

Danish Centre for Evaluation and Health Technology Assessment

PREVENTIVE OUTPATIENT TREATMENT IN AFFECTIVE DISORDERS. RESULTS FROM A HEALTH TECHNOLOGY ASSESSMENT

Summary

Lars Vedel Kessing¹, Hanne Vibe Hansen², Esben Hougaard³, Anne Hvenegaard⁴, Jens Albæk⁴

1. Department of Psychiatry, University Hospital of Copenhagen, Rigshospitalet
2. Psychiatric Department, H:S Amager Hospital
3. Department of Psychology, University of Aarhus
4. DSI, Danish Institute for Health Services Research

Preventive outpatient treatment in affective disorders. Results from a Health Technology Assessment (HTA)

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For further information please contact:

National Board of Health
Danish Centre for Evaluation and Health Technology Assessment
Islands Brygge 67
DK-2300 Copenhagen
Denmark
Phone: +45 72 22 75 48
E-mail: dacehta@sst.dk
Home page: www.dacehta.dk

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English executive summary

Depression and bipolar disorder are common mental disorders. The prognosis for patients with affective disorder is poorer than previously believed. The course of the disorders can be influenced by concrete prophylactic measures.

The present HTA reviews the course of both depressive disorder and bipolar affective disorder.

The technology section discusses the treatment in the form of prophylactic pharmacotherapy, prophylactic combination therapy involving pharmacotherapy and psychological treatment, and doctor-patient cooperation (adherence).

The HTA is comprised of five parts:

1. the disorder
2. the technology (treatment)
3. the patient
4. the organisation
5. the economic aspects.

Method

Literature search and Levels of Evidence

Literature search

A systematic review of the international literature has been done (for description and search strategy see Bilag 1 (in Danish)).

Levels of Evidence

Grades of Recommendation has been done using “Levels of Evidence and Grades of Recommendation”, National Health Service Research and Development Programme, Centre for Evidence-Based Medicine in Oxford, 1998 (Bilag 2).

In the Recommendation, level 1a is the highest level of evidence, e.g. conclusion from systematic review or meta-analysis of homogenous randomised controlled trials and 5 represents f.ex. an expert evaluation.

Whenever possible level of evidence was based on systematic reviews or meta-analysis. When such reviews or meta-analysis were not published level of evidence was made based on individual studies. This was f.ex the case with the effect of psychological treatment and for the effect of combined medical and psychological treatment.

Questionnaire survey among patients

The HTA includes a nation-wide questionnaire survey from autumn 2003 among out-patients who have had contact to hospital psychiatry with a diagnosis of affective disorder regarding their view and attitudes toward illness and treatment. The results have been published independently in four English written international papers.

Questionnaire survey among the Heads doctors at psychiatric hospitals in Denmark

The HTA includes a nation-wide questionnaire survey from autumn 2003 among the head doctors at psychiatric hospitals nation-wide in Denmark regarding outpatient treatment service for patients with affective disorders and their view on treatment service for these patients.

Register studies

Finally, the HTA includes a large number of previously published papers on the course of illness and contact to hospital psychiatry for patients with affective disorders.

Main points regarding the disorders and treatment

The disorder

Prevalence and course of depressive disorder

- depressive disorder is a serious mental disorder. The prevalence of depressive disorder among the population is high. As regards disease impact, the disorder comprised the fourth-most important disease in 2000 and according to the WHO is expected to comprise the second-most important disorder among all physical and mental diseases in 2020
- in Denmark, it is estimated that at any one time, just under 200,000 persons suffer from symptoms of depression. Of the 200,000 patients, approximately 40,000 have been hospitalised at least once with depression
- depression frequently occurs together with other physical or mental disorders, which often worsens the course of the disease
- depression is often recurrent, and among patients hospitalised for depression for the first time approx. 70% will suffer several depressive episodes, and just over 60% will develop depression three or more times
- the risk of developing a new depression is enhanced in patients who have mild persistent symptoms of depression following an episode of depressive disorder
- with each new episode of depressive disorder, the risk of worsening the course of the disease increases
- among patients with major depression, the course of the disease becomes chronic with persistent symptoms of depression lasting more than two years in around 20% of cases
- major depression is often accompanied by a long-lasting reduction in psychosocial functioning, i.e. a negative effect on the relationship with family, friends and work
- relative to patients with chronic general medical conditions such as diabetes, hypertension, recent myocardial infarction or congestive heart failure, the diminishment in social functioning and well-being is comparable or greater among patients with depression
- some patients with depressive disorder have learning and memory difficulties, even during periods without depressive symptoms, and depressive disorder seems to be a risk factor for the development of dementia
- it is estimated that just over half of the persons who commit suicide suffer from depression. Among persons who have been hospitalised due to major depressive disorder, the lifetime risk of suicide is estimated to be approx. 10%.

Prevalence and course of bipolar disorder

- it is estimated that approx. 1% of the adult population corresponding to 40,000 persons in Denmark suffer from bipolar affective disorder. A large proportion of these will periodically require hospitalisation in a psychiatry ward
- viewed over an extended period, 10-15% of patients with depressive disorder will prove to suffer from bipolar affective disorder
- bipolar affective disorder frequently occurs together with other physical or mental disorders, which can weaken the diagnostic certainty leading to erroneous or delayed treatment and worsening of the course of the disease
- bipolar affective disorder is nearly always recurrent. Virtually all patients who have had treatment-demanding mania will suffer further episodes of the disorder. The majority of patients will suffer three or more episodes
- on average, patients with bipolar affective disorder suffer symptoms of their disorder approximately half of the time, and approx. 10% of the patients have permanent symptoms

- among patients with bipolar affective disorder, depressive symptoms are three-fold more frequent than manic symptoms
- the level of psychosocial functioning is negatively affected by the number of previous depressive episodes in particular
- the level of psychosocial functioning is reduced between episodes of the disorder in 30-60% of patients with bipolar affective disorder. The reduction in psychosocial functioning encompasses the relationship to the patient's spouse, children, other family members and friends. In addition, it negatively affects the value and amount of leisure activities, degree of satisfaction, occupational status and income
- some patients with bipolar affective disorder have learning and memory difficulties, and the risk of developing dementia is possibly increased
- the risk of suicide is greatest when the patients are in the depressive phase, during which the suicide risk is just as great as for patients with depressive disorder.

Technology

Pharmacotherapy of depressive disorder

- antidepressive pharmacotherapy can reduce the risk of new episodes of depression or relapse of existing episodes by more than 50% relative to placebo (Evidence level 1a)
- in general, both the various groups of antidepressants and the various drugs within each group seem to be roughly equally effective in treating depression. Differences between the various groups of antidepressants are seen in relation to special clinical manifestations of the disorder, however
- danish and international studies have revealed that less than half of patients who suffer from depression receive the correct diagnosis and adequate treatment of sufficient duration in general practice
- a large proportion of patients who are discharged following psychiatric hospitalisation with depression do not subsequently receive prophylactic antidepressant treatment in sufficient doses and periods of time.

Pharmacotherapy of bipolar affective disorder

- lithium is the most well-investigated drug as regards prophylactic treatment of bipolar affective disorder. Lithium treatment can reduce the risk of new episodes of the disorder by approximately a third relative to placebo. The effect is greatest for mania, where the risk is reduced by approx. 40%, and less for depression, where the risk is reduced by approx. 25% (Evidence level 1a)
- although the evidence is sparse, several mood-stabilising and antipsychotic drugs seem to protect against new episodes of the disorder with the effect being variable, but comparable to that of lithium.

Combination therapy (pharmacotherapy and psychological treatment) of depressive disorder

- cognitive therapy given in the acute phase seems to some extent to be able to prevent relapse and the recurrence of new depressive episodes, but the scientific evidence is limited (Evidence level 1b)
- long-term psychotherapy is effective in preventing relapse/recurrence of depression. Combination therapy comprised of antidepressive pharmacotherapy and cognitive or interpersonal therapy seems to be more effective than monotherapy, and pharmacotherapy seems to be more effective than psychotherapy (Evidence level 1b)
- sequential combination therapy in which psychotherapy is given as succeeding or supplementary therapy following an initial period of pharmacotherapy alone has a prophylactic effect towards new depressive episodes (Evidence level 1b)
- in patients with chronic depression, combination therapy comprised of antidepressive pharmac-

otherapy and cognitive therapy seems to have a better effect on the patients' psychosocial functioning than the two treatments given independently.

Combination therapy (pharmacotherapy and psychological treatment) of bipolar affective disorder

- psychological treatment in the form of psychoeducation or cognitive therapy can reduce the number of new episodes of bipolar affective disorder (Evidence level 1b)
- combination therapy comprised of pharmacotherapy and psychoeducation or cognitive therapy has a better effect on psychosocial functioning than pharmacotherapy alone (Evidence level 1b).

Doctor-patient cooperation (treatment adherence)

- the doctor-patient cooperation can be expressed in terms of treatment adherence. The pharmacotherapy received by patients with depressive or bipolar affective disorder is often too short-lasting and the dosage too low, which is termed reduced treatment adherence
- reduced treatment adherence worsens the prognosis and enhances the risk of recurrence of new depressive episodes (in depressive disorder) or new depressive or manic episodes (in bipolar affective disorder)
- several treatment regimens are available that can improve treatment adherence to pharmacotherapy and reduce the impact of the disorder. These include cognitive therapy, psychoeducation and more integrated treatment programmes based on active participation of both general practitioners and practising specialists in combination with psychosocial support.

The organisation

The need to improve the outpatient treatment of patients with depressive disorder rests on five main arguments

1. the prevalence of depressive disorder among the population is high and increasing
2. only a minor proportion of patients with depressive disorder receive a correct diagnosis and treatment and the long-term course of illness is poor
3. prophylactic treatment and "shared care" improve course of illness
4. The professional standard of present-day outpatient treatment varies considerably
5. No specialised outpatient treatment facilities are available for patients with special treatment needs.

Antidepressant and psychological treatment reduce *mild and moderate depression* and prevent relapse of depression. Shared care (collaborative care between general practitioners and specialists in psychiatry) increases rates of response/remission and increases patient satisfaction.

Outpatient treatment of patients with *severe forms of depressive disorder* should include the following prophylactic treatment elements if it is to comply with the highest standard presently known:

- *pharmacotherapy*. Prophylactic antidepressive pharmacotherapy is the best-documented treatment of moderate to major depressive disorder. There is a need for regular quality assurance, quality development and research regarding long-term treatment with antidepressants. Likewise there is a need for improved knowledge of how the patients can best be kept on treatment
- *psychological treatment*. The evidence for the effect of psychotherapy as prophylaxis in the treatment of patients with depressive disorder is weaker than the evidence for the effect of prophylactic pharmacotherapy. Studies indicate, though, that psychotherapy in combination with pharmacotherapy can improve the course of the disease in patients with major and periodically hospitalisation-requiring depressive disorder. Many patients request psychotherapy at an early stage. Psychotherapy of patients with depressive disorder necessitates knowledge of and experience with treatment of depressive disorder as well as specific education and experience with psychotherapy for depressive disorder. It is considered important to expand and maintain expertise in psychotherapy, including the possibility to educate therapists within the field

- *relatives.* There is a strong desire among patients for their relatives to be better informed about and more involved in their treatment than is presently the case.

The majority of patients with mild to moderate depressive disorder are treated on an outpatient basis in the primary sector, especially by practising psychiatrists, general practitioners and practising psychologists. Patients with severe depressive disorders are treated partly in the primary sector and partly in district psychiatry clinics or outpatient clinics in psychiatry wards.

At present the treatment is dispersed among many different types of healthcare professionals, and there is considerable variation regarding knowledge of diagnosis, professional attitude and treatment practice among health care professionals who treat patients with depressive disorder.

It will continue to be the general practitioners who treat the greatest proportion of patients with depressive disorder. It is necessary to improve the knowledge of diagnosis and treatment of depressive disorder among general practitioners through guidance and clinical advice. Detailed knowledge of how best to design educational programmes and treatment programmes for use in general practice is lacking, however.

A small proportion of patients with depressive disorder need special treatment. This applies to patients with major and periodically hospitalisation-requiring depressive disorder and patients with depressive disorder and concomitant physical or other mental disorders. The prognosis for these patients is poor, and the risk of readmission and suicide is great.

Another group of patients with depressive disorder having special treatment needs are patients with major depressive disorder and forms of depressive disorder that are complicated to treat.

A third group of patients with depressive disorder having special treatment needs are women who are pregnant or considering pregnancy. Discontinuation of antidepressant drug treatment during pregnancy is associated with a high risk of relapse of depression, but on the other hand, treatment with antidepressants may be associated with increased risk of foetal abnormalities.

The need to improve the outpatient treatment of patients with bipolar disorder rests on five main arguments

1. bipolar affective disorder is one of the most serious psychiatric disorders, and a large proportion of the patients develop a chronic course with recurrent major episodes of illness and a reduced level of psychosocial functioning. In a large proportion of patients with bipolar affective disorder the course of the disease is complicated by abuse of alcohol or medicine
2. from the treatment perspective bipolar affective disorder is extremely complicated, and the patients periodically need intensive multidisciplinary treatment
3. combined pharmacological and psychological prophylactic treatment improves the course of illness
4. this patient group has “fallen through the net” in that the present treatment structure does not include any outpatient treatment programmes specifically directed at patients with bipolar disorder
5. no specialised treatment offer is available for patients with special treatment needs.

Outpatient treatment of patients with bipolar affective disorder should include the following prophylactic treatment elements if it is to comply with the highest standard presently known:

- *pharmacotherapy.* Pharmacotherapy is the best-documented prophylactic treatment of patients with bipolar affective disorder, and the majority of patients need permanent pharmacotherapy. Pharmacotherapy of patients with bipolar affective disorder necessitates great professional expertise and experience, and the treatment has to be continually monitored and adapted to the condition of the individual patient
- *psychological treatment.* The evidence for the effect of prophylactic psychological treatment of

bipolar affective disorder is weaker than the evidence for the effect of pharmacotherapy, but newer studies indicate that certain forms of psychological treatment – psychoeducation and cognitive therapy – are markedly effective in combination with pharmacotherapy. Psychological treatment has an independent effect, and it enhances patient adherence to pharmacotherapy. Psychoeducation and cognitive therapy necessitate a general knowledge of and experience with the treatment of bipolar affective disorder, as well as specific expertise in psychological treatment of bipolar disorder

- *psychosocial support.* Many patients with bipolar affective disorder have a problematic relationship with their family and friends, and their possibilities to cultivate recreational interests are diminished. Their association to the labour market is considerably poorer than could be expected from their educational and social status. Patients with bipolar affective disorder periodically need special support and guidance regarding how to maintain and improve their network, education and job competence.

Advantages and disadvantages of centralised affective disorder clinics (organisational aspects)

There is little evidence as to which concrete organisational measures best ensure optimal treatment of patients with major affective disorder. The recommendations set forth a number of treatment objectives that can in principle be implemented through various different organisational models.

The advantage of the present decentralised outpatient treatment of patients with major affective disorder is the closeness and continuity in the treatment. The disadvantages are that it varies due to the different interests and knowledge of the various therapists and that it is difficult to build up experience and specific expertise in treatment and research. Neither is it presently possible for patients with particularly complicated disorders to be referred to specialist assessment and/or treatment.

One of the advantages of centralised outpatient treatment facilities is that experience and expertise in treatment and research is ensured by a sufficiently large patient population, in contrast to the present decentralised treatment structure, where the individual physician in the district psychiatry centre or the individual practising psychiatrist or general practitioner will only see a few patients.

Another advantage of centralised outpatient treatment facilities is the possibility to provide treatment encompassing the treatment elements that are known to be effective, namely qualified pharmacotherapy and psychological treatment and psychosocial support. Combination treatment with pharmacotherapy and psychological treatment can enhance patient adherence to treatment, reduce the risk of relapse, reduce the symptoms and improve the level of psychosocial functioning. Practising psychiatrists and general practitioners rarely have the possibility to provide combination treatment. In some parts of the country, district psychiatry centres can provide outpatient treatment to very severe cases of affective disorder, but the treatment possibilities are geographically heterogeneous and in many places, especially in Greater Copenhagen, are considered to be inadequate. Most district psychiatry centres have built up expertise in and predominantly treat patients with major psychoses such as schizophrenia.

The establishment of central outpatient treatment facilities would also enable the referral of patients who are particularly difficult to treat and enable second opinions to be made.

The risk associated with the establishment of central treatment facilities is that they could entail a break in the continuity of treatment. The break in continuity could be counteracted by close cooperation between the central treatment facility and the primary therapist, in most cases the patient's general practitioner.

There is a great need to investigate which educational models and treatment models can enhance the efficacy of the treatment of patients with affective disorder, as well as for regular quality assurance and quality development of the treatment of patients with affective disorder. Additionally,

there is a need for research in the diagnosis and treatment of affective disorder. These needs are difficult to meet through the present decentralised treatment structure, but require treatment facilities with a larger patient population and experience in the treatment of a specific disorder.

It is well documented that patients with major affective disorder are at great risk of developing a more chronic course of illness with diminished psychosocial functioning, frequent readmission and suicide. A plausible assumption, but one that is not founded on research findings, is that *early intervention* with integrated outpatient treatment can improve the prognosis for this group of patients. It is therefore important that the validity of this assumption be tested.

The patient

Patient wishes

A large proportion of the patients would like the possibility to be referred to outpatient assessment and treatment at central treatment facilities. In response to a nationwide questionnaire survey among patients with major affective disorder, undertaken in 2003 in relation to the present HTA, more than half of the patients stated that they would prefer to receive outpatient treatment at a central specialised treatment facility rather than from their usual therapists. The same survey revealed that the patients were generally satisfied with the treatment. This did not apply to the involvement of relatives in the treatment, however, and involvement of relatives therefore needs to be accorded higher priority in any future treatment structure.

The economy

Economic aspects

Based on foreign clinical trials it is estimated that systematic outpatient combination treatment consisting of prophylactic pharmacotherapy and psychotherapy/psychoeducation can reduce bed-day utilisation by 20% for patients admitted for depressive disorder and by 40% for patients admitted with bipolar disorder in the first years after discharge.

The establishment of five to ten central outpatient treatment facilities will entail additional costs for setting up and running these treatment facilities. The economic model calculations indicate that outpatient treatment in affective disorder clinics can be cost-neutral as clinical trials show that this treatment reduces the hospitalisation needs of the patients. It is decisive, though, that a reduction in hospital bed-day utilisation is actually realised as a result of treatment in affective disorder clinics. Bed-day utilisation by the patients will have to be reduced by at least 10-15% the first two years after the patients' start at the clinics in order to cover the cost of the affective disorder clinics. If that is not the case, treatment in the affective disorder clinics will be a relatively more expensive form of treatment. In principle, the financial saving resulting from any decrease in bed-day utilisation should be reassigned to operation of the affective disorder clinics, which are a relatively more expensive form of outpatient treatment than the outpatient treatment presently available.

In principle, the potential savings in bed-day utilisation should be able to finance the costs for:

- supervision, guidance and education of the primary therapists (general practitioners, etc.) primarily responsible for outpatient treatment of patients with depressive disorder (shared care)
- specialised outpatient treatment of a small group of patients with severe treatment-resistant depressive disorder
- specialised outpatient treatment of patients with bipolar affective disorder
- second opinion assessment and the guidance and education of therapists in the diagnosis and treatment of patients with major affective disorder

- specialised outpatient treatment of pregnant women with major depressive or bipolar affective disorder
- research in affective disorder.

Difficulties

Nationwide outpatient centralised treatment of patients with major affective disorder necessitates the establishment of at least one treatment facility in each of the five Danish administrative regions.

In the short term the establishment of new outpatient treatment facilities with a need for highly qualified personnel could be associated with difficulties due to a general lack of qualified psychiatric personnel. In the longer term it is likely that improved educational possibilities and specialisation of the treatment could enhance interest in this psychiatric speciality and thereby enhance the personnel recruitment base.

This organisational change, in which the outpatient treatment of a patient group is moved from the current therapists, could potentially entail conflicts of interest.

Pilot projects

Knowledge of the influence of organisational structure on treatment efficacy in patients with major affective disorder is lacking. It is therefore natural to propose the establishment of pilot projects to test the effect of various organisational and treatment measures. It is important to underline that some questions will be difficult to answer on the basis of pilot projects alone. These include the effect of a shared care model, conditions applying to special patient groups such as patients with particularly complicated disorders and pregnant women, and enhanced possibilities for education and research in affective disorder. It is also difficult to measure the significance that the increased focus and specialisation of treatment as regards ensuring destigmatisation and acceptance of fellow citizens with mental disorders.

It is the organisational framework that determines the possibilities for the future treatment, education and research in affective disorders. It is therefore difficult to test the effect of organisational changes before they have been implemented. Conversely, it is important to point out that inappropriate organisational conditions can hinder development within a treatment area. It would be wise to regularly evaluate the consequences of organisational changes.

The authors of this HTA-report makes the following general recommendations

It is recommended that consideration be given to supplementing the current organisation of outpatient treatment of patients with depressive or bipolar affective disorder with 5-10 specialised clinics corresponding to 1-2 clinics in each of the coming five administrative regions of Denmark.

It is recommended that the purpose of *affective disorder clinics* should be:

Concerning depressive disorder

- to provide focussed supervision, guidance and education of the primary sector health care professionals (general practitioners, etc.) regarding outpatient treatment of patients with depressive disorder (shared care or collaborative care)
- to provide assessment (second opinion) and treatment of patients with major depressive disorder and forms of depressive disorder that are complicated to treat
- to provide guidance and treatment of women with depressive disorder who are pregnant or considering pregnancy.

Concerning bipolar disorder

- to provide treatment of patients with bipolar disorder during the phase around the onset of illness (diagnosis of the disorder) and during unstable phases
- to provide guidance and treatment of women with bipolar disorder who are pregnant or considering pregnancy.

General

- that outpatient affective disorder clinics should be a supplement to the present decentralised treatment
- that the clinics should provide treatment of the highest professional standard
- that the treatment should consist of both pharmacotherapy and psychological treatment
- that the clinics should regularly perform quality assurance and quality development of the treatment
- that the clinics should provide education and perform research in diagnosis and treatment of affective disorder.

It is recommended that patients with bipolar affective disorder be referred to specialised outpatient facilities at the time they first seek treatment for the disorder, after the first admission for the disorder or possibly during the phase in which the final diagnosis has not yet been made. It is also recommended that the patients be referred to specialised outpatient facilities during “unstable” phases of the disorder, i.e. phases during which the patients have pronounced symptoms of the disorder or are abusing alcohol or medicine, as well as in connection with stressful psychosocial events or social isolation. Finally, it is recommended that all women with bipolar affective disorder who are pregnant or considering pregnancy be referred to specialised outpatient facilities.