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A half-century of participant observation in psychiatry. Part III: psychopharmacology

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Summary

The third part of the triptych of my 50-year activity in psychiatry is about psychopharmacology. This way of treatment changed the picture of contemporary psychiatry. The introduction of neuroleptic (antipsychotic) drugs and tricyclic antidepressants in the 1950s resulted in a therapeutic revolution and contributed to the 'medicalization' of psychiatry and its therapeutic similarity to other non-surgical specialties. A discovery of prophylactic lithiumactivity in the 1960s initiated the mood-stabilizing drugs. During the last half-century, the most dynamic was the 1990s when most antipsychotic and antidepressant drugs of the so-called new generation were introduced. The twenty-first century marks a debut of next antidepressant and antipsychotic drugs, some of the latter having long-acting injectable preparations. An interestingevent was a demonstration of the antidepressant activity of ketamine. My research domain in psychopharmacology was lithium treatment of affective illnesses. Lithium makes the topic of many papers I authored, more than 150 of them are in the PubMed database. Many clinical and research aspects related to lithium administration have been reported as first in Polish literature and some are pioneering in the world. Recently, I wrote the book *Lithium – the amazing drug in psychiatry* which has also its English version. I have carried much research on antidepressant drugs, pharmacotherapy of treatment-resistant depression, and mood-stabilizing drugs for which I proposed a modern classification. I participated in European projects EUFEST and OPTIMISE on the optimization of using antipsychotic drugs in schizophrenia. I also performed much research on the antidepressant effect of ketamine and electroconvulsive therapy.

Key words: psychopharmacology

Psychopharmacology of the last half-century

The introduction of neuroleptic (antipsychotic) drugs [1] and tricyclic antidepressants [2] in the 1950s resulted in a therapeutic revolution in psychiatry and contributed to its 'medicalization' and therapeutic similarity to other non-surgical medical special-

ties. The beginning of my work in psychiatry, i.e., the 1970s was already witnessing a regular use by psychiatrists of neuroleptic drugs in schizophrenia and mania and tricyclic antidepressants in depression.

The mechanism of the therapeutic action of these drugs was interpreted in the 'neurotransmitter' context. The antipsychotic effect was perceived as a decrease in the activity of the dopaminergic system. It transpired later that it was mainly due to the dopaminergic D2 receptor blockade. In 1963, a psychopharmacologist from Gothenburg, Arvid Carlsson (1923–2018), was the first to demonstrate a connection between the dopaminergic system and antipsychotic drug activity [3]. For the whole of his research on dopamine, also in the context of neuroleptic drugs, he received the Nobel Prize in 2000. The mechanism of action of tricyclic antidepressants was viewed as enhancing noradrenergic and serotonergic neurotransmission due to blocking the reuptake of these neurotransmitters from the synaptic cleft. The eminent Polish psychopharmacologist, Jerzy Vetulani (1936–2017), working in the 1970s at the Vanderbilt University in Nashville, put forward a hypothesis that antidepressant activity is related to the adaptive reaction of noradrenergic receptors (so-called down-regulation of beta receptors) of neurons, appearing only after some time of antidepressant drug use [4].

At the turn of 1960s and 1970s, Spanish researchers initiated to use clomipramine, one of the tricyclic antidepressants having a predominant effect on the serotonergic system, in obsessive-compulsive disorder [5]. This research was led by Juan José López-Ibor Aliño (1941–2015), the latter President of the World Psychiatric Association (1999–2002). At the same time, a therapeutic activity of the first tricyclic antidepressant, imipramine, in panic disorder, was demonstrated. The main credit in this respect should be given to Donald Klein (1928–2019), named by some "the father of American psychopharmacology". He was also the author of a pathogenic concept of this disorder (called the suffocation false alarm theory) [6].

In 1949, an Australian psychiatrist, John Cade (1912–1980), showed therapeutic efficacy of lithium in manic states [7]. Whereas in the early 1960s, the reports appeared pointing to a possibility of preventing the recurrences of affective disorders by using lithium. They were authored by a British psychiatrist, Geoffrey (Toby) Hartigan (1917–1968), [8] and a Danish psychiatrist, Poul Christian Baastrup (1918–2002) [9]. In 1967, Danish psychiatrists, Poul Baastrup and Mogens Schou, summarized their experiences on longer administration of lithium (on average 6 years) in a large group of 88 patients with unipolar or bipolar mood disorder. The criterion for comparison was a duration of mood-disordered state (mania or depression). The results showed that the mean duration of mood disturbances per year of lithium treatment was more than six-fold shorter compared to before lithium. It followed with a great probability that lithium can exert a favorable prophylactic effect on the course of affective disorders [10].

Shortly after this, a very critical article on lithium research appeared in the prestigious medical journal *Lancet* having a characteristic title *Prophylactic lithium: Another therapeutic myth?* Its authors were British psychiatrists, Barry Blackwell and Michael

Shepherd. They expressed doubts about the results of Danish researchers and required studies using double-blind methodology [11].

This postulate was fulfilled in 1970–1973 when eight placebo-controlled studies on lithium prophylactic efficacy were performed in Denmark, Great Britain, and the USA. The analysis of all studies showed that the recurrences of mania or depression occurred on the average in 30% of patients who were given lithium and 70% of patients receiving placebo [12]. The first author of this analysis is Mogens Schou (1918–2005), the most outstanding lithium researcher in the second part of the 20th century. In the 1970s, the use of lithium for the prevention of recurrences of mood disorder began to rise, attaining its peak at the turn of the 1980s and 1990s.

The effect of lithium preventing affective recurrences is defined as mood-stabilizing. At the turn of the 1960s and 1970s, the reports appeared pointing on a possibility of mood-stabilizing action of anticonvulsant drugs such as valproate and carbamazepine. As to valproate, they were French authors led by Pierre Lambert [13], using valproic acid amide, and described its effect as "thymoregulatrice". Whereas the discovery of mood-stabilizing action of carbamazepine can be credited to Japanese researchers working under the leadership of eminent psychopharmacologist, Teruo Ōkuma (1926–2010) [14]. Coming back to lithium, in the early 1980s, Canadian authors were the first to demonstrate the augmentation of antidepressant drugs by lithium [15].

I have been witnessing a half-century of the history of clozapine, which began with turbulent events in Europe. The drug was introduced to psychiatry in the early 1970s by a Swiss company Wander, later named Sandoz. The observation of the clinical activity of clozapine contradicted the common view that the antipsychotic effect should entail, often severe, extrapyramidal symptoms. During clozapine treatment, only sialorrhea could be regarded as a parkinsonian symptom. Whereas in 1975, there was an epidemic of agranulocytosis in patients treated with clozapine, including 16 cases. Among them, eight patients died due to a secondary infection [16]. In connection with this, in the late 1970s, clozapine was withdrawn for several years and after this re-introduced, with the recommendation of close and frequent monitoring of the leukocyte system.

The beginning of the 1980s marks the inauguration of antidepressant drugs called selective serotonin reuptake inhibitors (SSRI). The basic mechanism of their action was inhibition of serotonin transporter, resulting in an increase of neurotransmitter level in the synaptic cleft of neurons in the central nervous system. Their elaboration was the aftermath of the serotonin concept of depression. The homeland of the SSRI is Sweden, thanks to the involvement of already mentioned eminent Gothenburg psychopharmacologist, Arvid Carlsson. The first drug of this series was zimelidine, which was shortly withdrawn due to the cases of Guillain-Barre syndrome reported with its use. On the other hand, fluvoxamine, initiated in1984, has been successfully used until now [17]. In the mid-1980s, a drug with dominant action on the dopaminergic system, bupropion, was introduced to the treatment of depression.

The late 1980s makes the startup of the SSRI drug, fluoxetine, with commercial name Prozac, in the USA. This can be regarded as a cultural event for the country.

A peculiar feature of fluoxetine was spectacular effect in mild depressions which were usually qualified for psychotherapeutic management. The presence of Prozac on the American market met a huge media response and the assessment of this phenomenon was often of extremely polarized character. In 1990, Prozac was hailed as the "Pill of the Year" in *Newsweek* magazine, whereas in the same year in its competitor, *Time*, the first clinical observations were quoted indicating that using the drug may increase the tendency to aggressive and suicidal behaviors.

The magic word 'Prozac' is included in the titles of numerous books. In 1993, a psychiatrist, Peter Kramer, wrote the book *Listening to Prozac*, in which he included a whole range of interesting observations. One of them concerned the possibility to achieve during therapy with fluoxetine desired changes of personality often requiring significantly longer psychotherapeutic conduct. Yet, Kramer expressed his concern over whether Prozac might initiate a field of so-called cosmetic psychopharmacology associated with modification of psychopathological symptoms of minimal severity [18]. In 1995, the book appeared in the Polish translation under the title *Wsłuchując się w Prozac. Przełom w psycho-farmakoterapii depresji* [19]. In subsequent years, books written by psychiatrists taking a skeptical approach appeared, such as *Talking Back to Prozac* [20] and *Beyond Prozac* [21]. The first of them discusses the drawbacks of fluoxetine, while the second considers the possibility of improving the serotonin system, not necessarily by using this drug. Another well-known book is *Prozac Nation*, written by Elizabeth Wurtzel. The author describes a struggle with depressive symptoms treated with Prozac, including in the context of her writing activity [22]. The book was a basis for the film made in 2001 under the same title. Finally, a crushing criticism of the drug is presented in the book *Prozac backlash. Overcoming the dangers of Prozac, Zoloft, Paxil, and other antidepressants with safe, effective alternatives* [23]. The book criticizes the use of SSRI drugs and highlights the dangers associated with it. Finally, the book *Better than Prozac* discusses a new generation of psychotropic drugs, elaborated by taking into account the achievements of neurobiology and molecular genetics [24].

Another important psychopharmacological event of the late 1980s in the USA was the introduction of clozapine to the treatment of schizophrenia. It did not result in such media response as in the case of fluoxetine, however, it can be said that in the USA clozapine experienced its second youth. Firstly, its therapeutic efficacy was confirmed in drug-resistant schizophrenia, i.e., the one in which the previously used drugs had not been effective. Furthermore, the observations of its activity in bipolar disorder (BD) and schizoaffective disorder brought about a conclusion that clozapine unquestionably has mood-stabilizing properties. It was suggested in the article from 1995, the first author of which was Carlos Zarate [25]. Therefore, clozapine became the first antipsychotic drug having recognized mood-stabilizing activity. Such properties were shortly demonstrated in subsequently introduced atypical antipsychotic drugs such as olanzapine and quetiapine.

The 1990s can be recognized as the golden age of psychopharmacology. During this time, a majority of new antidepressant drugs, mainly SSRI, were introduced as

well as the novel atypical neuroleptic drugs. It was also a period of great prosperity of pharmaceutical companies that were promoting these drugs. It was even associated with a significant influence of these companies on the direction of scientific research in psychiatry.

Besides already mentioned fluvoxamine and fluoxetine, three SSRI antidepressants (sertraline, paroxetine, citalopram) were introduced in the first half of the 1990s, and escitalopram – in 2001. These drugs have been the most frequently used group of anti-depressants until now. Apart from employing in depression, they have been widely used in various anxiety conditions such as obsessive-compulsive disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder. In the mid-1990s, venlafaxine and mirtazapine appeared, being the 'double-action' drugs acting on both serotonergic and noradrenergic systems, similar to tricyclic antidepressants.

After thirty years of neurotransmitter concepts of the therapeutic mechanisms of antidepressant drugs, at the turn of centuries the attempts were made to search for other mechanisms related to their therapeutic efficacy. A proposal was put forward for the regulation of inflammatory activity and/or hypothalamic-pituitary-adrenal axis by antidepressant drugs. However, the most important was probably a demonstration that antidepressant drugs improve neuroplasticity and stimulate neurogenesis. Some authors even postulated that stimulation of neurogenesis is an essential condition for the antidepressant effect [26].

In the 1990s, the new important properties of lithium such as antisuicidal and antiviral activity were discovered. The journal *Lithium* also appeared, operating in 1990–1994. Whereas a British researcher, Joanne Moncrieff, set herself the goal of discrediting lithium studies from 1970–1973 and undermining the evidence of the prophylactic effect of long-term lithium use [27]. However, most psychiatrists experienced in lithium treatment were not willing to accept her arguments. In 1999, on the 50th anniversary of introducing lithium to modern psychiatry, a Canadian psychiatrist of Czech origin, Paul Grof, presented a concept of the "excellent lithium responders", i.e., patients with BD in whom lithium monotherapy brings upon a complete recovery from the illness [28].

At the turn of the 20th and 21st century, there was a significant increase in valproate use with a concomitant decrease in lithium use both in Europe and the USA. In 2010, European researchers published the results of the BALANCE project (***B**ipolar **A**ffective Disorder **L**ithium/**AN**ti**C**onvulsant **E**valuation*), in which the prophylactic efficacy of monotherapy with valproate and lithium as well as combination of these drugs was compared. Three hundred-thirty patients with BD (110 in each group) were followed up for 2 years. The recurrence was observed in 54% of patients receiving drug combination, 59% of patients receiving lithium and 69% of those receiving valproate, which may indicate better efficacy of lithium monotherapy compared with valproate and the best effect of drug combination [29]. In the second decade of the 21st century, the neuroprotective and 'antidementia' activity of lithium was recognized in experimental, epidemiological and clinical studies [30].

In the 21st century, a few new psychotropic drugs have been introduced, however, many attempts were made to verify and optimize the application of the previous ones. The most important antidepressant drugs implemented in this time include duloxetine (2004), agomelatine (2009) and vortioxetine (2013). Each of them, when introduced to the market, was accompanied by attractive company data on therapeutic specificity for given symptoms of depression, and exceptional pharmacological mechanism. Thus, duloxetine was promoted for its potential pain-killing activity, agomelatine – for effect on biological rhythm disturbances and sleep, and vortioxetine – on cognitive functions. However, only agomelatine was certain pharmacological *novum* associated with its effect on melatonergic receptors M1 and M2.

The greatest repercussions to clinical practice in the area of antidepressant drugs came from the American project STAR*D (Sequenced Treatment Alternatives to Relieve Depression), including more than 3,500 patients. It was found that the percentages of remission after the first, second, third, and forth antidepressant treatment were 36,8%, 30,6%, 13,7%, and 13,0%, respectively. Compared to baseline, remission was obtained by 67% of patients. Therefore, even after several antidepressant treatments, a significant therapeutic intervention was necessary for 1/3 of patients [31].

The results of STAR*D re-emphasized the issue of so-called drug-resistant depression, usually perceived as a depression in which at least two antidepressant treatment did not bring a significant improvement. In psychopharmacology, this issue has been functioning since the 1980s. During this time, a number of effective methods for enhancing the therapeutic effect of antidepressants have been proposed such as a combination of antidepressants, adding thyroid hormones, or other substances, especially mood-stabilizing drugs. Among the latter, the first experiences were reported with lithium [15] and, in my opinion, augmentation of antidepressant drugs by lithium can be a second indication for using lithium, after the prevention of mood recurrences. In recent years, the potentiation of antidepressants with atypical antipsychotics has become increasingly popular. Physical methods have been also used, the most important is electroconvulsive therapy, as well as stimulatory techniques such as transcranial magnetic stimulation, vagus nerve stimulation and deep brain stimulation.

Important for discussion on depression were the years 2009–2010 when three books on this topic appeared. In the first of them, *The emperor's new drugs. Exploding the antidepressant myth*, Irving Kirsch undermines the results of studies on antidepressant drugs. According to his meta-analysis, in the majority of them, no advantage of antidepressants over placebo was demonstrated [32]. In the book *Manufacturing depression. The secret history of a modern disease*, Gary Greenberg points to the role of recognizing depression and the use of antidepressant drugs as the main factor of the social success of psychiatry in recent years [33]. Lastly, in the book *Anatomy of an epidemics. Magic bullets, psychiatric drugs, and the astonishing rise of mental illness in America*", Robert Whitaker suggests that the development of psychiatric diagnostics and psychopharmacology resulted in a doubling in a number of persons

with psychiatric disturbances in the USA in recent 20 years [34]. All these publications discredited the usefulness of using antidepressant drugs, however, not giving any reasonable alternative. Eminent European psychiatrists commented on these books indicating that they do not represent *bona fide* scientific knowledge and cause disinformation of public opinion [35].

In the field of antipsychotic drugs, some events can be noted in the 21st century. The drugs with specific action on the dopaminergic receptors appeared such as aripiprazole, brexiprazole, cariprazine, and lurasidone, sometimes called third-generation antipsychotics. For some, a mood-stabilizing activity was demonstrated (aripiprazole) as well as usefulness in depression in the course of BD (lurasidone, cariprazine). A number of atypical antipsychotics became available in long-acting injectable (LAI) form (risperidone, olanzapine, aripiprazole, paliperidone). There has also been a growing tendency to recommend the LAI in patients with schizophrenia, pointing to their purposefulness in the early period of the illness, even after the first psychotic episode. However, the views on the mechanisms of antipsychotic effect, as related to dopaminergic D2 receptor blockade, have not changed. The antipsychotic activity of an agonist of glutamatergic metabotropic receptors 2/3 has not been eventually confirmed [36]. The therapeutic action of pimavanserin, an inverse agonist of serotonergic receptor 5-HT2A was demonstrated in Parkinson's disease psychosis, however, the attempts for using the drug in schizophrenia are on very early stage [37].

In the first decade of the 21st century, two big projects comparing the efficacy of antipsychotic drugs in schizophrenia were performed on both sides of the Atlantic. The study carried out in the USA had the acronym CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness), and the European project was called EUFEST (European First Episode Schizophrenia Trial). In the first one, olanzapine, quetiapine, risperidone, and ziprasidone were compared with perphenazine in 1,493 chronic schizophrenia patients. 26% of patients completed the eighteen-month study. In the second study, olanzapine, quetiapine, amisulpride, and ziprasidone were compared with small doses of haloperidol in 498 patients with the first episode of schizophrenia. The one-year study was completed by 59% of patients. In both projects, olanzapine was found to be the most effective. In the EUFEST, a similar effect to olanzapine for general functioning was obtained by amisulpride. In CATIE, no differences between atypical antipsychotics and perphenazine were found, while in EUFEST, haloperidol was inferior to atypical antipsychotics as far as the remaining in the treatment and side effect were concerned [38, 39].

The last quarter of the century has confirmed the importance of clozapine as a gold standard for drug-resistant schizophrenia which has remained valid despite the introduction of new antipsychotic drugs. In the last years, more data has been accumulated on the efficacy of clozapine in severe and treatment-resistant schizoaffective disorder and BD. In patients with schizophrenia, it has been found that clozapine exerts antisuicidal activity and reduces the intake of psychoactive substances, especially psychostimulant ones. There has been a recommendation for using clozapine on earlier stages of

schizophrenia treatment. According to the European project OPTIMISE, clozapine can be introduced after two ineffective courses of treatment with antipsychotic drugs [40].

Despite many genetic and biochemical studies pointing to a significant role of the glutamatergic system in the pathogenesis of schizophrenia, the use of drugs influencing this system is scanty. The most data concern drugs acting on the glycine site of the glutamatergic receptor NMDA, used for the augmentation of antipsychotic drugs in the treatment of negative symptoms. [41].

The role of the glutamatergic system in psychiatric treatment received significant support when in 2006 appeared a paper of which the first author was Carlos Zarate, already mentioned as showing a mood-stabilizing effect of clozapine. Using a double-blind method with placebo, it was found that a single infusion of ketamine, a glutamatergic NMDA receptor antagonist, 0.5 mg/kg of body mass, results in rapid improvement, and even complete remission of depressive symptoms. Among patients with drug-resistant depression, the remission occurred in 29% and in 71% there was a significant reduction as early as 24 hours following infusion [42]. The same research group reported also the favorable effect of ketamine infusion as an add-on to mood-stabilizing drugs (lithium or valproate) in depression in the course of BD [43].

A demonstration of the antidepressant effect of ketamine made one of the most interesting achievements of the 21st century's psychopharmacology. Besides of pointing to a pathogenic role of the glutamatergic system, it undermined a view of a necessary 'delay' in the action of antidepressant drugs. In many studies, it was also found that ketamine infusion results in a rapid reduction of suicidal thoughts. To sustain the effect of ketamine, multiple infusions were also conducted and a number of specialist centers came into existence (mostly in the USA and Canada) to perform these procedures. In recent years, an important step in ketamine treatment was the elaboration of the drug as a nasal spray.

In my 50-year work in psychiatry, I have witnessed many distortions concerning the use of benzodiazepines in psychiatry and other fields of medicine. In the 1970s, these drugs were among the most prescribed in the world due to their usefulness in the treatment of anxiety states but also insomnia, restlessness, muscle tension, alcohol withdrawal syndrome, and premedication to surgical procedures. After introducing the SSRI drugs and promoting them in the treatment of anxiety disorders, a possible addicting potential of benzodiazepines was greatly exaggerated, and their use was actively discouraged. The example of terminological hypocrisy was naming a state of benzodiazepine cessation 'withdrawal syndrome', and that of SSRI – 'discontinuation syndrome'. The indoctrination of physicians and patients was so powerful that even nowadays some patients are more afraid of benzodiazepine dependence than suffering from the symptoms the drugs could effectively alleviate. However, the experienced clinical psychiatrists know that benzodiazepine dependence occurs mainly in patients vulnerable to abusing and depending on various substances and that in most subjects benzodiazepines can be safely administered even for a long time without the risk of dependence [44].

When beginning my psychiatric activity, electroconvulsive therapy (ECT) was more than 30 years old and began its new and safe history associated with general anesthesia and muscle relaxation. However, I myself witnessed several ECT treatments without anesthesia and relaxation, which always makes a dramatic impression. In 1975, the release of the movie *One flew over the cuckoo's nest* occurred, where the main character was given ECT in the old version. This gave the weapon for many years to the opponents of such therapy. Nowadays, ECT makes the main method of physical treatments in psychiatry. The compelling evidence has been accumulated for its efficacy in drug-resistant depression in unipolar and bipolar disorder and also in schizophrenia with suboptimal effect of clozapine. However, there have still been publications written by people who never saw the treatment with their own eyes but make a demand to immediately suspend the procedure [45].

Fortunately, in the second decade of the 21st century, the publications on the lack of efficacy of ECT as well as antidepressants are regarded by experienced clinical psychiatrists as similar to those of antivaccination movement or 'flat-earthers'.

Research contribution of the article's author to psychopharmacology

My research domain in psychopharmacology has been lithium treatment of affective disorders. This resulted in more than 150 articles on lithium included in the PubMed database and recently released book *Lit – niezwykły lek w psychiatrii* [46], with English edition *Lithium – the amazing drug in psychiatry* [47]. Many clinical and research aspects related to lithium administration have been reported as first in the Polish literature and some are pioneering in the world.

As early as in 1970, in the Psychiatric Clinic of Medical Academy in Poznan, it became possible to estimate lithium concentration in body fluids (blood and urine) as well as in red blood cells. The administration of lithium carbonate to patients with affective disorders for both therapeutic and prophylactic purposes was then started. A female patient in whom lithium was started in 1970 observes in this year a half-century of such treatment [48]. In 1972, the first publications on lithium therapy coming from Poznan center appeared. They concerned, among others, lithium intoxication [49] and a case of diabetes insipidus occurring during lithium administration [50]. In 1974, the results of the therapeutic effects of lithium in endogenous depression were published [51].

The years 1976–1977 mark my stay at the Department of Psychiatry, University of Pennsylvania, Philadelphia as the NIH Fogarty (John E. Fogarty International Center) research fellow. I was a member of the research group which as one of the first in the world identified the mechanism of transmembrane lithium transport on the red blood cell model. It transpired that the main mechanism transporting lithium out of the cell is the lithium-sodium countertransport. The activity of this mechanism determines the magnitude of the red blood cell lithium index [52]. In BD, the activity of the lithium-sodium countertransport is decreased, resulting in a higher red blood cell lithium index in these patients [53].

In 1980, we published in *Psychiatria Polska* an evaluation of a prophylactic lithium effect in 61 patients in which lithium was used for an average of 5 years. All these subjects had at least two affective episodes in the 2 years prior to lithium treatment. The so-called mirror image method was employed comparing the course of illness on lithium with an analogical period before lithium. The analysis showed that during lithium administration the number of recurrences decreased by 71%, and the number of hospitalizations by 72%. In 44% of patients, no recurrences were observed during lithium treatment [54].

The first Polish study on the augmentation of antidepressant drugs by lithium was published in 1987. The study covered ten depressive patients treated in the Psychiatric Clinic, Medical Academy in Bydgoszcz, including 7 patients with unipolar affective disorder in whom previous results of antidepressant treatment (mostly with tricyclic antidepressants) were unsatisfactory. Following lithium addition, in all of them an improvement was observed and in six patients, a complete remission occurred after four weeks [55]. Five years later, the same authors studied 51 patients and showed that the potentiating effect of lithium assessed after 28 days was better in bipolar than unipolar depression, in patients with lower symptom severity before lithium and in those with rapid significant improvement (within a few days after lithium introduction) [56].

In 1991, the results of the Polish-American study concerning the occurrence of labial herpes in patients receiving lithium for prophylactic purposes were presented in the journal *Lithium*. From the American side, the study was coordinated by Jay Amsterdam, director of the Depression Research Unit, Department of Psychiatry, University of Pennsylvania in Philadelphia. Polish group included 69 patients (24 men, 45 women) receiving lithium for an average of 8 years at the outpatient clinic, Department of Psychiatry in Poznan. Twenty-eight of them had recurrent labial herpes. During lithium administration, in 13 patients (46%) labial recurrences disappeared, in seven the frequency of recurrences decreased, in six it was the same and in two – increased. Better effect of lithium on labial recurrences was observed in patients with serum lithium concentration higher than 0.65 mmol/l and red blood cell lithium concentration higher than 0.35 mmol/l.

American population covered two groups of 52 subjects, matched for gender (21 male and 31 female subjects in each group), age (mean 45 years), and duration of pharmacological treatment (mean 5 years). The first group, including mostly patients with BD, received lithium, while in the second group, patients with recurrent depression were given antidepressant drugs. It turned out that the frequency of labial herpes recurrences compared with a five-year period before pharmacological treatment decreased in the lithium group by 73%, while no significant difference was observed in the antidepressant group (decrease by 8%) [57].

In the same year, the results of a joint study with the Department of Dermatology, Medical Academy in Bydgoszcz, appeared where excellent results of using lithium succinate ointment for topical treatment of skin (mostly labial) herpes were reported [58].

In 2001, an estimation of a percentage of so-called excellent lithium responders was made in Poznan center. A group of patients among whom lithium treatment was started in the 1970s was compared with a group in which lithium was introduced in the 1980s. Each group included 79 patients who were observed for 10 years. The percentage of excellent lithium responders, i.e., patients who completed a 10-year observation without the recurrence of the illness was similar in both groups and amounted to 34% and 27%, respectively [59].

In collaboration with the Department of Psychiatric Genetics, the molecular-genetic studies were performed showing a connection between lithium prophylactic efficacy and the polymorphisms of various genes. The association with some genes was described as the first time in the world. This was the case with the *BDNF* (brain-derived neurotrophic factor) gene [60], *DRD1* (dopaminergic D1 receptor) gene [61], biological clock gene [62], and stress axis genes [63, 64]. The association was also found between a polymorphism of the *GSK-3β* (glycogen synthase kinase 3-beta) gene and lithium-induced kidney changes [65]. In 2009, I was one of the founders of the International Consortium on Lithium Genetics (ConLiGen) [66], and patients from Poznan centers were included in the genome-wide association study prophylaxis [67]. In 2013, in the journal *Drugs*, I summarized pharmacogenetic data on mood-stabilizing drugs, with special consideration of lithium [68]. In 2016, together with Professor Alessandro Serretti from Bologna, I edited a book on pharmacogenetic factors associated with drugs used in schizophrenia, depression and BD [69].

In the Department of Adult Psychiatry, Poznan University of Medical Sciences, the effect of lithium on cognitive functions was also investigated. In 30 patients with BD showing a various degrees of lithium prophylactic efficacy, *the Wisconsin Card Sorting Test* was performed. Thirty healthy subjects matched by gender and age served as the control group. The subjects exhibiting poorer prophylactic effect of lithium obtained poorer results compared with those showing good prophylactic outcomes and with healthy subjects [70]. The aim of another study was a neuropsychological assessment and measurement of serum BDNF in 60 lithium-treated patients, among which thirteen met the criteria of excellent lithium responders. The CANTAB battery tests measuring attention and spatial working memory were used. The results obtained by excellent lithium responders were significantly better than those obtained by remaining lithium-treated patients and similar to those obtained by healthy control subjects. Interestingly, also serum BDNF in excellent lithium responders was comparable to healthy controls [71]. In 2016, I published a review paper on the effect of lithium on neurocognitive functions [72].

In the second decade of the 21st century, an attempt was made to assess the effect of long-term lithium treatment on kidney and thyroid function in patients of Poznan center. Kidney function was estimated in 80 patients with BD (26 men, 54 women), aged 60±11 years, receiving lithium for 5–39 (mean 16) years. The glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 was found in 38% of men and 16% of women, and urine specific gravity equal or less than 1.005 – in 21% of men and 14% women [73].

A five-year follow-up was also performed in four patients, aged 67–69 years, with mean duration of lithium treatment 27±9 years, with the excellent prophylactic effect of lithium, in whom the GFR was lower than 50 ml/min/1.73 m^2. In three patients with initial GFR 47–48 ml/min/1.73 m^2, kidney parameters such as GFR, serum creatinine and urine specific gravity did not change significantly, therefore a continuation of lithium as previously was recommended with a yearly check-up of kidney function. In a patient with GFR 32 ml/min/1.73 m^2, the GFR decreased by 14%, and serum creatinine increased by10%. In this patient, the dose of lithium was reduced by half, and frequent nephrological consultations were suggested [74].

For the assessment of thyroid function and morphology, 98 patients with BD receiving lithium for at least three years (mean 19±10 years) were compared with 39 patients with BD not receiving lithium, matched for gender, age and duration of the illness. In patients receiving lithium, TSH concentration and thyroid volume were significantly higher. Whereas the frequency of hypothyroidism was similar in both groups (24% vs. 18%), 3–4 fold more frequent in women than in men. It transpires from our as well as from other studies that the symptoms of hypothyroidism usually appear in the early stage of lithium treatment, also more frequently in persons with a family history of thyroid dysfunction. In patients receiving lithium, the frequency of goiter was not different in women and men (37% vs. 41%) [75]. A comparison of anti-thyroid antibodies did not show differences between groups [76]. The parameters of thyroid function were similar in patients receiving lithium for 10–20 years and more than 20 years [77].

In collaboration with the Szczecin center, we investigated the effect of long-term lithium treatment on the very small embryonic-like stem cells (VSELs) and the mRNA expression of neuronal and glial markers in peripheral blood of BD patients with long duration of the illness. Patients not receiving lithium had a significantly higher number of VSELs, correlated with the duration of the illness, and higher expression of the markers compared with healthy persons, matched for gender and age. This could indicate an intensification of regenerative and inflammatory processes during the course of BD. Whereas in lithium-treated patients, the number of VSELs was similar to that of healthy persons and was negatively correlated with the duration of lithium treatment and serum lithium concentration. Also, the expression of neural and glial markers was in most cases comparable to control subjects. It can suggest that lithium treatment can alleviate the exaggerated regenerative and inflammatory processes in BD [78].

In 2016, two male and three female patients, aged 64–79 years, receiving lithium with very good effect for more than 40 years were described. In four of them, lithium concentration was kept in the range of 0.60–0.65 mmol/l, and in one – 0.7–0.8 mmol/l. Both men had symptoms of nephropathy, however, without a significant progression. One woman had Hashimoto's disease and was taking thyroxine. All patients had cognitive functions on a similar level as in healthy persons of comparable age. They all were professionally active until 55–65 years of age and their family and social functioning was adequate. The beginning of lithium treatment usually was made within

the first three years of the illness [79]. Recently, one of these persons was presented with throughout successful 50 years of lithium prophylaxis [48].

In the field of the BD pharmacotherapy, I was a co-author of one of the first in the world report on the antimanic activity of clozapine [80]. Whereas in 2007, I proposed a classification of mood-stabilizing drugs into first – and second-generation, based on the chronology of their introduction into psychiatric armamentarium [81]. The first generation, besides lithium, included valproate and carbamazepine; their mood-stabilized activity was demonstrated in the 1970s and 1980s. The second generation started with the article of Zarate et al. in 1995 [25], and inclusion criteria have been consecutively met by clozapine, olanzapine, quetiapine, lamotrigine, aripiprazole, and risperidone [82].

Together with Anna Służewska, the studies were carried out on the anti-inflammatory effect of antidepressants. The article from 1995, with Anna as the first author, has obtained 260 citations in the Scopus database [83]. Following the previous research on the potentiation of antidepressants by lithium [55, 56], the studies in the Department of Adult Psychiatry were performed on such augmentation by carbamazepine [84], lamotrigine [85], thyroxine [86], omega-3fatty acids [87], and recently, by sleep deprivation with sleep phase advance [88].

In 2002–2006, I was a national coordinator of the European study on the first episode of schizophrenia, EUFEST, described previously in this paper. Thirteen European countries and Israel participated in the project, including four centers from Poland (Lublin, Lodz, Poznan, Warsaw). In Poland, 94 patients were recruited from a total of 498 patients in the project (19.3%). In 2011–2016, the Department of Adult Psychiatry in Poznan, as the only center from Poland, participated in the international project OPTIMISE concerning the optimization of antipsychotic drugs in the first episode of schizophrenia [40].

The application of ketamine infusions in the Department of Adult Psychiatry began in 2011. The most recent report includes 53 patients (40 women, 13 men), aged 22–81 (mean 47±13 years), with a depressive episode in the course of BD. All patients had received at least one first – (lithium, valproate, carbamazepine) or second-generation mood-stabilizer (clozapine, quetiapine, olanzapine, aripiprazole) for a minimum one year. Anti-depressant drugs that did not bring an improvement were discontinued at least 7 days before infusion of ketamine, 0.5 mg/kg foir40 min. The mean initial severity of depression assessed by the Hamilton scale was 23±5 points. This result decreased to 16±7 after 24 hours, to 13±7on the 7^{th} day, and 12±8 points after two weeks following the infusion. On the 7^{th} day after the infusion, twenty-seven patients (51%) achieved clinical improvement, defined as the reduction by $\geq$ 50% points in the Hamilton scale, and remission, defined as the severity of depression $\leq$ 7 points in the Hamilton scale, was obtained by 26% of patients [89]. In the studies carried on in Poznan, a connection between the efficacy of ketamine and changes in BDNF [90] as well as with vitamin B_{12} levels was found [91]. We also observed a rapid improvement of cognitive functions after ketamine, which was not correlated with the amelioration

of depression [92]. As the only non-American author, I was invited by Carlos Zarate to write a chapter in the book *Ketamine for treatment-resistant depression. The first decade of progress* [93].

During my work in psychiatry, I have witnessed the withdrawals of several efficacious psychiatric drugs of the so-called old generation by Polish pharmaceutical companies. A great detriment was the cessation of producing fluphenazine decanoate (Polish preparation Mirenil prolongatum), the first in the history antipsychotic drug used in long-acting injections. It is not known what was the reason for the withdrawal of the first tricyclic antidepressant, imipramine, as well as an antipsychotic, perphenazine, available also in long-acting injections. As mentioned previously, in the CATIE study, perphenazine compared favorably with atypical antipsychotics.

In the second decade of the 21st century, many studies were performed in the Department of Adult Psychiatry on the clinical efficacy and the mechanism of electroconvulsive therapy (ECT). Using ECT, very good results were observed in drug-resistant depression, both unipolar and bipolar one [94]. In the research on the effect of ECT on cognitive functions, no significant effect was found on various kinds of memory and executive functions [95], except for impairment of the autobiographical memory [96]. Using ketamine as an anesthetic drug in every other ECT session, compared with thiopental employed in each session, better antidepressant effects and worse results in verbal memory were found [97]. Recently, the Department of Adult Psychiatry in Poznan joined the International Consortium on the Genetics of Electroconvulsive Therapy and Severe Depressive Disorders (Gen-ECT-ic) [98].

As a clinical psychiatrist working for half a century, I can testify that practicing prudent and perfect psychopharmacology has enabled me to bring effective help to thousands of patients with psychiatric disorders. This was the source of my great personal gratification. An asset of psychopharmacology is that the results of studies in any place in the world, published in scientific journals or presented during scientific conferences, can be rapidly implemented into clinical practice. Certainly, psychopharmacological treatment should be conducted in the context of a given patient and his/her family, and with adequate psychotherapeutic support. In most patients, supportive psychotherapy, focused on their specific personality features and life situation can be usually sufficient.

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