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Filip Smit

We never know self-realisation.
We are two abysses – a well staring at the sky.

(from: *The Book of Disquiet*, Fernando Pessoa)

Colophon

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In dedication to the people
who kindly participated
in these studies
- It is their altruism that furthers science

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Depressive disorder affects 154 million people worldwide. It carries a poor prognosis, compromises quality of life, and is further associated with excess mortality. Given these characteristics it is perhaps not surprising that depression is one of the leading causes of disability, and it is projected to be the single leading cause of disability in the Western countries by the year 2030. This should place depressive disorder in the limelight of public interest.

Preventing the onset of the disorder would help to maintain quality of life in many and avoid the costs of the full-blown condition. It is this preventive approach to reducing the burden of depression that is being studied by Dr. Smit in this book. Undoubtedly, the case for prevention is a strong one, especially because Dr. Smit demonstrates that preventing depression is a viable option and can be done effectively. In addition, the book offers valuable insights in selecting target groups for prevention, such that prevention is likely to become a cost-effective endeavour.

This book is but one example of the work conducted by the Trimbos Institute. The institute has a staff of 220 people, organised in 14 programmes. We conduct cutting edge research and strive to be leading innovators in the field of mental health and the addictions with the aim to foster health, prevent mental illness and to treat and support people with mental problems. The institute has multiple local and international collaborations and works closely with policy makers and health planners. The Multidisciplinary Depression Guideline, and related guidelines for the anxiety disorders, ADHD, schizophrenia and personality disorders are good examples of our work. The Institute is successful in attracting significant research funds, lately a multi-million Euro grant for its Depression Initiative. This will yield valuable knowledge about cost-effective prevention and treatment of depressive disorder. Besides being useful in a Dutch context, our knowledge may also be used for the development of public health policies abroad. It is with this issue in mind, that it gives me pleasure to recommend this important book.

Dr. Jan Walburg
(CEO / President of the Trimbos Institute)



"Melancholia" by Albrecht Dürer (1514)

Antithesis:

A note to Albrecht Dürer's Melancholia

As a whole, Dürer's "Melancholia" (see title plate) is a somewhat disjointed composition; a mêlée of lavish allegory and harsh geometry. Nothing quite dominates the plate, and nothing lends it compositional unity. In fact, it is rather chaotic. However, the disharmony suggests hidden meaning and does so in a forlorn and forbidding way. It seems something is under construction, something will be revealed in due time, and yet, in the here and now, it resists decryption, both as a whole and in detail.

What do we see? The robed and winged figure of Melancholia sits at the corner of a building. We cannot see the face clearly. It is partly covered by a supporting hand, and for the remainder it is cast in shadows. Only two piercing eyes catch a flicker of light. The concentrated stare is unhappy in an unsentimental way. Observe this face. It is neither male nor female, and it looks strangely androgynous. It gazes at something we cannot see. The other hand of this figure rests on top of a closed book, and holds a drawing compass. Several keys dangle from a girdle. This suggests that something is closed, and can be opened, but we do not know what.

What else do we see? A greyhound lies on the ground, curled, starved and miserable. In fact, it looks rather less than a dog, and we find it difficult to recognise man's most loyal companion. Next to Melancholia sits a putto on a millstone. The little cherub sits there as the pendant of a sinister bat, which hovers in the sky, and has "Melencolia I" written across its wings. These figures are surrounded by a number of geometrical forms, some tools, and cosmic phenomena. At the front we see tools for construction: a plane, a saw, a measuring rod, and some nails. Further to the back: pincers, a hammer, and rising against the building, a ladder. Above the head of the putto are scales. There is also an hourglass and a magic square with numbers. In the bottom row we can read 1514, presumably the year when the engraving was made. The numbers are arranged as follows:

16	3	2	13
5	10	11	8
9	6	7	12
4	15	14	1

and show, upon closer inspection, a pattern of almost maddeningly internal consistency. In the backdrop is a shimmering sea, a moonlit coastline, a nocturnal sky with the arc of a rainbow, and a meteor falling. The whole is illuminated

by a dull light. The light, perhaps of the moon, falls from the upper right, and picks out the unconnected items one by one, and leaves them with barely a shadow. And there is the blinding, frontal, light of the ominous meteor. Caught in that black light is the pale arc of a rainbow.

Now, put this together, and think! It is neither day nor night: the meteor is a sign of the night, the rainbow of the day, and the two will not co-occur. This is an unworldly world, where the fluidity and animation of the allegorical figures stand out in sharp contrast to the stern shapes of geometry. This is life thrown out in an unconcerned, mathematical universe. This is *tedium vitae* pure and cold. This is a universe under partial construction – bare of harmony, without any connectedness – where even the distorted shape of the dog is hardly recognizable. But there is more. This is also the androgynous twin-cosmos of intellect and affect, of day and night, of male and female, of genius and foreboding, of the angelic putto and the demonic bat, the two pendants, the two aspects of the same world. It may look accidental and hapless, but there is method in this madness. Both the disparity, and the throwing together of the unconnected parts, create a world of new meaning. The numbers in the magic square add up to the same figure across the columns, across the rows, the diagonals, the four corners, and in the four corners. There is a pattern. There is encrypted meaning. The plate, as many have pointed out, may represent a spiritual self-portrait of Albrecht Dürer, one which links intellectual and artistic creation with melancholy, and makes them inseparable, as if the genius cannot, and will not, rise without depression.

This may be mere conjecture, but I fear the prevention of depression (never expected to be a complete success) may also invade this world of artistic and intellectual genius, this half-made world under permanent construction. Prevention of depression could perhaps save one precious thing, but at the expense of another. Let that serve as a warning for the remainder of this thesis.

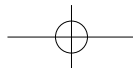
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Preventing Depression

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General introduction



Research questions

This thesis is about preventing depression. It is divided in four parts. Each part addresses one question. The questions are:

1. Do we need it?
2. Do we know where to begin?
3. Is it effective?
4. Is it cost-effective?

Clearly, these are common-sense questions. One may even find them unsurprising and simple. The amazing thing, however, is that the questions are rarely addressed jointly. However, the primary question, "Do we need prevention of depression?" cannot be answered without addressing the other questions. Assume for a moment that we have compelling reasons why we need depression prevention. However, if it is not effective, it remains a futile wish; and if it is not affordable, we have to replace this wish with another alternative that is economically more attainable. Accordingly, nothing comes of the original idea. In the same vein: we need to know where to begin with preventing depression, or else the whole venture will be reduced to a blindfold game of trial-and-error, which will be slow, painful and costly, and carries the risk that a possibly sound idea may be cast aside as impractical. Thus, all four questions are interrelated, like the numbers in Dürer's Magic Square – and answering one question will require that the others also be addressed.

In the following sections we will first clarify the key-concepts, depression and prevention, then we will present the outline of this thesis and describe some of its limitations.

Depression

Depressive disorder is characterised by an abnormal depressed mood (dysphoria) and loss of pleasure (anhedonia). This blunted affect is present most of the day, nearly all days, for at least two weeks. The resulting lack of motivation can be quite crippling. In addition there are a number of other symptoms causing marked functional impairment, such as sleep disturbance (insomnia or hypersomnia), lack of energy (anemia), poor concentration, a lack or increase in appetite, inappropriate feelings of self-reproach, recurrent morbid thoughts about death and suicidal ideation (APA, 1987).

Depression often carries an unfavourable prognosis. A depressive episode lasts

for six months on average (Kruijshaar et al, 2005) and in 20% of the cases it lasts longer than two years (Spijker et al, 2002). According to one estimate, there is a 85% probability that after recovery a new episode occurs in the five years following the index episode (Mueller et al, 1999), but other studies usually put recurrence rates somewhat lower (Fombonne et al, 2001; Keller et al, 1992; Piccinelli and Wilkinson, 1994). Compulsively contemplating death and suicide is often symptomatic of this disorder, and makes suicide a real risk. About 60% of all suicides are committed by people who were depressed (Marquet et al, 2005), and mortality rates are higher by a factor of 1.65 in people with depression (Cuijpers and Smit, 2002).

It is not only a disabling condition, it is also highly prevalent. Annually 737,000 people suffer from depression in the Netherlands (Meijer et al, 2006). The impairment caused by this disorder and its high prevalence combine to create a substantial disease burden at national level, which is equal to an annual loss of 157,700 quality adjusted life years in the Dutch population alone (ibid). According to the World Health Organisation depression is one of the major causes of non-fatal disease burden world wide (WHO, 2000). Finally, it is well known that people with depression make more frequent use of health services and stay absent from their work more often, which has substantial economic ramifications (see Chapter 1.2).

Why prevention of depression?

Treatment of depressive disorder is as successful as any other medical treatment (Beekman et al, 2006). Nevertheless, there are two compelling reasons why we should like to also have preventive interventions for depressive disorder.

First, the annual influx of new (that is, first-ever) cases of depression is substantial. On an annual basis there are 358,500 new cases in the Netherlands, which is 49% of the prevalent cases. This suggests that it would be a sound idea to reduce this influx, which, in turn, requires primary prevention.

Second, curative interventions can only reduce the disease burden of depression (expressed as years lived with disability) to something in between 10% - 20% at population level, because not all cases are recognised as such, and when recognised not all will receive appropriate treatment or comply with the given treatment (Andrews et al, 2004; Chisholm et al, 2004).

From a public health point of view it seems therefore appropriate to reduce the disease duration by cure and to reduce the influx of new cases by primary prevention (see Chapter 1.1).

Types of prevention

At this point it might be well to introduce some terminology to describe prevention. Conventionally, prevention is divided into primary, secondary and tertiary

prevention. Primary prevention is directed at avoiding new onsets, secondary prevention at early recognition and early intervention in people who have some preliminary symptoms of the disorder, while tertiary prevention aims to avoid impairments that may stem from a disease. It should further be noted that relapse prevention is aimed at avoiding relapse in remitting patients. Both primary and secondary prevention can also be described by a terminology introduced by Mrazek and Haggerty (1994). They distinguish between three types of prevention:

1. *Universal* prevention consists of interventions, often of a psycho-educational nature, directed at the whole population, regardless of risk status. The aim of universal prevention is to inform the general public about depressive disorder, how to recognise it, what people can do to avoid it, and how to improve the prognosis of its milder forms – and should the latter fail – to whom they can turn for help. Other forms of universal prevention may assume the form of screening programs, for example in schools or in the primary care setting. Universal prevention is important because it helps to create awareness in a population about the disorder, what can be done to prevent it, and what treatments are available. Sometimes it is thought that this awareness can act as a necessary catalyst to create a sense of readiness in a population to take a further step towards selective and indicated prevention, if so required.
2. *Selective* prevention is directed at population segments that are placed at a higher risk for depression because they have been exposed to risk factors known to be predictive of the onset of the disorder.
3. Finally, *indicated* prevention is directed at people who have some of the depressive symptoms, but do not meet the diagnostic criteria for the full-blown disorder. This group may be in an early disease stage, and is known to be at much higher risk of depressive disorder.

It is these latter forms of – selective and indicated – prevention that will be discussed in this thesis. The idea is that people can make a transition from a relatively good to a worse health state. Presence or absence of risk factors and protective factors may promote or inhibit these transitions. Hence, conducting prevention needs to be based on knowledge of the relevant risk and protective factors. The aim of prevention is to contain the adverse effects of risk factors and to strengthen the effects of protective factors. In other words, the task at hand is to reduce risks for unfavourable transitions and improve prognosis in the face of adversity.

Outline of the thesis

The overall outline of the thesis can be summarised as follows. Chapter 1.1 introduces the rationale of preventing depression alongside some key statistics that

underscore the importance, if not to say the necessity, of a much firmer role for prevention in public health. In Chapter 1.2 the economic costs of mental disorders are presented, providing, we hope, yet another incentive to attach greater value to the prevention of mental disorders, in particular that of depression. Both chapters help to answer the first question “Do we need it depression prevention?”

The next three chapters, 2.1 through 2.3, address the second question: “Do we know where to begin?” Here we employ epidemiological techniques and make use of large population-based psychiatric cohort studies: the Nemesis study, the Longitudinal Aging Study of Amsterdam (LASA) and the Amsterdam Study of the Elderly (Amstel study). The epidemiological studies are used to identify groups of people where prevention is most likely to yield substantial health gains with the least effort and hence for the lowest costs. To put it in another way, the epidemiological data sets are used to generate hypotheses about the possible cost-effectiveness of prevention of depression.

As always, the proof of the pudding is in the eating, and this brings us to the questions: “Is prevention of depression effective and cost-effective?” To answer these questions we present the outcomes of a randomised prevention trial in Chapter 3.1 and a meta-analysis of similar trials in Chapter 3.2. These chapters explore and synthesise the first evidence that prevention of depression is possible and effective. Chapter 4.1 is based on the same trial, but presents data on the cost-effectiveness of preventing depression. Again, this study is one of the first of its kind.

In the preceding chapters we made a shift from population-based epidemiological studies (to generate hypotheses) to a clinical trial (to test one of the hypotheses). A parallel approach was adopted for the economic studies. We started with a population-based cost-of-illness study and concluded this line of investigation with a trial-based cost-effectiveness analysis. Thus, the shifts are from the general to the specific, from hypothesis generating to hypothesis testing, and follow two parallel courses, one epidemiological, the other economic. In the final chapter, Chapter 4.2, the population-based epidemiological perspective is revisited in the form of a “risk-factor epidemiology of costs in mental health”. Here, former notions are brought together in a slightly new way, and we investigate the costs associated with risk factors for mental disorder. This chapter leads up to the General Discussion, which contains a summary of the main findings, followed by discussion, and directions for the future. I should like to mention that the latter section is partly borrowed from yet another study (Meijer et al, 2006), commissioned by the Netherlands Ministry of Health, to provide a scientific underpinning for a Policy White paper on the prevention of common mental disorders.

Limitations

This thesis has several limitations and it is only fair to point them out. First, it is restricted to the adult Dutch population, hence prevention of depression in children and adolescents will not be discussed.

Second, this thesis has a focus on selective prevention and to a larger extent an even more narrow focus on indicated prevention. In fact, our primary interest was to address the question how indicated prevention (in people with some early symptoms) could be made more restrictive by directing it towards ultra-high risk groups that do not only have some early symptoms, but are in addition exposed to a number of risk factors known to be predictive of the onset of depressive disorder. We took this angle for two reasons. Population segments having some depressive symptoms can be large, depending, of course, on the exact definition of "having some depressive symptoms". It is hard, then, to see how all these people can be offered preventive interventions as limited economic resources will impose restrictions. Although we do not explicitly address the ethical question when prevention is acceptable, ethical considerations played also a role in our decision to be restrictive. Selective prevention targets people who have been exposed to risk factors and have an increased risk of becoming depressed. Now, these people may have no knowledge about their risk status. Under those circumstances it might be inappropriate to offer them a (medical) intervention. After all, we cannot be sure that the disorder will occur without the intervention, and we can not be sure that the disorder will be avoided when the intervention is offered. In other words, some people in the target group will not benefit from the intervention, but will be confronted with a perhaps upsetting knowledge about their risk status. It is worth noting that these ethical considerations may take a different turn when it comes to indicated prevention. Now people have complaints and are likely to be aware about their condition. In fact, they may be looking for help or willing to accept help when it is offered.

Our approach to these logistic and ethical issues is to require that prevention is preferably directed at groups that have already some symptoms and are in addition exposed to risk factors indicative of an ultra-high calculable risk of depression. With the risk to create some terminological confusion: we wanted indicated prevention to become more selective. Hence the narrow focus.

Third, we should mention that this thesis represents work in progress. At one point prevention of depression in older people is discussed, at another we refer to younger adults. In other words, there are gaps, disconnected quantum leaps, and the answers to the research questions cannot be considered complete. More work remains to be done, and more work is being carried out. This thesis, then, is only a snapshot of the approaches we took to answer questions 1 through 4. Its relevance is that the approaches described in this thesis can be used for addressing similar questions about other mental disorders, in other age groups.

Indeed, it gives me great personal satisfaction to see that some of the research lines are being extended to other fields, such as anxiety disorder, problem drinking, and to younger age groups.

One final issue needs to be addressed here. There is no thesis without an antithesis. That is why an extra section has been inserted. This section is formed by the title plate, consisting of Albrecht Dürer's Melancholia, and a brief reflection on its possible meaning. The role of the antithesis is to make explicit that this thesis takes only one angle towards preventing depression. This is to say, that other views may be adopted, and must be adopted, in order to well and truly open up the debate.