Historical approach to reserpine discovery and its introduction in psychiatry

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Aproximación histórica al descubrimiento de la reserpina y su introducción en la clínica psiquiátrica

Summary

Reserpine, an alkaloid of the Rauwolfia serpentina *plant isolated during the middle of the 20th Century, represented a highly important clinical advance in the treatment of schizophrenia whose pharmacological tools were limited to chlorpromazine that was introduced in the clinical area two years before. Both agents would come into the history as the drugs that made possible the beginning of the psychopharmacological era. In the present article, a revision is made of the complicated process leading to the isolation and synthesis of reserpine, by the Swiss pharmaceutical company Ciba (Schlittler and Müller) and how its pharmacological properties (Bein) were discovered and studied, in the animals laboratory, mainly, the «tranquillizers». The introduction of this antipsychotic in psychiatry, which was initiated in 1954 (half a century ago), and the results obtained in the first clinical studies, as well as the role played by researchers such as Kline, Delay, Noce, Hollister, Altschule, etc. are then described. In addition, and from a historical perspective, the discoveryg of the adverse effects of this drug, especially those of extrapyramidal nature (dyskinesia and akathisia), are studied, concluding with the reasons that produced its rapid clinical decline, among which the genesis of depressive pictures (phenomenon presently questioned) may be emphasized. Finally, the conclusion reached was that, although the clinical relevance of reserpine was not as evident and long lasting as chlorpromazine, its initial contribution to the treatment of schizophrenic patients was of maximum importance.*

Key words: *Reserpine. History of Medicine. Antipsychotics. Schizophrenia. Extrapyramidal effects.*

Resumen

La reserpina, un alcaloide de la planta Rauwolfia serpentina *aislado a mitad del siglo XX, supuso un trascendental avance clínico en el tratamiento de la esquizofrenia, cuyo arsenal farmacológico se limitaba únicamente a la clorpromazina, introducida en la práctica clínica sólo 2 años antes. Ambos fármacos pasarían a la historia como los agentes que habilitaron el inicio de la era psicofarmacológica. En el presente trabajo se revisa el complejo proceso que condujo al aislamiento y la síntesis de la reserpina por parte de la compañía farmacéutica suiza Ciba (Schlittler y Müller) y cómo se descubrieron y estudiaron en el animal de experimentación sus propiedades farmacológicas (Bein), sobre todo las «tranquilizantes». A continuación se describe el paso de este antipsicótico a la clínica psiquiátrica, que se inició en 1954 (hace medio siglo), y los resultados aportados en los primeros estudios clínicos, así como el papel desempeñado en este sentido por investigadores como Kline, Delay, Noce, Hollister, Altschule, etc. Finalmente se aborda, desde la perspectiva histórica, el descubrimiento de los efectos adversos de este fármaco, sobre todo los de naturaleza extrapiramidal (discinesias y acatisia), concluyendo con los motivos que ocasionaron su rápido declive clínico, entre los que destacó la génesis de cuadros depresivos, fenómeno, por otro lado, cuestionado en la actualidad. Se concluye discutiendo el hecho de que, aunque la relevancia clínica de la reserpina no fue tan manifiesta y perdurable como la de la clorpromazina, su contribución inicial al tratamiento de los pacientes esquizofrénicos fue de suma importancia.*

Palabras clave: *Reserpina. Historia de la Medicina. Antipsicóticos. Esquizofrenia. Efectos extrapiramidales.*

INTRODUCTION

Until the middle of the XX century, the therapeutic approach of psychotic disorders was based on the application of debatable remedies, whose clinical efficacy was more than doubtful in most of the cases[1]. In this sense, the pharmacological treatments used since the second half of the XIX century were very unspecific in the control of schizophrenia symptoms. Opium, morphine, cocaine, hashish, codeine, digitalis tincture, chloral hydrate and fundamentally bromides are among the drugs used most in this era. The so-called biological therapies, such as pyretotherapy (by malaria induced fever, application of tuberculin or development of abscesses with turpentine), the induction of insulinic or cardiazolic comas, and, above all, electoconvulsive therapy, had much more success. These techniques

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were confirmed, from the beginning of the XX century, as the first specific treatments of psychotic disorders.

In this therapeutically inhospitable framework, there was a real revolution in the beginning of the decade of the fifties of the XX century in the approach to psychiatric disorders, above all the psychotic ones, thanks to the introduction in the clinical aspects of the first pharmacological tools specifically aimed at the management of schizophrenic patients[1-14]. This «psychopharmacological revolution» in the field of schizophrenia began with the clinical introduction of two pharmacological agents of different origin almost simultaneously in the psychiatric therapeutic armamentarium. These were chlorpromazine[15,16], a phenotiazine substance of chemical synthesis, and reserpine, an alkaloid having a natural origin, obtained from the root of an autocthonic plant from the Asiatic Indostan, the *Rauwolfia serpentina*[17]. Both drugs, which will remain in history as the agents that helped the onset of the psychopharmacological era, make up the first of the three important milestones that have marked significant advances in schizophrenia treatment. The later synthesis and clinical introduction of haloperidol and finally the discovery of the atypical characteristics of clozapine, which allowed for the development of new antipsychotic agents, shape the three milestones on which the present antipsychotic pharmacological armamentarium is based[1].

With the present study, it is aimed to recall the 50th anniversary of the therapeutic introduction of reserpine in the psychiatric practice, which occurred in 1954, and to describe the circumstances that made the synthesis and discovery of the neuroleptic properties of this alkaloid of *Rauwolfia* possible, as well as the substantial role it played in the development of psychiatry in those adventurous years of the fifties of the last century, known as «the golden decade of psychopharmacology»[12]. In this sense, although the clinical relevance of reserpine was not as manifest and long lasting as that of chlorpromazine, its initial contribution to the treatment of schizophrenic patients was extremely important.

THE DISCOVERY OF RESERPINE

Historic background on the use of *Rauwolfia serpentina* and the study of the pharmacological properties of its alkaloids

The history of the therapeutic use of *Rauwolfia serpentina* goes back to the origins of ayurvedic medicine. The therapeutic properties of this plant, called *sarpagandha* in the popular Hindu setting, are documented in the classical treatise Charaka Samhita (between 1000 and 2000 B.C.), in which its supposed sedative properties are collected[18] (fig. 1). Another local definition of this plant, *pagal-ka-dawa,* even means «herb against insanity».

The first report on the tranquilizing and sedative effects of *Rauwolfia serpentina,* based on studies performed with modern methodology, occurred in India in the beginning of the decade of the 30's[19], although the results of this study did not reach Western medicine until 1949, when the Indian cardiologist Rustom Jal Vakil published a study on the hypotensive effect of the extracts of the plant's roots in the *British Heart Journal*[20]. Simultaneously, the isolation of the first alkaloid of this root, ajmaline, occurred[21]. During the next 20 years, the drug studies continued, above all in India, tending to isolate the compounds responsible for the tranquilizing and hypotensive properties of serpentaria, such as the studies of the Chopra group in Calcutta, which, faced with the impossibility of isolating any alkaloid responsible for it, due to the limited development of the analytic methods of the era, spoke of «unknown active principles»[22].

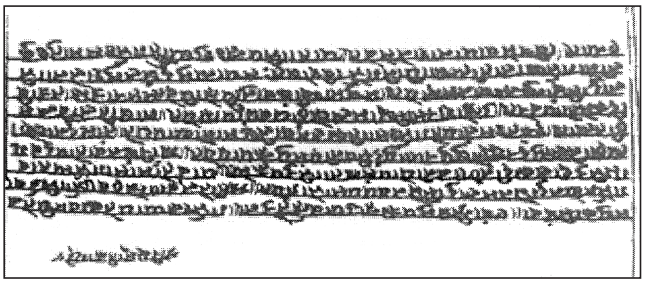

Figure 1. *Charaka samhita,* one of the classical treatise of ayurvedic medicine, in which the therapeutic use of *Rauwolfia serpentina* is collected. The image shows the facsimile of a part of the treatise in the Official Indian Library of London.

The final entry of *Rauwolfia* in Western medicine is attributable to Robert W. Wilkins, who, working in the General Hospital of Massachusetts (Boston), tested the effects of an extract of dry roots of *Rauwolfia serpentina* called «serpine» in his hypertensive patients. This study's conclusions were published in 1953, not only verifying the moderate hypotensive action of these extracts, but also an interesting sedative effect, associated to a sensation of relaxation by the patients[23].

Isolation of reserpine

During the same times in which Wilkins reported the effect of *Rauwolfia,* another group of investigators, from the Swiss pharmaceutical company Ciba, formed by Emil Schlittler, Johannes Müller and Hugo J. Bein, were successful in isolating the alkaloid responsible for most of its pharmacological effects.

In the middle of the 40's, the Swiss chemist Emil Schlittler, of the Research Division of Ciba Laboratories, in Basel, received a sufficient amount of crude extract of *Rauwolfia* from his branch in India to study its pharmacological properties, verifying the results of his Indian colleagues, that is, a moderate sedative and hypotensive efficacy. He was able to isolate some grams of crystalline ajmaline, similar to that obtained previously by Siddiqui, from its crude concentrate.

In September 1947, professor Sir Robert Robinson, of the University of Oxford, visited the Ciba headquarters

and was informed about the investigations of Schlittler, promising to more carefully study the chemical structure of ajmaline. Thus, in the beginning of 1948, a resinous liquid of *Rauwolfia,* very rich in ajmaline, was sent to him at Oxford, in order to perform the pertinent measurements. The surplus mother liquid, without ajmaline, continued to be studied by Schlittler, verifying its sedative and hypotensive activity in the drug tests in the experimental animal[18]. Coinciding with the publication of the study of Vakil, Schlittler requested the help of Johannes Müller to isolate, from the cloudy brown residue that remained, the principle responsible for these actions. This work was very difficult, due to the difference in the types of compounds isolated, according to the extraction method used, to the large amount of compounds present in the resinous liquid that showed pharmacological activity, even of anatagonic nature among some of them, and the important slowness in the onset of these activities[24]. Furthermore, the analysis methods in that era were not sufficiently sensitive and accurate to detect highly lipophilic compounds[25].

In spite of the technological and methodological difficulties, in 1951, the Schlittler and Müller group isolated, by chromatographic techniques, a fraction of study resin, whose microscopic appearance was a small group of brilliant white crystals. This active principle, scarcely soluble, was sent for study to the pharmacologist Hugo J. Bein (fig. 2A), who rapidly verified, in the pertinent studies in rabbits and dogs, that this alkaloid was responsible for most of the sedative and hypotensive activity of the *Rauwolfia* root, and that its effects were dose-dependent. The isolation of this fraction, in «pure crystalline form», was reported in September 1952, the alkaloid being called reserpine[26]. One year after (November 1953), the company Ciba Pharmaceutical Products marketed reserpine, with the name of Serpasol®, it being synthesized chemically in 1956 by professor Robert B. Woodward (fig. 2B), from Harvard[27].

Figure 3 shows the chemical structure of reserpine. At present, more than 30 phytochemical constituents have been isolated from the different species of *Rauwolfia*[28], although none have acquired such clinical or experimental importance as reserpine.

In 1953, Hugo Bein discovered the pharmacological properties of reserpine[29]; a potency one thousand times greater than the extracts of *Rauwolfia,* an initial reversible hypnotic action similar to that reported with chlorpromazine, an absence of anticonvulsant action, and the preservation of pupillary reflex and of different pain reflexes, which indicated absence of analgesic action. At low doses, reserpine did not interfere with the capacity to respond to conditioned stimuli in the experimental animal. At high doses, it was capable of causing an extrapyramidal syndrome or pseudoparkinsonian syndrome, event already observed with *Rauwolfia* in 1944 by De[2]. As Bein states[24], in 1953, during a scientific meeting in Summit (New Jersey), North American headquarters of Ciba, Frederick F. Yonkman used the term «tranquilizing» for the first time to describe the effect of reserpine in the central nervous system (CNS).

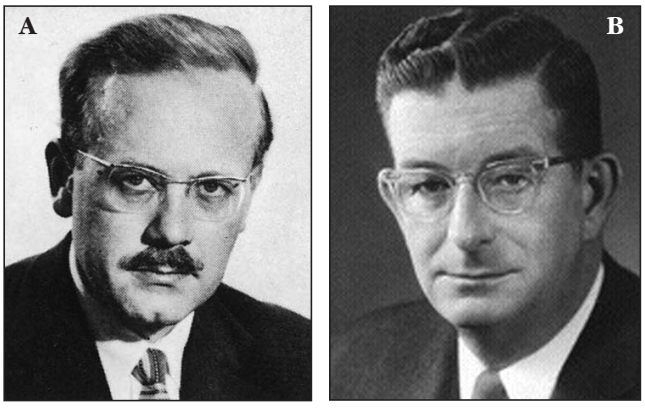

Figure 2. Key persons in the discovery and synthesis of reserpine. **A:** Hugo J. Bein (Switzerland). **B:** Robert Burns Woodward (United Kingdom), Chemical Nobel Prize in 1965.

The pharmacological profile of reserpine was studied in detail in many countries, including Spain, thanks to the work of professor Francisco G. Valdecasas, of the University of Barcelona. In fact, in 1954 (one year after its marketing and the same year it was introduced in psychiatric therapy), Valdecasas et al. described that low doses of reserpine significantly strengthened the tensional effect of epinephrine, based on, as textually quoted, «the interest that the alkaloids of *Rauwolfia*, and especially reserpine, have in the treatment of psychic disorders (which) has led us to study systematically this effect»[30]. In these experiments, the strengthening action of epinephrine induced by reserpine was also observed with cocaine and LSD-25. On the contrary, the action of chlorpromazine was clearly adrenolytic[31].

INTRODUCTION OF RESERPINE IN PSYCHIATRIC MEDICINE

The first publications on antipsychotic efficacy of reserpine (1954)

The pioneer of use of reserpine in the treatment of psychosis was Nathan S. Kline (fig. 4A), from Rockland

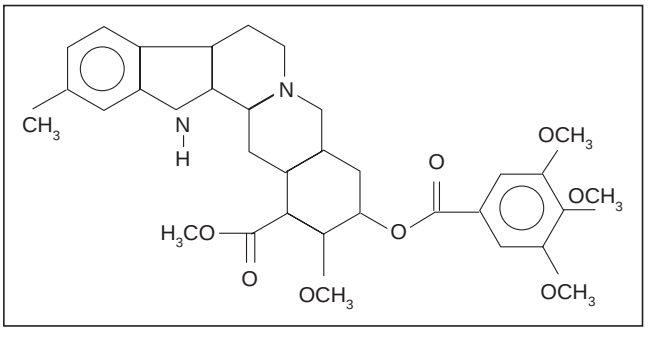

Figure 3. Chemical structure of reserpine.

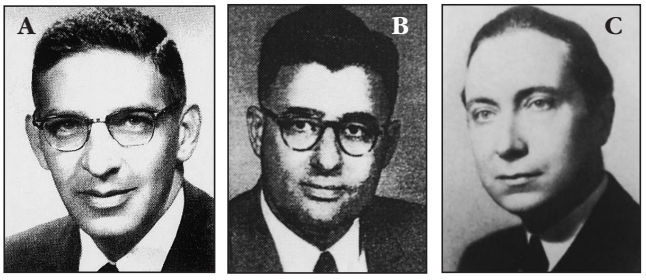

Figure 4. Key persons in the clinical introduction of reserpine in psychiatry. **A:** Nathan S. Kline (USA). **B:** Robert H. Noce (USA). **C:** Jean Delay (France). The first two were awarded the Lasker Award in 1957 for their studies on reserpine in psychiatry.

State Hospital of New York. As Caldwell states[2], in the spring of 1953, Kline read an interesting news from Bombay in the *New York Times*: in the course of the VI Gujarat and Saurashtra Provincial Medical Conference (Baroda, March 14-16), a special award was granted to Dr. R. A. Hakim (Ahmedabad) for a study titled «Indigenous drugs in the treatment of mental diseases»[32]. Hakim studied the effects of «Siledin», a mixture of medicinal plants, among which *Rauwolfia* was included, in a sample of 146 patients diagnosed of schizophrenic or manic-depressive disorder. The percentage of patients with positive response to treatment was 51% while the percentage of patients responding to combined Siledin and electroconvulsive therapy was 80%. These results, as well as the description of the pharmacological effects of the recent synthesized reserpine, led Kline to think that this substance could exert an action similar to that reported from France with the use of chlorpromazine.

In this way, Kline designed a clinical study in which 411 patients (94.4% schizophrenics) were enrolled and the efficacy of reserpine assessed[33]. Although in this study, the sedative, ansiolytic and antiobsessive effect as well as certain side effects (somnolence, nasal congestion or reduction of blood pressure) were verified, Kline did not observe a substantial antipsychotic effect, possibly due to the low dose of reserpine used (0.5-1 mg/day). The clinical experience of this pioneer of psychopharmacology was reported to the New York Academy of Science on April 30, 1954. Later studies of this same research team, using larger dosage regimes (initial dose of 5 mg intramuscular and 3 mg orally per day), verified the antipsychotic efficacy of reserpine in severe hospitalized schizophrenic patients (n = 200) treated for 9 months, with improvement percentages of 86%, and hospital discharge index of 22%[34].

The second publication on the use of reserpine in psychiatry is dated July 20, 1954[35]. This publication[36] collects the first data obtained with the new alkaloid by one of the pioneer groups in the development of psychopharmacology, that of the Hospital Sainte-Anne de Paris, directed by Jean Delay (professor of psychiatry in the Sorbonne and director of the Hospital Sainte-Anne) (fig. 4C), and formed by Pierre Deniker (chief of Men's Service of the same hospital), Y. Tardieu and Therese Lempérière. These authors studied the antipsychotic and adverse effects of reserpine, comparing them with those of chlorpromazine, predicting that reserpine could have an efficacy greater than chlorpromazine in chronic schizophrenic patients.

On his part, Robert H. Noce et al. (fig. 4B), also in the USA, performed a study on a sample of 89 patients (74 with psychiatric disorder and 15 with mental retardation), who were parenterally administered a daily dose of 2 mg of reserpine, for 7 months. The study results confirmed a high percentage of improvement (about 80% of the patients) as well as a decrease in the hospital practices of isolation and resort to electroconvulsive therapy[37].

To summarize, table 1 shows the 5 publications performed in 1954 on the use of reserpine in the field of psychiatry.

The «demonstration of the value of the derivatives of *Rauwolfia*, especially reserpine, in the treatment of mental disorders» allowed Nathan Kline to obtain the prestigious Lasker Award in 1957, together with Robert Noce for «their studies on reserpine and its use in mental diseases» and Rustom Jal Vakil for «his brilliant and systematic studies on *Rauwolfia* in hypertension and effective bridging of the gap between Indian experience and that of Western medicine». Henri Laborit, Pierre Deniker and Heinz E. Lehmann were also awarded the 1957 Lasker

TABLE 1. Psychiatric publications on reserpine in 1954, year of its clinical introduction in the psychopharmacology scope, according to chronological order

Date		*Authors*	*Title*	*Reference*
30 April	1	Kline	Use of *Rauwolfia serpentina* benth in neuropsychiatric conditions	33
19-25 July	2	Delay et al.	Premiers essais en thérapeutique psychiatrique de la réserpine. Alcaloïde nouveau de la *Rauwolfia serpentina*	36
30 October	2	Noce et al.	Reserpine (Serpasil) in the management of the mentally ill and the mentally retarded	37
November	2	Steck	Le syndrome extra-pyramidal et diencéphalique au cours des traitments au Largactil et au Serpasil	57

1: date of publication of the journal; 2: date of communication. Modified by Deniker[38].

Award for their contribution to the clinical introduction of chlorpromazine.

The scientific consolidation of reserpine as an antipsychotic agent (1955-1956)

Only one year after the psychiatric introduction of reserpine, a meeting sponsored by Ciba, to which many North American clinicians who had experimented with the use of reserpine were invited, took place in the New York Academy of Sciences[39]. Among the participants was Leonard Hollister, a Californian internist who presented the data that may have been the first placebo controlled study performed with reserpine in psychiatry. The results of this study were published in the *Annals of the New York Academy of Sciences*[40], although this volume was not seen until two years later, which, in the author's opinion[39], takes away an important degree of its originality. In spite of this, the publication, in the July 16, 1955 number of the journal *The Lancet*[41], of the first clinical trial with reserpine under the methodological principles proposed some years before by Bradford Hill[42] is attributed to Davies and Shepherd, of the Maudsley Hospital (London): double-blind, randomized, placebo controlled and previously designed study with the participation of statistical experts. In this multicenter study, 67 out-patients were enrolled, after applying the diagnostic criteria defined on anxiety. The patients from the reserpine group were treated with 0.5 mg dose, twice a day, for 6 weeks, obtaining, at the end of the treatment, statistically significant differences compared to the placebo in the evaluation of the efficacy, determined by the application of specifically designed questionnaires[41].

In addition, on August 9, 1955, Mark D. Altschule, from the McLean Hospital (Boston, Massachusetts), dictated on August 9 the Gordon Conference on Medicinal Chemistry of the Colby Junior College (New London, New Hampshire) on the use of this agent (and chlorpromazine) in mental disorders, published the following year in the *New England Journal of Medicine*[43]. In this review, all the clinical impressions and data published on the use of reserpine, in its first years of marketing, in the different psychiatric disorders as well as its profile of adverse effects are collected. The author specifies that although reserpine does not «cure» the psychiatric disorders, it does cause an important clinical improvement in these patients, above all in those with «self-limited psychotic syndromes associated with hyperactivity and agitation, as the manic disorders, schizoaffective states and some cases of early schizophrenia». In the same way, its efficacy stands out in other acute syndromes, such as delirium tremens and other manifestations of abstinence syndromes (anxiety attack in the deprivation of barbiturics, etc.) or the catatonic syndromes, and in certain chronic psychosis, such as senile psychoses, manic psychoses, chronic schizophrenic or behavior disorders in which aggressiveness, impulsiveness or hysterism are manifest symptoms. In all these cases, the advantages of the two new neuroleptic drugs (reserpine and chlorpromazine) were clear, both for the patients (with a high index of spontaneous recovery in cases of acute syndromes) as well as for their caretakers. The socio-health care translation of these facts (above all in chronic disorders) was the possibility of initiating a deinstitutionalization process, which Altschule stimulated, in those incipient moments of the psychopharmacological era, around 15%-20%. As a conclusion, Altschule verified that these two drugs «had totally changed the psychiatric practice».

The year 1955 was a key year in the history of reserpine, since a series of very important scientific acts took place. Besides the mentioned Gordon Conference on Medicinal Chemistry of the Colby Junior College, and the Meeting sponsored by Ciba in the New York Academy of Sciences, the first international conference on the new neuroleptics (I Coloquio Internacional sobre la Terapéutica Narcobiótica), organized by Professor Ramón Sarró, took place in Barcelona between March 29 and April 1. In September and October, there were two plenary conferences in Italy on reserpine and chlorpromazine (Convegno Nazionale su Sonno prolungato, Ibernazione artificale, Neuroplegici in Neuropsichiatria, Vercelli, and Symposium Nazionale sulla Reserpina e la Chlorpromazina in Neuropsichiatria, Milan). Finally, also in October, in the Hospital Sainte-Anne of Paris, Delay and his aid Deniker, organized the I Colloque International sur la Chlorpromazine et les Médicaments Neuroleptiques en Thérapeutique Psychiatrique (October 20-22, 1955) (fig. 5). This was attended by more than 400 psychiatrists from 22 countries (Germany, Austria, Argentina, Belgium, France, Brazil, Canada, Cuba, Spain, the United States, Great Britain, Greece, Holland, Italy, Luxembourg, Mexico, Peru, Portugal, Sweden, Switzerland, Turkey and Venezuela). It extensively dealt with the utility of the new chemical

Figure 5. Closing ceremony of the Colloque International sur la Chlorpromazine et les Medicaments Neuroleptiques en Therapeutique Psychiatrique, held in Paris (France) on October 20-22, 1955. The closing table was made up by: Rumke, Barahona-Fernandes, Delgado, Delay (standing), Overholser, Mayer-Gross and Hoff.

tools (chlorpromazine and reserpine) in the treatment of psychosis in more than 150 communications. Many authors have considered this scientific act, whose contributions were published the following year in a special number of almost one thousand pages in the journal *L'Encéphale,* as the first meeting of a new era en the field of psychiatry and of psychopharmacology.

Among the conclusions of this last event, collected in 1956 by Delay and Deniker[44], the following can be mentioned: the efficacy of the new neuroleptic tools in the treatment of different psychiatric disorders was confirmed, above all those that occurred with states of tension, agitation, aggressiveness and dysphoria, although the participants recognized that the support of psychotherapy and the importance of the patient's psychosocial readaptation should not be overlooked. Treatment with these agents was not innocuous, from the tolerance point of view, although the benefit-risk balance was clearly positive. Chlorpromazine and reserpine seemed to inaugurate a new era in the treatment of mental disorders, contributing substantial advantages compared to the existing biological treatments, above all compared to shock therapies. No consensus was established on the dosage regime that should be followed, the administration dose depending on the individual susceptibility to the products, on the nature of the disease and on the techniques used (hibernation techniques, in the case of chlorpromazine, induction therapies in sleep cures, or treatment in single drug therapy of psychotic patients, also call «neuroleptic cures» by some participants), although, in the case of reserpine, some authors reached a dose of up to 15 or 20 mg/day, doses 10 times greater than those administered in the internal medicine services for the treatment of hypertensive patients.

In the inevitable comparative analysis that took place between reserpine and chlorpromazine, thanks to the first clinical observations supplied by those attending, the French agent obtained a considerable victory in general lines. Among the advantages of chlorpromazine over reserpine mentioned by the speakers, an onset of a faster action and more potent, regular and constant antipsychotic effect may stand out. In the same way, in the most relevant specific comparative studies between the two drugs presented in this «colloquium»[45,46], it was concluded that the clinical response to chlorpromazine was superior in the treatment of schizophrenic disorders and that, in the treatment of the «acute psychosis», reserpine was not sufficiently effective[47]. On the contrary, in the management of «chronic psychosis», the main problem of the psychiatric hospitals, reserpine would play an especially relevant role in the opinion of Maurel et al.[47] The reserpinic cures in these patients, especially in the manics, would make it possible to eradicate psychomotor agitation, antisocial behaviors and aggressive reactions. However, the confusion existing in that time in regards to the management of the new therapeutic tools was evident. The statements of Maurel et al.[47] in relationship with reserpine, give proof of this: «Irreducible divergences are observed in the dosage, in the administration method, in the type of patient susceptible to being treated and in the intensity of the disease as well as in the technical and psychological conditions of the cures».

All these results were rapidly compared in the different countries. As conclusion, in Spain, professor Juan José López Ibor stated, in relationship with the new neuroleptic agents and the schizophrenic pictures, that «although the neuroleptic therapies do no more than subdue the morbid course - of the schizophrenia - they are socially and biologically of enormous value»[48].

The adverse effects of reserpine from the historical perspective

Parallelly to the knowledge of the clinical efficacy of reserpine, more knowledge was also obtained on its adverse effects. The possibility of gastric perforations, consecutive to the increase of gastric secretion, was possibly the most worrisome adverse effect of reserpine in the first years of its clinical introduction. In 1956, Hussar and Bruno[49] reported the first case of duodenal ulcer associated to treatment with reserpine, which was followed by another series of publications, but with the characteristic that doses of several milligrams daily of reserpine were used in all them. It was soon demonstrated that the capacity of reserpine to stimulate gastric secretion was practically null with daily doses lower than 0.25 mg[50], the incidence of dyspepsia being 1.5%. This subject was definitively settled, although unfortunately very late, with the study of cases and controls on the association between reserpine consumption and hospitalizations due to peptic ulcers, performed on a sample of elderly hypertensive patients of Medicaid[51]. These authors concluded that the relative risk of hospitalization due to peptic ulcer among reserpine users and non-users was 0.8, so that there was no type of association.

In the first clinical studies with reserpine, nausea, vomiting and diarrhea were also cited as frequent adverse effects and buccal dryness, nasal congestion and «parkinsonisms» were mentioned less frequently[43]. Precisely, as previously demonstrated, the induction of extrapyramidal motor adverse effects constitute one of the most representative characteristics of the so-called classical neuroleptics (phenothiazines, butyrophenones, reserpine). By 1952, Delay et al. had described a syndrome of psychomotor indifference with chlorpromazine similar to the akinetic syndrome described by Lhermitte in patients with lethargic encephalitis[52]. Two years later, Labhardt described an extrapyramidal syndrome in patients treated with chlorpromazine[53] and this same year, Thiebaux et al.[54] established a parallelism between this syndrome and that observed in patients treated with reserpine[55]. However, as Bein states[56], the Indian clinical investigators had already observed, during the two previous decades, certain neurological symptoms in their patients treated with *Rauwolfia,* that were reversed by atropine.

These extrapyramidal pictures (tremor and bradykinesia) having a reversible character were, as could be seen

by the Swiss psychiatrist Hans Steck, director of the Psychiatric University Hospital of Cery (Lausanne, Switzerland), in 1954, similar to the irreversible conditions of lethargic encephalitis described after the First World War[57]. These symptoms began with marked somnolence that gave way to different types of dyskinesias and hyperkinesias, finally ending up in a parkinsonism picture where localized (limbs and fingers) or generalized tremor was the clearest sign. However, contrary to the encephalitis, the syndrome described was observed while the drug was administered and disappeared when the treatment was discontinued[38]. In their speech at the International Meeting of Milan in 1957, collected in the work *Psychotropic Drugs,* Delay and Deniker state that «we are inclined to conclude that neuroleptics have the same trophism as the Von Economo encephalitis virus, so they produce a selective impregnation of the mesodiencephalic centres of the brain base»[58].

In the first years after the clinical introduction of reserpine, many clinicians observed that some of their patients had a sad appearance, with anxiety attacks, tendency to crying and non-expressive face, reactions that were listed, following Healy[10], as depressive. However, some psychiatrists, such as Steck[57] or Haase[59], interpreted these reactions as a new neurological affect attributable to reserpine, called akathisia. The proposal of the use of the term «akathisia» in 1954 to refer to «... a group of symptoms that were observed as a result of the administration of high doses of reserpine, especially», was precisely attributed to Haase[60].

The relationship between the extrapyramidal system and neuroleptics was so close during the decades of the 50's and 60's that the myth that the appearance of extrapyramidal adverse events was an essential condition for the drug to be considered as antipsychotic was consolidated. In fact, in such early times as the Colloquium of Paris, Delay et al.[61] had already stated that «the extrapyramidal symptoms are considered by some authors as a complication (of reserpine and other neuroleptics) and by others as an indicator of the medication's activity». This relationship was finally specifically approached and studied in a monographic meeting that took place in Montreal in November 1960 and, in 1961, Ayd published the first serious epidemiological data on the extrapyramidal adverse effects caused by neuroleptics[62].

THE CLINICAL DECLINE OF RESERPINE

During the second half of the decade of the 50's, reserpine was widely used based on its two important pharmacological activities (antipsychotic and hypotensive) and even, in some places (University Psychiatric Clinic of Burghölzli, Zurich), as a hypnotic agent to treat different sleep disorders. However, the introduction of new hypotensive agents, more effective orally, its relationship with some cases of mortality due to thrombosis, its association with breast cancer (later refuted, by controlled studies) and, above all, the description of reserpine induced depressive pictures, with the consequent risk of suicide, considerably reduced its use.

In the first publications on the clinical use of reserpine in the years 1954 and 1955, some cases of depressions induced by this agent had already been described, placing the mean incidence at 10%-15% of the hypertensive patients[63]. Freis published the first specific reports of depression in hypertensive subjects treated in the long term with high doses of reserpine in 1954[64]. The appearance of depressions, including some cases of suicide, in reserpinic therapy, above all those having a severe nature, was an eminently dose-dependent phenomenon, whose incidence increased when doses superior to 0.5 mg/day were administered, and could continue for 4 to 6 weeks after treatment was discontinued. In this sense, it must be kept in mind that during the decade of the 50's, administration of daily doses of 1-2 mg was very frequent, even reaching 5-10 mg intramuscularly in cases of hypertensive encephalopathy[65]. In fact, in some studies with large population samples, as is the case of Lemieux et al.[66], the mean dose of reserpine was 1.36 mg/day, a dose that was 6 to 14 times greater than that presently recommended. More recent studies, having a controlled and random design, have verified that the use of reserpine at effective antihypertensive doses of 0.05-0.125 mg/day is associated to a depression incidence less than 5%, values that are similar, for example, to those of beta-blockers[67].

A commentary on these safety problems by Titus H. Harris, of the Medical Department of the University of Texas (Galveston), in the *American Journal of Psychiatry*[68] in 1957 could mean a point of non-return in the clinical use of reserpine. Simultaneously, as has been well stated by Healy and Savage[63], since 1957, the first data that would support the catecholaminergic hypothesis of depression, based on the reduction of the monoamine rate on the central level, began to appear. In this way, a vicious circle was created in which reserpine was trapped: depression is due, from the biochemical point of view, to a decrease in the central levels of catecholamines and reserpine causes a depletion of these amines, ergo reserpine induces depression pictures.

However, in the distance, several authors[35,63,69] have questioned the real clinical importance of this phenomenon, which they consider to be overestimated, both in incidence and intensity. Lempèriére[35], one of the pioneers in the use of reserpine in Europe, remembers that, although he had to treat many depression cases in hypertensive patients treated with high doses of reserpine, severe depressions rarely appeared at the doses used in the treatment of psychotic patients, but rather mild dysphoric pictures. On their part, Healy and Savage[63] point to the possibility of a hyperdiagnosis of depressions, due to the lack of validated diagnostic instruments in the period and the absence of an adequate psychiatric training by the Primary Health Care professionals in the diagnosis of depressive disorders of their hypertensive patients. In fact, in the evaluations made by prestigious psychiatrists, such as Sarwer-Forner and Ogle[70] or Ayd[71],

it is concluded that the incidence of «depressive» and «anxious» reactions was similar between reserpine and chlorpromazine. Even more, for many years, after the decade of the 70's, reserpine has been used as a potentiation tool in case of depressions resistant to conventional antidepressive treatment[72].

Finally, after 1957, the clinical introduction of phenotiazines and haloperidol finally slowly eclipsed the therapeutic use of reserpine in psychiatry. Furthermore, the fact that this drug could not be patented, given its natural origin, and the impossibility of finding derivatives that contributed significant additional advantages, considerably limited the interest given it by the Pharmaceutical Industry. In spite of this, during the decade of the 50's of the last century, the «golden decade» of psychopharacology[12], reserpine was the most mentioned psychodrug in the scientific literature, even above chlorpromazine[73].

The actual validity of the clinical use of reserpine in psychotic disorders seems to be minimum, although some authors continue to give it a certain usefulness. Thus, Christison et al. in 1991 published their data based on eight double-blind, placebo controlled clinical trials and concluded that there was a possible utility of this drug in schizophrenic patients resistant to conventional neuroleptic treatment[74].

In conclusion, we can retrieve the words of Fraser[75], who stated that «the history of reserpine can be described as a classic example of the impact of false information, excessive therapeutic recommendations early dose and marketing strategies on prescribing fashions».

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