Therapy Resistant Schizophrenics Alprazolam Versus Carbamazepine "As Augmenting Therapy"


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 Gabaergic 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

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 preceding 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).


3. Topographic EEG using Brain Imager (Dantec-Sigen) where topographic mapping of the brain takes place in the form of colored maps that show the distribution of the brain electrical activity. It 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% no change in 52.6% 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 CGI 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; Kellner et 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., 1965). 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; Csernansky 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 benzodiazepenes 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 same 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 (Keller et al., 1976) and thus might be expected to facilitate or expedite those clinical responses 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 et al. (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).

<table>
<thead>
<tr>
<th>Group</th>
<th>Improved %</th>
<th>No change %</th>
<th>Worse %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZ</td>
<td>57.9</td>
<td>42.1</td>
<td>None</td>
</tr>
<tr>
<td>CZ</td>
<td>42.1</td>
<td>52.63</td>
<td>5.27</td>
</tr>
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Table (3): Comparison between AZ and CZ groups before treatment regarding different variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>AZ</th>
<th>CZ</th>
<th>&quot;t&quot;</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± S.D.</td>
<td>Mean ± S.D.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bprs scores</td>
<td>69.74 ± 7.06</td>
<td>72.74 ± 6.54</td>
<td>1.30</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Total subscores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thought disorder</td>
<td>9.78 ± 1.68</td>
<td>10.42 ± 1.21</td>
<td>1.36</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Anxiety depression</td>
<td>6.31 ± 0.20</td>
<td>6.68 ± 1.29</td>
<td>1.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hostility suspicion</td>
<td>14.21 ± 1.71</td>
<td>13.63 ± 2.54</td>
<td>0.87</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Retardation / Withdrawal</td>
<td>10.84 ± 6.55</td>
<td>12.26 ± 8.07</td>
<td>1.82</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CGI scores</td>
<td>5.52 ± 0.51</td>
<td>5.57 ± 0.060</td>
<td>0.29</td>
<td>&gt;0.05</td>
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</tbody>
</table>
Table (4): Comparison between AZ and CZ groups regarding the different variables six months after starting treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>AZ Mean ± S.D.</th>
<th>CZ Mean ± S.D.</th>
<th>&quot;t&quot; p</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPRS scores</td>
<td>60.16 ± 10.5</td>
<td>66.21 ± 9.8</td>
<td>1.84</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Total subscores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thought disorder</td>
<td>8.89 ± 1.56</td>
<td>9.10 ± 1.4</td>
<td>0.43</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Anxiety depression</td>
<td>5.75 ± 1.39</td>
<td>6.42 ± 1.89</td>
<td>1.17</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hostility suspicion</td>
<td>11.21 ± 3.04</td>
<td>11.89 ± 2.23</td>
<td>0.92</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Retardation / Withdr</td>
<td>10.42 ± 3.04</td>
<td>11.84 ± 3.16</td>
<td>1.41</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CGI scores</td>
<td>5.05 ± 2.90</td>
<td>5.31 ± 3.10</td>
<td>1.39</td>
<td>&gt;0.05</td>
</tr>
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Table (5): Mean differences of scores before and after treatment among AZ and CZ groups of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>AZ Mean ± S.D.</th>
<th>CZ Mean ± S.D.</th>
<th>&quot;t&quot; p</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPRS scores</td>
<td>9.85 ± 6.24</td>
<td>6.53 ± 2.04</td>
<td>6.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total subscores</td>
<td>0.89 ± 3.47</td>
<td>1.32 ± 3.5</td>
<td>2.56</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>thought disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety depression</td>
<td>0.56 ± 2.21</td>
<td>0.26 ± 4.49</td>
<td>2.38</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Hostility suspicion</td>
<td>3 ± 6.70</td>
<td>1.74 ± 6.2</td>
<td>4.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Retardation /</td>
<td>0.42 ± 3.80</td>
<td>0.42 ± 2.3</td>
<td>1.36</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Withdrawal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI scores</td>
<td>0.47 ± 1.9</td>
<td>0.26 ± 1.6</td>
<td>4.87</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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References


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


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علاج مرضى الفصام العدوانيين غير المستجيبين للعلاج بإستخدام عقار البرازولاتم مقابل كربامازبين "علاج معضد"

تم إجراء دراسة مفتوحة على 36 من مرضى الفصام العدوانيين غير المستجيبين للعلاج، وقد صنف المرضى إلى مجموعتين: أعلاى أفراد المجموعة الأولى كاربامازبين بينما أعطي أعضاء المجموعة الثانية البرازولاتم كعلاج مساعد مع مضادات الذهان. وقد قيمت النتائج قبل أسبوعين من بدء العلاج ثم بعد أسبوعين وبعد ستة أسابيع من العلاج مستعمرين اختبار معدل القياس النفسي المختصر واختبار الإدراكي الإكلينيكي الكلي. وقد تم عمل تخطيط المعالجة بالكمبيوتر لكل المرضى، وبالرغم من وجود تغييرات غير محددة وحيدة من حين إلى آخر فأنها لم تكن ذات صلة بالاستجابة لكل من العقارين.

ولقد أوضحت النتائج أن هناك تحسناً دلاًًلإحصائي في الإدراكي الإكلينيكي الكلي حيث أدى البرازولاتم إلى التحسن في 57.9% من الحالات إلى عدم التغيير في 42% ولم يحدث تدهور يذكر في حين أن الكاربامازبين قد أدى بالمقارنة إلى نسبة 52% و 36, 05, 04 %. وعلى الفرق بينهما لابد منها، واللذان أدى العلاج بالبرازولاتم إلى استجابة أفضل بالنسبة للإرتراب الفكري والأفكار غير العادية، بينما أدى البرازولاتم إلى استجابة أفضل في العدواني والتوحسي والاستتارية والقلق والاكتئاب، بينما كان لكل من الدواعين تأثير طفيف على البطء الحركي والإطواء وتبديل الوضع. ولقد قالت جرعات المراقبة بمضادات الذهان إلى الثلث بعد أربعة أسابيع من العلاج بأي من العقارين، ولقد يعزى هذا الخفض إلى تنไฮ ظاهرة الانضغاط أو زيادة نشاط الناقل العصبي "جابا" أو زيادة مستوى مضادات الذهان في سائل الدم "البلازما" وهي عوامل محتملة في تخفيف بعض الأعراض وتيسير استجابة المرضى لعلاجهم السابق بمضادات الذهان.