

# Today's Psychopharmacological Treatments: Results, Problems, New Perspectives

Mesut Cetin<sup>1</sup>, Feyza Aricioglu<sup>2</sup>, Cengiz Han Acikel<sup>3</sup>, Selim Kilic<sup>3</sup>

## ÖZET:

Günümüzde Psikofarmakolojik Tedavi: Sonuçlar, sorunlar, yeni açılımlar

Tüm çabalara rağmen, XXI. yüzyılın ilk çeyreğinin yarısında gelişmişlik düzeyimizde bile, psikiyatrik bozuklukların bir çoğunun tedavilerinin tam olarak yapılmadığı, kronik, hayat boyu süren hastalıklar grubunu oluşturdukları bilinir. Bu nedenle psikiyatrik bozukluklar ve bu bozuklukların ilaçla tedavisi herhangi bir bedensel hastalığın tedavisinden daha fazla ustalık ve özen gerektirmektedir. Psikofarmakoloji alanındaki gelişmelere, randomize klinik deneyler, preklinik araştırmalar, meta-analizler ve klinisyen deneyimleri oldukça faydalı bilgi kaynakları olmaktadır. Yine de, bu aşamada psikofarmakoloji alanındaki gelişmeler tüm karşı görüşlere rağmen oldukça hızlı ve tatminkardır. Ancak alınacak çok daha fazla yol vardır. Bu derlemede psikotropolarla ilgili etkililik, etkinlik, yan etkiler, advers etkiler, ilaç etkileşimleri, psikofarmakoloji alanındaki yeni açılımlar, farmakoekonomi ile jenerik ve referans ilaç tartışmaları gibi psikofarmakolojinin güncel konularına değinilmiştir.

**Anahtar sözcükler:** Psikofarmakolojik araştırmalar, etkinlik, etkililik, yan etkiler, advers etkiler, farmakoekonomi, bireye özgü tedavi, akılcı ilaç kullanımı

**Klinik Psikofarmakoloji Bülteni 2012;22(2):198-204**

## ABSTRACT:

Today's psychopharmacological treatments: results, problems, new perspectives

Despite all efforts even in the half of the first quarter of the twenty-first century, psychiatric disorders are still lifelong conditions, which cannot be treated fully and mostly continue to be chronic. Therefore, psychiatric disorders and their treatments require more skills and care than physical disorders. In the area of preclinical research in psychopharmacology, clinical trials, research, meta-analyses, and clinician experiences provide useful information for psychopharmacological applications. Although there is still a long distance to cover and at times opposing views, developments in the field of psychopharmacology are rapid and satisfactory. In this review, current issues in psychopharmacology, such as effectiveness, efficacy, new avenues of enquiry, side effects, adverse effects, and drug interactions of psychotropics, generic and reference drug issues, and pharmacoconomics will be discussed.

**Key words:** Psychopharmacological research, effectiveness, efficacy, side effects, adverse reactions, pharmacoconomics, individually tailored treatment, rational use of drugs

**Bulletin of Clinical Psychopharmacology 2012;22(2):198-204**

<sup>1</sup>M.D., Professor of Psychiatry, Editor-in-Chief, Bulletin of Clinical Psychopharmacology, GATA Haydarpaşa Training Hospital, Department of Psychiatry, Istanbul - Turkey  
<sup>2</sup>Ph.D., Professor of Pharmacology, Psychopharmacology Editor of Bulletin of Clinical Psychopharmacology, Marmara University, School of Pharmacy Department of Pharmacology and Psychopharmacology Research Unit, Istanbul - Turkey  
<sup>3</sup>Statistical Editors of Bulletin of Clinical Psychopharmacology, Department of Epidemiology, GATA Medical School, Ankara - Turkey

Yazışma Adresi / Address reprint requests to: Mesut Cetin, GATA Haydarpaşa Training Hospital, Department of Psychiatry, Istanbul - Turkey

Telefon / Phone: +90-216-464-2888

Faks / Fax: +90-216-464-5724

Elektronik posta adresi / E-mail address: mesutcetin@yahoo.com

Gönderme tarihi / Date of submission: 5 Nisan 2012 / April 5, 2012

Kabul tarihi / Date of acceptance: 10 Nisan 2012 / April 10, 2012

## Bağınıt beyanı:

M.C., F.A., C.H.A., S.K.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

## Declaration of interest:

M.C., F.A., C.H.A., S.K.: The authors reported no conflict of interest related to this article.

Despite all efforts, even at the current level of development, psychiatric disorders are lifelong conditions, that cannot be treated fully and remain mostly chronic. If we were to give an example, major depressive disorder is one of the most common psychiatric disorders and affects about 17% of the world's population; this disorder is chronic, recurrent and has a higher rate of total disability and economic burden than other psychiatric disorders (1). In the past fifty-five years, research about depression has focused on pathophysiology of depression and monoamine systems (noradrenaline (NE), serotonin (5-HT), dopamine

(DA)). In the process, tricyclic antidepressants, monoamine oxidase inhibitors, serotonin reuptake inhibitors, and dual acting antidepressant drugs were used in the treatment of depression (2-5). Contrary to the common belief that these drugs are effective and useful, there have been allegations that antidepressants are not more effective than placebo and books have been written supporting these allegations since the 1960's with the help of the antipsychiatry movement. One of the last examples of these papers was published in 2008 by Irving Kirsch, Professor of Psychology, and his colleagues at Harvard University. It is

a meta-analysis titled: "Initial severity and antidepressant benefits: A meta-analysis of data submitted to the Food and Drug Administration" (6). This and similar publications have created mistrust against antidepressant drugs (7-12). The high level of placebo effect observed in depression therapy and the 3 to 4 week-delay of the antidepressant effect from the initial start date of the drugs play the biggest roles in this creating this issue.

Regarding the effectiveness of the antidepressants, the Turkish Association of Psychopharmacology held the 4th International Congress on Psychopharmacology in Antalya from November 23 to 27, 2011. Professor Irving Kirsch and Ian Anderson, Professor of Psychiatry, debated the effectiveness of the antidepressants. As a result of this debate, the importance of individualized treatment has been emphasized once again as it has been concluded in many other different platforms.

Commonly prescribed antidepressants in the current market act mostly to modify the effects of 5-HT and/or NE. Furthermore, there are two more antidepressants that are effective through DA and melatonin receptors. However, very important systems such as glutamatergic and GABAergic systems have been neglected. Evidence has been increasing that, in particular, the glutamatergic system plays an important role in the neuropathology of schizophrenia and manic depression, as well as the neuropathology of depression. Research conducted at Yale University and published by Science Magazine in August 2010 (13) showed that a single dose of ketamine provides a rapid and long-lasting antidepressant response through the glutamatergic system. This discovery can be accepted as a drastic improvement in depression treatment. Ketamine blocks N-methyl-D-aspartate (NMDA) receptors, which receive neurotransmission mediated by glutamate; it is currently used as an anesthetic drug both in humans and animals. Therefore, the biggest obstacle in depression therapy, which is the delayed onset of antidepressant effect, may be overcome by using ketamine. However, because ketamine is an anesthetic drug, it is not preferred for use in the routine treatment of depressive patients. The mechanism of action of ketamine is rapid activation of the mammalian target of rapamycin (mTOR) pathway, which is one of the signal pathways in the nervous system. This invention is an important indication that the glutamatergic system should be taken into consideration in antidepressant drug development (14).

Although the basic rules of pharmacological drug administration, such as "right dose, right route, and right time", are followed correctly, psychiatric therapies may not always result in a response, or the treatment may be insufficient, and/or there may be undesirable effects following drug administration.

The reasons for this situation may include pharmacogenetic factors related to the patient, besides the nature of the disorder. When there is lack of response to an antidepressant, that drug may not be an appropriate for that specific patient. In most cases, a response to the treatment can be achieved by "individualized pharmacotherapy." Individualized pharmacotherapy interests not only clinicians, but also the pharmaceutical industry, health insurers, and reimbursement system authorities. By means of individualized pharmacotherapy, accurate therapeutic doses of the correct medicine can be achieved and early diagnosis, detection of side effects, drug interactions, and possible adverse reactions could be predicted and avoided. With the help of reliable biomarkers, "trial and error" prescribing will be replaced by "tailored" prescribing. (15).

On the other hand, there are unmet needs with antipsychotic treatment. These include efficacy / effectiveness issues, metabolic syndrome due to side effects, Parkinsonism, and prolactin elevation. Any of these may cause relapses, re-hospitalizations, treatment adherence issues, and deterioration of cognitive and social functioning. Without adequate medication adherence, relapses, re-hospitalization, and cognitive and social functioning declines are inevitable. The need for cost effective treatment must also be considered (16-49).

There have been many meta-analyses carried out to compare the efficacy/effectiveness, side effects, continuous medical treatment, and pharmacoeconomics of antipsychotics. One of these meta-analyses was published in 2009 in the American Journal of Psychiatry authored by Prof. Stefan Leucht and colleagues (16). This meta-analysis was conducted by reviewing the literature published between May 2007 and September 2007 and covers 9 second-generation antipsychotic drugs (SAGs) (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone, and zotepine) used in the treatment of schizophrenia and includes double-blind randomized studies. The meta-analysis compared head-to-head effectiveness of first and

SGAs and included 78 studies with the results of treatment from 13,588 patients. Olanzapine was found to be superior to aripiprazole, quetiapine, risperidone, and ziprasidone. Risperidone was proven to be more efficacious than quetiapine and ziprasidone, in reducing positive symptoms, but not negative symptoms. This study also revealed that amisulpride, which is not approved by the FDA, was as effective, according to the total PANNS score, as olanzapine, risperidone and ziprasidone, which are FDA approved and was considerably superior than these drugs with respect to negative symptoms.

The second large meta-analysis was conducted by Leucht and his colleagues was published in the January 2009 issue of *Lancet* (17), and is considered to be one of the most important meta-analyses on antipsychotics. In this meta-analysis, the authors searched (without language restrictions) the register of the Cochrane Schizophrenia Group, the U.S. FDA website, and previous reviews for comparisons of the second-generation antipsychotic drugs in oral formulations versus first generation antipsychotics (FGAs) in randomized controlled trials. In this meta-analysis 411 studies were identified and 107 of them were excluded. They analyzed the use of 9 SGAs (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone, zotepine) included in the first meta-analysis. The investigation covered 150 double-blind, mostly short-term studies consisted of 21,533 patients' data and 239 publications, but many of the open studies were excluded, since most found the SGAs to be more efficient. Ninety-five of these studies used haloperidol and 28 of them used chlorpromazine as the reference FGA. In the meta-analysis, SGAs were compared with FGAs for overall efficacy, positive, negative, and depressive symptoms, relapse, quality of life, extrapyramidal side effects, weight gain, and sedation. Amisulpride, clozapine, olanzapine, and risperidone were more efficacious than the FGAs, and aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine were not.

Additionally, there were only 14 relapses reported in the long-term studies. While olanzapine, risperidone, and sertindole have been found statistically significantly superior to the FGAs, there were no significant differences for amisulpride, aripiprazole, and clozapine. A total of 17 studies examined the quality of life and amisulpride, clozapine, and sertindole were found to be superior to the FGAs. In terms of extrapyramidal side effects, while all

SGAs have fewer side effects than haloperidol, in the comparisons made to chlorpromazine, which is a low-potency first-generation drug, only clozapine, olanzapine, and risperidone were found to be superior. In the weight gain related analysis, amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, and zotepine have been found statistically significantly different compared to haloperidol, while there were no significant differences for aripiprazole and ziprasidone. When chlorpromazine was compared to the SGAs, no significant differences were found. In terms of sedation, clozapine, quetiapine, and zotepine were found to have more sedative effects compared to haloperidol, but the sedative effects of aripiprazole were significantly lower. In the comparisons made with the second-generation psychotics to chlorpromazine, only clozapine's sedative effects were found to be significantly higher.

When industry-supported studies were ignored, even if the effectiveness of the SGAs was lower, they were found to be significantly superior to the FGAs in terms of overall improvement, with the exception of risperidone.

In conclusion, four of the SGAs (amisulpride, clozapine, olanzapine, and risperidone) were found to be significantly more effective than the FGAs, and others (aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine) were found to be only as effective as the FGAs.

In this meta-analysis, the main limitations pointed out by the writers were that the drug used in the comparisons in most cases was haloperidol and insufficient number of studies were conducted with the mid-potency FGAs.

These two meta-analyses, conducted by the support of National Institute of Mental Health (NIMH) and published in respectable and high impact journals, *Lancet* and *American Journal of Psychiatry*, are quite important, because Leucht and colleagues compared SGAs among each other and SGAs to FGAs, which provided a broad point of view of antipsychotic treatment. However, the meta-analysis raises two additional points of interest regarding the effects of psychotropic medications, i.e., efficacy and acceptability. Efficacy is the drug's power to produce the desired effect. Acceptability can be described as the use of medication without significant side effects and without interfering with the patient's quality of life. In addition to the difficulties that may be encountered in psychotropic drug research, the meta-analysis method has important limitations. Randomization quality of the studies

can not be assessed precisely. Some studies have been conducted with the sponsorship of drug companies and might be biased, which can't be measured. The inability to properly evaluate the reference studies, biases caused by the publications, sponsorship issues, retrospective studies, and evaluation of weight problems are just some examples of limitations and challenges. Considering all of these factors, this meta-analysis can still be accepted as quite important, because researchers did not sum up their daily information, but evaluated data from a great number of articles (30). As a result of these type of studies, it is usually expected that valuable evidence supporting every day applications should be found. Most people who write and evaluate meta-analyses go into further generalizations because of this need. Results of a meta-analysis, which is conducted on a particular group of patients for a particular group of drugs, should not be generalized for similar groups of patients or similar drugs.

Meta-analyses are valuable, but it should not be forgotten that they rely on randomized clinical trials (RCTs). In randomized clinical trials, patient selection (the correct diagnosis and differential diagnosis, whether the identification of inclusion and exclusion criteria were clearly specified or not), drug dosage, dose-titration, length of the study and patient compliance issues determine if the final results are correct and accurate (18-21). During the last decade, there have been many studies and meta-analyses published regarding effectiveness and side-effects (22-35) and new areas of application (36-46) for antipsychotics.

Another challenging issue is adverse reactions. As a result of combining psychotropics with each other or with different drug groups, adverse reactions may occur. For example, during antidepressant treatments, primarily decreased libido, sexual dysfunctions, various dermatological, cardiovascular, hematological, and neurological adverse effects might occur. In some instances, combinations of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have been shown to cause serotonin syndrome. If treatments with monoamine oxidase inhibitors (MAOIs), TCAs, and some new antidepressants such as paroxetine, venlafaxine are suddenly discontinued, withdrawal syndrome may be observed. Reports have shown that use of SGAs may result in adverse effects such as type II diabetes, insulin resistance, lipid profile abnormalities,

increased risk of angioedema and cardiovascular disease. Iatrogenic psychiatric problems caused by drugs like depression, psychosis, mania, and confusion may be seen frequently, as well (25,26,34,35).

Looking back over the 22-year history of the Bulletin of Clinical Psychopharmacology, most of the articles regarding clinical effectiveness and side effects of both antidepressants and antipsychotics conducted in Turkey were published in our journal, which is a huge source of pride for us (2-5,12,14,15,27-46,50,51).

Antidepressants and SGAs are not homogeneous groups and they are composed of different drugs in terms of effectiveness, side effects, and costs. Hence in our opinion, when clinicians prescribe antipsychotics their patients, they should keep the results of neutral meta-analyses in mind. They should consider the individual characteristics of their patients, patients' physical health and quality of life and choose the most effective and appropriately priced medication, in order to restore the patient's social and occupational function.

In many of the developing countries including Turkey, health budgets are limited. To get the most value out of limited resources, drugs should be prescribed rationally considering the overall assessment of the effectiveness, reliability, and cost. Most studies are designed to measure only the efficacy of drugs. In fact, there is a strong need to study economical and clinical comparisons of data as well. Pharmacoeconomics focuses on the costs and benefits of drug therapy. Rational prescribing of drugs is the process of planning, assessing risks and benefits of alternative drugs, implementing treatment with the chosen drug, and monitoring the response and adverse effects, in order to provide drug therapy that is effective, safe, and economical. Rational psychopharmacology, in the most basic sense means prescribing the right drug, at the right dose, for the optimal time, and for appropriate clinical indications, while keeping the cost as low as possible. Health economics aims to achieve the best possible public health level by optimizing the use of limited resources. Finding effective drug combinations, making appropriate health care investments, and promoting prevention and cost-effective services such as treatment guidelines are some strategies used in health economics.

As there is a limited budget for health services in our country, clinicians should make the best use of available resources, prescribe drugs in a rational way, and evaluate the effectiveness and reliability in terms of

pharmacoeconomics. According to the Employers' Union of the Pharmaceutical Industry (IEIS) data, in 2011, the Turkish prescription drug market grew 1.4% by cost, reaching 14 billion Turkish Liras (\$ 8.3 billion), and grew 9.1% by drug packages sold and reached 1.56 billion packages (47). Average drug consumption cost in 2011 was \$121 per person. According to the records of the Social Security Institution of Turkey (SGK), which controls health care expenditures of the government, total government spending in 2010 was 14,897,455 TL (48). Based on pharmaceutical industry data, the market research firm Intercontinental Marketing Services (IMS) reported that, out of the gross sales of all drugs, antipsychotic drugs were 5<sup>th</sup> with sales of \$18.2 billion and antidepressants were 7<sup>th</sup> with \$11 billion. The most prescribed psychotropics (by number of packages sold) were alprazolam with 47.8 million, zolpidem with 39.4 million, and citalopram with 37.7 million. In the U.S. among the most prescribed psychotropics, quetiapine had the first place, and was 5<sup>th</sup> on the overall list of drugs. At the same list, olanzapine took 10<sup>th</sup> place and aripiprazole took 13<sup>th</sup> place. In 2011, 264 million antidepressant prescriptions were written in the U.S. In 2010, in terms of cost, antipsychotics were in 7<sup>th</sup> place, with a cost of \$25.412 billion; antidepressants were in 9<sup>th</sup> place with a total cost of \$ 20.216 billion (49).

In this context, the reference drug vs. generic drug debate comes up. As it is known, the reference drugs are under protection of the patent laws in many countries and they are protected for a certain time and only after this period expires, the production of generic drugs is allowed. Generic drugs, should not only be, pharmaceutically equivalent to the reference drugs, but also they should be bioequivalent. Countries around the world, whom seek to reduce their health care costs, achieve significant savings through the use of generic drugs. Because generic drugs have no research and development (R & D) costs, they are 20-80% less expensive than reference products compared

to the reference product's price. It has been declared, that through the use of generic drugs between years 2004 and -2008 in Turkey, a total of 3 billion 879 million TL have been saved in health expenditures, in Turkey. Despite the decline in drug prices in recent years and the number of people connected to the SGK increased, SGK reimbursements for the prescriptions remain constant or even decreased in recent years, from our point of view; this could be the result of increase in the number of generic drugs' prescriptions.

Again, based on clinical observations and impressions gained from research, generic drugs produced and controlled according to the rules, laws and regulations, are as effective as reference drugs. However, despite the assurances given, there are some small instances where some of the clinicians are rightfully doubtful regarding the generic drug companies' drugs. Although very few, these cases of this kind of negative confidence issues could be solved by tighter controls from the government and other institutions, as well as through feedback from our colleagues (50,51).

As a result, when a clinician makes a final decision on a patient's regarding his/her treatment, he/she should not accept results of meta-analyses results as absolute truth, and has to consider meta-analyses' limitations and he/she has to take patient's needs under consideration by applying the "individually tailored medication" principal. Less important factors, such as drugs' superiority against each other shouldn't be considered as priority and individually tailored medication method has to be chosen, while; adverse reactions and serious side effects, such as weight gain, and metabolic syndrome, and prolactin increase elevation which may effect the patients physical health in negative way, as well as, his/her social, occupational and cognitive functions; have to be taken under consideration at all times, and daily treatment plans have to be made by not disregarding pharmacoeconomic principles.

## References:

1. [http://www.who.int/mental\\_health/management/depression/definition/en/](http://www.who.int/mental_health/management/depression/definition/en/)
2. Yildiz A, Gonul AS, Tamam L, Mechanism of actions of antidepressants: Beyond the receptors. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2002;12 (3):194-200.
3. Bird D, Haddad PM, Dursun SM An overview of the definition and management of treatment-resistant depression. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2002;12(2):92-101.
4. Altindag A, Ozkan M, The pharmacological treatment of psychotic depression. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2001;11(3):212-28. (Turkish)
5. Gulseren L, Gulseren S, Hekimsoy Z, Bodur Z, Kultur S. Efficacy of fluoxetine and paroxetine on depression-anxiety, quality of life, disability and metabolic control in diabetic patients with major depressive disorder: A single blind, comparative study. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2001;11 (1):1-10.
6. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration. *PLoS Med*, 2008; 5: e45doi:10.1371/journal.pmed.0050045.
7. Davis JM, Giakas WJ, Qu J, Prasad P, Leucht S. Should we treat depression with drugs or psychological interventions? A reply to Ioannidis. *Philos Ethics Humanit Med* 2011;6(1):8.
8. Cipriani A, Barbui C, Brambilla P, Furukawa TA, Hotopf M, Geddes JR., Are all antidepressants really the same? The case of fluoxetine: a systematic review. *J Clin Psychiatry* 2006;67(7):850-64.
9. Cipriani A, Geddes JR, Furukawa TA, Barbui C. Metareview on short-term effectiveness and safety of antidepressants for depression: an evidence-based approach to inform clinical practice. *Can J Psychiatry* 2007;52(9):553-62.
10. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 2009;373(9665):746-58.
11. Hotopf M, Barbui C. Bias in the evaluation of antidepressants. *Epidemiol Psychiatr Soc* 2005;14(2):55-7.
12. Cetin M. Antidepressants, antipsychotics: Reliability of meta-analyses. *Klinik Psikofarmakoloji Bülteni - Bulletin of Clinical Psychopharmacology* 2008;18(4):245-50. (Turkish)
13. Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, Duman RS. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* 2010;329(5994):959-64.
14. Karolewicz B, Cetin M, Aricioglu F. Beyond the glutamate N-methyl D-aspartate receptor in major depressive disorder: the mTOR signaling pathway. *Klinik Psikofarmakoloji Bülteni -Bulletin of Clinical Psychopharmacology* 2011;21(1):1-6.
15. Aricioglu F, Cetin M. Personalized drug therapy in psychiatry: Maybe a little old or a little new, but the treatment of future. *Klinik Psikofarmakoloji Bülteni- Bulletin of Clinical Psychopharmacology* 2010;20:269-73. (Turkish)
16. Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F, et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *Am J Psychiatry* 2009;166(2):152-63.
17. Leucht S, Corves C, Arter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta analysis. *Lancet* 2009;373(9657):31-41.
18. Leucht S, Kissling W, Davis JM. How to read and understand and use systematic reviews and meta-analyses. *Acta Psychiatr Scand* 2009;119(6):443-50.
19. Cetin M., Kilic S. How to comprehend the recent meta-analyses conducted on typical and atypical antipsychotics? *Klinik Psikofarmakoloji Bülteni- Bulletin of Clinical Psychopharmacology* 2009, 19(1):1- 4. (Turkish)
20. Leucht S, Heres S, Kissling W, Davis JM. Evidence-based pharmacotherapy of schizophrenia. *Int J Neuropsychopharmacol* 2011;14(2):269-84.
21. Hamann J, Mendel R, Meier A, Asani F, Pausch E, Leucht S, Kissling W. "How to speak to your psychiatrist": shared decision-making training for inpatients with schizophrenia. *Psychiatr Serv* 2011;62(10):1218-21.
22. Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Davis JM. Maintenance treatment with antipsychotic drugs for schizophrenia. *Cochrane Database Syst Rev* 2012;5:CD008016.
23. Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Salanti G, Davis JM. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet* 2012;379(9831):2063-71.
24. Kishimoto T, Agarwal V, Kishi T, Leucht S, Kane JM, Correll CU. Relapse prevention in schizophrenia: a systematic review and meta-analysis of second-generation antipsychotics versus first-generation antipsychotics. *Mol Psychiatry*. 2011 Nov 29. doi: 10.1038/mp.2011.143. [Epub ahead of print]
25. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Lobos CA, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Schizophr Res* 2010;123(2-3):225-33.
26. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Kissling W, et al. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophr Bull* 2012;38(1):167-77.
27. Herken H, Erdal ME, Esgi K, Virit O, Aynacioglu AS. The relationships between the response to risperidone treatment and 5-HT2A receptor gene (T102C And 1438G/A) polymorphism in schizophrenia. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2003; 13 (3):161-6. (Turkish)
28. Inanli IC, Eren I. The effect of olanzapine on cognitive functions of patients with schizophrenia. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2006;16(4):213-22. (Turkish)
29. Ozcan Y, Ozisik HI, Unal S, Ozcan ME. Efficacy of risperidone on positive and negative symptoms of schizophrenia and memory functions. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2000; 10(3):182-8

30. Gonul AS, Suer C, Oguz A, Ozesmi C, Yilmaz A, Yabanoglu. The effects of olanzapine, a novel antipsychotic, on auditory event-related potentials in schizophrenia. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2000; 10(1):1-8. (Turkish)
31. Yazici AE, Yazici K, Taneli B, Tot S, Kanik A. The efficacy of olanzapine and risperidone inpatients with schizophrenia: an open clinical study. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2002; 12(2):115-20. (Turkish)
32. Ebrinc S, Semiz UB, Basoglu C, Cetin M, Baykiz AF, Kandilcioglu H, Balibey H. Efficacy and safety of amisulpride treatment in schizophrenia: Comparison with haloperidol. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2004; 14(2):143-9. (Turkish)
33. Ebrinc S, Basoglu C, Cetin M, Filiz M, Sendogan N. the efficacy and safety of haloperidol and risperidone in patients with schizophrenia. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2002; 12(1):6-13. (Turkish)
34. Danaci AE, Mizrak S, Hekimsoy Z, İçelli I. Diabetes mellitus due to olanzapine use: a case report *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2003; 13:94-6. (Turkish)
35. Kurt E, Akman B, Alatas A, Dagdelen S, T Oral T, Comparison of cardiac influences of antipsychotic drugs in patients with schizophrenia. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2007;17(3):155-61. (Turkish)
36. Atmaca M, Kuloglu M, Tezcan AE. Monosymptomatic hypochondrial psychosis: a case report being used risperidone. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2001; 11(1):41-5. (Turkish)
37. Arman AR, Yazgan Y, Berkem M. The effects of risperidone on behaviors seen in children with pervasive developmental disorder and mental retardation in an educational setting. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2003;13(3):174-8. (Turkish)
38. Ozturk M, Sayar MK, Tuzun U. Risperidone in children with Asperger's disorder: a report of four cases. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2000; 10(1):51-5. (Turkish)
39. Yumru M, Savas HA, Kokaçya MH, Virit. Long acting risperidone in treatment of schizophrenia: a retrospective study. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2007;17(2):119-23. (Turkish)
40. Karaoglan Kahilogullari A, Orsel S, A. Sargin E, Hatiloglu U, Berber MS, Ozbay H. Changes in drug prescription patterns in schizophrenia in five years. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2008;18(3):162-6. (Turkish)
41. Sayin A, Karslioglu E, Yavas G, Candansayar S. The use of antipsychotic prescription for an university psychiatry clinic: A retrospective study. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2006;16(3):160-6. (Turkish)
42. Uzun O, Ozsahin A, Ozmenler KN, Doruk A, Battal S, Clozapine in treatment-resistant schizophrenia: followed-up study for three years. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2000; 10(2):74-80. (Turkish)
43. Soyul C, Bilici M, Bekaroglu M, Yildirim F. Clozapine in patients with treatment-resistant schizophrenia. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 1999; 9(1):34-8. (Turkish)
44. Herken H, Kaya N, Besiroglu L, Derman H, Ozkan I. A comparison of efficacy and safety of clozapine and sulpiride in treatment-resistant schizophrenia. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 1999; 9(2):148-51. (Turkish)
45. Alptekin K. New generation antipsychotics in the treatment of schizophrenia: dopamine stabilizing agents and aripiprazole. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2008;18(Suppl. 1): S21-S6. (Turkish)
46. Karamustafalioglu, Karamustafalioglu N, Tolerability and safety of aripiprazole in schizophrenic Patients. *Klinik Psikofarmakoloji Bülteni- Bulletin of Clinical Psychopharmacology* 2008;18(Suppl. 1):S35-S42. (Turkish)
47. [http://www.ieis.org.tr/asp\\_sayfalar/index.asp?sayfa=220&menuk=12](http://www.ieis.org.tr/asp_sayfalar/index.asp?sayfa=220&menuk=12)
48. <http://www.medimagazin.com.tr/ana-sayfa/sgk/tr-ilac-giderleri-artmadi-sgkli-sayisi-artti-1-4-35555.html>
49. <http://www.imshealth.com/portal/site/ims/menuitem.5ad1c081663fd9b41d84b903208c22a/?vgnnextoid=fbc65890d33ee210VgnVCM10000071812ca2RCRD&vgnnextfmt=default>
50. Cetin M, Aricioglu F. On the debate of original drug versus generic *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2009;19(4):211-4. (Turkish)
51. Cetin M, Aricioglu F. Pharmacoeconomics and its importance in psychiatry. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2010;20(1):1-4. (Turkish)