

— Review Article —

## Responsivity of Negative Symptoms to Typical Neuroleptic Drugs in Schizophrenia

Jagdishwar S. SRIVASTAVA<sup>1)</sup>, Yuji OKAZAKI<sup>2)</sup> and Yoshibumi NAKANE<sup>2)</sup>

1) Central Drug Research Institute, Lucknow, India

2) Department of Neuropsychiatry, Nagasaki University School of Medicine, Nagasaki, Japan

The psychopharmacological management of schizophrenia consists primarily of neuroleptics. These drugs have successfully changed the scenario of psychiatry since the 1950s. They have mainly been used for controlling positive symptoms in schizophrenia, but on closer look it is evident that positive and negative symptoms both respond to neuroleptics in the acute and chronic stages of schizophrenia separate reports are cited for acute and chronic stages with an aim to quantitate the response. The early as well as recent studies support these observations with few exceptions. However, greater responsivity has been observed in the acute stages of schizophrenia.

**Key Words :** negative symptoms, neuroleptic drugs, schizophrenia

### Introduction

The pharmacotherapy of schizophrenia began in late 1950s with the introduction of chlorpromazine. Thereafter, several antipsychotics belonging to various chemical groups were added to the armamentarium of psychiatrists. Gradually, with their increasing use in clinical psychiatric practice over the past four decades, the following limitations were observed :

1. It takes 2 to 3 weeks of administration for the antipsychotic effects to become apparent.
2. Nearly 5% to 20% of patients do not respond conventional neuroleptics and therefore are considered to be treatment-resistant.
3. The response of negative symptoms to the available antipsychotic drugs is not satisfactory.
4. They produce disturbing acute and chronic extrapyramidal effects and anticholinergic side effects of varying intensity.

This has led to continued efforts to develop newer antipsychotic agents with earlier onset of effect, improved therapeutic profile especially in resistant cases (including positive and negative symptoms both, and reduced extrapyramidal and anticholinergic side effects. However, the focus has narrowed down to the latter two objectives.

Based on these facts, there is an increasing tendency to classify neuroleptic agents into typical and atypical neuroleptics. Although, in strict sense, the atypical group should not be considered neuroleptic since they do not produce neurologic extrapyramidal side effects.

The negative symptoms are not unique to schizophrenia and have been described in depression<sup>3)</sup>, as a sequelae to institutionalization<sup>14)</sup> or even in neuroses<sup>15)</sup>. In schizophrenia, these can be present at various stages : prepsychotic stage, during acute exacerbation together with positive symptoms, and in the chronic residual state with or without positive symptoms. It is very difficult to identify them in prepsychotic stage and there are a few studies to provide their prevalence in acute and chronic stage which are referred to below.

It has long been considered that typical neuroleptic drugs have little or no effect on negative symptoms and this poor responsivity was even taken as one of the criteria for classifying patients as having type I and type II schizophrenia<sup>12)</sup>. However Goldberg<sup>13)</sup> has reformulated to state that schizophrenic patients with enlarged ventricles show symptoms of organicity (visual and olfactory hallucinations, disorientation and memory deficit) and only these tend not to respond to neuroleptics. The aim of the present synopsis is to review the effect of typical antipsychotic drugs on negative symptoms with emphasis on response rates for negative and positive symptoms to quantitate it. This approach was chosen in light of several recent articles concentrating mainly on atypical drugs, especially clozapine in neuroleptic nonresponsive chronic schizophrenic patients. If we want to study the effects of neuroleptic drugs on negative symptoms we should study them at different stages of schizophrenia. For the purposes of this article we will discuss the effects in the acute and chronic phases of schizophrenia for typical neuroleptic drugs separately.

### Acute Schizophrenia

During the acute stage, negative symptoms are concomitantly present with positive symptoms<sup>4, 6)</sup>. The pro-

**Table 1.** Studies in acute schizophrenic patients

AUTHOR/ <sup>REF NO</sup> YEAR	NO. OF PATIENTS	MEAN AGE (year)	DESIGN	DURATION (weeks)	DRUGS/DOSE (mg/day)	RATING SCALE	RESULTS
1. NIMH-PSC <sup>30, 31</sup> (1964, 1967)	344	28.2	Double Blind	6	CPZ : 654/ FPZ : 6.4/ TDZ : 700/PL	IMPS/ WBRs	Improvement in withdrawal, selfcare, speech
2. Goldberg et al. <sup>16</sup> (1967)	250	—	Double Blind	26	CPZ/FPZ/TDZ/ PL	Venable O'Connell	Withdrawal response earlier than paranoid
3. Johnstone et al. <sup>18</sup> (1978)	45	>16	Double Blind	4	Alpha/Beta FPN: Krawiecka 9 mg	Scale	No improvement in negative symp.
4. Kay & Singh <sup>22</sup> (1989)	62	25.2±6.5	Double Blind	12	CPZ/HLP (15.1 mg HLP <sub>eq</sub> )	PANSS	Positive (51.5%) Negative (35%)
5. Philips et al. <sup>36</sup> (1991)	401	31.0±10	Open	10	CPZ/PPZ/CLZ (518 mg CPZ <sub>eq</sub> )	SANS-CV/ SAPS-CV/	Positive (80%) Negative (47%)
6. Hill. et. al <sup>17</sup> (1992)	39	26.8±1.8	Open	4	—	BPRS	Improve ment+ on negative symp.
7. Kinon et al. <sup>22</sup> (1993)	115	29.4±7.0	Double Blind	8	FPZ : 80/HLP : 20	BPRS/ SANS	Higher initial negatives symp predict poor response
8. Plao et al. <sup>34</sup> (1994)	20	29.0±5.3	Double Blind	3	HLP (10, 20, 30)	SANS/ SAPS/ BPRS	Positive (80%) Negative (30%)

Drugs (CPZ = Chlorpromazine; FPZ = Fluphenazine; TDZ = Thioridazine; FPN = Flupenthixol; HLP = Haloperidol; PPZ = Perphenazine; CLZ = Clozapine; PL = Placebo) Scales (IMPS = Inpatient Multidimensional Psychiatric Scale; WBRs = Ward Behavior Rating Scale; PANSS = Positive and Negative Syndrome Scale; BPRS = Brief Psychiatric Rating Scale; SANS = Scale for Assessment of Negative Symptoms; SAPS = Scale for Assessment of Positive Scale; CV = Changed version)

minent negative symptoms were present in 54% of the first episode of schizophrenia at the time of admission and the overall severity of negative symptoms was similar to positive symptoms<sup>30</sup>. Therefore, it is important to know the effect of typical neuroleptic drugs on such symptoms in acute schizophrenic episodes since they are present in almost half of the patient population (Table 1). National Institute of Mental Health (NIMH) Psychopharmacology Service Center Collaborative Study Group for the first time reported the effect of neuroleptic drugs on negative symptoms in acute schizophrenia. The two double-blind studies published by NIMH<sup>30, 31</sup> included 344 patients with acute schizophrenia at nine hospitals who were treated with typical neuroleptic drugs (fluphenazine, thioridazine and chlorpromazine) for a period of 6 weeks. The response was evaluated on Inpatient Multidimensional Psychiatric Scale (IMPS)<sup>30</sup> and Burdock Ward Behavior Rating Scale (WBRs)<sup>31</sup>. Out the negative symptoms social withdrawal (WBRs), loss of self care (WBRs) and slow speech (IMPS) showed highly significant improvement emphasizing the overall effectiveness of phenothiazines in nearly 95% of the patients. Although the response rates were not given, the improvement in negative symptoms was as

great as in positive symptoms, giving a very optimistic view at that time. Rapid but partial improvement was observed in withdrawal syndrome in 5 weeks while the paranoid syndrome took as long as 13 weeks (although slow but more complete) when 250 acute schizophrenic patients were followed for up to 26 weeks<sup>16</sup>. Meltzer reviewed these NIMH Studies and found moderate improvement in negative symptoms of these relatively young acute schizophrenic patients treated with typical neuroleptics in 6 weeks<sup>30</sup>. From among the recent studies, we have included only those which clearly mention inclusion of acutely ill or recent onset or neuroleptic-naive newly admitted patients with schizophrenia. Johnstone et al<sup>18</sup> reported results obtained from 45 acute schizophrenic patients treated with flupenthixol (alpha and beta isomers) in a placebo-controlled double-blind study. The maximum dose of flupenthixol was 9 mg per day for 28 days and these patients were rated on the scale for symptoms basically developed by Krawiecka and colleagues for the rating of chronic psychotic patients<sup>34</sup>. No change was observed in negative symptoms but positive symptoms improved significantly with the alpha isomer of flupenthixol only. This is one of the studies quoted by

Crow<sup>12)</sup> to support differentiation between two types of schizophrenia depending on the basis of poor response to neuroleptic drugs along with structural brain abnormalities in such patients. Thereafter, Kay and Singh<sup>22)</sup> evaluated a total of 62 acute to subacute schizophrenic patients in a prospective longitudinal study. These patients underwent a drug-free placebo period, 3-4 months of double-blind neuroleptic treatment (chlorpromazine/haloperidol) and a 3-year poststudy follow-up. The dosages were individually titrated according to response and the mean daily dose across the study was 15.1 mg, expressed in haloperidol equivalence. The positive and negative syndrome scale (PANSS)<sup>30)</sup> was employed to rate the symptoms. They found significant neuroleptic-related improvement in both positive and negative symptoms but their data shows that the reduction in negative symptoms (35%) was less than that for positive symptoms (51.5%).

In a study of 401 newly admitted schizophrenic patients, 58% had prominent negative symptoms and 48% were first-episode drug-naive patients at the time of admission<sup>36)</sup>. These patients received neuroleptic treatment (chlorpromazine, perphenazine or clozapine) for nearly 10 weeks as inpatients, and the mean chlorpromazine equivalent dose was 518 mg per day for the duration of stay in the hospital. The positive and negative symptoms were evaluated on a changed version of the Scale for Assessment of Positive Symptoms (SAPS)<sup>2)</sup> and the Scale for Assessment of Negative Symptoms (SANS)<sup>3)</sup> to make it more suitable for Chinese patients<sup>36)</sup> and the response to negative symptoms (47%) was less marked than to positive symptoms (80%). In this study, 35% patients also received clozapine but there was no difference found in the efficacy of chlorpromazine, clozapine and perphenazine and the partial response of negative symptoms to these drugs indicates a neuroleptic-resistant component for negative symptoms.

Hill and colleagues<sup>17)</sup> evaluated the symptomatic response to standard neuroleptic drugs in 22 recent onset (less than 12 months) and 17 chronic recurrent (at least 3 years duration) schizophrenic patients with acute psychotic episode. The Brief Psychiatric Rating Scale (BPRS)<sup>32)</sup> was used for evaluation of both positive and negative symptoms but no details of treatment were mentioned. They found greater improvement of negative symptoms to standard antipsychotic treatment in chronic patients than in recent-onset patients. The patients with acute onset had lower mean withdrawal-retardation scores at the baseline than the chronic recurrent group and this could be responsible for the difference. However, there was a change in withdrawal retardation scores in 20 patients (51%) mainly consisting of the chronic recurrent schizophrenic group experiencing acute exacerbation. The BPRS scores of 25 patients (64%) decreased by one-third which mainly included improvement in positive symptoms.

In a study to identify possible predictors of relapse in an

initial course of neuroleptic treatment, 115 acutely relapsed schizophrenic patients were included<sup>22)</sup>. These patients were kept in an open (fluphenazine 20 mg per day) phase for 4 weeks and thereafter a double-blind (fluphenazine 80 mg per day/haloperidol 20 mg per day) phase for an additional 4 weeks. The negative symptoms were rated on SANS and found higher baseline ratings of anhedonia, asociality and attention deficit in the nonresponder group. Therefore, a particular degree of negative symptoms depending on severity during the initial treatment trial are associated with a less favourable clinical response to alternative neuroleptic therapy.

In a recent double-blind study, the response of fixed-dose haloperidol (10, 20 and 30 mg) treatment was assessed on positive and negative symptoms only for a short period of 3 weeks in 20 schizophrenic patients with acute exacerbation<sup>34)</sup>. They used SANS and SAPS for the rating of symptoms. A decrease of more than 40% was observed in positive symptoms in 16 (80%) patients. However, a reduction in negative symptoms of more than 30% was present in only 6 (30%) patients. This study also observed a differential response in negative symptoms with a significant change only in affective flattening and avolition whereas avolition and anhedonia remained unchanged.

In summary, current evidence from these three old and four recent studies suggests that negative symptoms definitely respond to conventional neuroleptic drugs in the same dosage and same time frame as for positive symptoms in the acute phase of schizophrenia. This also clarifies that the rate of improvement for negative symptoms is less than that for positive symptoms. One possible explanation is that negative symptoms either follow or take more time to respond than positive symptoms in disappearance upto certain extent with neuroleptic therapy, and then either reduce with continued medication or persist in the form of chronic schizophrenia with remissions and exacerbations. The last study<sup>22)</sup> found improvement of negative symptoms only in a small number of patients during the early course of drug therapy. These studies show a difference of upto two times between response rates for positive and negative symptoms. Further, there is some evidence for poor response or impending relapse when the initial scores of avolition, anhedonia and asociality were high during neuroleptic therapy in acute schizophrenic patients<sup>21, 24)</sup>. It is also noteworthy that, except for Johnstone and coworkers, no other study shows improvement in positive symptoms without amelioration of negative symptoms. However, none of these studies have observed an increase in the severity of negative symptoms.

#### *Chronic Schizophrenia*

Negative symptoms are prominently present in chronic

**Table 2.** Studies in chronic schizophrenic patients

AUTHOR/ <sup>REF NO</sup> YEAR	NO. OF PATIENT	AGE (yrs)	CHRONI CITY(yrs)	DESIGN	DURATION (weeks)	DRUG/DOSE (mg/day)	RATING SCALE	RESULT
1. a. Casey et al. <sup>9</sup> (1960)	692	36	10 (D)	Double Blind	24	OPZ : 400/PMZ : 400/PHB : 200	MRSPP	Improvement+ withdrawal, selfcare
b. Casey et al. <sup>10</sup> (1961)	462	38	8.2 (H)	Double Blind	20	CPZ/ : 200-600/ IMI : 60/TFP : 30 /ISX : 30	IMPS/PRP	No advantage on combining
2. a. Prien et al. <sup>37</sup> (1968)	838	41.6 ±8.6	13.1 (H)	Double Blind	24	CPZ = 2000 vs 300 mg	IMPS/BPRS	Improvement+ in high dose
b. Prien et al. <sup>38</sup> (1969)	360	41.8	15 (H)	Double Blind	24	TFP = 80 vs 15 mg	IMPS/BPRS	Improvement+ in high dose
3. Serafetinides et al. <sup>40</sup> (1972)	57	22-61	15 (D)	Double Blind	12	CX : 205/CPZ : 830/HLP : 12/PL	Venable O'Connor	Improvement+ on withdrawal
4. Clark et al. <sup>11</sup> (1972)	57	25-50	>5 (H)	Double Blind	20	CPZ : 800/PHB 480	Oklahoma Scale	No effecton negative symp.
5. Angrist et al. <sup>5</sup> (1980)	21	27.9 ±1.3	—	Open	6	HLP*	BPRS	No improvement on negative symp.
6. Brier et al. <sup>7</sup> (1987)	19	28.0 ±8	12 (D)	Double Blind	8	FPZ : 27±12	BPRS/EBS	No improvement on negative symp.
7. Tandon et al. <sup>42</sup> (1990)	40	30.0 ±6	6 (D)	Open	4	HLP/THTX*	BPRS/SANS	Positive (38%) Negative (34%)
8. Tandon et al. <sup>43</sup> (1992)	80	29.0 ±8	8 (D)	Open	4	HLP/THTX*	BPRS/SANS	Positive (35%) Negative (26-30%)
9. Serban et al. <sup>41</sup> (1992)	30	43.5 ±9.1	15 (D)	Open	12	THTX : 26.75	BPRS/SANS	Positive (29%) Negative (27%)

Chronicity (H = hospitalization ; D = duration of illness); Drugs (CPZ = Chlorpromazine ; PMZ = Promazine ; PHB = Phenobarb ; IMI = Imipramine ; TFP = Trifluoperazine ; ISX = Isocarboxazid ; FPZ = Fluphenazine ; HLP = Haloperidol ; CX = Clopenthixol ; THTX = Thiothixene ; PL = Placebo); \* = Individualized dosage; Scale (MRSPP = Multidimensional Rating Scale for Psychiatric Patients ; IMPS = Inpatients Multidimensional Psychiatric Scale ; PRP = Psychotic Reaction Profile ; EBS = Emotional Blunting Scale ; BPRS = Brief Psychiatric Rating Scale ; SANS = Scale for Assessment of Negative Symptoms)

schizophrenia and are considered responsible for the deterioration in occupational and social adjustment in the postpsychotic phase. Although accurate prevalence rates of negative symptoms in chronic residual schizophrenia in a drug-free state are difficult to cite, there is evidence that a subgroup exists that is poorly responsive to neuroleptic drugs with prominent negative symptoms and the prevalence of such patients has been estimated a between 5 and 20%<sup>28</sup>. Kolakowska et al.<sup>29</sup> did a cross-sectional study of 77 patients with schizophrenia and found a poor outcome in 26% patients as these patients were characterised by persistent hallucinations and delusions along with moderate to severe negative symptoms. It was also observed that, in these patients, the illness started at an early age and negative symptoms were more prominent during their first episode. The studies for chronic schizophrenic patients are summarized in Table 2. There are some important early observations as Casey and colleagues from the

Veteran Administrations Cooperative Group reported two studies on drug therapy of chronic schizophrenia. In the first study<sup>9</sup>, including 692 chronic schizophrenic patients, the majority labelled as chronic undisturbed were randomised to receive chlorpromazine, promazine, phenobarbital or placebo daily for a period of 24 weeks in a double-blind design. The chlorpromazine was superior in improving withdrawal, self depreciation (depression) and self care than promazine and phenobarbital. In the second study<sup>10</sup>, chlorpromazine was combined with amphetamine, trifluoperazine, imipramine, isocarboxazid or placebo for a period of 20 weeks in 462 chronic schizophrenic patients. The improvement was observed in all groups and combination with other drugs offered no advantage over chlorpromazine alone.

Prien and coworkers in the 1960s showed, with chlorpromazine<sup>37</sup> and trifluoperazine<sup>38</sup> in high-dose therapy for 24 weeks in chronic schizophrenic patients, that there is

improvement in some of the negative symptoms. The chronicity of these patients was measured by the number of years they were in the hospital and the patients who had shown response were comparatively younger (below 40 years of age) and had a stay of less than 10 years in the hospital. The high-dose groups (chlorpromazine 2000 mg per day; trifluoperazine 80 mg per day) showed significantly more improvement particularly on psychosocial adequacy and community adjustment potential, both of which are desirable for discharge from the hospital.

Serafetinides et al.<sup>40)</sup> studied 57 chronic schizophrenic patients to compare the effects of haloperidol, clopenthixol, chlorpromazine and placebo over 12 weeks. The negative symptoms evaluated on BPRS showed no improvement but when Venable-O'Connor scales<sup>44, 45)</sup> were applied separately for paranoid and withdrawal symptoms, improvement was observed in withdrawal symptoms in these patients with neuroleptic drugs. Another study was carried out to evaluate the effects of chlorpromazine in 57 chronic schizophrenic women for lag in the onset of effects<sup>41)</sup>. This study failed to find any significant effect on withdrawn and selusive behavior throughout the 20-week period of active medication in these female schizophrenic patients.

The above-mentioned studies were primarily designed to evaluate the efficacy of phenothiazines in various dose groups or amongst themselves, and during the course of therapy improvement was observed in negative symptoms. There are some recent retrospective studies, not shown in the table due to methodological problems, which have attempted to evaluate the effects of typical neuroleptic drugs on negative symptoms especially in view of the favourable response to chlozapine in chronic schizophrenic patients. Overall and Rhoades<sup>38)</sup> reanalyzed the data of 473 chronic schizophrenic patients evaluated on BPRS predominantly withdrawn disorganized profile from a data bank of total of 2623 psychiatric patients drawn from Early Clinical Drug Evaluation Units (ECDEU). No significant effect of typical neuroleptic drugs on these negative symptoms was observed. Meltzer<sup>36)</sup> retrospectively analyzed the effects of neuroleptic drugs (chlorpromazine or trifluoperazine) in 171 chronic schizophrenic patients. Negative symptoms improved in 21 patients (38.2%) out of 55 patients showing marked negative symptoms at the time of admission compared to improvement in positive symptoms in 44 (56.4%) out of 78 patients. Meltzer<sup>27)</sup> reanalysed this study with two separate negative subscales: negative depressive symptoms (loss of interest, slow speech, slow improvement and depressed appearance); negative disorganization items (inappropriate affect, poverty of thought content, incoherence and loosening of association) and blunted affect was included as a third category. The improvement was present in both the previous category of negative symptoms (depressive and disorganization items) with no significant change in

blunted affect.

There are some recent prospective studies in which the effect of neuroleptic drugs on negative symptoms was systematically evaluated. We begin with a study cited by Crow<sup>12)</sup> for two disease concepts in schizophrenia. Angrist and coworkers<sup>5)</sup> reported a study to evaluate the effect of amphetamine and haloperidol on positive and negative symptoms in 21 male schizophrenic patients. There was no beneficial effect found on negative symptoms by haloperidol during the 6-week study.

Breir et al.<sup>7)</sup> studied the effect of neuroleptic drugs in 19 young chronic schizophrenic patients using withdrawal reinstatement design under a double-blind placebo-controlled condition. The positive and negative symptoms both increased with the withdrawal of neuroleptic drugs and then decreased significantly during 4 weeks of therapy with fluphenazine at a mean dose of 31 mg. The patients were divided into four categories depending upon symptom dominance and high negative-high positive group comprised of 53% (10) patients in neuroleptic-free state. With neuroleptic therapy, only one patient was left in this group whereas 4 patients remained in the high-negative group.

Tandon and colleagues from the Michigan Schizophrenia Program carried out two studies in non-overlapping chronic schizophrenic patient populations. In their first study<sup>42)</sup>, 40 patients were treated with haloperidol or thiothixene in individualised dosages for a period of 4 weeks. The positive and negative symptoms were evaluated on BPRS and SANS separately. There was a significant decrease in negative symptoms (34%) and positive symptoms (38%). In their second study<sup>43)</sup>, they included 80 chronic schizophrenic patients with a similar protocol. The improvement for negative symptoms was 26% and 30% on BPRS and SANS, respectively, and for positive symptoms it was 35% on BPRS.

Serban et al.<sup>41)</sup> in an open trial treated 30 patients with chronic schizophrenia with thiothixene for 3 months. Moderate improvement was observed in 19 patients (64%), mild improvement in 5 (16%), and 6 (20%) remained unimproved. Of the five factors for negative symptoms (alogia, avolition, anhedonia, affective flattening and attention deficit) improvement was present in all of them at the time of discharge. They reported a significant improvement in positive (29.3%) and negative (27.5%) symptom but the negative symptoms persisted longer than positive symptoms in the unimproved group. When Andreasen's classification<sup>1)</sup> was applied to the unimproved group, 4 patients still belonged to negative schizophrenia, one was mixed, while the sixth patient developed severe extrapyramidal reactions and was withdrawn from the study. Therefore, the degree of improvement appears to be only marginally higher for positive symptoms, almost the same as reported by two previous studies of Tandon and colleagues.

Amongst chronic studies, the four early studies<sup>9, 10, 37, 38)</sup>

showed significant improvement in negative symptoms with neuroleptic therapy but no advantage was gained in combination with other psychotropic drugs. Serafetini-des<sup>40</sup> observed a rapid but partial improvement of withdrawal symptoms but Clark et al<sup>11</sup> failed to find any such effects. In retrospective analysis, Overall and Rhoades<sup>20</sup> found no effects on withdrawal-disorganized profile in contrast to the observations of Meltzer and associates that up to 38% of patients show improvement in negative symptoms with standard antipsychotic drugs. The decrease in severity of negative symptoms ranged between 26% and 34% in comparison to a maximum of 38% for positive symptoms<sup>7, 42, 43</sup>. This clearly shows a drop in the response rates for two types of symptoms in chronic stages of schizophrenia moreso in the case of positive symptoms. Although there is a marginal difference between the rates for positive and negative symptoms, the overall response for positive symptoms is present in a greater porportion of patients<sup>36, 41</sup>. These findings are clinically significant even though only a few studies are available to report separately on positive and negative symptoms responsivity to typical neuroleptic drugs in chronic schizophrenic patients.

### Conclusion

The negative symptoms present during the acute phases of schizophrenia show an encouraging response although the response rates have been found to be variable, ranging from 30% to 47% for negative symptoms as compared to up to 80% for positive symptoms. Further, the time frame of this response is similar to that for positive symptoms. However, the presence of a certain degree of negative symptoms can predict a poor response to conventional neuroleptic drugs.

This level needs to be further determined, but the responsivity of both positive and negative symptoms is decreased in chronic schizophrenic patients. Negative symptoms and also positive symptoms persisting over a long time become less responsive to conventional neuroleptic drugs, and the role of atypical drugs at this stage has proven to be beneficial not only for negative but also for positive symptoms<sup>19</sup>.

### Acknowledgement

We gratefully acknowledge Prof. Tsukasa Koyama, Department of Psychiatry, Hokkaido University School of Medicine and Dr. Toru Tsujimura, Assistant Prossessor, Nagasaki University School of Medicine for their help.

Dr. J. S. Srivastava vistied Japan for 6 months under the auspices of India National Science Academy-Japan Society for Profmotion of Science (INSA-JSPS) bilatrcal scientific exchange programme in the year 1995-96.

### References

- 1) Andreasen NC: Negative versus positive schizophrenia: definition and validation. *Arch. Gen. Psychiatry* 39: 784-788, 1982
- 2) Andreasen, NC: Scale for assessment of positive symptoms (SAPS). Iowa City: University of Iowa, 1984
- 3) Andreasen, NC: Scale for assessment of negative symptoms (SANS). Iowa City: University of Iowa, 1984
- 4) Andreasen NC: The diagnosis of schizophrenia. *Schizophr. Bull.* 18: 17-24, 1987
- 5) Angrist B, Rostrosen J, Gershon S: Differential effects of amphetamine and neuroleptics on negative vs. positive symptoms in schizophrenia. *Psychopharmacol.* 72: 17-19, 1980
- 6) Arndt S, Andreasen NC, Flaum M, Miller D, Nopoulos P: A longitudinal study of symptom dimensions in schizophrenia. *Arch. Gen. Psychiatry* 52: 352-360, 1995
- 7) Breier A, Wolkowitz OM, Doran AR, Roy A, Boronow J, Hommer DW, Pickar D: Neuroleptic responsivity of negative and positive symptoms in schizophrenia. *Am. J. Psychiatry* 144: 1549-1555, 1987
- 8) Burdock EI, Hakeren G, Hardesty AS, Zubin J. A ward behavior rating scale for mental patients. *J. Clin. Psychol.* 15: 246-247, 1960
- 9) Casey JF, Benett IF, Lindley C, Hollister LE, Gordon MH, Springer HH: Drug therapy in schizophrenia. A controlled study of the relative effectiveness of chlorpromazine, promazine, phenobarbital and placebo. *Arch. Gen. Psychiatry* 2: 210-220, 1960
- 10) Casey JF, Hollister LE, Klett CJ, Lasky JJ, Caffey EM: Combined drug therapy of schizophrenics. *Am. J. Psychiatry* 117: 997-1003, 1961
- 11) Clark ML, Ray TS, Ragland RE: Chlorpromazine in chronic schizophrenic women: rate of onset and rate of dissipation of drug effects. *Psychosom. Med.* 25: 212-217, 1972
- 12) Crow TJ: Molecular pathology of schizophrenia: more than one disease process. *Br. Med. J.* 280: 66-68, 1980
- 13) Ernst K: Neurotische und endogene Residualzustands. *Arch. Psychiatr. Neurol.* 203: 61-84, 1962
- 14) Goffman E. *Asylums*: Anchor Books, New York, 1961
- 15) Goldberg SC: Negative and deficit symptoms in schizophrenia do respond to neuroleptics. *Schizophr. Bull.* 11: 453-456, 1980
- 16) Goldberg SC, Schooler NR, Mattson N: Paranoid and withdrawal symptoms in schizophrenia: Differential symptoms reduction over time. *J. Nerv. Ment. Dis.* 145: 158-162, 1967
- 17) Hill C, Keks NA, Jackson H, Kulkarni J, Hannah D, Copolov D, Singh B: Symptomatic response to antipsychotics differs between recent onset and recurrent chronic schizophrenic patients. *Austral. New Zeal. J. Psychiatry* 26: 417-422, 1992
- 18) Johnstone EC, Crow TJ, Frith CD, Carney NWP, Price JS: Mechanism of the antipsychotic effect in the treatment of acute schizophrenia. *Lancet* 1: 848-851, 1978
- 19) Kane J, Honigfeld G, Singer J, Meltzer HY: Clozapine for the treatment resistant schizophrenic. *Arch. Gen. Psychiatry* 45: 789-796, 1988
- 20) Kay SR, Fiszbein A, Opler LA: The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13: 261-276, 1987
- 21) Kay SR, Singh MM: The positive-negative distinction in drug free schizophrenic patients. *Arch. Gen Psychiatry* 46: 711-718, 1989
- 22) Kinon BJ, Kane JM, Chakos M, Rafael M: Possible predictors of neuroleptic resistant schizophrenic relapse. Influence of negative symptoms and acute extrapyramidal side effects. *Psychopharmacol. Bull.* 29: 365-369, 1993
- 23) Kolakowska T, Williams AO, Ardern M, Reveley MA, Jambor K, Gelder MG, Mondelbrote BM: Schizophrenia with good and poor outcome. I: Early clinical features, response to neuroleptics and signs of organic dysfunction. *Brit. J. Psychiatry* 146: 229-239, 1985
- 24) Krawiecka M, Goldberg D, Vauhan M: Standardized psychiatric assessment scale for rating chronic psychotic patients. *Acta Psychiat. Scand.* 55: 299-308, 1977
- 25) Lorr M, Klett CJ, McNair DM, Lasky JJ. *Inpatient multi-dimensional psychiatric scale (manual)*. Consulting Psychologist Press, Palo Alto, 1963
- 26) Melzer HY: Dopamine and negative symptoms in schizophrenics: critiques of the type I-type II hypothesis. In: Alpert M (ed.) *Controversies in schizophrenia: changes and constancies*. Guilford Press, New York: 110-136, 1985

- 27) Meltzer HY: Pharmacologic treatment of negative symptom. In: Greden H, Tandon R (ed.) *Negative schizophrenic symptoms: pathophysiology and clinical implications*. American Psychiatric Press, Washington, DC: 217-235, 1991
- 28) Meltzer HY: Treatment of neuroleptic nonresponsive schizophrenic patient. *Schizophr. Bull.* 18: 515-542, 1992
- 29) Meltzer HY, Sommers AA, Luchins DJ: The effect of neuroleptics and other psychotropic drugs on negative symptoms in schizophrenia. *J. Clin. Pharmacol.* 6: 329-338, 1986
- 30) National Institute of Mental Health-Psychopharmacology Service Center Study Group: Phenothiazine treatment in acute schizophrenia. *Arch. Gen. Psychiatry* 10: 246-61, 1964
- 31) National Institute of Mental Health-Psychopharmacology Service Center Study Group: Clinical effects of three phenothiazines in acute schizophrenia. *Dis. Nerv. Syst.* 28: 369-383, 1967
- 32) Overall JE, Jordan D: Brief Psychiatric Rating Scale. *Psychol. Rep.* 10: 799-812, 1962
- 33) Overall JE, Rhoades HM: Refinement of phenomenological classification in Clinical Psychopharmacological Research. *Psychopharmacol.* 77: 24-30, 1982
- 34) Palao DJ, Arauxo A, Brunet M, Bernardo M, Ferrer J, Gonzalez-Monclus E: Positive versus negative symptoms in schizophrenia: response to haloperidol. *Prog. Neuropsychopharmacol. & Biol. Psychiat.* 18: 155-164, 1994
- 35) Phillips MR, Wei Z, Zhao ZA: Issues involved in the use of Scales for Assessment of Negative and Positive Symptoms in Mental Disorders (Chinese). Wuhan, PRC: Hubei Scientific Press, 1990
- 36) Philips MR, Zhao Z, Xiong X, Cheng X, Sun G, Wu N: Changes in the positive and negative symptoms of schizophrenic inpatients in China. *Br. J. Psychiatry* 159: 226-231, 1991
- 37) Prien RF, Cole JO: High dose chlorpromazine therapy in chronic schizophrenia. Report of NIMH-Psychopharmacology Research Branch Collaborative Study Group. *Arch. Gen. Psychiatry* 18: 482-489, 1968
- 38) Prien RF, Levince J, Cole JO: High dose trifluoperazine therapy in chronic schizophrenia. *Am. J. Psychiatry* 126: 305-313, 1969
- 39) Prosser ES, Csernansky GC, Kaplan J, Thiemann S, Beeker TJ, Hollister LE: Depression, Parkinsonian syndrome and negative syndrome in schizophrenics treated with neuroleptics. *J. Nerv. Ment. Dis.* 175: 100-105, 1988
- 40) Serafetinides EA, Collins S, Clark MI: Haloperidol, clopenthixol and chlorpromazine in chronic schizophrenia. *J. Nerv. Ment. Dis.* 154: 31-34, 1972
- 41) Serban G, Siegel S, Gaffney M: Response of negative symptoms of schizophrenia to neuroleptic treatment. *J. Clin. Psychiat.* 53: 229-234, 1992
- 42) Tandon R, Goldman RS, Goodson J, Greden JF: Mutability and relationship between positive and negative symptoms during neuroleptic treatment in schizophrenia. *Biol. Psychiatry* 27: 1323-1326, 1990
- 43) Tandon R, Rebeiro SCM, Dequardo JR, Goldman RS, Goodson J, Greden JF: Covariance of positive and negative symptoms during neuroleptic treatment in schizophrenia: A replication. *Biol. Psychiatry.* 34: 495-497, 1992
- 44) Venable PH: A short scale for rating "activity-withdrawal" in schizophrenia. *J. Ment. Sci.* 103: 197-199, 1957
- 45) Venable PH, O'Connor N: A short scale for rating paranoid schizophrenia. *J. Ment. Sci.* 105: 815-818, 1959