Implementation of evidence-based treatment for schizophrenic disorders: two-year outcome of an international field trial of optimal treatment

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According to clinical trials literature, every person with a schizophrenic disorder should be provided with the combination of optimal dose antipsychotics, strategies to educate himself and his carers to cope more efficiently with environmental stresses, cognitive-behavioural strategies to enhance work and social goals and reducing residual symptoms, and assertive home-based management to help prevent and resolve major social needs and crises, including recurrent episodes of symptoms. Despite strong scientific support for the routine implementation of these 'evidence-based' strategies, few services provide more than the pharmacotherapy component, and even this is seldom applied in the manner associated with the best results in the clinical trials. An international collaborative group, the Optimal Treatment Project (OTP), has been developed to promote the routine use of evidence-based strategies for schizophrenic disorders. A field trial was started to evaluate the benefits and costs of applying evidence-based strategies over a 5-year period. Centres have been set up in 18 countries. This paper summarises the outcome after 24 months of 'optimal' treatment in 603 cases who had reached this stage in their treatment by the end of 2002. On all measures the evidence-based OTP approach achieved more than double the benefits associated with current best practices. One half of recent cases had achieved full recovery from clinical and social morbidity. These advantages were even more striking in centres where a random-control design was used.

Key words: Evidence-based treatment, schizophrenia, effectiveness, field trial, outcome, multicentre

In the past three decades, treatment strategies have been developed for treatment and rehabilitation of schizophrenic disorders that have been shown to markedly reduce the clinical, social and carer morbidity and improve the efficiency of mental health resources. Several reviews of the clinical trials literature have concluded that every person with a schizophrenic disorder should be provided with the combination of a) optimal dose antipsychotics, b) strategies to educate himself or herself and carers, usually relatives, to cope more efficiently with environmental stresses, and c) assertive home-based management to help prevent and resolve major social needs and crises, including episodes of symptoms (1-6).

Despite strong scientific support for the routine implementation of these 'evidence-based' strategies, few services provide more than the pharmacotherapy component, and even this is seldom applied in the manner associated with the best results in the clinical trials (4). Further, although a 5-year outcome is considered the minimal time period for evaluating modifications in the natural course of major disorders by effective treatment, very few field trials of psychiatric treatment strategies have evaluated prospectively the benefits and risks of treatment for more than one year.

In 1994, an international collaborative group was established with the goal of promoting the routine use of evidence-based strategies for mental disorders with continued evaluation of clinical, social, carer and economic outcomes. This collaboration became known as the Optimal Treatment Project (OTP). This paper reports preliminary results for a cohort of cases with schizophrenic disorders.

METHODS

More than 80 centres in over twenty countries have begun the project since 1994. Lack of research funding and administrative difficulties limited the number of centres with unselected cases that have received 'optimal treatment' according to the project protocol for at least 24 months to 14. These were Ankara (Turkey), Gothenburg, Svenljunga and Lysekil (West Sweden), Como and Benevento (Italy), Trondheim (Norway), Athens (Greece), Bonn (Germany), Valencia (Spain), Auckland (New Zealand), Tokyo (Japan), Budapest and Szekesfehervar (Hungary).

'Optimal treatment' includes the strategies listed in Table 1. In each centre, a multidisciplinary team of psychiatrists, psychologists, social workers, nurses and occupational therapists received between 60 and 100 hours of workshop training in these strategies. Once they had been certified as competent, they began to enter cases in the

Table 1 Evidence-based treatment strategies used in the Optimal Treatment Project (OTP)

- Minimally effective antipsychotic drug strategies targeted to changing symptom profiles (7-9)
  - Choice of medication based on symptom profiles, side effects and response
  - Education about benefits and problems
  - Adherence training and maintenance
  - Side effects prevention and minimization
  - Early warning signs of exacerbation
- Education of patients and informal carers in stress management strategies (10,11)
  - Education to enhance understanding of the nature of psychotic disorders and their clinical treatments
  - Training in effective interpersonal communication and structured problem solving to achieve personal goals and manage life stresses
- Assertive case-management (12)
  - Development and maintenance of effective social support - housing, finances, health and safety
  - Early detection and intensive care to resolve clinical and social crises in the settings most conducive to full and rapid recovery
- Goal-oriented social and occupational skills training (9,13)
  - Training patients and informal carers in the skills they need to achieve their personal goals for friendships, close relationships, work and recreational activities
  - Supporting patients to access the full range of social and occupational opportunities available in their communities
- Specific pharmacological and/or psychological strategies for residual or emerging symptoms (8,14-17)
  - Coping with persistent psychosis
  - Managing negative symptoms
  - Coping with anxiety and panic
  - Coping with mood swings, dysphoria and suicidal thoughts
  - Managing substance misuse
  - Managing anger and frustration
  - Managing sleep disorders
  - Managing nutritional problems

project. Patients with a DSM-IV diagnosis of a schizophrenic disorder were selected. Clinical diagnoses were based on standardised interviews. These included the Structured Clinical Interview for DSM-IV (SCID-I, 18), the Schedules for Clinical Assessment in Neuropsychiatry (SCAN, 19) or the Current Psychiatric State, 50-item version (CPS-50, 20). No specific exclusion criteria were used: in particular, cases with comorbid psychiatric, neurological, physical or substance misuse problems were included so that the sample represented typical clinical cases. Cases entered the study once they were stabilised from any recent exacerbations. In four centres (Ankara, Gothenburg, Trondheim and Benevento), cases were randomly assigned to OTP or routine case management.

A core battery of global measures was used in each centre. These included: a) the Mental Functions Impairment Scale (MFIS, based on 21), a 7-point scale which measures the proportion of time each day the subject experiences impairment in mental functioning as a result of all types of symptoms; b) the Disability Index (DI, based on 22), a 7-point scale which measures limitations of subjects' ability to perform interpersonal and social functions in accordance with their cultural expectations; c) the Global Carer Stress (GCS, 23), a 5-point scale which measures the subjective stress experienced by the key caregiver associated with the patient's mental disorder. Ratings were translated, and at each centre two or more raters who were independent of the clinical teams were trained to apply the scales to a high level of reliability (intraclass correlation coefficient > 0.90). The ratings were made at 3-month intervals by the clinical teams, and at least at baseline and at 12 and 24 months by the independent assessors. Ratings were made after interviews with both the patient and his or her key caregiver, with supplemental information available from charts and case managers when necessary. Background information on residence, work and social functioning was also collected by the independent raters at 3 month intervals. In addition to these core measures, several centres used other standardised clinical, social, economic and neuropsychological assessments. A manual describing the assessment battery and its standardisation was produced (20).

Paired t-tests were used to assess the changes in the cohorts from before treatment to 24 months of treatment. Cohen's d was used to calculate effect sizes (24).

RESULTS

At the end of 2002, 1012 cases had entered the project, with 603 having completed at least two years of 'optimal treatment'. Table 2 summarises the background characteristics of this cohort. Complete data was available on 594 cases, 99% of the sample. Included in this cohort were 58 cases that had withdrawn partially or fully from participation in the clinical protocol of the project but were evaluated at 24 months. Thus the analysis was conducted on an intention-to-treat basis. A further 9 cases were unavailable for evaluation at 24 months. Thus, a total of 67 cases, or 11%, could be considered project drop-outs.

Fidelity in applying all the evidence-based strategies was examined on a random selection of cases at each service. This usually ranged from good to excellent, with fidelity tending to improve the longer services participated in the program. The most common problems involved applying pharmacotherapy according to the project guidelines, that aimed to target specific symptoms, to maximise adherence and to minimise side effects. Other problems included engaging families and other informal caregivers in services where routine contact previously had been rare, and applying supportive goal-oriented methods to assist patients to enhance their social networks and to gain constructive occupation. Further training and supervision usually remedied these deficits.

Table 3 shows the results on the clinical, social and carer indices. Significant improvements occurred on all measures over the 24 months. These benefits appeared to have clinical significance, with average percentage changes of 41% on the impairment index, 39% on disability and 48% less stress on carers. The cases assigned to continue their routine case management showed similar improvements, but these appeared to have less clinical significance: impairment 12%, disability 13% and carer stress 15%.

Table 2 Characteristics of cohorts at each centre

Centre	N (% total)	Age: years (SD)	Sex: male (%)	Marital status: unmarried (%)	First episode (%)	Duration of illness >10 years (%)	Optimal treatment (%)
Trondheim	49 (8)	25.2 (4.6)	28 (57)	46 (94)	49 (100)	0 (0)	29 (59)
Auckland	24 (4)	27.1 (8.3)	15 (63)	21 (88)	22 (92)	2 (8)	24 (100)
Tokyo	19 (3)	36.1 (7.7)	12 (63)	11 (58)	0 (0)	4 (21)	19 (100)
Valencia	102 (17)	26.3 (6.0)	69 (68)	91 (89)	18 (18)	14 (14)	102 (100)
Athens	51 (9)	35.4 (6.9)	25 (49)	46 (90)	0 (0)	51 (100)	51 (100)
Bonn	18 (3)	33.6 (6.3)	11 (61)	10 (56)	0 (0)	6 (33)	18 (100)
West Sweden	88 (15)	38.3 (8.3)	55 (63)	80 (91)	0 (0)	53 (60)	56 (64)
Hungary	35 (6)	33.4 (10.4)	14 (40)	25 (72)	8 (23)	7 (20)	35 (100)
Benevento	24 (4)	30.0 (2.0)	19 (79)	23 (96)	0 (0)	0 (0)	12 (50)
Ankara	100 (17)	28.9 (7.0)	66 (66)	55 (55)	19 (19)	13 (13)	50 (50)
Como	93 (15)	61.0 (8.8)	52 (56)	90 (93)	0 (0)	93 (100)	47 (51)
TOTAL	603 (100)	35.7 (13.8)	366 (61)	501 (83)	120 (20)	243 (40)	443 (73)

The direct comparison between cases randomly assigned to OTP (n=146) or routine case management (n=114) in the centres of Ankara, Trondheim, Benevento and Gothenburg showed an even greater contrast between the two treatment approaches, with OTP cases presenting more than twice the benefits observed by blind, independent raters on routine case management. The Cohen's d for impairment was 1.49 for OTP (48% improvement) vs. 0.56 for routine case management (21% improvement). The corresponding figures for disability were 1.41 (53% improvement) vs. 0.56 (16% improvement), and those for carer stress were 1.22 (63% improvement) vs. 0.33 (15% improvement).

An analysis of the rates of recovery (full = no significant impairment or disability; partial = substantial improvement in impairment and disability) showed that 35% of OTP cases met the criteria of full recovery at 24 months vs. 10% of those on routine case management. When the recent-onset group (onset of psychotic symptoms within 10 years) was considered separately, 43% had made a full recovery vs. 6% in the contrast group. However, a very similar proportion of both groups (74 vs. 73%) showed patterns of substantial recovery from impairment and disability, with similar proportions making little or no progress (26 vs. 27%). This would appear to suggest that the rate of recovery with OTP was more rapid and complete than with routine case management.

DISCUSSION

This interim report of a five-year international field trial supports the hypothesis that consistent benefits are derived from evidence-based treatment strategies when

Table 3 Clinical impairment, social disability and carer stress at start of project and after 24 months

	Number of cases	Impairment mean (SD)	Disability Index mean (SD)	Carer Stress mean (SD)
At start of 'optimal treatment'	434	3.57 (1.57)	3.16 (1.32)	2.29 (1.34)
After 24 months of 'optimal treatment'	434	2.12 (1.46) d = 1.04	1.94 (1.25) d = 0.92	1.09 (1.14) d = 1.10
At start of continued current treatment	160	3.79 (1.89)	3.78 (1.53)	2.76 (1.29)
After 24 months of continued current treatment	160	3.32 (1.58) d = 0.25	3.29 (1.46) d = 0.32	2.34 (1.17) d = 0.33

d = Cohen's effect size

they are applied in a systematic way for schizophrenic disorders. It may be concluded that the combination of pharmacological and psychosocial strategies that have proven efficacious in controlled trials can be applied and evaluated in routine practice without additional resources, apart from the obvious need to ensure adequate training and monitoring of the fidelity of the strategies. The effect sizes and percentage improvements indicate that the clinical and social benefits associated with two years of optimal treatment are substantial, and with a clear trend towards recovery from clinical impairment and social disability.

In common with most field trials, this study can be criticised for its lack of methodological rigour. The lack of random allocation of all cases to a standardised comparative treatment approach with blind ratings should be set against the completeness of the data gathering and the broad range of cases sampled across a range of cultures with widely differing health care delivery systems. It is commonly observed that efforts to improve the scientific methodology of trials result in a reduction in the estimates of specific benefits that are associated with more naturalistic studies. In contrast, in this project the sub-sample of centres that provided a random controlled comparison between the evidence-based approach and more traditional case management programmes showed greater benefits on all core measures than those treating consecutive cases without a randomly controlled comparison.

It should be noted that significant improvements on all measures were observed when the traditional case management approach that was used as the control condition was provided over the 24-month period, reflecting the high clinical standards of the centres that entered the project. However, the lower effect sizes suggest that these benefits were less clinically significant and did not lead to the major improvements achieved from the attempts to adhere to the evidence-based protocol.

The OTP project provides further strong evidence for a change in the prognosis of schizophrenic disorders. In recent years there has been much speculation about the origins of the apparent improved outlook for patients diagnosed with these disorders (25,26). Biomedical and psychosocial factors have been implicated. Until now there has been little evidence that treatment has contributed to anything more than stabilising the course of the acute episodes of the disorder, without enhancing the rate or extent of recovery (2,27,28). On the basis of these preliminary results, it could now be hypothesised that integrated optimal pharmacotherapy and psychosocial treatment programmes may play a major role in expediting recovery from these disorders. Almost half the cases that began evidence-based treatment within 10 years of onset of their disorders showed a pattern of excellent recovery after two years. This apparently dramatic benefit should be interpreted with caution. Not all these cases were totally free of all psychiatric symptoms or social disability, nor does this interim report indicate that this recovery was stable. Residual symptoms of anxiety and depression, cognitive and learning difficulties, and the unavailability of social and occupational opportunities for patients were often more distressing and handicapping than the psychotic and deficit symptoms specific to the schizophrenic syndromes. The services that participated in the project were trained in the application of a broad range of evidence-based psychological strategies for drug-resistant psychotic and deficit symptoms, as well as strategies for managing anxiety, depression, suicidal ideation, anger, sleep and nutritional problems. Many of these strategies have not been tested specifically for residual symptoms and problems of patients with a first line diagnosis of schizophrenia (14,17). However, as in other branches of medicine, the goal/problem oriented approach to case management suggests that both pharmacological and psychosocial approaches may be effective when targeted to specific problems rather than merely to the core symptoms of each diagnostic category. The single-case evaluation that is necessary to establish the validity of the treatment plan for every case would appear to be a key component in the application of the wide range of treatment strategies over the entire course of a disorder. This approach was an integral part of optimal clinical management of cases in this project and may have contributed to the better than expected outcome of many cases, including many of those with disorders of long duration (29).

While the positive outcomes were striking, it is important to note that one in four cases of recent onset and first episode cases, and 40% of chronic cases showed no improvement after two years of optimal treatment. This substantial minority represents a significant challenge to clinicians and researchers. Although worthwhile advances have been made in pharmacotherapy and psychosocial treatments, there is much work still to be done. However, this lack of effectiveness of new strategies for *all* cases of schizophrenia should not excuse services from providing the full range of evidence-based strategies in a competent and optimistic manner to all cases.

The 5-year outcome data from this project will help establish whether the benefits from these methods are stable and continue to accrue. Unfortunately during the course of this project it has become very clear that few mental health services are provided with the resources to deliver continued optimal treatment programmes of this kind. Relatively short-term intensive treatment that produces worthwhile but incomplete improvement is still considered ethical in the mental health field. This acceptance of inadequate treatment led to most of the centres of excellence that began this OTP withdrawing because they were unable to ensure continued comprehensive treatment beyond the first year. The evidence gathered from this project is that two years of comprehensive evidence-based treatment is not sufficient for at least half the cases and that progress continues far beyond this point. To aim to achieve full and lasting recovery from mental disorders

should not be considered idealistic, but rather a societal necessity, and we should all fight to ensure that the resources are provided to implement optimal treatment for all disorders until this objective is met.

In addition to the core methodological weaknesses already discussed, this project suffered several other limitations. First, although every effort was made to include all cases of schizophrenic disorders within specific catchment areas, this was achieved in few centres. In almost all centres individual psychiatrists maintained personal control over the treatment programme provided to patients assigned to their care, and most were unwilling to follow an evidence-based protocol for a large proportion of their cases. This included an unwillingness to adhere to the principles of pharmacological practice, to discuss aspects of diagnosis and treatment rationales with patients and their informal carers, or to consider psychological strategies as adjuncts to pharmacotherapy for persisting and residual symptoms. Thus, the cohort included in the field trial may not be representative of schizophrenic disorders in the community. In particular, cases who showed rapid and full recovery after relatively brief psychotic episodes were seldom considered to need any psychosocial strategies in order to ensure full and lasting recovery of clinical and social functions and to prevent future episodes, despite the fact that such interventions could be brief and tailored to the individual strengths and weaknesses of patients and their carers. However, the multi-centred, cross-cultural nature of this project adds strength to the conclusion that an evidence-based approach applied within a individualised goal and problem oriented framework may be effective in routine clinical practice for both recent-onset and long-term cases of schizophrenia.

The relationship between clinical and social benefits and specific treatment strategies was not clearly defined. Although we attempted to ensure that all cases adhered to the treatment protocols, this was not always evident. It was clear that poor adherence to the treatment methods was not only due to poor compliance by the patient, but frequently to poor compliance by the professionals in applying the treatment strategies. Attempts to increase the flexibility of structured treatment methods beyond the parameters established under controlled trial conditions all too frequently become a license to implement methods in a highly idiosyncratic way, providing only part of the strategy, delaying implementation or avoid using those approaches that are clearly indicated in favour of those that are more convenient or those supported by marketing incentives. Careful and assertive monitoring that maximises adhesion to protocols in controlled trials appears just as necessary in routine practice if similar benefits are to be achieved.

Finally, it is important to note again that this is a report of work in progress and that the final results after five years of continued optimal treatment may show a different picture to that reported here. Prognostic factors and random effects that had less influence on the outcomes at two years may have greater impact on the course of the disorders after five years. The advent of improved medicines or psychological strategies may improve the outcomes, while new problems, such as a further reduction in the capacity of services to maintain fidelity to treatment protocols, may emerge to limit the benefits of treatment strategies that have proven effective in the short term.

Appendix

The other members of the OTP Collaborative Group are Ken Burnett (Victoria, Australia), Carla Belotti (Como, Italy), Massimo Casacchia (L'Aquila, Italy), Scott Clark (Sydney, Australia), Giulio Corrivetti (Salerno, Italy), Naomi Cowan (Auckland, New Zealand), Dave Erickson (Vancouver, Canada), Bo Ivarsson (Boras, Sweden), Tommy Norden (Lysekil, Sweden), Joan Obiols (Andorra, Andorra), Alexandra Palli (Athens, Greece), Esterina Pellegrini (Como, Italy), John Pullman (Taranaki, New Zealand), Rita Roncone (L'Aquila, Italy), Kei Sakuma (Koriyama, Japan), Zsolt Unoka (Budapest, Hungary), Atilla and Zsusa Varga (Szekesfehervar, Hungary) and Joseph Ventura (Los Angeles, USA).

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