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Reducing Dosage in Maintenance Treatment of Schizophrenia

Review and Prognosis

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This paper reviews the assumptions and efficacy of two strategies for dose reduction during maintenance treatment in schizophrenia: low dose and targeted medication. Studies of low-dose treatment suggest that it can be used for relatively short periods of time or if the dosage reduction is moderate. Studies of targeted treatment suggest that relapse risk increases significantly compared with standard-dose treatment and that there are few offsetting advantages. The paper also reports initial findings from the NIMH Treatment Strategies in Schizophrenia Study, which compares low dose, targeted treatment and a standard dose in the context of two forms of family treatment. Early stabilisation of patients is lower than expected, but patient characteristics are useful in predicting likelihood of stabilisation.

The efficacy of antipsychotic medication for the prevention of relapse in schizophrenia is a well established fact in clinical psychopharmacology. Davis's (1975) review of 24 placebo-controlled clinical trials concluded that 65% of patients would relapse without medication, compared with 30% who continue treatment. His summary included trials ranging in length from one month to two years. In a series of five experimental studies of the role of guaranteed medication administration, relapse rates for patients who received injectable antipsychotic medication varied from 8% to 40% during trials lasting from 10 to 24 months. A review (Schooler, 1985) concluded that these studies provided evidence that some patients do relapse despite taking their medication.

More recently, attention turned in earnest to strategies that would maximise the reduction of risk of relapse that can be achieved with medication, while at the same time reducing unwanted side-effects. In particular, the alarm had sounded regarding tardive dyskinesia, which in the late 1970s was still perceived as both progressive and dependent on cumulative dose received (Baldessarini *et al*, 1981). Other side-effects – pseudo-Parkinsonism, neuroleptic-related depression, akathisia and akinesia – as well as complaints about medication from patients and families, stimulated efforts to test medication strategies that might address these problems while still protecting patients from the consequences of relapse. The basic goal of the strategies that were developed was to reduce the amount of antipsychotic medication administered.

Two strategies have received extensive experimental study:

(a) continuous 'low dose' treatment: medication is administered continuously but at doses that are lower than those conventionally used to treat psychotic symptoms either acutely or for long-term maintenance
(b) targeted treatment, intermittent treatment or early intervention: medication is administered only during periods when patients experience either prodromal signs or frank psychotic symptom exacerbation.

This paper reviews the assumptions regarding treatment that underlie these two strategies and summarises research regarding their clinical effectiveness. A more detailed review of this research is reported elsewhere (Schooler, 1991). The paper also discusses initial results of the National Institute of Mental Health (NIMH) Treatment Strategies in Schizophrenia Study, which is the first to compare low-dose and targeted treatment with each other and to standard-dose maintenance medication with antipsychotic drugs.

Assumptions of dosage-reduction strategies

The use of the term maintenance treatment implies that acute treatment goals have been met. A major goal for the maintenance phase of treatment is to ensure that the level of symptom remission or stability that has been achieved will not be lost. A secondary goal may be to achieve gains beyond that level, often in areas of functioning that go beyond symptoms of psychopathology. In studies of mood disorder, the maintenance phase of treatment has been divided conceptually into continuation treatment and long-term preventive therapy (Prien,

1984). The distinction is between the maintenance of control over the acutely treated episode in continuation treatment and the prevention of a subsequent episode of illness. This distinction may not always define an unvarying temporal sequence in schizophrenia, but may represent a distinction among patients whose acute episode has been treated. For some patients, the medication may continue to suppress symptoms of the illness, while for others the episode may be over. In these latter cases, the goal of treatment with medication is long-term prevention of a subsequent episode of illness. This distinction between continuation treatment and treatment for prevention of a subsequent episode is useful in differentiating the assumptions of continuous low-dose and targeted treatment.

Clinical implementation of both treatment strategies assumes, and indeed requires, that there is ongoing monitoring of patients to detect signs or symptoms that may signal an impending relapse or emergence of psychosis. Monitoring systems utilise a wide range of treatment structures, involving clinicians, family members and patients. All need to be educated about the nature of early signs and symptoms and appropriate action to take if they are detected. Herz & Melville (1980) found that patients and family members could recall early signs of schizophrenic decompensation and, further, that they could agree on their presence during a given episode of illness. They developed the Early Signs Questionnaire to monitor symptoms prospectively.

Continuous low-dose medication

The primary assumption underlying use of continuous low-dose medication during maintenance treatment is that patients require a lower dose of medication to maintain symptom remission or stability than was needed to treat acute symptomatology. A secondary assumption is that symptoms that emerge while a patient is receiving a low dose will be treated more easily than symptoms that occur while a patient is medication-free, either because the process of relapse is more gradual in patients on medication, or because relapse is 'milder' in patients on medication. Thirdly, the need to increase medication in response to symptom exacerbation does not mean that the patient will require the higher dose indefinitely. Once the symptoms that triggered the dose increase have remitted, the dose can be lowered again. The use of continuous low dose does not require discrimination of whether the patient's symptomatic state is being controlled by medication (the patient is in the continuation phase of treatment) or would be symptom-free off medication (the patient is in the prevention phase of treatment).

Targeted or intermittent treatment

Targeted treatment is based on the assumption that patients require neuroleptic medication only during times of symptom exacerbation. Medication serves to treat the exacerbation but does not prevent it. However, treatment of prodromal signs can avert the development of more florid symptoms. According to this model of the role of medication in schizophrenia, the major advantage provided by continuous medication administration is that it ensures the presence of medication at the times it is needed. Thus, users of a targeted strategy are explicit about the need to identify times when medication should be administered and the creation of a treatment-delivery structure to do this. In fact, the Early Signs Questionnaire (Herz & Melville, 1980) was developed to allow the implementation of an intermittent treatment programme. A variety of delivery structures have been used, but contact and/or observation must be sufficiently frequent to ensure that early signs of relapse are detected and medication is initiated before a major symptom exacerbation has occurred.

Targeted treatment seems to be most applicable to patients who are in the preventive phase of maintenance treatment. Indeed, in their studies of this strategy, Herz *et al* (1982, 1991) explicitly restricted study inclusion to patients who were symptom-free following an eight-week medication-withdrawal phase of treatment and for whom medication was not 'controlling' current symptoms.

Review of clinical trials

Continuous low-dose medication

As reviewed by Schooler (1991), five groups of investigators have reported comparisons of continuous low dose of medication to a 'standard' dosage in outpatients (Goldstein *et al*, 1978; Kane *et al*, 1983, 1985, 1986; Marder *et al*, 1984, 1987; Johnson *et al*, 1987; Hogarty *et al*, 1988). All studies used injectable antipsychotic medication to insure that covert noncompliance did not compromise the dosage differences. None of the studies included a placebo comparison group. In an early in-patient study, Caffey *et al* (1964) compared standard dose, low dose and a placebo. They found 5%, 15% and 45% relapse rates respectively in these groups over a four-month period. The relapse rate in the reduced-dose group was intermediate between the standard and placebo

rates, suggesting that the low dose was indeed better than a placebo.

All the studies, with the exception of the six-week study by Goldstein *et al*, lasted at least a year. Whether a lower dose was less effective than a standard dose depended on several factors. In an early stage of treatment (Goldstein *et al*), low dose (6.25 mg of fluphenazine enanthate every two weeks) resulted in a higher relapse rate. If the dose was very low (1.25–5 mg fluphenazine decanoate every two weeks) (Kane *et al*) it led to a higher relapse rate, defined by an increase in psychotic symptoms during the first year. If treatment continued for a second year (Marder *et al* and Hogarty *et al*), low dose led to increased exacerbations or minor episodes, but not increased relapse. Johnson *et al* found a significant increase in relapse within the first year after dose reduction. Although the reduction studied (50%) was less than that in the other studies cited and patients had been stable for longer than in the other studies, the average doses administered in the reduced-dose and standard-dose conditions were not dramatically different.

All the long-term studies, with the exception of that by Johnson *et al*, reported that dosage reduction resulted in a decrease in extrapyramidal side-effects and fewer symptoms of anxiety or negative symptoms. However, all found an increased risk of psychotic exacerbation. Clearly, some patients can tolerate dose reduction; the systematic examination of patient characteristics associated with stability despite reduced dose would be valuable. Further, in all the long-term studies cited, inclusion of patients was restricted to those who were maintained on moderate dosage, equivalent to about 25 mg fluphenazine decanoate every two weeks. The efficacy of dose reduction in patients being maintained on higher doses has not been investigated.

Targeted or intermittent treatment

As reviewed by Schooler (1991), targeted or intermittent treatment has been studied by four groups (Herz *et al*, 1991; Carpenter *et al*, 1990; Jolley *et al*, 1989, 1990; Pietzcker and his colleagues – Pietzcker *et al* (1986), Gaebel (this supplement)). The design of all the targeted-treatment studies involved discontinuation of medication in the experimental group following a stabilisation period which ranged from eight weeks after discharge (Carpenter *et al*) to at least six months in an out-patient clinic. Treatment in all studies was for two years. Patients were randomly assigned to continuation at their maintenance dose or to discontinuation in all studies, but only the Herz and the Jolley groups maintained double-blind conditions throughout treatment. The study by Pietzcker and colleagues included a third treatment group, 'neuroleptic crisis intervention'. Patients in this group received medication only when a relapse occurred, rather than when prodromal signs were identified. The 'neuroleptic crisis intervention' group provides an interesting and extremely valuable comparison, since it allows test of the hypothesis that introducing treatment at the first signs of symptom exacerbation is better than waiting until a full episode has developed, and represents a direct test of the hypothesis that early intervention at prodromal signs is better than treatment only of frank psychotic episodes.

In all studies, implementation of a targeted strategy was demonstrated to be feasible. Patients randomised to targeted treatment received significantly less medication over the two-year treatment period than those assigned to continuation treatment, and showed significant reduction in side-effects, particularly extrapyramidal symptoms. However, the likelihood of relapse was significantly higher in the targeted-treatment group than in the continuous-treatment group during the first and second year of treatment in all studies. The increase in risk of relapse or of prodromal symptoms did not appear to be offset substantially by a broad range of symptomatic benefit or of clinically significant reduction in risk of developing tardive dyskinesia.

Targeted treatment may be effective for a limited period of time, as suggested by the Jolley group's finding of no differences in hospital readmission during the first year and only a trend toward increases in relapse. Inspection of the life tables published by the Carpenter, Herz and Jolley groups suggests that a difference between the treatment groups emerged earlier in the Herz and Carpenter studies than in the Jolley study. This may have been because Jolley and his colleagues used injectable fluphenazine decanoate for all patients: the slow reduction in plasma concentrations reported with this drug following medication discontinuation (Wistedt *et al*, 1981) may have delayed relapse.

Gaebel (this supplement) found that although early intervention leads to a significantly higher relapse rate than continuation of medication, it affords a lower relapse rate than delayed crisis intervention.

An early-intervention strategy is feasible, is superior to intervention only when a relapse has occurred, and offers reduced side-effects. It does increase risk of relapse compared with continuous medication and in general does not improve social functioning compared with continuous medication. Both the Herz and Carpenter groups have suggested

that the strategy may be clinically useful for patients who are reluctant to take medication but who may be amenable to monitoring while medication-free. This recommendation is supported by Gaebel's findings that an early-intervention strategy is superior to resuming antipsychotic medication only when full symptoms have emerged.

NIMH Treatment Strategies in Schizophrenia Study

Design

In all the studies reviewed above, either targeted early intervention or low dose was compared with standard dose of medication. None of the studies cited compared these two strategies directly. This comparison is valuable because, as described above, the two strategies make different assumptions regarding the role of medication in the long-term treatment of schizophrenia. Further, they represent substantially different clinical options for long-term medication management. The NIMH Treatment Strategies in Schizophrenia Study will, when completed, provide this needed comparison of low-dose, targeted-treatment and standard-dose medication (Schooler *et al*, 1989).

In addition, the study compares two forms of family treatment: 'applied' and 'supportive' family management (Keith *et al*, 1989, 1991). The combination of three medication and two family-treatment conditions results in a 3×2 factorial design that allows the investigation of additive and interactive effects of medication and the psychosocial treatment. Among other reasons for interest in this interaction, the psychosocial treatment is hypothesised to offset increased risk of relapse incurred through dose reduction. Both forms of family treatment are based on a psycho-educational approach to the treatment of schizophrenia and include a workshop for family members early in the course of the patient's treatment and monthly family support groups throughout the course of study treatment, all conducted in the clinic. Applied family management further incorporates a version of home-based behavioural family therapy developed by Falloon *et al* (1984).

Schizophrenic patients and their families at five clinical centres in the USA were recruited during an acute exacerbation of the illness and randomly assigned to one of the two forms of family treatment, which was initiated as soon as clinically feasible. Patients' treatment with antipsychotic medication during an initial six-month phase had the goal of clinical stabilisation on a dose of 12.5–50 mg of fluphenazine decanoate every two weeks (standard dose). Successfully stabilised patients were further randomised, under double-blind conditions, to continuation of standard dose, a continuous low dose that was 20% of the standard (2.5–10 mg every two weeks) or targeted treatment (vehicle-only injections every two weeks) for up to two years of treatment. Family treatment also continued throughout the two years of double-blind treatment. However, home family visits in the applied family management condition were conducted only until the end of the first year following randomisation to double-blind medication; they were on a weekly schedule for 13 sessions, then fortnightly for 13 more sessions and then monthly.

The five clinical sites that participated in the trial were not a random sample of facilities offering treatment to schizophrenic patients, but they differed in ways that could influence treatment outcome, such as location, demographic characteristics of the patient population served and length of hospital stay. The inclusion of a range of clinical facilities, if findings are consistent, enhances the ability to generalise results.

Initial results

The outcome of the three maintenance-medication strategies and their interaction with family treatment has not yet been reported. Results regarding clinical stabilisation have been reported for the first half of the sample ($n = 239$) randomised to family treatment (Schooler *et al*, 1989). Stabilisation was defined by the moderate-dosage range of fluphenazine decanoate, the absence of dosage changes during the month prior to initiation of double-blind medication, and by rating-scale criteria using the Brief Psychiatric Rating Scale – Anchored Version (BPRS) (Woerner *et al*, 1988). These rating-scale criteria required no ratings above 'moderate' on items reflecting psychotic symptoms.

The study design incorporated a two-stage randomisation because of the need to allow enough time for clinical remission so that patients could be considered suitable for a maintenance-treatment strategy involving dose reduction. The original study plan was conceived with the expectation that approximately 90% of patients would enter the double-blind medication treatment. Schooler *et al* (1989) found that only 149 (62% of the sample) could be successfully stabilised within six months of an index hospital stay and randomised to double-blind medication condition. This lower than expected stabilisation rate allowed examination of predictors of successful stabilisation. Patients who did not enter double-blind treatment

were categorised as non-stabilised ($n=50$, 21%), non-cooperative ($n=35$, 15%) or administratively withdrawn ($n=5$, 2%). The non-stabilised group included some patients who had shown substantial clinical improvement but at doses of neuroleptic medication above the range utilised in the study. The non-cooperative group included patients and families who initially consented to participate in the study but later withdrew consent or dropped out of treatment.

Three groups were compared: those stabilised within the dose range; those not stabilised; and those who were not cooperative with treatment. Predictors of stabilisation from a number of domains were examined: demographic characteristics; psychiatric-treatment history; diagnosis; psychopathology; extra-pyramidal side-effects; initial exposure to applied or supportive family management; and social adjustment. Comparisons among groups for continuous variables used analysis of variance; categorical variables were evaluated using χ^2 tests. Table 1 presents information on characteristics that differed significantly among the groups.

There were no differences among the five sites in the percentages of successfully stabilised patients. The percentages ranged from 54% to 70%. Among the demographic characteristics examined (gender, age, race, marital status and living setting prior to study entry), only race was differentially associated with stabilisation outcome (Hargreaves *et al*, 1989). The percentage of non-white patients successfully stabilised (70%) was higher than the percentage of white patients (55%). In terms of psychiatric treatment history (age at first hospital admission, number of prior hospital stays, prior receipt of neuroleptic medication and psychosocial treatment, rapidity of symptom onset and length of index hospital stay), only the number of prior hospital stays differentiated patients who were successfully stabilised from those who were not (Hargreaves *et al*, 1989): non-stabilising patients had more prior hospital stays (mean 5.3) than those who entered the double-blind study (3.0) or who were classified as non-cooperative (2.6).

DSM–III–R criteria for schizophrenia (American Psychiatric Association, 1987) were met by 81% of

Table 1
Significant predictors of stabilisation status

Variable	Stabilisation status		
	Entered double-blind treatment ($n=149$)	Non-stabilised ($n=50$)	Non-cooperative ($n=35$)
Race ($\chi^2=5.83$)*			
Percentage of white patients ($n=108$)	55.0	27.0	18.0
Percentage of non-white patients ($n=126$)	70.0	17.0	13.0
Number of prior hospital admissions (mean) ($F=7.64$)***	3.0	5.3	2.6
Severity of illness (mean) ($F=7.32$)***	4.0	4.6	4.4
Brief Psychiatric Rating Scale - Anchored Version			
Thought disturbance (mean) ($F=4.64$)**	2.3	3.0	2.5
Activation (mean) ($F=2.89$)*	1.5	1.6	1.8
Hostile suspiciousness (mean) ($F=7.52$)***	1.9	2.2	2.7
Anxiety–depression (mean) ($F=4.97$)**	2.2	2.4	2.9
somatic concern (mean) ($F=3.80$)*	2.3	2.3	3.2
anxiety (mean) ($F=2.54$, $P>0.05$, <0.10)	2.8	3.2	3.7
Neurological Rating Scale			
Overall score (mean) ($F=2.96$)*	1.4	1.5	1.6
gait (mean) ($F=4.89$)**	1.5	1.8	2.1
arm-dropping (mean) ($F=6.99$)***	1.4	1.4	1.9
shoulder-shaking (mean) ($F=3.40$)*	1.4	1.6	1.8
Attendance at psycho-education workshop ($\chi^2=11.37$)**			
Percentage of those attending ($n=176$)	69.0	20.0	11.0
Percentage of those not attending ($n=58$)	48.0	24.0	28.0
Social adjustment			
In household (mean) ($F=4.08$)*	4.2	4.8	4.2
Overall (mean) ($F=3.03$)*	4.6	5.1	5.0
Family judgements			
Burden (mean) ($F=3.92$)*	2.3	3.0	2.2
Patient's severity of illness (mean) ($F=4.74$)**	2.3	2.9	2.5

*$P\leqslant0.05$, **$P\leqslant0.01$, ***$P\leqslant0.001$.

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patients, but the likelihood of successful stabilisation was not different for them than for the smaller numbers of patients who satisfied criteria for schizo-affective of schizophreniform disorder (Keith *et al*, 1989). The severity of the key symptoms required for diagnosis at the height of the episode (delusions, hallucinations and conceptual disorganisation) did not differentiate those who would be successfully stabilised within six months from the other two groups either (Keith *et al*, 1989).

However, some symptoms of psychopathology rated during the stabilisation period did differentiate the groups (Hargreaves *et al*, 1989). These ratings were made on average about a month following hospital admission. Therefore, they reflect initial response to treatment and, on average, reveal lesser symptom severity than ratings made at the height of the episode. Both the BPRS and the Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1982) were completed. As shown in Table 1, overall severity of the illness, and severity of thought disturbance, activation and hostile suspiciousness on the BPRS distinguished the groups (Hargreaves *et al*, 1989). For all these factors, the least symptom severity was seen in the group that was successfully stabilised. The greatest overall severity and thought disturbance characterised patients who failed to stabilise; the greatest activation and hostile suspiciousness characterised the non-cooperative group. None of the ratings of negative symptoms, anergia on the BPRS or SANS global ratings differentiated the groups. Severity on the BPRS factor of anxiety–depression was highest in the non-cooperative group, parallelling the finding with activation and hostile suspiciousness. Since this factor includes items that reflect depressive mood and guilt, which may be more closely related to negative symptoms, each item was examined separately (Glick *et al*, 1989). Of the four items in the factor, only somatic concern was significantly related to likelihood of stabilisation; anxiety showed a trend. In both cases, non-cooperative patients had highest symptom levels. Guilt and depression did not differentiate the groups, as was the case with all negative symptoms, whether rated on the BPRS or the SANS.

Patients who were not cooperative with treatment showed the highest levels of extrapyramidal symptoms, indexed by a total score on the Neurological Rating Scale, a modification of the Simpson–Angus Scale (Simpson & Angus, 1970). This reflects significantly higher scores in this group in stiff gait, arm-dropping and shoulder-shaking, all measures of Parkinsonian rigidity, although in all cases mean scores were in the 'normal' to 'mild' range. Presence of abnormal involuntary movements related to tardive dyskinesia was unrelated to likelihood of stabilisation (Glick *et al*, 1989).

There was no difference in likelihood of successful stabilisation between patients assigned to applied family management and those assigned to supportive family management, but patients whose families did not attend the initial psycho-educational workshop were less likely to be successfully stabilised. They were more likely to fall in the non-cooperative group, as shown in Table 1 (Keith *et al*, 1989). Ratings of overall social adjustment made one month after discharge specifically in the household and global functioning–were poorer in patients who were not subsequently stabilised. Also, family members judged the non-stabilised patients as more severely ill and a greater burden (Hargreaves *et al*, 1989).

Comment

Review of dosage-reduction studies

The completed studies involving both continuous low dose and targeted treatment represent a substantial corpus of clinical research regarding maintenance treatment in schizophrenia. They provide information both about the course of schizophrenic illness and the impact of treatment on that course. First, if we needed a reminder of the importance of antipsychotic medication in long-term treatment of schizophrenia, these studies provide it through their findings, ranging from a reduction in clinical stability to an increase in psychotic symptoms when the moderate doses that patients were receiving were reduced or discontinued. Equally important, in only a few studies was there an increase in hospital readmission associated with either reduction or discontinuation of dose. Second, all the studies involved the implementation of clinical care systems that went beyond the standard care available in the facilities where the studies were being conducted. The clinical infrastructures in the research clinics all involved a clinical contact at least every other week. It may be that the clinical support system provided accounted in part for the general absence of increased hospital admission. Positive effects of dose reduction have been seen in a number of areas, particularly involving reduced side-effects, lower ratings of anxiety and depression and, in the Kane *et al* study, improved ratings by family members of satisfaction and burden.

From a methodological perspective, none of the low-dose studies directly addressed the important clinical question of the lowest possible dose. Only the Kane *et al* study included more than two doses. The results of that study suggest that the intermediate dose studied was indeed intermediate in efficacy

between the two others. In the other studies there were only two doses, one that defined the routine maintenance dose and one that represented the reduction. Therefore, it was not possible to determine whether an even lower dose would have been less effective. The reductions included 50% of the standard (Johnson *et al*), 20% of the standard (Goldstein *et al*, Hogarty *et al*, Kane *et al* and Marder *et al*) and 10% of the standard (Kane *et al*). In all cases, the samples were restricted to patients who were already receiving moderate doses. The effects of dose reduction in patients who are receiving high maintenance doses have not been studied, nor have there been studies that examine multiple doses that will aid in determining an optimal dose or dose range.

The targeted or intermittent treatment or early intervention strategy studies have been informative as well. First, they suggest that the treatment strategy can be implemented. Because patients do not immediately receive a full dose of medication, there is a significant difference in the amount of medication received under the two conditions. At this stage of research development, that may seem obvious, but it was a subject of active discussion when the studies reviewed here were being designed. Second, all the studies reviewed hypothesised that early intervention would, at best, be 'as good as' continued medication in prevention of relapses or symptom exacerbation, but not better. The hypothesised advantages were in reduction of tardive dyskinesia risk and improvement in emotional responsiveness, energy and motivation. These expectations have not been supported.

Efficacy of dose-reduction strategies with family treatment

The initial findings from the NIMH Treatment Strategies in Schizophrenia Study raise a number of important points about treatment of schizophrenia. The first is that not all acutely symptomatic patients will respond to antipsychotic medication well enough within six months to be candidates for a medication strategy that entails dose reduction. These stabilisation rates are, though, remarkably consistent across a range of facilities that treat schizophrenia. Neither diagnosis nor symptom severity at the height of the episode identify the patients who will stabilise, but early response of positive symptoms to treatment does. Further, the early implementation of two forms of family treatment based on the same principle, psychoeducation, does not distinguish those who stabilise successfully from others. But family participation in a psycho-educational workshop does. This finding is complemented by the finding that family members' judgements both of the patient's severity of illness and of burden are also useful predictors.

The reason why patients did not enter the double-blind dosage-reduction study has substantial importance. Distinguishing between clinically not stabilised patients and non-cooperative patients is useful. Non-stabilised patients are more likely to be white, to have more prior hospital admissions, higher severity of thought disturbance and poorer social adjustment following discharge, and are seen as more severely ill and a greater burden by their families. Patients who fail to be stabilised because they (and their families) are not cooperative are less likely to attend the psycho-educational workshop, and are likely to have higher levels of a number of specific symptoms of psychopathology and extrapyramidal side-effects of medication: these include anxiety, activation, hostile suspiciousness and Parkinsonian rigidity in a number of body areas.

Although review of findings from completed studies indicates that targeted, early intervention significantly increases risk of relapse without substantial offsetting advantages, the addition of a family-treatment factor to the NIMH Treatment Strategies in Schizophrenia Study makes this study of targeted treatment different from the earlier studies. Experimental studies of family treatment report both significant reduction in relapse and symptom improvement (e.g. Falloon *et al*, 1985; Hogarty *et al*, 1986; Leff *et al*, 1985). In view of the finding that family behaviour and judgements early in treatment are related to likelihood of stabilisation in the NIMH Treatment Strategies in Schizophrenia multicentre study, and the findings of prior research, the hypothesis of interactive effects of dosage reduction and family treatment on longer-term outcome has substantial importance.

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References

American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders* (3rd edn, revised) (DSM-III-R). Washington, DC: APA.

ANDREASEN, N. C. (1982) Negative symptoms in schizophrenia. *Archives of General Psychiatry*, **39**, 784–788.

BALDESSARINI, R. J., COLE, J. O., DAVIS, J. M., *et al* (1981) *Tardive Dyskinesia Task Force Report 18*. Washington, DC: American Psychiatric Association.

CAFFEY, E. M. Jr, DIAMOND, L. S., FRANK, T. V., *et al* (1964) Discontinuation or reduction of chemotherapy in chronic schizophrenics. *Journal of Chronic Disease*, **17**, 347–358.

CARPENTER, W. T. Jr, HANLON, T. E., HEINRICHS, D. W., *et al* (1990) Continuous vs. targeted medication in schizophrenic outpatients: outcome results. *American Journal of Psychiatry*, **147**, 1138–1148.

DAVIS, J. M. (1975) Overview: maintenance therapy in psychiatry – I. Schizophrenia. *American Journal of Psychiatry*, **132**, 1237–1245.

FALLOON, I. R. H., BOYD, J. L. & MCGILL, C. W. (1984) *Family Care of Schizophrenia: a Problem Solving Treatment for Mental Illness*. New York: Guilford Press.

———, ———, ———, *et al* (1985) Family management in the prevention of morbidity of schizophrenia. *Archives of General Psychiatry*, **42**, 887–896.

GLICK, I. D., JACOBS, M., LIEBERMAN, J., *et al* (1989) Prediction of short term outcome in schizophrenia: depressive symptoms, negative symptoms, and extrapyramidal signs. *Psychopharmacology Bulletin*, **25**, 344–347.

GOLDSTEIN, M. J., RODNICK, E. H., EVANS, J. R., *et al* (1978) Drug and family therapy in the aftercare of acute schizophrenics. *Archives of General Psychiatry*, **35**, 1169–1177.

HARGREAVES, W. A., KANE, J. M., NINAN, P. T., *et al* (1989) Demographic characteristics, treatment history, presenting psychopathology and early course in schizophrenia. *Psychopharmacology Bulletin*, **25**, 340–343.

HERZ, M. I. & MELVILLE, C. (1980) Relapse in schizophrenia. *American Journal of Psychiatry*, **137**, 801–805.

———, SZYMANSKI, H. V. & SIMON, J. C. (1982) Intermittent medication for stable schizophrenic outpatients: an alternative to maintenance medication. *American Journal of Psychiatry*, **139**, 918–922.

———, GLAZER, W. M., MOSTER, M. A., *et al* (1991) Intermittent vs. maintenance medication in schizophrenia. *Archives of General Psychiatry*, **48**, 333–339.

HOGARTY, G. E., ANDERSON, C. M., REISS, D. J., *et al* (1986) Family psychoeducation, social skills training, and maintenance chemotherapy in the aftercare of schizophrenia. *Archives of General Psychiatry*, **43**, 633–642.

———, MCEVOY, J. P., MUNETZ, M., *et al* (1988) Dose of fluphenazine, familial expressed emotion, and outcome in schizophrenia. *Archives of General Psychiatry*, **45**, 797–805.

JOHNSON, D. A. W., LUDLOW, J. M., STREET, K., *et al* (1987) Double-blind comparison of half-dose and standard flupenthixol decanoate in the maintenance treatment of stabilised out-patients with schizophrenia. *British Journal of Psychiatry*, **151**, 634–638.

JOLLEY, A. G., HIRSCH, S. R., MCRINK, A., *et al* (1989) Trial of brief intermittent prophylaxis for selected schizophrenic outpatients: clinical outcome at one year. *British Medical Journal*, **298**, 985–990.

———, ———, MORRISON, E., *et al* (1990) Trial of brief intermittent neuroleptic prophylaxis for selected schizophrenic outpatients – clinical and social outcome at two years. *British Medical Journal*, **301**, 837–842.

KANE, J. M., RIFKIN, A., WOERNER, M., *et al* (1983) Low-dose neuroleptic treatment of outpatient schizophrenics. *Archives of General Psychiatry*, **40**, 893–896.

———, ———, ———, *et al* (1985) High dose vs. low dose strategies in the treatment of schizophrenia. *Psychopharmacology Bulletin*, **21**, 533–537.

———, WOERNER, M. & SARANTAKOS, S. (1986) Depot neuroleptics: a comparative review of standard, intermediate, and low dose regimens. *Journal of Clinical Psychiatry*, **47** (suppl.), 30–33.

KEITH, S. J., BELLACK, A., FRANCES, A., *et al* (1989) The influence of diagnosis and family treatment on acute treatment response and short term outcome in schizophrenia. *Psychopharmacology Bulletin*, **25**, 336–339.

———, MATTHEWS, S. M. & SCHOOLER, N. R. (1991) A review of psychoeducational family approaches. In *Advances in Neuropsychiatry and Psychopharmacology, Vol. I. Schizophrenia Research* (eds C. A. Tamminga & S. C. Schulz), pp. 247–254. New York: Raven Press.

LEFF, J., KUIPERS, L., BERKOWITZ, R., *et al* (1985) A controlled trial of social intervention in the families of schizophrenic patients: two year follow up. *British Journal of Psychiatry*, **146**, 594–600.

MARDER, S. R., VAN PUTTEN, T., MINTZ, J., *et al* (1984) Costs and benefits of two doses of fluphenazine. *Archives of General Psychiatry*, **41**, 1025–1029.

———, ———, ———, *et al* (1987) Low and conventional dose maintenance therapy with fluphenazine decanoate: two year outcome. *Archives of General Psychiatry*, **44**, 518–521.

PIETZCKER, A., GAEBEL, W., KOPCKE, W., *et al* (1986) A German multi-center study on the neuroleptic long-term therapy of schizophrenic patients: preliminary report. *Pharmacopsychiatry*, **19**, 161–166.

PRIEN, R. F. (1984) Long term maintenance pharmacotherapy in recurrent and chronic affective disorders. In *The Chronically Mentally Ill: Research and Services* (ed. M. Mirabi), pp. 159–174. New York: Spectrum.

SCHOOLER, N. R. (1985) Treatment of schizophrenia: maintenance strategies and pharmacologic tactics. In *Controversies in Schizophrenia* (ed. M. Alpert), pp. 366–380. New York: Guilford Press.

——— (1991) Maintenance medication for schizophrenia: strategies for dose reduction. *Schizophrenia Bulletin*, **17**, 311–324.

———, KEITH, S. J., SEVERE, J. B., *et al* (1989) Acute treatment response and short term outcome in schizophrenia. *Psychopharmacology Bulletin*, **25**, 331–335.

SIMPSON, G. M. & ANGUS, J. W. S. (1970) Drug-induced extrapyramidal disorders. *Acta Psychiatrica Scandinavica* (suppl.), **212**, 17–19.

WISTEDT, B., WILES, D. & KOLAKOWSKA, T. (1981) Slow decline of plasma drug and prolactin levels after discontinuation of chronic treatment with depot neuroleptics. *Lancet*, *i*, 1163.

WOERNER, M. G., MANNUZA, S. & KANE, J. M. (1988) Anchoring the BPRS: an aid to improved reliability. *Psychopharmacology Bulletin*, **24**, 112–117.

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