# A Combined Depot (Flupenthixol and Zuclopenthixol) in Neuroleptic Non-Responsive Schizophrenia*

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## Abstract

A combination of flupenthixol and zuclopenthixol depot was given every 3 weeks to 40 neuroleptic (NL) resistant schizophrenic patients who had tried at least three types of NL of both oral and depot forms including zuclopenthixol or flupenthixol separately. BPRS and CGI showed statistically significant evidence of response. On dividing the BPRS into positive and negative symptoms again statistically significant results were obtained. It is hypothesized that the combination of flupenthixol and zuclopenthixol may have a synergistic effect that leads to adaptation and regulatory functions at the receptor level. Flupenthixol and zuclopenthixol have an effective occupancy on D1 and D2 and to a slight extent of 5HT receptors. It seems that their combination may produce an effect on receptors similar to that of atypical NL. Further studies on drug naive schizophrenic patients and on relapse prevention are recommended.

**Introduction:** It has been shown in many studies that 5-25% of schizophrenics are unresponsive to neuroleptics (NL) and that 5-10% are intolerant to therapeutic doses i.e. 10-35% of schizophrenics are non responsive to classical NL. For the last three decades, at least 40 placebo controlled studies have shown that most schizophrenic relapses can be prevented by neuropletic maintenance treatment. NL have an impressive prophylactic efficacy and reduce the average relapse rate from 75 to 15% (Kissling, 1991). Under normal treatment conditions 50% of patients suffer one or more relapse within the first year episode. Non compliance is one of the main causes of relapse. Other causes involve side effect, especially EPS and lack of understanding and awareness of the patient and family of the nature of the disorder.

There is relative absence of evidence that patients respond substantially better to one NL than to another (although side effect profiles and patients' tolerance differ markedly) albeit the receptor occupancy of the new atypical NL.

In principle, the antipsychotic effect is the same for both oral and depot NL. However, depot NL are preferred because they improve compliance, reduce periods of hospitalization and reduce relapse rate.

The receptor binding of NL may differ in their occupancy of dopamine (DA) receptors and a combination of two compatible depot NL may have a synergistic effect and an adaptational mechanism on DA receptors.

Previous studies have shown that flupenthixol may have an energizing effect and an antidepressant quality, while zuclopenthixol is said to have a sedative effect. Both have a relevant DA receptor occupancy equivalent to their antisychotic effect.

This study aimed to investigate the effect of a combined therapy, in one injection, of both flupenthixol 40 mg and zuclopenthixol 200 mg every two weeks given to NL non responsive schizophren-

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ic, including those who received flupenthixol or zuclopenthixol in a separate setting. The efficacy of this attempt is hampered by the fact that those patients were already unresponsive to NL. The only similar trail known to us is that carried out by Hallen (1991) on four cases report.

**Methodology:** Forty resistant schizophrenics were selected randomly from a sample of resistant schizophrenic patients in a psychiatric university clinic in Cairo. The diagnosis was based on DSM-III R criteria. Patients' age ranged from 21 to 48 years. The patients had been ill for at least three years and the duration of the schizophrenic disorder ranged between 3 to 12 years, with an average mean duration of 5.5 years.

All patients had tried at least three types of NL of both oral and depot forms, chlorpromazine 800-1000 mg/day or its equivalent of haloperidol, trifluperazine, Clozapine 100-300 mg, depot forms of flupherazine up to 50 mg/2 weeks, haloperidol depot 200 mg/4 weeks, flupenthixol 80 mg/2 weeks or zuclopenthixol up to 500 mg/3 weeks for some patients. During the course of their illness all patients had received courses of ECT during the acute phases or exacerbation of the schizophrenic disorder.

Despite all lines of treatment, selected patients, with moderate or severe psychopathology, showed poor response to NL and tolerance to high dose.

To identify 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 receding five years with NL (for at least 2 chemical classes). Doses should be the equivalent to a greater than 1000 mg/day of chlorpromazine for 6 weeks without significant relief.
2. Cross sectional: Brief Psychiatric Rating scale (BPRS) score of at least 45. Clinical Global Impression (CGI) score of at least 4 and a score of at least 4 (moderate) for two of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior and unusual thought content.
3. Prospective: Failure to decrease BPRS by 20% or below 35 or failure to decrease CGI to 3 (mildly ill) after a 6 weeks trial of haloperidol (dose up to 60 mg/day).

All patients and families consented to try the combination flupenrhixol 40 mg and zuclopentixol 200 mg injection IM every two weeks, for the whole period of study of twelve weeks. Adjuvant therapy of chlorpromazine or thioridazine (200-600 mg/day) was allowed for those patients who needed sedation.

Zuclopenthixol decanoate and cis (Z) flupenthixol decanoate can be mixed in a syringe and given as one injection (co-injection) as both esters are dissolved Viscoleo. This is convenient to the patient and the nursing staff. The depot formulation of Zuclopenthixol and cis (Z) flupenthixol cannot be mixed with depot formulations, using sesame oil as the vehicle (as in all other depot formulations, because this would result in definite changes of the pharmacokinetic properties. (Jann et al. 1985).

Patients were assessed three times. At the outset of the study, after 6weeks and after 12 weeks, using the following:
1. The Clinical Global Impression test (CGI) which was used to assess the severity of the disorders and the therapeutic effect (Guy, 1976).
2. The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962).

Diagnosis and ratings on the BPRS and the CGI were all done by at least two experience a psychiatrists in a common interview setting. Also a chart of the side effects were evaluated. Antiparkinsonian agents were added when required.

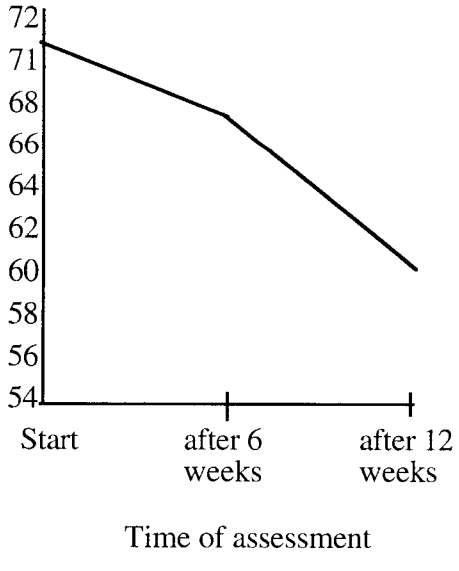
Statistical analysis were done using the mean, standard deviation ant the t-test.

**Results:** *1. BPRS Total Score*
Twenty six patients (65%) showed improvement in the BPRS total score at the time of the second assessment (after 6 weeks), while 10 patients (25%) showed no change in the total score. Half of the later group (12.5%) showed improvement by the time of third assessment (after 12 weeks). 4 patients (10%) showed worsening of the scores after 6 week, but half of those (5%) showed improvement after 12 weeks.

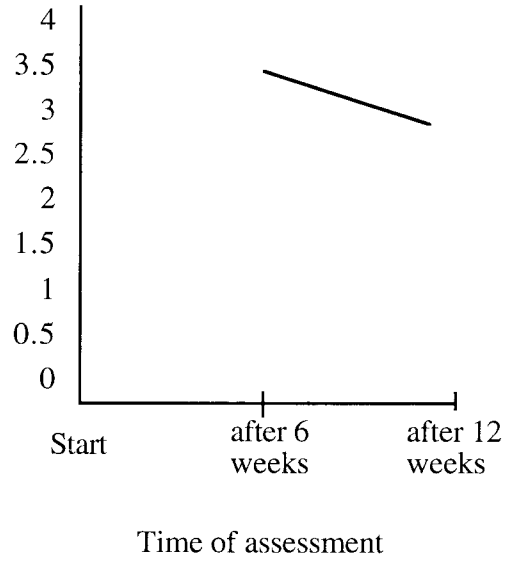
Regarding the mean score of BPRS, significant improvement was observed after 6 weeks ($p< 0.050$., with more improvement after 12 weeks ($p<0.001$)[Graph I].
The mean total score at the start was 70.75±3.55, decreased to 68.35±4.4 after 6 weeks $t=2.68$, $p<0.05$) and then again to 60.8±7.35 ($t=7.71$, $p<0.010$) after 12 weeks.

*2. CGI score (Severity and Improvement Score):*
The mean score on the severity scales was 4.9±0.25 at the beginning of the study with no change after 6 weeks and a decrease to 4.65±0.18 after 12 weeks, which was not a statistically significant difference ($t=1.63$, $p>0.05$) [Graph II].
On the improvement scales the mean score was 3.63±0.63 after 6 weeks, with more improvement to 2.8±0.95 after 12 weeks ($t=4.44$, $p<0.010$) [Graph II].

**Graph I: Mean BPRS scores**




**Graph II:Severity of illness scores**



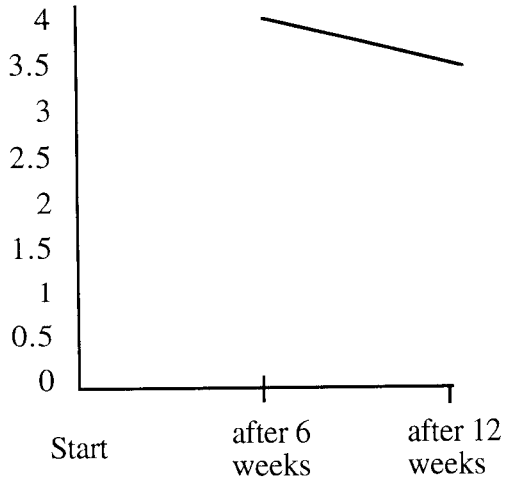
*3. Items of the positive syndrome scale:*
Concerning positive symptoms only (e.g. conceptual disorganization, delusions, hallucinatory behavior, suspiciousness, excitement, grandiosity and hostility) the mean score at the start was 28.90±4.8, with some improvement after 6 weeks (mean score =27.6±4.2) although not reaching the level of statistical significant. More improvement was observed after 12 weeks, which was statistically significant (mean score=24.0±4.05, t=5, p<0.01) [Graph IV].

*4. Items of the negative syndrome scale:*
Regarding negative syndromes only (e.g. emotional withdrawal, blunted affect), the mean score at the start was 10.75±1.95, which improved to 10.35±1.6 after 6 weeks, with more significant improvement to 9.15±1.32 after 12 weeks (t=4.3, p<0.01) [Graph V].

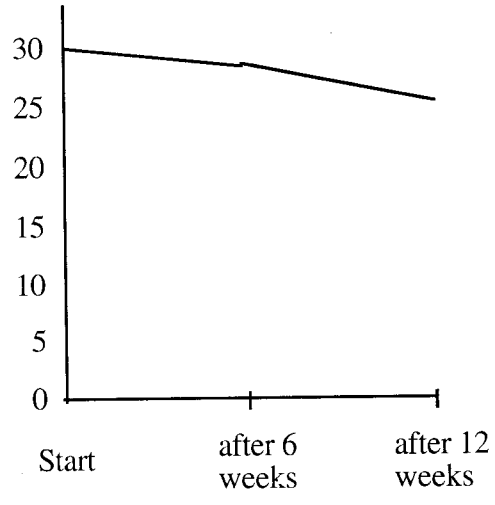
*5 Anxiety somatization scale:*
As regards to symptoms of anxiety and somatization, the mean score was 8.2±1.4 at the start improved to 7.8±1.28 after 6 weeks (p>0.05, insignificant), with more improvement after 12 weeks (mean score 6.95±1.01, t=4.95, p<0.01) [Graph VI].

*6. Depression scales:*
No statistically significant differences has been found on the depression scales between the mean scores at the start, after 6 weeks and after 12 weeks of treatment. Mean scores were 2.45±0.85 at the start, 2.40±8.2 after 6 weeks and 2.35±0.80 after 12 weeks, p>0.05) [Graph VII].

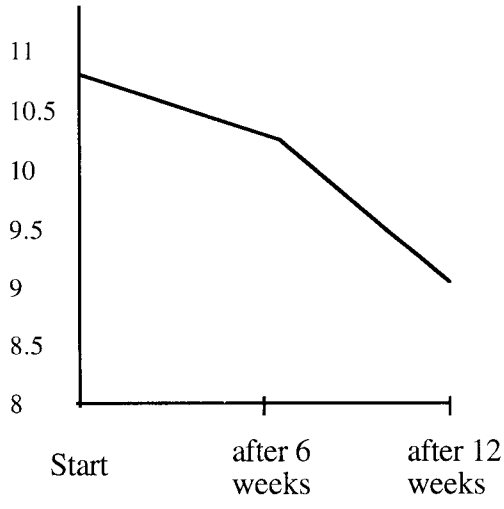
**Graph III:Improvement Scores**



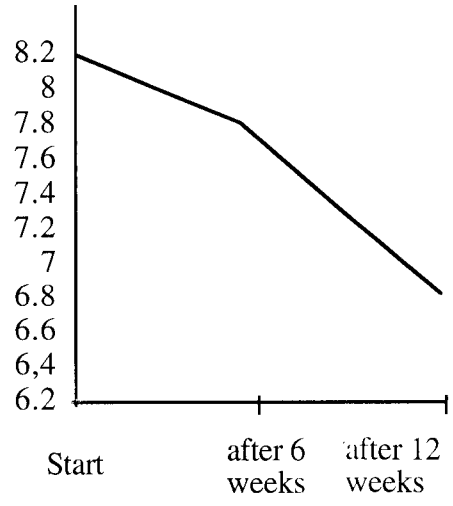

**Graph IV:Mean Scores on Positive Symptom Scale**



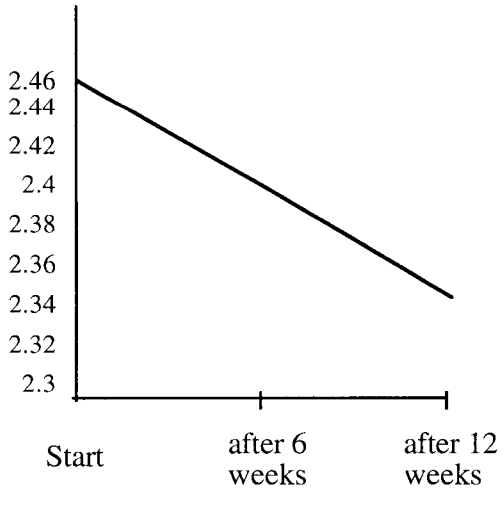
**Graph V:Mean Scores on Negative Symptom Scale**




**Graph VI:Anxiety Somatization Scores**




**Graph VII:Depression Scores**




*7. Dropouts, side effects and tolerability:* All patients completed the study with no drop outs. In 34 patients (85%) only mild side effects were reported. These were mainly autonomic and extrapyramidal side effects, which did not significantly interfere with the patients' functioning. In 5 patients (12.5%) the side effects (mainly extrapyramidal ) significantly interfered with the patients' functioning and necessitated increase of the antiparkinsonian drug dosage. Only one patient (2.5%) developed side effects (both autonomic ad extrapyramidal) which outweighed the therapeutic effect.

*8. Drug responders verses non responders:*

-Patients were divided into two subgroups:

1. Those patients who showed improvement in total scores of BPRS = drug responders.
2. Those who showed no change or worsening of the total scores of BPRS after 12 weeks assessment = drug non responders.

Scores on illness severity and on positive and negative symptoms, as measured by the BPRS, showed no statistically significant difference between the two groups, indicating that neither the level of negative or positive symptoms nor illness severity seem to predict the future response to therapy.

**Discussion:** Clinical treatment studies give strong support to the importance of DA receptor blockade in the alternation of psychotic symptoms. In a clinical study by Johnsone et al. (1978) two isomeric forms of flupenthixol were compared with placebo in the treatment of acute schizophrenia. The alpha isomer, which blocks DA receptors, reduced psychotic symptoms significantly in comparison with both placebo and beta isomer. The importance of DA system is further supported by the finding that alpha methyl tyrosine (an inhibitor of tyrosine hydroxylase which decreases the feedback activation of DA neurons following DS receptor blockade, therefore strengthening the NL blockade of DA receptors), strengthens the antipsychotic action of subthreshold doses of NL (Wahlinder et al. 1976). Patients treated with chemical distinct antipsychotic drugs were found to have similar D2 receptor occupancy levels in the brain (Farde et al. 1992). In patients treated with conventional NL receptor occupancy of D2, levels were in the range of 70-89%.

It seems that the chemical structure of the NL compounds determine to what degree the receptors were occupied. Perphenazine and sulpiride did or seem to interact with D1 receptors, while Thioridazine (30%) and flupenthixol (44%) seemed to do so, but to a much lower degree than with D2 receptors. Clozapine showed the highest degree of D1 receptor occupancy 36-52%, indicating that this drug may have similar receptor occupancy for both D1 and D2. It may be speculated that a similar receptor occupancy of the D1 and D2 receptor is synergistic, and therefore will result in full antidopaminergic effect, in analogy with the finding that a full behavioral dopaminergic response requires the activation of both D1 and D2 receptor (Longoni et al 1987).

The statistically significant improvement in both positive and negative symptoms through BPRS by combining both flupenthixol and zuclopenthixol reported in our study, can be attributed to the synergistic occupancy of D1 and D2 dopamine receptors. With the aid of molecular genetics and PET studies, several new types of DA receptors have been identified:D3 (Sokoloff et al., 1990), D4 (Tol et al., 1991) and D5 (Sunahara et al., 1991).However the significant of these for the therapeutic effect of antipsychotic compounds is not yet known. Recently genetic polymorphism has been demonstrated for the D4 Dopamine receptor (Tol et al., 1992). The D4 receptor variants showed different properties to antagonists and these may underlie individual responses to antipsychotic treatment. A pronounced blockade of D2 receptors occurs after the first dose of a NL (Nordstoem et al., 1992), but the period of time required for the development of the antipsychotic effect seems to range between a few hours and several months. However, the antipsychotic effect of NL treatment is multidimensional. This has been convincingly demonstrated in maintenance treatment studies, in which relapse rates were lowered by family treatment, group treatment and social training (Goldstein et al., 1978, Falloon et al., 1985; Leff et al., 1985 and Hogarty et al., 1991).

Even if the primary effect of antipsychotic medication could be related to DA blockade, complex interactions among several different neuronal systems in var-

ious regions also have to be considered in this connection. In addition to their effect on DA systems, NL also interact with several other neuronal transmitter systems, including the neuropeptides. Evaluation of the clinical importance of these other systems in relation to the mechanisms of action of antipsychotics remains incomplete.

The unique therapeutic properties of clozapine has been attributed to combined blockade of 5HT2 and D2 receptors at therapeutic doses. The D1 receptors may be a target for atypical NL. Should we consider flupenthixol an atypical as its occupancy involves D1, D2 and to a lesser extent 5HT2 receptors?

It has been suggested that a balance of 5HT and D2 like antagonism might contribute to an atypical antipsychotic response pattern. In a study by Sieberns (1986), the profile of various depot NL was identified where flupenthixol had very good efficiency in emotional withdrawal, motion retardation, uncooperativenes and blunted affect, while zuclopenthixol showed very good efficacy in hostility and suspiciousness, compared with fluphenzine with highest efficacy un hallucination and exaggerated self esteem. Haloperidol showed good efficacy in emotional withdrawal, guilt feelings, suspiciousness, hallucination, uncooperativenes , unusual thought context, but did not reach the level of improvement achieved by other depot NL in the above items (fig. 1).

DA receptors blockade is certainly a prominent effect of neuroleptics and no doubt this blockade contributes to the antipsychotic effect. Affinity to certain receptors other than DA receptors is often implicated in side effects. The alpha 1 adrenoceptor blocking effect is claimed to be responsible for cardiovascular side effects such as orthostatic hypotension and tachycardia. An antihistaminic effect is considered responsible for sedation and drowsiness, and an anticholinergic effect for dry mouth. constipation, urine retention and visual disturbances. However, one cannot exclude the possibility that affinity for these receptors - in some parts of the brain - may have a beneficial effect.

Since the blockade of S2 receptors seems to be common to all neuroleptics it is tempting to relate this effect also to antipsychotic effect. It is claimed that hallucinations caused by hallucinogenic drugs are mediated by 5-HT. The similarity of these hallucinations and those experienced by some schizophrenic patients supports the idea of an involvement of 5-HT in certain schizophrenic symptoms. Thus 5-HT receptor blockade could be expected to be of value in controlling these symptoms.

Finally the D-1 receptor blockade effected by certain neurolptics has attracted a great deal of attention. The experiments by Rosegarten et al. (1983) showing that perioral movements in rate were dependent on D1 receptor stimulation may lead to the suggestion that D1- receptor activation is responsible for similar effect in man i.e. dyskinesias.

Since tardive dyskinesia is often claimed to develop upon long-term treatment with neurolptices blockade of D-1 receptor should therefore be advantageous. Furthermore since tardive dyskinesia is caused by the development of DA receptor hypersensitivity, the neuroleptics least capable of including this should be used. The neuroleptics including the least tolerance and hypersensitivity are thioxanthenses, which should therefore be regarded as the drug of choice for long-term maintenance therapy.

Butyrophenones, diphenyl-butyl-piperidine and benzamindes interact preferentially with D2 receptor. In contrast,

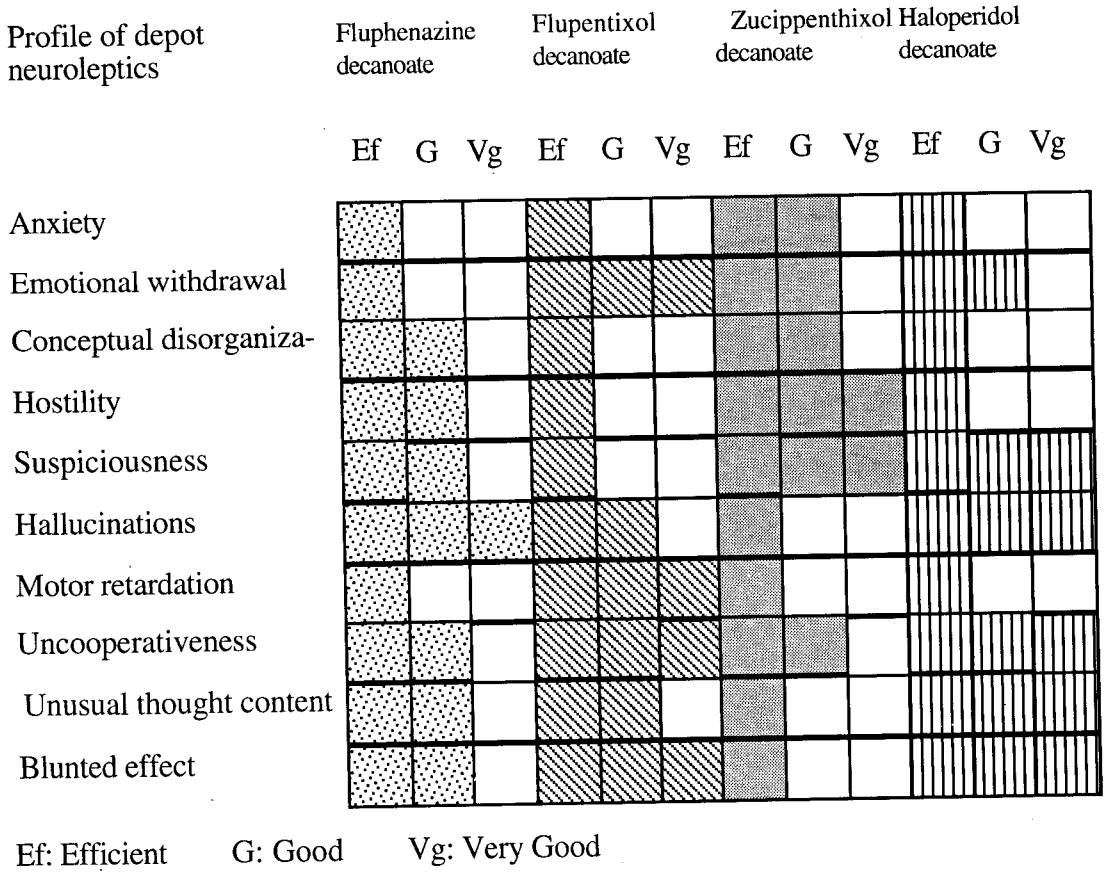



**Fig 1 Profiles of depot neuroleptics After Sieberns S (1986)**

thixoanthenes like Cis (Z) flupenthixol and zuclopenthixol have high affinity for both D1 and D2 receptors. In our study the combination of flupenthixol and zuclopenthixol gave results similar to those of Seiberns (1986). Our combination of both induced a synergistic effect, i.e. an overlap of the profiles, of both drugs.

Most NL also react with other receptor systems. Cis (Z) flupenthixol and zuclopenthixol show affinity mainly for serotonergic (5HT2 and S2) receptors and for alpha adrenergic receptors, whereas the affinity for histaminergic (H1) is very weak. Both drugs do not show noteworthy anticholinergic effect. The results obtained in the study namely the improvement in both negative and positive symptoms have an analogy with the improvement of NL resistant schizophrenia to Clozapine which works throughout its effect D1 and D2 and D3 receptors and also 5HT receptors.

The combination therapy of flupenthixol and zuclopenthixol may have a synergistic effect on D1, D2, 5HT2 receptors leading to an adaptation process that yield some changes in negative and positive symptoms. Attempts with this combination to as a first choice in the management of schizophrenia, which is non responsive to NL, may prove to be an encouraging procedure. The same may hold true for prophylaxix against schizophrenic relapse.

It seems that the combination of flupenthixol and zuclopenthixol as a single depot in injection has the benefit of synergistic receptor occupancy of both D1 and D2 giving it an atypical NL response, affecting both positive and negative symptoms as assessed by BPRS in the non responsive NL schizophrenics.

A replication of this study on drug-naive schizophrenic patients may reveal an even higher statistically significant improvement in the psychothalogical profile of symptoms than that reported in our case.

Further studies are recommended for comparing the efficiency of the combined flupenthixol and zuclopenthixol depot, not only in reducing the severity of psychopathology but also in reducing the relapse rates and increasing levels of socialization.

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## استخدام مزيج من عقارى الفلوبنثيكول و الزوكلوبنثيكول فى علاج الفصاميين غير المستجيب

تم إعطاء مزيج من الفلوبنثيكول و الزوكلوبنثيكول (المتخزن) فى شكل حقنة مرة كل ٣ أسابيع إلى ٤٠ مريض بالفصام ممن يقاومون العلاج . و الذين سبق لهم تناول أنواع غلى الأقل من مضادات الذهان عن طريق الفم أو الحقن بما منهم بما فيهم العقارين سالفى الذكر كل على حدة. و قد بينت نتائج اختبارات "الانتباع الكلينيكيالعام" CGI و" مقياس التقدير السيكترى المختصر" وجود فروق ذات دلالة فى الاستجابة. و عند تقسيم الاستجابات فى مقياس التقدير السيكترى المختصرإلى أعراض سلبية و إيجابية ظهرت مرة أخرى فروق ذات دلالة بين النوعين. و لذلك فقد افترضنا أن الجمع بين الفلوبنثيكول و الزوكلوبنثيكول قد يكون له تأثير تدعيمى مساند يؤدى إلى تكييف و تنظيم الوظائف فى مستوى المستقبلات. و ولهذين العقاريين تأثيرعلى عدة مستقبلات و يبدو أن الجمع بينهما بنتج تأثير على المستقبلات مشابها لتأثيرللعقارات غير النمطية المضادة الذهان. وتوصى الدراسة بمزيد من البحث غلى مرضى الفصام السذج و على منع الانتكاسة.