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Neuroleptics and the neuroleptic-induced deficit syndrome

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The first central pharmacodynamic action of chlorpromazine to be described was sedation without narcosis. The antipsychotic action and extrapyramidal symptoms were observed later. Sedation can be separated into nonspecific sedation (drowsiness, somnolence) and specific sedation (psychomotor inhibition and psychic indifference). Both types are parts of the clinical profiles of classical neuroleptics. The sedative properties of neuroleptics may contribute to the overall efficacy in the treatment of psychotic patients, depending on the clinical situation. In most patients, however, sedation is only needed for a short period, or not at all. The drug induced sedation may adversely affect the patients' well-being and functional capabilities. The term neuroleptic-induced deficit syndrome (NIDS) has been coined to focus attention on the adverse mental effects of neuroleptics. NIDS still needs to be properly defined and to be differentiated from the deficit syndrome of schizophrenia and postpsychotic depression. Assessment methods are needed to establish the incidence and prevalence of NIDS, to evaluate the importance of NIDS in the overall treatment outcome in psychoses and to facilitate development of better antipsychotic agents.

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The main features of neuroleptics, mainly based on the observations of chlorpromazine, were summarized by Deniker (1) as follows:

- a powerful sedative action without narcotic effect;
- a favourable action on excitement, restlessness, and aggressiveness;
- therapeutic effect in psychosis;
- frequent associations of central vegetative changes; and
- a primary subcortical action.

Interestingly, extrapyramidal symptoms induced by chlorpromazine were observed but were not included in the early definition of neuroleptics. The word neuroleptic (Greek to grasp, seize or take hold of the neuron) was invented by Delay to differentiate chlorpromazine from ataractics (sedatives and hypnotics, such as barbiturates). The neuroleptic syndrome observed in animals and in humans referred to psychomotor retardation, emotional neutrality or indifference, reduced initiative and slowing of thought processes. Recent definitions of the world neuroleptic focus on "the effects on cognition and behavior of antipsychotic drugs, which produce a state of apathy, lack of initiative, and limited range of emotion and in psychotic patients cause a reduction in confusion and agitation and normalization of psychomotor activity" (*Dorland's illustrated medical dictionary*; 2). French and German medical dictionaries have similar definitions, and have adopted the word *neurolepsie* (German *Neurolepsie*), in Sweden *neurolepsia* (Latin) to indicate the psychic indifference, detachment and the state of apathy induced by neuroleptics. The word neurolepsy does not seem to have found its way into the English vocabulary. Neuroleptics have also been used in anaesthesiology in connection with neuroleptanalgesia or neuroleptanaesthesia. The combination of a neuroleptic (often droperidol) and a strong analgesic (such as leptanal) is used to induce a state of emotional indifference and pain control to allow surgery to be performed.

Since chlorpromazine was introduced, several neuroleptics have been developed. Most authors agree that this class of compounds share the actions described by Delay, Deniker and others for chlorpromazine, but to varying degrees. With the advent of atypical neuroleptics, such as sulpiride, and atypical antipsychotics, such as clozapine, there was a need for subclassifications. These have been based on chemical structure pharmacological actions. The

most elaborate subclassifications have been developed in French psychiatry (3). The most commonly used subdivision is classical (low potency *vs* high potency and sedative *vs* non-sedative) versus atypical neuroleptics. In North America the term antipsychotic agents has been favoured over neuroleptics (4); the word neuroleptic is mainly used to refer to the extrapyramidal actions of antipsychotics.

Relationships between mental and motor actions of neuroleptics

In 1983, Deniker (5), in a review article, stated: "From the outset, the syndrome of psychomotor indifference of chlorpromazine was described; it was later ascribed to akinesia". Thus, the connection between *neurolepsia* and extrapyramidal symptoms (EPS) was made already in the early 1950s, but this connection is not generally recognized. The neuroleptic threshold is a concept introduced by Haase in 1954 (6). At a certain individual dose level of a neuroleptic, fine motor activity is inhibited as demonstrated by micrographia, and there is a reduction of the psychoenergetic level without disturbance of consciousness, the psychoneuroleptic action. The neuroleptic threshold dose was considered to be the optimal antipsychotic dose level for an individual, whereas doses inducing coarse EPS (bradykinesia, rigidity, tremor, dystonia and dyskinesia) were considered to be toxic, indicating overdose. With newer antipsychotic agents, such as clozapine and remoxipride, there seem to be a separation between the antipsychotic dose level and the dose inducing EPS (7, 8). Atypical antipsychotics have not yet been studied clinically with regard to fine motor side effects and the psychoneuroleptic action, however.

Nonspecific and specific sedation

In Scandinavia and northern Europe, clinical psychopharmacologists (9, 10) routinely divide the sedative actions of neuroleptics into nonspecific and specific sedation. Nonspecific sedation refers to the presence of drowsiness or somnolence, whereas specific sedation refers to psychomotor inhibition in patients with agitation, excitation and aggressiveness. Compounds such as levomepromazine, chlorpromazine and thioridazine have both nonspecific and specific sedative properties; others, such as haloperidol, fluphenazine and perphenazine, induce mainly specific sedation, and also have a high propensity to induce EPS.

Since chlorpromazine was developed, many neuroleptics have been developed with sedative actions varying in degree of specific *vs* nonspecific sedative properties. Neuroleptics without nonspecific sedation do not seem to have less antipsychotic activity and can be used in most patients. In clinical practice, concomitant sedative agents are used occasionally when needed. In patients with prominent or persistent agitation, excitation and aggressiveness, neuroleptics high in specific sedation are often preferred.

Studies of neuroleptics in healthy volunteers utilizing psychomotor test batteries and subjective ratings clearly show a difference between chlorpromazine on the one hand and such compounds as perphenazine, trifluoperazine and haloperidol on the other (11–14). Whereas chlorpromazine induced nonspecific sedation in a dose-dependent fashion, trifluoperazine and haloperidol caused only slight drowsiness but a slowing of thought processes and verbalization and a sense of indifference were still prominent, mainly signs of specific sedation.

Mechanisms of action of nonspecific and specific sedation

Nonspecific sedation of neuroleptics is generally attributed to central antihistaminergic, anti-α-adrenergic and possibly anticholinergic (antimuscarinic) actions of some classical neuroleptics (4, 15, 16). Preclinical data with selective dopamine D_1 antagonists suggest that D_1 receptor antagonism alone or in combination with dopamine D_2 receptor blockade may contribute to this type of sedation (17). Some classical neuroleptics are nonselective with regard to subtypes of dopamine receptors and may block D_1 receptors at clinically relevant tissue drug concentrations.

The antipsychotic action of neuroleptics is attributed to dopamine D_2 receptor antagonism (4, 18, 19). Dopamine D_2 receptor blockade is also responsible for the EPS induced by neuroleptics. As mentioned above, there is a relationship between akinesia in patients, psychomotor inhibition and psychic indifference, that is, between some EPS and specific sedation. It is therefore a reasonable assumption that the specific sedative effects of classical neuroleptics are mediated via antagonism of central dopamine D_2 receptors. It has not been clarified, however, how atypical neuroleptics and antipsychotics retain their antipsychotic action while the EPS and the specific sedation are reduced or absent if all actions are mediated through dopamine D_2 receptor blockade. Regional or cellular selectivity for D_2 receptors within the central nervous system (CNS) may be one explanation; other explanations may be selectivity for other subtypes of dopamine receptors, such as D_3 or D_4 receptors, or selectivity for subpopulations
of functionally coupled D_2 receptors (19). One should not disregard the possibility that other mechanisms that have not yet been discovered may be involved.

The neuroleptic-induced deficit syndrome (NIDS)

The mental effects induced by neuroleptics, which include nonspecific and specific sedation, psychic indifference and actions on the cognitive, conative, affective and motivational faculties of the psyche may be beneficial or detrimental to the individual depending on the clinical situation. It has been mentioned that neuroleptics are used for treatment of psychomotor excitation in psychotic patients in the acute phase or in chronic schizophrenia and mania (chemical straitjacket). However, in most acute-phase patients and during maintenance treatment of psychotic patients in remission or with residual symptoms, neither nonspecific nor specific sedation is needed, and sedation may be detrimental. Thus, such mental effects may reduce wellbeing and the quality of life and compliance with medication and thereby worsen the therapeutic outcome (20–23). They may also adversely affect the success of other treatment modalities such as psychotherapy, behaviour and cognitive therapy and may prevent rehabilitative measures. Even in patients resuming employment, such symptoms may lead to suboptimal work performance. Such adverse mental effects of neuroleptics have been referred to as the neuroleptic-induced deficit syndrome (24).

Definition of NIDS

The subjectively experienced and objective signs of neuroleptic-induced mental side effects have been well known since the discovery of chlorpromazine (5, 6, 25). However, attention has only occasionally been brought to this issue (20, 26, 27), probably since other types of antipsychotic medication have not been available. These adverse mental experiences have been referred to as the dyscognitive syndrome (26), neuroleptic dysphoria (28, 29), akinetic depression (21) and subjective aspects of akathisia (30, 31). The importance of all these adverse symptoms for successful treatment outcome has been made clear, however (22, 32, 33). A generally accepted definition of NIDS has not yet been formulated. It is hoped that the present symposium will initiate a broader discussion and a more widespread awareness of the size and the severity of the problem and lead to agreement on a definition of NIDS.

It is emphasized that, similarly to EPS, all patients may not experience adverse mental reactions. Thus, van Putten (20) reported that approximately 45% of schizophrenic patients were reluctant to comply with neuroleptic medication for this reason. In a recent study of 68 schizophrenic patients undergoing neuroleptic treatment using rating scales and a semistructured interview, subjective side effects related to sedation, dysphoria, and akinesia, including emotional, perceptual and cognitive complaints, occurred in up to 47% (34).

Handling of NIDS

As for EPS, the first measure to be taken to avoid or reduce mental side effects is to reduce and to individualize the dose of the neuroleptic (6, 29). This must be balanced against the risk of underdosing the patient. Centrally active anticholinergics may also be used (6). However, even if such treatment elevates the threshold for the appearance of NIDS and EPS, these agents may introduce their own side effects, such as memory impairment, confusion or delirium, as well as peripheral anticholinergic side effects. Anticholinergics may also lead to therapeutic reversal of neuroleptics (6, 35). It is to be hoped that future antipsychotic agents will have fewer neuroleptic-induced mental (and other) side effects. In fact, such nonneuroleptic antipsychotics should be searched for; neuroleptic antipsychotics are already available in abundance.

NIDS and the deficit syndrome of schizophrenia

For more than a decade, the negative symptoms of schizophrenia have been a major issue in schizophrenia research (36–41). There is a widespread belief that negative symptoms are not improved by classical neuroleptics. However, several reviews of this issue (41–43) clearly show that a number of studies demonstrate improvement of negative symptoms in acute-phase and chronic schizophrenia. Carpenter et al. (38) and others (44–46) have pointed out the difficulty in diagnosing negative symptoms and the deficit syndrome of schizophrenia. In particular, primary or core negative symptoms must be kept separate from negative symptoms secondary to positive symptoms, bradykinesia and other neuroleptic-induced EPS, neuroleptic-induced dysphoria, postpsychotic depression, institutionalization personality disorders and mental retardation. Thus, these authors have pointed out the difference between symptoms of NIDS and the deficit syndrome of schizophrenia.

Several rating scales of the negative symptoms of schizophrenia (39, 40, 47) include items related to mental constructs such as cognitive, affective and conative functions, anhedonia and EPS (Table 1). These symptom items are in fact very similar to the neuroleptic-induced symptoms already described by the early writers on chlorpromazine and other neuroleptics (1, 5, 6). It is important to note that the construction, validation and reliability testing of many negative symptom or deficit symptom scales have not been done in patients who are neuroleptic-free; up to 100% of the patients are said to be on

Table 1. Congruence of mental side effects of neuroleptics and negative, or deficit, symptoms of schizophrenia

Mental function	Neuroleptic side effect	Negative symptom
Vigilance	Drowsiness, somnolence	Attentional impairment
Cognition	Reduced speed of thinking Concentration difficulties "Narrowing of mind" "Fuzzy head"	Alogia Poverty of speech
Conation	Apathy Lack of energy "Weak, tired"	Avolition, apathy Diminished sense of purpose
Affectivity	Flat affect Indifference	Affective blunting Restricted affect
Emotionality	Lack of feeling *Dysphoria* "Dead inside"	Diminished emotional range
Motivation	Anhedonia Reduced drive Reduced initiative	Anhedonia, asociality Curbing of interest Diminished social drive Diminished curiosity

The wording of negative symptoms has been borrowed from Andreasen (47) and Carpenter et al. (38).

neuroleptics. Reassuring statements, such as the absence of akinesia or co-administration of central anticholinergics to alleviate EPS, do not meet reasonable requirements of scientific rigor. The mental side effects of neuroleptics (and central anticholinergics) have not usually been taken into consideration and are rarely mentioned as a source of bias. It seems important for the future of schizophrenia research that patients be studied both on and off neuroleptic (and other) drugs. If not, the growth of knowledge of schizophrenia as a disorder and of antipsychotic agents runs the risk of being retarded by false conclusions.

NIDS and postpsychotic depression

Postpsychotic depression is a concept described by Mayer-Gross in 1920 (48), that is before the neuroleptic era. Since Bowers and Astrachan (49) reopened this issue, a large number of studies have been published, usually in patients on maintenance treatment with neuroleptics. A possible causal relation between treatment with neuroleptics and postpsychotic depression, at least in a proportion of patients, has been proposed (50–53). Neuroleptic dysphoria, sometimes accompanied by akinesia and subjective experiences of akathisia, can be induced even by single doses of at least some classical neuroleptics, such as haloperidol, in healthy volunteers and in patients (11, 21, 54–59). It is therefore probable that the neuroleptic treatment *per se* may contribute to the syndrome of postpsychotic depression in susceptible individuals. Further clinical studies of this issue are needed.

NIDS: pending issues

In order to expand knowledge of schizophrenia and its treatment it seems that NIDS needs recognition, a clear definition and criteria for its presence. Its delineation from neuroleptic dysphoria, subjective aspects of akathisia and akinesia, negative symptoms and the deficit syndrome of schizophrenia and postpsychotic depression may be difficult but is an important task. Assessment methods of NIDS both with regard to its incidence and prevalence and degree of severity need to be developed. Self-rating scales, observer rating scales, psychomotor and neuropsychological tests and various neurophysiological methods (such as cEEG and evoked potentials) are immediate possibilities. Studies should be performed both in healthy volunteers and in patients in various phases of their illness (acute, residual and in remission) and on and off drug treatment.

Conclusion

It seems well recognized and documented that classical neuroleptics have several pharmacodynamic effects in the CNS beside the antipsychotic action. The nonspecific and specific sedative effects referred to above as the neuroleptic syndrome are beneficial and contribute to overall efficacy in a number of clinical situations. However, the potentially detrimental effects on several psychic functions in patients in remission or with mild to moderate residual symptoms have been poorly understood and neglected. On the one hand, neuroleptic antipsychotics permit recovery from psychotic symptoms, but on the other hand, mental adverse effects also set limits to their therapeutic usefulness. The time is ripe, it seems, for a closer look at the neuroleptic-induced deficits both from a scientific and from a practical clinical perspective. A research program on NIDS as outlined above seems important both for our common knowledge of psychotic disorders, including schizophrenia, and for the development of new antipsychotic agents with improved overall efficacy and tolerability, leading to a better quality of life and social functioning for patients and better health economics for society.

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