

DEPRESSION

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# The review of antidepressants

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A summary

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# Why carry out pharmaceutical reviews?

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This is a summary of the TLV's review of antidepressants. It is the fifth pharmaceutical review of the total of 49 therapeutic groups which the TLV is tasked with reviewing. On adopting new reimbursement rules in October of 2002, it was not practically possible to review all medicines according to the new rules overnight. Therefore, the LFN is now conducting a review of approximately 2,000 medicines to see if they should continue to be given reimbursement status in the future. Each of the medicines will be tried according to the new rules and will either retain or lose reimbursement status or be granted restricted reimbursement.

## More health for our money

The purpose of the new reimbursement rules is to extract as much health as possible for every tax crown expended on medicines. We eliminate those medicines that do not show sufficient effectiveness in relation to what they cost. However, this does not mean that we aim only to have inexpensive medicines in the pharmaceutical reimbursement system. If a medicine has positive effects on a person's health and quality of life, and on a socio-economic level as a whole, then it may also be expensive.

## Three principles for our decisions

In reimbursement decisions for a medicine, we shall evaluate whether or not it is cost-effective. This means that we weigh the effectiveness of the medicine against its cost. We also incorporate other principles into our evaluation: the needs and solidarity principle, which means that those who have the greatest medical needs shall receive more of our healthcare resources than other patient groups; and the human value principle, which means that we must respect the equal value of all individuals.

## 49 therapeutic groups to be reviewed

In this review we are evaluating medicines in one therapeutic area after another. The review encompasses a total of 49 groups of medicines and the order in which they are tried is determined by how large the sales figures were for each respective group in 2003. The medicines that sold the most will be reviewed first. At [www.tlv.se/genomgang](http://www.tlv.se/genomgang) we present the therapeutic groups being reviewed right now, the medicines included in those reviews and more.

## Extensive research and groundwork

Before any decision is made, we perform a comprehensive investigation and analysis of data on medical effect and cost-effectiveness which we request from pharmaceutical companies in regard to their medicines. We also review the scientific, medical, and health economic literature available for the group of medicines to be reviewed. In addition, we sometimes need to construct our own health economic models. We publish each completed review in a final report. The report documents the existing body of scientific knowledge for the group in question. We also prepare a synopsis of the report to be printed separately.

## Assessment by independent external experts

The assembled body of knowledge in regard to medical effect and health economic documentation which we present in the final report has been assessed by independent external medical experts. The report has also been circulated for comments to the SBU (The Swedish Council on Technology Assessment in Health Care), Medical Products Agency and the National Board of Health and Welfare. The companies and patient organisation groups concerned, as well as the county councils' pharmaceutical reimbursement group, have also had the opportunity to give input.

# The review of medicines against depression

## The TLV's decisions in brief

In the review of medicines used for treating depression the TLV has found that there is a need for a number of medicines to treat depression and anxiety. These illnesses lead to great societal costs and to great losses in quality of life for the persons afflicted. The medicines in this therapeutic group are not the most expensive and a successful treatment is cost-effective. It is urgent to reimburse a broad range of medicines because less than half of all treated patients receive sufficient effect from the first treatment. Many experience side-effects leading to the cessation of treatment or that they must try a number of medicines until they try one which works. All active substances in the therapeutic group of antidepressant medicines therefore are granted continued reimbursement with one exception:

The active substance fluvoxamine is removed from the reimbursement system.

According to our analysis the active substance fluvoxamine results in a considerably lower number of cured patients than the other antidepressant medicines. The cost of treatment is considerably higher than for the SSRI medicines where there is competition in the form of generics.

For pharmaceutical substances where there are copies available there is no reason to grant continued reimbursement for expensive brand name drugs. We have decided that this group of medicines may not cost more than 3 Skr per tablet in the strength sold most of, in packages in sizes of 100 tablets or the equivalent. This has led to a number of companies decreasing their prices. The original brand name drugs which did not decrease their prices and are thereby removed from the reimbursement system are

- Remeros (mirtazapine)
- Fontex (fluoxetine)
- Seroxat (paroxetine).

These decisions free up 40 million Skr and come into effect on the 1st of April, 2009.

The TLV, Dental and Pharmaceutical Benefits Agency, has completed its review of the therapeutic group of medicines called antidepressants. The review was presented in December 2008. This is a summary of the report which is available for download on [www.tlv.se/depression](http://www.tlv.se/depression) and may also be ordered by mailing to [registrator@tlv.se](mailto:registrator@tlv.se)

## Antidepressant medicines - areas of use

Antidepressant medicines are not only used for treating depression but also for various anxiety-related symptoms. We deal with the use of the medicines for treating depression and anxiety but in this evaluation put the emphasis on the treatment of depression. There are both older and newer medicines in this therapeutic group. Usage is dominated by the SSRI medicines, which represent two-thirds of usage and comprise a number of well-known brands such as Cipramil and Zoloft.

## As much health as is possible for our tax money

The review of medicines used for treating depression is part of the TLV's general review of the entire list of

reimbursed medicines. The objective of the review is to ascertain if medicines should continue to be part of the high cost threshold. There are three principles which shall lay the foundation for our decision for whether a medicine should be reimbursed using State funds:

- The principles are
- cost-effectiveness principle
- needs and solidarity principle
- human value principle.

In order to judge whether usage of a medicine is cost-effective we weigh the value obtained against the cost from a societal perspective. We also consider that those in the greatest medical need shall have more of the resources available within healthcare. The equal value of all people is also part of our evaluation. The purpose of our work is to extract as much health as possible for the tax money expended on medicines. Our reviews free up money which can be used for other urgent areas of treatment within healthcare.

## The fifth review

This is the fifth review we are presenting. The first one was on migraine medicines and was completed in 2005. Following this we presented the review of medicines against stomach acid, then one on medicines used for treating asthma, COPD and coughing, and then the review on medicines against hypertension. You can read more on these and the currently ongoing reviews on our website at [www.tlv.se/genomgang](http://www.tlv.se/genomgang).

## What is depression and anxiety?

Depression is a word used in many different contexts and can cover many different meanings. In a medical context the term depression is used to describe a cluster of symptoms which often occur together, but where the underlying causes may vary. Depression is characterised by extended periods of dysphoria, feelings of meaninglessness and hopelessness. For doctors to be able to see and diagnose "depression" it is also necessary for the patient to have difficulties in his/her working or private life. Many patients suffering from depression are also afflicted with anxiety. Anxiety can be described as a group of non-specific unpleasant symptoms which are similar to the reactions to horror and fear. The threat can be experienced by the patient as external or internal. Conditions counted as belonging to the sphere of anxiety are phobias, panic attacks, compulsive thoughts and compulsive actions.

## 4 to 10 percent meet the criteria for depression

Depression-related illnesses are one of the most common causes of ill health, productivity losses and the inability to work in the world. Sweden is no exception. These illnesses carry great losses in quality of life both for those afflicted and their closest circle. It is estimated that 4 to 10 percent of the adult population in Sweden meet the criteria for depression. The number of women is twice as high as the number of men. Those affected by depression once are often at risk again, at least one more time during their lives. Depression can also be connected to severe physical diseases such as cancer and cardiovascular diseases. Many affected by the disease also have other psychological disorders.

## 700 000 people treated during 2007

According to the latest figures the annual societal cost for depression and anxiety is approximately 40 billion Skr. The societal costs arising from these conditions are costs for healthcare, including medicines, sick leave, early pension and also premature death. Every year about 1000 people commit suicide in

Sweden, of which a large share is due to depression. Not even half as many die from traffic accidents each year. Just over 700 000 people were treated with antidepressants during 2007. According to a study by the Board of Health and Welfare this usage is not unreasonably large, but there is probably over-treatment of certain patient groups and under-treatment of others. The costs for antidepressant medicines in 2007 were 990 million Skr and society reimbursed these costs to the value of 660 million Skr, which was approximately 3 percent of the total pharmaceutical reimbursement bill in Sweden. The decisions in this review will free up 40 million Skr per year.

## SSRI medicines dominate

There are different ways of treating depression and anxiety. Medicine is one treatment alternative and psychological treatment another. During the spring of 2009 the National Board of Health and Welfare will present national guidelines for the treatment of depression and anxiety. With these national guidelines treatment using pharmaceuticals will be put into a larger context. Our task is to take a stance on which antidepressants should be included in the pharmaceutical reimbursement system. We have evaluated the 17 active substances included in the ATC system's group for antidepressant drugs, N06A.

Up until the 1980s tricyclics were mainly used as antidepressants. These medicines are effective but can have uncomfortable side-effects. During the 1980s a new class of antidepressants called SSRIs were launched. One of the first of these was Prozac, sold in Sweden under the brand name Fontex. These drugs are also effective but do not have as much uncomfortable side-effects as the tricyclic drugs. This led to a heavily increased use of antidepressants during the 1990s. Other substances have also emerged such as mirtazapine (Remeron and Remeron-S), venlafaxine (Efexor) and duloxetine (Cymbalta). The use of antidepressants has continued to increase since the year 2000, but not at the same rate as during the 1990s. SSRI drugs stand for the greatest use. In 2006 they made up almost 70% of the volume in the range of antidepressant drugs.

## Our own meta-analysis and health-economics analysis

A great number of clinical studies have been carried out to document the effect of antidepressants. The factual material is quite comprehensive but simultaneously difficult to interpret and too contradictory to answer the question of differences in effect between these medicines.

To augment the existing reviews we have carried out our own review and analysis, focused on how many patients recover following treatment with antidepressants. The analysis is based on information on 20 000 patients treated for depression.

We also needed to carry out a health economics analysis in order to understand how cost-effective the treatment of depression using antidepressants is in Sweden.

### **SSRI as first line. Important with a broad range of products**

According to most current recommendations the treatment of depression should be started using SSRI drugs. This concurs with what we have found to be most cost-effective. However, we can also state that not even half (only 40-50 percent) of the patients achieve a satisfactory result from the medicine they first try as a treatment. For some there is no effect. For others the medicine may give an effect but due to issues such as side-effects it is quite common that patients stop treatment. Changing to another medicine can have an effect, regardless if the switch is to another medicine within the same drug class or to a medicine in another drug class. For this reason it is important that there are a number of substances to choose from within the high cost threshold.

On the whole we see that antidepressants have an effect on treating depression, but there are differences in efficacy between different substances. In an analysis limited to the four SSRI medicinal preparations which have generic alternatives, there is in practice no difference in efficacy. In our health economics analysis the result indicates a somewhat better effect for the SSRI substance called escitalopram (Ciprallex) than for the other antidepressants when it comes to how many patients recovered. The model also points to a somewhat lower societal cost even if the difference is small. The medical efficacy of fluvoxamine (Fevarin) does not however measure up to its current price.

### **Expensive original brand drugs lose reimbursement – all substances except for one remain in the reimbursement system**

In order for as many patients as possible to receive satisfactory treatment for depression and anxiety it is important that there is an opportunity to test one's way towards the best treatment result. We have taken this into account and decided that all substances in the antidepressants group shall continue to be

reimbursed, excepting the SSRI substance fluvoxamine (Fevarin). The price for fluvoxamine is considerably higher than for SSRI copies. Fluvoxamine's medical effects and qualities do not motivate the higher price.

In the group of antidepressant medicines there are original brand name drugs whose patents have expired, and copies which have the same medical effect. Our evaluation shows that there are price differences between original brand name drugs and the copies. We can also see that doctors prefer to prescribe the more expensive originals despite there being copies available with the same medical effect at a considerably lower price. It is not cost-effective to reimburse the original brand name drugs whose patents have expired as the copy is much cheaper. Some of the original drugs result in a treatment cost of 8 Skr per day, whereas the comparable cost for treatment per day for the cheapest copy is not even 1 Skr.

For this reason we have decided that expensive original brand drugs, which have cheaper generic copies, shall no longer be reimbursed. We have also decided that the highest price for a tablet within the SSRI group shall be 3 Skr in the most popular strength in the 100-tablet package size. Due to this most of the companies chose to decrease their price for their original brand drugs in order to retain reimbursement status in the future.

These decisions come into force on the 1st of April, 2009.

### **More expensive medicines can be more cost-effective**

As depression and anxiety cause both suffering and decreased quality of life for those afflicted with the conditions as well as considerable societal costs, small differences in effect can motivate the price differences which exist. In relative numbers the price differences may appear to be large, but in absolute terms, that is in Swedish crowns, they are small. Antidepressants are in other words not in the expensive range of medicines. Both our review and the reviews conducted by others indicate that some new and more expensive medicines may have a better effect and cost-effectiveness than older medicines.

### **The healthcare system does not have the information it needs to treat patients effectively**

Depression-related illnesses are so common that they should be treated as a health problem for society as a whole. Pharmaceutical treatment can contribute to alleviating the symptoms of depression-related conditions but a precondition for this is a choice of well-researched antidepressants for treating patients. Another precondition for the best use of pharmaceuticals is a collaboration which functions well between the caregiver and the patient. The cost for making the wrong decision could be high, in both human and economic terms.

We see gaps in the information needed by those working in healthcare to make decisions in regard to the treatment of patients – not least in comparing medicines to other forms of treatment.

Our review gives more knowledge on antidepressants to those in positions of responsibility within healthcare. But we also realise that there are many areas where research is needed for depression and anxiety, and that more knowledge on these medicines is needed for patients to receive an effective treatment.

## **What makes a cost-effective medicine?**

When we try whether or not a medicine should be granted reimbursement, we shall evaluate whether or not the medicine is cost-effective or, put more simply, if the medicine is worth its price. That is if treatment with the medicine costs an amount of money reasonable for society in relation to the healthcare benefits that the medicine delivers. How large the cost of a medicine is, is therefore not a good measure of whether or not we are using the right medicine or even a sufficient amount of it. However what is important, is that the use of a medicine is cost-effective, not just for healthcare, but for society as a whole. Investigating how cost-effective a medicine is gives us a foundation for being able to prioritize and therefore use our resources in the best possible way

### **The value derived is balanced against the cost incurred**

What then, does it mean, for use of a medicine to be cost-effective? Firstly, it does not mean that all inexpensive medicines are cost-effective, while more expensive ones are not. When determining if a medicine is cost-effective, all the expenses associated with the medicine being used must first be added up. There is, first and foremost, the cost of the medicine. However, costs can also arise due to the patient visiting a physician to receive the medicine, if any other additional healthcare assistance is needed, as well as any side-effects that the medicine may cause.

This total cost is weighed against the benefit that the medicine provides, primarily in the form of healing, alleviation of pain and increased quality of life for the patient. One must also consider that use of the medicine may also entail savings in other areas of healthcare, in that the patient does not need to visit the doctor as often, avoids hospitalisation, operations, etc. However, all this is still not enough to gain a societal perspective. We also have to account for whether or not a medicine allows a patient to work and earn a living and contribute to our common welfare instead of being on sick leave or even being forced into early retirement. Here benefits go to the individual in production, and to the state, who then avoids fees for sick leave and early retirement. If the patient is older, it is possible that use of the medicine may lead to the individual's being able to take better care of himself or herself and thereby require less assistance from elderly care services or relatives. This is also a socio-economic benefit on the plus side of a cost-effectiveness analysis

### **Cost-savings are not obligatory**

Sometimes the positive effects of a medicine are so great that they entirely compensate for the medicine's costs. Then it can be said that the treatment is cost-saving. But we do not make such high demands to consider use of a medicine to be cost-effective; in other words that it has a reasonable cost when seen in relation to the effect and therefore should be reimbursed. That people are healthy, without pain, and able to live a more normal life by taking a medicine constitutes a great value for which society is prepared to pay.



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