Schizophrenia Bulletin Open
https://doi.org/10.1093/schizbullopen/sgac053

History of ECT in Schizophrenia: From Discovery to Current Use

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Eighty years ago, schizophrenia was the first indication for electroconulsive therapy (ECT), and likewise ECT was one of the first treatments used for schizophrenia. This paper presents the history of ECT in the treatment of schizophrenia and its evolution, from it's discovery in the 20th century, which is an example of empiricism with a sequence of "*shock*" therapies. Following this discovery, the use ECT in schizophrenia has been in expansion during several decades, in a context of lack of efficacy of the treatment in schizophrenia. Then, after World War II and the derivative use of ECT in Germany, the use of ECT has decline during several decades. However, in the last decades, the use of ECT in schizophrenia has reemerged. Indeed, among patients in schizophrenia, rates of resistance to treatment have always been and still are high. In 2017, the concept of "*ultra-treatment resistant schizophrenia*" was defined when clozapine was tried and failed; and ECT, that had been long since abandoned in the treatment of schizophrenia until recent renewed interest, has emerged especially concerning the add-on of ECT to clozapine. However, ECT remains highly stigmatized and underutilized. This article looks at the history of the practice of ECT in schizophrenia with a historical and clinical approach and makes connections between the history of the treatment and its influence on its current recommendation and practice.

Key words: electroconvulsive therapy/electroshock/schizophrenia/resistant/schizophrenia

Introduction

Eugen Bleuler's conception of schizophrenia finds its origins in Emil Kraeplin's conception of "*dementia praecox*". At the congress of the German Association of Psychiatrists in 1908, Eugen Bleuler pronounced for the first time the word "*schizophrenia*".[1] Shortly thereafter, in 1936, electric shocks became one of the most widespread treatments for schizophrenia. Antipsychotics, discovered first in 1952, were seen as a significant improvement in treatment, and electroconulsive therapy's (ECT) use in schizophrenia has gradually become a last resort approach.

Nowadays, several recommendations and expert reviews recognize the potential benefit of ECT for treating schizophrenia, and some recent research has shown a renewed interest for the use of ECT in conjunction with clozapine.[2,3] Indeed, the rate of treatment-resistant schizophrenia (TRS) to antipsychotics has remained high, between 20 and 33%.[4,5] Furthermore, in 2017, only 40% of TRS treated with clozapine, the standard treatment for TRS, met criteria for a clinical response.[6] Moreover, schizophrenia remains one of the leading causes of reduction in disability-adjusted life years (DALY).[7] However, ECT remains underutilized and highly stigmatized.

The aim of this paper is to explore the history of the development, use, and recommendations for ECT in schizophrenia from its discovery until the present day. We aim to highlight the influence of history in the current approach to the use of ECT in treating this specific psychiatric disorder. After a brief history of the nosography of demantia praecox and schizophrenia, this paper follows a chronological approach in five parts. In the first section, we will introduce the successive discoveries which led to the discovery of the therapeutic effect of electroshock treatment. In the second part, we will focus on the discovery of electroshock. The third section will present the successive

historical events during the 20th century that have had an influence on the interest in and conversely, reluctance for the use of ECT in schizophrenia. The fourth section will summarize the practice of ECT at the end of the 20th century. Finally, the last part will summarize its current use, hypotheses on the mechanism of action, and societal approach to the stigmatization of ECT.

A Brief History of the Nosography of Demantia Praecox and Schizophrenia

In the mid-19th century, several clinical concepts were used to characterize psychotic disorders, such as hebephrenia and catatonia. These appeared respectively in 1871 with Ewald Hecker and in 1874 with Karl Ludwig Kahlbaum, two German psychiatrists working together at Kahlbaum's clinic in Görlitz, Prussia, in the early 1870s.[8] It was in 1852 that the term "*dementia praecox*" was first introduced by Benedict Morel, a French psychiatrist working at the asylum of Saint-Yon. If he associated the word dementia with the qualifier "precocious" or "juvenile", it is for chronological precision, to specify that manifestations of dementia appear at a premature age.[9] The psychiatrist Emil Kraepelin was the first to characterize dementia praecox in 1893 in the 4th edition of his textbook write when he was department head at the University of Heidelberg, Baden-Württemberg, Germany. Dementia praecox then belonged to the category of degenerative psychic processes, such as catatonia and paranoid dementia. It is in the 5th edition of his textbook that Emil Kraepelin clarified the clinical picture and the evolution of dementia praecox, distinguishing it from paranoia which did not lead to dementia. This element is of particular importance for positioning the prognosis as the determinant of the diagnosis. In the 6th edition of his textbook, Emil Kraepelin extended the concept of dementia praecox, a single disease with three principal clinical forms: hebephrenic, catatonic and paranoid.[10,11]

Eugen Bleuler was a Swiss psychiatrist, professor at Burghölzli and director of the mental asylum in Rheinau, Switzerland. The term "*schizophrenia*" is itself attributed to him with the first publication in "*Dementia praecox oder Gruppe der Schizophrenien*", in 1911.[12] First, he clarified that the progression to dementia, and therefore, the prognosis, did not characterize all of these patients. According to Eugen Bleuler's concept of schizophrenia, the splitting of different psychological functions (concept that approaches the more current disorganization phenomenon) resulting in a loss of unity of the personality, was the most important sign. Thus, he proposed the less static and stigmatizing neologism, by juxtaposing the Greek roots schizen ("σχίζειν", "to split") and phren—("φρήν", originally denoting "diaphragm" but later changing by metonymy, to "soul, spirit, mind").[13] The plural "*schizophrenias*" in the title of Eugen Bleuler's monograph highlighted his view that the illness had a variety of clinical presentations. He did not challenge Emil Kraepelin's approach of lumping hebephrenia, catatonia, and dementia paranoid into one diagnosis.[14]

The Beginning of Shock Therapy: an Example of Empiricism

Electroshock, as the name suggests, was a "*shock*" therapy. This term comes from Constance Pascal (1877–1937), a Romanian psychiatrist who worked in France and was interested in the treatment of mental illness by shocks at the beginning of the 20th century. As the name suggests, she used this term to show that an important event—a *shock*—, was needed to treat mental illness. Indeed, she believed that mental illnesses came from anaphylactic reactions in the brain and that the balance of the brain could be restored using a reverse shock.[15] She explained that the body might be shocked by certain substances or practices, such as fever therapy which Julius Wagner-Jauregg (1857–1940) had invented just a few years prior.[16] Indeed, at the beginning of the 20th century this Austrian neurologist and psychiatrist at university of Vienna, developed the first "shock" therapy—using fever—which subsequently opened the way to convulsive therapy. At that time, "*general paralysis*" (currently known as "*terciary syphilis*"), with a dementia syndrome, delusions and hallucinations, was a major problem in psychiatry. Julius Wagner-Jauregg was inspired by the "*centuries-old observation that mental patients following an incidental febrile disease occasionally show great improvement*".[17] He wanted to know if the fever was responsible for this improvement. After using typhoid, he tried tuberculin injections, and, in 1917, when his medical wards were unusually full of soldiers infected with malaria, he used injections of malaria into patients suffering from general paralysis. He showed that patients improved following fever peaks. Of note, he obtained the Nobel Prize in medicine in 1927 for this discovery.[17,18] Given the clinical similarity between schizophrenia and general paralysis, this was a starting point for treating schizophrenia.[17]

Following these studies on the role of fever, Manfred Sakel (1900–1957), an Austro-Hungarian psychiatrist and neurophysiologist researcher working at the University of Vienna's Neuropsychiatric Clinic, discovered insulin coma therapy. Initially, he used insulin to treat addiction to morphine in 1930s.[19] During an accidental coma after an insulin injection, he found that the symptoms of schizophrenia improved.[20] Thus, in 1933, he proposed an insulin cure for patients with schizophrenia.[21] He believed that hypoglycemia targeted damaged nerve cells in schizophrenia.[22] At that time, only the coma was considered as treatment by Manfred Sakel and not the convulsions, which were then considered complications of the treatment.[20]

At the end of the 1920s, Ladislas von Meduna (1896–1964) began to understand the benefits of epileptic seizures

in schizophrenia. Ladislas von Meduna was born and studied in Budapest. For the first 6 years of his medical career, he worked as a neurologist and a neuropathologist in the famous Research Institute for Neuropathology under Schaffer. Then, in 1927, he worked as a neuropathologist at the University Clinic for Nervous and Mental Diseases in Budapest and continued his neuropathological studies at the local psychiatric hospital. During these first years, Ladislas von Meduna established his observations, based on this dual approach of neuropathology and psychiatry, which were to be the beginning of his discoveries.[23] First, Ladislas von Meduna examined brain tissues of epileptic patients who had died in status epilepticus and then brain tissues of patients suffering from schizophrenia. He found a lower density of glia cells in the patients suffering from schizophrenia than in patients with epilepsy.[24] He also used the work of Gyula Nyírő, (1895–1966), a Hungarian psychiatrist at the University of Szeged, to develop his own. In 1929, Gyula Nyírő noticed that epileptic patients who developed symptoms of schizophrenia had fewer epileptic seizures: 1% recovered from uncomplicated epilepsy, while 16% recovered from epilepsy accompanied by symptoms of schizophrenia. This led to the hypothesis of an antagonistic effect between schizophrenia and epilepsy. Gyula Nyírő wanted to cure epilepsy with schizophrenia, not the opposite. Thus, he followed Julius Wagner-Jauregg's thought, and injected blood from patients with schizophrenia into patients with epilepsy. Faced with poor results, he abandoned his hypothesis.[24]

Based on Gyula Nyírő's findings, Ladislas von Meduna used the hypothesis of antagonism. By causing convulsions, he aimed to increase the production of glia cells and thus create unfavorable territory for the development of schizophrenia. Interestingly, almost 100 years later the hypothesis of antagonism between epilepsy and schizophrenia is still up for debate, and some clinicians still note a strong link between the two diseases[17,25,26] (Thanks to functional MRI, functional brain networks and graph theory (a mathematical framework allowing the quantitative modeling and analysis of these networks) compared temporal lobe epilepsy (ELT) and schizophrenia: the functional brain networks in schizophrenia would tend toward a randomized topology whereas it would be more regularized in ELT.[26] However, ECT would modify the dynamics of these brain networks. The question is therefore to know if ECT could regularize the topography of the brain networks of schizophrenia and thus make them close to those of epilepsy.[26] The hypothesis of an affinity between the two disorders is also supported, notably with the sharing of common genetic factors.[27,28]. Ladislas von Meduna also noticed an opposition between the two bodytypes of patients: patients with epilepsy were like "*a stocky, raw-boned man of athletic build with a massive head and powerful muscles*", whereas patients with schizophrenia were of the "*asthenic-leptosomatic type*" with a long body and face. Of note, he didn't make this physical distinction a rule, but rather another argument for antagonism between the two disorders.[22,29] Accordingly, in November 1933 he began intramuscular camphor injections to induce seizures; and after 2 months, he used pentylenetetrazol (better known as cardiazol) which was less painful and had a lower latency of seizure induction.[24,30] He stated that it is "*an ideal circulatory stimulant; but if this dose is increased* [. . .]*, then reacts on the central nervous system and produces epileptiform*".[22] cardiazol was often fatal and required the patient to be in good physical condition, despite marked individual variability.[22,30,31] Interestingly, Ladislas von Meduna found that insulin shock was more effective in catatonic and paranoid schizophrenia, while cardiazol was rather effective in simple and stuporous schizophrenia.[22] Thus, it seems that Ladislas von Meduna included patients with catatonia in addition to patients with schizophrenia, corresponding with Kraeplin and Eugen Bleuler's concept. The extension of cardiazol therapy to non-schizophrenia psychoses, which also led to positive results, made it possible to deduce that it was the specific action of epileptic seizure and not an antagonism of epilepsy on schizophrenia specifically.

The Discovery of Electroshock

The use of electricity in medicine dates back to ancient times. It was used to treat pain, headaches, as well as in hemiplegia.[32] Wilhem Erb, a German neurologist (1840–1921) affiliated with the University of Heidelberg, discovered that the skull is conductive but not excitable.[30] In 1870, the excitability of the cerebral cortex was demonstrated by treating a head injury and then observing a contralateral muscle response to the injury.[30,33]

In 1900, Stéphane Leduc (1853–1939), a French biologist in Nantes, studied the action of electric currents on the brain, in particular to induce sleep. He used a low internal resistance generator, with a collector and a switch. He described the induction of an epileptic seizure by electricity through the intact skull of an animal (Congrès international d'électrologie et de radiologie médicales. 2nd, 1903). Ugo Cerletti (1877–1963), an Italian physician who studied neurology and neuropsychiatry, and Lucio Bini (1908–1964), an Italian psychiatrist, were both pioneers in electroshock therapy. Ugo Cerletti was firstly appointed head of the Neurobiological Institute, at the Mental Institute of Milan, and then, he became the director of the Neurobiological Institute of the psychiatric hospital of Mombello, in Milan, and professor at the University of Genoa. At this moment, he was already interested in epilepsy.[30,34] Then in 1936, when he finally became the Chair of the Department of Mental and Neurological Diseases at the University of Rome La Sapienza, he followed the work of Stéphane Leduc and Ladislas von Meduna and studied the effects of epilepsy

in dogs through the application of an electric current with the aim of treating patients with schizophrenia. His aim was to replace cardiazol, which was poorly tolerated.[35] First, electrical stimulation was applied on the mouth-anus axis of the dogs, thus passing through the heart, and half of the animals died. The work of Jean-Louis Prévost (1790–1850) and his assistant Federico Batelli (1867–1941) found that the bi-temporal axis led to fewer deaths.[30] In 1937, Ugo Cerletti and Lucio Bini learned that a slaughterhouse used electricity to anaesthetize pigs before killing them.[36] They found that tolerance, time to onset of seizure and rates of death were different according to the intensity of the electrical stimulation, and that there was no observed brain injury when the duration and the intensity delivered was just what was necessary to induce seizure.[35,37] Thus, Lucio Bini gave more precise regulation of the intensity and the flow time of the current. According to Ferdinando Accornero, a student of Ugo Cerletti and Lucio Bini at the University of Rome, the two were equally involved in the discovery of electroshock: the first was at the origin of the concept, and the second was at the origin of its experimental realization.[35]

In April 1938, at the Clinic for Mental and Nervous Diseases in Rome, a 39 year-old man received electroshock treatment for the first time.[35] The patient was brought by the police to the clinic a few weeks before the session as he had been wandering the streets of Rome. This patient with schizophrenia could not give any precise information about himself or his family. He often spoke "*in jargon of his own invention*", verbalized "*illusions*" and "*his thoughts were disorganized, without logic*". He was "*emotionless, living passively like a tree that does not bear fruit*".[35] The patient was prepared as follows: he was shaved, lying on a bed, wearing a mouthguard modeled out of a copper tube covered with a compress and had large electrodes placed in the fronto parietal regions of the skull.[30] No anesthesia was used. A first shock was delivered at 80 V for one tenth of a second. The patient had a strong muscle contraction and a tonic spasm. He did not lose consciousness, but he also did not remember the experience. A second shock was delivered at 90 V for one tenth of a second. The patient fell into a spasm similar to the first, but for a longer duration. The patient "*turned pale for a few seconds, and then relaxed with a deep breath* [. . .]. *After about a minute, he opened his eyes, shook his head, sat up, and started to sing a popular, dirty song*". A third and final shock was delivered at 110 V for two tenths of a second. A tonic spasm occurred without relaxation, followed by rythmic spasms. The patient then had a tight mandible and presented bodily pallor and cyanosis up until the 48th second.[35] The shocks were repeated at 14 intervals, 11 complete and 3 incomplete, over a period of 2 months. According to Ferdinando Accornero, the patient had a complete remission of his schizophrenia symptoms.[18,35,37] According to Ugo Cerletti, there were *"too few observations* [. . .] *but the seizure was the same as that obtained with cardiazol"*.[38] As compared with cardiazol, convulsions with electroshock tended to be less severe and had a lower fracture rate, less severe cardiac stress, less patient anxiety, and shocks could be repeated where cardiazol injections could not. Clinicians argued that it was simple in application and easier than a injection, and less expensive.[39] Thus, electroshock allowed for an expansion of the targeted indication and population.

Ugo Cerletti announced good results with 80% complete remission and 20% significant improvements a few months after electroshock treatment; the improvements mainly concerned catatonic schizophrenia (the rates were the authors' estimation, the details regarding participants were not published).[30] Other clinicians noticed similar improvements. For instance, Paul Delmas-Marsalet (1898–1977), a French psychiatrist working in Bordeaux and particularly interested in electroshock, had reported the benefit of electroshock in schizophrenia with 40% complete remission, 30% incomplete remission and 30% failure for 24 patients.[30]

Regarding the pathophysiological mechanisms of electroshock treatment, Ugo Cerletti's main hypothesis was based on the existence of "*acro-agonins*". According to his research in 1940, electric current could activate a series of biological reactions in the body. In 1945, Pierre Doussinet and Elisabeth Jacob, French psychiatrists, affirmed the existence of a massive discharge of antibodies and antitoxins in reaction to electrical stress. Ugo Cerletti used these observations to test his hypothesis. Inspired by how rabies vaccines were developed, he crushed the brains of pigs that had received multiple electric shocks, diluted them in phenolic solution and injected himself with it to prove the harmlessness of the solution obtained. He did not experience any harmful effects; he then injected the solution into patients like a vaccine. He stated that "*out of 36 patients* [that received the solution]*, 11 were cured during treatment, 20 showed more or less remarkable improvement and 5 remained the same*". These substances were "*acroagonins*"[40,41] (nowadays it is thought that ECT could stimulate neurogenesis, which is associated with synaptic remodeling and glial activation.[42,43] The Brain Derived Neurotrophic Factor (BDNF), is believed to be one of the markers of neurogenesis. This could be thought of as a descendant of Ugo Cerletti's acro agonine. Several studies have reported an increase in BDNF after ECT, in depression but also in schizophrenia, but with heterogeneous results.[42,44]

Evolution of the Use Electroshocks and ECT in Schizophrenia in the XXth Century

Expansion

For several years, the first indications for electroshocks was primarily schizophrenia, especially in the case of acute attacks and recent onset of schizophrenia.[45] Machines for delivering electroshock were quickly

developed. In Paris (France), in 1941, Marcel Lapipe and Jacques Rondepierre, psychiatrists, created their own machine called the "*sismothère*". Paul Delmas-Marsalet offered his device in 1942. The Siemens–Reiniger company also began to produce machines.[46]

Electroshocks gradually garnered attention as a medical treatment for schizophrenia across Europe and, in the early 1940s, in the United States.[47,48] Of the first 46 Italian machines, about a third were sold abroad. Switzerland was the second country after Italy to have machines and to develop electroshock therapy, especially with Max Muller (1894–1980), a Swiss psychiatrist.[49] Switzerland was followed by Germany in 3rd position with the Danish psychiatrist Arild Faurbye (1907–1983) and the German psychiatrist Adolf Bingel (1901–1982), who was the pioneer of electroshock therapy in Germany, at the University of Hambourg, with the help of Siemens-Reiniger-Werke company.[46,50] Once the device was obtained, expenses were limited and therefore the economic advantage was quickly evident compared to the other available treatments.[41]

While side effects were reported, the practice also became safer. Side effects were primarily fractures of the limbs, spine, and teeth as well as other maxillofacial trauma. Initially, drugs were used to increase the intensity of the seizure, but this worsened these complications. Mechanical restraints, hyperextension of the spine, injection of insulin before electroshock, and anesthesia of the marrow with metrazol (convulsing agent) were used without success. In 1948, curare began to be used to paralyze muscles during a seizure and to partially protect the patient from the traumatic complications of electroshock. Succinyl–choline–iodide, discovered in 1949, improved the effect and tolerance of curare and allowed for safer practice.[51–53] Other side effects included confusion and impairments in attention and memory.[54]

Changes in practice highlight a willingness to improve tolerance, protect, and reassure patients. The copper tooth protector with compresses was replaced by an inter-dental tampon to limit odontological complications as much as possible. The frontal region was given preference because it was already hairless. Degreased with ether, this region offered an abnormally low resistance to direct current, a constant temperature, and the absence of a psychogalvanic or electrodermal reflex (sweating). Clinicians also gave more consideration to contraindications to electroshock treatment by instating a systematic eye fundus examination to rule out neurological origin of the psychiatric disorder.[30] Even though anesthesia was not yet systematically used, the patient was required to fast prior to the session which often took place in an equipped room with a nursing protocol that was gradually established.[55]

The practice of electroshock therapy enjoyed growing success until the 1960s. In fact, it was very popular, with a favorable opinion among nearly 80% of psychiatrists according to a survey by the American Psychiatric Association (APA) in 1950.[56]

Decline

1) The state before decline: increasing number of indications of electroshocks in psychiatry

After its initial success in schizophrenia, electroshocks began to show impressive results in mood disorders (i.e., "manic-depressive" illness, or "melancholy"). Therefore, from 1940 interest in the use of ECT gradually spread to depression, and eventually surpassed its use in schizophrenia.[57] As this extension showed positive results, the popularity and interest in the practice of ECT grew, and the treatment, because of its simplicity and relative safety, became commonplace. This then led to an overuse of ECT, which was extended to the treatment of certain pathologies with a "*nervous*" background such as asthma, psoriasis, prurigo and alopecia areata.[37] To illustrate, in 1949 at the Stockton State Hospital (California), up to 60% of patients, nearly 3000 people, were receiving this treatment.[58] All psychiatric manifestations had become an indication for electroshock sessions, including personality disorders.[59] Even the onset of anxiety and behavioral disturbances after ECT sessions were themselves an indication to prescribe an ECT session.[48]

In addition to this increasing number of indications, other practices helped create a negative image of ECT. In 1942, Lucio Bini (1908–64), an Italian psychiatrist working with Ugo Cerletti at the University of Rome, maintained that certain forms of chronic paranoid schizophrenia necessitated a "*destruction*" of the psychic life of the patient.[10] Many clinicians joined him to practice regressive and/or intensive ECT.[60] In intensive ECT, the number of ECT sessions was predetermined according to the severity of the patient's illness. Sessions were repeated 2–4 times a day, over the course of several days or weeks.[61,62] In regressive ECT, sessions were performed several times a day until provoking the onset of an acute brain syndrome with memory loss, confusion, disorientation, apathy, and dysarthria.[60,61,63,64] Lucio Bini sought the suppression of the patient's individual memory and pathological experience.[41] This practice contributed to the condemnation of this therapy.[60]

2) The trauma of Word War II (WW2)

Initially, the Nazi regime limited the distribution of the "*Konvulsator*", a German machine, in psychiatry departments as a pressure tactic to deny treatment to the sick.[46] However, a "*seismotherapie*" machine was built in forced labor camps, a far cry from ethical psychiatric care. The aim was to "heal" the emotionally disturbed prisoners as a way to make them capable of working.[46] However, according to Heinz Reinhold Faulstich (1927–2014), a German psychiatrist, the significant extension of shock therapy in psychiatry during WW2 was more myth than reality.[65] Indeed, a review of archived patient charts revealed that electroshock therapy was rarely used.[66] Aktion T4—a secret Nazi organization intended

to exterminate patients with mental health problems[60] main approach was starvation.[46]

In 1944, psychiatrists of the Nazi regime, and in particular Emil Gelny (1890–1961), used a derivative of seismotherapie named "Elkra II", adding four extra electrodes to the wrists and ankles of his victims in order to administer lethal electrical shocks causing electrocution.[31] Emil Gelny had not received an order from the T4 organization, but he had turned to them. Emil Gelny's criminal case remains the only officially known murder of patients using a converted electroshock therapy machine.[31,46] As Gábor Gazdag et al.[31] stated, Emil Gelny *"might have reduced the patient's resistance by explaining that they would receive ECT for therapeutic reasons"*.

The derivative use of electroshock, manipulation and outright lies to patients on the basis of medical argument, and intensive/regressive electroshock sessions led to a logical reluctance towards this treatment. The concept of stigma refers to "*negative attitudes and discriminatory judgments or negative thoughts and feelings, such as anxiety or hatred*".[67] Therefore, these historical events contributed to the decline and gradually built the stigma against this practice.

3) The discovery of neuroleptics

During the 1950s, alternative treatments for schizophrenia appeared, and in particular the discovery of the role of so-called "*neuroleptics*" (currently referred to as antipsychotics). Indeed, in 1952 in France, in the hospital Sainte-Anne (Paris), Jean Delay's publication[68] on the discovery of the first neuroleptic agent, i.e., chlorpromazine, was a major revolution, transforming the fate of patients. Consequently, the frequency of ECT use fell dramatically. Neuroleptic treatments were easier to use and were not stigmatized in the same way.[24,69]

4) Stigma of electroshock therapy and its role in the decline of its use: antipsychiatry

From the 1950s to the 1960s, a movement directed against psychiatry developed, particularly in Europe. In Italy, from the 1960s, the management of patients with psychiatric disorders was questioned by psychiatrists themselves. Franco Basaglia (1924–1980), an Italian psychiatrist affiliated with multiple universities in Italy, then created a so-called "*anti-institutional*" movement also known as the deinstitutionalization movement whose motivations were political as well as social.[70] In England, during these years, psychiatry was seen as a tool of social repression or institutional violence against certain individuals (outsiders, opponents, etc.). David Cooper (1931–1986), graduated from the University of Cape Town who then wored in London, edited "*Psychiatry and Antipsychiatry*" which appeared in 1967 and thus created the term "*Antipsychiatry*". In his view, schizophrenia was its starting point: "*the most effective way to explore the possibilities of such anti-discipline seems to me to be to study* [. . .] *the sphere known as schizophrenia"*.[71]

ECT was one of the medical practices criticized by the antipsychiatric movement.[47] In his writings, David Cooper often associated it with lobotomy; for instance, he described how he treated patients "*belonging to the diagnosis of schizophrenia*": "*We did not use any of the so-called shock treatments, nor lobotomy*".[71] ECT is also described as being used as a deterrent, probably reminiscent of the use of electroshock at the end of the WW2, with the aim of controlling patient behavior. David Cooper refers to a conversation between a psychiatrist and Antonin Artaud (1896–1948), a French artist and patient who received ECT: "*If you still talk about bewitching, Monsieur Artaud, you will have sixty-five electroshocks*".[71] Rather than being effective, according to David Cooper, ECT resulted in "*less intelligibility and less vitality in the patient's existence*" which could go as far as "*distorting*" the personality of patients.[71]

The Revival

The term electroshock was gradually abandoned during the 1950s.[72] The term electron-convulsive therapy appeared starting in 1946. Later, in 1951, the term "*modified ECT*" was coined. This term specified that ECT was to be used with anesthesia, to reduce the orthopedic/traumatic complications. Thus, it highlighted a breakthrough in practice. Standard curare, poorly tolerated on a respiratory level, was replaced by succinyl–choline in 1952 (still used currently).[24] Clinicians wanted to specify and improve tolerance and, thus, reduce stigma.

Research on the cognitive impact of ECT is part of a desire to decrease anxiety and stigma around this treatment. As early as 1942, with improved techniques, seizures were maintained while decreasing power of the electrical current and, potentially, reducing the cognitive impact.[45] In addition the efficacy of unilateral stimulation, and no longer bilateral, was quickly noticed. In 1958, the electrode was placed half an inch above half of the segment between the lateral edge of the orbit and the external ear canal. The second electrode was placed 3 inches from the first at an angle of 70°.[73] These two placements, on the side of the non-dominant hemisphere, showed a reduced cognitive impact.[73] From the 1960s, fewer confusional syndromes and less memory loss was reported than had been with bilateral stimulation.[74,75]

Moreover, administration of pure oxygen over a period of 30–60 s before and after the shock, decreased the degree of hypoxemia.[76] Starting in the 1950s, the benefits of hyper-oxygenation were seen both in the prolongation of seizures and in the reduction of cognitive impairment.[24,76,77]

Along the same lines, clinicians began to limit the number of sessions (20 has been mentioned) while maintaining efficacy.[78] During the same period, there was also a decline in the use of other treatments for schizophrenia. In 1958, chlorpromazine began receiving criticism: a high

rate of recurrence after stopping treatment, a high rate of non-compliance, and therefore a lower remission rate compared to the risk of antipsychotics was observed.[78] At the same time, insulin coma therapy was gradually abandoned given the significant risk to life. In this context, ECT was reconsidered with its good overall response, rather good tolerance, and simple nursing care.[78]

ECT at the End of the XXth Century

The concept of treatment-resistant schizophrenia (TRS) began to appear at the end of the 20th century.[79] It is stated that a fifth to a third of patients with schizophrenia do not respond sufficiently to drug treatments.[5] These patients are resistant even when anti-psychotics of different classes and doses are tried.[80] For patients with TRS, hospitalizations are more frequent and longer, while these patients often receive high doses of anti-psychotics.[5,81] For example, in 1968, a study by Robert F. Prien and Jonathan O. Cole wanted to show if high doses of chlorpromazine could improve outcomes in schizophrenia patients. There was a group of patients receiving more than 2000 mg of chlorpromazine. About half of them had at least one moderate to severe side effects during treatment, and 10% had serious side effects.[82] Thus, clinicians were then led to consider other treatments which could be effective in TRS, while maintaining acceptable tolerance.[80]

Before 1988, resistance to treatment often meant chronic hospitalization and/or frequent admissions.[5] In 1988, John Kane et al. of the Multicenter Clozapine Trial defined TRS as the persistence of positive symptoms, sufficiently intense to induce a relapse, and which are not responsive to an adequate antipsychotic treatment. The concept of duration of treatment resistance was also introduced: at least three periods during the last 5 years of treatment without significant symptom relief.[79] Chronicity alone could no longer accurately predict the probability of response to an antipsychotic, both the effects of drug non-compliance and extra-pyramidal side effects can mimic true treatment resistance.[5] In 1990, Herbert Y. Meltzer et al. suggested that the persistance of positive symptoms as well as negative symptoms, and the overall severity (at least moderate) of the disease and its impact on quality of life, should also be taken into account when considering the response to treatment.[83]

Clozapine was discovered much earlier, in 1960. However, double-blind trials only started on this molecule 10 years later. It was in John Kane et al. study (1988) that clozapine was found to be effective in TRS.[79] In fact, in 1990, the only real indication for clozapine approved by the Food and Drug Administration was TRS.[5] Data from John Kane et al. (1988) strongly suggested that about a third of those with TRS would show a considerable improvement with clozapine. Improvement was confirmed on positive, negative symptoms and on global scales.[80] However, the studies also showed a mediocre tolerance profile with significant side effects. In addition, an economic debate was taking place about the price of clozapine in the United States: expensive clinical and biological monitoring was weighed against improving the disorder with shorter treatment times overall.[84]

After the successive phases of expansion, global reluctance and sidelining because of psychiatric mood disturbances, followed by a revival, ECT in schizophrenia was still controversial at the end of the 20th century. For example, in 1978, in a large American survey comprising about 3000 APA psychiatrists, 25% of psychiatrists believed that ECT was an appropriate treatment for patients with schizophrenia, 59% considered its use inappropriate in this indication, and 15% were undecided.[85] Moreover, as we have seen, the definition of TRS was still unclear. In addition, there was a significant lack of data. In 1962, Riddell found ten scientifically acceptable studies among most of the early clinical reports of ECT in schizophrenia. The other articles did not meet the rigorous criteria for diagnosis, methods, control groups, and double-blind status.[86] Twenty years later, in 1980, Salzman made the same observation highlighting the paradox between the age of the treatment and the lack of data.[64]

There was already a consensus that ECT impairs memory capacities. During the last years of the 20th century, research began to clarify the type and duration of these changes: anterograde and retrograde amnesia, and the concept of subjective memory impairment also began to be examined.[87–89]

Moreover, in schizophrenia, certain specific indications appeared. For acute episodes of schizophrenia, some improvement has been described with ECT alone in uncontrolled clinical trials. However, some authors have highlighted the weakness of the methodology in these studies.[64,90,91] In 1986, Robert O. Friedel concluded that some patients may benefit from being treated with ECT in the acute psychotic phase.[92] In parallel, Gretchen L. Haas et al.[93] supported the hypothesis that a rapid resolution of acute psychosis may be essential in preventing long-term deterioration.

With regard to so-called "*chronic schizophrenia*" in the late 20th century, many studies have highlighted the limitations of ECT and suggested that it was ineffective.[90] However, an important distinction seems to be whether ECT should be used alone or in combination with antipsychotic medications.[80] Positive symptoms such as delusions, hallucinations, agitation and hostility (as well as depression) improved more rapidly in patients who received a combination of therapies compared to antipsychotics alone. These symptoms refer to paranoid schizophrenia. Some studies have shown that a combination of ECT and phenothiazines (such as chlorpromazine) is significantly better than either drugs or ECT alone in chronic schizophrenia.[94–98] This difference in improvement seems to disappear after 4–6 months after treatment.[94,97,98] Max Fink has shown that it often takes

up to 20 sessions to achieve a reduction in psychotic symptoms, though 12 sessions have also been observed as sufficient, suggesting a certain amount of inter-individual variability.[80,96] Of note, ECT doesn't significantly improve negative symptoms—related to hebephrenic schizophrenia—in most current studies.[99]

In agreement to Ugo Cerletti's results, other clinical forms of schizophrenia were more likely to respond to ECT, such as catatonia.[64,80] All forms of catatonia are included, as well as neuroleptic malignant syndrome, in which ECT has been shown to be effective.[100,101] Catatonia has a historical nosography that is important to contextualize. It was recognized by Karl Kahlbaum in 1874 and then by Emil Kraeplin who related it as a form of dementia praecox. When Eugen Bleuler relabeled Emil Kraepelin's image of dementia praecox as "*schizophrenia*", he retained catatonia as its marker. Therefore, at the beginning of the 20th century, clinicians thought that catatonia was a form of schizophrenia. According to Max Fink, an American neurologist and psychiatrist known for his work on ECT, this last conviction was shared for about a century, in repeated editions of the official diagnostic classifications until the latest revision, the DSM-5. However, current scientific data reports a multitude of pathologies leading to catatonia: psychiatric, neurological, or iatrogenic causes, etc.[102] Thus, catatonia is nowadays considered as a specifier of a psychiatric disorder or associated to a general medical condition.[103] Of note, there currently is robust and consistent evidence of an improvement in catatonic symptoms after ECT[104]—which helps in understanding Ladislas von Meduna and Ugo Cerletti's positive results.

According to the study by Marshal M. Folstein et al.[105] in 1973, the presence of affective symptoms also may make the response to ECT more effective; however, depression and suicide often accompany schizophrenia. Emotional symptoms were not necessary for a response in patients with schizophrenia.[98,106]At the very end of the 20th century, the beginnings of a promising association started to appear. The interest in ECT combined with clozapine (ECT-CLZ) increased relatively quickly as nine case-reports, comprising 23 patients with TRS, appeared between 1992 and 1999. Twenty-one in 23 patients reportedly responded well to the ECT-clozapine combination.[107] However, the scientific evidence for potential efficacy in patients with schizophrenia remained very poor.

Practice of ECT in Schizophrenia in the XXIth Century

Ultra-Treatment-Resistant Schizophrenia

In 2011, according to Agid et al.[4], 20–33% of patients with schizophrenia were resistant to treatment. This proportion is stable when compared to the 1997 data.[5] In 2017, Oliver D. Howes et al. conducted a systematic review of randomized clinical trials (RCTs) of antipsychotics in TRS. They highlighted the heterogeneity of these definitions and therefore defined criteria, such as negative and cognitive symptoms, time to onset of resistance, and adherence to treatment. Oliver D. Howes et al., unlike John Kane et al. in 1988, did not set a limit of time, adding that "*duration of treatment resistance relates to treatment onset and not illness onset, otherwise it could be confounded by duration of untreated psychosis*".[108] Clozapine is now considered to be effective in schizophrenia which is resistant to first and second generation antipsychotics, especially with regard to positive symptoms, as well as the number and duration of hospitalizations.[109] However, 60% of TRS treated with clozapine failed to meet clinical response criteria.[6]

Therefore, Oliver D. Howes et al. (2017) brought up the concept of ultra-treatment-resistant schizophrenia (UTRS) or clozapine resistant schizophrenia, corresponding to resistance as they defined it and where clozapine was tried and failed. There must be at least two dosages of serum samples of clozapine, at least 1 week apart, and these dosages should be stable, and above a certain threshold (350 ng/ml). If a clozapine serum dosage is not available, Oliver D. Howes recommends a minimum dose of 500 mg/day if tolerability is good enough. There is no consensus on the duration of treatment with clozapine; Oliver D. Howes et al.[108] have proposed a trial of at least 3 months after reaching therapeutic plasma levels.

Clozapine Combined with ECT

Several recent recommendations and expert reviews have recognized the usefulness of ECT in schizophrenia.[31,43,110] Since the 2000s, studies tend to show the effectiveness of ECT-CLZ. The meta-analysis of John Lally et al.[2] is the first to study ECT-CLZ in TRS. The 2 RCTs that have shown favorable results for ECT-CLZ comparing to ECT alone or clozapine alone, are the Abbas Masoudzadeh and Alireza Khalilian[111] and by Georgios Petrides et al.[112] studies. This latest single-blind cross-over RCT study has drawn interest in ECT combined with antipsychotics, including clozapine, to treat UTRS (i.e., clozapine resistant). Fifty percent of the ECT-CLZ group showed a significant response. None of the patients in the clozapine alone group responded, while 47.4% responded after the cross-over.[112]

The meta-analysis by Gang Wang et al. (2018) joined the conclusions of reviews and other meta-analyses on the benefit of this treatment. For the first time, they included Chinese studies—which were often not used due to the language barrier—with a total of 18 randomized clinical trials. The limitations of these studies include the lack of control groups, few details on the blinded assessment, and a lack of information on the applicability to other racial or ethnic groups.[3]

Overall, in 2022, Randall T. Espinoza and Charles H. Kellner have gathered indications for ECT according to guidelines from major psychiatric associations.

Indications in schizophrenia are: TRS (APA), after 3 or 4 other treatments have failed (Royal Australian and New Zealand College of Psychiatrists, and World Federation of Societies of Biological Psychiatry) or not considered (Canadian Network for Mood and Anxiety Treatments).[113]

As the risk of relapse has been found to be high in the first 6 months after ECT in TRS,[114] some clinicians suggested that maintenance ECT sessions should be used.[115,116]

Some Current Data on the Tolerance of ECT

In 2017, a literature review estimated the death rate from ECT at 2.1 per 100,000 treatments based on studies covering 766,180 ECTs administered over 40 years in multiple countries (developed and developing). In this review, Nina Tørring et al. (2017) added: "*if we calculated a crude, hypothetical ECT-related yearly mortality rate for an individual receiving ECT three times per week throughout a year (although this many treatments in a year is unrealistically high), it would equal 0.003 (0.000021 deaths per treatment × 3 treatments per week × 52 weeks per year*)". The authors pointed out a decrease in this rate over time: 4 deaths per 100,000 ECT, in 1997.[117,118] According to authors, this decrease is mainly due to the improved safety of general anesthesia. Indeed, there has been an overall decrease in mortality associated with general anesthesia during surgical procedures. In addition, ECT can reduce mortality related to the pathologies themselves. Psychotic disorders associated with severe suicidal ideations, catatonia and/or delusions can also cause complications including death; treating them decreases mortality.

However, data on memory alterations have seen few significant changes. As we have seen, from the first years after the discovery of ECT, there was concern around ECT because of its cognitive impact. This concern is logical for maintenance ECT due to its long-term nature. Since the time of Emil Kraepelin's dementia praecox, the cognitive deficits associated with schizophrenia itself are well-known. Indeed, schizophrenia causes alterations in attention, memory, executive function and social cognition including recognition of facial expression of emotions and theory of mind.[119,120] These elements make it difficult to interpret the results of cognitive tolerance of ECT in schizophrenia as cognitive impairment could be due either to ECT or to schizophrenia itself.

Current Hypotheses Concerning the Pathophysiological Mechanism of Action of ECT in Schizophrenia

Among the possible mechanisms of action of ECT in schizophrenia—such as the antagonism between epilepsy and schizophrenia, or Ugo Cerletti's acroagonine and the synaptic remodeling and glial activation—another theory considers schizophrenia, like depression, to be a pro-inflammatory pathology. To illustrate, post-mortem data have shown an increase in microgliosis and an activation of astrocytes (macroglia cell). ECT might work by inhibiting glial activation in schizophrenia. In addition, this hypothesis is supported by the observation of a decrease in plasma levels of TNFα, a pro-inflammatory cytokine, after ECT, although the patients included also suffered from depression thus potentially confounding the results. This hypothesis could correspond with the idea put forth by French researchers mentioned above of a discharge of antibodies and antitoxins.[121]

Continued Stigma of ECT, and Barriers to Use

ECT remains one of the most stigmatized aspects of psychiatry. The stigmatization of ECT inherited the history of the representation of ECT. Today, the representation of ECT is primarily transmitted through media such as movies and television series. In 2016, Pascal Sienaert et al. analyzed 82 films and television series.[122] The first known appearance of ECT is in the movie *"The Snake Pit"* (1948). This film "*depicted (ECT) in a neutral, even positive way, and portrayed accurately for the era*".[123] Then, in the 1960s and 1970s, corresponding to the emergence of the antipsychiatry movement, ECT was depicted as a tool of torture and punishment. This is the case in "*Shock Treatment*" (1964) or "*Shock Corridor*" (1964) where the ECT represented is used without anesthesia. One of the most iconic of these representations is "*One Flew Over the Cuckoo's Nest*" (1975), adapted from Ken Kesey's 1962 book.[123] Of note, this film is still ranked 18 in the 2022 list of World's Best Movies on the Internet Movie Database (IMDb). In 2016, a study analyzed 39 scenes showing ECT from films and tv shows released between 2000 and 2014. This study showed that these representations don't reflect the way ECT is practiced nowadays.[124] In 2002, Garry Walter et al. showed how viewers' opinions of ECT (medical students) on ECT was influenced by watching scenes depicting this therapy.[125]

This stigma and reluctance regarding ECT are barriers to treatment. The lack of knowledge about ECT underlies this reluctance.[126] Certain information and psychoeducation programs could be effective in reducing stigma in patients who are treated with ECT.[67] In parallel, the antipsychiatry movement, such as the "Citizens Commission for Human Rights" (CCHR), founded in 1969 by Thomas Szasz (1920–2012) a Hungarian psychiatrist, still exists. In May 2020, on the home page of their website, ECT was referred to as "*Therapy or TORTURE, the truth about electroshock*" recalling David Cooper's position on ECT, which he saw as a weapon of deterrence and rebuke.[71]

Conclusion

Eugen Bleuler said "*The evolution of the concept of dementia praecox constitutes a good part of the evolution of theoretical psychiatry in general*".[10] In parallel, the

history of ECT in schizophrenia could be a model for understanding the evolution, or life trajectory, of a given treatment in psychiatry. Indeed, the discovery of ECT in schizophrenia was purely empirical, and this empiricism was gradually built upon until anti-psychotics, a specific treatment and a revolution at that time for schizophrenia, was created. Then, as may be the natural progression of any new treatment; new indications such as mood disorders were found, abuses took place such as intensive or regressive ECT, details of adverse effects were reported, historical events such as the WW2 were encountered, and the result greatly influenced the evolution of the practice of ECT in schizophrenia. Consequently, the reluctance and opposition to this treatment gradually built up and contributed to the stigma that still persists today. Knowledge of the history of this treatment, information and psychoeducation could be a tool to fight against this stigma.

Concurrently, TRS has become a major public health issue in recent years and ECT, after a long decline, has experienced renewed interest as a treatment for this disorder, particularly when associated with clozapine. This combination tends towards efficacy with good tolerance and reassuring current data. However, the problems of the past persist and point to a need for supervised use and more data. Though the methodology is difficult to establish, continued research is needed to understand the mechanisms of action of ECT in schizophrenia without aggravating the stigma. Despite these considerations, ECT remains an effective therapeutic option in treatment-resistant schizoprenia, as was the case when the effect of electrochocks was discovered 80 years earlier.

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