INTERMITTENT NEUROLEPTIC LONG-TERM TREATMENT IN SCHIZOPHRENIA: STATE OF THE ART

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ABSTRACT

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). This has stimulated the search for modifications and alternatives to maintenance treatment. In particular, neuroleptic low-dose treatment strategies obviously compare quite favorably with standard-dose treatment concerning relapse prevention and side effects. Alternatively, on the basis of reports on prodromal symptoms preceding a relapse, early intervention, time-limited, targeted neuroleptic treatment strategies have been developed. However, all recently completed controlled two-year studies of early intervention treatment have not confirmed this strategy to be as effective as maintenance treatment in preventing relapse, although total drug exposure could be significantly reduced and social adjustment seems to be unaffected.

1. INTRODUCTION

The efficacy of long-term treatment in schizophrenia has been empirically proven[1]. Prevention of relapse can be attained in approximately 70% of patients treated according to treatment standards. However, about 50% of the patients do not profit from long-term treatment due to non-compliance[2]. In approximately 15% the occurrence of tardive dyskinesia must be expected[3]. Finally, about 20-30% of the patients are non-responders or partial responders to a long-term neuroleptic treatment; under placebo an approximately similar percentage does not experience any relapse[4]. Low dose long-term treatment above a certain minimum dosage is equivalent to standard treatment with respect to its relapse prophylactic efficacy along with a lower incidence of side effects[5]. As a potential treatment alternative intermittent drug treatment with early neuroleptic intervention has been investigated.

2. INTERMITTENT NEUROLEPTIC LONG-TERM TREATMENT

2.1 Clinical Rationale

A psychotic decompensation develops stepwise via intermediate stages in the course of several days[6,7]. Psychotic relapses are frequently preceded by unspecific prodromal symptoms[8]. Consequently the rationale of an "early intervention, time-limited, targeted pharmacotherapy" has been developed[9]. Pilot studies confirmed the clinical feasibility of this treatment strategy[9,10,11] which was then tested under controlled conditions.

2.2 Results of Controlled Studies

According to several controlled two-year studies on early neuroleptic intervention relapse prevention is less effective compared to neuroleptic maintenance treatment[12,13,14,15,16]. *Jolley et al. (1990)*[15] reported significant differences in the relapse rates between long-term medication and early intervention treatment (12 % vs. 50 %) and *Carpenter et al. (1990)*[13] reported a significantly higher rate of decompensation per patient (2.8 vs. 4.2). *Carpenter et al (1987)*[12] found an insignificantly higher rate of relapses (52 % vs. 45 %) and *Herz et al. (1991)*[16] also reported an insignificantly higher relapse rate under intermittent (30%) compared to maintenance treatment (16%). Social adaptation under both treatment strategies was not significantly different. Drop-out rates were significantly higher under early neuroleptic intervention in all studies (*Carpenter et al. 1990*[13]*:* 51%*; Jolley et al. 1990*[15]*:* 56 %*; Herz et al. 1991*[16]*:* 62 %). The cumulative neuroleptic dosage under intermittent treatment, however, was lower, whereas the rate of side effects did not reveal any major differences between the treatment strategies[15,16]. Comparable results were obtained in a recently completed NIMH study[17].

None of the above studies have explicitly investigated whether prodromal symptoms are actually valid predictors of relapse. This important aspect was assessed in a German multicenter study (ANI study) on intermittent neuroleptic long-term treatment[18,19,20]. 364 patients with schizophrenia and schizo-affective psychoses according to ICD-9 and RDC were included in this study. 159 (=44%) of the patients completed the two-year treatment phase. Following a three months' post-discharge stabilization phase three treatment strategies with random assignment of patients were compared in an open study design. In neuroleptic **Maintenance Treatment** (MT) patients were stabilized on a minimal neuroleptic maintenance dosage (100 mg CPZE). In neuroleptic **Early Intervention** (EI) medication was gradually withdrawn and was only to be reinstalled in case of prodromal symptoms occured. In neuroleptic **Crisis Intervention** (CI) the medication was also discontinued, yet treatment was resumed only upon occurrence of a relapse ("crisis") as defined according to psychopathological criteria. The occurrence of prodromal symptoms recorded according to a modified list developed by *Herz & Melville (1980)*[8] had therapeutic consequences in the EI group only.

The overall results of this large study were similar to those cited above. Under intermittent treatment conditions drop-out rates were significantly higher (EI: 60%, CI: 67%) than under maintanance treatment (MT: 43%). Drop-outs were mainly patients who already at the beginning of the study showed poorer remission and received higher neuroleptic doses. Furthermore all three treatment strategies differed significantly in relapse/rehospitalisation rates (MT: 23%/24%, EI: 49%/37%, CI: 63%/43%). With respect to social adaptation, subjective well-being, and side-effects no significant treatment differences were obtained. Cumulative neuroleptic dosage was highest under MT and lowest under EI.

Concerning the predictive quality of prodromal symptoms there was no significant relationship between prodromal symptoms and relapse, in particular under th condition of CI, which was introduced into the study design as a control strategy[21]. According to a low positive predictive value (43%), prodromal symptoms are obviously ambiguous in their predictive quality. They could be useful as early warning signs, which may or may not predict impending relapse.

3. CONCLUSIONS

According to the above study results, standard dose neuroleptic long-term treatment represents the most effective pharmacological strategy of relapse prevention. However, it still has to be clarified why early neuroleptic intervention produces poorer results concerning relapse prevention. In particular, the neurobiological and hence clinical consequences of intermittent neuroleptic treatment are not yet fully understood[22]. Future research should concentrate on the development of more valid relapse predictors[23] under stronger consideration of neurobiological variables[24]. The search for more effective and safer therapeutic alternatives to neuroleptic maintenance treatment in schizophrenia nevertheless has to go on in the future. To our present knowledge for the majority of patients intermittent treatment with early neuroleptic intervention is not an appropriate therapeutic alternative. Since some selected patients, however, may actually benefit from it[25], research should also aim at better identification of the potential treatment responder.

4. REFERENCES

1. Davis, J.M., Schaffer, C.B., Killian, G.A., Kinard, C., Chan, C., "Important Issues in the Drug Treatment of Schizophrenia", *Schizophrenia Bulletin* **6**, 70-87 (1980).
2. Johnson, D.A.W., "Observations on the use of long-acting depot neuroleptic injections in the maintenance therapy of schizophrenia", *J. Clin. Psychiatry* **45**, 13-21 (1984)
3. Gaebel, W., "Tardive Dyskinesien unter Neuroleptika-Behandlung", *Deutsches Ärzteblatt* **90**, 1041-1046 (1993).
4. Hogarty, G.E., Goldberg, S.C., Schooler, N.R., Ulrich, R.F., "Drug and Sociotherapy in the Aftercare of Schizophrenic Patients: Two Year Relapse Rates", *Arch. Gen. Psychiatry* **31**, 603-608 (1974).
5. Schooler, N.R.,"Maintenance Medication for Schizophrenia: Strategies for Dose Reduction", *Schizophrenia Bull.* 17, 311-324 (1993).
6. Donlon, P.T., Blacker, K.H., "Stages of Schizophrenic Decompensation and Reintegration", *J. Nerv. Ment. Dis.* **157**, 200-209 (1973).
7. Docherty, J.P., Van Kammen, D.P., Siris, S.G., Marder, S.R., "Stages of Onset of Schizophrenic Psychoses", *Am. J. Psychiatry* 135,**135**, 420-426 (1978).
8. Herz, M.I. and Melville, Ch., "Relapse in Schizophrenia", *Am. J. Psychiatry* **137**, 801-805 (1980).
9. Herz, M.I., Szymanski, H.V., Simon, J.C., "Intermittent Medication for Stable Schizophrenic Outpatients: an Alternative to Maintenance Medication", *Am. J. Psychiatry* **139**, 918-922 (1982).
10. Carpenter, W.T., Stephens, J.H., Rey, A.C., Hanlon, T.E., Heinrichs, D.W., "Early Intervention vs. Continuous Pharmacotherapy of Schizophrenia", *Psychopharmacology Bull.* **18**, 21-23 (1982).
11. Carpenter, W.T., Heinrichs, D.W., "Early Intervention, Time-limited, Targeted Pharmacotherapy of Schizophrenia", *Schizophrenia Bull.* **9**, 533-542 (1983).
12. Carpenter, W.T., Heinrichs, D.W., Hanlon, T.E., "A Comparative Trial of Pharmacologic Strategies in Schizophrenia", *Am. J. Psychiatry* **144**, 1466-1470 (1987).
13. Carpenter, W.T., Hanlon, T.E., Heinrichs, D.W., Summerfelt, A.T., Kirkpatrick, B., Levine, J., Buchanan, R.W., "Continuous versus Targeted Medication in Schizophrenic Outpatients: Outcome Results", *Am. J. Psychiatry* **147**, 1138-1148 (1990).
14. Jolley, A.G., Hirsch, S.R., McRink, A., Manchanda, R., "Trial of Brief Intermittent Neuroleptic Prophylaxis for Selected Schizophrenic Outpatients: Clinical Outcome at One Year", *Brit. Med. J.* **298**, 985-990 (1989).
15. Jolley, A.G., Hirsch, S.R., Morrison, E., McRink, A., Wilson, L., "Trial of Brief Intermittent Neuroleptic Prophylaxis for Selected Schizophrenic Outpatients: Clinical and Social Outcome at Two Years", *Brit. Med. J.* **301**, 837-842 (1990).
16. Herz, M.I., Glazer, W.M., Mostert, M.A., Sheard, M.A., Szymanski, H.V., Hafez, H., Mirza, M., Vana, J., "Intermittent vs Maintenance Medication in Schizophrenia. Two-year Results", *Arch. Gen. Psychiatry* **48**, 333-339 (1991).

17. Schooler, N.R., Keith, S.J., Severe, J.B., Matthews, S.M., "Treatment Strategies in Schizophrenia: Effects of Dosage Reduction and Family Management on Outcome", *Schizophrenia Res.* **9**, 260 (1993).
18. Pietzcker, A. "A German Multicenter Study on the Long-Term Treatment of Schizophrenic Outpatients", *Pharmacopsychiatry* **18**, 333-338 (1985).
19. Pietzcker, A., Gaebel, W., Köpcke, W., Linden, M., Müller, P., Müller-Spahn, F., Schüssler, G., Tegeler, J., "A German Multicenter Study on the Neuroleptic Long-Term Treatment of Schizophrenic Patients. Preliminary Report", *Pharmacopsychiatry* **19**, 161-166 (1986).
20. Pietzcker, A., Gaebel, W., Köpcke, W., Linden, M., Müller, P., Müller-Spahn, F., Tegeler, J., "Continuous vs Intermittent Neuroleptic Longterm Treatment in Schizophrenia - Results of a German Multicenter Study", *J. Psychiatric Res.*, in press (1993).
21. Gaebel, W., Frick, U., Köpcke, W., Linden, M., Müller, P., Müller-Spahn, F., Pietzcker, A., Tegeler, J., "Early Neuroleptic Intervention in Schizophrenia: are Prodromal Symptoms Valid Predictors of Relapse?", *Brit. J. Psychiatry* **163** (suppl. 21), 8-12. (1993).
22. Glenthøj, B., Hemmingsen, R., Allerup, P., Bolwig, T.G., "Intermittent versus continuous neuroleptic treatment in a rat model", *Eur. J. Pharmacology* **190**, 275-286 (1990)
23. Gaebel, W. and Awad, G., "Prediction of Neuroleptic Treatment Outcome in Schizophrenia - Concepts and Methods", *Springer, Vienna*, in preparation (1994)
24. Lieberman, J., "Prediction of Relapse in Schizophrenia", *Arch. Gen. Psychiatry* **44**, 597-603 (1987).
25. Chiles, J.A., Sterchi, D., Hyde, T., Herz, M.I., "Intermittent Medication for Schizophrenic Outpatients: Who is Eligible?", *Schizophrenia Bull.* **15**, 117-121. (1989).