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Effect of neuroleptics on positive and negative symptoms and the deficit state

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Abstract. The concept of negative symptoms tries to operationalize a deficit syndrome observed in schizophrenia, but also in other disorders. The instruments for the measurement developed so far are unclear in their dimensional structure and validity. Further methodological development is needed. A new scale for measuring negative symptoms was derived from the AMDP-system and applied to results of drug trials with clozapine, fluperlapine, and haloperidol. The three drugs were equally effective on negative symptoms of acute and chronic schizophrenics.

Key words: Negative symptoms – Rating scales – Fluperlapine – Clozapine – Haloperidol

The concept of negative symptoms

The terms "negative" and "positive" symptoms were coined by the English neurologist Jackson (1884) in connection with a hierarchical model of cerebral functions. Strauss et al. (1974) applied the terms in 1974 to a new concept of negative and positive symptoms as predictors of the outcome of schizophrenia. According to Sommers' review, the main negative symptoms concern affect, arousal, cognition, and social functioning (Sommers 1985), reflected, for instance, by blunted affect, apathy, attentional deficit, poverty of thought or speech, and social withdrawal. Some of these symptoms are elements of the deficit syndrome already described by Bleuler (1911) as "core symptoms of schizophrenia" or by Huber (1957) as "basic symptoms of schizophrenia". The concept of negative symptoms has been elaborated on by many authors, for instance, Andreasen (1982), Andreasen and Olsen (1982), Koehler and Sauer (1984), Ban et al. (1985), Carpenter et al. (1985), Crow (1985), Goldberg (1985), Sommers (1985) and Zubin (1985). Recently Carpenter et al. (1985) tried to distinguish between primary negative symptoms which are intrinsic of the schizophrenic disorder and secondary negative symptoms.

Negative symptoms in the course of schizophrenia

Negative symptoms can occur in all stages of the course of schizophrenia. As Table 1 indicates, they can manifest themselves in the prepsychotic period, then during a productive psychotic episode together with positive symptoms. During this stage negative symptoms can be hidden by positive symptoms. Later, negative symptoms can come up again in the postpsychotic stage as a residuum or defect, again, with or without residual positive symptoms.

Depression also produces negative symptoms. A recent study by Prosser et al. (1987) showed clearly that negative symptom scores and depression are associated in schizophrenia. Depression is very common in the course of schizophrenia in the prepsychotic period, described, for instance, extensively by Conrad (1958) or in the postpsychotic period (Möller and v. Zerssen 1981). Therefore, negative symptoms can be observed in the frame of a postpsychotic depression, which can be endogenous or reactive, as described by Mayer-Gross (1920) and as postremissive exhaustion by Heinrich (1967).

Diagnostic specificity of negative symptoms

Negative symptoms are not specific for schizophrenia. Negative symptoms as a syndrome can occur, as already mentioned, in depression (Ciompi and Lai 1969) or in schizoaffective psychoses, in neuroses (Ernst 1962), in schizoid or schizotypal personality disorders, and they can be quite characteristic for mild organic brain syndromes. They can also occur in the context of a drug-induced Parkinson syn-

Table 1. Occurrence of negative symptoms

1. *In the course of schizophrenia*
Prepsychotic period (Conrad, Huber)
Productive psychotic period:
– mixture of positive and negative symptoms
– negative symptoms may be hidden
Postpsychotic period:
– residuum or defect with or without positive symptoms
– "postpsychotic depression", endogenous or reactive (Mayer-Gross 1920) postremissive exhaustion (Heinrich 1967)
2. *Of other origin*
Depression and schizo-affective psychoses
Drug-induced depression
Neuroses and personality disorders
Mild organic brain syndromes
Drug-induced Parkinson syndromes
Institutionalization

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drome and hyperkinesia or as a consequence of institutionalization (Goffman 1961) and substance abuse.

Unfortunately, we cannot distinguish between negative symptoms in depression and negative symptoms in schizophrenia. Some authors believe that neuroleptics can induce depression. The problem of drug-induced depression has certainly been overestimated and may not exist to a relevant extent at all. Our own studies with neuroleptic drugs show a marked decrease of depressive symptoms in schizophrenia (Woggon and Angst 1976), a finding which was confirmed by the studies of Hirsch and Knights (1982) and by Möller and v. Zerssen (1986).

Prognostic relevance of negative symptoms

The schizophrenic deficit states or residua have always been considered as being chronic and partially resistant to treatment, but they are not irreversible. Three extensive European follow-up studies of schizophrenic patients (Bleuler 1972; Ciompi and Müller 1976; Huber et al. 1979) all described spontaneous remissions from chronic defects in some cases. Analyzing the prognostic relevance of negative symptoms, it is important, from a methodological point of view, to control the variable chronicity.

Assessment of negative symptoms

The methodology of drug trials was mainly developed in the 1950s by Anglo-Saxon authors. They were the first to carry out short and long-term double-blind trials with neuroleptic drugs. They were also the first to develop suitable rating scales, for instance, the BPRS of Overall and Gorham (1962), which is still in use today. Some of these instruments are widespread because they are reliable, sensitive for measuring change and, above all, short. The great disadvantage is that they are not comprehensive and do not assess the whole psychopathological symptom pattern which is, for instance, possible with the CPRS or the AMDP system (Angst and Woggon 1983; Ban et al. 1985). In face of the restricted item pool of standard instruments, Anglo-Saxon authors were forced to develop new scales measuring side effects and, more recently, negative symptoms. This development is certainly desirable, but one has to realize that due to the restriction to noncomprehensive instruments, the information collected in the past decades by hundreds of well designed double-blind drug trials was limited. Many questions about the effect of neuroleptic drugs on negative symptoms and the deficit states could now be the subject of extensive meta-analyses if the relevant information had been collected earlier.

Some new instruments developed for the measurement of negative symptoms are the SANS of Andreasen (1982) and the NSRS of Iager et al. (1985), the PANSS of Kay and Opler (1987), furthermore, the SADS-C negative symptom scale and the NOSIE defect scale (Lewine et al. 1983) and the subscales of the AMDP system.

In studies of drug effects on positive and negative symptoms one has to measure simultaneously schizophrenic, affective, psycho-organic and neurological symptoms. The only instrument which is suitable for this purpose is the AMDP system, which still needs further revisions in the future.

Are negative symptoms resistant to neuroleptic drugs?

Neuroleptic drugs were from the beginning considered to be less effective against non-productive symptoms, for instance, against the so-called dynamic reduction of Janzarik (1959), which is a core negative symptom of schizophrenia. Glatzel (1967) even hypothesized that residual states of schizophrenia would occur more frequently as a consequence of neuroleptic treatment. On the contrary, the large investigations of Bleuler (1972) and of several Russian authors are at variance with this assumption, showing over the past decades an increase in recurrence at the cost of chronic schizophrenia (Angst and Dinkelkamp 1974). Nevertheless, there is wide agreement that neuroleptic drugs are more efficient in productive or so-called positive psychotic symptoms than in negative ones, although this difference may be partially explained by chronicity.

Studying the effect of neuroleptics on negative symptoms, one should therefore specify in which stage of the psychosis the trial is carried out. Positive and negative symptoms are equally prevalent in acute and chronic schizophrenia, but in chronic cases there is more stability (Kay and Opler 1987) and the clinical syndrome is usually more dominated by the negative symptoms. Drug effects on negative symptoms may be better in the early stage of the disorder.

Neuroleptic drugs and anti-depressants usually reduce the whole psychopathological symptom pattern, but there may be differences when the symptoms start to improve. The symptoms do not develop or disappear simultaneously. Due to a sedative or inhibitory effect, insomnia and psychomotor agitation may respond first, delusions and hallucinations second, depression may respond third, and negative symptoms fourth. However, there is no data supporting the widespread hypothesis of a time lag of action of psychotropic drugs. The positive effect of drugs usually starts within the first few days; this is also true for anti-depressants.

Conventional neuroleptic drugs do act on negative symptoms, shown by a multitude of drug studies over the past decades. A review on the effect of neuroleptics and other psychotropic drugs on negative symptoms in schizophrenia was published by Meltzer et al. (1986). It shows again the necessity to consider chronicity as an intervening variable in studying drug effects on positive and negative symptoms.

One question today is whether there are differential effects of certain drugs on negative symptoms. Examining this question, we have to be aware that comparing two drugs in their efficacy usually ends with unsignificant differences. Most of the drug studies on negative symptoms in schizophrenia report favorable effects. Apart from conventional neuroleptics, the diphenylbutylpiperidines have attracted special attention and the review of Meltzer et al. suggests that they may produce greater improvements in some negative symptoms. Drugs enhancing dopamine activity, like L-dopa and amphetamine, have been administered too, as well as benzodiazepines and beta-blockers. It seems premature to draw definitive conclusions about the differential efficacy of all these drugs.

Contrary to this more sceptical conclusion, there is substantial progress in developing new drugs with differential profiles of side effects. In regard to the development of negative symptoms, neurological side effects are very relevant. It has been shown that negative symptom scores cor-

relate positively with a drug-induced Parkinson syndrome (Hoffman et al. 1987; Prosser et al. 1987). Furthermore, there is a correlation between negative symptoms and hyperkinetic neurological symptoms such as akathisia and dyskinesia (Csernansky et al. 1983; Barnes and Braude 1985; Waddington et al. 1985, 1987; Waddington and Youssef 1986). We may therefore conclude that drugs without extrapyramidal side effects may be preferable in treating negative symptoms or syndromes.

Clozapine and fluperlapine in the treatment of negative symptoms

Clozapine and fluperlapine are known to have no or almost no extrapyramidal activity. Therefore, a meta-analysis of

Table 2. Negative symptoms in the AMDP system

1. Concentration disturbances
2. Inhibited thinking
3. Retarded thinking
4. Restricted thinking
5. Blocking
6. Incoherence
7. Loss of feeling
8. Blunted affect
9. Parathymia
10. Affective rigidity
11. Lack of drive
12. Mutism
13. Social withdrawal
14. Decreased libido

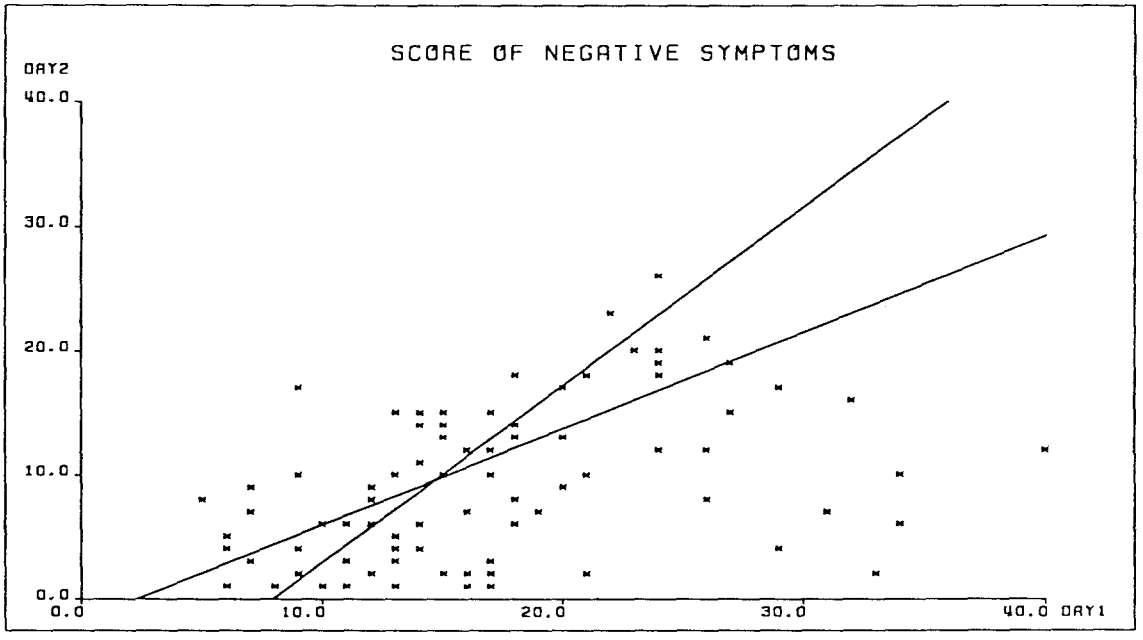

Fig. 1. Haloperidol

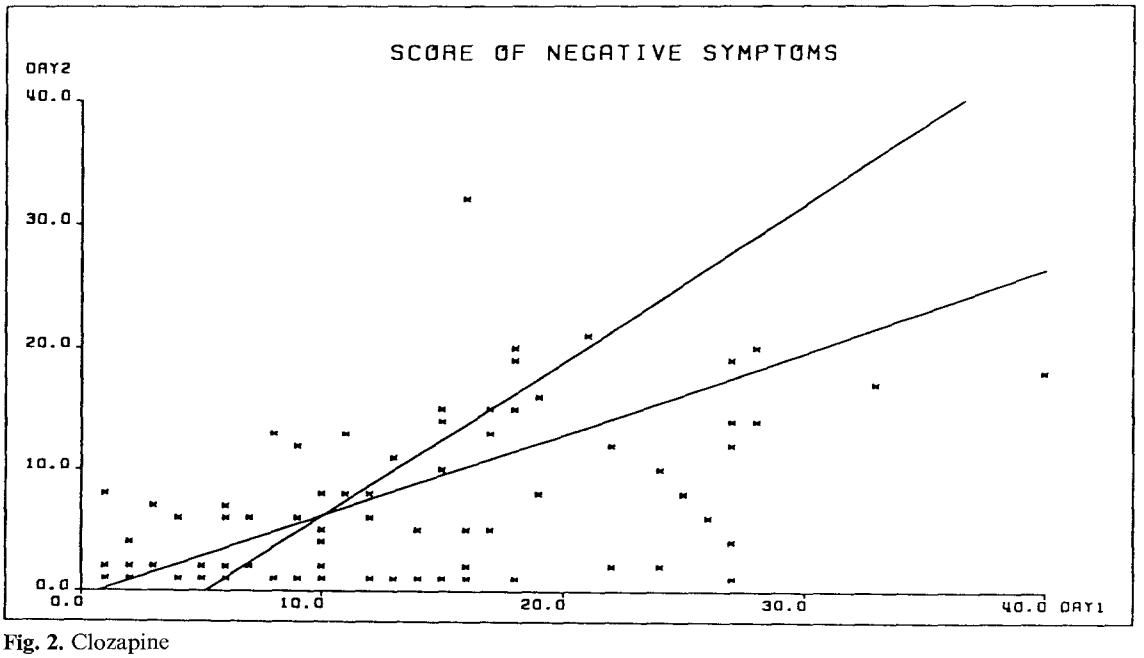

Fig. 2. Clozapine

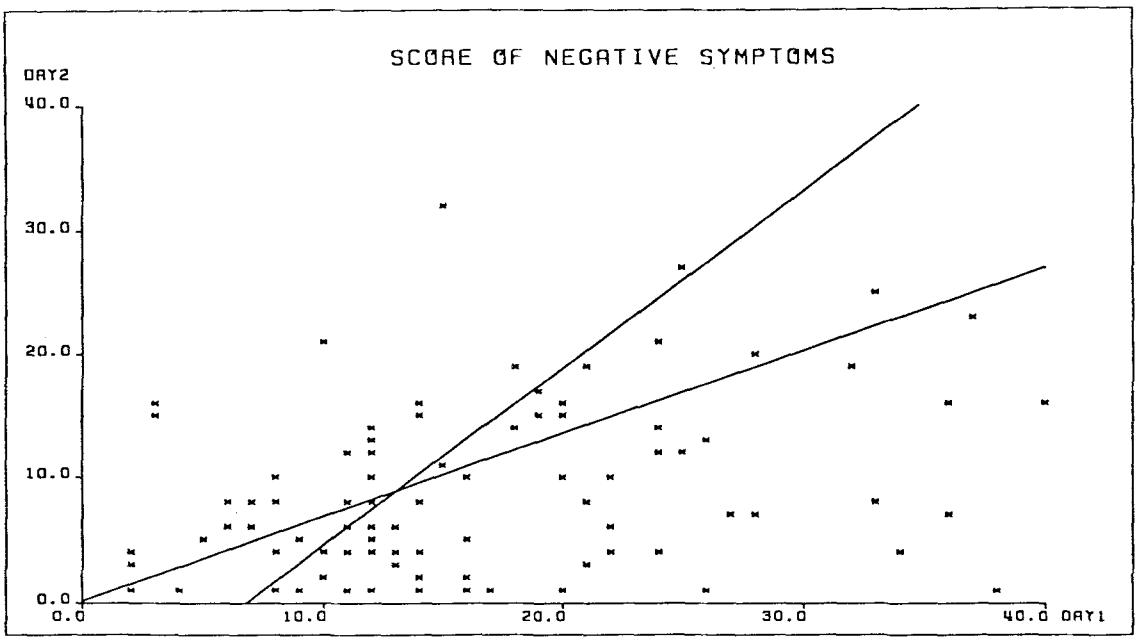

Fig. 3. Fluperlapine

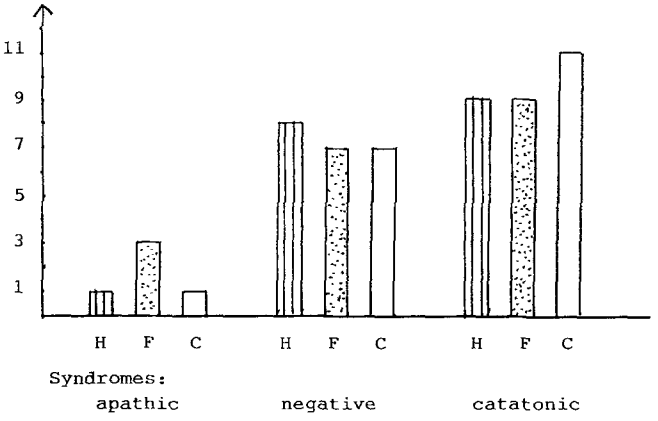

Fig. 4. Mean difference between day 0 and day 20 ↓. H = Haloperidol; F = fluperlapine; C = clozapine

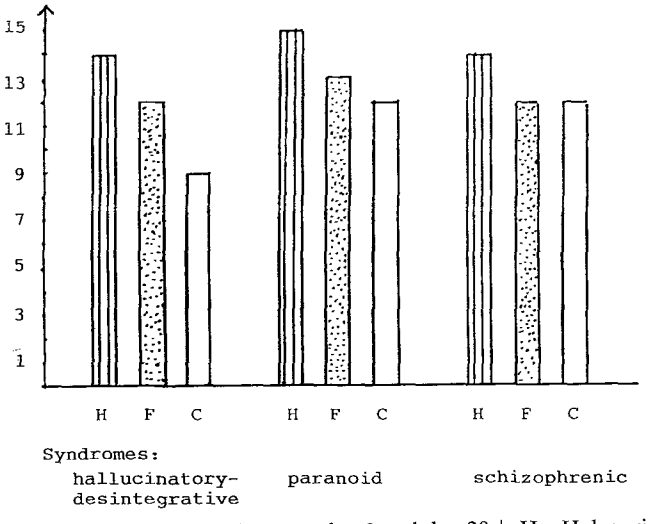

Fig. 5. Mean difference between day 0 and day 20 ↓. H = Haloperidol; F = fluperlapine; C = clozapine

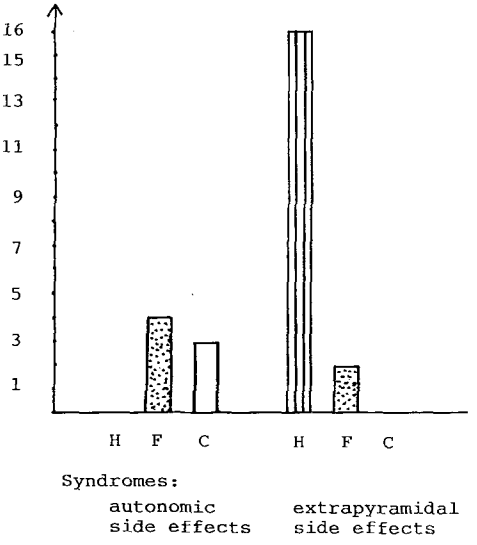

Fig. 6. Mean difference between day 0 and day 20 ↑. H = Haloperidol; F = fluperlapine; C = clozapine

their effect on negative symptoms is interesting. As an example, let us briefly compare the results of 90 patients treated with haloperidol, 90 patients treated with fluperlapine, and 89 patients treated with clozapine. The first two groups come from a multicenter double-blind trial (Woggon et al. 1986), the latter from five different trials on clozapine carried out in Zurich, two of them with a double-blind design. For the analysis of the data, 14 scales of the AMDP system and a new ad hoc scale for negative symptoms were used. According to a methodological study of Straumann (1988) and Good (1988), 14 AMDP symptoms correlated highly with the SANS and the NSRS and were therefore considered to be negative symptoms. They are listed in Table 2 as a tentative NAMDP scale.

In a first step, we analyzed the three samples separately, treated with haloperidol, fluperlapine and clozapine, respec-

tively, and comprising 90 patients each, in order to determine changes in syndrome scores during treatment. The improvement in the NAMDP score can be visualized by so-called scatter plots in which values of the first measurement and those of the second measurement (20 days later) are plotted against each other (Figs. 1–3). A clear and almost identical reduction of NAMDP score values shows up in all three samples (Figs. 4–6). This reduction is satisfactorily homogeneous within the populations, as indicated by correlation coefficients between the two measurements of 0.685 (fluperlapine), 0.738 (haloperidol), and 0.726 (clozapine). However, no significant differences among the three drugs could be revealed with respect to changes in the NAMDP score.

In a second step, the three samples were combined and subsequently broken up with respect to chronicity (acute versus chronic cases). Such a break-up was motivated by the inhomogeneity of the scatter plots. Contrary to our expectations, the NAMDP score could not be used to distinguish between drug effects in acute and chronic cases. On the other hand, clear differences could be revealed on the basis of the AMDP scales "Apathic syndrome", "Somatic-depressive syndrome", "Paranoid syndrome", and "Catatonic syndrome".

The failure of the negative AMDP (NAMDP) score to distinguish drug effects between acute and chronic cases is probably due to the fact that negative symptoms are multidimensional, a hypothesis which had already been put forward by Gibbons et al. (1985), Grau et al. (1986), and Meltzer and Locascio (in preparation). To our knowledge, the presently available instruments to assess specifically negative symptoms are not factor analyzed yet. What we really need is more methodological development, providing us with well constructed, dimensionally clean scales measuring the supposedly different aspects of negative symptoms. Our findings would suggest that researchers of the AMDP should be motivated for such studies, because the AMDP system seems to be especially promising. The suggested methodological development is a prerequisite for further statements about the differential effect of psychotropic drugs on negative symptoms.

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