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CLINICAL MANIFESTATIONS OF EXTRAPYRAMIDAL SIDE EFFECTS OF NEUROLEPTICS

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Abstract: Neuroleptics or antipsychotic drugs constitute one of the main groups of modern psychotropic drugs and occupy a central place in clinical psychopharmacology. Neuroleptic drugs include drugs belonging to different chemical groups and possessing a number of general psychopharmacological properties.

These characteristics were more fully expressed by J. Delay and P. Deniker (1961): 1) psychopathic effect without the effect of sleep; 2) an effect that eliminates various types of excitation, including manic excitation; 3) Effects that eliminate some acute, chronic, and experimental psychosis; 4) the ability to cause specific neurological and vegetative disorders; 5) The predominant influence of the CNS on subcortical structures. A. Carlsson and co-authors (1963-1987) later found that the clinical effects of neuroleptics are linked to their general neurochemical properties, which include the ability to compensately increase dopamine biosynthesis and metabolic rate in the corresponding brain structures by selectively blocking dopamine D2-receptors in various parts of the brain (stratum, nucleus accumbens, cerebral cortex).

The development of neurological side effects of classic neuroleptics is associated with the blockade of D2-dopamine receptors in the brain's neurostrial system. The main characteristic of the new generation of neuroleptic drugs (Ryspoleptic, Ziprex, etc.) is that they do not cause significant or general extrapyramidal side effects. This property is determined by their spectrum of neurochemical activity.

Atipic neuroleptics have a selective effect on the mesolymbic and mesocortical dopaminergic systems of the brain and a weakly expressed effect on the nihrostrial system. Furthermore, atypical neuroleptics simultaneously block dopamine receptors and 5HT2-serotonin receptors.

The relationship between dopamine and serotonin receptor blockade plays an important role in the mechanism of action of atypical antipsychotics (R. Baldessarini, 1987; H. Meltzer, 1989; F. Bamaster et al., 1997).

It has been established that blockade of 5HT2-serotonin receptors leads to a compensatory increase in dopamine concentration in the nigrostrial system, thereby reducing the severity of extrapyramidal side effects due to the dopamine-blocking activity of these neuroleptics (C. Saller et al., 1990).

According to the DSM-IV American classification, all extrapyramidal motor disorders associated with the use of neuroleptics are divided into Parkinsonism, acute dystonia, acute cirrhosis, and late dyskinesia.

Diagnostic criteria for extrapyramidal neuroleptic disorders according to DSM-IV are presented in Table 1.

Table.

Criteria for diagnosing Parkinsonism arising from the use of neuroleptics according to DSM-IV

A. The presence of one or more symptoms arising against the background of neuroleptic therapy:

1. Tremor (legs, head, tongue)
2. Muscle rigidity and the "tooth roller" symptom, accompanied by increased muscle plastic tone
3. acini

Symptoms of group B. A appear within the first few weeks after the start of neuroleptic therapy or when the dose of previously administered neuroleptics is increased, and decrease after the appointment of antiparkinsonian correctors.

C. Symptoms of group A should not be associated with mental illness (catatonia, negative symptoms in schizophrenia, motor inhibition in major depressive syndrome, etc.).

The development of symptoms in group A should not be associated with the use of other medications, neurological or somatic diseases (Parkinson's disease, Wilson's disease, etc.).

Criteria for diagnosing acute dystonia (acute dyskinesia) caused by the use of neuroleptics according to DSM-IV

A. The presence of one or more symptoms arising against the background of neuroleptic therapy:

1. Incorrect head and neck position relative to the body (retrocolic, torticollis)
2. Snail muscle spasms (trizm, spasm, facial contortion)
3. Difficulty swallowing (dysphoria), speech or breathing problems (laryngopharyngeal spasms, dysphonia)
4. Inaccurate and complicated speech as a result of language enlargement or hypertonia (diarrhea, macroglossia)
5. language output
6. Eye muscle spasms (ocular crises)

Group B. A symptoms appear within the first few weeks after the start of neuroleptic therapy or with an increase in the dose of previously administered neuroleptics and decrease after the appointment of antiparkinsonian correctors.

C. The origin of Group A symptoms should not be associated with mental illness (e.g., a catatonic form of schizophrenia)

The appearance of symptoms in group A should not be associated with the use of other medications, neurological or somatic diseases.

Criteria for diagnosing acute acothia caused by the use of neuroleptics according to DSM-IV

a) The appearance of subjective complaints, such as discomfort, after the use of neuroleptics

b) Presence of any of the following symptoms:

Discomfort

Restless walking with the intention of changing posture to alleviate discomfort.

To be unable to stand or sit for a few minutes

Symptoms of group C.A and B appear within the first four weeks after the start of neuroleptic therapy or with an increase in the dose of previously administered neuroleptics and decrease after the appointment of antiparkinsonian correctors.

c) Symptoms of groups A and B should not be associated with mental illness (psychomotor disturbances in schizophrenia, agitated depression, manias, hyperactivity disorder, etc.)

d) Symptoms of groups A and B should not be associated with the use of other medications, neurological or somatic diseases.

Diagnostic criteria for late dyskinesia arising from the use of neuroleptics according to DSM-IV

a) Compulsory movements of the tongue, cheeks, body, and limbs, which arise in connection with the appointment of neuroleptics

b) Compulsory actions are observed for at least 4 weeks and are characterized by the following manifestations:

1. choreographic movements
2. Athetoid movements
3. rhythmic movements (stereotypes)

Signs of group C. A and B appear during treatment with neuroleptics or within 4 weeks after the discontinuation of simple neuroleptics and within 8 weeks after the discontinuation of deponeuroleptics

D. Treatment with neuroleptics should be at least 3 months (1 month if the patient is 60 years old or older)

E. Signs of group A and B should not be associated with neurological or general somatic diseases (Hentington's chorea, Wilson's disease, Siddengham's chorea, etc.), as well as with the use of other medications (L-Dopa, bromocriptine).

Signs of group A and B should not be a manifestation of acute neuroleptic dystonia (acute dyskinesia).

Different neuroleptics have different extrapyramidal activity. It has been established that classical neuroleptics cause extrapyramidal disorders by increasing the number of aliphatic phenothiazine derivatives to piperazine derivatives and butyrophenones according to a known pattern.

In this case, the nature of unwanted extrapyramidal effects also changes from the dominant acineto-rigidity syndrome to hyperkinetic and dyskinetic syndrome (G.Ya. Avrutskiy, I.Ya. Gurovich, V.V. Gromova, 1974). The development of extrapyramidal disorders by atypical neuroleptics depends on the dosage used. Risolept and ziprex in moderate therapeutic doses lead to the appearance of extrapyramidal symptoms with the same frequency as placebo. As the dosage increases (more than 6 mg per day of risolept and more than 10 mg per day of ziprex), the frequency of development of extrapyramidal side effects exceeds that of placebo, but is significantly lower than that of haloperidol (Peuskens J., 1992; F. Muller-Spahn, 1992; D. Sasey, 1997). According to our data, patients with schizophrenia with residual organic brain damage may be excluded, and low doses of drugs in these patients may also cause extrapyramidal disorders. Comparative characteristics of extrapyramidal side effects of neuroleptics are presented in Table 2.

Neuroleptic parkinsonism occurs in more than 50% of cases during treatment with classic neuroleptics during the first week or before the start of neuroleptic therapy, when the dose of the received neuroleptics is increased, and is characterized by a state of hands bent on elbows and drawn to the body, limited general mobility, trembling of the limbs, acathasia and vegetative disorders accompanied by it (facial fatigue,

sweating, sebosis). Muscle tone increased in the plastic type with the sign "toothed wheel." Various types of unstable hyperkinesis can be observed.

Treatment. As a rule, extrapyramidal symptoms decrease after the appointment of antiparkinsonian correctors - cyclodol, akineton, etc. (Table 3). In patients with residual cerebral organ failure, symptoms may persist - according to I.Ya. Gurovich, "prolonged extrapyramidal syndrome" (1971).

In such cases, antiparkinsone correctors are prescribed in combination with high doses of nootropic drugs, the dose of the received neuroleptics is reduced, and drugs with minimal extrapyramidal activity are prescribed (see Table 2). Our research has shown that the use of extracorporeal detoxification methods - plasmapheresis and hemosorption - yields effective results in the severe, prolonged course of extrapyramidal neuroleptic syndrome.

2. Comparative characteristics of extrapyramidal side effects of neuroleptics (based on literary data and personal experience in the use of drugs)

Drug	Parkinsonism	Hyperkinetic Manifestations (tremors, hyperkinesias, acathiasis)	Diskinesias
		Aliphatic derivatives of phenothiazine	
Aminazine (Chloropromazine)	++	+	+
Propazine (promazine)	+	+	+-
Thyzercin	+	+	-
(Levomepromazine)			
Teralen (alymeazine)	+	+	+-
		Piperazine derivatives of phenothiazine	
Phenolone (metaphenazine)	+	+	+
Etaperazine (Perfenazine)	++	+	+
Triphthazine (trifluoperasine)	++	++	++
Majeptil (thioproprazin)	++	+++	+++
Moditen (fluorfenazine)	++	+++	++
Meterazine (prochloroperazine)	++	++	++
		Pyperidine derivatives of phenothiazine	
Sonapax (thioridazine)	+	+-	+-
Neuleptyl (periciazine)	++	+	+
PIPORTYL	++	++	++

(PIPOTIAZINE)			
		Butyrophenone derivatives	
Galoperidol	++	++	++
Trisedyl (trifluperidol)	+++	+++	++
		Diphenylbutylpiperidine derivatives	
Orap (pimozid) *	+	++	+
Imap (flush pyrene) *	+	+	++
Semap (Penfluoridol)	+	++	+
		Dibenzodiazepine derivatives	
Leponeks (Clozapine) **	+-	+-	-
Olanzapine (Ziprexa) **	+-	+	+-
		Thioxanthine derivatives	
Chloroprotexene (trucsal)	+	-	-
Clopixole (Zuclopenticol)	++	+	+
Fluanceol	++	+	+
(fluopenticol)			
Tiotixen (navan)	++	++	++
		Substituted benzamides	
Eglonil (sulpyride)	+-	+	-
Topral (sultopride)	++	++	+
thiapride (thiapridal)	+	+	+
		Benzisoxazole derivatives	
Risperidone (risperdal) **	+-	+	+-

Note. The sign (+) indicates an approximate effect of the drug when used in moderate therapeutic doses; the sign (-) - no effect;
* - currently, these drugs are not produced;
** - Atypical antipsychotics practically do not lead to the development of extrapyramidal side effects and do not cause a significant increase in prolactin in the blood plasma, but can lead to weight gain and edema due to high secretion of antidiuretic hormone.

Acute dystonia (or early dyskinesia) occurs in 25-75% of cases within the first 7-10 days after the start of treatment with classic neuroleptics or with an increase in the dose of previously prescribed drugs and is characterized by the appearance of sudden spastic tetanomorphic motor disorders. Motor disorders may be localized and encompass a specific muscle group, occur in typical areas of the body, or are generalized in nature, with general motor disturbances accompanied by anxiety, anxiety, tingling, and vegetative disorders (puffiness, hypersalivation, tear flow, vasomotor reactions, etc.). In local dystonia, there are tongue wrinkles, hyperkinesias in the facial muscles, thyrism, visual spasms (ocular crises), deviation of the neck, opistotonus, dyspnea, etc. Oral syndrome (Kulenkampff-Tarnow) is also illuminated, the clinic of which is manifested by sudden tonic contraction of the muscles of the mouth and neck, tongue exhalation,

respiration, and impaired phonation. In some cases, these symptoms can be assessed as epilepsy or a manifestation of infectious CNS diseases (meningitis, encephalitis, etc.).

Treatment. In the development of local dystonia, intramuscular or intravenous administration of akineton at a dose of 5 mg yields effective results (G.Ya. Avrutskiy, D.I. Malin, 1994). In the absence of the drug, dystonic symptoms can be eliminated by administering 25-50 mg of aminazine intramuscularly and 2 ml of 20% caffeine solution subcutaneously (G.Ya. Avrutskiy, I.Ya. Gurovich, V.V. Gromova, 1974).

In cases of generalized dystonia, it is recommended to prescribe aminazine or tizercin in doses up to 50 mg intramuscularly and antiparkinsonic correctors (acineton 5 mg intramuscularly) simultaneously. Acute dystonia can be eliminated by administering 20 mg of diazepam (relanium) intravenously slowly or intramuscularly. To prevent the recurrence of dyskinesias, antiparkinsonian correctors are prescribed or their dosage is increased.

Acacia occurs within the first 4 weeks after the start of neuroleptic treatment or when the dose of neuroleptics is increased and manifests as complaints such as discomfort, inability to sit comfortably, constant movement, and the need to change body position. Patients are restless and are forced to constantly walk to change their body position, eliminate discomfort, and not sit or stand for a few minutes in any place. Acacia can be combined with neuroleptic Parkinsonism. "Late" forms of acacia are also described, in which the appointment of antiparkinsonian correctors and a decrease in the dose of neuroleptics does not immediately reduce the clinical symptoms of acacia. These conditions are difficult to distinguish from late dyskinesias (M. Munetz, C. Corners, 1982).

Treatment. Antiparkinsonic correctors are cyclodol, akineton, etc. It is also effective to prescribe tranquilizers - diazepam, clonazepam, and fenazepam in moderate therapeutic doses.

Late dyskinesias are one of the most serious neurological complications of neuroleptic therapy and develop in 20-30% of patients who regularly take classic antipsychotics. The frequency of late dyskinesias in young people receiving neuroleptic therapy for one year is 5%, while in the elderly it is 25-30%. Late dyskinesias develop relatively rarely when treated with atypical neuroleptics (rispoleptic, ziprex). According to a study by P. Lemmens et al., 1999, late dyskinesias were noted in 0.23% of patients treated with rhinoplasty within a year.

According to DSM-IV data, motor impairments in late dyskinesias persist for more than 4 weeks after the termination of neuroleptic therapy. They may arise against the background of prolonged antibiotic use or within the first 4 weeks after discontinuation of traditional antibiotic use and within 8 weeks after discontinuation of long-acting neuroleptics.

The clinical manifestation of this complication is characterized by the gradual development of various hyperkinesias (oral, ateoid, choreiform, torsion-distonic), their transition to a generalized form. In other cases, hyperkinesis may arise after discontinuation of neuroleptics. Hyperkinesias often increase during intervals between treatment courses, while other extrapyramidal disorders decrease.

Simultaneously with neurological changes, persistent changes can occur in the psychological sphere. The sum of these symptoms is described as a manifestation of psychopharmacotoxic encephalopathy (I.Ya. Gurovich, E.P. Fleiss, 1969). They are characterized by low activity, high psychological and physical exhaustion, affective instability, slowness of intellectual processes, controllability in patients, as well as states of "sterification" of the psyche due to the tendency of existing dyskinesias to intensify.

Treatment. As soon as the first signs of late dyskinesias appear, it is necessary to discontinue neuroleptics (if the patient's mental state allows this). In cases where it is impossible to stop therapy, treatment is continued with atypical antipsychotics (azaleptin, risolept, ziprex), in which the risk of developing

complications is significantly lower. In many cases, it has been established that late dyskinesias resolve after discontinuation of drug administration. In this case, dyskinesias may worsen after the discontinuation of neuroleptics, and in most cases, improvement occurs within a few months (J. Kane, J. Smith, 1982).

The use of the antioxidant alpha-tokoferol (vitamin E) is effective in reducing dyskinesia. Due to the presence of organic brain insufficiency in many patients, the therapy regimen should include neurometabolic drugs (nootropil, picamilon, pantogam, phenibut, etc.), general strengthening therapy, and physiotherapy. If dyskinesias do not disappear, patients are prescribed neuroleptics in small doses - sonapax 50-150 mg/day, and leptoneks 50-100 mg/day. The use of thiapridal at a dose of 200-600 mg per day is more effective. It is also recommended to take benzodiazepines - diazepam 10-30 mg/day, clonazepam 2-6 mg/day.

The use of antiparkinsone correctors with central cholinolitic activity is considered ineffective in chronic extrapyramidal neuroleptic syndrome. Some reduction in the severity of dyskinesias can be achieved through the use of akineton, which, in our opinion, has a more effective effect on hyperkinetic disorders compared to other antiparkinsonian drugs. Furthermore, the presence of an ampullary form of akineton allows its use for parenteral intramuscular and intravascular drip administration, which enhances the therapeutic effect (Avrutskiy G.Ya., Malin D.I., 1994). Some authors note the possibility of increasing dyskinesia when using anticholinergic correctors (T. Friis, J. Gerlach, 1983; W. Greil et al., 1984). Our research has shown that if there are cases of Parkinsonism in the form of a complex of amistatic symptoms, accompanied by a simultaneous plastic growth of muscle tone with dyskinesias, then anticholinergic correctors have a positive effect. It is assumed that the development of dyskinesia is associated with high sensitivity of dopamine receptors. It is impossible to deny the involvement of autoimmune mechanisms in this process. Recently, it has been established that the autoimmune process can affect the structures of the dopamine system, directly at the level of dopamine receptors, producing anti-receptor antibodies with stimulating and blocking effects (G.I. Kolyaskina, T.P. Sekirina, 1990). Based on these views, the use of detoxifying and immunocorrective methods of extracorporeal detoxification can be theoretically justified.

Our research results showed that after plasmapheresis and hemosorption, along with a decrease in motor impairments, there was an improvement in mental and general physical condition - a decrease in apathy, increased activity, normalization of sleep, and rest. Therefore, along with extrapyramidal symptoms, it also affects the reduction of symptoms of psychoorganic syndrome.

Table 3. Treatment of extrapyramidal side effects of neuroleptics

Side effects	Treatment
Parkinsonism	Anticholinergic correctors: cyclodol 2-18 mg/sec akineton 2-24 mg/s tremblex 0.25-0.5 (2-4 ml) benzotropin intramuscularly 3-9 mg/s
Acute dystonia	Akineton 5-10 mg/s intra-muscular, intravenously Relanum 10-20 mg intramuscularly, intravenously Aminazine in the absence of acineton 25-50 mg intramuscularly + 2 ml 20% caffeine solution subcutaneously For the purpose of prevention, the dose of correctors is increased
Acacia	Anticholinergic correctors Tranquilizers - diazepam, clonazepam, and fenazepam in moderate therapeutic doses.
Evening Diskinesias	Non-high doses of some neuroleptics: sonapax 50-150 mg/s;

	Lyuphoneks 50-100 mg/s
Hazardous neuroleptic syndrome	The most effective: thiaprid 200-600 mg/s Tranquilizers - clonazepam 2-6 mg/s; diazepam 20-30 mg/s In some cases, acineton is effective Vitamin E Nootropics Extracorporeal methods of detoxification (plasmapheresis, hemosorption) Cancellation of neuroleptics Intensive infusion therapy (from 2.5 to 6 liters per day) Nootropics Bromokriptin 7.5-15 mg/sec Dantrolene 100 mg/s Plasmapheresis, hemosorption

The prevention of complications should be carried out taking into account risk factors. It has been established that late dyskinesias are more commonly caused by the following factors: 1) the presence of cerebral organ deficiency; 2) old age; 3) Continuous use of neuroleptics in high doses, especially pyperazine derivatives of phenothiazine and butyrofen; 4) Predisposition to the development of massive extrapyramidal symptoms with a predominance of prolonged hyperkinesias. In the presence of the aforementioned factors, especially when they combine, it is necessary to conduct therapy with great caution, taking into account possible complications (G.Ya. Avrutskiy, I.Ya. Gurovich, V.V. Gromova, 1974).

Literature:

1. Авруцкий Г.Я., Гурович И.Я., Громова В.В. Фармакотерапия психических заболеваний. М.: Медицина, 1974; 470.
2. Авруцкий Г.Я., Малин Д.И. Социальная и клин. Психиатрия. 1994; 2: 70-5.
3. Baldessarini R. Amer J Med 1987; 83: 95-103.
4. Bymaster F, Rasmussen K, Calligaro D. et al. J Clin Psychiatry 1997; 58 (Suppl. 10): 28-36.
5. Carlsson A, Lindquist M. Act Pharmacol 1963; 20: 140-4.
6. Casey D. J Clin Psychiatry 1997; 58 (Suppl. 10): 55-62.
7. Delay J, Deniker P. Methodes chimiotherapeutiques en Psychiatrie. 1961; Paris: Masson, 1961, 496 p.
8. Friis T, Gerlach J. Acta psychiatr Scand 1983; 67: 178-87.
9. Greil W, Haag H, Rossnagl G, Ruther E. Brit J Psychiat 1984; 145: 304-10.
10. Lemmens P, Brecher M, Van Baelen B. Acta Psychiatr Scand 1999; 97: 1-11.
11. Kane J, Smith J. Archives General Psychiatry 1982; 39: 473-81.
12. Meltzer H. Psychopharmacology 1989; 99: 18-27.
13. Muller-Spahu F. and the International Risperidone Research Group. Clin Neuropharmacol 1992; 15 (Suppl. 1): 90A.
14. Peuskens J. Janssen Clinical Research Report RIS-INT-2. (March 1992).
15. Saller C, Czupryna M, Salama A. J Pharmacol Exp Ther 1990; 253: 1162.