On the so-called psychopharmacological revolution: the discovery of chlorpromazine and the management of madness

CAPONI, Sandra. On the so-called psychopharmacological revolution: the discovery of chlorpromazine and the management of madness. *História, Ciências, Saúde – Manguinhos*, Rio de Janeiro, v.28, n.3, jul.-set. 2021. Available at: http://dx.doi.org/10.1590/S0104-59702021000300003.

Abstract

This article analyzes the shortcomings and problems of the thesis that a true revolution took place in the field of biological psychiatry between 1952 and 1954 thanks to the discovery of chlorpromazine. To do so, it analyzes the discourses and strategies that led to the discovery of this drug, which became a model for the production of new psychopharmaceuticals. It seeks to understand, also, what is meant by "therapeutic efficacy" with regard to this drug.

Keywords: chlorpromazine; history of psychiatry; psychopharmacology; therapeutic efficacy.

Sandra Caponi[i]

[i] Professor, Departamento de Sociologia e Ciências Políticas/ Universidade Federal de Santa Catarina, *campus* Trindade. Florianópolis – SC – Brasil

orcid.org/0000-0001-8180-944X

sandracaponi@gmail.com

Received on 4 Sep. 2019.

Approved on 13 Jan. 2020.

Translated by Catherine Jagoe.

http://dx.doi.org/10.1590/S0104-59702021000300003

In October 2000, the American Psychiatric Association (APA) published a special issue of the journal *Psychiatric Services* to commemorate the organization's fiftieth anniversary. It contained an article by Lieberman, Golden and Stroup titled "Drugs of the psychopharmacological revolution in clinical psychiatry." In it, they referred to the discovery of neuroleptics in the early 1950s as a moment of real transformation or revolution in the field of psychiatry:

> The development of antipsychotic drugs in the 1950s heralded the golden age of psychopharmacology. Their discovery was comparable to the discovery of antibiotics for infectious diseases, anticonvulsants for epilepsy, and antihypertensive drugs for cardiovascular disease. The antipsychotic drugs soon became the cornerstone in the pharmacopoeia for the treatment of psychiatric illnesses, and enthusiasm for their potential pervaded the mental health field (Lieberman, Golden, Stroup, 2000, p.1255).

References to the existence of a real revolution in the field of psychiatry have been repeated from 1957, when the Albert Lasker Clinical Medical Research Award was first granted, up to the present day (Ban, 2007; Baumeister, 2013; Fond, 2013; Healy, 2000; López-Muñoz, Alamo, Cuenca, 2002; Mazana, Pereira, Cabrera, 2012; Shorter, 1997). In these references we find, among many other things (Gaudillière, Thoms, 2015; Kunz, 2014; Missa, 2008), the argument that there was a process of radical transformation in psychiatric knowledge between 1952 and 1954. Supposedly, that inaugural moment allowed for "a true revolution in the approach to psychiatric disorders" (López-Muñoz, Alamo, Cuenca, 2002).

This meant claiming that neuroleptics had made it possible to avoid the drawbacks of the high-risk treatments used in hospitals prior to that point. Thus, drugs such as morphine, used in conjunction with shock therapies, lobotomy, and containment therapies, were no longer necessary.

References to a transformation or revolution in the field of psychiatry thanks to chlorpromazine can be seen as early as 1957, when Henri Laborit, Pierre Deniker, Heinz Lehmann, Nathan Kline and Robert Noce received the prestigious Albert Lasker Clinical Medical Research Award. The first three, a surgeon and two psychiatrists, received it for discovering chlorpromazine, and the last two for discovering reserpine. The Lasker Foundation's rationale for awarding this important prize was described as follows:

> This work firmly established a whole new phase of psychiatric treatment and research. It demonstrated on a vast scale and incontrovertibly that a medication could influence the clinical course of the major psychoses; the problems of psychiatry had been brought within reach of the experimental laboratory as never before, and the future was suddenly more bright and promising (Lasker Foundation, 1957).

The goal of this article is to show the shortcomings of this widely-held thesis that the discovery of chlorpromazine led a true revolution or epistemological shift in the field of biological psychiatry. In order to do so, we need to analyze the discourses and intervention strategies that led to the era of neuroleptics, observing the continuities with and departures from the therapies used before the discovery of chlorpromazine (Parada, 2016).

Given that it is impossible to cover all the literature on the history of chlorpromazine, I shall begin with Judith Swazey's book (1974) *Chlorpromazine in psychiatry: a study of*

therapeutic innovation. Based on my reading of this work, I propose a dialogue both with primary sources and with the numerous authors who have critiqued the discovery of chlorpromazine (Breggin, 2016; Freitas, Amarante, 2016; Gotszche, 2016; Moncrieff, 2008; Amarante, Pitta, Oliveira, 2017; Whitaker, 2010; Pignarre, 2006; Rose, 2019).

A triumphalist narrative

When we analyze the history of psychopharmacology in general and the history of chlorpromazine in particular, we find one reference repeated again and again. Various authors (Whitaker, 2017; Moncrieff, 2013; Healy, 2000, 2002; Henckes, 2011; Missa, 2006, 2008; López-Muñoz, Alamo, Cuenca, 2002; Gaudillière, Thoms, 2015) insist that the most complete history to date on the discovery of chlorpromazine is Judith Swazey's book (1974).

Her book contains an overview ofthe main reference texts as well as interviews with actors who contributed directly or indirectly to the discovery; it presents relevant data and provides a very clear and helpful historical chronology. However, it would appear to be a history without problems, or a history whose central theme revolves around precursors.

Swazey (1974) offers a detailed "hagiographic history," with a succession of great names and great victories, presenting the ideas circulating among a group of scientists obsessed with discovering a medication like penicillin that could save the lives of people condemned to madness. She lays out the methodological paths of discovery and identifies scientifically established norms that made it possible to overcome the existing "ideological barriers" (p.193).

Each chapter of *Chlorpromazine in psychiatry* is presented as a step on the path towards a "psychopharmacological revolution" that led to the victory of a "therapeutic innovation" that superseded the retrograde ideological views held at the time. Or, as the author puts it, a discovery that made it possible to "break the ideological barriers" in place (Swazey, 1974, p.193). And Swazey sees psychoanalysis as one of those ideological barriers. This is how she refers to the role of psychoanalysis in 1950:

> One important factor was that American psychiatry in the mid-1950s was dominated by what Armor and Klerman have termed the psychotherapeutic ideology, generated over the course of a half-century by Freudian psychoanalysis and the new movements that evolved from Freud's tenets (Swazey, 1974, p.196).

Swazey celebrates the fact that despite those barriers, use of the drug expanded so much in the United States that it eventually became an almost universal treatment. Swazey's position is not shared by psychoanalysts like Gladys Swain (1994, p.271), who emphasizes the historical relationship between the use of neuroleptics and psychanalytic therapy. Swain argues, however that this complex relationship is rarely discussed. She writes: "we practice chemotherapy and psychotherapy, but we only speak of psychotherapy, because it is the respectable cultural object while the other is unmentionable" (p.269).[1]

Unlike Swain, Swazey contrasts what she terms "psychotherapeutic ideology" to somatotherapy, in which disordered behaviors are seen as due mainly to alterations in brain

function. Swazey (1974) argues that even though there was some resistance to biological psychiatry and somatotherapy, which were favored by opponents of psychoanalysis, they became the dominant approach over the course of the 1950s, when "only a few fanatics" refused to use chlorpromazine (p.197).

Edward Shorter (1997) makes the same arguments as Swazey in his book *A history of psychiatry: from the era of asylum to the age of Prozac*, in which he claims that chlorpromazine ushered in a revolution in psychiatry comparable to the introduction of penicillin in general medicine. This claim was repeated in 2001 by a psychiatrist from the Lierneux Hospital in Belgium, interviewed by Missa (2006): "For me Largactil (the brand name of chlorpromazine in Belgium) is just as important as penicillin."

In 1975, a year after Swazey's book was published, Deniker wrote a short paper titled "Qui a inventé les neuroleptiques?" ("Who invented neuroleptics?") in which he distances himself from Swazey's perspective. He points out that her book was commissioned and funded by the National Academy of Sciences in the United States. At that point, the history of the discovery of chlorpromazine was not very well known in France, except among the scientists directly involved. In Deniker's view, that history was popularized in 1970 thanks to a short text by Ann Caldwell (1970) titled *Origins of psychopharmacology from CPZ to LSD*, devoted largely to the figure of Laborit and American researchers. A few years later, the National Academy of Sciences decided it would be a good idea to fund a more fully-documented work, and they gave the job to Judith Swazey, who specialized in the history of science.

Even though Deniker believes her study was well-documented, he points out certain limitations. He claims that she makes no reference to the concept of "neuroleptics" and that she minimizes the role of Jean Delay's group at the Sainte-Anne Hospital. He lists the group's publications, including their early papers on the use of chlorpromazine for psychosis, arguing that Swazey's text does not respect the chronological order of publications, instead listing the dates when different researchers received samples of the drug:

> Thus, the specialists who regularly worked in laboratories took credit for [the discovery], even though their work appeared much later than others'. Therefore, of the two American investigations, the first lacks basic objectivity (Caldwell, 1970), and the second (Swazey, 1974), by presenting 'unpublished' elements helped lend more visibility to the French and American pharmaceutical industry (Deniker, 1975, p.8).

My discrepancy with Swazey's work is based on its failure to critique the side effects of chlorpromazine. Even though she does mention the drug's unwanted side effects, which had already been well documented by Delay and Deniker, she makes virtually no reference to its profound sedative effects, nor to the sense of apathy and indifference to the world and to treatment seen in patients who took it (Caponi, 2019).

I shall now analyze the arguments presented by the winners of the Lasker Award for the discovery of chlorpromazine: the surgeon Henri Laborit (Laborit; Huguenard, 1952) and the psychiatrists Pierre Deniker (Delay, Deniker, 1952a) and Heinz Lehmann (Lehmann, Hanrahan, 1954).

On the therapeutic efficacy of chlorpromazine

Judith Swazey (1974) claims that, like many other drugs, chlorpromazine was discovered by accident. In fact, the medication was initially created and designed as an antihistamine by the French pharmaceutical company Rhône-Poulenc in the 1940s. Initially, the company was interested in studying phenothiazines for controlling worm infestations. Although their research proved unsuccessful on that front, some of the phenothiazines turned out to be effective antihistamines. One of the antihistamines Rhône-Poulenc studied, promethazine, also had anesthetic and sedative properties, and it started to be used in sleep therapies. It was a powerful antihistamine that was also useful for treating allergies. Chlorpromazine's trajectory continued thanks to the observations of Henri Laborit, a French naval physician who was investigating the use of antihistamines to help augment anesthesia during operations on service men. Laborit asked the Rhône-Poulenc laboratory to send an antihistamine that was stronger than the promethazine Phenergan in order to improve conditions during surgeries. Subsequently, Laborit observed that patients treated with the new phenothiazine, chlorpromazine, showed a marked change in behavior, becoming more calm, peaceful and sleepy, without losing consciousness.

Chlorpromazine was initially used by Laborit (1951) to produce artificial hibernation, as a vegetative stabilizer. In 1952, Laborit published the first article on 4560RP. In it, he stressed "the patient's lack of interest in what is going on around him, going as far as to describe it as 'pharmacological lobotomy'"(Missa, 2006, p.255). The molecule known as 4560RP was tested by various teams to explore its efficacy as an anesthetic, as well as for Parkinson's disease and pain treatment. Laborit claimed that his studies showed that chlorpromazine represented a significant advance in relation to promethazine, particularly in the emotional indifference to pain it produced (Laborit, Huguenard, 1952, p.206).

The studies Laborit received from Rhône-Poulenc on the 2460RP molecule had been performed on animals. Such research is no different from the studies still carried out today to test psychoactive drugs (Cynowiec, 2017). Rats had been trained to respond by pressing an escape switch when exposed to a physical threat, such as an electrified floor, for example. However, even when they knew the escape strategy to avoid an electric shock, the rats treated with compound 4560RP, later known as chlorpromazine, appeared insensible and completely unable to react.

Laborit (1951) used this molecule in patients who underwent any kind of surgery and found that it left them in a state that he described as "artificial hibernation," similar to animals that have adapted to extremely cold conditions. Using the analogy to the phenomenon of hibernation, physicians often sought to augment chlorpromazine's effect by submerging patients in ice, a procedure often used as an aid to anesthesia. Laborit eventually suggested that chlorpromazine might be used in the psychiatric field, since it produced effects similar to lobotomy but made it possible to avoid the surgery, which was irreversible, although considered effective. Nowadays it may seem strange to defend a medication on the grounds that it could induce what was described as "chemical lobotomy," but at the time, this amounted to praise. The Portuguese neurologist Egas Moniz had recently received the 1949 Nobel Prize for Medicine for inventing lobotomy (Nobel Prize,

1949). Chlorpromazine proved capable of transforming patients who were agitated and stressed on arrival at the operating room, rendering them calm, apathetic and indifferent to surgery, just as if they had undergone a lobotomy.

Swazey's book only refers to that feeling of indifference indirectly; it is sometimes mentioned, but never questioned or discussed by the author. When we look at the chronology of publications about chlorpromazine, which went into use in 1952, we see that the first was by Laborit in February 1951. Even though he was writing from an anesthesiological perspective, Laborit stressed the psychological effect of the drug, "disinterest." That was the starting point for chlorpromazine's entry into the psychiatric field. Medicated patients were people who belonged in the closed space of hospital and chlorpromazine seemed an excellent management aid for wards with agitated patients. Swazey (1974, p.146) simply repeats at some points in her book that, according to some observers, the most noticeable psychiatric response to chlorpromazine was "somnolence" and "indifference" in patients. In 1952, Delay and Deniker (1952b, p.115) described the psychic effects of the medication as follows:

> From the psycho-physiological point of view, in conditioned rats, we noted indifference to external stimuli. ... The psychological effects observed in patients were: somnolence, passing the majority of the time sleeping, and when woken they remain dazed. ... In general patients treated with it remain sleepy and as if indifferent. However, the term 'chemical lobotomy' that has been proposed to characterize the state of these patients, does not seem correct to us.

That same apathy had been described by Laborit from his observations of patients treated with chlorpromazine for surgical procedures. Their indifference appeared also in circumstances not involving surgery, even potentially dangerous ones, as seen in the studies carried out on animals. According to Healy (2002), in view of this aboulia or indifference to external threats, Laborit recommended that chlorpromazine be used to control stress reactions in extreme situations such as on the battlefield. "Following this recommendation chlorpromazine was included in the medical kits of US soldiers in the KoreanWar" (p.37).

Chlorpromazine at the Sainte-Anne Hospital

As we have seen, chlorpromazine began its pharmacological trajectory as an antihistamine, was next used as an anesthetic and only then brought into psychiatric wards as a treatment for psychotic patients. In order to understand this use of the drug, we need to look at the Sainte-Anne Psychiatric Hospital in Paris in 1952. At that time the hospital director was Jean Delay, a key figure who oversaw the work done by Pierre Deniker's team on the discovery of chlorpromazine. Healy argues that the history of this discovery could have turned out very differently, because before Deniker or anyone else claimed that the drug could help treat schizophrenia, Henri Baruk (1967, p.54) and his colleagues, also from the Sainte-Anne Hospital, had administered it to laboratory animals and concluded that it produced experimental catatonia and that rather than curing schizophrenia, it could actually cause it.

Pierre Deniker and his team began studying psychotic inpatients at the Sainte-Anne Hospital. In 1952, Delay and Deniker (1959) presented six co-authored papers. The titles (translated here from French into English) were: "Use in psychiatric therapy of a preferred centrally-acting phenothiazine (4560 RP)," published in *Annales Médico-Psychologiques* on May 26, 1952; "Treatment of states of excitation and agitation by a medication method derived from hibernotherapy," published June 23, 1952 in the same journal; "Treatment of states of confusion via chlorpromazine (4560RP)," also published in *Annales*, on July 7, 1952; "Treatment of psychosis using a neuroleptic method derived from hibernotherapy (4560RP), used as a prolonged and continuous treatment," published in the *Actes du Congrès des Médecins Aliénistes et Neurologues de France et des Pays de Langue Française*, issue 50, on July 27, 1952; "38 cases of psychosis treated with prolonged and continuous use of 4560RP," published in *Actes du Congrès* on the same date; and lastly, "Biological reactions observed during the course of chlorpromazine treatment," their third paper presented at the same conference (Deniker, 1975, p.9-10).

These six studies reveal how the Sainte-Anne Hospital team understood the drug's action. Deniker (1975) argued that there were three possible options for understanding how medications worked and reconstructing the history of a drug's discovery: (1) the chemopharmacological route, (2) the human physiology route, of anesthesiology and reanimation, and (3) the search for specific psychiatric medications. The first two options refer specifically to the discovery of the drug and how to apply it, that is, to studies (like Laborit's) on its mechanisms of action and its potential to induce the desired effects, in this case, hibernation and anesthesia. According to Deniker, the first two methods are indirect and do not help us understand the extent and importance of the drug in the field of psychiatry. He felt that the third method was the only one that might lead to the discovery of the specific action of chlorpromazine in the psychiatric field, and that is the one the researchers at the Sainte-Anne Hospital were pursuing.

> One idea we had in mind was the possibility of discovering a specific medication for the treatment of mental illnesses. ... Nevertheless, the idea of possibly discovering specific psychiatric medications had not been considered by specialists until that point (Deniker, 1975, p.14).

Among the studies by Delay and Deniker that appeared in 1952, the one that will be analyzed here is the paper titled "38 cases of psychosis treated with prolonged and continuous use of 4560RP." In it, Delay and Deniker (1952a) examine the effects of the drug on a set of patients who were divided into five groups: "psychic excitation and agitation;" "confused states;" "anxious and downcast states;" "schizophrenia" and lastly, the group made up of "the delirious, hallucinatory and obsessives."

As we can see, it was very difficult to speak about the therapeutic efficacy of chlorpromazine for a given pathology, because it was not used to treat a specific type of diagnosis but was being tested for various diagnoses, with some overlap between them. There were behaviors or symptoms that were repeated in different clinical cases, such as agitation, excitation, and mental confusion. We note that at the time those diagnoses were defined, the authors resorted to what we would now call "symptom grouping." In

the first case, the following behaviors appeared: manic episodes, mental confusion, great agitation, aggressive reactions; in the second, there was mental confusion and delirium. Many of these symptoms were repeated in cases defined as "anxious and depressive states." In the majority of these cases, the recommended treatment varied from five to 25 days, since in some cases there was more than one treatment. The dose used did not change, and remained between 50 and 150mg.

In general, the results obtained were seen as effective in terms of sedation, reduced anxiety, disappearance of confusion, and control of abnormal movements. A temporary improvement was also reported. In some cases, the patients were pronounced cured and discharged from hospital. As for the patients in the third group, the majority showed no signs of recovering from their depression, although the authors did observe progress in terms of symptoms of mania and agitation. In the case of the schizophrenic patients, there was no mention of hallucinations or delirium, and the results recorded were: (patient 27) disappearance of confusion and anxiety; (patient 28) sedation of agitation; (patient 29) disappearance of abnormal movements; (patient 30) improvement in agitation and excitation; (patient 31) remission of agitation; (patient 32) calm and improved rapport (Delay, Deniker, 1952a, p.506-508). As for the last group, the same therapeutic effects described earlier were seen: sedation and control of agitation, but there was an initial rise in hallucinations. It is important to stress that many of these patients had already undergonevarious rounds of electroconvulsive therapy, insulin therapy and other shock therapies.

The study shows that chlorpromazine was not used exclusively for cases of schizophrenia, as it was later. Its main therapeutic function seemed limited to controlling agitation and anxiety and producing sedation. The drug did not seem to be effective for depression, but it did work for cases of motor agitation and mania. "The neuroleptics are effective against mania and on rare occasions can induce a certain level of depression (like reserpine)" (Deniker, 1990, p.86).

Some years later, in 1956, Deniker y Delay published an article in the journal *L'Encéphale* evaluating the effects of the use of chlorpromazine in mental patients treated at a clinic from 1952-1955. This overview was based on a total of three hundred case histories of inpatients and outpatients who received chlorpromazine over a period of almost four years. The authors state that it is difficult to establish a comparison to other research, given the ambiguity and discrepancy between nosological classifications used in these studies. Deniker and Delay's (1956, p.528) article focuses on three aspects: the action of chlorpromazine in acute psychoses; its action in depression; and the role of long-term cures made possible by the use of chlorpromazine in the treatment of chronic psychoses.

They state that as regards the first group, acute psychoses, their initial expectations for the efficacy of chlorpromazine were confirmed, since the drug proved to have rapid effects. Their study shows that a large number of patients were cured and discharged. They note that the average duration of hospital stays was lower than in patients who received electroshock. Another fact they note is that for women, the length of hospitalization was longer than for men. As for those diagnosed with depression, they state that "simple depressive syndromes, as well as so-called reactive depressions, can react favorably to treatment exclusively with neuroleptics" (Deniker, Delay, 1956, p.532).

Finally, for long-term treatment of chronic psychosis, they studied a total of 116 patients, including cases of schizophrenia. They evaluated the use of chlorpromazine by itself or in conjunction with electroshock and other medications as well as lobotomy, and came up with results they saw as positive. They underline the importance of oral outpatient treatment, in which the medication could be continued after leaving the asylum (Deniker, Delay, 1956, p.533).

This text helps us understand what Deniker and Delay saw as an effective, successful result from the therapeutic point of view. They state that chlorpromazine does not reduce hallucinations or delirium:

> Producing a state of indifference or disinterest with regard to the delirium is what seems to constitute the originality of this treatment. The problem of whether the hallucinations or the delirious activity really disappear is more complex. Although in some cases they seem to stop, frequently the patient continues to believe the delirium. He continues to live with the existence of 'delirious ideas' about which he no longer manifests concern after treatment, but indifference (Deniker, Delay, 1956, p.535).

Here we see, once again, that the issue of indifference (whether that meant indifference to the world, the patients'environment or the symptoms of their disease) seems key to understanding how the drug actually worked. That is, the feeling of indifference seems to be directly linked with what was seen as the drug's therapeutic efficacy. Thus, although patients treated with chlorpromazine would continue to have hallucinations, they seemed indifferent to their visions.

Delay and Deniker's works describe the efficacy of chlorpromazine in calming patients on psychotic wards. Some studies carried out later at the Sainte-Anne Hospital and others show that patients claimed they had stopped hearing voices telling them to go home, and they had the sense that they had recovered some normality (Healy, 2000). However, the success of chlorpromazine was not as immediate as this suggests. Even though Delay and Deniker sought to spread the word about their observations by publishing in prestigious medical journals and international conferences, their research did not immediately have the impact they hoped for. Many psychiatrists argued that psychosis was impossible to treat and that chlorpromazine was merely a fairly effective sedative. As Healy (2002, p.92) put it, "Henri Ey endorsed chlorpromazine as useful in the delivery of sleep therapies but would not go further. Even within the Sainte-Anne, the new treatment was not immediately adopted by everybody." There may have been powerful reasons for this skepticism.

Reading Deniker's papers, we can see clearly that he called for skepticism and caution. As the discoverer of chlorpromazine, he soon encountered the drug's adverse effects and insisted on the need for extreme caution, stressing that the use of chlorpromazine could lead to a condition called tardive dyskinesia in patients. This caused involuntary movements of the limbs and face, accompanied by muscular rigidity and tremors. This adverse effect of chlorpromazine had been described by Delay and Deniker in 1956, in an article titled "Extrapyramidal movement disorders during chlorpromazine and reserpine therapy; clinical and electromyographic studies" (Delay, Deniker, Bourguignon, 1956) published in

the journal *L'Encéphale*. Deniker (1989) returned to this topic at different points, including in an article published almost 35 years later, "From chlorpromazine to tardive dyskinesia: brief history of the neuroleptics."

However, although the drug's side effects proved devastating, it appeared to achieve the desired effect of calming patients down while keeping them awake. Deniker's studies showed that chlorpromazine was much more than merely a sedative. Missa thus summarizes the effects of the drug as presented by Delay and Deniker:

> The most constant psychological effect was the syndrome of inertia and indifference. Stimuli from the outer world seemed to arrive muffled. They respond to stimuli with a slight delay, in a neutral or indifferent tone, gazing downwards. Sunk in sweet indifference, they seem separated from their surroundings by an invisible screen (Missa, 2006, p.259).

Heniz Lehmann and emotional indifference

As we saw earlier, the American Public Health Association awarded the 1957 Lasker Award to Heinz E. Lehmann for introducing chlorpromazine into the field of psychiatry, and in particular for his 1954 article co-authored with G.E. Hanrahan, on "Chlorpromazine: new inhibiting agent for psychomotor excitement and manic states," in the *Archives of Neurology and Psychiatry* (Lehmann, Hanrahan, 1954).

Lehmann won the Lasker Award for creating a clinical model for chlorpromazine use, laying out the benefits and drawbacks of the drug and minimizing its risks. According to the Lasker Award web page, the prize was given because:

> In his first important publication on the subject, Dr. Lehmann was able to outline the clinical guidelines so clearly, describe the results so accurately and evaluate the dangers so frankly that, with this paper alone, any other psychiatrist was in a position to apply this medication with confidence and safety. He noted not only the effect on the individual patient but the overall ward effect on groups, and especially disturbed wards (Lasker Foundation, 1957).

Although the award was granted for the "use of chlorpromazine to treat schizophrenia," Lehman (1955) only referred to schizophrenic patients a year later, in his paper "Chlorpromazine in psychiatric conditions." Lehmann's two texts help us see which elements were considered relevant to the therapeutic efficacy of chlorpromazine. In an interview with Swazey (1974) shortly before his death, Lehmann said that chlorpromazine revolutionized the field of psychiatry and made it a true medical specialty, able to treat mental illnesses like any other illness, that is, with medication (Lehmann, Swazey, 1974, p.157).

Lehmann's first study was based on an experiment done at the Protestant Hospital in Verdun, where 71 psychiatric patients aged 18-82 were treated with chlorpromazine for a period of four months. This study was done on patients diagnosed with acute and chronic mania, schizophrenia, senile dementia, mental deficiency and others who had been lobotomized.

The patients who showed the best recovery were those who had been treated the longest with chlorpromazine at the highest doses. Some of them had received as much as 800mg, much more than the 150mg that Deniker recommended as the maximum dose. For the authors, the study showed the drug to be effective for "symptom control" in excited states, without the need for auxiliary treatments like electroshock. Figure 1 contains a table showing the results of Lehmann's first study.

*Therapeutic Results with Chlorpromazine**

	Averted	Recovered	Much Improved	Improved	Unchanged	Still Under Treatment	Total
Schizophrenia	2	..	3	9	7	1	22
Schizoaffective	..	..	1	2	..	..	3
Manic, acute	2	5	2	7	..	3	22
Manic, chronic	..	4	1	3	1	3	12
Psychoneurotic	..	1	..	1	2	..	4
Postlobotomy	..	..	..	2	1	1	4
Mental deficiency	..	..	..	..	1	..	1
Senile psychosis	..	..	..	3	..	..	3
Total	4	13	7	27	12	8	71

* Averted means arrest of imminent psychotic attack during prodromal stage; recovered, sustained cessation of symptoms within 40 days; much improved, reduction of symptoms to the point where the patient is able to leave hospital within 40 days; improved, sustained lessening of symptoms within 40 days but patient unable to leave hospital.

Figure 1: Therapeutic results with chlorpromazine (Lehmann, Hanrahan, 1954, p.233)

The table shows that even though Lehmann received the Lasker Award for discovering the therapeutic effect of chlorpromazine for schizophrenia, his first study seemed to indicate that no such effect existed. As the author put it:

> Most of the patients who showed no lasting improvement with the drug were chronic schizophrenics presenting considerable deterioration. We have not observed a direct influence of the drug on delusional systems or hallucinatory phenomena (Lehmann, Hanrahan, 1954, p.232).

The effect of chlorpromazine in the treatment of patients diagnosed with schizophrenia was the topic of a study published by Lehmann a year later. In it he claimed, contrary to the results presented in his first study, that chlorpromazine could indeed reverse some cases of schizophrenia. In Judith Swazey's interview of Lehmann, he said that he had reached that conclusion after observing a group of schizophrenic patients who participated in the first study and had accidentally received the medication for a longer time period. These patients appeared to have improved.

> At the time, we thought we were just treating excited states with CPZ and attributed the improvement that the schizophrenics showed to that effect of the drug. But then, about 3 months after the trial had ended, we discovered that some of the chronic, backward schizophrenics had been accidentally left on large doses of CPZ. And incredibly, to us, four or five of these backward patients were getting better. No one believed that a pill could cause remission in schizophrenia, and we seemed to be getting the best results with chronic paranoids, the group most refractory to treatment (Lehmann, Swazey, 1974, p.157).

In this second research project, the same strategy was used as in the previous one. Patients in different clinical states were observed, including mania, depression, schizophrenia and patients who had undergone a lobotomy. Within that range of cases, patients in whom the drug worked best for symptom control were observed under the rationale that chlorpromazine was the appropriate therapy for those illnesses. In his 1955 study, Lehmann said that chlorpromazine could guarantee the remission of schizophrenia symptoms (Lehmann, 1955).

In the interview by Swazey mentioned earlier, Lehmann explained that his interest was not limited to using the drug to calm agitated patients, regardless of their diagnosis, but that, in the studies he performed in 1954 and 1955, he was pursuing the ambitious project of finding the psychopharmacological bases of schizophrenia. We know that neither Lehmann nor any other psychiatrist achieved this goal, the "Holy Grail" still being sought today, almost fifty years later. This is how Lehmann characterized his work in 1974:

> So, I decided to try CPZ. Since we had no research funds in 1953, and only about six doctors for 1,600 patients, we used some of our own money for research, as sort of a side hobby. We were interested in finding a psychophysiological base to support clinical psychiatric diagnosis. I'm still seeking that Holy Grail (Lehmann, Swazey, 1974, p.155).

Lehmann argued that chlorpromazine had led to a revolution in the psychiatric field for two reasons: (1) chlorpromazine gave psychiatry an instrument that brought it closer to other branches of medicine. While the psychophysiological basis for mental illnesses remained unknown, he presented chlorpromazine as a medication that could reverse symptoms (and in some cases cure) mental illness, the same way that a medication could cure a biological pathology; (2) chlorpromazine allowed patients to leave hospital and return home, which led to outpatient services.

In the table in Figure 1, we can see that there is a difference between the categories of "much better" and "better." In the first case, this meant a reduction of symptoms after forty days, allowing the patient to leave hospital. In the second, it meant a sustained reduction of symptoms in less than forty days, "but the patient cannot leave hospital." This was a relevant distinction for Lehmann, because chlorpromazine allowed for outpatient management of patients who would continue on medication outside the psychiatric hospital.

Lehmann and Hanrahan's text (1954, p.234) ends with five questions for evaluating the inclusion of chlorpromazine in the list of therapeutic agents in the psychiatric field, so that its value and legitimacy could be recorded. The questions are:

(a) Does it control symptoms as well as or better than other established treatments?

(b) Does it compare favorably with regard to ease of administration and unpleasant side-effects?

(c) Is there less risk associated with its use?

(d) Does it improve the underlying pathological condition?

(e) Does it permit sustained psychotherapeutic rapport?

As regards the first question, Lehmann argues that manic and agitated patients who were prescribed chlorpromazine recovered and their disease symptoms diminished. However, to address the therapeutic efficacy of the drug, it was necessary to define which symptoms

were controlled. Lehmann observed a greater level of recovery in manic psychosis, without specifying the symptoms or explaining how the diagnosis was made. It is worth pointing out that the *Diagnostic and Statistical Manual of Mental Disorders* (DSM I), the manual of the American Psychiatric Association, had appeared two years earlier, in 1952, and that it defined the symptoms of the manic type of manic-depressive psychosis as follows:

> This group is characterized by elation or irritability, with overtalkativeness, flight of ideas, and increased motor activity. Transitory, often momentary, episodes of depression may occur, but will not change the classification from the manic type of reaction (APA, 1952, p.25).

If we consider this diagnosis, it is easy to imagine that the desired symptomatic effect of the drug was simply to achieve a degree of calm, limit voluble speech, induce psychomotor deceleration, and control irritability. The parameters for what was considered an effective therapeutic outcome in determining whether the drug was acting in a satisfactory way were defined along those lines. According to the authors of the study:

> The aim is to produce a state of motor retardation, emotional indifference, and somnolence, and the dose must be increased accordingly as tolerance develops. After the first week of treatment the patients remain retarded but are less sleepy. In most cases it has not been necessary to exceed a dose of 800mg per day, while some patients may require only 100mg or less daily. The course of treatment may last from three days to four weeks (Lehmann, Hanrahan, 1954, p.229).

As regards the second question (ease of administration and side effects), Lehmann presented a series of procedures to make the use of chlorpromazine easier. This was one of the main reasons he received the Lasker Award: for providing clear guidelines for using the drug in 13 steps that covered the form of use, the dose, diet, required rest etc.

On the third question (risk), the Lasker Award rationale also stressed Lehmann's frank evaluation of the dangers of using chlorpromazine, which helped other psychiatrists to know in what conditions they could apply the medication confidently and safely. Lehmann did not seem unaware or heedless of the drug's adverse effects. He describes how patients became apathetic, disengaged, less "alert," and the "vacant expression" he noticed in their faces. He also stated that many complained that chlorpromazine made them feel "empty" and that they disliked the treatment, reporting the somnolence and weakness that accompanied use of the drug. Like Deniker, Lehmann also observed Parkinson's symptoms in patients treated with chlorpromazine, although he claims those symptoms could be reversed after a certain time. However, despite having listed all these problems linked to the use of chlorpromazine, Lehmann states that:

> Patients receiving large doses of chlorpromazine exhibit definite motor retardation, with an unsteady gait, while the facial expression becomes rather wooden and the general appearance resembles that of Parkinsonism but there is no muscular rigidity. With smaller doses these phenomena are less pronounced. There is usually marked drowsiness, which may increase to the point of somnolence. ... These symptoms are reflected in the patients' statement that they feel cold, drowsy, faint, and weak (Lehmann, Hanrahan, 1954, p.228).

He adds that: "Some patients dislike the treatment and complain of their drowsiness and weakness. Some state that they feel 'washed out,' as after an exhausting illness, a complaint which is indeed in keeping with their appearance" (Lehmann, Hanrahan, 1954, p.230).

Lastly, Lehmann asks, "Does [the drug] improve the underlying pathological condition?" (Lehmann, Hanrahan, 1954, p.234). This is when the analogy between the therapeutic procedures used by medicine and psychiatry appears. We know that it was through identifying with medical explanations that psychiatry finally achieved epistemological legitimacy and prestige (Foucault, 2003). This explains the efforts to show that chlorpromazine was a medication just like any other, for example, penicillin: a medication capable of acting on and reversing the underlying biological processes of the pathology, even though the drug's mechanism of action remained unknown:

> The mode of action of chlorpromazine has not yet been established. Several theories have been advanced. It has been surmised that the drug operates through an effect on general metabolism by lowering the cellular 0_2 requirements. We have not been able to confirm the findings of Delay and Deniker that basal metabolism is lowered after chlorpromazine administration. ... Nor could we corroborate their findings of a significant drop in the eosinophile count with chlorpromazine. We therefore do not feel justified at this time in assuming that the drug exhibits its specific effects through the adrenals or any other endocrine glands (Lehmann, Hanrahan, 1954, p.236).

Given the lack of knowledge about the underlying biological processes, Lehmann sought to define the best way to administer the drug and to list its side effects, the correct dose, and its effect on symptoms. Since the biological bases for mania or schizophrenia were unknown, chlorpromazine's efficacy seemed limited to the effect of conscious sedation seen in earlier studies, but it did not diminish delirium or hallucinations. Therefore, in 1954, Lehmann describes chlorpromazine's mechanism of action on patients as follows:

> Chlorpromazine has a pronounced inhibitory effect on certain functions of the central nervous system. Patients receiving the drug become lethargic. Manic patients often will not object to bedrest, and patients who present management problems become tractable. Assaultive and interfering behavior ceases almost entirely. The patients under treatment display a lack of spontaneous interest in the environment, yet are easily accessible and respond as a rule immediately and relevantly to questions even if awakened from sleep. As Delay and Deniker described them, they tend to remain silent and immobile when left alone and to reply to questions in a slow monotone (Lehmann, Hanrahan, 1954, p.230).

Lastly, the final question deals with the drug's ability to "permit a sustained psychotherapeutic rapport," a question that is both epistemological and political. It involves knowing whether the drug allows a therapeutic relationship to be established with the patient. All the analogies with shock therapies mentioned in the text seem to negate that possibility. Nevertheless, the authors write that chlorpromazine could help create a psychotherapeutic rapport. As Lehmann acknowledges: "Many of us have in recent

years lost sight of our essential task of understanding our patients, as we subject them to a sequence of comas, shocks, convulsions, confusion, and amnesia, all of which render them incapable of relating to the psychiatrist in a consistent and meaningful manner" (Lehmann, Hanrahan, 1954, p.234).

We might ask how chlorpromazine could help establish a therapeutic rapport based on empathy, which had been impossible with previous shock treatments. We should bear in mind that even though Lehmann stresses the differences between the neuroleptics and earlier interventions used, such as electroshock (Lehmann, Hanrahan, 1954, p.234), he continues to associate chlorpromazine use with lobotomy, just like Laborit. In 1955, he wrote that,"[i]n the management of pain in terminal cancer cases, chlorpromazine may prove to be a pharmacological substitute for lobotomy" (Lehmann, 1955, p.97). Even though he was talking about sedation for cancer pain, the high doses recommended for treating mania and schizophrenia, 800mg, could produce similar effects to a chemical lobotomy. This fact seems to indicate that the patient would have difficulty engaging in psychotherapy or talk therapy. Even though Lehmann does not go so far as to equate it with lobotomy, his descriptions of lethargy, somnolence, vacant expression, motor retardation, unsteady gait, wooden facial expressions, motor rigidity, and Parkinsonian movements, all produced by chlorpromazine, would seem to indicate that the patients' capacity for verbalization and reflection were clearly compromised, although they might have been capable of giving simple answers to specific questions.

A quiet ward

Jean Noel Missa published a long interview from 1999 with a nurse who worked in a Canadian psychiatric hospital. She analyzed the therapeutic relationship with patients before and after neuroleptics were used on the ward where she worked. She recalled that previously, they used to dance and sing, and described what she observed on a day-to-day basis:

> Before the era of neuroleptics, you could talk to the patients. I spent years listening to patients. One woman used to come up, pull up a stool next to me and start telling me her story. I would listen to her. Now we have people drooling and shaking and shaking. I think those psychotropic medications leave them in a dreadful state. What they go through on psychotropics, what goes on in their heads is terrifying. The patients changed because of those medications, they're not the same any more. I prefer the patients alive, even if they're delirious. Now they seem like robots (Missa, 2006, p.299).

Lehmann, on the contrary, saw this passivity in a positive light. He felt that the use of chlorpromazine produced a different type of sedation than barbiturates or shock treatments. He argued that the desired therapeutic effect seemed to have been achieved. Even though their hallucinations persisted, patients could live with them better, there was no screaming going on in hospitals anymore and the goal of controlling psychomotor excitation, manic states and psychotic episodes in schizophrenics seemed to have been achieved.

A psychiatrist interviewed by Missa (2006, p.297), speaking of his work on the wards in the late 1950s, said: "Largactil was effective, but it didn't cure them. Any more than now. …

The patient was better off. Calm and disciplined… although still having hallucinations." As Lehmann (1955) stated, chlorpromazine made it possible to manage chronic psychotic patients' "behavior problems." Returning to Lehmann's 1955 text once again, we can better understand what this award-winning psychiatrist meant by the drug's therapeutic effectiveness:

> Chlorpromazine can usually be relied on as a last resort when other measures have failed. The nursing personnel son learned to appreciate its favorable effects, and the introduction of the drug has indeed changed the whole aspect of the acute treatment and observation wards through considerable reduction of noise and confusion, previously often associated with the management of acutely disturbed patients (Lehmann, 1955, p.92).

The idea that chlorpromazine brought peace and quiet to psychiatric hospitals was a commonplace repeated endlessly by psychiatrists throughout the 1950s and 1960s. The following is a description from 1964 of how American psychiatric hospitals changed:

> Do you remember the lobotomies – the broken glass – the subhuman screams in the night – the windows under which you would not walk lest excreta of some sort drop on you? Do you remember the interminable locking and unlocking of doors? Do you remember the beat-up patients and the beat-up attendants? (Swazey, 1974, p.218).

After chlorpromazine, psychiatric interventions were no longer limited to straitjackets or electroshock; now, madness could be treated with a drug, just as in any other branch of medicine, although shock treatments did not disappear. In 1953, referring to the 4560RP compound, the statement was made that: "It's an incontrovertible fact that thanks to that phenothiazine derivative, we were able to release all our patients from their straitjackets and the disturbed ward is impressively calm" (Parada, 2016, p.148).

Again and again, people spoke of the "revolutionary" effect of chlorpromazine in psychiatric hospital wards and in patients' behavior. Now they were silent and indifferent, as we can see from this account from 1955:

> In the American hospitals, the atmosphere of disturbed wards has been completely revolutionized. Patients now remain clothed; they are quiet; they do not annoy each other; they conform to the conventions, take an interest in their personal appearance and in the appearance of the ward (Overholser, 1956, p.199).

Following this same line of argument, Judith Swazey (1974, p.220) says that:

> Along with CPZ's effects on disturbed behavior, hospitals across the country reported significant reductions in the destruction of personal belongings and hospital furnishings, in accidents and injuries to patients, and in the need to use sedative or physical restraints or seclusion to control patients.

The transformation of psychiatric hospitals had profound implications. With a medication considered effective for treating psychosis and producing calmer patients and wards, psychiatry could finally gain the desired professional respect of its colleagues in the field of medicine: a respect that psychiatry seemed to have lost due to the succession of coercive interventions and technologies used in insane asylums. At last, it seemed possible to speak of updating the management of disturbed patients.

This new form of management implied not only reorganizing the space of the asylum, with wards that were more calm and peaceful, but also managing madness outside the hospital. Thus, in his book *Toucher le cerveau, changer l'esprit,* Carlos Parada (2016) stresses that chlorpromazine proved just as effective for managing the internal space of the hospital as it was for dealing with outpatients. Interventions gradually ceased to be momentary, isolated and sporadic, such as electroshock, but accompanied patients throughout their lives, both in hospital and out of it. Thus began a process of chronification of mental illness that required continuous treatment throughout the patient's entire life (p.157).

Final considerations

Chlopromazine not only brought calm to psychiatric wards for the disturbed, it also allowed some patients treated with neuroleptics to be considered less agitated and calmer, so that they could return home, at least for some time. These patients, now calm and indifferent, would remain bound to psychiatry by prescription renewals and dose adjustments.

From 1956 on (Delay, Deniker, Bourguignon, 1956), it has been known that this so-called technological revolution in the management of madness, this major tranquilizer (also known as an ataraxic, in reference to the indifference or ataraxia it caused) left indelible marks on patients' bodies. This was not merely a matter of unwanted side effects, a problem shared with many other psychiatric medications, but something more; the drug simultaneously calms agitation and aggressiveness but causes syndromes due to its mechanism of action. As Deniker pointed out in 1956, it produced extrapiramidal and vegetative syndromes that were inseparable from its action. Henri Baruk (1972, p.54) writes:

> The nature of the neurological syndrome caused by neuroleptics has been interpreted in different ways. Delay and Deniker see the neurological syndrome as perpetually linked to the action of these medications. Some authors argue that it is necessary for patients to develop the neurological syndrome in order to be able to determine the psychological effects of the drug. In another sense, Baruk and Berges' work has shown, for the first time, that beginning with chlorpromazine and then with other neuroleptics, experimental catatonia is one of the psychomotor disorders linked to use of the drug.

We know that neuroleptics are directly linked to Parkinson's symptoms and that they produce severe adverse reactions; however, the use of classic or atypical antipsychotics has continued to rise in recent decades. From what we have seen so far, we can conclude that the persistent use of neuroleptics despite exhaustive knowledge of the harm they produce is due to the fact that this type of medication fulfils precisely the goals for which it was created: to induce calm and to control agitation on psychiatric wards; to provide long-term treatment for chronically disturbed people outside the asylum; and to render patients indifferent to what is happening to them both in and outside the psychiatric hospital. In other words, chlorpromazine proved to be an excellent aid to calming and disciplining psychotic patients both in and outside asylums.

Delay and Deniker's description (1952b) of people treated with chlorpromazinestressed patients' apparent indifference or delayed response to external stimuli, their neutral

emotions and flat affect, and their reduced initiative; this was repeated by Deniker in a text published in 1987. In it, referring to research he did in 1957, he compares the experimental data obtained for laboratory rats to the clinical descriptions of patients. He sums up those data in the table in Figure 2, which synthesizes the psychophysiological characteristics of neuroleptics.

TABLEAU 8

Caractéristiques psychophysiologiques des neuroleptiques (1957)

DONNÉES EXPÉRIMENTALES	DONNÉES CLINIQUES
1. Création d'un état d'indifférence psychomotrice spéciale	
Hypersomnie *réversible* par stimulus banals (E.E.G. de sommeil physiologique avec étalement des stades initiaux, rareté des rythmes rapides de veille et abondance d'ondes lentes. Absence des fuseaux).	
Diminution de l'activité locomotrice spontanée et provoquée. Inhibition des *réflexes conditionnés* et de l'apprentissage. Tendance à la *catalepsie*.	Rareté et lenteur des mouvements, hypo- ou amimie. Indifférence psychique, diminution de l'initiative. Neutralité émotionnelle et affective. Pas d'altérations grossières de la conscience ni des facultés intellectuelles.
2. Efficacité vis-à-vis des états d'excitation et d'agitation	
Tranquillisation des animaux naturellement agressifs. Action sur la sham-rage des animaux décortiqués. Suppression de l'hyperkinésie des « souris tournantes IDPN » sans narcose ni parésies.	Efficacité vis-à-vis du *syndrome maniaque*. Effet sur l'excitation et l'agitation psychotiques en général. Action sur l'agressivité et l'impulsivité.

Figure 2: Psychophysiological characteristics of neuroleptics (Deniker, 1987, p.48)

The first physiological characteristic identified in patients taking neuroleptics is their "psychic indifference, diminished initiative. No alterations in consciousness," data which matches the laboratory animals' "reduction in locomotor activity and tendency to catalepsia" (Deniker, 1987, p.48).

If we bear in mind that this tendency towards indifference had already been identified by Laborit, who referred to indifference to pain, and by Lehmann, who referred to indifference to delirium, everything seems to point to the fact that the feeling of "indifference," both to the environment and to the treatment, was a desired therapeutic effect. Indifference was associated with diminished agitation, aggressiveness and impulsiveness, as well as fewer escape attempts and more acceptance of treatment. The discoverers of chlorpromazine seem thus to have come close to the way Foucault (2003, p.268) defined the action of psychiatric medications: "Finally, drugs – mainly opium, chloroform, and ether – were, like drugs still today, an obviously disciplinary instrument for maintaining order, calm, and keeping patients quiet."[2]

Thus, the so-called "psychopharmacological revolution," far from representing a departure from the shock treatments that preceded neuroleptics, seems to represent a continuation in whatwas considered therapeutic efficacy, both before and after. Whether we are speaking of insulin shock, lobotomy, electroshock, opium, ether, or the discovery of chlorpromazine, the desired effects remain the same: achieving the indifference, calm and silence necessary for managing madness.

ACKNOWLEDGMENTS

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil. Finance code 001. Process n.88881.121008/2016-01 (Senior Internship Abroad).

NOTES

[1] [Translator's note] In this and other citations from texts originally published in French, the translation into English is based on the Spanish-language versions.

[2] [Translator's note] Citation in English from Foucault (2003) was sourced from Michel Foucault, *Psychiatric power*, London, Macmillan, 2006, p.235.

REFERENCES

AMARANTE, Paulo; PITTA, Ana; OLIVEIRA, Walter. *Direitos humanos e saúde mental*. São Paulo: Hucitec, 2017.

APA, American Psychiatric Association. *DSM-1*. Arlington: APA, 1952.

BAN, Thomas. Fifty years chlorpromazine: a historical perspective. *Neuropsychiatric disease and treatment*, v.3, n.4, p.495-500, 2007.

BARUK, Henri. *Les thérapeutiques psichiatriques*. Paris: Presses Universitaires de France, 1972.

BARUK, Henri. *La psychopathologie expérimentale*. Paris: Presses Universitaires de France, 1967.

BAUMEISTER, Alan. The chlorpromazine enigma. *Journal of the History of the Neurosciences*, v.22, n.1, p.14-29, 2013.

BREGGIN, Peter. Rational principles of psychopharmacology for therapists, healthcare providers and clients. *Journal of Contemporary Psychotherapy*, v.46, n.1, p.1-13, 2016.

CALDWELL, Ann. *Origins of psychopharmacology from CPZ to LSD*. Springfield: Charles C. Thomas, 1970.

CAPONI, Sandra. *Uma sala tranquila: neurolépticos para uma biopolitica da indiferença*. São Paulo: Liber Ars, 2019.

CYNOWIEC, Esteban. *Análisis epistemológico de la construcción y utilización de modelos animales para el estudio de alteraciones psiquiatricas humanas*. Tesis (Doctorado en Ciencias Biológicas) – Universidad de Buenos Aires, Buenos Aires, 2017.

DELAY, Jean; DENIKER, Pierre. Efficacy of tofranil in the treatment of various types of depression: a comparison with other antidepressant drugs. *Canadian Psychiatry Association Journal*, v.4, p.100-112, 1959.

DELAY, Jean; DENIKER, Pierre. 38 cas de psychoses traitées par la cure prolongée et continue de 4560RP. In: Congrès des Médecins Aliénistes et Neurologistes de France et des Pays de Langue Française, 50., 1952, Luxembourg. *Comptes rendus*. Paris: Masson, 1952a. p.503-511.

DELAY, Jean; DENIKER, Pierre. Utilisation en therapeutique psychiatrique d'une phenithiazine d'action centrale élective (4560 RP). *Annales Médico-Psychologiques*, v.110, n.2, p.112-131, 1952b.

DELAY, Jean; DENIKER, Pierre; BOURGUIGNON, André. Extrapyramidal movement disorders during chlorpromazine and reserpine therapy. *L'Encéphale*, v.45, n.4, p.1093-1098, 1956.

DENIKER, Pierre. The neuroleptics: a historical survey. *Acta Psychiatrica Scandinavica*, v.82, p.83-87, 1990.

DENIKER, Pierre. From chlorpromazine to tardive dyskinesia: a brief history of the neuroleptics. *Psychiatric Journal of the University of Ottawa*, v.14, n.1, p.253-259, 1989.

DENIKER, Pierre. *Psychopharmacologie: les médicaments et drogues psychotropes*. Paris: Ellipses, 1987.

DENIKER, Pierre. Qui a inventé les neuroleptiques? *Confrontations Psychiatriques*, v.13, p.7-11, 1975.

DENIKER, Pierre; DELAY, Jean. Étude de 300 dossiers de malades psychotiques traités par la chlorpromazine en service fermé depuis 1952. *L'Encéphale*, v.39, p.528-535, 1956.

FOND, Guillaume. L'éloge de la fuite: hommage à Henri Laborit (1914-1995). *Tunisie Medicale*, v.91, n.8, p.487-489, 2013.

FOUCAULT, Michel. *Le pouvoir psiquiatrique*. Paris: Gallimard, 2003.

FREITAS, Fernando; AMARANTE, Paulo. Mad in Brasil: um novo espaço para reflexões e debates sobre medicalização e desmedicalização. In: Amarante, Paulo; Pitta, Ana; Oliveira, Walter (org.). *Patologização e medicalização da vida: epistemologia e política*. São Paulo: Zagodoni, 2016. p.163-170.

GAUDILLIÈRE, Jean-Paul; THOMS, Ulrike. *The development of scientific marketing in the twentieth century research for sales*. London: Pickering and Chatto, 2015.

GOTSZCHE, Peter. *Psicofármacos que matam y denegación organizada*. Barcelona: Los Libros del Lince, 2016.

HEALY, David. *The creation of psychopharmacology*. Cambridge: Harvard Universty Press, 2002.

HEALY, David. Pioneers in psychopharmacology. *International Journal of Neuropsychopharmacology*, v.3, n.4, p.351-354, 2000.

HENCKES, Nicolas. Reshaping chronicity: neuroleptics and changing meanings of therapy in French psychiatry, 1950-1975. *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences*, v.42, n.4, p.434-442, 2011.

KUNZ, Eduard. Henri Laborit and the inhibition of action. *Dialogues in Clinical Neuroscience*, v.16, n.1, p.113-117, 2014.

LABORIT, Henri. L'hibernation artificielle par moyens pharmacodynamiques et physiques. *Presse Medicale*, v.59, p.1329, 1951.

LABORIT, Henri; HUGUENARD, Pierre. Un nouveau stabilisateur végétatif (le 4560RP). *Presse Medicale*, v.60, p.206-208, 1952.

LASKER FOUNDATION. *Chlorpromazine for treating schizophrenia*, 1957. Disponible en: http://www.laskerfoundation.org/awards/show/chlorpromazine-for-treating-schizophrenia/. Acceso en: 17 mayo 2021.

LEHMANN, Heinz. Chlopromazine in psychiatric conditions. *Canadian Medical Association Journal*, v.72, p.91-99, 1955.

LEHMANN, Heinz; HANRAHAN, M. Chlorpromazine: new inhibiting agent for psycomotor excitement and manic states. *Archives of Neurology and Psychatry*, p.227-237, 1954.

LEHMANN, Heinz; SWAZEY, Judith. Lehmann, Swazey interview. In: Massachusetts Institute of Technology (org.). *Chlorpromazine in psychiatry: a study of therapeutic innovation*. Cambridge, MA: The Massachusetts Institute of Technology, 1974.

LIEBERMAN, Jeffrey; GOLDEN, Robert; STROUP, Scott. Drugs of the psychopharmacological revolution in clinical psychiatry. *Psychiatric Services*, v.51, n.10, p.1254-1257, 2000.

LÓPEZ-MUÑOZ, Francisco; ALAMO, Cecilio; CUENCA, Eduardo. Aspectos históricos del descubrimiento y de la introducción clínica de la clorpromazina: medio siglo de psicofarmacología. *Frenia*, v.2, n.1, p.77-107, 2002.

MAZANA, Javier Sebastián; PEREIRA, J.; CABRERA, R. Cincuenta años de clorpromazina. *Revista Española de Sanidad Penitenciaria*, v.4, n.3, p.101-113, 2012.

MISSA, Jean-Noël. La psychopharmacologie et la naissance de la psychiatrie biologique. In: Missa, Jean-Noël; Doron, Claude-Olivier. *Les maladies mentales*. Paris: PUF, 2008. p.131-147.

MISSA, Jean-Noël. *Naissance de la psychiatrie biologique: histoire des traitements des maladies mentales au XXe siècle*. Paris: PUF, 2006.

MONCRIEFF, Joanna. *Models of drug action*, 2013. Disponible en: https://joannamoncrieff.com/2013/11/21/models-of-drug-action. Acceso en: 17 mayo 2021.

MONCRIEFF, Joanna. *The myth of the chemical cure*. London: Palgrave MacMillan, 2008.

NOBEL PRIZE. *The Nobel Price in Physiology or Medicine 1949*: Egas Moniz (Biographical), 1949. Disponible en: https://www.nobelprize.org/prizes/medicine/1949/moniz/biographical/. Acceso en: 17 mayo 2021.

OVERHOLSER, Winfred. Has chlorpromazine inaugurated a new era in mental hospitals? *Journal of Clinical and Experimental Psychopatholy*, v.17, n.2, p.197-201, 1956.

PARADA, Carlos. *Toucher le cerveau, changer l'esprit*. Paris: PUF, 2016.

PIGNARRE, Philippe. *Les malheurs des psys: psychotropes et médicalisation du social*. Paris: La Découverte, 2006.

ROSE, Nikolas. *Our psychiatric future*. Cambridge: Polity Press, 2019.

SHORTER, Eduard. *A history of psychiatry: from the era of the asylum to the age of Prozac*. New York: John Wiley and Sons, 1997.

SWAIN, Glasys. *Dialogue avec l'insensé*. Paris: Gallimard, 1994.

SWAZEY, Judith. *Chlorpromazine in psychiatry: a study of therapeutic innovation*. Cambridge, MA: The Massachusetts Institute of Technology, 1974.

WHITAKER, Robert. La psiquiatría defiende sus antipsicóticos: un caso práctico de corrupción institucional. *Informe MIA*, 2017. Disponible en: https://madinamerica-hispanohablante.org/la-psiquiatria-defiende-sus-antipsicoticos-un-caso-practico-de-corrupcion-institucional-robert-whitaker/. Acceso en: 4 sep. 2019.

WHITAKER, Robert. *Mad in America: bad science, bad medicine and the enduring mistreatment of the mentally ill*. New York: Basic Books, 2010.