Therapy Resistant Schizophrenics Alprazolam Versus Carbamazepine "As Augmenting Therapy"

Okasha A., Raafat M., Khalil A.H. ,Seif El Dawala A., Effat S. and Shohdy A.

Abstract

An open study was carried out on 36 therapy resistant aggressive schizophrenics. Patients were classified to two groups, the first receiving Carbamazepine (CZ), the second had Alprazolam (AZ) as an adjunct to their neuroleptics (NL). Assessment was made before and after two weeks, then six weeks after treatment, using Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression (CGI). Topographic EEG was done to all patients and in spite of non-specific changes and occasional focal abnormality, it has no relationship to the response to either CZ or AZ. The results showed significant improvement in CGI where AZ produced improvement in 57.9%, unchanged in 42.1%, and none of the cases became worse, while CZ showed 42.1%, 52.63%, and 5.27% respectively, but the differences were non significant. CZ showed better response in conceptual disorganization and unusual thoughts ($p>0.002$), while AZ had a better response with hostility, suspiciousness, excitement ($p>0.001$), anxiety and depression ($p>0.03$). Both drugs had a slight effect on motor retardation, withdrawal and blunted affect. The required maintenance treatment on NL was reduced by one third after four weeks of therapy with either CZ or AZ. The possible role of reducing kindling phenomena, increased Gabanergic activity and increasing NL plasma level are probable factors in ameliorating some symptoms and facilitating the response of the patients to their previous NL

Abbreviations

CZ:	*Carbamazepine.*	*AZ:*	*Alprazolam.*
NL:	*Neuroleptics.*	*BPRS:*	*Breif Psychiatric Rating Scale.*
CGI:	*Clinical Global Impression.*		

Introduction Psychiatrists are faced in their daily clinical practice with a group of schizophrenics who are non-responders to the classical NL agents. However, given the relative absence of evidence that patients respond substantially better to one NL than to another (although side effects profiles and patient's tolerance differ markedly), considerations of adjunctive treatment with non-neuroleptic agents such as lithium, anti-convulsants, benzodiazepines, non-classical neuroleptics may be given higher priority than it was only a decade ago. Kane et al. (1988) indicated a conservative estimate that 10-20% of schizophrenic patients "derive little benefit from typical NL drug therapy. Recent data suggest an adjunctive role for AZ and CZ in the treatment of neuroleptic resistant symptoms in a subgroup of chronic schizophrenics. Some authors claim the target effects of both drugs on either positive or negative symptoms of schizophrenia.

Methodology Thirty six resistant male schizophrenics were selected randomly from a sample of resistant schizophrenic patients in a psychiatric unit in Cairo. The diagnosis was based on the DSM-III-R criteria (Table 1). The patients ages ranged between 22-48 years. The patients had been ill for at least 2 years, the duration of the schizophrenic disorder ranging between 3 to 12 years with an average mean duration of 5.5 years. All patients were on maintenance treatment of NL and the majority were on a combined regime of depot injection and oral NL (at least two types).The depot NL on which patients were maintained at the beginning of the trial were either fluphenaine enanthate (25mg every two weeks) or flupenthixol decanoate (40 mg every two weeks). The oral medication was either trifluperazine (18.4 ± 4.3 mg/day) or haloperidol (29.8 ± 6.2 mg/day). All patients received courses of ECT

during the acute phases or exacerbations of the schizophrenic disorder.

In spite of all lines of treatment, all patients showed poor response to NL and a tolerance to high doses in cases with moderate or severe psycho-pathology. For resistant patients we followed the rigorous set of research criteria proposed by Kane et al. (1988) which is as follows:

1. Historical: no period of good functioning within the preceeding five years with NL (for at least two chemical classes) at dose equivalent to or greater than 1000 mg/day of chlorpromazine or 6 weeks without significant relief.

2. Cross-sectional: BPRS score of at least 45, CGI score of at least 4, and item scores of at least 4 (moderate) for two of the following four items: conceptual disorganization, suspiciousness, hallucinatory behaviour and unusual thought content.

3. Prospective failure to decrease BPRS by 20% or below 35, or failure to decrease CGI score to 3 (mildly ill) after a 6 week trial of haloperidol (dose up to 60 mg/day).

All patients and their families agreed to the addition of the two new treatments as an adjunctive to their NL. A written consent was taken.

CZ was given to 18 patients and the same with Az in an alternative sequence. No reduction of their maintained medications was made except after four weeks. The average doses of AZ were 3.4 ± 1.2 mg/day and those of CZ were 600 ± 150 mg/day.

Patients were rated initially on entry and after two and six weeks using the following:

1. The Clinical Global Impression (CGI) which was used to assess the severity of the disorder and the therapeutic effect *(Guy, 1976; McGlashan, 1983).*

2. The Brief Psychiatric Rating Scale (BPRS). *(Overall and Gorham, 1983).*

3. Topographic EEG using Brain Imager (Dantec-Sigen)l where topographic mapping of the brain takes place in the form of colored maps that show the distribution of the brain electrical activity 1 was done to all patients at entry to find any possible correlation between response to CZ or AZ and any epileptogenic activity.

The diagnosis and the rating on the BPRS and the CGI were all done by at least two experienced psychiatrists in a common interview setting.

Serum concentration of both AZ and CZ was not done as facilities were not available and dosage increment was based on the progress of the clinical condition and improvement.

Results Tables (2, 3, 4) show the severity of symptoms at the beginning and at the end of the trial. In spite of the absence of any significant difference between the ameliorating effects of either AZ or CZ. AZ seemed to have a better effect at the end of a six weeks follow up period.

Using the CGI addition of AZ showed 57.9% improvement 42.1% unchanged and none became worse, while CZ showed improvement in 42.1%1 no change in 52.63% and worsening in 5.27% of cases (Table 2). The differences were statistically significant.

The percentage of improvement was dependent on the changes of scores of CGI from severe to moderate and/or mild.

Applying the paired "t" test, both drugs induced a significant clinical improvement but there was no statistical significance of the superiority of either; the CGl of the augmenting effect of AZ was significant at the level of p >0.0011 and that of CZ at the level of p >0.05 (Table 5)

The average total score of BPRS at the beginning of the trial was 69.74 for AZ and 72.74 for CZ, i.e. showing no significant differences neither in total nor in sub-scores. After six weeks, it declined to 60.16 and 66.21 respectively (Tables 3,4) with significant augmenting effect of p <0.001 with AZ and p <0.005 with CZ.

Comparing both drugs regarding their clinical effects showed no statistical difference between both. The improvement of augmenting NL with AZ was at the level of p> 0.05 and similar in the case of CZ.

On applying statistical analysis to the subscales of BPRS, in anxiety and depression, AZ showed a significant improvement of p>0.05

while in the case of CZ the improvement was insignificant p< 0.05.

In conceptual disorganization and unusual thought content, CZ was superior to AZ with a significance of p< 0.002 for the former drug and p<0.02 for the latter.

The response to hostility, suspiciousness and excitement to the adjunctive therapy revealed that AZ was superior to CZ with a significance of p <0.001 for AZ and p <0.02 for CZ. Improvement in motor retardation, withdrawal and blunted affect with either drugs was non-significant (p> 0.05) (Table 5).

More than two thirds (29) of our schizophrenic patients on medication had abnormal topographic EEG, mainly in the form of generalized cerebral dysfunction. The presence or absence of abnormality did not have any statistically significant effect on the response to addition of CZ or AZ to NL medication.

TEEG was repeated in 4 patients of each group (i.e. AZ and CZ therapy) and there was no change of any significance as compared with the pre-treatment TEEG.

Four weeks after the initiation of the trial an attempt was made to reduce the dose of the maintenance treatment of NL. A reduction of about one third of the dosage of NL did not affect or alter the clinical condition and diminished the intensity of side effect.

Discussion Twelve double-blind studies have evaluated the efficacy of benzodiazepines as adjunctive treatment in combination with NL in the treatment of schizophrenia. Of these studies, six reported some positive effects *(Atamura et al.,1987; Guz et al., 1972; Kellneret al.,1975; Lingjaerde,1982; Lingjaerde et al.,1979; Wolkowitz et al.,1988),* three reported negative effects *(Hanlon et al., 1960, 1970; Karson et al., 1982),* and three reported mixed effects *(Csernansky et al., 1988; Holden et al., 1968; Michaux et al., 1966).* It must be noted that many of the early studies had methodological flaws, including non-uniform diagnoses, nonspecific rating scales and poor statistical analyses. When studies conducted since 1975 only were examined, six of the seven studies *(Altamura et al., 1987; Csemansky et al., 1988; Kellner et al., 1975; Lingjaerde, 1982; Lingjaerde et al., 1979; Wolkowitz et al., 1988)* reported some positive effects, although in some of the studies the positive effects were modest, transient, or specific for certain symptoms. Those studies examined the effects of different benzodiazapenes and it is unknown if specific benzodiazepines are more clinically effective than others.

Few studies have examined dose-response relationship in benzodiazepine treatment of schizophrenia or possible benzodiazepine-neuroleptic pharmacokinetic interactions. Csernansky et al.(1988) reported that mean plasma AZ levels were inversely correlated with withdrawal-retardation ratings, although those results were largely determined by two outlying patients.

In an open-label trial of AZ augmentation in treatment resistant schizophrenics, Douyon et al,(1989) similarly found that patients with higher plasma AZ levels (greater than 25 ng/ml) responded more favourably (with reductions in ratings of positive and negative symptoms) than did patients with lower levels and they raised the possibility of adjusting AZ doses to achieve plasma levels of 60-80 mg/ml. They also observed that AZ increased haloperidol or fluphenazine levels by an average of 23%, but they suggested that the clinical effects they observed were not secondary to this. The study of Wolkowitzetal (1988) found that the clinical response was not correlated with plasma AZ levels: the average plasma AZ level attained in the receptors was only 18.5 mg/ml. They also found that AZ administration did not significantly alter plasma fluphenazine levels.

It is unknown if benzodiazepine responsivity represents a "state" (transient) or "trait" (enduring) characteristic of individual patients. The data of Kellner et al. (1975) suggest that some but not all patients who initially responded to benzodiazepine augmentation continue to show favourable responses when the sarne benzodiazepine was readministered.

It should also be noted that several studies with AZ augmentation *(Csernansky et al., 1984; Douyon et al., 1989; Kahn et al., 1988; Wolkowitz et al., 1986)* have commented on clinical changes in individual patients that are not characteristic of NL effects, such as

improvements in social and emotional relatedness, spontaneity, sociability, affability, humor and increased interest in family and social life.

In using benzodiazepines in schizophrenia, two perspectives are conceptualized in explaining their efficacy. By reducing anxiety, benzodiazepines help patients with prominent anxiety symptoms and anxiety agitated patients. Indeed, retrospective and prospective studies have found benzodiazepines to lower doses of NL *(Salzman et al 1985).*

In addition to having anti-anxiety and sedation effects, benzodiazepines may have more specific anti psychotic effects via two additional mechanisms. Animal studies have shown that benzodiazepines decrease pre-synaptic dopamine release in the brain *(Singhal* et *al., 1983; Wood, 1982)* and to modulate the stress/benzodiazepine-sensitive prefrontal cortical dopamine system *(Deutsch* et *al., 1985; Lavielle et al., 1978; Tamand Roth, 1985).*

A more recent elaboration of the dopamine hypothesis proposes that neuroleptic induced post synaptic receptor blockade is the first action in a chain of events that ultimately leads to a decrease in pre-synaptic dopamine release; the time course of this decrease in dopamine release more closely parallels that of clinical efficacy *(Pickar,* 1966; *Pickar et al.,* 1984, 1986). Animal and human studies indicate that NL acutely increase dopamine turnover, reflected by increased levels of homovanillic acid (HVA). Benzodiazepines have been found to blunt the acute neuroleptic induced rise in HVA in the rat brain *(Kelleretal., 1976)* and thus might be expected to facilitate or expedite those clinical reponses dependent on decreases in presynaptic dopamine release.

Benzodiazepines also shift to the left the dose response curve relating haloperidol doses to catalepsy in rats, providing behavioural evidence that benzodiazepines, added to neuroleptics, further decrease dopamine activity at the post synaptic receptor *(Keller et al., 1976).*

The first study to report an open clinical trial of the addition of CZ to neuroleptics in schizophrenic patients was that of *Hakola and Lauluma* (1982). Their study focused on schizophrenic women with abnormal EEGs and frequent violent outbursts. The patients had been tried on neuroleptics up to "high" doses (mean 2.040 chlorpromazine equivalents). The authors reported that violent behaviour and symptoms of psychosis were decreased when CZ was introduced. The degree of response could be assessed because no rating scales were used, but the overall outcome in a patients' population that is difficult to treat provided new enthusiasm for the use of CZ.

Unlike lithium added to NL, the early articles on the addition of CZ to NL focused on specific subtypes of schizophrenia (e.g. patients with schizophrenia who were still violent despite neuroleptic treatment). The *Kidron* etal. (1985) study was actually the first to address non responders not selected for the treatment of violence, abnormal EEG, or epilepsy. In their group of 11 subjects, none improved enough to be considered for further treatment with CZ. An important part of the study was the description of dramatically lowered haloperidol blood levels following added CZ.

We suggest that augmenting NL in a subgroup of therapy resistant schizophrenics with AZ or CZ have significant beneficial effect. AZ is more helpful in hostility, suspiciousness, excitement, anxiety and depression, while CZ is better in conceptual disorganization and unusual thought content.

The addition of AZ or CZ may allow us to reduce the dosage of NL which has a beneficial effect on diminishing side effects whether extrapyramidal or anticholinergic.

The mode of action is unknown, but is probably through decreasing of the presynaptic

dopamine release, increasing gabanergic activity, affecting the kindling phenomenon of aggression and hostility, or through synergistic effects of altering the plasma level of NL. The anti convulsive properties of CZ and AZ cannot explain the mode of action, as the TEEG abnormalities did not have any positive correlates with the clinical effect.

Table 1: DSM-III-R Criteria For Schizophrenia 295-xx

A Presence of characteristic psychotic symptoms in the active phase: either (1), (2) or (3) for at least one week (unless the symptoms are successfully treated):

(1) two of the following:

a) Delusions.

b) Prominent hallucinations (throughout the day for several days or several times a week for several weeks, each hallucinatory experience not being limited to a few brief moments.

c) Incoherence or marked loosening of associations.

d) Catatonic behaviour.

e) Flat or grossly inappropriate affect.

(2) Bizarre delusions (i.e involving a phenomenon that the person's culture would regard as totally implausible, e.g. thought broadcasting, being controlled by a dead person).

(3) Prominent hallucinations (as defined in [1b] above) of a voice with content having no apparent relation to depression or elation, or a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices conversing with each other..

B. During the course of the disturbance. functioning in such area as work, social relations, and selfcare is markedly below the highest level achieved before onset of the disturbance (or when the onset in childhood or adolescence, failure to achieve expected level of social development.).

C. Schizoaffective disorder and Mood disorder with psychotic features have been ruled out.

D. Continuous signs of the disturbance for at least six months.

E- It cannot be established that an organic factor initiated and maintaind the disturbance.

Table (2): Improvement of CGI after six weeks of treatment with AZ and CZ

Group %	Improved %	No change %	Worse %
AZ	57.9	42.1	None
CZ	42.1	52.63	5.27

Table (3): Comparison between AZ and CZ groups before treatment regarding different variables

Variable	AZ	CZ	"t" p	P
	Mean ± S.D.	Mean ± S.D.		
Bprs scores	69.74 ± 7.06	72.74 ± 6.54	1.30	>0.05
Total subscores				
Thought disorder	9.78 ± -1.68	10.42 ± -1.21	1.36	>0.05
Anxiety depression	6.31 ± -0.20	6.68 ± -1.29	1.05	>0.05
Hostility suspicion	14.21 ± -1.71	13.63 ± -2.54	0.87	>0.05
Retardation / Withdr	10.84 ± -6.55	12.26 ± -8.07	1.82	>0.05
CGI scores	5.52 ± -0.51	5.57 ± -0.060	0.29	>0.05

Table (4): Comparison between AZ and CZ groups regarding the different variables six months after starting treatment

Variable	AZ Mean ± S.D.	CZ Mean ± S.D.	"t" p	P
Bprs scores	60.16 ± 10.5	66.21 ± -9.8	1.84	>0.05
Total subscores				
Thought disorder	8.89 ± -1.56	9.10 ± -1.4	0.43	>0.05
Anxiety depression	5.75 ± -1.39	6.42 ± -1.89	1.17	>0.05
Hostility suspicion	11.21 ± -3.04	11.89 ± -2.23	0.92	>0.05
Retardation / Withdr	10.42 ± -3.04	11.84 ± 3.16	1.41	>0.05
CGI scores	5.05 ± -2.90	5.31 ± -3.10	1.39	>0.05

Table (5) : Mean differences of scores before and after treatment among AZ and CZ gtoups of patients

Variable	AZ			CZ		
	Mean ± S.D.	"t" p	p	Mean ± S.D.	"t" p	p
BPRS scores	9.85 ± 6.24	6.24	< 0.001	6.53 ± 2.04	3.14	< 0.005
Total subscores thought disorder	0.89 ± 3.47	2.56	< 0.02	1.32 ± 3.5	3.58	< 0.002
Anxiety depression	0.56 ± 2.21	2.38	< 0.03	0.26 ± 4.49	0.59	< 0.05
Hostility / suspicion	3 ± 6.70	4.44	< 0.001	1.74 ± 6.2	2.8	< 0.02
Retardation / Withdrawal	0.42 ± 3.80	1.36	> 0.05	0.42 ± 2.3	1.8	> 0.05
CGI scores	0.47 ± 1.9	4.87	> 0.001	0.26 ± 1.6	2.15	< 0.05

References

Altamura, AC, Mauri MC, Mantero M, et al (1987): Clonazepam / Haloperidol combination therapy in schizophrenia: a double blind study. Acta Psychiatry Scand 76: 702 - 706.

Csernansky JG, Lombrozo L, Gulevich G, et al (1984): Treatment of negative schizophrenic symptoms with alprazolam: a preliminary open-label study. J. Clin. Psychophaemacol 4: 349 - 352.

Csernansky JG, Rieny SJ, Lombrozo L, et al (1988): Double blind comparison of alprazolam, diazepam and placebo for the treatment of negative schizophrenic symptoms. Arch Gen. Psychiatry 45: 556-659.

Deutsch AY, Tam SY, Roth RH (1985): Footshock and conditioned stress increase 4.3 dihydroxy phenylacetic acid (DOPAC) in theventral tegmental area but not substantia nigra. Brain Res 333: 143-146.

Douyon R, Angrist B, Peselow E, et al (1989): Neuro-leptic augmentation with alprazolam: Clinical effects and pharma cokinetic correlation. Am. J. Psychiatry 146:231-234.

Guz L, Moraea R, Sartoretto JN (1972): The therapeutic effects of lorazepam in psychotic patients treatedwith haloperidol: a double blind study. Current Therapeutic Research. Clinical andExperimental 14: 767-774.

Hakola HPA, Lauluma VA (1982): Carbamazepine in treatment of violent schizophrenic: Lancet 1: 1358.

Hanlon TE, Otaky, Agallianos DD et al (1969): Combined drug treatment of newly hospitalized, acutely ill psychiatric patients. Diseasesofthe Nervous System 30: 104-116.

Hanlon TE, Ota KY, Kurland AA (1970): Comparative effects of fluphenazine, fluphenazine-chlordiazepoxide and fluphenazine imipramine. Diseases of the Nervous System 31: 171 -177.

Holden JMC, Itil TM, Keskiner A, et al (1968): Thioridazine and chlordiazepoxide, alone and combined, in the treatment of chronic schizophrenia. Compr Psychiatry 9:633-643.

Kahn JP, Puertollano MA, Schane MD (1982): Adjunctive alprazolam for schizophrenia: negative results in a double blind, placebo controlled trial. AM.J . Psychiatry 139: 1627-1628.

Kane J, Honigfeld O, Singer J, et al (1988): Clozapine for the treatment of resistant schizophrenic. Arch Gen Psychiatry 45: 789-796.

Karson CN, Weinberger DR, Bigelow L, et al (1982): Clonazepam treatment of chronic schizophrenia: negative results in a double blind, placebo-controlled trial. Am J. Psychiatry139:1627-11628.

Keller H H, Schaffner R, Haefely W (1976): Interaction of benzodiazepines with neuroleptics at central dopamine neurons, Naunyn Schmiedebergs. Arch Pharmacol 294: 1-7.

Keller R, Wilson RM, Muldawer MD, et al (1975): Anxiety in schizophrenia: The responses to chlordiazepoxide in an intensive design study. Arch Gen Psychiatry 32: 1246-1254.

Kidron R, Averbuch I, Klein E, et al (1985): Carbamazepine-induced reduction of blood levels of haloperidol in chronic schizophrenia Biol Psychiatry 20: 219-222.

Lavielle S, Tassin J, Thierry A, et al (1978): Blockade by benzodiazepines of the selective high increase in dopamine turnover induced by stress in mesocortical dopaminergic neurons of the rat. Brain Res 168: 585-694.

Lingjaerde O (1982): Effect of benzodiazepine derivative estazolam in patients with auditory hallucinations: a multi center double-blind, cross-over study. Acta Psychiatry Scand 65: 339-354.

Lingjaerde O, Engstrand E, Ellingsen P, et al (1979): Antipsychotic effect of diazepam when given in addition to neuroleptics in chronic psychotic patients: a double-blind clinical trial. Current Therapeutic Research. Clinical and Experimental 26: 505-514.

Michaux MH, Kurland AA, Agallianos DD (1966): Chlorpromazine chlordiazepoxide and chlorpromazine-imipramine treatment of newly hospitalized, acutely ill psychiatry patients. Current Therapeutic Research. Clinical and Experimental 8: 117-152.

Pickar D (1988): Perspectives on a time-dependent model of neuroleptic action. Schizophr Bull14: 255-268.

Pickar D, Labarce R, Linnoila M, et al (1984): Neuroleptic-induced decrease in plasma homovanillic acid and antipsychotic activity in schizophrenic patients. Science 225: 954-957.

Pickar D, Labarca R, Doran AR, et al (1986): Longitudinal Measurement of plasma homovanillic acid levels in schizophrenic patients. Arch Gen Psychiatry 43: 669-676.

Salzman C, Green A, Rodriguez-Villa F, et al (1986): Benzodiazepines combined with neuroleptics for management of severe disruptive behaviour-Psychosomatics 27: 17-21.

Salzman C (1988): Use of benzodiazepines to control disruptive behaviour in patients. J Clin. Psychiatry 49: 13-15.

Singhal RL, Rastogi RB, Lapierre YD (1983): Diazepam potentiates the effect of neuroleptics on behavioural activity as well as dopamine and norepinephrine turnover: do benzodiazepines have antipsychotic potency? J Neural Transm 56: 127-138.

Tam Sy, and Roth RH (1985): Selective increases in dopamine metabolism in the prefrontal areas by the angiogenic beta-carboline FG-7142. Biochem Pharmacol 34: 1595-1598.

Wolkowitz OM, Pickar D, Doran AR, et al (1986): Combination alprazolam-neuroleptic treatment of the positive and negative symptoms of schizophrenia. Am J Psychiatry 143: 85-87.

Wolkowitz OM, Breier A, Doran A, et al (1988): Alprazolam augmentation of the antipsychotic effects of fluphenazine in schizophrenic patients. Arch Gen Psychiatry 45: 664-671.

Wood PL (1982): Action of GABAergic agents on dopamine metabolism in the nigrostriatal pathway of the rat. J Pharmacol Exp ther 222: 674679.

Authors

Okasha A.

Professor and Chairman of Neuro-Psychiatric Department, Faculty of Medicine, Ain Shams University, Abbasia, Cairo, Egypt.

Rafafat M.

Assistant Professor, Neurology- Department of Neuropsychiatry, Ain Shams University.

Khalil H.

Professor of Psychiatry Department of Neuropsychiatry Ain Shams University.

Seif - El Dawala A.

Lecturer of Psychiatry Department of Neuropsychiatry, Ain Shams Universitry.

Effat S.

Lecturer of Psychiatry Department of Neuropsychiatry, Ain Shams Universitry.

Shohdy A.

M.D. Psychiatry

Address of Correspondence

Prof. Okasha A.

P.O. Box 22 Deir El Malak, Cairo 11657.

علاج مرضى الفصام العدوانيين غير المستجبين للعلاج بإستخدام عقار البرازولام مقابل كربامازيبين "كعلاج معضد"

تم إجراء دراسة مفتوحة على ٣٦ من مرضى الفصام العدوانيين غير المستجيبين للعلاج، وقد صنف المرضى إلى مجموعتين: أعطى أفراد المجموعة الأولى كاربامازيبين بينما أعطى أعضاء المجموعة الثانية البرازولام كعلاج مساعد مع مضادات الذهان. وقد قيمت النتائج قبل أسبوعين من بدء العلاج ثم بعد أسبوعين وبعد ستة أسابيع من العلاج مستعملين إختبار معدل القياس النفسى المختصر واختبار الإنطباع الإكلينيكى الكلى. وقد تم عمل تخطيط المخ الكهربى بالكمبيوتر لكل المرضى، وبالرغم من وجود تغيرات غير محددة وبؤر شاذة من حين إلى آخر فأنها لم تكن ذات صلة بالإستجابة لكل من العقارين.

ولقد أوضحت النتائج أن هناك تحسنا ذا دلاله إحصائية فى الإنطباع الإكلينيكى الكلى حيث أدى البرازولام إلى التحسن فى ٥٧,٩٪ من الحالات وإلى عدم التغير فى ٤٢٪ و لم يحدث تدهور يذكر فى حين أن الكاربامازيبين قد أدى بالمقارنة إلى نسبة ٤٢٪ و ٥٢,٦٣٪ و ٥,٢٧٪، غير أن الفرق بينهما لايعتد به. وقد أدى العلاج بالكاربامازيبين إلى إستجابة أفضل بالنسبة للإضطراب الفكرى والأفكار غير العادية، بينما أدى البرازولام إلى إستجابة أفضل فى العدوانية والتوجس والإستثارة والقلق والاكتئاب، بينما كان لكل من الدواءين تأثير طفيف على البطء الحركى والإنطواء وتبلد الوجدان. ولقد قلت جرعات المداومة بمضادات الذهان إلى الثلث بعد أربعة أسابيع من العلاج بأى من العقارين، ولقد يعزى هذا الخفض إلى تقليل ظاهرة الاضرام أو زيادة نشاط الناقل العصبى "جابا" أو زيادة مستوى مضادات الذهان فى سائل الدم "البلازما" وهى عوامل محتملة فى تخفيف بعض الأعراض وتيسر إستجابة المرضى لعلاجهم السابق بمضادات الذهان.