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ORIGINAL PAPER

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Review: Treatment of schizophrenia

State of the art

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Abstract As a result of the multifactorial etiopathology of schizophrenia, a treatment strategy combining drug therapy with psychosocial measures is indicated. Depending on the stage of the disease and on the individual condition of the patient, the accent is set alternatively more on one approach or on the other. However, under aspects of symptom reduction and relapse prophylaxis, the therapy with neuroleptics plays the most important role. In order to keep their side effects to a minimum during acute and long term treatment, there is nowadays a trend towards administration of the lowest possible dose. Under this aspect, the use of so called atypical neuroleptics should be taken into consideration. The treatment of negative symptoms, especially in the context of chronic residual syndrome, is still a problem which hasn't been solved to satisfaction. Beside the use of atypical neuroleptics, treatment with antidepressives should be tried. During the long term relapse prophylactic treatment, it is important that not only the criterion "reduction of the relapse rate" but also that of individual risk/benefit relation be considered. Concerning psychosocial therapies, especially focused behavioural therapy approaches, for example educational programs and specific family therapeutical intervention following the high-EE-concept, as well as training of social and cognitive competences have proved useful beside supportive psychotherapy and the whole range of sociotherapeutical measures. However they need further evaluation before they get integrated in routine treatment.

Key words Treatment of schizophrenia · Negative symptoms · Neuroleptics · Psychosocial therapy

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General aspects

The diagnosis of schizophrenia should be made according to one of the modern operationalized classification systems: ICD 10 or DSM IV. The diagnosis is based on an intense psychopathological as well as somatic check-up including blood analyses and brain imaging. The differential diagnosis of other functional psychoses and especially of exogenic psychoses has to be carefully considered.

Based on the multifactorial etiopathogenesis of schizophrenia, a multidimensional therapy approach is suggested, in which psychopharmacological and psychosocial methods are combined.

The results of control group studies show that for the treatment of the acute phase and the relapse prevention, the efficacy of neuroleptics is very well proven. With respect to psychosocial intervention, which seems to be indicated especially after the full or partial remission of psychotic symptoms, adequate control group designs are rare and the results are often not consistent (Möller and von Zerssen 1986, Hirsch and Weinberger 1995, Deister and Möller in press).

Medication of the acute phase

The psychopharmacological treatment of psychotic symptoms can be performed principally with any neuroleptic (Kane and Marder 1993). However there is clinical experience with individual patients who appear to respond better to one medication than to another (Gardos 1974).

As a rule, a monotherapy should be applied. A combination of different neuroleptics only seems rational under special conditions, for example if one wants to connect the highly potent antipsychotic effect of some butyrophenones with the sedative, respectively sleep-inducing effect of the less potent neuroleptics from the phenotiazine-group or a benzodiazepine.

When choosing a neuroleptic, the psychopathological state of the patient as well as his individual risk for certain unwanted effects have to be taken into account.

When treating a patient suffering from a severe schizophrenic episode, one should begin with a sufficiently high dosage of the chosen neuroleptic. Often so called high potent neuroleptics are recommended in such cases. A much smaller dosage may be used to start with if the psychotic state is less severe. The adequate dosage can then be "titrated" through stepwise increase. In extremely severe psychotic states which can usually only be treated under inpatient conditions, particularly when there is a risk of endangerment for self or others, or when the patient's cooperation is insufficient, a parenteral start of the treatment with a high potent neuroleptic is indicated (Möller et al. 1982). In cases of agitation, excitement states or psychotic sleep problems, a comedication with a low potent phenothiazine (e.g. levomepromazine or thioridazine) or a benzodiazepine (e.g. diazepam) may be administered as single or multiple dosage in order to attain additional sedation. A further increase of the neuroleptic dosage after having reached dosages which are generally considered as being antipsychotic (Baldessarini et al. 1988) (500–1000 chlorpromazin-aequivalents) should not be carried out in the first four weeks of treatment because it is well known from clinical experience that the full response to neuroleptic treatment needs several weeks (Lieberman et al. 1993). After four weeks without a sufficient partial response of the productive symptoms, an increase of dosage might be advisable, however, there is no sufficient evidence from controlled studies for such a procedure.

Based on PET findings showing that striatal D_2-receptors are nearly totally blocked with relatively low dosages of high potent neuroleptics (Nordstrom et al. 1993) – e.g. 5 mg haloperidol – there is a tendency also from the clinicians to treat patients with very low dosages compared to those which used to be widespread in clinical practice. It was suggested that 350 to 700 mg chlorpromazine equivalents might be sufficient for the average schizophrenic patient (Reardon et al. 1989, Rifkin et al. 1991, van Putten et al. 1990). However the PET-findings should not be overinterpreted: it might be that the antipsychotic effect is not only a matter of D_2-blockade, but that other transmitter systems (e.g. the serotonergic) are involved (Kane et al. in press) and are influenced by higher dosages of a classical neuroleptic. Evidence for a comparatively low dosage, in this case titrated on an individual base according to the neuroleptic threshold concept (Bitter et al. 1991), comes from a study of McEvoy et al. (1991). They compared the treatment results of an individually titrated low dose which induced only very mild parkinsonian symptoms (3.7 ± 2.3 mg/d) with higher dosages (11.6 ± 4.7 mg/d). They did not find an improved efficacy in those patients who were switched to the higher dosage. However, a pitfall of this study might be a too short duration (14 days) of the control-group design and a possibly too small sample size to find differences.

For reasons of a flexible adaptation of the dosage to the individual clinical conditions, the treatment of the acute phase should not begin with a depot-neuroleptic. An exception is when lacking compliance of the patient renders a therapy with a depot-neuroleptic advisable. In such a case the depot-neuroleptics with short term effect should be preferred to others to keep at least some flexibility.

If after 6 weeks of therapy with the first neuroleptic and in spite of increased dosages- a high dosage approach using up to tenfold higher dosages than the standard therapy is not further recommended – *an unsatisfactory therapy result* has been achieved, another neuroleptic, if possible from another pharmacological class, should be administered. However this suggestion is only based on clinical evidence, but not on evidence of controlled clinical studies. There are only very few studies focusing on this issue. Kinon et al. (1993) found little benefit in switching from fluphenazine to haloperidol after four weeks, however, Shalev et al. (1993) reported that the great majority of patients improved after consecutive trials of different conventional antipsychotics, but without controlling for the time effect.

Well founded empirical data support clozapine for the treatment of refractory patients. Among others the excellent study of Kane et al. on severely refractory patients (1988) shall be mentioned here. A clozapine treatment for such patients should last up to six months because it has been demonstrated that the treatment response can occur after a long delay (Meltzer 1989) and the dosage should be increased up to 800 mg p.d. Augmentation strategies like the administration of carbamazepine, lithium or benzodiazepines have been reported as helpful in refractory patients (Schulz et al. 1990). However the empirical evidence is weak (Meltzer 1992). As ultima ratio ECT should be considered although there exist only few data to support such an approach (Sagatovic and Meltzer 1993).

In therapy resistance and when unexpected side effects are encountered, measures of serum levels should be made in order to better adapt the dosage of the medication.

Among others fast metabolizers (caused e.g. by genetic disposition, by enzyme induction) and slow metabolizers can be detected in this way. Especially the problem of enzyme induction during treatment with neuroleptics should be carefully considered. It is still an unsolved problem whether there exists a certain therapeutic range for certain neuroleptics (Baldessarini et al. 1988, Dahl 1986).

In cases of *catatonic stupor,* if the neuroleptic treatment does not lead to a clear therapeutic success already during the first days, ECT has to be applied in order to avoid an endangerment of the patient's life by the development of febrile catatonia. Recently high dosages of lorazepam have been suggested as an alternative to the neuroleptic treatment of the catatonic stupor (Benkert and Hippius 1996).

The *schizoaffective psychoses* have a special position, under therapeutic aspects. Schizodepressive episodes are treated with a combination of a neuroleptic and an antidepressant (Möller and Morin 1989, Goodnick and Meltzer 1984). In schizomanic episodes a monotherapy with one neuroleptic is usually regarded as sufficient. Because of

the risk of neurotoxic complications, an additional dose of lithium may not be harmless, at least when relatively high dosages of the neuroleptic are administered. The efficacy of an additional treatment with carbamazepine or valproate is not yet definitively proven.

Generally neuroleptic treatment focuses on positive symptoms as outcome criterion. However *negative symptoms* are an important part of schizophrenia and should be considered carefully in the treatment of schizophrenia (Möller and Rao 1996). Meanwhile there is some evidence that not only positive symptoms, but also negative symptoms respond to neuroleptics (Möller 1993a, Möller et al. 1995). However in most studies only negative symptoms secondary to positive symptoms have been addressed, while there is still some uncertainty whether also primary negative symptoms, especially the chronic deficit syndrome can be influenced by neuroleptics.

Especially atypical neuroleptics, like clozapine, zotepine, recently also risperidone and olanzapine demonstrated relatively good results in the treatment of negative symptoms. Also substituted benzamides like sulpiride or amisulpride in a dosage which is known to act preferentially on dopamine release by blocking the presynaptic D_2-receptors, e.g. less than 600 mg sulpiride p.d., should be considered. An attempt can be made also with activating antidepressants especially in cases of pure negative symptoms (Siris et al. 1978). Possible causal factors for secondary negative symptoms have to be carefully considered and as far as possible eliminated, e.g. overdosage of neuroleptics, social understimulation, depression (Carpenter et al. 1985).

In cases of *postpsychotic depression*, a reduction of the neuroleptic dosage should be tried, if clinically possible. Anticholinergics can be administered under the hypothesis of an akinetic depression, also if no clear parkinsonoid syndrome is detectable. Finally, an antidepressant treatment should be considered, although its efficacy in this indication is not as well established as for major depression without schizophrenia (Siris 1995). To counter the risk of symptom provocation (Prusoff et al. 1979), which is attributed to antidepressants, a simultaneous neuroleptic medication should be administered. It is not well enough investigated which type of antidepressant is preferable under this condition. The classical tricyclics are problematic because of sedation and anticholinergic side effects, disturbances of vigilance and cognitive capacities (cognitive dysfunction is an important core symptom of schizophrenia). SSRI and MAO-I might be preferable under such effect aspects, however they are not well investigated in this indication.

After a clear improvement of the psychotic symptomatic and a period of relative stability, the dosage can carefully be reduced in small steps over a relatively long period. Even if under neuroleptic treatment the symptoms completely disappeared, it is necessary to administer a maintenance therapy for at least 6 months, better one year, to prevent a reappearance of the psychotic symptoms.

Under treatment with neuroleptics, different undesirable side-effects may appear, which can be mostly controlled by dosage adjustment, change of neuroleptic or additional medication and which only in rare cases (for example malign neuroleptic syndrome) necessitate a withdrawal of the medication. Most frequently the different kinds of EPMS are of clinical importance (Tab. 1). Especially under this aspect so called atypical neuroleptics are advantageous (Möller 1995). Relative or absolute counterindications for a neuroleptic medication are rare.

Table 1 Extrapyramidal side effects (modified after Baldessarini et al. 1991 and Hinterhuber and Haring 1992)

Side effect	Symptoms	Frequency of symptoms relative to the total number of patients treated with neuroleptics	Time at which symptoms first appeared relative to the start of treatment	Cause	Treatment
Acute dyskinesia/ acute dystonia	muscle spasms (eyes, face, tongue, throat, extremities, back)	5% (max. 30%)	1–5 days	unclear; excessive dopamine synthesis?	anticholinergics are diagnostic and curative (initial dose i.m. or i.v., then p.o.)
Akathisia	tormenting motor restlessness, urge to move about	25%	5–70 days	unclear	dose reduction or medication switch, lowdose propranolol; anticholinergics or benzodiazepines may be helpful
Parkinson syndrome	akinesia, rigor, tremor, gait disturbances, vegetative symptoms	20% (max. 40%)	5–30 days	dopaminergic hypoactivity or cholinergic hyperactivity	anticholinergics (p.o.); dopamine agonists dangerous?
Tardive dyskinesia	orofacial dyskinesia, choreiform and athetoid movements; not painful, patients often unaware of symptoms	20% (max. 30%)	months to years	increase of D_1/D_2 ratio or hypoactivity of specific GABAergic projections	prophylaxis the best course; if possible, discontinuation of neuroleptics or switch to less potent drug or to clozapine; low-potency neuroleptics to suppress extreme dyskinesia even in the absence of psychotic symptoms; slow spontaneous remissions in about 50%

Sufficient attention should be given to the side-effects which are "only" subjectively disturbing, because they are of great relevance under compliance aspects (Fleischhacker et al. 1994). Among others even a slight parkinsonoid or a slight akathisia should be avoided as far as possible. For this reason a neuroleptic dosage which is sufficient but as low as possible should be aimed at, eventually (when using classical neuroleptics) through careful titration under exact clinical control. However it can happen that a severe parkinsonism has to be put up with, in order to obtain a sufficient therapeutic effect by a "classical", "typical" neuroleptic.

A regular labmonitoring is advisable in order to avoid particular medical complications of the neuroleptic therapy.

Long-term medication

In particular after repeated remanifestations of the disease in the last years before the actual manifestations, a long term relapse prevention is indicated (Möller et al. 1992, 1993b). To this effect, neuroleptics have to be administered in a much lower dosage than in the acute treatment. It is particularly important that side-effects be kept as low as possible by an adaptive treatment regimen. The optimal dosage has to be individually determined for each patient. The minimal effective dosage seems to be for fluphenazine decanoate 6.5–12.5 mg every 2 weeks, for flupenthixol decanoate 20 mg every 2 weeks, for haloperidol decanoate 50–60 mg every 4 weeks, for oral haloperidol 2.5 mg daily and for oral fluphenazine hydrochloride 2.5 mg daily (Kissling 1994). The experience shows that the dosage which has been chosen at the end of the treatment of the acute phase can be considerably reduced in the following months/years (Johnson 1975).

The EPMS which may impair considerably the quality of life of the patient and particularly the development of tardive dyskinesia – an incidence rate of 4% per year is reported in the prospective study of Kane et al. (1986) – have to be considered carefully. Particularly because of the risk of tardive dyskinesia the dosage of neuroleptics should be kept as low as possible. One should avoid a long-term administration of anticholinergics in order not to conceal a chronic irritation of the extrapyramidal system caused by a too high dosage of neuroleptics. When tardive dyskinesia appear, administration of the neuroleptic should be stopped and replaced by clozapine as the only substance which until now seems to have no risk for tardive dyskinesia.

Because of the well known compliance problems, the use of depot-neuroleptics (Barnes and Curson 1994) for the long-term prophylaxis has proven particularly useful. However in controlled studies the efficacy of depot-neuroleptics compared to oral neuroleptics was not as superior as hypothesized (Möller 1990). Advantages (reduction of the dosage due to absence of first pass-effect, relatively stable blood levels, guarantee that the patients take the drug) and disadvantages (lack of acute dose adjustment, "early peak"-phenomenon) of the depot-neuroleptics therapy have to be carefully balanced in the decision for the individual patient. In particular when the patient's insight into the disease and the compliance are sufficient, and when the doctor-patient relation is good, the oral long-term medication with its broad range of drugs (including among others atypical neuroleptics) can have advantages.

As an alternative strategy to the continuous neuroleptic long-term medication with a standard dose, the *"low dose strategy"* was tested. It appeared to be efficacious only when the dosage was not lowered too much (not more than about 1/5 of the standard dosage) and only when selected patients (among others history of neuroleptic stabilization with relatively small dosages, no destabilization during change to these low dose treatments) were treated (Kane et al. 1983, Marder et al. 1987). The *"early intervention strategy"*, that is the discontinuation of the neuroleptic treatment after the treatment of the acute manifestation, and renewed administration of neuroleptics after the appearance of unspecific early warning symptoms (nervosity, insomnia etc.) could not prove sufficient efficacy compared to the continuous neuroleptic long-term medication (Gaebel et al. 1993; Carpenter et al. 1992; Herz et al. 1991, Hirsch et al. 1987). It should at the most be taken into consideration in cases of patients who cannot be motivated for a standard or low dose relapse prevention strategy.

For *schizoaffective psychoses*, at least for the ones with a strong affective component, the relapse prevention with lithium, or with carbamazepin in cases of lithium intolerance, is indicated (Goodnick and Meltzer 1984, Möller and Morin 1989). If the therapy does not show enough success, it is advisable to administer a neuroleptic long term medication and if the patients do not respond to this, a combination of a neuroleptic and lithium should be tried. In cases of patients suffering from a schizoaffective psychosis with a strong schizophrenic component, a relapse prophylaxis with neuroleptics should be preferred from the beginning.

In cases of *chronic productive psychoses*, a symptom suppressive maintenance therapy with neuroleptics has to be applied, with dosages such as to reduce the psychotic symptoms as far as possible on the one hand, and keeping the unwanted side-effects as low as possible on the other. Especially with such patients, a careful consideration of the benefit-risk-ratio is necessary and under this condition the reduction of the productive symptom-complex should not be overstressed. Chronic negative symptoms (chronic deficiency syndrome) should be treated according to the strategies mentioned above.

Psychosocial therapy

The whole range of classical sociotherapeutic approaches is regarded as a very important part in the treatment of schizophrenia. Among others occupational therapy, vocational rehabilitation etc. shall be mentioned (Wing 1976, Muijen and Hadley 1995).

There is a broad consensus that psychotherapeutic approaches are only meaningful in combination with a neuroleptic therapy (Hogarty et al. 1979). In widespread use are supportive and educational approaches. The doctor has to help the patient to carry the heavy burden that such a disease represents and has to give him, in a realistic measure, hope and courage. Actual problems of different social role areas should be discussed. Information about the complex causation of the disease and about its treatment necessities and possibilities are of great importance for the patient himself and his relatives among others to increase the compliance. Special attention should be given to the problem of over- or understimulation, which is of particular importance for schizophrenic patients. Understimulation can be caused by a lack of challenge at the work place, by an overprotective family or by a poor institutional situation. Overstimulation can be caused by any form of stress, among others too high performance requirements and emotional stress. In this context the "high expressed emotion" paradigm has to be mentioned (Vaughn et al. 1982).

As to specfic psychotherapeutic methods beyond supportive psychotherapy, only behavior therapy oriented approaches could prove some positive effects in controlled studies, for example in improving social skills, in coping with stress, in reducing cognitive disturbances (Brenner et al. 1987, Eckman et al. 1992, Liberman et al. 1986, 1995, Mueser and Bellack 1995). In this context especially family therapy programs based on the "high expressed-emotion-concept" could prove positive effects and even demonstrate relapse prevention properties (Hogarty et al. 1986, Buchkremer et al. 1995).

Concerning all psychotherapeutic procedures, it should be kept in mind, that they may not only have positive effects, but can in some cases lead to negative consequences, in particular when elements of the therapeutic strategy are too stressful for the patients. It is a more or less widely accepted rule that psychotherapeutic procedures should only be conducted by psychotherapists who have experience with the special needs and risks of schizophrenic patients. Furthermore, they should only be applied after sufficient stabilization from the acute disease and under the condition of a neuroleptic medication.

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