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Augmentation of Clozapine Due to Inadequate Treatment Response in Schizophrenia: Comparison of Patients with Augmented and Non-augmented Treatments

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SUMMARY

Objective: Clozapine is considered to be a gold standard antipsychotic in treatment resistant schizophrenia. This study aims to investigate clozapine augmentation methods utilized in schizophrenia and compare the sociodemographic characteristics, clinical features and remission states of patients whose treatments are augmented and not.

Method: This study included 122 outpatients diagnosed with DSM-IV schizophrenia. Patients were assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders, Positive and Negative Syndrome Scale, Clinical Global Impression Scale, Global Assessment of Functioning, Calgary Depression Scale for Schizophrenia, Panic Agoraphobia Scale, Yale-Brown Obsessive Compulsive Scale and the World Health Organization Disability Assessment Schedule II. The remission state of the patients was assessed utilizing the Remission in Schizophrenia Working Group criteria for schizophrenia.

Results: Combined antipsychotic drug use was the most prevalent method utilized for clozapine augmentation. Patients on augmentation treatment were on higher daily clozapine doses and their remission rates were lower. In addition, the severity of psychopathology related with schizophrenia and comorbid symptoms, the level of functioning and disability were worse in this particular patient group. History of antipsychotic combination use prior to clozapine was found to predict the future use of clozapine augmentation.

Conclusion: Adding a second antipsychotic seems to be the most common method of augmenting clozapine treatment in schizophrenia. The group of patients whose clozapine treatment is augmented appears to represent a "more difficult to treat" patient group before clozapine is initiated.

Keywords: Schizophrenia, clozapine, augmentation, treatment resistant

INTRODUCTION

A wide spectrum of randomised controlled research and meta-analyses demonstrating the superiority of clozapine over the first and second generation antipsychotics in the treatment of schizophrenia have been reported in the literature (Taylor and Duncan-McConnell 2000, Chakos et al. 2001, Wahlbeck et al. 1999, Wahlbeck et al. 2000, Leucht et al. 2009, Leucht et al. 2013). A recent large scale meta-analysis reported on the Cochrane database has shown that clozapine was the most effective antipsychotic agent for the short and long term treatment of the positive symptoms of schizophrenia, and that this superiority was valid for the total and negative symptoms in short term therapies. It was also determined that the high level of psychosis scores better predicted the outcomes and that the value of the 'number needed to treat' was 9 (Siskind et al. 2016). Another current meta-analysis on the one to one comparison of the long term effectiveness of second generation antipsychotics on the symptoms of psychopathology has demonstrated that clozapine and olanzapine were superior to all the other agents (Kishimoto et al. 2019). Given these multiple and consistent evidence on its effectiveness on treatment resistant schizophrenia, clozapine currently stands as the "gold standard" drug recommended in the therapeutic guidelines (Moore et al. 2007, Lehman et al. 2004, NICE 2014, Taylor 2017).

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Nevertheless, 45-70% of the patients respond partially or inadequately to clozapine treatment (Vayısoğlu and Anıl Yağcıoğlu 2013, Tiihonen 2009). An additional meta-analysis by Siskind (2017) indicates that 40% of the cases respond positively to clozapine while 12-20% constitute an ultra-resistant subgroup. Heterogeneity of the treatments received by this ultra-resistant subgroup who, despite recommendations of augmented therapy, at best respond partially to the first and second lines of therapy, and the inadequacy of reported data present difficulties for effective therapeutic approaches.

Majority of the augmentation methods recommended for patients who respond partially to clozapine involve addition of another antipsychotic agent to the protocol. However, the effects of adding antidepressants, mood stabilisers, glutamatergic agents, sex hormones, cholinesterases and phosphodiesterase inhibitors have also been investigated for augmenting clozapine efficacy. The favourable reports on the use of especially fluvoxamine, duloxetine, mirtazapine, omega 3 fatty acids and electroconvulsive therapy need to be supported with further evidence (Sommer et al. 2012, Gürel and Anıl Yağcıoğlu 2018, Anıl Yağcıoğlu and Gürel 2018).

The aim of this study was to investigate the methods of augmentation of clozapine treatment in outpatients being followed at the Department of Psychiatry at Hacettepe University Faculty of Medicine, for inadequate response to clozapine; to compare the data on remission, sociodemographic and clinical characteristics of patients receiving augmented and nonaugmented treatment and to determine the variables significantly predicting the indication for augmentation.

METHOD

Participants

Outpatients being followed at the Department of Psychiatry at Hacettepe University Faculty of Medicine were assesed cross-sectionaly between January 2015 and March 2016. Patients who met DSM IV criteria (American Psychiatric Association-APA 1994) for schizophrenia, and were 18-65 years old and had been using clozapine for at least 6 weeks were recruited in the study after giving informed consent. The aim and the design of the study received approval (code no: GO15-4801) by the Hacettepe University Ethical Committee for Noninterventional Clinical Research.

Of the total of 147 patients interviewed, 122 were included in the study while 13 patients refused to participate and 12 were excluded on grounds of Parkinson's disease (n:1) and schizoaffective disorder (n:11) diagnosed on the SCID-I criteria. Inadequacy of improvement in the positive symptoms in response to clozapine monotherapy was the main reason for using augmentation methods investigated in this study. The information on the augmentation methods was acquired both during the interviews with the participating patients and the specific data on the patient registration forms; and use of additional psychotropic agents not related to augmentation were excluded from the analyses.

Assessment Tools for Clinical Evaluation

All participants were assessed by SCID - I to confirm the diagnosis of schizophrenia (Özkürkçügil et al. 1999). The information subsequently acquired on the Sociodemographic and Clinical Questionnaire including query on current cigarette smoking is summarised in Table 1.

In order to assess the symptoms and the severity of psychopathology and the level of disability the participants were assessed by the Positive and Negative Syndrome Scale-PANSS (Kay et al. 1987, Kostakoğlu et al. 1999), Clinical Global Impression Scale-CGI (Guy et al. 1976), Global Assesment of Functioning –GAF (Endicott et al. 1976), Calgary Depression Scale for Schizophrenia-CDSS (Addington et al. 1990, Aydemir et al. 2000), Yale Brown Obsessive-Compulsive Scale-YBOCS (Goodman 1989, Karamustafalıoğlu et al. 1993, Tek et al. 1995), Panic and Agoraphobia Scale-PAS (Bandelow et al. 1995, Tural et al. 2000) and World Health Organization Disability Assesment Schedule-II- WHO-DAS-II (WHO 1999, Uluğ et al. 2001).

The symptomatic remission state of the patients were determined by using the criteria which included stability of the clinical status, absence of hospitalization, any change in the treatment protocol and change in severity of psychopathology in the last 6 months according to information gathered through the psychiatric interview, file records and patients' physician responsible for follow up.

Clinical Laboratory Investigations

The levels of clozapine and clozapine/norclozapine ratio in the blood samples of participants on augmented and non-augmented clozapine treatment were assessed during the routine control visits, as part of the research plan. Blood level of clozapine was estimated by high performance liquid chromatography (HPLC) as the trough concentration of the drug 12 hours after taking the last dose. The measured values were recorded if the patient was on a maintained clozapine dose at the time of the follow up interview and the blood test had been made within the previous 2 months.

Statistical Analysis

Statistical analyses were carried out on the IBM SPSS Statistics 22.0 Windows version. Numerical variables were expressed in terms of the mean±standard deviation, the

median [minimum–maximum] values. Categorical variables were expressed in numbers and percentages.

Intergroup differences in categorical variables were calculated by the Chi square test or the Fisher exact test. The Kolmogorov Smirnov test was used to check normality in the distribution of the numerical variables and the homogeneity of the variances was analysed by the Levene test. The differences in numerical variables between two independent groups were analysed using the T test for independent samples when conditions of parametric test assumptions were satisfied, or by the Mann Whitney U test when these assumptions were not met. Correlation between numerical variables was analysed using the Spearman correlation analysis. Changes in the categorical variables before and after clozapine treatment were investigated by the McNemar test. Factors predicting remission after clozapine treatment and also the requirement of clozapine augmentation were assessed by the multistep logistic regression analysis. The p value of <0.05 was accepted to express statistical significance.

RESULTS

The participants of this study consisted of a total of 122 schizophrenia patients with a mean age of 41.4 (±10.6) years who applied the outpatient clinic of the Department of Psychiatry at Hacettepe University Faculty of Medicine between January 2015 and March 2016 and were followed up on clozapine treatment. Majority of the participants were male (53.3%), single (70.5%) and domiciled in urban towns (95.9%). The mean duration of education was 11.5 (±3.5) years with the majority being high school graduates.

Age at onset of illness of the whole group was 21.7 (±6.2) years. Switching to clozapine treatment was determined by treatment resistance in 90.2% of the participants and the mean duration of the time taken for the switch was 118.3 (±92.7) months. The mean total scores of the group were determined to be 58.56 (±17.52) on the PANSS, 27.95 (19.37) on the WHO-DAS-II and 3.56 (±1.08) on the CGI-Severity. The GAF scores mostly ranged between 41-60 (n:66, 45.1%) and 61-80 (n:37, 30.4%).

File records and information obtained from the participants, particularly during the interviews for cross sectional evaluation, in order to determine whether or not the participants were on clozapine agumentation therapy, indicated that 26% (n=32) were, at the time, on augmentation while 74% (n=90) were not; while 16% (n=21) had previously been on augmentation therapy that was discontinued. This information was used to place the participants in two groups as users of augmented and nonaugmented clozapine treatment.

Comparison of the two groups on the basis of age, gender and education level, family history of mental and psychotic disorders and cigarette smoking did not yield any statistically significant differences. Significant differences were also not demonstrated between the two groups on employment status and, marital status before and after treatment with clozapine, age at onset of illness, time taken for switch to clozapine treatment and the duration of clozapine treatment (Table 1). The two groups were found not to differ significantly when they were queried on the total number of antipsychotics and the combined typical/atypical antipsychotics used before the switch to clozapine treatment. The history of the participants on clozapine augmentation on grounds of resistance to clozapine monotherapy was also investigated for treatment with combination of antipsychotics before starting to use clozapine. These participants were found to have used combined antipscyhotics more frequently in comparison to the participants on nonaugmented therapy (n=18, 56.3% x n=24, 30%), the intergroup difference being statistically significant (p=0.017). The sociodemographic and important clinical features of the participants on augmented and nonaugmented therapy have been summarised in Table 1.

Comparisons showed that the clozapine dose used by the participants on nonaugmented clozapine treatment was

Table 1. Sociodemographic and Clinical Characteristics of the Participants on Augmented and Nonaugmented Clozapine Treatment

	Participants on Augmented therapy (n=32)		Participants on Nonaugmented therapy (n=90)		*p*
	number (n)	%	number (n)	%	
Gender					
Female	17	53.1	40	44.4	0.523
Male	15	46.9	50	55.6	
Family History of Mental Disease					
Yes	20	62.5	55	61.1	1.000
No	12	37.5	35	38.9	
Family History of Psychotic Disorder					
Yes	12	37.5	36	40	0.970
No	20	62.5	54	60	
Cigarette Smoking					
Yes	16	50.0	31	34.4	0.180
		Mean ± Std. Deviation	Mean ± Std. Deviation		*p*
Age		40.9±9.4	41.5±11.0		0.776
Education (years)		10.9±3.7	11.8±3.4		1.000
Disease Onset Age		20.9±5.3	22.7±7.0		0.121
Clozapine Use Duration (months)		109.8±62.6	110.1±68.4		0.970
Time Before Initiation of Clozapine (months)		113.5±85.3	113.6±85.5		0.984

Table 2. Serum Levels of Clozapine and Clozapine/Norclozapine Ratio in Participants on Augmented and Nonaugmented Clozapine Treatment

	Participants on Augmented Therapy (n=32)	Participants on Nonaugmented Therapy (n=90)	*p*
	Mean ± Std. deviation	Mean ± Std. deviation	
Clozapine Dose (mg/day)	432.0±176.4	363.3±155.9	0.039
Serum Clozapine Level (ng/mL)	916.3±473.4	796.0±433.2	0.320
Serum Norclozapine Level (ng/mL)	388.6±191.9	355.9±203.4	0.391
Clozapine/Norclozapine Ratio	2.4±0.8	2.4±0.9	0.826

significantly lower, but that the blood levels of clozapine did not differ significantly between the two groups (Table 2).

Among the augmentation methods used, the most frequently implemented method had been the addition of another atypical antipsychotic agent (56.3%) to the existing treatment. It was seen that each patient was on a single main augmentation treatment at the time of assessment (Table 3).

Comparison of the results of clinical tools for assessing the severity of psychopathology showed that the scores of the participants on nonaugmented clozapine treatment were significantly lower on the PANSS, the CDSS, the YBOCS total and obsession subtest and the CGI disease severity and WHO-DAS-II scores. These were reflected in the lower severity of schizophrenia, the comorbidities and disability and the higher level of functioning in the same group of participants. However, significant intergroup differences were not observed in the scores on the PAS, the YBOCS compulsion subtest and the CGI subtests on improvement and side effects (Table 4).

In order to determine the factors predicting the requirement of clozapine augmentation, multi step logistic regression analysis was carried out using the variables gender, age, age at onset of illness, antipsychotics used before switching to clozapine treatment, time taken to switch to clozapine, duration of clozapine use and blood level of clozapine. The result indicated that the use of combination antipsychotics before the switch to clozapine treatment predicted clozapine augmentation such that the probability of augmentation increased up to 2.7 fold (at 95 % confidence interval :1.120-2.775; p=0.028)

Table 3. The Implemented Methods of Clozapine Augmentation in the Study Participants

	Participants (n)	(%)
Atypical AP*	18	56.3%
Typical AP**	7	21.9%
MS	3	9.4%
Benzodiazepine	1	3.1%
ECT	3	9.4%
TOTAL	32	100%

AP:Antipsychotic, MS: Mood Stabilizer; ECT: Electroconvulsive Therapy
*Frequency of Atypical AP Use:
Risperidone>Amisulpride>Aripiprazole>Sulpride>Quetiapine=Olanzapine
** Frequency of Typical AP Use : Fluphenazine>Zuclopenthixol

Table 4. Clinical Assessment Scores for the Severity of Psychopathology, Comorbidities and Disability in the Participants on Augmented and Nonaugmented Clozapine Treatment

	Participants on Augmented Treatment (n=32)		Participants on Nonaugmented Treatment (n=90)		*p*
	Mean ± SD	Median (Mini.-Maxi.)	Mean ± SD	Median (Mini.-Maxi.)	
PANSS	64.7±19.7	63.5(35-122)	56.3±16.2	54(32-115)	0.027
CDSS	5.0±3.9	4(0-17)	3.3±3.6	2(0-13)	0.013
YBOCS Obsession	6.9±5.9	6(0-19)	4.3±5.3	2(0-17)	0.034
YBOCS Compulsion	8.4±5.7	10(0-19)	6.1±5.3	5(0-18)	0.081
YBOCS Total	15.3±10.5	14(0-38)	10.4±9.6	8(0-31)	0.020
PAS	8.8±12.0	1.5(0-36)	3.8±6.3	0(0-27)	0.148
GAF	6.7±1.5	7(21-30–81-90)	7.3±1.2	7(21-30–81-90)	0.053
CGI-severity	3.9±1.2	4(2-6)	3.4±1.0	3(2-6)	0.022
CGI-improvement	2.3±0.8	2(1-4)	2.1±0.7	2(1-4)	0.201
CGI-side effect	2.0±0.2	2(1-3)	2.1±0.3	2(2-4)	0.355
WHO-DAS-II	38.1±21.9	39.2(4.8-81.3)	24.3±17.1	20.1(2.8-78.5)	0.002

PANSS: Positive and Negative Syndrome Scale, CDSS: Calgary Depression Scale for Schizophrenia, YBOCS: Yale-Brown Obsession-Compulsion Scale, PAS: Panic Agoraphobia Scale, WHO-DAS-II: World Health Organization Disability Assesment Schedule-II-, GAF Global Assesment of Functioning, CGI: Clinical Global Impression Scale

DISCUSSION

This study, carried out on 122 participating patients diagnosed with schizophrenia on the DSM-IV criteria at the outpatient clinic of the Department of Psychiatry at Hacettepe University Faculty of Medicine, investigated the use of clozapine augmentation methods for resistance to clozapine monotherapy with reference to the sociodemographic and clinical characeristics of the participants. The entire group of participants displayed a typical course of disease onset on the basis of the data on sociodemographic and clinical parameters and had been under treatment for nearly two decades. Analyis of the clinical assesment tools for psychopathology revealed that the clinical severity of disease, disability and the loss of functionality indicated a moderate level of disorder.

Although clozapine has been proven to be the most effective antipsychotic agent for the management of treatment resistant schizophrenia, only 45-70% of these patients are observed either to respond partially or not at all to monotherapy with clozapine (Vayısoğlu and Anıl Yağcıoğlu 2013, Tiihonen et al. 2009). Augmentation of clozapine is being attempted in cases with lack of response. In our study, 26% of the participants currently used and 16% had previously received augmented clozapine treatment, while 58% of the participants were on nonaugmented clozapine treatment. The prevalence of augmented clozapine treatment in Turkey is not known. The incidence of using augmented clozapine treatment was 24% among 86 patients studied in our clinic in 2002 (Anıl et al. 2002) which matches the results of the present study. However, higher incidences of implementing augmentation therapy elsewhere in the world have been reported. In Australia, for example, 84% of the 84 treatment resistant schizophrenia patients investigated in a cross-sectional study were on clozapine treatment augmented with antipyschotic agents (72%), antidepressants (30%) or mood stabilizers (17%) (Pai et al. 2012). The variation in selecting and implementing clozapine augmentation in different clinical environments may be associated with multiple factors including, the point of view regarding polypharmacy and definition of response inadequacy to treatment, as well as the individual clinical variations on disease severity and duration, comorbidities and opportunity of hospitalisation. Heterogeneity in the results of the reported work in the literature on clozapine augmentation complicates the progress to a common approach to the problem. Comparative evaluation of our results with those in the literature is prevented since most of the factors investigated in the present study as possible indications for augmentation have not been included within previous research reported in the literature. The participant groups of this study on augmented and nonaugmented clozapine treatment did not differ significantly on the basis of gender, age, education, marital status, employment status, family history of mental disorders, age at onset of illness, time taken to switch to clozapine treatment and duration of clozapine use. These results agree with the demonstration of the lack of differences on the basis of age, gender, education level, marital and employment states between patients on augmented and nonaugmented clozapine treatment in the previous study undertaken in our clinic (Anıl et al. 2002).

It is shown here that the clozapine dose used by the participants on augmented treatment was higher than the dose used by the participants on clozapine monotherapy. The inadequacy of the response to clozapine by this group of participants despite being on high dosage was attributed to the progressive increases in the clozapine dosage before starting augmentation. The observed increase in the therapeutic dose was not reflected in the levels of clozapine and clozapine/norclozapine ratio in the blood. The possibility of an association of this observation with pharmacogenetics and multiple drug use was considered. It, however, becomes difficult to comment on a possible effect of cigarette smoking on the blood level of the clozapine/norclozapine ratio since the participants on augmented and nonaugmented therapy did not differ in either respect.

It was observed that 78.2% of the participants were put on clozapine augmentation with atypical (56.3%) or typical (21.9 %) antipsychotics, this distribution being in agreement with the relevant literature (Elkis and Buckley 2016). Given the limited number of participants, it was not possible to analyse in this study which of the augmentation approaches were more effective on the clinical response. The evidence for the efficacy of clozapine augmentation was categorised after evaluating the combined data of 21 meta-analyses in a current meta-review. The highest achieved evidence level was associated with the systematic review of high quality case control or cohort studies. The methods supporting this level of evidence for treatment efficacy comprised the use of the first and the second generation antipsychotics in combination, the use of ECT for persistent positive symptoms and the use of the antidepressants fluoxetine, duloxetine and citalopram for persistent negative symptoms (Wagner et al. 2019).

When the patients who are on remission with clozapine are compared with the ones who are not, with respect to use of augmentation treatment, patients who are not in remission are found to have higher rate of augmentation treatment.

This can either be attributed to the low efficacy of the augmentation therapies in inducing remission or the inadequacy of clozapine monotherapy which results in more resistant schizophrenia patients being put on treatment with augmentation methods to achieve remission. It is not possible to discern within the scope of this crossectional study which of these explanations is valid, indicating that longitudinal follow up studies are required.

After comparing the results on clinical assessments of severity of psychopathology, comorbidity and disability and impairment of functioning between the participants on augmented and nonaugmented clozapine treatment, significant intergroup differences were seen in all scores except those on the PAS, the YBOCS compulsion subtest and the CGI subtests on improvement and side effects. This finding was attributed to increased resorting to augmentation treatment when the impairment of functioning and the severity of psychopathology, depression, obsessive symptoms and disabilities increased.

Finding that 16% (n=21) of the participants had a history of augmentation treatment that was terminated on grounds of inefficacy is noteworthy, and trials on their cases with different augmentation methods should be expected in the course of future follow up. It must therefore be kept in mind when implementing augmentation treatment that there are patients with a similar history, which may require new and different augmentation methods. In this context, it is worth considering that having conducted this study in a single center may have caused a bias in the selection of augmentation methods.

It has been shown in this study that the participants on augmented clozapine treatment had previously used significantly more number of treatments with combination of antipsychotics. Since the users of augmented treatment had also given inadequate response to therapy before switching to clozapine, it was thought that they had been exposed to treatment combinations not given a high level of efficacy in the guidelines.

Having a history of treatment with combination antipsychotics before switching to clozapine treatment was found to be the only variable to predict the requirement of starting augmentation of clozapine. It was thought that the increased incidences of using alternative combination therapies in a subgroup of participants was due to their considerable difficulty in responding to monotherapy. Although this subgroup was assumed to have the severest disease symptoms before the initiation of clozapine treatment, the cross sectional design of the study precluded the explanation of this situation. Repeated investigation of the data on the subject indicated that 56% of the participants with a history of using combination antipsychotics were also users of augmented clozapine treatment during the evaluation interviews at the outset of this study. In summing up, the presence of a subgroup of schizophrenia cases can be cited as being the 'most resistant to treatment'.

Participation in this study was refused by 13 patients. There may have been unsettled symptoms and rather severe clinical conditions underlying these refusals. This gives reason to believe that the severity of the psychopathology in those patients who agreed to participate in the study was relatively moderate and their compliance with treatment was therefore better.

Not being designed as a progressive follow up study, exclusion of a follow up period for the given treatments, use of crossectional data and requirement of retrospective investigations are among the most significant limitations of this study. Also, not having reached remission may have been due to incompliance of the participant with the recommended therapeutic regimen rather than being caused solely by the inefficacy of the chosen treatment. In that context, not including the investigation of treatment compliance within the scope of the study can also be considered as a limitation.

In conclusion, despite the insufficieny of the existing evidence, it can be seen that the use of a second antipsychotic agent to enhance the effectiveness of clozapine on psychotic symptoms is the most frequently implemented augmentation method. Until the development of agents superior to clozapine, it should be aimed to design new and more effective methods of augmenting its efficacy and to introduce those found beneficial to clinical application.

REFERENCES

Addington D, Addington J, Maticka-Tyndale E (1993) Assessing depression in schizophrenia: the Calgary depression scale. Br J Psychiatry (Suppl Dec 22): 39-44

American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (Translation Editor: E Köroğlu). Ankara, Hekimler Yayın Birliği.

Andreasen NC, Carpenter WT Jr, Kane JM et al (2005) Remission in schizophrenia: proposed criteria and rationale for consensus. Am J Psychiatry 162:441-9.

Anıl AE, Turgut İT, Kabakçı E et al (2002) Klozapin tedavisi alan hastaların özellikleri, tedaviye yanıtı, başvurulan güçlendirme yöntemleri, tedavi emniyeti ve ek ilaç kullanımı: Geriye dönük dosya analizi bilgileri. 3P Dergisi 10:129-40.

Anıl Yağcıoğlu AE, Gürel ŞC (2018) Şizofrenide tedaviye direnç. TPD Şizofreni ve Diğer Psikotik Bozukluklar. Güncellenmiş 2. Baskı. Editörler: Esen Danacı A, Böke Ö, Saka MC, Erol A, Ulusoy Kaymak S. Türkiye Psikiyatri Derneği Şizofreni ve Diğer Psikotik Bozukluklar Bilimsel Çalışma Birimi. Türkiye Psikiyatri Derneği Yayınları, Bilimsel Çalışma Birimleri Dizisi 22, s: 494-518.

Aydemir Ö, Esen Danacı A, Deveci A et al (2000) Sensitivity and specifity of the Turkish version of Calgary depression scale for schizophrenia. Arch Neuropsyhiatr 37:82-6.

Bandelow B (1995) Assessing the efficacy of treatments for panic disorder and agoraphobia. II. The Panic and Agoraphobia Scale. Int Clin Psychopharmacol 10:73-81.

Chakos M, Lieberman J, Hoffman E et al (2001) Effectiveness of second-generation antipsychotics in patients with treatment resistant schizophrenia: a review and meta-analysis of randomized trials. Am J Psychiatry 158:518-26.

Elkis H, Buckley P (2016) Treatment-resistant schizophrenia. Psychiatr Clin North Am 39:239-65.

Endicott J, Spiltzer RL, Fleiss JL et al (1976) The global assessment scale. A procedure for measuring overall severity of psychatric disturbance. Arch Gen Psychiatry 33:766-71.

Goodman WK, Price LH, Rasmussen SA et al (1989) The Yale-Brown obsessive compulsive scale. I. development, use, and reliability. Arch Gen Psychiatry 46:1006-11.

Guy W (1976) ECDEU Assessment Manual for Psychopharmocology- Revised. U.S. Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, National Institute of Mental Health; Psychopharmacology Research Branch; Division of Extramural Research Programs. p. 218–22.

Gürel ŞC, Anıl Yağcıoğlu AE (2018) Şizofrenide elektrokonvulzif tedavi ve diğer beyin uyarımı tedavileri. TPD Şizofreni ve Diğer Psikotik Bozukluklar. Güncellenmiş 2. Baskı. Editörler: Esen Danacı A, Böke Ö, Saka MC, Erol A, Ulusoy Kaymak S. Türkiye Psikiyatri Derneği Şizofreni ve Diğer Psikotik Bozukluklar Bilimsel Çalışma Birimi. Türkiye Psikiyatri Derneği Yayınları, Bilimsel Çalışma Birimleri Dizisi- No:22, s. 473-93.

Karamustafalıoğlu OK, Üçışık MA, Ulusoy M et al (1993) Yale Brown obsesyon kompulsiyon derecelendirme ölçeğinin geçerlilik ve güvenirlik çalışması. Serbest Bildiri, 28. Ulusal Psikiyatri Kongresi Bursa

Kay SR, Fiszbein A, Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13:261-76.

Kishimoto T, Hagi K, Nitta M et al (2019) Long-term effectiveness of oral second-generation antipsychotics in patients with schizophrenia and related disorders: a systematic review and meta-analysis of direct head-to-head comparisons. World Psychiatry 18:208-24

Kostakoğlu AE, Batur S, Tiryaki A et al (1999) Reliability and validity of the Turkish version of the posiitive and negative syndrome scale (PANSS). Turkish Journal of Psychology 14:23-32.

Lehman AF, Lieberman JA, Dixon LB et al (2004) Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry 161 (Suppl 2):1-56.

Leucht S, Corves C, Arbter D et al (2009) Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 373:31-41.

Leucht S, Cipriani A, Spineli L et al (2013) Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 382:951-62.

Moore TA, Buchanan RW, Buckley PF et al (2007) The Texas medication algorithm project antipsychotic algorithm for schizophrenia: 2006 Update. J Clin Psychiatry 2007;68:1751-62.

National Institute for Health and Clinical Excellence (NICE): Guidance (2014) Psychosis and schizophrenia in adults: treatment and management: updated edition https://www.nice.org.uk/guidance/cg178

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Özkürkçügil A, Aydemir Ö, Yıldız M et al (1999) DSM-IV eksen I bozuklukları için yapılandırılmış klinik görüşmenin Türkçeye uyarlanması ve güvenilirlik çalışması. İlaç ve Tedavisi Dergisi 12:233-6.

Pai NB, Laidlaw M, Vella SC (2012) Augmentation of clozapine with anotherpharmacological agent: treatment for refractory schizophrenia in the 'real world'. Acta Psychiatr Scand126:40-6.

Siskind D, McCartney L, Goldschlager R et al (2016) Clozapine v. first- and second generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. Br J Psychiatry 209:385-92.

Siskind D, Siskind V, Kisely S (2017) Clozapine response rates among people with treatment-resistant schizophrenia: data from a systematic review and meta-Analysis. Can J Psychiatry 2017 62:772-7.

Sommer IE, Begemann MJH, Temmerman A et al (2012) Pharmacological augmentation strategies for schizophrenia patients with insufficient response to clozapine: a quantitative literature review. Schizophr Bull 38:1003-11.

Taylor DM, Duncan-McConnell D (2000) Refractory schizophrenia and atypical antipsychotics. J Psychopharmacol 14:409-18.

Taylor DM (2017) Clozapine for treatment-resistant schizophrenia: still the gold standard? CNS Drugs 31:177-80.

Tek C, Uluğ B, Rezaki BG et al (1995) Yale-brown obsessive compulsive scale and US national institute of mental health global obsessive compulsive scale in Turkish: reliability and validity. Acta Psychiatr Scand 91:410-3.

Tiihonen J, Lonnqvist J, Wahlbeck K et al (2009) 11-year followup of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). Lancet 374:620-7.

Tural Ü, Fidaner H, Alkın T et al (2000) Panik agorafobi ölçeğinin güvenirlik ve geçerliği, Turk Psikiyatri Derg 11:29-39.

Uluğ B, Ertuğrul A, Göğüş A et al (2001) Reliability and validity of the Turkish version of the World Health Organisation disability assessment schedule-II (WHO-DAS-II) in schizophrenia. Turk Psikiyatri Derg 12:121-30.

Vayısoğlu S, Anıl Yağcıoğlu AE, Yağcıoğlu S et al (2013) Lamotrigine augmentation in patients with schizophrenia who show partial response to clozapine treatment. Schizophr Res 143:207–14.

Wagner E, Löhrs L, Siskind D et al (2019) Clozapine augmentation strategies-a systematic meta-review of available evidence. Treatment options for clozapine resistance. J Psychopharmacol 33:423-35.

Wahlbeck K, Cheine M, Essali A et al (1999) Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. Am J Psychiatry 156:990–9.

Wahlbeck K, Cheine M, Essali MA (2000) Clozapine versus typical neuroleptic medication for schizophrenia. Cochrane Database Syst Rev 2:CD000059.

World Health Organization (1999) The World Health Organization Disability Assessment Schedule Phase II Field Trial Instrument. The World Health Organization, Geneva, Switzerland