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THE TREATMENT OF DEPRESSION IN CLINICAL PRACTICE

A public health perspective

By

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List of papers

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Introduction

Depression is a public health concern of great magnitude and possibilities of effectively treating the illness have been available for more than 40 years. That these treatments were under-used is a well known fact, and the expression “the iceberg of depression” has illustrated this (1). The use of antidepressants has steadily become more common, however, and during the last decade it has grown rapidly (2-4). Although this increasing use of antidepressants has been considered rational and a probable cause of decreasing suicide rates (2, 5), concern has also been expressed regarding over-use and misuse. Allegations have been put forward that the use of antidepressants continues for years without any benefit and without any attempts to withdraw the medication. The indications for treatment have been questioned (6). Alarming messages have been voiced that “½ million Swedes use antidepressants”, that the medications are used in order to suppress “normal emotional reactions” and that human problems are “medicalized” (7-11). Based on the generally small effect sizes of antidepressant medications in clinical trials, it has been claimed that the placebo effect in treating depression is as good as the effect of antidepressant medication, and also that the antidepressive effect as such does not contribute to the decrease in suicides (12). In the recently published report from SBU - the Swedish Council on Technology Assessment in Health Care - it is stated that there is no evidence that it would be of value to screen individuals for depression at primary care centers (13).

This project focuses on the treatment of depression in a public health perspective and it aims at finding answers to questions like: Are antidepressants prescribed to too many people? Or to too few? Are antidepressants widely used on proven indications? Are the antidepressant treatments going on “for ever”? Or in summary, would it be of value for the public health to further improve the detection and treatment of depression? The project approaches these questions in four studies. It considers firstly, the use of antidepressant medications in the

general population, secondly the indications and outcome of antidepressant treatments in individual patients at primary care centers, thirdly, the use of antidepressants in individuals committing suicide, and fourthly, the actual treatment received by the depressed individuals in the general population .

The Swedish county of Jämtland was found to be very suitable for this study. Jämtland county had, compared to other Swedish counties, a history of a low use of antidepressants while the suicide rates were among the highest in the country (14). An unique source of data was the prospective individual-based prescription database, going on in Jämtland since 1970, which makes it possible to study the individual purchases of medications on prescription. Finally, an intervention had been going on since 1995, a continuous educational effort for general practitioners focused on the detection and treatment of depression, not least in an attempt to reduce suicide rates (15-18). This education program has been followed by a larger increase in the use of antidepressants than in Sweden on average, and furthermore, the high suicide rates have been reduced to the average Swedish level (19, 20).

Depression

History of depression

The psychiatric use of the word “depression” was introduced in the middle of the 19th century by the German psychiatrist Wilhelm Griesinger, although descriptions of depression had been described earlier by e.g. Arateus (AD 150): “And yet in certain of these cases there is mere anger and grief and sad dejection of mind.....those affected with melancholy are not every one of them affected according to one particular form but they are suspicious of poisoning or flee to the desert from misanthropy or turn superstitious or contract a hatred of life. Or if at any time a relaxation takes place, in most cases hilarity supervenes. The patients are dull or stern, dejected or unreasonably torpid.....they also become peevish, dispirited and start up

from a disturbed sleep". Descriptions of the association of depression with suicide are already given in the Old Testament I, Samuel 31:3-5, when king Saul committed suicide.

Characteristics of depression

In 1896 Kraepelin offered the following symptoms of depression: mental retardation, tiredness, inability to concentrate, slow-wittedness, hopelessness, lack of confidence, social withdrawal, loss of spontaneity and initiative, self neglect, inactivity, and without hallucinations or marked delusions. There is a feeling of illness but the insight is often partial. Somatic complaints also accompanied the depressive states: reduced appetite and loss of weight, disturbed sleep or insomnia. These symptoms could then progress into stupor, or a sense of persecution and guilt often in the form of delusions, and such ideas could be repeated monotonously and without affect (21). These early descriptions seem modern.

The symptoms that constitute a major depressive episode are defined in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) from 1994 (22) (Appendix 1.) and a major depressive episode can be part of a major depressive disorder (single episode or recurrent) or bipolar disorder.

Other disorders with depressed mood characterized in DSM-IV are: dysthymic disorder, mood disorder due to a general medical condition, substance-induced mood disorder, cyclothymic disorder and adjustment disorder with depressed mood.

Depressive disorders in the general population

The prevalence rate of depression is mainly expressed as either a point or a period prevalence rate, but life time prevalence rates can also be used although they are much less reliable (23) e.g. the Cross-National Study of 10 countries (Canada, the U.S., Puerto Rico, France, Italy, West Germany, Lebanon, Taiwan, Korea, and New Zealand) all used the Diagnostic Interview Schedule for DSM-III (DIS) but showed great variability (1.5% in Taiwan to 19%

in Beirut). In this study major depressive disorder was twice as common in women than men but bipolar disorder was equally distributed (24)

The point prevalence rate of major depressive disorder has generally been estimated to be about 4% and if bipolar disorder is added it is 5% (23, 25).

Methods and instruments in modern epidemiological studies

Modern community surveys use standardized interview instruments in order to study the prevalence of depressive disorders. These interviews are designed to be administered by trained lay interviewers. In connection with the U.S. Epidemiologic Catchment Area (ECA) study (26), a comprehensive structured interview, the National Institute of Mental Health Diagnostic Interview Schedule (DIS) was developed. By combining aspects of the DIS and the Present State Examination (27), a more structured diagnostic interview - the Composite International Diagnostic Interview (CIDI) (28) - was developed, and this provides a DSM-III-R (the predecessor of DSM-IV) diagnosis. Another approach to the study of psychiatric epidemiology is the two-phase epidemiological survey (29) that has been used to assess the prevalence of depressive disorders. The first step is to identify possible cases of depression in the study population by using a questionnaire such as the Beck Depression Inventory (BDI) (30), and the second step is to interview the possible cases in order to establish the diagnosis utilizing structured instruments like the Structured Clinical Interview for DSM-IV (SCID) (31) or the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (32). The SCAN interview yields a DSM-IV or ICD-10 diagnoses.

A third study approach is the longitudinal design where the risk of depressive illness can be calculated.

Recent epidemiological surveys using structured layman interviews in the general population.

During the 1990s, trained lay interviewers used the standardized interview instrument Composite International Diagnostic Interview (CIDI), in order to establish a DSM-III-R diagnosis of major depressive disorder in several studies. The National Comorbidity Survey (NCS) in the U.S, where a random sample of 8098 subjects aged between 15 and 54 years, was selected and 82.6% responded between 1990 and 1992 (33), the Netherlands Mental Health Survey and Incidence Study (NEMESIS) where a representative sample of 7076 persons aged 18-64 years were interviewed at home in 1996 with a 69.7% response rate (34), and a Norwegian psychiatric epidemiological study performed in Oslo between 1994 and 1997 where a random population sample of 3590 subjects aged 18-65 years was selected and the response rate was 57.5% (35). The NCS was replicated in 2001-2002 (NCS-R) and designed to update the prevalence of DSM-IV disorders (36). Nine thousand and ninety subjects age ≥ 18 years were asked to participate and the response rate was 73%. These studies estimated the life time and the 12-month prevalences of mental disorders including major depression. The 12 month prevalence of major depressive disorder in the NCS was 10.3% (with an estimated prevalence of current major depression of 4.9%), in the NEMESIS 4.3% (6 month prevalence), in the Oslo study 7.3% and in the NCS-R 6.6%.

Recent (after 1990) findings of prevalence rates in large populations (> 3000 subjects) when CIDI was used for diagnosis are summarized in Table 1.

Table 1. Recent epidemiological community survey prevalence rates (%) for major depression (MD)

Author, year	Country	N	Age group	% MD
Kessler, 1994	USA	8098	15-54	10.3
Spijker, 2001	Netherlands	7076	18-64	4.3
Kringlen, 2001	Norway (Oslo)	3590	18-65	7.3
Kessler, 2003	USA	9090	≥18	6.6

Recent two-phase epidemiological surveys in the general population

The European Outcome of Depression International Network (ODIN) study of depressive disorders included 9 centres (5 urban and 4 rural) in Europe (37) and 14 387 subjects belonged to the target sample. The Beck Depression Inventory was used for the screening and SCAN for the interview. The prevalence of depressive disorders found (ages 18-65) varied considerably between the centres (range 2.6-17.1%) probably due mainly to the different sampling procedures employed, and the combined sample gave an overall prevalence of 8.6%.

Epidemiological studies of risk for depressive disorder in the population

The prospective Lundby study in 1957 and 1972 of a geographically defined normal Swedish population of 2612 has found that until 70 years of age, the cumulative probability of suffering a first episode of depression was 27% in men and 45% in women. Although they did not use DSM criteria, the authors have reported that a majority fulfilled such criteria (38).

Summary

Depression is a common illness in the general population. Prevalence rates are usually presented as point or period prevalence rates (ca. 5 % and 10 % respectively).

Burden of Depression

The World Health Organization conducted the Global Burden of Disease study in 1992. The World Bank and Harvard University had developed a measure to allow for comparisons between many (more than 100) different disease conditions. The measure, called the Disability Adjusted Life Years (DALYS), includes both death (years of life lost because of premature death=YLL) and disability (years of life lived with disability=YLD) (39). The years of life lost due to a disease was added to the years lived with the disability due to the disease itself (DALYS=YLL+YLD) (40). The research data showed that the burden of mental illness had been heavily underestimated; using YLD it was found that major depression was the leading cause of disability world wide, and, using DALYS, major depression was the second (to ischemic heart disease) leading disease burden in established market economies (41).

Major depression has a median onset in the mid-to late-20's, bipolar disorder around the age of 20 (24), so that depressive disorders thus frequently start early in life. Major depression is a highly recurrent (75-80%) disease (23). It tends to run a chronic course. In a study by

Solomon et al (42), subjects who were treated for depression and who had recovered from their intake episode of unipolar major depressive disorder were prospectively followed for 10 years within a multicenter naturalistic study. Survival analytical techniques were used to examine the probability of recurrence after recovery from the index episode. It was found that the cumulative probability of recurrence of unipolar major depression for a patient with one recurrence at 1 year after recovery was 25%; at 2 years, 42%; and at 5 years, 60%. The cumulative probability of recurrence for a patient with two recurrences at 1 year after recovery was 41%; at 2 years, 59%; and at 5 years, 74%. The risk for recurrence progressively decreased as the duration of recovery increased. An early onset and a chronic course thus produce substantial disability across the life span.

The direct (in- and out-patient care, drugs) and indirect (sick leave, morbidity and premature mortality) costs for depressive disorders (cost of illness) to the Swedish society have been estimated to be SEK 10.4 billion in 1997 (an increase of 55% from 1987, although the costs for in-patient care decreased) (43). During the same period, the sales of antidepressant medication increased four-fold in Sweden. The major part (71%) of this increase took place between 1994 and 1996. Between 1990 and 2000, the change in the economic burden of depression was estimated in the U.S. A human capital approach was used and prevalence-based estimates of 3 major cost categories were developed: (1) direct costs, (2) mortality costs arising from depression-related suicides, and (3) costs associated with depression in the workplace. It was found that the economic burden had risen by 7% although the treatment rate increased by 50% (44).

Suicide

There is a clear association between suicide and depression. A report by Guze and Robinson (45) from 1970 derived largely from follow-up studies of severely depressed inpatients, estimated that about 15% of patients suffering a major depression will eventually die by

suicide. However, people who have been admitted to inpatient treatment may be at higher risk of suicide than those with a less severe symptomatology, whereas the majority of depressed people are treated as outpatients or not treated at all.

New approaches to statistical analysis allow for the more exact specification of lifetime risk. Guze and Robinson used proportionate mortality to estimate suicide rates. Proportionate mortality is calculated by dividing the number of subjects who have died of suicide by the number of subjects who have died from all causes during the follow-up period. If all the subjects were followed throughout their life span, proportionate mortality would correctly estimate the probability of suicide. However, if subjects are not followed for their entire lives, the proportionate mortality method will overestimate the risk of suicide. Inskip et al (46) using a statistical modelling approach to correct for the problem of limited follow-up periods estimated, on the basis of data from 1921-1975, that the life time risk of suicide for affective disorder was 6%.

A second approach to calculating suicide risk is case fatality prevalence. This approach compares the number of persons who have died by suicide to the number of persons originally in the cohort being followed. For instance, Helgason (47) followed a cohort of Icelanders for 61 years and found that 7.2% of the patients with affective disorder died by suicide. When the cohort was split into two groups, one “psychotic” and one “neurotic”, the suicide rates bifurcated: patients with primarily psychotic depression 14.5 %, and patients with primarily neurotic depression: 1.8%. The Lundby study found a rate of suicide in depressed males of 650/100 000 person years compared to 8.3 in males without any psychiatric disorder (48). In a review published in 2000, Bostwick and Pancrantz (49) presented results from a meta analysis of studies that included data on affective illness and suicide. The estimated lifetime prevalence of suicide for inpatients assessed as suicidal was 8.6%, for inpatients without specified suicidality 4.0%, for a mixed inpatient/outpatient population 2.2% and for the non-

affectively ill population less than 0.5%. They proposed a hierarchy of risk based on the intensity of the treatment setting.

A third approach to calculating suicide risk is the standardized mortality ratio (SMR), calculated by dividing the observed mortality of a cohort by the expected mortality of an age- and gender-matched cohort representative of the general population. In Sweden, Ösby et al (50) found a strongly increased SMR for suicide in psychiatric inpatients with a first hospital diagnosis of bipolar (males 15, females 22.4) and unipolar (males 20.9, females 27) disorder from 1973-1995, most pronounced in young patients and in the first year after the first diagnosis.

Blair-West et al (51) in 1994, using a mathematical algorithm, calculated a 3.4% suicide risk in major depression in the U.S.; and male:female ratios of 10:1 for youths under 25 and 5.6:1 for adults.

Treatment of depression

Treatment options

Electroconvulsive therapy (ECT) was introduced in 1938 by Cerletti and Bini as a technical modification of v. Medunas pharmacologic convulsive therapy, and ECT emerged as the first effective antidepressive treatment although it was first used in Italy on a schizophrenic patient.

The first antidepressant medication introduced in Sweden was imipramine 1957 (synthesised in 1948), and in the 1960s other antidepressants with a similar tricyclic chemical structure were introduced.

The treatment of depression may not, however, be only pharmacological (or ECT).

Psychosocial interventions with evidence-based positive effects for mild and moderate depression are: cognitive behavioural therapy and interpersonal psychotherapy (13, 52). There is also a limited support for brief psychodynamic therapies and counselling (when used in depression in primary care) (13). Available treatment modalities can in the great majority of cases lead to a full recovery from depressive symptoms, and restored capacity for work and social life. The aim of treatment therefore should be recovery (13).

Antidepressant medication

All antidepressants increase neurotransmission for one or more of the monoamines - serotonin, noradrenaline (norepinephrine), or dopamine – and this leads to the postulation of a monoamine hypothesis for affective disorders (53). The antidepressants act in one of three ways: (1) blockage of presynaptic monoamine transporter proteins, which remove released transmitter from the extracellular space, (2) inhibition of monoamine oxidase, which degrades monoamine neurotransmitters or (3) inhibition or excitation of pre- or postsynaptic receptors that regulate monoamine transmitter release and/or neuronal firing rates (52).

The definition of a treatment response is a 50% decrease during the first 4-8 weeks of treatment in a symptom rating on a depression rating scale such as the Montgomery Åsberg Rating Scale (MADRS) or the Hamilton depression rating scale (54). The response rate is about 60% regardless of the type of antidepressant medication used for major depression.

In Sweden, 17 antidepressant drugs (ATC group N06A) are currently marketed (Appendix 2).

Evidence-based treatment with antidepressant medication should continue for at least six months after response in order to minimize the risk of a relapse, and a continuation therapy for a year decreases the relapse rate further. If there have been previous recurrent episodes or severe episodes, a continuation therapy up to 3 years reduces the relapse rate by 50% (13).

The first so-called tricyclic antidepressants (TCAs) were effective treatment tools, but their use was limited, probably because of their disturbing side-effects. The first serotonin reuptake inhibitor (SSRI) was introduced in 1982. It was called zimelidine and was synthesised in Sweden (55). It had less disturbing side effects than the TCAs, and it had a low toxicity in overdose. Unfortunately, it had to be withdrawn from the market already in 1983 after a rare side-effect (Guillain-Barré syndrome) was recognised (56). The SSRIs currently available were in Sweden introduced in the first half of the 1990s (fluvoxamine, citalopram, paroxetine, sertraline and fluoxetine). A reversible monoamine oxidase-A inhibitor moclobemide and other types of antidepressants have also been introduced for clinical use (mianserin, mirtazapine, venlafaxine and reboxetin).

Prevalence of antidepressant medication for the treatment of depression in the general population

Ohayon et al (57) investigated the relation between the use of psychotropic medication and current mental disorder in four European countries (France, Germany, Italy, and the United Kingdom) during 1993-1997 by means of telephone interviews directed by the Sleep-EVAL expert system. Of 18 679 subjects aged ≥ 15 years, representative of the general population, 78.8% participated. It was found that 7% of the depressed individuals in the general population were being treated with antidepressants.

In 1996 in the Netherlands, 69.7% out of 7 076 subjects aged 18–64 years, selected as a representative sample of the general population, were interviewed at home and diagnosed using the CIDI as part of the The Netherlands Mental Health Survey and Incidence Study (NEMESIS). They were asked about antidepressant treatment and it was found that 45.3% of individuals with a major depressive episode in the 6 months prior to the interview received professional care, and that 42.6% of these (19.3%) received antidepressant medication (34).

In Cache County (Utah, USA) in 1995-1996, Steffens et al (58) examined 4559 non-demented individuals (aged 65 to 100 years, representing 90% of the elderly population) for current major depression using a modified version of the Diagnostic Interview Schedule (DIS). The medication use in these depressed individuals was determined through a structured interview and a "medicine chest inventory." Point prevalence of major depression was estimated at 3.6%, and 35.7% were taking an antidepressant (1.3% of the population base).

Laukkala et al (59) reported that as part of the Finnish Health Care Survey, in which 5,993 subjects aged 15–75 years in a random sample of Finns were interviewed face-to-face by professional interviewers in 1996 using the Short Form of the University of Michigan Composite International Diagnostic Interview Finland for diagnosis, questions were asked about medication. They found that, although antidepressant use increased over four-fold between 1989 and 1998, among those 9.3% with a major depressive episode during the preceding 12 months, only 13% (up to 25% for recently diagnosed subjects) used antidepressants.

Table 2 presents a summary of recent (2000) epidemiological data for the use of antidepressants in relation to depression.

Table 2.

Recent epidemiological data from studies in Europe and US on antidepressant medication among depressed individuals in the general population.

Author, year	Country	N	Age group	% antidepressant medication
Ohayon, 2002	France, Germany, Italy and The U.K.	18679	≥15	7
Spijker, 2001	Netherlands	7076	18-64	19.3
Steffens, 2000	U.S.	4559	65-100	35.7
Laukkala, 2001	Finland	5993	15-75	13

Primary care

Most patients suffering from major depression consult a primary care physician. There are studies indicating that 4-10% of patients who consult a general practitioner suffer from major depression (60-62). Several studies have however found that the general practitioners recognise the depressive disorder in about half the cases and that of these only 1/2-2/3 receive

treatment (63-67). In general practice, the treatment is mostly pharmacological, with antidepressants (68, 69).

Effects on the public health

One Swedish study of a prescription database has found that the use of antidepressants, mainly TCAs, was associated with increased prescriptions for other drugs, indicating widespread health problems among the antidepressant users (70). The use of medical services (general medical care and mental health services) among depressed individuals has been estimated in different studies. The Dutch study NEMESIS found that 45.3% of individuals with major depression received professional care, and the American NCS found 27.7% (34, 71).

Since the introduction of the SSRIs, the sales of antidepressant has increased five-fold (2). Large increases are seen in other countries as well (3, 4). The Swedish Diagnosis and Therapy Survey in 2000 found depression as the indication for 68% of the prescriptions of antidepressants (72).

The public health effects of this increased use of antidepressants has been disputed. Suicide rates have been reported to have decreased in Sweden, Denmark, Norway, Finland, USA, England & Wales, Northern Ireland (older individuals), Australia and Hungary (2, 5, 73-76). In Iceland, the effects of the five-fold increase in sales of antidepressants (14.9 DDD/1000/day in 1989 to 72.7 in 2000) were studied with regard to suicide, disability, hospital admissions and outpatient visits. No significant changes could be noted (77). A partial explanation may be that the Iceland population is only about 300 000 and that suicide rates have been low (around 10/100 000). That is only about 30 suicides per year in absolute numbers, compared to 2000 in Sweden, or 30 000 in the USA. In Jämtland, on the other hand, with about 30 suicides per year, a clear decrease has been established.

Prevention of suicide

Public and general suicide-prevention campaigns (often at a national level) have tried to encompass psychological, biological, and social areas. Directed strategies usually target risk populations. In the case of suicide prevention, the target has usually been people who have committed deliberate self harm or parasuicide, which to some extent represents an attempt to commit suicide (78). For example, it has been found that young adult men, who were assessed at an emergency unit after self harm, constituted a high risk group that could be targeted (79). Another high risk group is patients with depression who have been admitted to a psychiatric hospital because of a suicide attempt (80). Low CSF 5-HIAA in mood disorder patients who had attempted suicide predicted an almost threefold increase within one year after the attempt (81). However, in the Swedish county of Västerbotten, a study of the epidemiology of parasuicide between 1989-1995, comparing the different parishes/communities of the county, found an inverse correlation between parasuicide rates and suicide rates (82). A prevention scheme in Stockholm, Sweden that was directed towards suicide attempters found no differences in outcome (mortality, suicide mortality, registered sickness, criminality, abuse of alcohol and social assistance) (83). Since systematic clinical investigations of consecutive suicides have found depressive syndromes in 30-87% of the cases (84-93), it seems logical that the treatment of depression should be an effective means of suicide prevention. Naturalistic studies have found empirical evidence for this e.g. in Sweden, where there was a four-fold increase in the sales of antidepressants during the 1990s and a 25% decrease in suicides during the same period with a lack of alternative causes (2). Similar patterns have been found in Hungary (73). In Australia, changes in suicide rates and exposure to antidepressants for 1991-2000 were significantly associated, particularly in older age groups, in which rates of suicide decreased substantially in association with an increased exposure to antidepressants (5). Further, long term medication (antidepressants alone or with a

neuroleptic, or lithium in combination with antidepressants and/or neuroleptics) lowered the suicide rate in hospitalised affective disordered patients who were followed for 34-38 years (94). Several analyses have found that the suicide risk in bipolar patients was radically lower during periods of long-term lithium treatment (95).

Jämtland county

In the county of Jämtland, the object of the studies in this thesis, modern antidepressive treatment with electro-convulsive treatment (ECT) was first used in 1941 when a convulsator was delivered after Olof Dagberg, one of the doctors at Frösö hospital (the state mental hospital), had learned the technique in 1940 from Cerletti in Bern, Switzerland (96). Antidepressant medication (imipramine) was introduced 20 years later.

Jämtland county is a vast and mostly rural area and situated in the middle of Sweden. Its area constitutes 12 % of Sweden, but it has only 130 000 inhabitants (1.5 % of the Swedish population). There are 2.6 inhabitants per km², compared to 21.6 per km² in Sweden as a whole. Östersund is the only city and county administrative centre, and it has the only hospital in the county (Östersund General Hospital) (97). The Jämtland population is older than that of Sweden as a whole. The mean age of the Jämtland population was 42 years in 2000 and for Sweden as a whole 40.3 (19.9% aged 65 years and over in Jämtland and 17.2% in Sweden as a whole). Twenty five percent of the population in the county between the ages of 20 and 64 have a tertiary education compared to 28% in the rest of Sweden. Of all the inhabitants in the County of Jämtland, 43% were gainfully employed in 1999, compared to 45% of the national population. In Jämtland county compared to Sweden as a whole, the sick rate (number of days on sick leave) was higher (23.4 compared to 16.8 days per year). The incapacity rate (sick rate, rehabilitation, work injury or disability pension per registered insured living or working in Sweden) in the year 2000 was 46.5 days and in Sweden as a whole 38.7 days.

From 1915 until 1969, most of the psychiatric care was within the Frösö Hospital. In the 1970s a modern community-based psychiatric organisation started to develop and in 1991 the mental hospital was closed. All psychiatric in- and outpatient care was located within the

General Hospital. In parallel with this trend, psychiatric conditions were increasingly managed in an expansive primary care organisation, not least for depressive disorders.

In 1987, 1988 and 1990, Göran Isacsson, psychiatrist in Östersund, held lectures for all general practitioners in Jämtland, demonstrating findings from the county that people committing suicide were to 85 % untreated or mistreated depressed patients, and he encouraged a more frequent use of antidepressants (14). Against a background trend of an increase in the use of antidepressants in all Sweden, Jämtland then approached the Swedish average during 1988-1989 (98).

In 1994, there was a need for new educational efforts directed to primary care physicians in the skills of detecting depression as well as improving the quality of the treatment of depression. Inspired by the positive outcome of the Gotland study, a similar project - the Jämtland project - was started in 1995 (99-101). The general goal of the Jämtland project was to improve the treatment of depression in primary care through a continuous education program, which would hopefully, as in Gotland, lead to an increase in the use of antidepressants and a decrease in suicide rates. The educational program coincided, however, with the increased use of antidepressants in all Sweden due to the advent of the SSRIs, and in parallel with that, decreasing suicide rates. This made the original purpose of the present research project almost impossible, namely to evaluate the effects of the education. The new antidepressants were accompanied by an intense marketing aimed at influencing the physicians' prescribing behaviour (102). The marketing also included many educational efforts. The physicians were also influenced by an intense coverage and debate in the public media regarding the use of SSRIs. Rather than attempting to evaluate the educational effort as planned, the research project was redirected to the study of the effects of the rapidly

increasing use of antidepressants. The individual-based prescription database in Jämtland provided an unique tool for the study of such effects (103).

Description of the educational program

The educational model was inspired by the educational program on the island of Gotland in Sweden, 1983-1984, which was directed by the Swedish Committee for Prevention and Treatment of Depression (104). The Gotland study was followed by an increased use of antidepressants and a lowered suicide rate, which was however only temporary (101). With the support of the Board of the Jämtland County Council, a steering committee for an educational program on depressive disorders was formed in 1994. The group consisted of two general practitioners (Hans Beijer and Anders Berglund), two local psychiatrists (Svante Henriksson, then head of the Department of Psychiatry, and Robert Öhman), as well as one representative from H. Lundbeck Sweden AB, manufacturer of the SSRI citalopram (Solveig Osséen). The costs of the education program were covered by the County Council with the exception for the fees and travels for lecturers which were covered by H. Lundbeck Sweden AB. The latter had no influence on the content of the educational program. In 1995, all general practitioners and resident practitioners were offered a two-day seminar which was to be repeated annually until 2001. The intention was to have less than 20 physicians participating at each seminar in order to facilitate an interactive educational approach. Seminar I was carried out on three occasions (twice in the fall of 1995 and once in the spring of 1996). Seminar II was given twice in the the fall of 1996. In 1995 and 1996, 88 primary care physicians were working in Jämtland. Forty-eight of them participated in seminars I and II (35 participated in both). From 1995 to 2001, a total of 78 doctors have taken part in at least one seminar. Seventy-three (83%) of the 88 primary care physicians who worked in

Jämtland county in 1995 were still working in the county in 2001. From 1997, the length of the seminars has been one day.

The seminars comprised lectures, case discussions and videotape presentations.

In 1995, the following topics were covered: genetics, epidemiology, classification, etiology, pathogenesis, gender perspectives, personality disorders, the management of depression, empathy, psychopharmacology, suicidology, and psychotherapy of depression. In 1996, the following areas were covered: depressive illness in the elderly, depressive disorders in childhood and adolescence, indications for antidepressants, as well as case seminars including cases of suicide. In all the seminars, local psychiatrists as well as national experts were employed as lecturers .

The seminars in 1997-2001 contained the following additional subjects: substance abuse and depression, atypical or masked depression, depression in the post partum period, chronic stress and depression, prescription patterns of antidepressants in Jämtland and suicide, suicide trends in the world, suicide risk assessment and national guidelines, and work-related depression. There were also follow-ups on personality disorders, suicidology and new developments within psychopharmacology with an emphasis on antidepressants. Cases prepared and presented by the participating physicians were regularly discussed. Video tape sessions included cases of depression, grief, suicidal ideation and assessment of risk for suicide.

The present study

Aims of the study

The overall aim was to study the effects of the new opportunities for adequate antidepressant treatment of depressed individuals in the general population. Individual data were obtained from the prescription database, medical records, the cause-of-death register, forensic toxicological investigations, and field interviews and the results were reported in four papers with the aims of studying:

1. The prescription patterns of different antidepressants.
2. Whether the increased use of antidepressants has been beneficial for depressed individuals.
3. The pharmacological treatment prescribed to, and consumed by, individual suicides.
4. The use of antidepressant medication in depressed individuals from a representative sample of the general population.

Methods

The prescription database

In Jämtland county, prescription drugs dispensed to a representative sample of 13% of the population of 136 000 have been monitored since 1970 (i.e. 18 000 individuals, selected as being born on 4 particular days of each month). Information concerning the patients' personal identification number, category of prescribing physician (i.e. psychiatrist, resident, general practitioner, etc.), and the strength, volume, and dosage of drugs dispensed can be obtained from the database (103) .The annual publication 'Swedish Drug Statistics' presents incidence and prevalence rates for the use of medications by age and sex (105). These basic pharmacoepidemiological data require the inclusion of the personal identifier from the prescription in the database. It is not, however, possible to obtain information on the indications for the prescriptions from this source.

In all the *papers (I-IV)*, the prescription database was used to retrieve unbiased information on the individual use of prescription drugs, in particular antidepressant medications. The study design of each paper in the present study is indicated in Table 3.

Table 3.

Description of study design and inclusion criteria for participating individuals.

<i>Paper</i>	Study design	N	Inclusion Criteria	Year
<i>I</i>	Naturalistic	1034	A first prescription of an antidepressant after ≥ 2 years without such a prescription	1991-96
<i>II</i>	Naturalistic	191	A first prescription of an antidepressant after ≥ 5 years without such a prescription	1995
<i>III</i>	Case-control	59	Suicide death	1985-95
<i>IV</i>	Cross-sectional	2048	Age 18-85, living in 3 parishes in Östersund	2001-02

In *paper I*, a naturalistic study design was used. The prescription database was the only source of information for this study which included those 1034 individuals who had had a first

prescription dispensed for an antidepressant during the period 1991-1996 after ≥ 2 years without such a prescription.

In *paper II*, a naturalistic study design was also used by examining notations of indications for and outcome of antidepressant treatment in medical records of those 191 individuals who, in 1995, had had a first prescription dispensed for an antidepressant after ≥ 5 years without such a prescription.

The use of prescription drugs in 59 cases who committed suicide between 1985-1995 and 118 controls who were included in the prescription database was compared in a case control design in *paper III*. Psychiatric records for the suicides and cases were examined. Results from the forensic toxicological screening were also examined for the suicides.

In *paper IV*, a cross sectional epidemiological design, consisting of a screening questionnaire (mailed to a sample of 2048 individuals from the prescription database), and, for those individuals who had a positive screening for a depressive episode, a diagnostic interview were used in order to identify depressed individuals. The use of antidepressants in depressed and non-depressed individuals could then be established with data from the prescription database.

Medical records

In *paper II*, medical records from the psychiatric and other departments of Östersund Hospital as well as those from primary care centres all over the county were retrieved, and notations of indications and outcome of antidepressant medication were examined and registered.

All the psychiatric records of suicide cases and controls were examined in *paper III* for information regarding clinical diagnosis.

Psychiatric records of individuals were used in order to validate information regarding prior psychiatric care that was given during the diagnostic interviews reported in *paper IV*.

Suicide statistics

In *paper III*, suicide cases were investigated for their use of prescription drugs and antidepressants in particular. Information about the suicide cases was obtained from Statistics Sweden (SCB). This information consisted of personal identification number, date and cause of death of all 396 certain suicides (ICD-9 diagnoses E 950-9) and uncertain suicides (E 980-9) in Jämtland during 1985-95. Fifty-nine (15%) out of the 396 suicide cases were found in the prescription database, 46 men (median age 45 years, range 19-89), and 13 women (median age 55 years, range 25-77). Of these, 33 men and 9 women belonged to the certain suicide (E 950-9) category while 13 men and 4 women belonged to the uncertain (E 980-9) cases. The uncertain category was included in order not to exclude actual suicides due to overdose, since a definite confirmation of a diagnosis of suicide in such cases may be impossible.

For each case, two controls were selected from the county census register in order to compare the use of prescription drugs between the two groups. The controls were selected as the persons of the same gender listed (by age) immediately before and after each case in the census register, and they were included in the database during the same time period as the case. The two groups were thus matched for age and gender.

Forensic toxicology

The medications received by the suicide cases in *paper III* were studied in detail for the three-month period prior to suicide. In order to assess what drugs the subjects who committed suicide were actually taking at the time of death, the forensic toxicological screening data were examined. These data were obtained from the National Board of Forensic Medicine.

Depression screening questionnaire

In *paper IV*, a questionnaire was mailed in order to screen for depression in the sample of 2048 individuals that was selected from general population. They were selected from the prescription database as those living in three parishes in the Östersund area. The questionnaire included the Major Depression Inventory (106). Individuals with a probable depressive episode were contacted by telephone in order to arrange for a face-to-face psychiatric interview.

Diagnostic interview (SCAN)

The diagnostic interviews in *paper IV* were all made by one experienced clinical psychiatrist (SH) utilising a structured clinical interview schedule, the computerized SCAN (Schedules of Clinical Assessment in Neuropsychiatry) 2.1 system (I-Shell) (107, 108). Typically, the interview took 2-3 hours. During the interview, data were directly entered into a laptop computer. Using SCAN, the interviewer has to assess the severity of symptoms and whether they have been present during the month before examination. The "present state" option was chosen for all cases. The generated diagnoses used were on the basis of DSM-IV categories (22). The intensity of the depressive psychopathology covering the past three days was rated according to the Montgomery Åsberg Depression Rating Scale (MADRS) (109).

Statistical methods

For the statistical analysis, the SPSS software was used (110). Standard methods were used to calculate mean values and standard deviations. The chi-square test for 2x2 tables with Yate's correction for continuity or Fischer's Exact Test were used for the comparison of categorical variables. The Student's t test was used for continuous variables. For linear relationships between variables with ordinal data the Spearman rank correlation coefficient was used. The minimum statistical significance level for all analyses was $p < 0.05$.

Ethical aspects

In all *papers*, the individual-based prescription database was used. The database has been in operation since 1970 (111) and it has been approved by the Swedish Data Inspection Board (98, 111). The purpose of starting and managing the database was to be able to research drug utilisation. For the general public in Jämtland, the information about the registration is posted at all local pharmacies, and for those individuals whose prescription data are included (individuals born on the 4 particular days of the month) instructions are given as to what to do if they do not want to participate. The possible ethical problems involved are foremost the integrity of those individuals who are registered. The personal identification number can be used as a link to other databases in which this personal identification number is used. Several studies using the prescription database have been published previously (14, 111-124)

In *paper 1*, no such linkage to other sources of information was made and the data were only analysed on an aggregated level. Due to the strengthened formal requirements since then, the ethics of the study was retrospectively approved on March 30, 2004 by senior lecturer Tom Mjörndal (at the time of the study, acting chairman of the Ethics Committee at the Faculty of Medicine at Umeå University), professor Gösta Holmgren and professor Bruno Hägglöf.

In *paper II*, the problem of the integrity of the patients as well as that of the prescribing physicians was considered from the start and relevant measures were taken. Written information about the study was given to all prescribers in the county and the aims of the study were presented at meetings with primary care physicians where the issue of integrity was discussed. In some instances, telephone contacts were made. It was agreed that the prescribing physician should inform the patient and ask for permission for participation in the study. With this procedure, the study was approved by the Ethics Committee at the Faculty of Medicine at Umeå University (Um dnr 96-301).

In *paper III*, suicide victims were compared to controls found in the population census register. Relatives of the deceased were not contacted, nor were the controls. No real ethical problems, other than the general problems with register data mentioned earlier, were considered to exist in this study. No ethical approval was, therefore, asked for at the time of the study. For the same reasons as for *paper I*, the study, however, has been reviewed in retrospect on March 30 2004 by the Ethics Committee at the Faculty of Medicine at Umeå University, and it was found that the study would have been approved (assessed by senior lecturer Tom Mjörndal, at the time of the study acting chairman, professor Gösta Holmgren and professor Bruno Hägglöf). In *paper IV*, individual data from the prescription database concerning antidepressant medication were compared with personal data about depression which were asked for in a mailed questionnaire. Information about the study was included in the leaflet containing the questions. The questionnaire might have disturbed some people. They might, however, also gain from the investigation. When individuals were interviewed (SCAN) in the diagnostic stage of the study, those individuals with a psychiatric disorder were always offered referral to a doctor (psychiatrist or general practitioner) if necessary. The collected prescription, questionnaire and diagnostic data were registered and managed in accordance with the Swedish Personal Data Protection Act (PUL) effective as of October

1998. The study was approved by the Ethics Committee at the Faculty of Medicine at Umeå University (Um dnr 98-245).

Results

Paper I

With the advent of the new generation of antidepressants (foremost the SSRIs), the total yearly incidence of antidepressant treatment doubled during 1991-1996 (from 0.76% to 1.33%). The total one year prevalence increased from 2.0% to 3.8%. For men and women this increase is shown in Table 4.

Table 4.

Increase (%) in yearly incidence and prevalence of antidepressant medication according to gender.

1991-1996	Men	Women
Incidence	0.58	0.57
Prevalence	1.3	2.2

In 1991, 3% of the index prescriptions were for the SSRIs and in 1995 66%, which increased in 1996 to 70%. The average daily dosage after titration was for clomipramin 82% ≤ 75mg, amitriptyline 94% ≤ 75mg, citalopram 12% < 20mg and paroxetine 88% = 20mg. Regardless of whether first prescription was for an SSRI or a TCA, 35% of the subjects did not have a second prescription dispensed during the study period. The pattern considered adequate, with

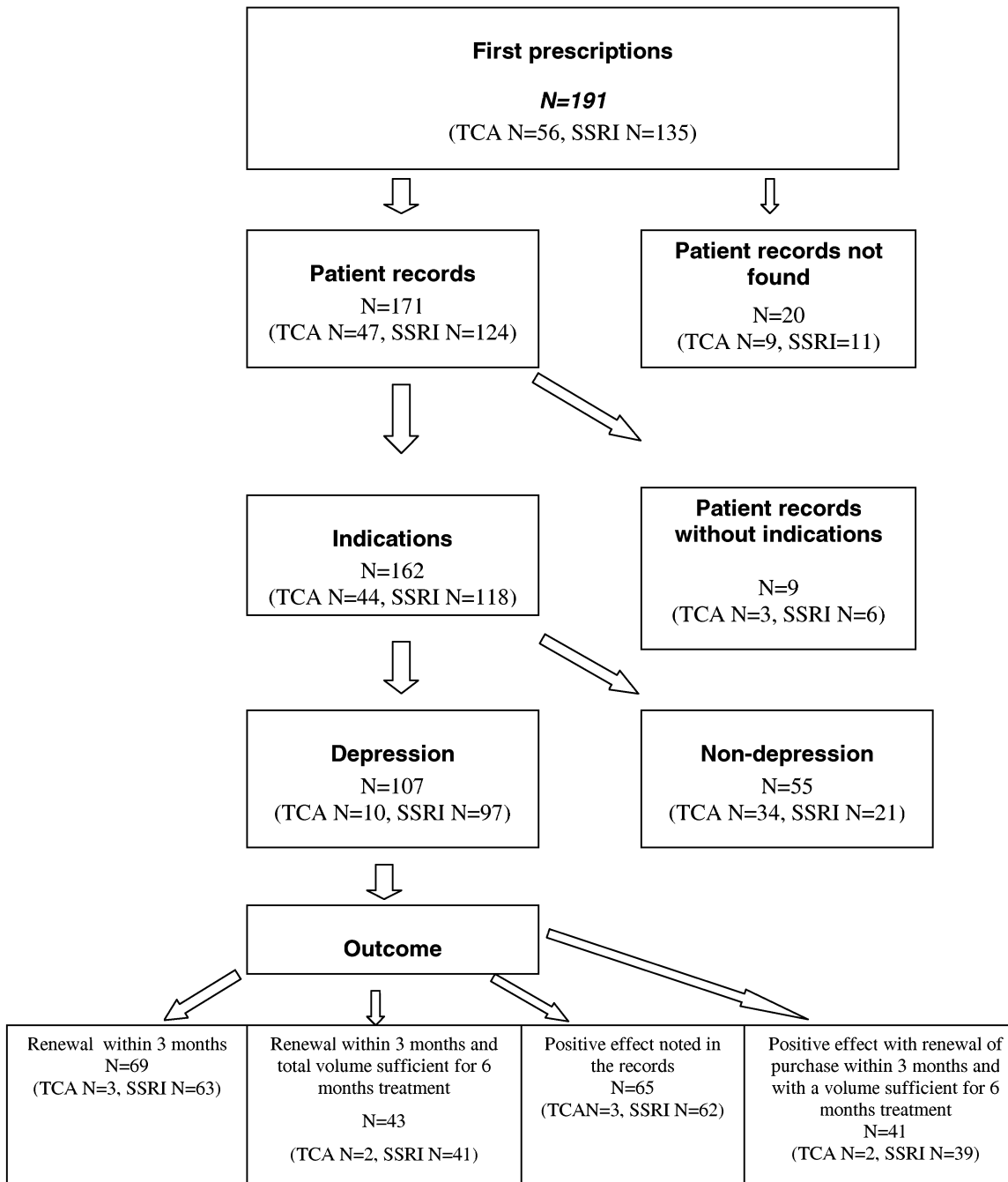
repeated dispensations of a first renewal of purchase within 3 months and a total volume sufficient for at least 6 months of treatment, grew three-fold (0.17% to 0.52%). Such adequate treatments were more frequent with the SSRIs than TCAs (42% and 27% respectively, $p < 0.001$). Several criteria were fulfilled indicating a successful antidepressant treatment: an increased treatment prevalence, a more adequate dosing, a more commonly adequate duration of treatment. However, the extent to which this prescribing was for depressed individuals and whether it was of any benefit to them could not be assessed, and this led to the investigation of indications and outcome in paper II.

Paper II

From the prescription database, the 191 individuals who started a new antidepressant treatment in 1995 were selected. For 171 (90%) of them, the medical records could be retrieved. In 107 cases, these records contained sufficient information on the indications and outcome of the treatment that was identified in the prescription database. Depression was found to be the indication in 2/3 of the cases. For the SSRI treatments, depression was the indication in 82 % of the cases compared to 23 % for the TCA treatments ($p < 0.001$). Figure 1 illustrates the different steps in the study. A successful treatment of depression, defined as a positive effect with a renewal of purchase within 3 months and with a volume sufficient for 6 months treatment, was found in 39 (40%) of the SSRI cases and in 2 (20%) of the TCA cases. There was thus evidence that the increased use of antidepressants had been beneficial for depressed individuals.

Figure 1.

Study flow chart of indications for and outcome of antidepressant treatment.



Paper III

The 59 suicide cases received dispensations of twice as many prescription drugs.

Psychotropics and vitamins accounted for most of this difference. More cases than controls had received psychiatric care, indicating severe psychopathology. Nine (50%) of 18 cases who received psychiatric care had a clinical diagnosis of depression. However, during the last 3 months before death, 21 cases had had no prescription dispensed, 31 had had prescriptions dispensed from a GP or other physicians and 7 from psychiatrists. Five of 7 cases with prescriptions from a psychiatrist were prescribed an antidepressant compared to 2 of 31 with prescriptions from general practitioners or others ($p < 0.001$), thus a total of 7 (12%) cases were dispensed antidepressants. In total, 21 (36%) of the suicides were dispensed psychotropics. Toxicological analysis was performed in 48/59 (71%) cases and in 2/3 the prescribed psychotropic drug could not be retrieved. The majority of suicides obviously occurred among individuals who were not being treated for depression.

Paper IV

Sixty-two individuals (4.5%) out of the 1375 responders to the questionnaire were diagnosed with depressive episodes (major depression, dysthymia, depression due to a general medical condition, and Alzheimer's disease with depression), and 17 (27 %) of these acutely depressed individuals were taking antidepressant medication. A further 44 respondents without current depression were receiving antidepressant medication. A telephone interview of 28 of these revealed that 18 of them took antidepressants as a continuation treatment after depression. In table 5, these findings are summarized in relation to the study population of 1375 individuals.

Table 5.

Prevalence of antidepressant use among depressed individuals in Jämtland county 2001-2002 (study population N=1375).

Diagnosis (SCAN)	Antidepressant N=61 (%)	No antidepressant N=1314 (%)	Total N=1375 (%)
Depression	17(1.2)	45(3.3)	62(4.5)
No depression	44(3.2) ^a	1269(92.3)	1313(95.5)

^a 18 (1.3%) of these individuals were prescribed their antidepressant as continuation treatment after depression

The frequent use of antidepressants as expressed in defined daily doses (in Jämtland 54.9 DDD/1000 inhabitants/day, during 2001) would match the prevalence of depression if the indication for prescribing were depression and the DDD actually reflected the doses used. The actual doses used however are higher for the treatment of depression. The prescribed daily dose is equivalent to nearly 1.5 times the DDD (Table 6.).

Table 6.

Actual used doses (mean prescribed daily doses-PDD) compared to defined daily doses (DDD).

Drug	PDD (Mean)	DDD	PDD/DDD
Citalopram	30mg	20mg	1.5
Sertraline	75mg	50mg	1.5
Fluoxetine	30mg	20mg	1.5
Paroxetine	30mg	20mg	1.5
Venlafaxine	150mg	75mg	2
Mirtazapine	45mg	30mg	1.5
Amitriptyline	25mg	75mg	1/3
Bupropion (N07B)	150mg	300mg	1/2

Discussion

The illness of depression is a major public health concern, causing great suffering to the depressed individuals and their relatives, and major costs to the whole of society. Depressive illness carries with it an increased risk of other morbidity and mortality (mainly but not only suicide). For the treatment of depression effective antidepressant drugs, TCAs and monoamine oxidase inhibitors, have been available for more than 40 years. The use of antidepressants in the population was on a low level, however, and few depressed individuals were treated. There was a gradual and slow increase in the use of antidepressants until the early 1990s when the new generation of antidepressant drugs, foremost the SSRIs, were introduced. With the advent of these new drugs, a great increase in the use of antidepressant medication occurred. This dramatically increased use was considered to be rational and was suggested as a possible reason for the drop in suicide rates. However, this was also disputed with allegations of misuse and over-use. The present project focused mainly on whether the increased use of antidepressants was beneficial to depressed individuals in the general population, to what extent individuals who committed suicide had been treated with antidepressants, and at what rate depressed individuals were actually being treated.

The project extracted all its study subjects from the prescription database population in the County of Jämtland. The information relating to prescribed antidepressants gathered from this database could then be used as an unbiased source of information on the use of antidepressants and other prescription drugs in *papers I-IV*. The prescription data were compared with information collected retrospectively in *paper II and III*, while the information relating to depression diagnosis in *paper IV* was collected at a single point in time (at the interview).

In *paper I*, the only data used were from the prescription database. Medical records, including psychiatric records, were the sources of information concerning the reasons behind the physicians' choice of particular antidepressants and the possible effects of that treatment in *paper II*. These records gave information based on the clinical opinions and decisions of a large number of different physicians and thus they were not standardised diagnoses or effect measures, and this must be kept in mind when drawing conclusions from this study. The object for study in this project is solely actual clinical practice. In *paper III*, information regarding suicide cases was gathered from Statistics Sweden (SCB) and, for the controls, from the population census register. Information regarding psychiatric care for both cases and controls were retrieved from psychiatric records (with the above-mentioned potential limitations), and data from the toxicological analyses in the suicide cases were provided by the National Board of Forensic Medicine. In order to acquire facts about the rate of depression, the diagnostic process in *paper IV* used a screening questionnaire which yielded possible depressed individuals, and these were interviewed face-to-face in a second step by means of the structured SCAN interview. The questionnaire included the Major Depression Inventory which has been shown to have an acceptable sensitivity and specificity. This produced scientific diagnoses in contrast to the clinical diagnoses in *paper II*. The weaknesses of this study were the limited size of the study population and the fact that the sensitivity and specificity relevant to the diagnostic procedure used in this particular study could not be determined due to limited interviewing capacity, since all the subjects were interviewed by the same clinically experienced psychiatrist (the author). On the other hand, this may have guaranteed that the diagnostic procedure was of good quality.

Prescription patterns of different antidepressants

Among new users of antidepressants, the SSRIs became the dominant drug in 1995, and both men and women increased their use. Our incidence data suggest, provided they are representative for Sweden as a whole, that compared to 1991, 47 000 more individuals who started an antidepressant treatment in 1996 were being treated for the first time. More SSRI- than TCA-users had been dispensed doses in accordance with recommendations, actually only 18% of clomipramine-treated individuals and 6% with amitriptyline had dosages above 75 mg. These findings of more appropriate dosing with the SSRIs are in agreement with the results of other studies (63, 66). However, only 1/3 renewed their first prescription, regardless of type of drug, suggesting that they did not start taking the medication. The SSRI and TCA treatments regarding adherence to guidelines differed when the duration was examined. Treatments with 2 refills within 3 months of the first purchase and a volume sufficient for ≥ 6 months, the quality criterion, were twice as common among the new SSRI users than among the TCA users (42% and 22% respectively, $p < 0.001$). These differences are probably explained by the fewer side effects of the SSRIs. For elderly patients more sensitive to side effects, TCAs were not tolerated at all, particularly not in adequate doses. For the prescriber it is easier to manage an SSRI treatment in practice (not as elaborate a titration process as with the TCAs). Whether these results were actually of benefit for depressed individuals could not be established in this paper, since it was important to identify the patients prescribed antidepressants for depression in order to be able to study the outcome of treatment in these patients. This was done in *paper II*.

Was the increased use of antidepressants beneficial for depressed individuals?

In *paper II*, it was found that the indication for the first use (in 5 years) of an antidepressant in 2/3 of the cases was depression (the rest were other proven indications such as anxiety and pain). More remarkable was that 82% of the SSRI prescriptions were for depression but only 23% of the TCA prescriptions ($p < 0.001$). These findings are in agreement with the Swedish Diagnosis and Therapy Survey in 1995, where SSRIs and TCAs were prescribed for depression in 73 and 42 % of the cases, respectively (125), and the National Disease and Therapeutic Index physician survey index in the US where 86% of the SSRIs were used for the treatment of depression (126). This implies that the increased use of antidepressants has been targeted towards depressed individuals. Further it was found that, in the depressed individuals, the outcome, according to our criteria, was successful twice as often in those prescribed SSRIs as in those prescribed TCAs. If the results from *papers I and II* are combined it can be assumed that 38% more depressed individuals had been successfully treated in 1996 than in 1991. These studies suggest that the SSRIs actually offer a better outcome for depressed individuals, but naturalistic studies are not conclusive.

The pharmacological treatment prescribed to, and consumed by, individual suicides.

The suicide cases had twice as many prescriptions dispensed as the controls (psychotropics and vitamins exclusively accounted for the difference) and they received psychiatric care three times as often, indicating psychiatric disorders among suicide cases. This finding is consistent with the finding from systematic clinical investigations of consecutive suicides ('psychological autopsies') that suicides have psychiatric disorders in more than 90% of the cases (84-93, 127). However, prescriptions of psychotropics were dispensed in 1/3 of the suicides and antidepressants only in 1/10. These findings are almost identical to the finding in a previous study carried out between 1970 and 1984 in Jämtland County (14). A period of 26

consecutive years of medication received by a representative sample of all suicides in Jämtland has thus been studied. The medication that was dispensed (purchased by the individual) was not necessarily consumed by the time of the suicide, so forensic toxicological findings were also analysed. This analysis revealed that 2/3 of the psychotropic drugs that had been dispensed during the 3 months prior to death were not retrieved. The antidepressants were too few for a separate statistical analysis. If it is assumed that most of the suicide cases were suffering from depression, the fact that most of them had not been prescribed (had not purchased) antidepressants may have been a causal factor behind the suicide. This study does not provide detailed knowledge about the life circumstances, diagnoses or actual physician contacts.

The use of antidepressant medication in depressed individuals from a representative sample of the general population.

In *paper IV*, reliable and valid individual-based epidemiological data were combined with information regarding the use of antidepressants as retrieved from the prescription database. The main result was that the prevalence of currently depressed individuals was 4.5 % (62 / 1375), and that, among these, only 27 % (17 / 62) were receiving antidepressant medication. In comparison, 3.4% (44 / 1313) of the individuals without current depression used antidepressants ($p < 0.001$). Eighteen out of these 44 had had their antidepressant prescribed as a prophylactic treatment of depression in remission. The 4.5% rate of depressive episodes in the general population was in agreement with what has been found in other larger European studies using comparable diagnostic procedures, the Camberwell Needs for Care Survey found an estimated month prevalence of 3.1%, and one of the centers (Turku, Finland) in the ODIN study 6.2% (37, 128).

Information regarding the use of antidepressants among depressed individuals in the general population has usually been obtained by interviewing patients. For example, it was found in

Finland that only 13% of the individuals with major depression in 1996 reported the current use of antidepressant medication (59), and in the Netherlands 19.7% (34). No comparable data where information has been collected from a prescription data base could be found in the literature. In *paper IV*, the prescribed daily doses of antidepressants in depressed individuals were 1.5 times higher than the defined daily doses (129). Assessing the prevalence of antidepressant use simply by employing rates of defined daily doses (DDD/1000 inhabitants/day) is therefore misleading. For example the antidepressant sales of 54.9 DDD/1000 inhabitants/day in Jämtland 2001, would if approximated to 5.49 % be on a parity with or higher than the prevalence rate of depression (4.5 %). More correct would be $5.49/1.5 \% = 3.7 \%$. Considering that about 30 % of the prescriptions are for other indications than depression, and, further, that antidepressants are used as frequently for continuation treatment of depression as for acute treatment, the finding that only 1-in-4 of acutely depressed were taking antidepressants in spite of the large sales of 54.9 DDD/1000 inhab./day, does not seem so remarkable. Since the result of *paper I* suggest that the non-compliance rate among those who have purchased a first antidepressant may be 30 % it is obvious that there is still much to do to ensure that the depressed individuals in the population receive adequate treatment.

Further research is needed regarding questions like:

- Is it rational to treat all individuals with major depressive disorder with antidepressants? Or only those above a particular severity score?
- In a perspective of suicide prevention: must all depressed be treated or is it possible to limit the target? What would be reliable predictors to determine suicide risk in the depressed?
- How should factors like non-compliance and therapy-refractoriness be handled in studies like this?

- What would be the best criteria for a successful outcome of treatment in a naturalistic setting?

Conclusions

From this thorough investigation of experiences from the County of Jämtland may be reasonable to draw the following conclusions:

1. Almost every 20th individual was currently depressed.
2. Not more than one in four of the currently depressed individuals was prescribed an antidepressant.
3. Modern antidepressants were mainly prescribed for the treatment of depression but also for other proven indications. The use for unproven indications was minimal.
4. More than one third of the individuals who started a new treatment course with antidepressants did not comply regardless of type of antidepressant.
5. Less than half of the individuals who began a new treatment course with antidepressants took the medication for six months which is the recommended minimal duration.
6. The SSRIs were prescribed at recommended doses in contrast to the TCAs which were prescribed at lower doses than recommended.
7. A successful outcome of treatment of depression appears to have been more common when an SSRI antidepressant rather than a TCA was prescribed.
8. Few, if any, suicides were taking a course of antidepressants at the time of death.
9. The increased use of antidepressants has been an improvement which has been of benefit for people afflicted with depression and may have prevented a number of suicides.

Summary

Introduction. Depression is a major public health problem with a reported point prevalence of 5%. Depressive illness causes great suffering and disability. Effective treatment with antidepressant drugs has been available for more than 40 years. Although there has been an increase in the use of antidepressant drugs, the prevalence of their *reported* use among depressed individuals is between 7% and 19.7%. The principal aim of this project was to investigate the evidence for the rational use of antidepressant medication for the treatment of depression in the general population.

Methods. Information about the use of antidepressants and other medication was collected from an individual-based prescription database. All the individuals included in the study were selected from this prescription database, and they were representative of the population in Jämtland county, Sweden. Medical records were used to identify indications for and the effect of antidepressant medication. The suicide cases and the controls were obtained from Statistics Sweden and the population census register, respectively. Psychiatric records were used to obtain information about received psychiatric care. Forensic toxicological analysis of the suicide cases was retrieved from the National Board of Forensic Medicine to determine to what extent the purchased medication was in the blood stream at the time of death. For a screening of depression, a questionnaire was mailed and individuals who screened positive were interviewed face-to-face for a psychiatric diagnosis of depression.

The data from the prescription database was compared with the other sources of information.

Results. The incidence of dispensed antidepressant drugs doubled between 1991 and 1996. In 1995 and 1996, the majority of dispensations were serotonin reuptake inhibitors (SSRIs). More than one-third did not renew their dispensation regardless type of antidepressant. For the SSRIs, more often than for the tricyclic antidepressants (TCAs), recommended doses were prescribed. Significantly more SSRI than TCA treatments continued for at least 6 months. Depression was the indication for 82% and 23% of the SSRI and TCA treatments, respectively. Twice as many SSRI-as TCA-treated depressive cases were successful. Suicide cases were dispensed drugs twice as often as the controls, and three times more suicides received psychiatric care and half of them were clinically depressed. During the 3 months prior to death 36% of the suicide cases were dispensed a psychotropic and 12% an antidepressant. About one-third of the psychotropic drugs were retrieved in post-mortem toxicology. One-quarter of the 4.5% depressed individuals in the population at study were dispensed antidepressant medication, which is a 1.2% prevalence rate for acute therapy. The prevalence rate of continuation therapy was 1.3%.

Conclusions. Almost every 20th individual was currently depressed but not more than one in four was prescribed an antidepressant. Modern antidepressants were mainly prescribed for the treatment of depression at recommended doses and more often, compared to the old antidepressants, provided a successful outcome. Few, if any, suicides were taking a course of antidepressants at the time of death. The increased use of antidepressants has been an improvement which has been of benefit for people afflicted with depression and may have prevented a number of suicides.

Personal reflections

There is still too infrequent treatment of depressed individuals, who would otherwise benefit from such treatments. What is needed for the future? In the public health perspective, the trend of increased use of antidepressants still has not reached a sufficient level to provide treatment for all the depressed individuals. Rapidly acting antidepressant drugs are wanted for clinical use as well as appropriate antidepressants with treatment strategies tailored for young depressed individuals. Depression treatment care programs which involve both primary care and psychiatric services should be implemented. Such programs could be shaped jointly in order to serve the caregivers with continuous educational efforts, primarily directed at the prescribing physicians, and guide lines for the management of depressive disorders.

Depression detection and treatment teams should be organised within the primary care system in order to reach depressed individuals (especially the young). It would be appropriate for each team to have one psychiatrist to consult with. These teams could help to improve adherence to treatments and thereby the numbers treated for longer periods would increase (reducing risk of recurrences). The goal of treatment should be full recovery. Research is needed to develop better diagnostic methods including easy to use laboratory tests. The diagnostic understanding could support an improved use of available treatment opportunities and maybe enhance the treatment of individuals at risk for suicide. Making available screening procedures, such as self reporting questionnaires of depressive symptoms, in primary care centres or pharmacies, might be tried. Information to the public could be improved by a different and modern approach from the mass media, more reflecting the major progress concerning treatment options and the risks involved if depressed individuals fail to seek treatment. It is necessary to gather more and better knowledge about the duration aspects of depression, individual long term outcome of untreated and treated individuals. The issue of

depression, comorbidity and the use of medication needs to be more investigated. At what rates and which are the most prevalent comorbid illnesses? What are the problems involved e.g. pharmacological interactions. Investigations are needed to study the rates and distribution of possible subtypes of depression and, perhaps, if there are different treatments that should be employed.

Appendix 1. Diagnostic criteria for Major depressive episode

A) Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations

1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood.

2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.

4) insomnia or hypersomnia nearly every day

5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

6) fatigue or loss of energy nearly every day

7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B) The symptoms do not meet criteria for a Mixed Episode

C) The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D) The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism)

E) The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Appendix 2. Antidepressants (N06A)

Non selective reuptake inhibitors (TCAs)

<i>Tertiary amines</i>	<i>Year of registration</i>
Imipramine	1962
Amitriptyline	1963
Trimipramine	1964
Clomipramine	1973
Venlafaxine	1995

Secondary amines

Nortriptyline	1965
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Selective serotonin reuptake inhibitors (SSRIs)

Fluvoxamine	1990
Paroxetine	1991
Citalopram	1992
Sertraline	1995
Fluoxetine	1995
Escitalopram	2001

Selective noradrenaline reuptake inhibitors (sNRIs)

Reboxetine	1997
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Monoamine oxidase A inhibitors

Year of registration

Moclobemide

1989

Other

Maprotiline

1977

Mianserin

1990

Mirtazapine

1996

Appendix 3. Summary in Swedish (Svensk sammanfattning)

”Behandling av depression i klinisk praxis. Ett folkhälsoperspektiv.”

Depression

Depression är en vanlig sjukdom. Genom att slumpmässigt välja människor i den allmänna befolkningen och fråga dessa om depressionssymptom, och, som i en del studier, i ett andra steg låta psykiatrer eller psykologer intervjua dem med misstänkt depression för att ställa diagnos, har kunskap inhämtats om hur vanligt det är med depression. Det beräknas att ca. 5% av befolkningen är drabbad (23, 25). Risken, att någon gång under livstiden insjukna, har i Sverige, i den s.k. Lundbystudien som genomförs genom att totalbefolkningen i ett skånskt samhälle intervjuas av en psykiater vid upprepade tillfällen under många år, uppskattats till 45% för kvinnor och 27% för män (38). Symptom på depression är t.ex. nedstämdhet, brist på glädje eller intresse, nedsatt aptit, sömnstörningar, långsamhet i tankar och rörelse, trötthet, koncentrationssvårigheter, social tillbakadragenhet, känslor av hopplöshet och återkommande tankar på döden och självmord (21, 22). Världshälsoorganisationen – WHO – har räknat antal år som förlorats pga. för tidig död (YLL) och antal år levda med funktionell oförmåga (YLD), och därefter beräknat sjukdomsördan – DALY – i befolkningen avseende olika sjukdomar genom att ta hänsyn till båda dessa mått (39). Depression var den främsta orsaken i hela världen till antal för tidigt förlorade år (YLL), och den näst främsta (efter ischemisk hjärt sjukdom) i västvärlden till sjukdomsörda (DALY) (41). Bakgrunden till denna svåra sjukdomsörda är att depressionssjukdomar börjar tidigt i livet (de flesta i 20-årsåldern) (24), ofta är av återkommande natur (23, 24) och medför en förhöjd dödlighet inte minst är risken

för självmord förhöjd (45-51). För den deprimerade individen, anhöriga och samhället leder depression till stort lidande och stora kostnader.

Depressionsbehandling

Effektiva läkemedel för depressionsbehandling s.k. tricykliska (TCA) finns tillgängliga sedan ca 40 år. Andra effektiva metoder är el behandling (ECT), effektivt också för svåra depressioner, och psykoterapi (kognitiv beteende terapi och interpersonell psykoterapi) effektivt för lättare depressioner (13, 52). Målet för all depressionsbehandling ska vara tillfrisknande (13). Emellertid söker en minoritet deprimerade individer läkare (1) och genom att fråga deprimerade individer i den allmänna befolkningen om de hade fått behandling med antidepressiva läkemedel vet man att en minoritet deprimerade erhåller sådan behandling (34, 57-59). Förskrivningen av antidepressiva läkemedel har ökat dramatiskt i Sverige liksom i många andra länder (2-4). Merparten av denna ökning utgörs av serotonin återupptags hämmare (SSRI) (2). Självmordstalen har gått ner i flera länder och det har framförts att det finns ett möjligt orsakssamband till den ökade användningen av antidepressiva läkemedel (2, 5, 73-76).

Effekterna på folkhälsan av denna ökade användning av antidepressiva läkemedel har diskuterats. Det har hävdats i den allmänna debatten att det sker en överanvändning alternativt felanvändning (6-11), att den antidepressiva effekten i sig inte är bättre än placeboeffekten och att den saknar betydelse för att motverka självmord (12).

Jämtlands län, som har haft en låg användning av antidepressiva läkemedel och höga självmordstal jämfört med Sverige i sin helhet (98), och där det finns en unik receptundersökning vars information kan användas för att studera individuella läkemedelsuttag, lämpade sig väl för att studera frågan om användningen av antidepressiva

läkemedel är rationell. Dessutom har, inspirerat av ett framgångsrikt projekt på Gotland i början av 80-talet, en fortlöpande vidareutbildning av primärvårdens läkare i att känna igen och behandla depressioner pågått sedan 1995 och denna utbildningsinsats har följts av en ökning av användningen av antidepressiva läkemedel som är större än för Sverige i övrigt samt en minskning av självmorden till den genomsnittliga nivån i Sverige.

Syfte

Det allmänna syftet för detta forskningsprojekt var att försöka utvärdera "Jämtlandsprojektet". Det blev emellertid tidigt uppenbart att utbildningsinsatsen var – om än betydande - bara en av många faktorer som påverkade allmänläkarna och befolkningen med avseende på depression. Ankomsten av den nya generationen antidepressiva har på ett avgörande sätt påverkat den allmänna debatten, befolkningens kunskap och inställning till depression och depressionsbehandling. Inte minst har läkare i Jämtland såväl som över hela landet blivit exponerade för olika utbildningsinsatser – oftast via läkemedelsindustrin. Syftet med detta forskningsprojekt fick därför anpassas till att med Jämtland som exempel studera och utvärdera vilka effekter de nya möjligheterna till adekvat depressionsbehandling haft på allmänläkare, förskrivningsmönster och folkhälsan.

Arbete I

Via Apoteket ABs individbundna receptundersökning i Jämtlands län (ett representativt urval ur befolkningen, 18 000 personer) studerades förskrivningsmönster för individer som erhållit ett första recept på ett antidepressivt läkemedel 1991-96. Det befanns att den ökade förskrivningen av antidepressiva läkemedel (SSRI) 1991-96 innebar en fördubblad incidens (från 0,76% till 1,33%) av antidepressiv medicinering men att 1/3 oavsett läkemedelstyp (SSRI eller TCA) inte förnyade sitt första uttag. Det var vanligare att SSRI i jämförelse med TCA förskrevs i adekvata doser. Incidensen av itererade uttag som möjliggjorde en

behandlingsduration på rekommenderade 6 månader ökade trefaldigt från 0,17% till 0,52%, SSRI behandlingar med ett sådant förskrivningsmönster var dubbelt så vanliga jämfört TCA (42% respektive 27%).

Arbete II

Resultaten från arbete I tillät inte en bedömning av huruvida det förändrade förskrivningsmönstret innebar en reellt förbättrad behandling för deprimerade patienter. Via receptundersökningen (se ovan) selekterades de 191 individer som under 1995 expedierats ett första recept på ett antidepressivt läkemedel och indikationen för deras antidepressiva medicinering söktes via journaler. I 171 fall kunde sjukhus och/eller primärvårdsjournaler studeras avseende indikation för förskrivning av det antidepressiva läkemedlet liksom behandlingseffekt. Indikationen var depression hos 2/3, fördelat på 82% av de med SSRI uttag och 23% TCA. Positivt behandlingsutfall bedömdes föreligga hos dubbelt så många av de SSRI behandlade som TCA behandlade (41% respektive 20%).

Arbete III

Via receptundersökningen och psykiatriska sjukjournaler undersöktes 59 självmordsfall och 118 kontroller mellan 1985-95. För suicidfallen studerades också rättsmedicinsk toxicologi. Fallen hade dubbelt så många uttag av receptbelagda läkemedel som kontrollerna och hade fler vårdtillfällen, tydande på att självmordsfallen hade en större sjuklighet inte minst psykiatrisk. Nio av de 18 som erhöll psykiatrisk vård vid något tillfälle hade en klinisk depressions diagnos. Under 3 månadersperioden före döden hade endast 7 (12%) av 59 självmordsfall tagit ut antidepressivt läkemedel. För 5 av 7 fall som hade tagit ut recept förskrivet av psykiater under de sista 3 månaderna före självmordet hade antidepressivt läkemedel ordinerats medan endast 2 av 31 uttagna recept som förskrivits av distriktsläkare avsåg antidepressiva. I 48 av de 59 fallen (81%) erhöles toxikologisk analys från den

rättsmedicinska obduktionen och endast 1/3 av de, under de 3 månaderna närmast före självmordet, uttagna psykofarmaka kunde återfinnas i den döda kroppen.

Arbete IV

Från receptundersökningen selekterades 2048 individer som 2001-2002 via enkät fick besvara frågor om depressionssymptom. Av de 1375 individer som svarat erbjöds de med misstänkt depression att intervjuas diagnostiskt (SCAN). Information om deras antidepressiva användning erhöles från receptundersökningen. Depressions prevalensen var 4.5% och av dessa hade 1/4 pågående antidepressiv medicinering. Profylaktisk antidepressiv medicinering pga. depression återfanns hos 1.3% av befolkningen. Sammantaget används åtminstone antidepressiva pga. depressionsindikation hos minst 2.5% av befolkningen. De förskrivna dagliga doser antidepressiva som används är i genomsnitt 1,5 gånger högre än de definierade dagliga dygnsdoser som används som tekniskt frekvensmått på mängden använt läkemedel. Den totala antidepressiva försäljningen var 54.9 DDD/1000 invånare/dag och av den mängden användes 2/3 till depressionsbehandling.

Slutsatser

Utifrån denna grundliga undersökning av erfarenheter från Jämtlands län kan skäl finnas att dra följande slutsatser:

1. Nästan var tjugonde individ hade en pågående depression.
2. Färre än var fjärde deprimerad individ behandlades med antidepressivt läkemedel.
3. Moderna antidepressiva läkemedel förskrevs pga. depression i de flesta fall, men också på andra godkända indikationer. Användningen vid icke godkända indikationer var minimal.

4. Minst 1/3 av de individer som har förskrivits antidepressiva mediciner för första gången, oavsett typ av preparat, brister i följsamhet.

5. En minoritet av dem som påbörjade en förstagångs behandling med antidepressivt läkemedel pga. depression fortsatte behandlingen i de rekommenderade sex månaderna.

6. SSRI preparaten förskrevs i rekommenderade doser till skillnad mot TCA som förskrevs i lägre doser.

7. En framgångsrik behandling var vanligare vid SSRI- än TCA- förskrivning.

8. Få, om än några, självmordsfall hade vid dödstillfället pågående behandling med antidepressiva läkemedel.

9. Den ökade användningen av antidepressiva läkemedel har varit till fördel för depressionsdrabbade individer och kan ha förebyggt ett antal självmord.

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