects are augmented by other substances, especially tranquilizers and alcohol. Users of the drug tend to find

amitriptyline less tolerable than most of the newer antidepressants (Rose 2018). Given all this, the Nepali doctors' allegiance to amitriptyline seemed strangely stubborn. But in 2018, many Nepali psychiatrists felt vindicated for sticking with the old.

"Simple, effective and inexpensive methods of treatment are now available"

Amitriptyline came to Euro-American markets in the same year that is regarded as the birth year of Nepali psychiatry: 1961. The institutional history of psychiatric services, both governmental and non-governmental, are essential to understanding how amitriptyline became so firmly entrenched in the clinics.

Unlike most other countries in South Asia, Nepal has never been under direct foreign rule. India, Nepal's immediate neighbour to the South, had been a British colony until Independence in 1947. The British established psychiatric institutions in Ranchi, Bangalore, and the major port cities (Calcutta, Bombay, Madras), initially to care for British troops, not for locals (Ernst 1991). Nothing similar happened in Nepal. The country's first psychiatrist was Dr. B. P. Sharma, who returned to Kathmandu in 1961 after training in the UK. He treated the first psychiatric patients in an outpatient clinic at Kathmandu's Bir Hospital. A number of psychiatric beds were added in several Kathmandu hospitals. In 1975, a psychiatric ward was established at Kathmandu's Military Hospital. In 1984, the psychiatric department at Bir Hospital split off and

became a separate mental hospital at Lagankhel in the Kathmandu Valley. Later foundations were the Institute of Medicine (IOM) under Tribhuvan University and the B. P. Koirala Institute of Health Sciences (BPKIHS) at Dharan, 400km southeast from Kathmandu. The B. P. Koirala Institute, established in 1993, is an Indo-Nepali collaboration modelled after the All India Institute of Medical Sciences (AIIMS) at Delhi (Aich 2010). The majority of Nepali psychiatrists since the 1960s trained in India, many of them at AIIMS.

The Psychiatrists' Association of Nepal (PAN) was established in 1990. In the early 2000s, there were just 22 psychiatrists active in Nepal (Acland 2002). In 2020, there were around 150. Their numbers are still so small that psychiatrists are able to rank themselves on a shared timeline. In my interviews, Nepali psychiatrists would say that they are "Number Four" or "Number 13" in the order of when they entered the field. For example, Dr. PSY-S described the early years of Nepali psychiatry by placing himself in this genealogy: "Dr. B. P. Sharma, he was the first psychiatrist. He came to Bir hospital, he started mental health services in Bir hospital in 1962. Then the second one, Dr. Deshraj Bahadur Kunwar ... then the third psychiatrist was Dr. Romal Shrestha ... I did my degree in 1985. So you can call me Number Four. And Dr. Mahendra Nepal, he did in 1986. (*So he is Number Five?*) He's Number Five, like that." Most of the older psychiatrists said they did not enter the field out of their own interest, but were asked to take up psychiatry by their seniors. "Those who treat the mad are also mad (*pagal*),"

people would say. Psychiatrists also felt stigmatized by other biomedical doctors. Even in the 2010s, Nepali psychiatrists complained that other doctors continued to stigmatize them: "If I ask a gastroenterologist, why don't you refer, he says that the patient will get angry" (Dr. PSY-T). Some doctors even warned patients against going to a "mad doctor." Nevertheless, the stigma had lessened: "We have turned this around, maybe by our behaviour, maybe by not acting crazy ourselves, that did the trick" (Dr. PSY-A). Awareness and acceptance of psychiatry had also improved, but even by 2020 it was still far away from where it should be.

Some, like Dr. PSY-S, said that they genuinely wanted to become psychiatrists even during their student days: "Crazy people fascinated me. I was in the main hostel at Calcutta Medical School. Our batch was 150 students. A strong batch. Every batch has two or three crazy students, and they all ended up in the main hostel. So there was a whole group of friends there. So I just wanted to study psychiatry." This made him, as he said, the first who "picked up psychiatry by choice." First-generation psychiatrists worked in government service, under the Ministries of Health, Education (for teaching hospitals), Homes (police hospitals), and Defence (army hospitals). Work in private hospitals became more common during the 2000s. By 2020, private hospitals have gained a sizeable chunk of the psychiatric market. Private colleges were credited with expanding numbers of psychiatrists (Dr. PSY-T).

Psychiatric services remain concentrated in the Kathmandu Valley. Dharan and Pokhara are the only larger centres further afield. In the rural areas, availability of trained psychiatrists is limited. Several psychiatrists said that the "treatment gap" is, in Nepal, entirely an urban/rural treatment gap. In the Kathmandu Valley, it is easy to get treated, but not in the provinces. Just around 20% of Nepalis live in cities, 80% live in rural areas. Most urban people live in the Kathmandu Valley. The Terai lowlands, south of Dharan, have seen big population increases, but most parts of the country remain sparsely populated. Nepal's extreme geography put community-based approaches on the agenda from the beginning. Dr. B. P. Sharma is credited for both founding Nepali psychiatry and for starting community psychiatry in the 1960s. In Dr. Sharma's days, that meant regular trips to areas beyond the Kathmandu Valley. He initiated day clinics and trained health workers in Bharatpur, Hetauda, Birgunj, Baglung, and several other provincial areas. Pokhara was first visited by Dr. Sharma and has become well served over the years: "They've got three women psychiatrists practicing there. Dr. S goes every month, Dr. O goes every month, Dr. K goes every month, so in Pokhara there's lots of input" (Dr. PSY-S).

From early on, Nepali community psychiatry was focused on psychopharmaceuticals. Even Dr. Sharma emphasized drugs. Like most other low-income countries, Nepal's approach to mental health was heavily pharmaceuticalized (Biehl 2007). Dr. PSY-S, who began to work in 1976 after graduating from the UK, was

part of the early community work: "Dr. B. P. Sharma ran the training. He saw the patients. Based on drugs only" (Dr. PSY-S). Since Dr. Sharma's days, Nepali psychiatrists regularly travelled to rural areas to see patients. This is still common practice today. The sponsorship of these trips has shifted from the government to pharmaceutical companies: "We are all going to the rural side, to earn money. The government salaries are very low" (Dr. PSY-T).

All the first-generation psychopharmaceuticals were available in the 1970s: "I remember amitriptyline was there, in 1971 ... we were using neuroleptics like chlorpromazine, trifluoperazine, clomipramine, imipramine, trimipramine. Lithium came in 1976" (Dr. PSY-S). Fluoxetine was first introduced to Nepal by the Indian company Cadila. Soon other SSRIs came to Nepal, first from Indian and gradually from Nepali companies. Availability was good in the Kathmandu Valley, but in rural clinics, the choice was very limited.

Nongovernmental organizations developed mental health projects from the 1980s onwards. The most influential intervention came from the United Mission to Nepal (UMN), a multinational Christian missionary organization. Its motto is "We serve, Jesus heals." UMN's approach shaped Nepali diagnosing and prescribing for decades. UMN launched its mental health project in 1984 (Acland 2002). This was Nepal's first mental health intervention by an NGO, though most of the work was done in collaboration with government institutions. It included psychiatric outpatient work, training of health

workers, drug abuse prevention, community mental health outreach, and work in jails. UMN built on the community approach developed by India's National Institute of Mental Health and Neurosciences at Bangalore (Acland 2002: 121; Seale-Feldman 2020: 33). The chief architect of UMN's mental health programme was Dr. Christine Wright, a British psychiatrist. The first draft of Nepal's Mental Health Policy was prepared with assistance of UMN (Acland 2002).

In the first 15 months of UMN's work in five community clinics in Lalitpur (Nepal's third-largest city, also in the Kathmandu Valley), 210 patients were treated. Epilepsy was the most common diagnosis (32%), followed by psychosis (24%), depression (18%), and mental retardation (10%) (Seale-Feldman 2020: 36). Another UMN study, of treatments administered over a four-year period in Morang district, recorded 4,878 treatments of epilepsy, 1,124 treatments of depression, 557 treatments of psychosis, 144 treatments of neurosis, and 34 treatments of mental retardation.

The UMN programme was built on psychopharmaceuticals. UMN pitted modern/rational treatments against the traditional/irrational hokum performed by ritual healers. In the training materials developed for primary health workers, UMN lobbied for a turn from magic to science. The first training card distributed by UMN in the mid-1980s reads as follows:

"Of the many health problems (illness) the causes and treatment of mental illness are poorly understood by the general public. As a result people seek non-medical

help from healers, priests, witch-doctors and often visit places of pilgrimage for help. People using these methods often can harm the patient by delaying proper treatment. *Following major scientific development in the field of psychotropic drugs and modern techniques of treatment, simple, effective and inexpensive methods of treatment are now available* for almost all the mental disorders ... The traditional beliefs and practices in our community have been there for many years. They can not be replaced in a short time ... Your repeated efforts to give the correct information would lead to change" (UMN training card, in Seale-Feldman 2020: 34; my emphasis).

UMN only used a narrow set of medications: phenobarbitone for epilepsy, chlorpromazine and depot fluphenazine for psychosis, and amitriptyline for depression (Acland 2002: 134). Trihexphenidyl, an anticholinergic, was added to chlorpromazine to control the side effects (Seale-Feldman, 2020, personal communication). UMN adopted amitriptyline as their drug of choice for two reasons. First, it was the only antidepressant on the World Health Organization's essential drugs list. Second, the drug was already widely available in Nepal, first as imports from India, later also from Nepali drug manufacturers. UMN did not establish amitriptyline, rather they found it when they came: "In 1983, two expat psychiatrists came, one was Chris Wright ... They had to work together with the government ... So it is not that amitriptyline was not there. It was there already. Amitriptyline has been there long before" (Dr. PSY-S).

The UMN programme started out by dispensing psychopharmaceuticals for free. UMN used donor funding to purchase the drugs and then handed them to patients in its various clinics. The more patient numbers grew, the harder it became to sustain this giveaway, but UMN continued for nearly a decade. Then, in 1993, UMN were told off by the Nepal government's Director General of Health. He wrote to them that they should stop giving drugs without charge, because eventually the government would have to pick up where UMN left, and the government would not be willing or able to continue UMN's giveaway (Acland 2002: 142). UMN complied with this request. The end of free drug distribution was a "major setback" for UMN's psychiatric outreach activities (ibid.). On the other hand, inexpensive generics were widely available, so "patients will buy their medication in the bazaar" (ibid.).

UMN introduced many psychiatric outpatient services. One of them was inserted in the UMN hospital at Tansen, a municipal town in western Nepal. The work of the psychiatric OPD at the Tansen hospital has been studied in detail by Harper (2014: 83-102). The UMN hospital catered to people from the surrounding villages. "Multiple physical complaints" was the most common presentation. Once physical problems had been excluded, this condition was diagnosed as somatized depression.

A key part of the UMN community work was the invention of a less stigmatizing idiom for mental disorders. Instead of speaking of "mental" problems, UMN doctors wrote new clinical guidelines that coined the concept of "nerve disease" (*nassako rog*).

Psychiatric treatment needed compliance from patients, and compliance could only be achieved if the patients believed in the treatment: "*Without belief in the doctor who is prescribing and advising, even the best advice and therapies will have difficulty in producing a positive outcome.* 'Nassako rog.' *An approach to patient education.* Nerves travel from the brain to all parts of the body and thus when the nervous system is sick symptoms occur all over the body" (cited in Harper 2014: 85; emphasis in the original). This idiom of nerve disease proved to be more acceptable than local idioms of "madness." It also eliminated the need for metaphors that became popular elsewhere, such as "neurochemical imbalance" (Rose 2003).

Together with government health workers, UMN also conducted many training sessions for primary care workers in the district, schooling them in the recognition of "nerve disease" and in the prescribing of first-line medications. Amitriptyline was the drug of choice for depression and a spectrum of mood disorders. It was also used in combination with other drugs, such as chlorpromazine. It was easily available in the local medicine shops and patients could refill their prescriptions without going back to a prescriber (Harper 2014: 86). The Tansen OPD exemplifies UMN's approach: insert psychiatric prescribing into the existing health infrastructure; work closely with primary care providers; train nonspecialists to diagnose and medicate; destigmatize psychiatric illness through reworking local idioms; base all prescribing routines on the local availability and affordability of drugs.

Nepali psychiatrists first collaborated with UMN and later continued the same programme on behalf of the government. Talking about the training of health assistants, one psychiatrist said that its beauty was its simplicity: "We don't want to confuse them. So we have three diseases and three medications: schizophrenia, chlorpromazine; depression, amitriptyline; epilepsy, phenobarbitone" (Dr. PSY-U). Amitriptyline became the standard because it was available, and it was available because it was standard. None of the country's violent upheavals of the last decades has changed anything about amitriptyline's position as go-to drug for disordered moods. Almost every psychiatrist I interviewed said that "old is gold" in reference to the drug. Political regimes changed drastically, the drug regimen stayed the same, because the country's relative poverty stayed the same.

Looking back at the commercial success of amitriptyline, Frank Ayd highlighted that family physicians "loved it because it was sedative, it had some definite antianxiety as well as antidepressant properties" (in Healy 2001: 99). This reception was not clearly visible in Ayd's original article, which was published in 1960. Ayd's study would not meet any standards of good evidence today. The diagnostic categories he used are very different from those used for clinical trials since DSM-III (APA 1980). Ayd found that "mildly depressed manic-depressives who were lethargic and seldom had physical complaints" and who "dubbed themselves 'tired businessmen' or 'tired housewives'" (Ayd 1960: 321-322) were a type that responded particularly well to amitriptyline. He

also mentions that amitriptyline could work for anxiety: "Dramatic therapeutic results were seen in those patients often diagnosed anxiety hysteria because their depression was overshadowed by severe anxiety with hysterical features" (Ayd 1960: 322).

In Ayd's original study with US patients, the side effects profile was said to be "not serious, seldom required counteracting measures, and subsided as the drug was continued" (Ayd 1960: 324). He found that the most frequent side effects of amitriptyline were constipation and dry mouth (both 60% of patients), followed by dizziness, blurred vision, and weakness/fatigue (both 20%). The common side effects that Ayd described in 1960 are similar to how they are listed six decades later.

Constipation and dry mouth are still high on the list of the most common side effects, caused by the drug's anticholinergic action. However, in terms of the "personality" that the drug fits best, Ayd's American "housewives and businessmen" are the opposite of what Nepali psychiatrists describe as typical. In Nepal, the quintessential patient for amitriptyline is the rural somatizer: a villager, with little to no education, who presents with multiple somatic aches and pains coupled with insomnia and agitation (Kohrt 2005; Harper 2014).

All the Kathmandu psychiatrists described the rural somatizer in these terms. They thought that Nepali people from rural areas could not express their feelings: "In Nepal, patients cannot express emotions. So this gets expressed through bodily symptoms: headaches, chest pain, dizziness. They are alexithymic" (Dr. PSY-B). Alexithymia is the

inability to identify and describe emotions, which can accompany several mental illnesses. For Nepali psychiatrists, this alleged inability to express emotions was a general cultural feature. Depression appeared underneath physical multimorbidities and not as an isolated mental health problem: "We call this 'multisystem' complaints: no appetite, not getting sleep, stomach gets upset. Headache, dizziness, aches and pains. There are innumerable symptoms. But we have to explore the mental side" (Dr. PSY-U). Depression without any comorbidity was very rare. The doctors mentioned similar sets of symptoms that were most common in Nepal, but they varied in how frequently they were presented. Dr. PSY-S, for example, thought that a tingling or numb sensation in hands and feet were most common, followed by "burning pain" and "gastric" problems.

The prevalence of the tingling or numb sensations as somatic expression of depression is well-known. In Nepali, it is called *jhum-jhum* (Kohrt 2005). The importance of *gyastric* complaints that focus on stomach, bowels, and digestive disturbances, has also been described (Harper 2014). Nepali psychiatrists have similar perceptions of the primacy of somatized depression as their Indian colleagues. For example, the Indian psychiatrists studied by AUTHOR (2013) also said that people somatize their emotional distress. The Nepali ethnophysiology of *jhum-jhum* overlapped with *gyastric*: "pressure comes up from the belly through the arms and travels through to the fingers" (Dr. PSY-S).

Like Indian psychiatrists, Nepali psychiatrists are aware of the high levels of stigmatization of "mental" problems, which are quickly branded as "madness." Like UMN's rebranding of depression as *nassako rog*, Nepali psychiatrists also use a language of "nerve" disorders: "I think it is very difficult to make them understand that they are suffering from depression. They completely refuse. So we have to modify how we say what we diagnose. We say, you have some kind of stress, and the stress affects your nerves, and because of the nerve problem, you have these symptoms. If you tell them straight away that they have a 'mental' problem, they will not come back to you" (Dr. PSY-A). "Nerves" made sense because they went all across the body, so any medication that treated the body could also act on the brain, and vice versa: "Neurochemical discharges are happening, and when we give medicines, they can balance neurotransmitters" (Dr. PSY-B). No stigma attached to "nerve" problems.

"Nerves" were thought to be channels running between the body and the brain. The "channel" image of nerves could be extended to explain mental problems as excess weight: "If we pick up a bucket, without water it will be very light. But with water, it will be very heavy, you can't pick it up. Similarly, our brain has a limited capacity. If you have too much thinking in there, it creates a lot of weight, so the brain becomes tense, just like a muscle" (Dr. PSY-N). The brain-as-bucket image explained both overthinking and fatigue.

In Nepal, both governmental and non-governmental psychiatric services started out with an emphasis on diagnosing and treating somatized depression. This tradition, which dates back to the pioneer years of the 1960s to the 1980s, remains strong even in the 2020s. Along with this primacy of somatized depression comes the primacy of amitriptyline because it targets both physical pains and mental symptoms.

Why old is so gold

When choosing between different kinds of therapies, prescribers have to compare them by a set of criteria to make a call on which therapy is "best," both by individual features as well as overall. This is a biocommensation, that is, a comparison between different entities towards which enhances a patient's life most (AUTHOR 2021). To biocommensurate means putting entities into a value comparison towards the pragmatic goal of making a patient better. A prescriber's task is to arrive at an overall commensuration that weighs all the salient features of different drugs and then decides which has the overall best profile. The prescriber's problem is that there is not one overarching criterion that surpasses all other criteria. Instead, to value pharmaceuticals, a whole range of criteria must be considered in relation to each other (Orsi 2015: 103). For antidepressants, these criteria include efficacy, toxicity, side effects, affordability, availability, accessibility, acceptability, novelty, confidence in using them, and range of symptoms treated. When Nepali psychiatrists compare different antidepressants to each

other, amitriptyline comes out as the overall best choice because it fulfills the criteria in the overall best way. Amitriptyline is clearly not perfect, but it is regarded as overall best for how Nepalis experience depression, for how much they can spend on medications, and for how they can access the medications. In the following, I present a detailed analysis of how Nepali psychiatrists biocommensurate amitriptyline in comparison to other drugs, especially the SSRIs, and how they arrive at their valuation of amitriptyline as old but gold.

For Nepali psychiatrists, a key advantage of amitriptyline over newer antidepressants was that it took care of agitation along with depression and somatic pains. "Most of the patients in Nepal have some kind of agitation, insomnia, or panic. For them, tricyclic antidepressants are still the gold standard" (Dr. PSY-U). Since amitriptyline was able to "control tension," there was no need to add a tranquillizer, such as diazepam or alprazolam. This broad-spectrum action saved patients money that they would otherwise have to spend on several different medications, for example, fluoxetine combined with a tranquillizer.

The idea that amitriptyline "controls tension" extended to the prescribers themselves. The drug has been in use for such a long time and doctors were so experienced in using it that it inspired much confidence in them. "Old is gold," they kept repeating. Dr. PSY-S, for example, said that "old is gold" for most depression cases. Dr. PSY-A described the "old" amitriptyline as "gold" when comparing it to the

drugs that came later: "Always we say old is gold. We are much more confident using the older drugs, very much confident because we have seen the patients responding very well." The beauty of amitriptyline was that it did not just take care of the patients' worries, it also eased the prescribers' worries of choosing the right medication. Amitriptyline was the trusted workhorse for any disordered mood.

The psychiatrists pointed out that, from among all antidepressants, amitriptyline best fulfilled the "four As" of community medicine: affordability, availability, accessibility, and accountability. Minding the four As was more important than optimal efficacy. Dr. PSY-S regarded prescribing by the "four As" as ethically superior to purely biomedical rationales: "Suppose there are two patients. One gets fluoxetine and goes back to his village. The other gets amitriptyline and goes back. The patient on amitriptyline does not have to come back to Kathmandu, he can continue the treatment in the village. He will only be referred back by the primary health workers if they cannot handle it themselves. But the patient on fluoxetine, he has to come back to Kathmandu. I see that as unethical." The community health workers were trained to detect the key symptoms of depression and to give amitriptyline up to a maximum dose of 150mg. They are also given a simple guide on what they should do when that fails. He continued to say that, "from a scientific point of view," amitriptyline was not better overall than other drugs, in fact it might be overall worse because of its high risks. But

again, the old amitriptyline was "gold" because its affordability and availability trumped its risk profile.

Patients could buy it from any private medicine shop but also get it from all the government health posts. Fluoxetine was added to Nepal's essential drug list in the late 2000s, but continued to play second fiddle to amitriptyline: "The government is committed to amitriptyline" (Dr. PSY-N). Another doctor said that affordability came first: "Say there is a poor farmer, of course we go for amitriptyline. No two opinions about it" (Dr. PSY-B). Affordability is critical in a country as poor as Nepal, both for individuals paying out-of-pocket and for the government. "Price is a major criterion. Even just one *paisa* [US\$0.000084] makes a difference. That's why we hold on to amitriptyline" (Dr. PSY-S). Nepal continues to be one of the world's poorest countries, with GDP per capita at just over US\$1,000 [ca. NPR120,000] in 2019. All other antidepressants are also cheaply available in generic form, and most of them are manufactured by domestic companies. Yet the low income levels made choosing between different medications far more price-sensitive than in other Asian countries. In the 2000s, amitriptyline cost about NPR1 per tablet, fluoxetine around NPR2 per tablet. In the 2010s, amitriptyline cost around NPR3 per tablet, fluoxetine around NPR6 per tablet. In absolute terms, the difference is microscopic: amitriptyline is US\$0.025 compared to US\$0.05. But in relative terms, fluoxetine continued to be twice as

expensive as amitriptyline, and for poor people in a poor country, that makes a big difference.

Price made a difference in favour of amitriptyline, yet even in terms of therapeutic efficacy, most Nepali psychiatrists thought that the newer drugs were not better than the old ones: "I still have to meet anyone who can impress on me that fluoxetine is better than amitriptyline" (Dr. PSY-S). For better-off patients, SSRIs could be considered. Without doubt, amitriptyline had many more side effects than SSRIs, the psychiatrists said. Pre-existing heart disease was one of the contraindications against using amitriptyline. The drug was certainly more toxic than SSRIs and the dose could easily be too high. The risk of giving a patient too much amitriptyline was mentioned by the psychiatrists as one reason why primary care prescribers were often giving far too little. They "spoil" the case by giving too low a dose. Sometimes they tried to offset the low dose by adding benzodiazepines. Many primary providers thought that the recommended dose for amitriptyline was too high for Nepali bodies and had to be lowered. They believed that Nepalis are at a higher risk of drug side effects when Euro-American dosage standards are applied. The psychiatrists dismissed this as a superstition. One of them said that Nepalis and westerners were "of the same Aryan race" and that drugs were metabolized in the same way in Nepal as in the west. If there is a difference in pharmacokinetics, it is that Nepalis are poorer and have a lower body mass, hence that a full therapeutic dose is reached more quickly. Alcoholism was a

major problem in the country, and this increased the risk from all psychotropic medications.

SSRIs had, on the whole, far fewer side effects than amitriptyline, but they bore many other risks. Nepali psychiatrists highlighted that fluoxetine had many gastric side effects: pain, abdominal contractions, loss of appetite, and nausea. It could lead to "gastric lesions" in patients with pre-existing gastritis. Insomniacs responded badly to fluoxetine, they often got more restless. Hence for anxious and insomniac patients, fluoxetine could only be used as a "daytime antidepressant." Sexual problems associated with fluoxetine were practically universal in men. Loss of libido, erectile dysfunction, and problems ejaculating were extremely common. The drug caused "impotence for most patients" (Dr. PSY-T). Some of the psychiatrists found that an additional prescription of sildenafil (Viagra) helped some of the patients, but it was not an ideal situation. Switching to other SSRIs could lower the sexual side effects, especially escitalopram seemed to work better for such patients. The problem with escitalopram was its high price, so for poorer patients who could not tolerate amitriptyline, it had to be fluoxetine. Sertraline, another SSRI, seemed to work well in cases where depression came with strong anxiety, obsession, and panic disorder. Nepali psychiatrists found that in cases where a patient had "pure" depression without any pains, anxiety, or sleep problems, SSRIs could work well.

Nepali psychiatrists warned that SSRIs could produce "paradoxical anxiety" (Dr. PSY-K). Patients could get more anxious and fearful than they were before without the drug. This was linked to a heightened suicide risk. The doctors mentioned that many Indian manufacturers brought out fixed-dose combinations of SSRIs with tranquillizers. The combination of alprazolam 0.25mg with fluoxetine 20mg was popular. The rationale for mixing SSRIs with tranquillizers was that depression and anxiety disorder are the "twin sisters" among the mood disorders. A related rationale was that depression, in any age group, diminishes the ability to make decisions, including decisions whether to harm oneself. Initiating treatment with an antidepressant lifted the indecisiveness just enough to flip into impulsiveness, so someone with depression has suddenly enough energy to put suicide plans into action. Even in combination, fluoxetine was not a great drug for anyone actively suicidal, amitriptyline worked better because of its sedative effects. Another problem with fluoxetine was that it took longer to kick in and show results. Many patients were too impatient, and discontinued before any effects were visible.

Prescription routines varied by institutional habits. Prescribers in the Kathmandu Valley and in most outer areas preferred amitriptyline. A few places preferred newer antidepressants. In particular, doctors at BPKIHS Dharan were less likely to use amitriptyline. The majority of Nepali psychiatrists trained in India, and all had ties to Indian colleagues. Those ties to India were strongest at Dharan, and with them came a

marked preference for newer drugs: "The Dharan folks, they studied outside and came back with book knowledge, they prefer fluoxetine. They have Delhi prescription patterns. They have no experience of the community. They have no idea of the hassles that a villager faces when you give him newer medicines. When you look at a prescription, you can make out, 'this is a Dharan guy'" (Dr. PSY-M). Prescribing differences could also be explained by the institute having younger staff, and younger psychiatrists were more open to newer drugs, doctors said.

There were individual exceptions to these rules. Some psychiatrists liked the newest drugs, such as venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), but it depended on how deep the "patients' pockets" were. Although venlafaxine was also available in generic form, no Nepali company produced it, and the Indian producers charged around NPR8 per tablet in the late 2010s. One psychiatrist outside Kathmandu was known for his love of citalopram: "He prefers citalopram left and right. There are so few psychiatrists, we can very well locate local sales patterns. Maybe he is company-driven. He is younger" (Dr. PSY-B). On the whole, however, the "old is gold" principle made Nepali prescribers resistant against newer prescribing trends. Indian psychiatrists were more driven by fashions and fads, whereas Nepalis stuck to the tried and tested.

Will the old amitriptyline still be gold in the future? Will the tenacity of local affordances continue to overrule global changes in evidence and health policy into the 2020s? In the 1990s, more international NGOs entered the fray of mental health in

Nepal. NGO work focused on post-disaster psychosocial interventions. Waves of NGO work were spurred by ethnic Nepalis fleeing from Bhutan to Nepal's eastern provinces since the 1990s (Hutt 2003), by trauma among people caught up in the Maoist insurgency (Pettigrew 2013), and by trauma related to the earthquakes of 2015 (Kane et al. 2015). The NGO sector has since become far more prominent. Several NGOs extend community psychiatry in the pattern established by UMN. Indeed, from the days of UMN's mental health project in the 1980s, there has been a "consistent present of Nepal as an important site in the production of knowledge for the field of global health and now global mental health, providing data, case studies, and evidence, and serving as a node through which experts within the network of global mental health have circulated" (Seale-Feldman 2020: 39). The newer NGOs tend to work with *mhGAP* guidelines (Chase et al. 2018), which explicitly favour fluoxetine over amitriptyline. It remains to be seen if the growing influence of international organizations and donors is able to break amitriptyline's 60-year run as Nepal's first-line drug for depression.

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