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Intermittent medication – an alternative?

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Neuroleptic maintenance medication is clearly effective for relapse prevention in schizophrenia. However, besides benefits for the majority of patients, there are also failures and/or serious risks for some patients (e.g., tardive dyskinesia). Since the risk-benefit ratio is often difficult to predict in the individual case, this has stimulated the search for modifications and alternatives to maintenance treatment. In particular, neuroleptic low-dose treatment strategies obviously compare quite favourably with standard-dose treatment concerning relapse prevention and side effects. Alternatively, on the basis of reports on prodromal symptoms preceding a relapse, early intervention, intermittent neuroleptic treatment strategies have been developed. However, all recently completed controlled 2-year studies have not confirmed this strategy to be as effective as maintenance treatment in preventing relapse, although total drug exposure is significantly reduced and social adjustment seems to be unaffected. Therefore, for the majority of patients, intermittent treatment cannot be recommended.

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Key words: schizophrenia; relapse prevention; prodromal symptom; early neuroleptic intervention; intermittent treatment

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The efficacy of neuroleptic maintenance treatment in schizophrenia has been empirically proven. Prevention of relapse can be attained in approx. 70% of all patients treated according to present treatment standards (1). The mechanism of relapse prevention, however, has not yet been clarified.

Whereas long-term prognosis in schizophrenic patients has improved markedly by introducing long-term neuroleptic treatment, its proper application is restricted by several factors. On the one hand, many patients do not benefit from long-term treatment due to limited compliance, the amount being estimated up to 50% for outpatients. On the other hand, in approx. 15% the occurrence of tardive dyskinesia (TD) must be expected. Finally, an average of 20–30% of the patients are nonresponders or partial responders to long-term neuroleptic treatment; under placebo an approximately similar percentage does not experience any relapse. Therefore, in setting up an indication for long-term prophylaxis, an individual risk-benefit weighing is required for which, however, few reliable decisive criteria are available so far.

As treatment alternatives, 2 modifications of neuroleptic standard treatment have been investigated. It has been shown, on the one hand, that low-dose long-term treatment – as long as it is not reduced below a certain minimum dosage – is equivalent to standard treatment with respect to its relapse prophylactic efficacy along with a lower incidence of side effects (2). Low-dose treatment nowadays can be considered as a widely accepted alternative to standard treatment. A second alternative is intermittent treatment with early neuroleptic intervention, whose rationale is presented here.

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Is there a rationale for intermittent treatment?

Clinical observations

According to earlier clinical observations, a psychotic decompensation develops stepwise via intermediate stages (cognitive perceptive loss of control, depressive retreat, affective emotional disinhibition and prepsychotic thought process) in the course of several days (3). Based on retrospective reports of patients and their relatives, Herz & Melville (4) found that psychotic relapses are frequently preceded by unspecific prodromal symptoms, such as sleep disturbances, nervousness and restlessness, as well as depressive mood. Considering these observations, the treatment rationale of early neuroleptic intervention was developed based on the idea that a full-blown psychotic relapse may be prevented by neuroleptic intervention at the time of onset of prodromal symptoms. The adjoint assumption is that, with this procedure, the neurolep-

tics could be possibly discontinued completely during the remitted, psychosis-free intervals and should only be readministered in case of occurrence of prodromal symptoms. This treatment strategy has been described accordingly as "early intervention, time-limited, targeted pharmacotherapy" (5). With the assumption that a longer lasting stability is attainable without neuroleptics and, on the other hand, a beginning relapse may be recognized and prevented in time, this treatment alternative promises a temporary exemption from medication and thus a lower lifetime exposure to neuroleptics, which might be of considerable importance with respect to side effects.

Actually, this procedure corresponds to what under naturalistic conditions is often practised by the patients themselves: if they feel better following a psychotic decompensation, they often discontinue medication due to a lack of insight into the necessity of treatment or due to side effects and start treatment again either on their own or on medical advice on anticipation of a recurrence. This yet rather unsystematic method could be utilized as a targeted application under the corresponding therapeutic setting.

Pilot studies confirmed the principal feasibility of this treatment strategy with mainly positive treatment results (5–7). These results were then tested under controlled conditions.

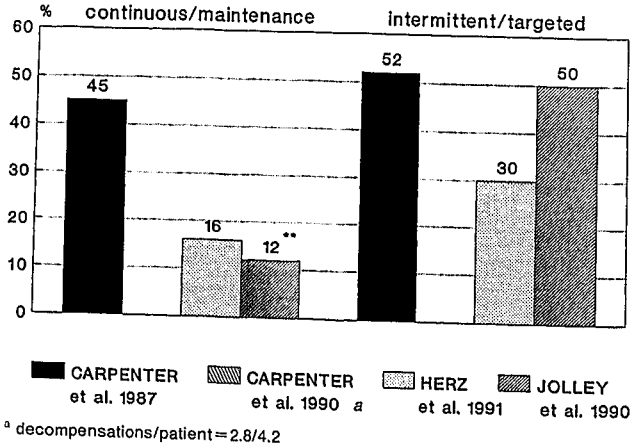
Results of controlled studies

Meanwhile, the results of several international controlled 2-year studies on early neuroleptic intervention have been published (8–12). In summary, despite differences in design these studies demonstrate that the early neuroleptic intervention treatment produces poorer results concerning relapse prevention compared with standard neuroleptic long-term treatment (Fig. 1).

Jolley et al. (11) reported significant differences in the relapse rates between long-term medication and intermittent therapy (12% *vs* 50%), and Carpenter et al. (9) reported a significantly higher rate of decompensation per patient (2.8 *vs* 4.2). Carpenter et al. (8) and Herz et al. (12) reported a nonsignificantly higher relapse rate under intermittent compared with continuous long-term treatment. Rehospitalization rates were also nonsignificantly higher under intermittent treatment. Whereas the social adaptation of the patients under both treatment strategies was not significantly different, the drop-out rates under early neuroleptic intervention were significantly increased in most studies (Fig. 2).

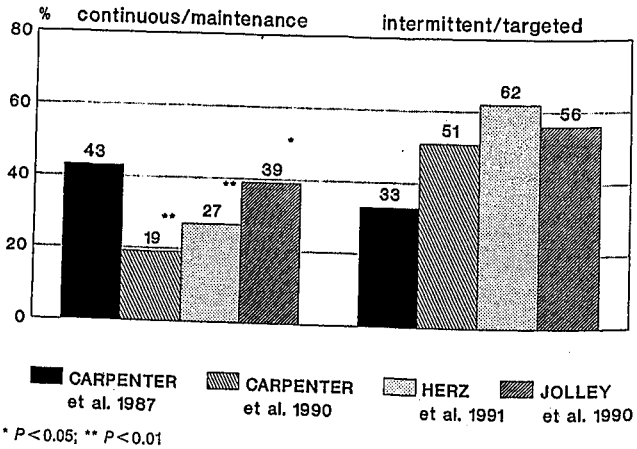
These results indicate that intermittent neuroleptic treatment is applicable to only a few patients. Finally, all studies demonstrated that the total neuroleptic dosage under intermittent treatment is lower and the rate of side effects (tardive dyskinesia in particular) does not reveal significant differences between the therapeutic strategies (11, 12). Quite similar results were found in a recently completed but not yet completely published US National Institute of Mental Health study by Schooler et al. (13), which compared standard, low-dose and intermittent treatment. Concerning relapse rate, standard treatment did best, intermittent treatment did worst and low-dose treatment was in between.

In summary, intermittent treatment with early neuroleptic intervention does not prevent relapses to the same extent as neuroleptic long-term treatment, although there are no essential differences as far as social adaptation and other target criteria are concerned. At the same time, intermittent treatment is applicable to only some of the patients, as the relatively high rates of drop-out show.



[a] decompensations/patient = 2.8/4.2

Fig. 1. Two-year results of controlled studies on maintenance *vs* intermittent neuroleptic long-term treatment: relapse rates.



* $P<0.05$; ** $P<0.01$

Fig. 2. Two-year results of controlled studies on maintenance *vs* intermittent neuroleptic long-term treatment: dropout rates.

Are prodromal symptoms valid predictors of relapse?

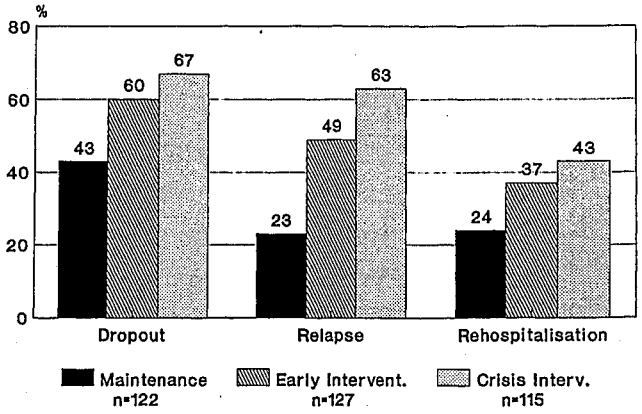
It remains unclear why early neuroleptic intervention leads to poorer results in preventing relapse. The treatment rationale is based on the assumption – as mentioned above – that prodromal symptoms represent valid predictors of relapse, and in case of their occurrence, reinstituting neuroleptic treatment may prevent the outbreak of a relapse. However, none of the mentioned studies investigated the question explicitly and prospectively, whether or not prodromal symptoms actually are valid predictors of relapses. This fundamental aspect of early intervention was investigated in a multicentre study in Germany (ANI study) on intermittent neuroleptic long-term treatment (14–16). This study was carried out at the psychiatric departments of the university hospitals of Berlin, Düsseldorf, Göttingen and Munich. Of 364 patients with schizophrenic and schizoaffective psychoses, classified according to ICD-9 and Research Diagnostic Criteria, 159 (44%) completed the 2-year treatment and observation phase. Three treatment strategies to which the patients had been randomly assigned after a 3-month post-discharge stabilization phase were compared in an open study design.

In long-term neuroleptic treatment, patients were stabilized on a minimal neuroleptic maintenance dosage ($\geq$ 100 mg chlorpromazine equiv.). In neuroleptic early intervention treatment, medication was gradually withdrawn and drugs were not reintroduced before prodromal symptoms occurred. In neuroleptic crisis intervention treatment, too, the medication was discontinued step by step, yet the treatment was resumed only on the occurrence of a relapse ("crisis") as defined according to psychopathological criteria (the Brief Psychiatric Rating Scale, Clinical Global Impression and Global Assessment Scale).

The occurrence of prodromal symptoms was recorded according to a modified list of prodromal symptoms (4) at each therapeutic contact in all 3 treatment groups, yet it was of therapeutic relevance only in the early intervention group. By means of crisis intervention, the extent to which prodromal symptoms actually – without intermediate neuroleptic intervention – predict the occurrence of a relapse was investigated.

The results of this study are in accordance with those of the above-mentioned studies. All 3 treatment strategies differed significantly as far as the observed relapse or rehospitalization rates are concerned (Fig. 3).

Accordingly, early intervention (49%/37%) as opposed to crisis intervention (63%/43%) may rather prevent relapse and rehospitalization but



Kruskal-Wallis *H*-test: $P < 0.01$ each

Fig. 3. ANI study on maintenance *vs* intermittent neuroleptic long-term treatment: 2-year results.

still furnishes poorer results than long-term medication (23%/24%). No differences were found as to psychosocial adaptation, subjective wellbeing and side effects (tardive dyskinesia) between the three therapeutic regimens. Only the cumulative neuroleptic dosage was significantly lower under intermittent treatment procedures; it was the lowest in the early intervention group. Furthermore, the drop-out rates in the 2 intermittent therapeutic strategies were significantly higher than under long-term treatment (Fig. 3). This must be attributed to the fact that in patients under intermittent treatment neuroleptic medication could not (or not for a long period) be discontinued without an exacerbation of symptoms, and thus these patients had to be removed from the study as per definition. These were mainly patients who already at the beginning of the study showed a poorer remission and received higher neuroleptic doses.

The predictive validity of prodromal symptoms, in particular in the crisis intervention group, could not be established (17). Whereas comparably high specificity values (70%–93%) indicate that the non-occurrence (no relapse) along with lacking prodromal symptoms can be predicted fairly well (few false-positive predictions), according to the very low sensitivity values (8%–14%), the occurrence of relapse is not predicted adequately (many false-negative predictions). From relatively low positive predictive values (15%–43%) it must be concluded that the prodromal symptoms are ambiguous in their predictive quality. Hence, in clinical practice the occurrence of prodromes should be taken as a potential warning sign initiating an early neuroleptic intervention.

The prodromal symptoms used are of insufficient predictive value. This may be due to the fact that psychotic "prodromal" symptoms (such as hallucinations), which already must be con-

sidered as indicators of relapse, were not included. Alternative explanations for predictive failure could either be that the mean frequency of at least one contact every 2–4 weeks had been too little to register all prodromes or that no special psychosocial interventions were provided. However, all cited studies produced similar unsatisfactory results, independent of the density and/or intensity of the psychosocial programme offered. One task of future research will be the assessment of objective (biological) markers of psychotic episodes, enabling the clinician to detect the earliest – subclinical – stages of an exacerbation of illness or relapse proneness more precisely and in time. Another related task will be the development of biological predictors of relapse and treatment response in the context of a conceptually and methodologically improved prediction research in schizophrenia (18).

These results may explain that a strategy whose therapeutic rational is empirically not verified cannot display full efficacy. Yet it is still not clear why, in spite of this insufficient empirical basis, early intervention produces better results than crisis intervention. One possible explanation could be that the strategy as per definition of the "treatment in case of doubt" has assimilated early intervention treatment to a (still less sufficient) kind of low dose long-term intervention.

The effects of intermittent medication from a neuropsychopharmacological perspective

How far does our knowledge on psychopharmacological mechanisms of action and their time course support the rationale of neuroleptic intermittent treatment? On the one hand, we know that the development of a neuroleptic steady-state plasma level of neuroleptics takes between several days to weeks. On the other hand it can be shown by means of positron emission tomography that, under administration of clinical doses of neuroleptics, a certain saturation of the dopamine (D_2) receptors in the striatum and supposedly in other dopaminergic pathways (19) between 65% and 85% takes place within hours (20). If this were the therapeutically decisive mechanism of action, a fast clinical response would be expected. This is not the case; although the clinical onset of action can be established within hours to days and represents one of the most reliable predictors of response (21), the full clinical efficacy develops only after weeks or months. The underlying mechanisms of this type of therapeutic latency effect according to present knowledge are feedback-directed adaptive processes in the presynaptic neurons that, over days or weeks, lead to a reduction of activity (depolarization blockade), especially in the nigrostriatal and mesolimbic pathways, along with increased inhibitory activities in the mesocortical tracts (22). Both mechanisms together lead to a reduction of activity in the mesolimbic dopaminergic pathways, which is considered to be of therapeutic relevance.

Furthermore, the extent of receptor blocking seems to be of no decisive value for the question of response or nonresponse (23). Responders and nonresponders do not differ as to the extent of receptor blockade. Thus response-relevant adaptive mechanisms in the postsynaptic signal transduction systems must be presumed, which may ultimately lead to alterations in gene expression. These processes, under the term of plasticity of the involved neural systems under neuroleptic therapy, require some time, of course. This is also true for the reverse process on withdrawal discontinuation of drugs, as can be seen from latencies of about 3–6 months prior to the occurrence of a psychotic relapse, even though the neuroleptics release the receptor within a few days after discontinuation (23).

Summarizing these results in view of the above issues, doubts arise as to the adequate neurobiological foundation of intermittent neuroleptic treatment. Even if one succeeded in recognizing and treating a psychotic relapse at an early stage, it probably takes weeks up to months until a new adaptive balance on the molecular level is established. It remains an open question to what extent such repeated interventions in the molecular regulatory dynamics of the neuronal systems could lead to irreversible alterations along with impaired therapeutic response in the long run. Such an unfavourable correlation has been suspected, at least for the occurrence of tardive dyskinesia (24). Also, within the conception of the vulnerability-stress model the neuroleptic interval treatment leads to a repeated shifting of the balance between vulnerability and protective factors – a strain not only under neurobiological but also under psychological and social aspects, as the results of Herz et al. (12) in their study investigating the higher family burden of schizophrenics under interval treatment revealed.

Clinical implications

Is there any indication for the application of early neuroleptic intervention (Table 1)?

At first, only patients with a prognostically favourable, periodically remitting course, which can be observed in clinical populations with long-term follow-up in only 20% of the cases, should be taken into consideration. As a rule, these are also the patients with favourable prognostic character-

Table 1. Contraindications to the use of intermittent medication. Source: Chiles et al. (1989)

Basic contraindications
Interfering baseline symptoms
Unstable outpatient course
Current stress
Hospitalized in past 3 months
Relative contraindications
Routinely uncooperative
Other psychoactive medication
Suicidal or assaultive
Alcohol or drug abuse
Medical problems
Organic brain syndrome
Management contraindications
Absence of a significant other
Travel problems
Disability

Table 2. Clinical application of intermittent treatment

General requirements
Cooperation by patient and relatives
Psychoeducation & information
Psychosocial management
Evaluation of prodromal symptoms
Drug withdrawal period
Gradual dose reduction
Drug-free treatment period
Monitoring for stressors
Monitoring for prodromal symptoms
Frequent contacts
Early intervention period
Crisis management
Drug and dose selection
Monitoring for side effects

istics as well as good response to an acute and relapse preventing long-term treatment. The intermittent strategy may thus be suitable for patients who remit completely under neuroleptics and who do not merely expose a suppression of symptoms. Fundamental contraindications thus are chronic persisting positive symptoms as well as an unstable course under neuroleptics. Chiles et al. (25) found these exclusion criteria to be fulfilled in 62% of an unselected sample. Furthermore, they considered additional exclusion criteria: an acute conflict or stress situation as well as a recent relapse that led to hospitalization and after which complete stabilization has not been reached yet. "Relative" contraindications, e.g., lack of cooperation (33%) and self-endangering or endangering others (16%), as well as "management" contraindications, e.g., lack of relatives or a distance too far to the hospital, were also considered. According to all criteria, only 13% of the initial sample remained, for which an intermittent treatment with early intervention would have been indicated. These figures reveal that this is a highly selective strategy of treatment whose relapse prophylactic efficacy has not been ascertained satisfactorily in selected cases. Nevertheless, it is beyond question that individual patients benefit from this strategy. However, valid predictors are still lacking to identify these patients in advance.

If, in the individual case, the decision based upon the aforementioned criteria is to carry out an interval treatment, its clinical application has to follow certain guidelines (Table 2).

The general and individual prodromal symptoms must be discussed with the patient and relatives in detail and become the basis of the therapeutic proceedings for all concerned. Explanations and information about the models of disease and treatment belong to the context of treatment, along with psychosocial management. A high frequency of contacts (one contact per week, more often in case of an acute crisis) is mandatory, with the additional offer of a crisis management around the clock, also on weekends. In general, this demand will be secured by the medical stand-by service of the hospitals, which has to be instructed and trained accordingly. Yet for the patient this means a higher threshold of approach with the familiar team not being available.

Withdrawal of the medication will take place over several weeks. In case of exacerbation this strategy will not be continued. If the withdrawal is successful, the actual observing phase begins with continuous monitoring on eventual prodromal symptoms. In case of their occurrence, one can decide on the "safe side" and start early treatment. Many patients who gained sufficient experience in the course of their disease do so on their own. The onset of medication will be, as a rule, with the same neuroleptic drug and at least same dosage with which the patient had been stabilized prior to withdrawal. It must be taken into consideration that all previous side effects may again occur to their full extent and precautions must be taken accordingly. If stabilization takes place without any occurrence of a psychotic relapse, the same procedure will be started anew.

Conclusions

Summarizing the above mentioned study results and neuropsychopharmacological considerations, the low-dose neuroleptic long-term treatment still represents the most effective method of relapse prevention. Only in comparison with the utilized cumulative neuroleptic dosage is it inferior to intermittent treatment strategies, without producing differences in the incidence of side effects in the periods of treatment observed so far. Yet it has not

been clarified why the early neuroleptic intervention produces poorer results in preventing relapses. Further studies will have to scrutinize the time factor and the correlation between prodromal symptoms and psychotic relapses while considering neurobiological indicators. At present intermittent treatment is not a suitable alternative for the majority of patients. The usefulness of an early intervention strategy for the patients starting to relapse on low-dose neuroleptics has still to be evaluated.

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