

# 40 Years History of Lithium Treatment in Bipolar Disorder in Turkey

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## ÖZET:

Türkiye’de iki uçlu bozuklukta Lityum kullanılmalarının 40 yıllık öyküsü

İki Uçlu Mizaç Bozukluğu’nun klasik tedavi seçeneği olarak lityum’un kullanılış tarihçesi Türkiye’de de dünyadaki kullanımına paralel seyretmiştir. Bu duruma, FDA (US Food & Drug Administration) tarafından lityumun sürdürüm tedavisinde onaylanması sürecinde etkili olan çalışmaları yapan Dr. Mogens Schou’nun Türkiye’de konferanslar vermek yolu ile gösterdiği etkin çabanın katkısı olduğunu düşünmekteyiz. Bu editoryal yazıda Lityum’un klinik uygulamada rutin kullanımı ile ilgili öncül klinik uygulamaları başlattığını ifade eden Dr. Niyazi Uygur’la yapılan biyografik çalışmadan alıntılar da bulunmaktadır. Bu çalışma vesilesi ile Türkiye’de yapılmış lityum kullanımı ile ilgili kaynakça da ulaşılabilen en eski tarihlere kadar taranmış ve okuyucuya sunulmuştur. Ulaştığımız literatür bilgileri, ülkemizde de 1970’li yıllarda lityum kullanmaya başlamış ve halen tedavisini sürdüren iki uçlu mizaç bozukluğu hastalarının bile mevcudiyetine işaret etmektedir. Türk psikiyatrisi pek çok alanında olduğu gibi, iki uçlu mizaç bozukluğu tedavisinde de lityum devrimine çok erkenden katılarak öncü rolünü sergilemiştir.

**Anahtar sözcükler:** Lityum, iki uçlu mizaç bozukluğu, tarihçe, Türkiye, Mogens Schou

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## ABSTRACT:

40 years history of Lithium treatment in bipolar disorder in Turkey

The historical background of using lithium as a choice of classical treatment of bipolar disorder in Turkey had a trend parallel to that of the world. We think that what contributed to this end was the successful efforts of Dr. Mogens Schou in giving lectures on the issue in Turkey. Dr. Schou was the one who conducted the trials which contributed to the process of approving lithium as a maintenance medication by the FDA (US Food & Drug Administration). This editorial article contains quotations from the biographic study made with Dr. Niyazi Uygur who stated that he had started the initial trials relating to the routine use of lithium in clinical practices. Owing to this study, the bibliography on the use of lithium in Turkey was screened back to the earliest dates and presented to the reader. The information in the literature we could reach indicates that lithium started to be used in 1970s also in Turkey and there still are bipolar patients whose treatment is in progress at present. As in many areas, Turkish Psychiatry has joined the lithium (in treatment of bipolar disorder) revolution at a very early stage and demonstrated its leading role.

**Key words:** Lithium, bipolar disorders, historical background, Turkey, Mogens Schou

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## Bağıntı beyanı:

M.N., N.K.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

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Dear Readers,

In this edition, we wanted to address to you with an editorial about the historical background of lithium medication which achieved an unrivaled privilege in treating Bipolar Disorder in Turkey. As known by many, after its initial discovery as a mineral, lithium was introduced to medical practices in the world in the 19<sup>th</sup> Century when it was used by Garrod in treating gout in 1859 (1). After a long period of silence lasting for 90 years following this date, Australia based research on its use in bipolar disorder was carried out by Dr. John Cade. Dr. Cade saw in 1949 that convulsion and agitation symptoms of the guinea pigs poisoned by urea could be prevented by

lithium and with the inspiration he received from it, he wanted to try lithium in patients with excitation (2). The studies made by Mogens Schou and Poul Christian Baastrup on lithium resulted in the FDA approving its use in acute mania in 1970 and in maintenance treatment in 1974 (3,4). The world-wide developments of this long adventure related to the use of lithium salts in bipolar disorder are explained in a quite informative way in the article of Dr. Şengül and associates titled “Story of Lithium in its Fifty-fifth Year” (5). Interestingly enough, however, the information on the introduction of lithium salts in Turkey was not mentioned either in this article or any other written source.

Recently, in his electronic mail sent to the editor of our journal Prof. Dr. Haluk A. Savaş, Dr. Niyazi Uygur says:

*“Dear Haluk,*

*First let me congratulate you and your colleagues for your new endeavor, the (JMOOD) journal. I am sure Turkish Psychiatry family will have a quality journal owing to your labor and efforts as long as no compromise is made or no deviation occurs from the publication principles.*

*For years, I could not make my colleagues who are in an academic chauvinism accept that I had started the first lithium administration in treating bipolar disorders in Turkey in 1971. They overlooked all my assertions.*

*I am sending you a section from my personal background so that you can disclose this historical truth:*

*In 1971, I listened to the conference of Prof. Mogens Schou from Denmark, who pioneered in introducing lithium salts for psychiatric treatment, and then I personally met him and immediately started the first lithium treatment in Turkey [There was no clinical application in Turkey except for Dr. Rafet Saygılı's (associate professor) thesis based on a 1-month application].*

*After I became a specialist and began working as a chief resident in 1974, I presented my practices over a period of 5 years in a series of three seminars where I symmetrically evaluated pre- and post-Lithium (2,3) conditions of each patient. During my presentations, Lider Atasev asked the question “Niyazi, the therapeutic limit and toxic limit of this medication are very close to each other, are you not afraid to poison the patients?”, which I never forget. At that time, this question was right and relevant, because there was not any photometer to directly measure the lithium plasma level. I was sending the blood samples of wealthy patients to London. I was sending the blood samples of patients with limited means to Dr. Chestakov, the biochemistry specialist of Pasteur French Hospital. He was measuring the Lithium level using an indirect method. Many of our colleagues who were aware of Lithium were administering lithium capsules as a single dose as if they were sedatives.*

*I also have the video of three of my patients who have been taking lithium since 1972. This video, which was shot in accordance with the ethical rules, shows my*

*patient from Gaziantep visiting me together with his wife due to my health problems; he said he would not hesitate to talk to anybody who wishes face-to-face if necessary. This video was played by Dr. Timuçin Oral to the participants in the 15th Spring Symposium.*

*It was quite difficult in those years to find a journal in Turkish and to cue for a publication. When you look at the April and May 1978 editions of the “Tıp Dünyası” journal and the references herein, you cannot see any publication on clinical applications besides mine. Those who started 10 years after me are trying to claim it now. I hope you will approach the matter in terms of the ethics of science and publication and spare a place for this mail of mine in your journal. I repeat my wishes of success and extend my regards and greetings.*

*P.S.: I will send the 16-17 minute video attached if I can manage. I can also give the person's telephone number for you to meet him if he agrees.”*

Upon this mail, the issue also attracted our attention as the editorial board of JMOOD. We take pride in the fact that lithium started to be used in bipolar disorder in our country in 1970s almost concurrently with the western world. It shows how closely Turkish Psychiatry really monitors bipolar disorders and their treatment. Therefore, these thoughts and feelings directed us to examine the issue and an attempt was made by Dr. Melike Nebioğlu and Dr. Numan Konuk to have a face-to-face interview with Dr. Niyazi Uygur and to attain the early literature in Turkish and the historical information on the issue from their source.



Assoc. Prof. Numan Konuk and Dr. Niyazi Uygur (date: May 10, 2011)

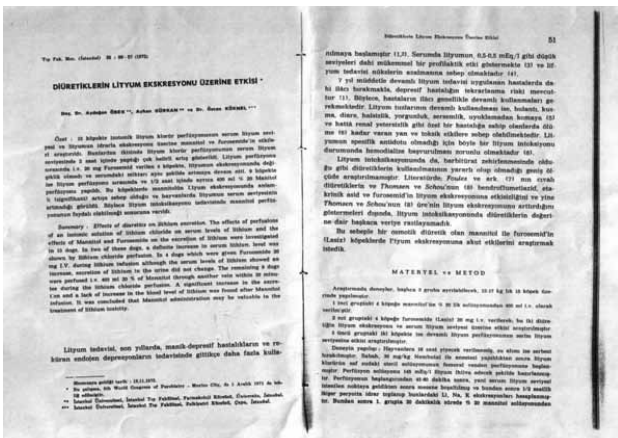


Dr. Melike Nebioğlu and Dr. Niyazi Uygur (date: May 10, 2011)

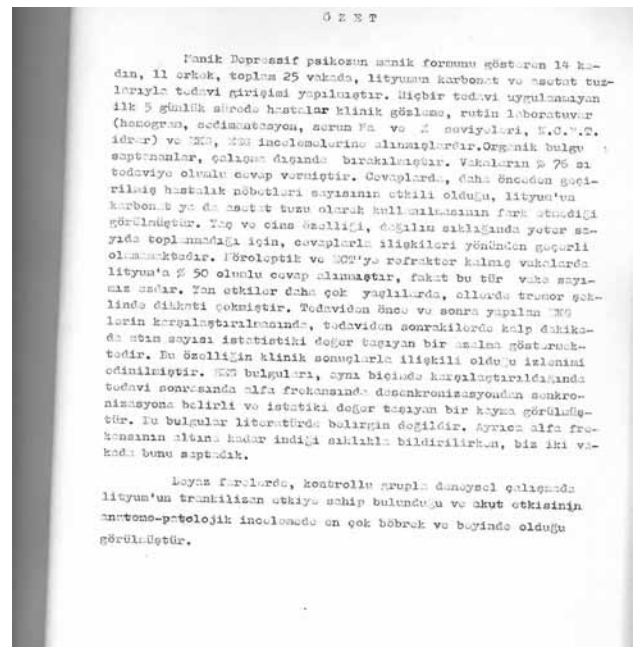
The earliest written source in the medical literature in Turkish we could reach was the (Associate Professor) thesis titled *“Clinical and Psychopharmacologic Trial with Lithium in Manic Excitation”* prepared by Refet Saygılı at the Aegean University in 1970 (6). This was followed by the experimental research article titled *“Effect of Diuretics on Lithium Excretion”* which we understand to have been presented in 1971 at the *“5<sup>th</sup> World Congress of Psychiatry – Mexico City”* by Dr. Aydoğan Öbek et. al and then published in the Istanbul Medical School Journal in 1972 (7). This article mentions that “Lithium therapy started to be used increasingly more in recent years in the treatment of manic depressive diseases and recurrent endogenous depressions”, “...even low levels of lithium such as 0.5 mEq/L in serum had a perfect prophylactic effect”, “...cessation of the medication had the risk of

relapse even in patients who uninterruptedly used lithium for 7 years...”, “...continuous use of Lithium salts could have side- and toxic effects such as nausea, vomiting, diarrhea... and even coma and death.”, “...it becomes necessary to resort to hemodialysis in case of Lithium intoxication because there is no antidote for it...” Since they could not encounter “any other data” about the values of diuretics in lithium intoxication, this trial was carried out “to investigate the acute effects of mannitol, which is an osmotic diuretic, and furosemide on lithium excretion in dogs”. As we understand from this article, the indication of lithium in bipolar disorder, its therapeutic and toxic level, the side-effects and indication of lithium and the treatment of intoxication were very well known at a theoretical level at the time when the said article was published.

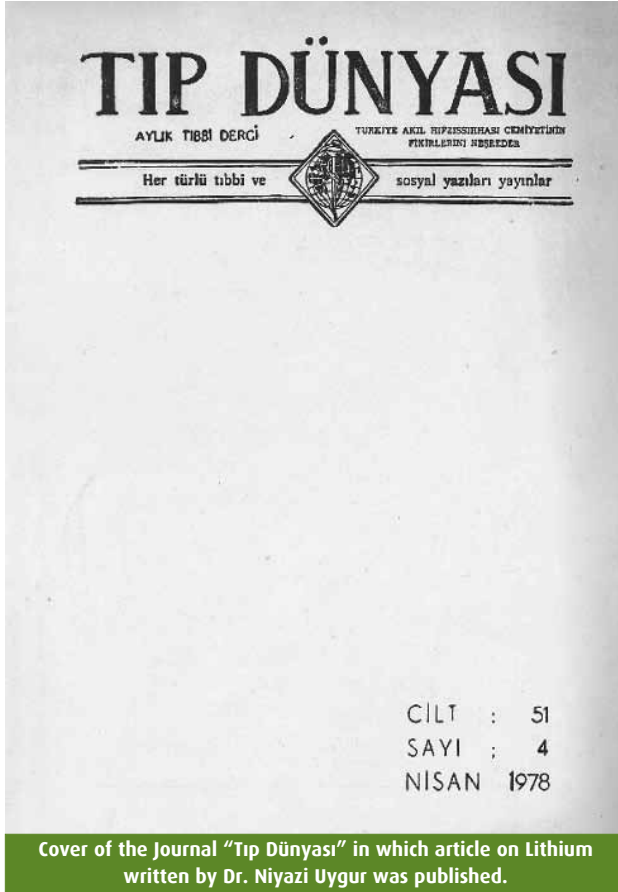
Interestingly, we could not find any literature indicating the existence of clinical applications although the infrastructure to make experimental studies with lithium was available in Turkey. The first literature on the routine clinical practice is the comprehensive review article of Dr. Niyazi Uygur titled *“Pharmacologic Characteristics of Lithium and its Salts”* which also includes headings about administration, supervision and its psycho-pharmaceutical value (8). Dr. Uygur’s claims are strengthened by the fact that along with this article a



Article on the subject in the journal of “Istanbul Tıp Fakültesi Mecmuası” in 1972 written by Aydoğan Öbek et al.



Abstract of the associate professorship dissertation of Dr. Refet Saygılı on Lithium. (Ege University, Izmir, 1970)



Cover of the Journal "Tıp Dünyası" in which article on Lithium written by Dr. Niyazi Uygur was published.

video of a Turkish patient, who began to be treated with lithium in 1972 and regularly monitored by Dr. Niyazi Uygur, was presented at the Spring Symposium of the Turkish Psychiatry Association (TPA). Along with the recordings of this patient, we present the following extracts from the interview held with him on May 10, 2011 at his home in the lines below, which also include the details of using lithium in clinical practices.

**“There were some research articles, but were you the one who first used Lithium in Turkey and published a study article about the clinical use of it?”**

*At that time, there was only the dissertation of Refet Saygılı before me. It was very difficult to detect the blood levels. The blood samples of wealthy patients were being sent to London or Doctor Chestakov, the biochemistry specialist in Pasteur French Hospital, was looking at Li level through K and Na using an indirect method. I started using lithium in the clinic when I was a resident. I listened to Mogens Schou during his seminar in Çapa Medical*



An example of Lithium advertisement from a drug company in 1980's.

*Faculty in 1971 and I immediately began using it on volunteered patients in Rahmi Duman Clinic. Then I became a specialist, in 1976, I monitored some patients for 5 years and some others for 3 years on a pre- and post-Lithium basis on charts; I presented my results together with a fellow resident named Necati Yüksel in a series of 3 seminars using case samples within the scientific activities of Bakırköy (Uygur N. Yüksel N. Tıbbi tedavide lithium tuzlarının yeri ve değeri. Bakırköy Ruh ve Sinir Hastalıkları Hastanesi'nde 3.dizi seminer, 1977.) (9). I was the first one who did it except for the professorship thesis of Mr. Refet.*

**Where did you get Lithium from?**

*We had lithium carbonate prepared as a magistral drug in pharmacies. Shortly after that, its Kilonum Retard capsule 450 mg form came from Germany. A domestic firm called Yurtoğlu launched it later under the name Litinat. ...No, it was a very cheap medicine anyway, they could not carry on with it and that firm was closed down later.*

**You said that you started it when you were a resident?**

*I began using it on one of my patient in firstly 1971. My 3<sup>rd</sup> patient whom I began lithium treatment in 1972 is from Gaziantep, I have his video recording.*



**You said that some doctors had been administering lithium for sedative purposes?**

*Yes, there were many colleagues who were recommending 1lithium a night!*

**Is there a sample of a prescription or a document written at that date?**

*Why is this country losing? All the hospital documents were sent away during the 12 September coup d'etat! There were not many journals to publish articles. I have a copy of the April 1978 edition of the "Tıp Dünyası" Journal; there is a mention of the seminars in Bakırköy in the references section of it.*

**There is an emphasis on prophylaxis in the presentation of Schou, what else did he emphasize?**

*There was an emphasis especially on recurrent mania. Its effectiveness on recurrent depression was being debated. We were very optimistic in those years. We were talking about a success rate of up to 70%. Our optimism faded away in time.*

**Have you used lithium for anything else other than bipolar disorder?**

*I must have definitely tried it in recurrent mood disorders.*

**Have you experienced toxicity many times?**

*Dr. Lider Atasev used to ask me "Are you going to poison people?". I have not experienced much toxicity, but there have been people coming in with toxicity.*

**Have you experienced long-term side-effects other than intoxication?**

*A general surgeon applied a thyroidectomy to a retired nurse saying "your goiter seems very large" without asking the medication she used; unfortunately I saw this. Diabetes insipidus, tremor... We have seen such innocent side-effects."*

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According to the data we obtained from the sources we could reach (Pubmed, Turkish Medical Index, Thesis Center of Turkish Higher Education Board, library catalogues of Istanbul University School of Medicine, Cerrahpaşa School of Medicine and Aegean University School of Medicine), many studies on the issue started to be seen nearly 10 years after this date. For example, the article with a closest date to that of Dr. Uygur's was published in 1984 by Dr. Arkonaç under the heading 'Lithium in Psychiatry Clinic' (10). The poster presentation 'Initial Results of a 'Lithium Clinic' Practice: A Prophylactic Activity' prepared by Dr. Refet Saygılı together with Dr. Simavi Vahip and Işık Tuğlular was presented in 1988 at the 24<sup>th</sup> National Psychiatry and Neurological Sciences Congress (11). 1990s were the years when studies started to appear, where patients with bipolar disorder who were administered lithium were being compared to those who were administered other mood regulators such as carbamazepine and the number of studies made after this date showed an increasing trend and can be made subject to a separate review (12).

## CONCLUSION

It is seen that the practices of treating bipolar disorders in Turkey went parallel to those of the western world and this is documented at least for lithium applications. Reflection of the lithium revolution in Turkey in such a rapid way was largely influenced by the interest and sensitivity of the Turkish psychiatrists of the period as well as the energetic approach of Mogens Schou in promoting his researches (13). We think these pioneering works stand behind the fact that lithium can still be extensively used by all the concerned clinicians in Turkey. We extend our sincere thanks to all the psychiatrists who contributed to this process.

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