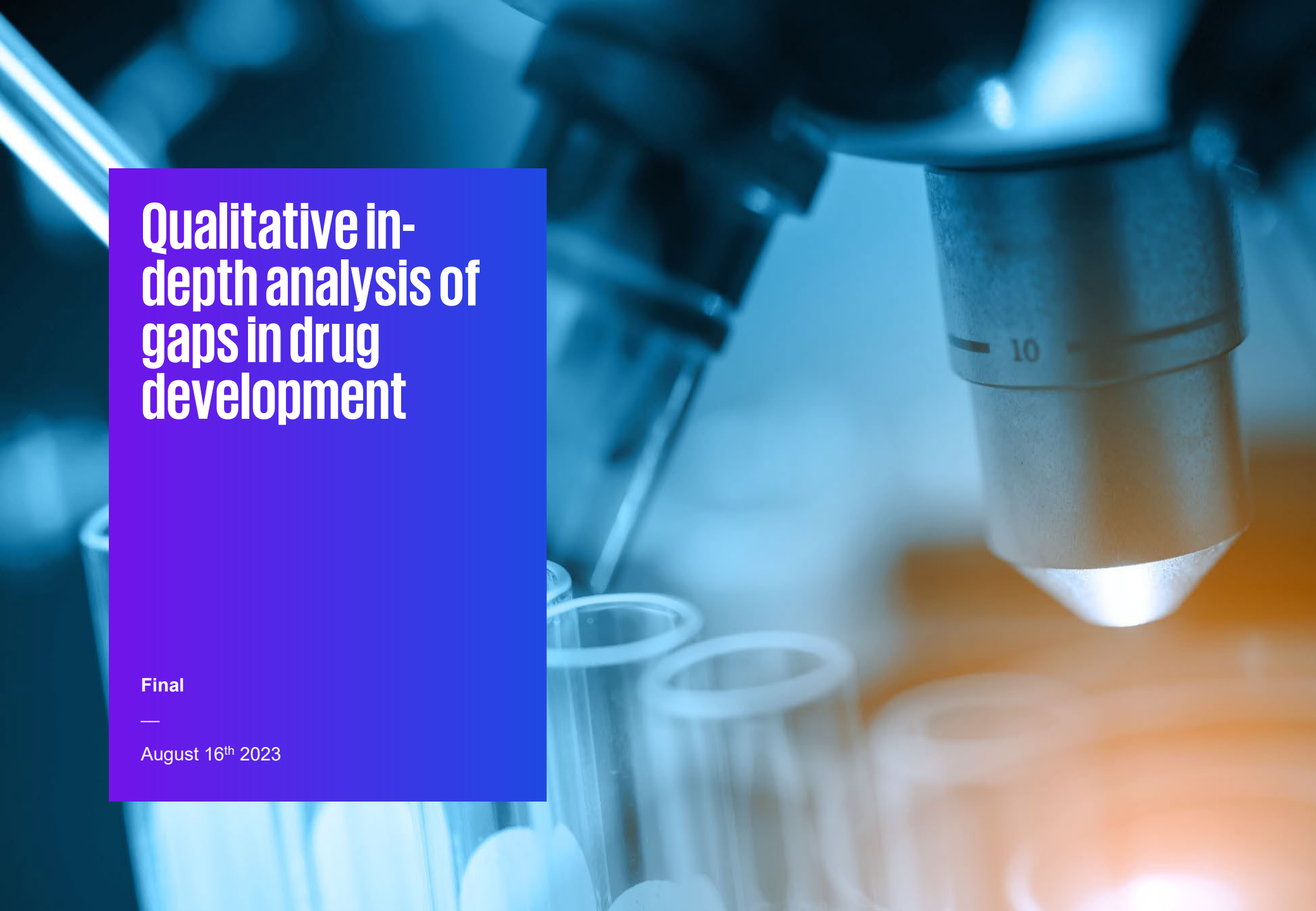


Qualitative in-depth analysis of gaps in drug development

Final

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August 16th 2023

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Executive summary

Improved balance between financial and social benefits of drug development is desirable

Background and purpose of the study

A study into the financial ecosystem of drug research & development (R&D) shows that, logically, commercial potential is a key driver of drug research. However, drugs with commercial potential are not necessarily drugs for conditions with the highest burden of disease. That begged the question of to what extent R&D activity into new drugs is answering the societal need (as expressed in burden of disease).[1]

As a result of a possible suboptimal alignment of drug development to the societal need, there may be conditions for which pharmacological treatment is desirable, but for which no or only limited medication is developed. In this study, this is referred to as "gaps in drug development". Other terms often used to indicate the discrepancy between the development of drugs and the societal need for drugs are unmet medical need or pharmaceutical blind spots.

The Dutch Ministry of Health, Welfare and Sport asked KPMG to study "gaps in drug development". KPMG translated this into the following research questions:

Research question 1: For which conditions is R&D activity in imbalance with the societal need? Can the need for medicines for these conditions be categorised?

Research question 2: Can these conditions be broken down into subindications?

Research question 3: What are the causes of limited R&D activity and what can the government do to encourage R&D activity for these conditions?

Funnel approach to identify gaps in drug development

The above research questions were answered using the funnel approach. This research approach is presented in Figure 1.

Starting point of this study are the 33 conditions with the highest burden of disease

In a previously conducted quantitative drug development study, 33 conditions with the highest annual burden of disease were defined. For these conditions it was mapped out which drugs had been newly registered in the period 1995-2021 and for which indications drugs are currently being developed.[2] The quantitative study describes the numbers of registered and expected new drugs. This report contains the results of subsequent qualitative research, describing for which of these 33 conditions there are gaps in drug development and what the pharmacological need for these conditions consists of. The factors contributing to the emergence of these gaps and the possible solutions are also explored in a qualitative manner.

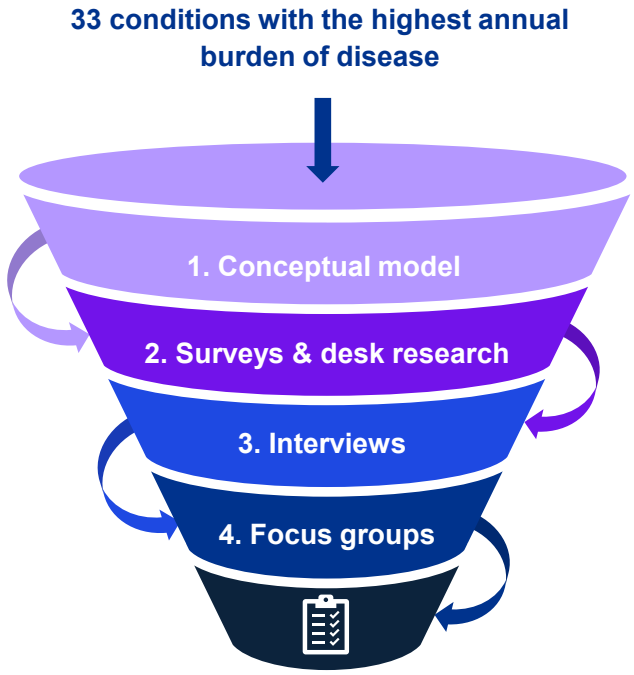


Figure 1: Funnel study approach

Source:
1. The Financial Ecosystem of Pharmaceutical R&D
2. Output current R&D ecosystem

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Funnel approach for identifying gaps in drug development

Step 1: Conceptual model

A conceptual model was drawn up to enable a comparison of the 33 conditions. This conceptual model consists of three composite indicators that together define the gaps in drug development. The three selected indicators are:

— **Societal need (Y-axis)**

The societal need is defined as burden of disease expressed in Disability Adjusted Life Years (DALYs).

— **Relative potential improvement in R&D activity (X-axis)**

This indicator shows that more R&D activity is possible and that, given the state of knowledge, this R&D activity is considered promising. Because there is no unit for improvement in R&D activity and it concerns a mutual comparison, this is referred to as 'relative' potential improvement in R&D activity.

— **Potential improvement in pharmacological treatment (colour coding)**

This indicator indicates whether better pharmacological treatment is possible because there is no effective drug yet, or because there is a need for drugs with a different form of administration or fewer side effects.This dimension has been made into a categorical variable, where the categories are displayed in different colours.

The conceptual model is populated with the 33 conditions with the highest annual burden of disease; an overview of these conditions is shown on page 14. The populated conceptual model can be plotted as a graph. Conditions on the curve have equal improvement potential based on societal need and relative potential improvement in R&D activity. (The potential improvement in pharmacological treatment is not included in this yet). The two variables are inversely related. That is the reason why an inverse curve is used to identify gaps in drug development. Conditions above the curve have the greatest improvement potential based on societal need and the relative potential improvement in R&D activity.

Step 2: Desk research and survey

Approach

The conceptual model is populated based on desk research and a survey Existing data was used to fill in the societal need expressed in DALYs and for the initial detailing of the other two indicators. Existing data was obtained using desk research. For a qualitative analysis of the potential improvement in R&D activity and the potential improvement in pharmacological treatment and to populate the rest of the conceptual model, a survey was conducted. The organisations approached for this are listed in Appendix A, the survey questions are included in Appendix B.

Results

A condition-specific survey was conducted among members of scientific associations and patient associations. This survey was completed 102 times; the response rate is 77.9%. In addition, a general survey was conducted among members of coordinating scientific associations and professors of pharmacology. This survey was completed 60 times; the response rate is 42.9%. The input from the surveys and desk research was used to plot the conceptual model.

Conditions on the curve have equal improvement potential based on societal need and relative potential improvement in R&D activity. (The potential improvement in pharmacological treatment is not included in this yet). The two variables are inversely related. That is the reason why an inverse curve is used to identify gaps in drug development. The curve is placed at the position where it makes a clear distinction visible, with some ten conditions above the curve (as such, it can be seen as a 'cut-off curve', so to speak).

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The conceptual model shows 11 conditions with a possible gap in drug development.

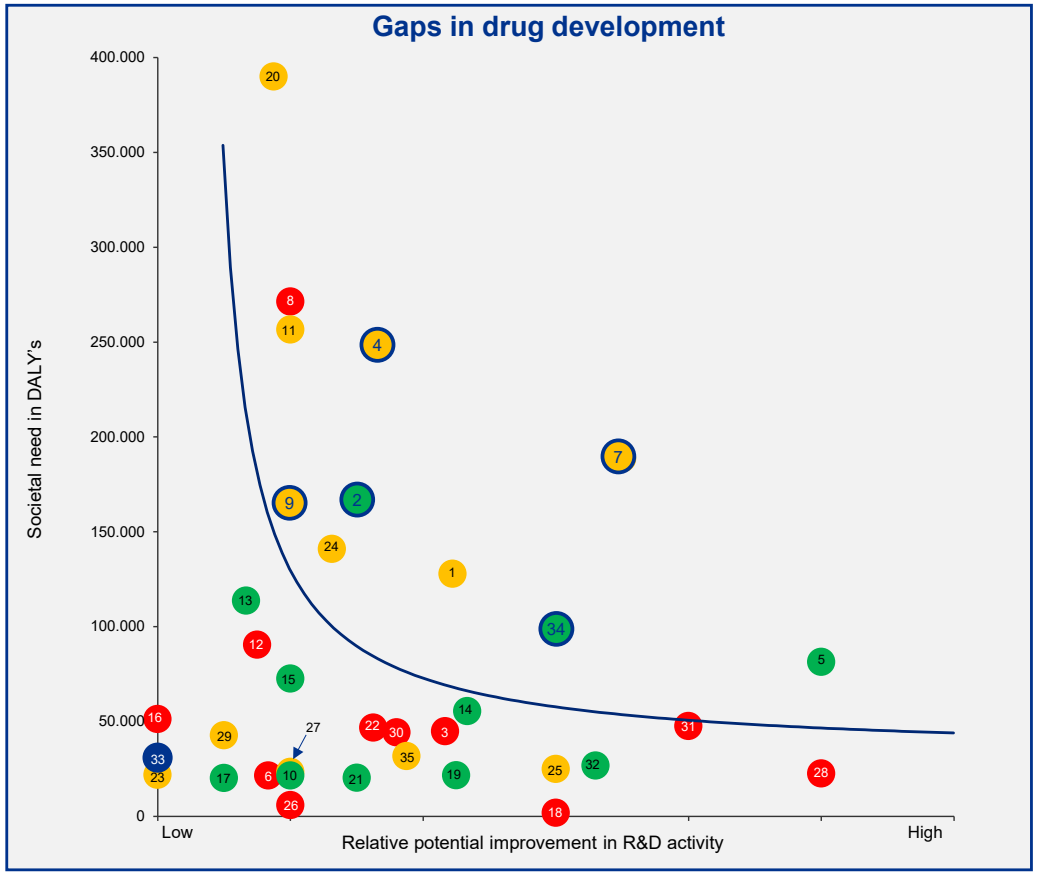


Figure 2: graphic representation of results of conceptual model

Caption:

Y-axis: Societal need in DALYS per year for the Dutch population

X-axis: Relative potential improvement in R&D activity Relative measure, therefore no unit is shown on the x-axis.

Colour: Potential improvement in pharmacological treatment:

Low potential | Medium potential | High potential | No results from survey | Selected for qualitative in-depth analysis

Explanatory list:

1. Anxiety disorders
2. **Arthrosis**
3. Asthma
4. **Stroke**
5. Breast cancer
6. Contact eczema
7. **COPD**
8. Coronary heart disease
9. **Dementia**
10. Diabetes mellitus
11. Diabetes mellitys type II
12. Colon cancer
13. Hearing disorders
14. Eye disorders
15. Heart failure
16. Cardiac arrhythmias
17. Brain cancer
18. HIV infections
19. Skin cancer
20. Hypertension
21. Upper respiratory infections
22. Lower respiratory infections
23. Leukemia
24. Lung cancer NSCLC
25. Lung cancer SCLC
26. Multiple myeloma
27. Multiple sclerosis
28. Non-Hodgkin lymphoma
29. Pancreatic cancer
30. Prostate cancer
31. Rheumatoid arthritis
32. Schizophrenia
33. Oesophageal cancer
34. **Mood disorders**
35. Parkinson's disease

Explanation of figure 2:

- The interviews and the survey retrieved for which conditions there are subindications for which a distinction must be made in the remainder of the study. This distinction has been made for Diabetes Mellitus type I and type II and for small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC).
- The 33 conditions with the highest annual burden of disease (35 conditions including subindications) are presented in Figure 2. The 11 conditions above the curve were included in a longlist of conditions for which a gap in drug development may exist. Based on the interviews, five conditions were selected from this longlist for which a qualitative in-depth analysis was carried out. These are the conditions that are printed in bold and underlined in the explanatory list, and indicated with a blue circle in figure 2. Breast cancer was not selected for a further in-depth analysis on the basis of the interviews; for a detailed explanation, see pages 22 to 27.
- For hypertension, only data on the indirect burden of disease is available. Because hypertension is a risk factor for many other conditions, the indirect burden of disease is high. It is estimated at 390,000 DALYs.
- For multiple myeloma no burden of disease expressed in DALYs is available for the Dutch population. Every year, approximately 1,300 people are diagnosed with multiple myeloma. There are some 6,500 people with this form of cancer. Multiple myeloma was included in the previous quantitative study because of the large number of new drugs.

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A qualitative in-depth analysis was carried out for arthrosis, stroke, COPD, dementia and mood disorders

Step 3: Interviews

Approach

The interviews were used to validate whether the 11 conditions on the longlist were recognised and whether any other conditions had to be included in the list. We also asked interviewees whether there are any subindications for the conditions studied, the pharmacological need for these conditions, and the current level of R&D activity. Subsequently, a selection was made from the longlist of conditions for which further qualitative in-depth analysis was carried out.

Results

A total of seven interviews were held with representatives of the pharmacological industry, investors, professors of pharmacology and interest representatives. The conditions arthrosis, stroke, COPD, dementia and mood disorders were selected from the longlist for further qualitative in-depth analysis.[a]

Step 4: Focus groups with experts

Approach

For each of the five selected conditions, further qualitative in-depth analysis was carried out in focus groups. For the focus groups, a heterogeneous group of experts was invited to shed light on the different perspectives of the pharmacological need and R&D activity. The following experts were invited for the focus groups: patients/patient representatives; healthcare professionals pharmacists; professors of pharmacology; representatives of the pharmacological industry and investors. Not all experts were represented in every focus group. The results described are not exhaustive, but only present the findings from the focus groups.

Three main themes were discussed in the focus groups:

— What is the pharmacological need for these conditions?
Questions included whether the need concerns the condition as a whole or specific subindications, whether the need consists of an improvement of current medication the development of new medication, and whether this medication is available on other markets (e.g. Japan or China).

— What are the possibilities/impossibilities of drug development?
This addressed the current level of R&D activity. In the case of lagging R&D activity, the reasons for this were explained, such as a lack of funding or the current state of science.

— What potential solutions exist to better meet the pharmacological need?
This last theme included questions about concrete solutions that national and international governments could facilitate.

Results

Below, the main findings from the qualitative in-depth analysis in the focus group are described for each condition.

Arthrosis

There currently is no preventive, curative or disease-modifying pharmacological treatment for arthrosis. There is, therefore, no need for improvement of existing medication, but a need for new therapies. Arthrosis has many different manifestations, each of which requires its own form of treatment. Recognising these manifestations is necessary for better treatment: there is a need for patient stratification. Enabling patient stratification requires facilitating diagnostics, such as advanced imaging or use of biomarkers.

To demonstrate the effectiveness of disease-modifying arthrosis therapies, major long-term - and therefore expensive - trials must be conducted. It is advocated as a starting point not to look for a solution for the entire patient population, but to first demonstrate the effectiveness of pharmacological treatment for a selected subgroup of patients: a proof of concept.

The availability of new drugs can be simplified by rationalising the regulatory framework for the approval of experimental drugs. One suggestion that was put forward is the conditional approval of promising experimental drugs being studied.

Note: a. These are not by definition the five conditions with the greatest improvement potential, but conditions that have been selected for further qualitative in-depth analysis on the basis of the outcomes of the conceptual model and validation with experts.

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Encouraging drug development requires customisation

Stroke

There have been a lot of developments in the treatment of the acute phase of stroke. There currently is little need for improvement of medicines for the acute phase of stroke. There is, however, a need for drugs that can limit brain damage in the phase immediately afterwards, for instance for swelling or inflammation. Lowering the burden of disease of a stroke for the largest group of patients requires other measures than drug development. Most can be gained from preventing strokes, which requires recognition of patients with risk factors and prevention.

COPD

To understand the drug need for COPD, a classification according to treatable traits is necessary. These include inflammation, bronchoconstriction and mucus formation. A total of twelve treatable traits have been defined.[3] These treatable traits offer different starting points for drug treatment.

In terms of new drugs, there is a need for disease-modifying drugs that prevent loss of pulmonary tissue, such as biologicals. There is also a need for pharmacological regeneration of pulmonary tissue.

With regard to the need for improvement of existing medication, corticosteroids are mentioned most often. These only work in some COPD patients and cause many side effects. These patients need an effective anti-inflammatory.

There is also a need for anti-inflammatory drugs that effectively combat inflammation without general immunosuppressive effect.

A possible solution put forward is encouraging the synergistic effect between academia and industry.

Dementia

It has been indicated that there is a lot of R&D activity in the field of disease-modifying treatment of dementia. There are several trials with positive results, as well as a few approved medicines. However, the effect of these drugs is limited, the costs are high and there are significant side effects. That is why it is emphasised to stimulate economies of scale now.This can be enabled by more continuity in funding and a more favourable research and investment climate.

Mood disorders

Mood disorders include both bipolar disorder and major depressive disorder. The pharmacological need is greatest for depression, both unipolar and bipolar depressions.

It is indicated that the treatment of mood disorders requires further development of existing medication. There is a need for faster acting drugs with fewer side effects. It is also indicated that there is a need for new drugs. These new drugs are quicker acting and take effect in a different way. Drug repurposing of psychedelics is mentioned as the most promising option.

Investing in setting up networks is mentioned as a precondition for more effective treatment. These networks seek to collect patient data, such as patient characteristics, treatment and course of the disease. These networks ultimately make it possible to better predict which treatment will work for which type of patient on the basis of patient characteristics.

Source: 3. Treatable traits: toward precision medicine of chronic airway diseases - PubMed (nih.gov)

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Patient stratification necessary for drug development for different conditions

General views from focus groups on opportunities to stimulate drug development

The focus groups mentioned several possible solutions to fill the gaps in drug development for each condition. In addition to the condition-specific solutions, there are a number of general solutions that were a recurrent theme in all focus groups. Below is an overview of the possible solutions mentioned:

— Improving public-private partnership. Many good ideas originate in academia, but it is usually the industry that has the investment power to scale up an idea. Improving collaboration between the two will make it easier for universities and the industry to jointly develop an idea up to the phase as a registered medicine. An additional benefit would be that talented researchers can better be retained for academia, where expertise in the current situation sometimes leaks away to, among others, the pharmaceutical industry because it can offer more financial security and there are more opportunities for further development of their ideas. Agreements on intellectual property are mentioned as facilitator for improving public-private partnerships.

— Simplifying the regulatory framework. The experts indicate that there is a culture in the Netherlands in which the safety and rights of participants in scientific research are properly safeguarded. However, the downside of this regulatory framework is that it hinders conducting research in the Netherlands. International collaborations in particular could increase sample sizes.

— More national and international control. For various conditions it is indicated that other developments are preconditions for acceleration of drug development. These include cooperation with primary care, the development of advanced diagnostics and the possibility of patient stratification. Participants in the focus groups do not expect that research into this will be initiated by the industry. That is why international governments are called upon to take the helm.

— Improving the infrastructure. The Dutch research landscape is fragmented. Improving the infrastructure would promote collaboration between universities, authorities, primary care and patients. As a result of the concentration of care, every healthcare institution has to deal with an increasingly selective patient population. This affects the research populations in medical scientific research. Access to complete and representative research populations and materials (such as biobanks) must be guaranteed despite the centralisation of care.

Conclusions

Based on a funnel approach, this study identified for which conditions gaps in drug development may occur. From these, five conditions were then selected for further qualitative in-depth analysis. This shows that the emergence of gaps in drug development is more complex than simply the lack of commercial potential of drugs. Factors such as the state of knowledge, access to research populations and an existing infrastructure for collaboration also play a key role. The extent to which each of these factors applies varies per condition, is difficult to determine exactly and is also subjective.

There are specific drug needs for the conditions mentioned. However, what all selected conditions have in common is the need for patient stratification. In the past, drugs for many conditions were developed for the patient group as a whole. However, based on the current knowledge, it is clear that different conditions comprise different subgroups that respond differently to treatments. There is a need to better recognise these groups and develop treatments that target specific subgroups.

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1.

Background of the study

The current R&D ecosystem results in gaps in the development of medicines

Background

The study “The Financial Ecosystem of Pharmaceutical R&D”, published in 2022, has shown that investors and industry weigh the commercial potential, the investment costs and the potential of a medical breakthrough given the state of knowledge before deciding on the development or further development of a drug.[1] The relative importance of the various factors can differ per investor and the stage of development of the drug. This study shows that, logically, commercial potential is a key driver determining whether a drug will be developed to launch. This makes the development of new drugs in part dependent on the willingness of governments and insurers to pay for these drugs.

However, drugs with commercial potential are not necessarily drugs for conditions with the highest burden of disease. New drugs that are developed do not necessarily meet the societal need for new drugs. As a result, there are conditions for which there is a societal need for new medication but for which insufficient new drugs are developed. In this study, the discrepancy between the drugs that are actually being developed and the drugs for which there is a societal need is described **“gaps in drug development”.**

Research questions

The Ministry of Health, Welfare and Sport has asked KPMG to conduct a study into “gaps in drug development”. KPMG translated this into the following research questions

Research question 1: For which conditions is R&D activity in imbalance with the societal need? Can the need for medicines for these conditions be categorised?

Research question 2: Can these conditions be broken down into subindications?

Research question 3: What are the causes of limited R&D activity and what can the government do to encourage R&D activity for these conditions?

Reader’s guide

Chapter 2 describes the research approach used. In Chapter 3, we explain how we selected conditions for which in-depth analysis was carried out on the basis of this approach. Chapter 4 outlines the in-depth results for the selected conditions. Chapter 5 contains the recommendations. Appendix A provides an overview of all organisations that were asked to participate in the surveys. Appendix B comprises the complete surveys. Finally, Appendix C lists additional results for the condition ‘anxiety disorders’.

Source: 1. The Financial Ecosystem of Pharmaceutical R&D

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2.

Research approach used

Identification of gaps in drug development by means of a funnel approach

To identify gaps in drug development, we used a funnel approach, as presented in Figure 3. Starting point were 33 conditions with the highest annual burden of disease. This was followed by the following four steps:

1. Development of a **conceptual model** for mutual comparison of the gaps in drug development for these 33 conditions
2. Plotting conditions in the conceptual model based on a **survey and desk research**
3. Validation and refinement of the outcomes of the conceptual model in various **interviews**
4. Qualitative in-depth analysis of a selection of conditions in **focus groups**

The steps in the study approach are discussed in more detail on this and the following pages.

Starting point of this study are the 33 conditions with the highest annual burden of disease

The 33 conditions with the highest annual burden of disease were taken as a starting point for this study. These conditions follow from the research report “Output current R&D ecosystem”. This report describes the number of market introductions of new drugs between 1995 and 2021 for the 33 conditions with the highest annual burden of disease. An overview of these conditions is presented on the next page.

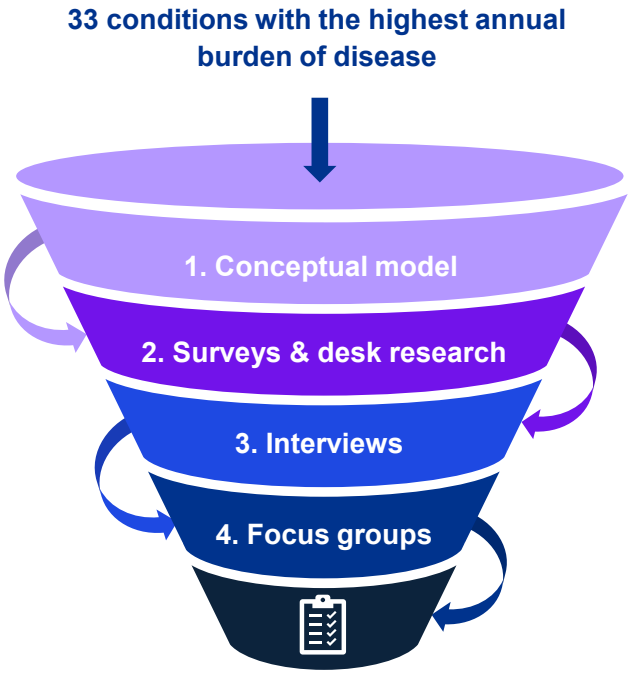


Figure 3: funnel study approach

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Overview of the 33 conditions with the highest annual burden of disease

Conditions with the highest annual burden of disease[2, 4, a]		
1. Anxiety disorders	12. Hearing disorders	23. Lung cancer
2. Arthrosis	13. Eye disorders	24. Multiple myeloma[b]
3. Asthma	14. Heart failure	25. Multiple sclerosis
4. Stroke	15. Cardiac arrhythmias	26. Non-Hodgkin lymphoma
5. Breast cancer	16. Brain cancer	27. Pancreatic cancer
6. Contact eczema	17. HIV infections	28. Prostate cancer
7. COPD	18. Skin cancer	29. Rheumatoid arthritis
8. Coronary heart disease	19. Hypertension[b]	30. Schizophrenia
9. Dementia	20. Upper respiratory infections	31. Oesophageal cancer
10. Diabetes Mellitus	21. Lower respiratory infections	32. Mood disorders
11. Colon cancer	22. Leukaemia	33. Parkinson's disease

Source: 2. Output current R&D ecosystem
4. Burden of disease in 2018 via Vzinfo

Note: a. This overview was created by selecting the forty conditions with the highest burden of disease. Of these, only those conditions were included in which pharmacological treatment plays at least a reasonably large role. The overview was then extended by including conditions for which the burden of disease has fallen sharply due to the recent introduction of drugs. This resulted in an overview with a total of 33 conditions.[2]
b. The disease burden for hypertension and multiple myeloma is not available via VZinfo. Hypertension has a high indirect burden of disease. Multiple myeloma is included in the overview because of the large number of new drugs and the expected growth in the number of drugs.[2]

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Step 1: A conceptual model with three indicators for mutual comparison of the conditions

Conceptual model allows comparison of conditions

Conceptual model allows comparison of conditions

A conceptual model was drawn up to enable a comparison of the 33 conditions. The conceptual model consists of three composite indicators that together define the gaps in drug development. The three selected indicators are:

1. Societal need, expressed in burden of disease based on DALYs
2. The relative potential improvement in R&D activity
3. The potential improvement in pharmacological treatment

The three indicators were plotted in a two-axis colour-coded model, as presented in Figure 4 below. The following pages provide a more detailed explanation of each indicator and how the input for each indicator was collected.

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Input

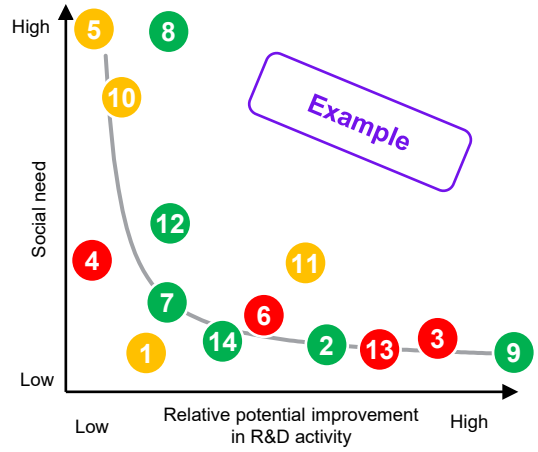
- Disease burden in DALY's a year for the Dutch population
- Extent of R&D activity into new drugs + availability of logical explanation of any low R&D activity
- Availability of medication + pharmacological treatment compared to other treatment options
- Potential improvement of existing medication

Calculation

- **Indicator 1 (y-axis):** Societal need
- **Indicator 2 (x-axis)** Relative potential improvement in R&D activity
- **Indicator 3 (color-coding):** Potential improvement in pharmacological treatment

Output

Display of the conceptual model output



Caption color-coding: Indicator Potential improvement in pharmacological treatment

Low potential | Medium potential | High potential

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Together, the three indicators of the conceptual model define the gaps in drug development

Indicator 1: Societal need

In this study, the societal need for drug development for a condition is expressed in disease burden based on Disability-Adjusted Life Years (DALYs). The burden of disease is the relative loss of health due to a condition. This includes loss of future years of healthy life and loss of quality of life compared to a healthy person. One DALY is equivalent to the loss of one year of life in complete health.[5, 6] This study looked at the total number of DALYs for the entire patient population in the Netherlands, consisting of the burden of disease per patient times the number of patients in the Netherlands. This information was collected by means of desk research – see next pages.

Indicator 2: Relative potential improvement in R&D activity

The potential to improve R&D activity depends on two factors: The extent to which there already is R&D activity and the extent to which there is a logical explanation for any low R&D activity.[a] A low score for this indicator means:

— A great deal of R&D activity, as a result of which little improvement is possible; or

— Little R&D activity, for which there is a logical explanation. For example, because a breakthrough is not considered promising on the basis of the current state of knowledge or because drugs are already available in other markets (such as Japan or China).

In that case, little improvement is possible. A high score for this indicator means that there is little R&D activity and that there is no logical explanation for this low activity. In that case, improvement is possible.

As it concerns a mutual comparison of the conditions, this is not expressed with its own unit, but in terms of relative potential improvement in R&D activity. This information was collected using desk research and a survey – see next pages.

Indicator 3: Potential improvement in pharmacological treatment

The indicator 'potential improvement in pharmacological treatment' addresses the following questions:

1. Is medication currently available, and is it the most appropriate treatment? (Or are other treatments, such as surgery, physical therapy or lifestyle interventions more appropriate?)
2. Is there a need for improvement of existing medication? For example reducing side effects or a more user-friendly form of administration.

This information was collected using desk research and a survey – see next pages.

Two methods were used to populate the conceptual model: desk research and a survey. The information collected in this way was quantified and plotted in the conceptual model. This is explained on the next pages.

Source: 5. Disability-adjusted life years (DALY's) (who.int)
6. Annexes to the report 'Overview 50% of the Dutch disease burden: conditions with a lead in outcome information and suitable for shared decision-making'

Note: a. The indicator 'Relative potential improvement in R&D activity' does not include the number of new market introductions in the past few years, as this does not properly reflect the improvement potential in R&D activity. After all, the number of past market introductions cannot predict current R&D activity. It is possible, for example, that high R&D activity has not yet resulted in a new drug.

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Step 2: The conceptual model is populated using desk research and surveys (1/2)

Initial population of conceptual model based on desk research

The conceptual model was populated as much as possible using the results of desk research. This resulted in an initial overview of conditions for which there may be potential for improvement in aligning supply and demand for pharmacological treatment. To find the societal need (expressed in DALYs), the number of DALYs per condition was retrieved from the VZinfo database. For the other two indicators, we consulted the report 'Output current R&D ecosystem', the website of the National Institute for Public Health and the Environment (RIVM) and nationally applicable guidelines for the various conditions.[2, 7]

Subsequently, specialist knowledge of the conditions was collected by means of a survey

After the initial population based on desk research, a survey provided more depth and insight into whether, and if so where, there are gaps in drug development for the 33 conditions. The survey was distributed among members of patient associations, members of scientific associations and professors of pharmacology. To obtain a representative picture, five members of scientific associations and three members of patient associations were approached for each condition. Appendix A lists the organisations that were asked to participate in the survey. The questions of both surveys are presented in Appendix B.

Two surveys to match the content with the expertise of the respondents The survey was distributed among a heterogeneous group of respondents. In order to match the content of the survey as closely as possible with the expertise of the respondents, it was decided to draw up two different variants of the questionnaire.

1. **Condition-specific survey:** This survey contained questions for one specific condition and was distributed to members of the patient associations and members of the scientific associations of the relevant condition. The survey was completed 102 times and the response rate was 77.9%.[a]
2. **General survey:** This survey contained questions for all 33 conditions, with respondents having the option to complete them for the conditions they had knowledge of. This general survey was distributed to experts with a broad view of the pharmaceutical landscape, such as professors of pharmacology and members of general scientific associations. This survey was completed 60 times; the response rate is 42.9%.[a]

Translation of collected information to conceptual model

The collected information was finally translated into a value for each indicator plotted in the conceptual model:

1. Indicator societal need: The disease burden in DALYs was determined for all 33 conditions on the basis of the VZinfo.nl database.7 The DALYs for each condition are presented as absolute values that are plotted directly on the Y-axis of the conceptual model.
2. Indicator relative potential improvement in R&D activity: In the surveys, respondents were asked how they describe current R&D activity on new drugs by biotech and pharmaceutical companies for the respective condition. It concerned a multiple-choice question in which a score was assigned to each answer: a high score means a lot of improvement potential, a low score means little improvement potential. The average score of all respondents resulted in a value that was plotted in the model. As there is no unit for potential improvement in R&D activity, the term 'relative' was added to this indicator.
3. Indicator potential improvement in pharmacological treatment: In the surveys, respondents were asked how they would describe the current situation of medicines on the market, and what proportion of patients treated with pharmacological products can be effectively treated with that medication. These were also multiple-choice questions to which scores were assigned. The scores were categorised into 'low', 'medium' and 'high', after which the corresponding colour coding was added.

Source: 2. Output current R&D ecosystem
7. Ziektelast in daly's | Ziektelast | Volksgezondheid en Zorg (vzinfo.nl)

Note: a. Response rate is an approximation, calculated based on the number of times the questionnaire has been sent. The questionnaire may have been further distributed within participating organisations.

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Step 2: The conceptual model is populated using desk research and surveys (2/2)



As there is an inverse relationship between indicator 1 and indicator 2, an inverse curve is presented in the conceptual model to identify the conditions for which there may be a gap in drug development. Conditions on the curve have equal improvement potential based on societal need and relative potential improvement in R&D activity. The curve is positioned such that it makes a clear distinction visible, with some ten conditions above the curve (as such, it can be seen as a 'cut-off curve', so to speak).

Finally, the findings from the conceptual model were confronted with explanations from the open answers from the survey and the desk research results. For a small number of conditions, this resulted in manual adjustment of the positions of conditions in the model.

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Step 3: Validation of outcomes of conceptual model in interviews
Step 4: In-depth analysis of selection of conditions in focus groups

Step 3: Findings from the conceptual model were validated in interviews to create focus for conditions for qualitative in-depth analysis

After populating the conceptual model based on desk research and the surveys, a longlist of conditions with possible gaps in drug development was drawn up. The longlist comprised conditions that are above the curve in the conceptual model and have a medium to high potential for improvement in pharmacological treatment.

A total of seven interviews were conducted. The interviewees were representatives of the pharmaceutical industry, investors in the pharmaceutical industry, professors of pharmacology, pharmacists and patient representatives.

The results of the conceptual model were validated in the interviews with the various experts. For the 33 conditions that were taken as a starting point, it was tested whether subindications exist within these conditions and, if so, whether these subindications should be investigated separately in the remainder of the study. Other questions served to collect information on whether the conditions on the longlist were recognised and whether any conditions had to be added to the list. The list of conditions shows where the need lies and what the status of R&D activity is.

Throughout the study, we have worked as accurately as possible. Nevertheless, it is virtually impossible to obtain a complete overview of R&D activity on drug development. While the experts interviewed have extensive knowledge of drug development, they do not always have a complete picture. It is therefore emphasised that the research results in this report are only an approximation of reality.

Based on the insights from the interviews, the longlist was reduced to a selection of five conditions for which further qualitative in-depth analysis took place through focus groups.

Which five conditions were selected is described in the next chapter.

Step 4: In-depth analysis of five conditions in focus groups with experts

A focus group was held for each selected condition. The purpose of the focus groups was to analyse the selected conditions in more depth with experts and to better understand what is going on in the field of drug development for the conditions in question. Three main themes were discussed in a two-hour digital meeting:

1. An in-depth look at the pharmacological needs of each condition, with, where necessary, a distinction according to subindications.
   Within this theme, it was asked whether the need concerns the condition as a whole or specific subindications, whether the need consists of an improvement of existing medication or the development of new medication and whether this medication is available in other markets (e.g. Japan or China).

2. An in-depth look at the possibilities/impossibilities of drug development for the condition.
   This addressed the current level of R&D activity. In the case of lagging R&D activity, the reasons for this were explained, such as a lack of funding or the current state of science.

3. Exploration of the possible solutions to fill the gap in drug development for the conditions in question.
   This last theme included questions about concrete solutions that national and international governments or the Ministry of Health, Welfare and Sport could facilitate.

The results of the focus groups are described in Chapter 4. In the focus groups we talked to only a limited number of experts. The information obtained from the focus groups may not be exhaustive, but only reflects the findings obtained in this manner.

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3.

Selection of conditions

The conceptual model shows 11 conditions with a possible gap in drug development

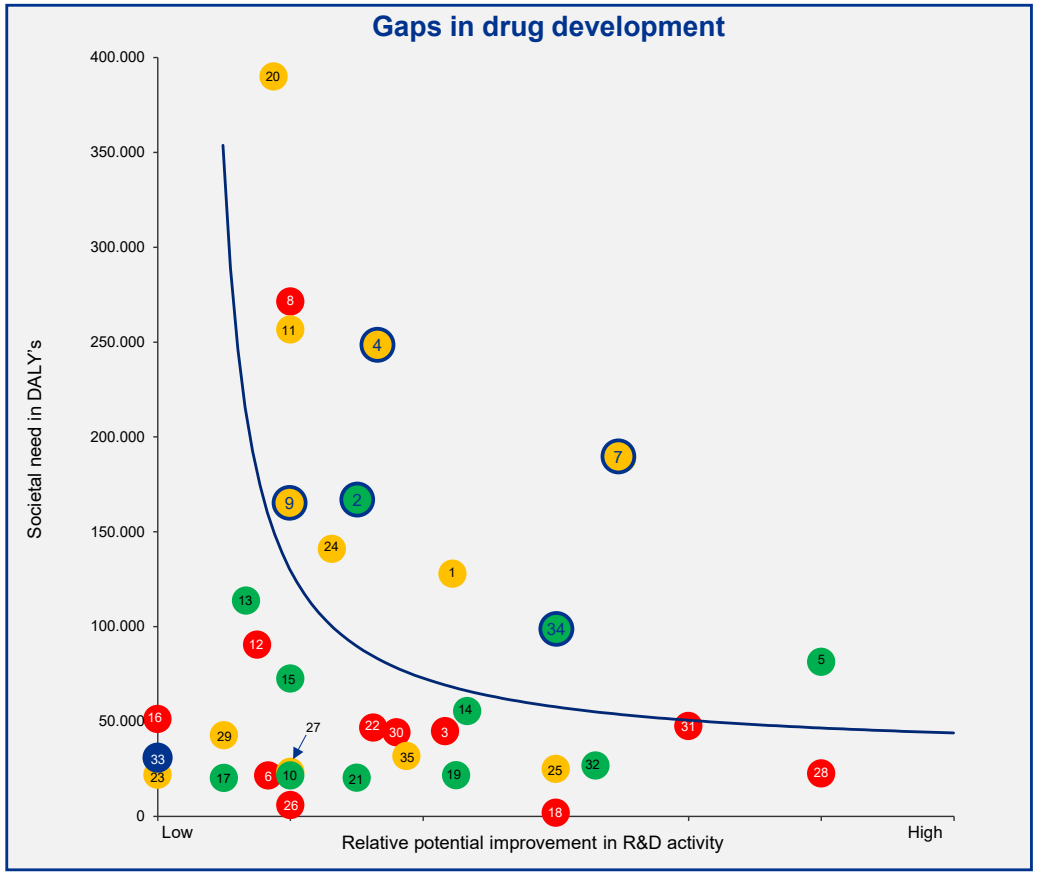


Figure 4: graphic representation of results of conceptual model

Caption:

Y-axis: Societal need in DALYS per year for the Dutch population

X-axis: Relative potential improvement in R&D activity Relative measure, therefore no unit is shown on the x-axis.

Colour: Potential improvement in pharmacological treatment:

Low potential | Medium potential | High potential | No results from survey | Selected for qualitative in-depth analysis

Explanatory list:

1. Anxiety disorders
2. **Arthrosis**
3. Asthma
4. **Stroke**
5. Breast cancer
6. Contact eczema
7. **COPD**
8. Coronary heart disease
9. **Dementia**
10. Diabetes mellitus
11. Diabetes mellitys type II
12. Colon cancer
13. Hearing disorders
14. Eye disorders
15. Heart failure
16. Cardiac arrhythmias
17. Brain cancer
18. HIV infections
19. Skin cancer
20. Hypertension
21. Upper respiratory infections
22. Lower respiratory infections
23. Leukemia
24. Lung cancer NSCLC
25. Lung cancer SCLC
26. Multiple myeloma
27. Multiple sclerosis
28. Non-Hodgkin lymphoma
29. Pancreatic cancer
30. Prostate cancer
31. Rheumatoid arthritis
32. Schizophrenia
33. Oesophageal cancer
34. **Mood disorders**
35. Parkinson's disease

Explanation of figure 4:

- The interviews and the survey retrieved for which conditions there are subindications for which a distinction must be made in the remainder of the study. This distinction has been made for Diabetes Mellitus type I and type II and for small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC).
- The 33 conditions with the highest annual burden of disease (35 conditions including subindications) are presented in figure 4. The 11 conditions above the curve were included in a longlist of conditions for which a gap in drug development may exist. Based on the interviews, five conditions were selected from this longlist for which a qualitative in-depth analysis was carried out. These are the conditions that are printed in bold and underlined in the explanatory list, and indicated with a blue circle in figure 4. Breast cancer was not selected for a further in-depth analysis on the basis of the interviews; for a detailed explanation, see pages 22 to 27.
- For hypertension, only data on the indirect burden of disease is available. Because hypertension is a risk factor for many other conditions, the indirect burden of disease is high. It is estimated at 390,000 DALYs.
- For multiple myeloma no burden of disease expressed in DALYs is available for the Dutch population. Every year, approximately 1,300 people are diagnosed with multiple myeloma. There are some 6,500 people with this form of cancer. Multiple myeloma was included in the previous quantitative study because of the large number of new drugs.

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Validation of the longlist in interviews results in in-depth analysis of arthrosis, COPD, mood disorders, stroke and dementia(1/6)

Based on the graph on page 21, a longlist of 11 conditions was drawn up. In in-depth interviews, this longlist of conditions was presented to experts. The table below shows for each condition what the most important findings were and why the condition was or was not selected for further qualitative in-depth analysis. The selected conditions are not necessarily the conditions with the greatest improvement potential. These are conditions for which their position in the graph on page 21 shows that there are gaps in drug development and for which, based on the interviews, there is also potential for improvement. The findings described for the selected conditions mentioned also serve as an example for the other conditions.

Condition		Key findings	Selected for further qualitative in-depth analysis
Anxiety disorders	Societal need:	127,800 DALYs. The high number of DALYs can be explained by the large patient population.	ϟ Given the overlap in the treatment of anxiety disorders and mood disorders, it has been decided to study only one of the two in more depth. In the mood disorders focus group, similarities and differences with anxiety disorders were briefly discussed (see Appendix C).
	Potential improvement in R&D activity:	Although the disease burden of anxiety disorders is slightly higher than that of mood disorders, the potential improvement in R&D activity has been reported to be greater for mood disorders.	
	Pharmacological treatment:	There is a lot of improvement potential in terms of pharmacological treatment. Because there is overlap with the treatment of mood disorders, it was decided to discuss mood disorders in the focus groups.	

Caption:

✓ Selected for qualitative in-depth analysis

ϟ Partial qualitative in-depth analysis in combination with other condition

— Not selected for qualitative in-depth analysis

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Validation of the longlist in interviews results in in-depth analysis of arthrosis, COPD, mood disorders, stroke and dementia(2/6)

Condition		Key fndings	Selected for further qualitative in-depth analysis
Arthrosis	Societal need:	165,800 DALYs. Concerns a large population. Immobility due to arthrosis has an additionally negative health effect.	✓
	Potential improvement in R&D activity:	Now that it is becoming increasingly clear that arthrosis is more than wear and tear, there are more targets for its treatment.	Arthrosis was selected due to the high burden of disease, increasing incidence and major direct and indirect effects on other health aspects. Arthrosis is also relevant given the new treatment options created by recognition of different subindications.
	Pharmacological treatment:	Only drugs for symptomatic treatment are available. No preventive, modifying or curative treatment possible	
Stroke	Societal need:	248,000 DALYs. Does not only affect a large group of patients, but also their informal caregivers.	✓
	Potential improvement in R&D activity:	A stroke can be divided into different phases. In the acute phase, there is a need for anticoagulant medication and the possibility of reversing the effects of prophylactic anticoagulant medication. There is also a need for neuroprotective drugs.	Stroke has been selected due to the high burden of disease. Based on the interviews there is greater scope for potential improvement in pharmacological treatment than the results from the conceptual model suggested.
	Pharmacological treatment:	Existing prophylactic medication cannot protect all patients yet. They also have side effects. Existing medication can be improved and new drugs can be developed.	

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Validation of the longlist in interviews results in in-depth analysis of arthrosis, COPD, mood disorders, stroke and dementia(3/6)

Condition		Key fndings	Selected for further qualitative in-depth analysis
Breast cancer	Societal need:	81,300 DALYs for all forms of breast cancer together. The disease burden at population level for the triple negative variant of breast cancer only is low compared to other conditions.	—
	Potential improvement in R&D activity:	There already is a lot of R&D activity with respect to most oncological conditions. There is a need for more R&D activity in particular for the triple negative variant of breast cancer.	For most oncological conditions there is little scope for improvement in R&D activity. As regards breast cancer, there is scope for improvement for the triple negative variant. However, the disease burden of this specific variant is relatively low compared to that of other conditions. It was therefore decided not to analyse breast cancer in more depth.
	Pharmacological treatment:	Scope for improvement, primary treatment is still tumour resection.	
COPD	Societal need:	188,500 DALYs. As a result of air pollution, the number of lung diseases may increase further, so there is a growing need for the development of drugs for the treatment of COPD.	✓
	Potential improvement in R&D activity:	For COPD, it is indicated that there is a lot of overlap with the treatment of asthma, despite the fact that the pathophysiology is different. No disease-modifying treatment is available yet.	COPD has a high disease burden and there is a lot of scope for improvement in R&D activity. This was confirmed in the interviews, which is why COPD was selected for in-depth analysis.
	Pharmacological treatment:	Current medication has side effects and is not always easy to titrate. In order to better influence the disease and its consequences, the most potential is seen in pharmacological treatment.	

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Validation of the longlist in interviews results in in-depth analysis of arthrosis, COPD, mood disorders, stroke and dementia(4/6)

Condition		Key fndings	Selected for further qualitative in-depth analysis
Coronary heart disease	Societal need:	271,300 DALYs; there is a great societal need because of the combination of a large patient population and a high burden of disease.	–
	Potential improvement in R&D activity:	Based on the survey, R&D activity is low, which seems to be explained by the treatment options that are already available and the expectation that the greatest developments will come from non-pharmacological therapies.	Despite the high disease burden, the interviews show that the low R&D activity can be explained. It has therefore been decided not to analyse coronary heart disease in more depth.
	Pharmacological treatment:	It is indicated that compliance is a more limiting factor than the availability of medication. In addition, more is expected from minimally invasive interventions.	
Dementia	Societal need:	163,600 DALYs. In addition to the burden of disease in DALYs, there is also a great need among informal caregivers of patients with dementia for new and different pharmacological treatment.	✓
	Potential improvement in R&D activity:	Investments made in recent years have not yet led to groundbreaking new treatment.	Dementia has a high disease burden. The interviews show that the pharmacological treatment of dementia is gaining momentum; there is more scope for improvement in R&D activity than appears from the surveys. It was therefore decided to analyse dementia in more depth.
	Pharmacological treatment:	There is a need for preventive, curative and disease-modifying treatment.	

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Validation of the longlist in interviews results in in-depth analysis of arthrosis, COPD, mood disorders, stroke and dementia(5/6)

Condition		Key fndings	Selected for further qualitative in-depth analysis
Diabetes Mellitus Type II	Societal need:	The disease burden of both types of diabetes together totals 201,000 DALYs. Diabetes Mellitus Type II has the greatest share in this.	—
	Potential improvement in R&D activity:	It is indicated that there are relatively many treatment options, therefore there is little room for improvement in R&D activity with regard to new drugs.	Due to the great need in areas other than drug development, it was decided not to study Diabetes Mellitus Type II in more depth.
	Pharmacological treatment:	The greatest need consists of other forms of administration of existing medicines and treatments in the form of lifestyle adjustments.	
Hypertension	Societal need:	No disease burden for hypertension itself can be determined. Hypertension often underlies other conditions; the indirect burden of disease is estimated at 390,000 DALYs.	—
	Potential improvement in R&D activity:	There are a lot of effective treatment options. Currently little scope for improvement in terms of R&D activity.	It is explicitly stated that the greatest need for the treatment of hypertension is not pharmacological but through other routes. It was therefore decided not to analyse hypertension in more depth.
	Pharmacological treatment:	For hypertension, it is indicated that no improvement potential is seen in *pharmacological* treatment. There is room for improvement in terms of lifestyle and adherence to therapy.	

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Validation of the longlist in interviews results in in-depth analysis of arthrosis, COPD, mood disorders, stroke and dementia(6/6)

Condition		Key fndings	Selected for further qualitative in-depth analysis
Lung cancer (NSCLC)	Societal need:	The disease burden of lung cancer is 165,800 DALYs Approximately 80% of lung cancer cases concerns NSCLC.	–
	Potential improvement in R&D activity:	The surveys indicate that there is a need for more pharmacological treatments specifically for NSCLC, but the interviews show that R&D activity is high for almost all oncological diseases. Based on the interviews, there is less room for improvement in R&D activity than previously thought.	Based on the interviews, there seems to be less relative potential improvement in R&D activity than the graph shows. It was therefore decided not to analyse lung cancer (NSCLC) in more depth.
	Pharmacological treatment:	In addition to surgical treatment, it is expected that there will be an increasing role for pharmacological treatment.	
Mood disorders	Societal need:	98,200 DALYs. This is a little less than for anxiety disorders.	✓
	Potential improvement in R&D activity:	There is relatively little understanding of the underlying pathophysiology. As there is a lot to be gained in this area, relatively much potential is seen in the improvement of R&D activity.	Although the burden of disease is slightly lower, so much more potential is seen in the improvement in R&D activity that it was decided to analyse mood disorders in more depth.
	Pharmacological treatment:	There is a lot of potential for improvement of existing medication.	

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4.

In-depth analysis of selected conditions

Selected conditions were analysed in more depth in focus groups

Based on the outcomes of the conceptual model and the interviews, five conditions were selected for further qualitative in-depth analysis. This was conducted in focus groups. For all focus groups, a heterogeneous group of experts was approached consisting of healthcare professionals, researchers, representatives of the pharmaceutical industry, investors, patient representatives, hospital pharmacists and professors of pharmacology.

In the focus groups, three main themes were discussed with the experts: the pharmacological need, the possibilities and impossibilities of drug development and an exploration of the solution options to fill the gap in drug development.

All the experts asked to participate had a broad view of trends and developments in the field of drug development. Despite this, each focus group remains a representation of the findings retrieved in a selected group. As such, the results are subjective and possibly not complete.

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Arthrosis: A key prerequisite for optimisation of pharmacological treatment is patient stratification (1/2)

In the Netherlands, approximately 1.5 million people suffer from arthrosis. This joint disorder can present in one or more joints. Arthrosis affects the quality of the cartilage and can cause inflammation of the tissues in the joint and changes in the bone at the joint. Arthrosis is accompanied by pain and stiffness, affected joints can become swollen and unstable and creak when moved.[8] Arthrosis can lead to changes in posture. As a result of the symptoms of arthrosis, patients often become less mobile, which has an indirect negative effects on health.

Subindications

Arthrosis has long been considered a homogeneous form of joint wear. There are, however, different manifestations (we do not speak of subindications, but of manifestations). Patients can suffer from one or more manifestations of arthrosis, and the manifestations can change over time in a patient. Examples are: inflammatory arthrosis, post-traumatic arthrosis, arthrosis as part of metabolic syndrome or arthrosis as a result of stress or strain.[9, 10] In addition, there are probably even more - undiscovered - forms of arthrosis.

1. Description of the need for drug development for arthrosis

The currently available treatment focuses solely on pain management. There is little need for improvement of existing medication. At present, no preventive or curative treatment of arthrosis is possible. In addition to prevention and cure, the need for medical treatment of arthrosis consists of disease-modifying treatment. Disease-modifying medication should enable inhibition of cartilage degeneration. Of the different manifestations of arthrosis, the potential of pharmacological treatment is greatest for inflammatory arthrosis.

2. Possibilities/impossibilities of drug development for arthrosis

— Patient stratification is a prerequisite for further development of medication

The different manifestations of the condition make the group of patients suffering from arthrosis heterogeneous. The different manifestations have their own target for treatment, and relatively much is known about possible targets for disease-modifying treatment in arthrosis. However, patient stratification is an important precondition for effective use of resulting treatments. To enable patient stratification, more research is needed into different forms of diagnostics such as advanced imaging and the use of biomarkers.

— Drug repurposing for disease-modifying medication is a promising option

Drug repurposing means that existing medicines are also used or investigated for other indications. This concerns both registered and non-registered medicines. In the past, a lot has been invested in the development of a generic treatment for arthrosis. These drugs often proved ineffective in phase II research (exploratory and therapeutic). As a result, development of many drugs foundered in this phase. However, these drugs were tested for effectiveness in the patient population as a whole. The experts indicate that when better patient stratification is possible, these medicines can be administered in a more targeted manner to subgroups of patients and may be effective. The experts see opportunities via this route for repurposing of drugs that were originally developed for arthrosis. As the safety of these drugs has already been demonstrated, phase I medicine research can be skipped. This could lead to faster drug development at lower costs.

— Accelerated further development of medication due to proof of concept

The experts state that it is important to set realistic goals. There has been a long search for a drug that can inhibit cartilage degeneration for the entire group of patients. An action that could lead to a step forward in the treatment of arthrosis is a proof of concept study, in which cartilage degeneration can be demonstrably inhibited in a selected group of patients. Demonstrating effectiveness of disease-modifying treatment in a selected group of patients increases confidence in the success rate. As a result, investors will be more inclined to invest in further development of arthrosis medication. In this way, a proof of concept can have a reinforcing effect on drug development.

Source:
8. Artrose | Alles wat je moet weten • ReumaNederland
9. Artrose toch een inflammatoire aandoening? | NTvG
10. Living with Inflammatory Arthritis: What You Need to Know | HSS

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Arthrosis: A key prerequisite for optimisation of pharmacological treatment is patient stratification (2/2)

3. Suggestions for improvement in R&D activity for arthrosis

— Improved national cooperation

The development of diagnostics to enable patient stratification is not expected to come from the pharmaceutical industry. The experts indicate that coordination of research to make this stratification possible should come from, for example, a national arthrosis working group, in which various stakeholders are represented. In the Netherlands, a great deal of tissue is available for research. To facilitate research, good access to tissues via biobanks is a requirement.

— Simplifying research

The experts indicate that the duration of phase II drug research (exploratory and therapeutic) is very long. That is why the experts in the focus groups advocate a system in which experimental treatment is possible with a lower threshold under controlled conditions.

— Alternative forms of reimbursement

Medicines are only reimbursed when they have been approved and registered. Due to the long duration of phase II research into arthrosis medication, the experts from the focus groups argue for an alternative form of (partial) reimbursement, whereby there is already a reimbursement for the drug while Phase II or Phase I research is still ongoing.

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Stroke: In order to reduce the burden of disease as a result of stroke, there is a particular need for prevention (1/2)

Each year, approximately 43,000 people in the Netherlands suffer a stroke.[11] Stroke ranks second in the Netherlands in terms of disease burden.[12] Another name for stroke is CerebroVascular Accident (CVA).

Subindications

There are two different forms of CVA:

— Ischaemic CVA: as a result of a blockage of a blood vessel, the underlying brain tissue does not receive oxygen. This may cause brain tissue damage. This form is also called infarction or non-haemorrhagic CVA.[11, 13]

— Haemorrhagic CVA: as a result of a leaking or ruptured blood vessel in the brain. The bleeding can also cause damage to the brain tissue.[11, 13]

Depending on the location in the brain, a stroke may have different symptoms. A commonly used acronym to identify the main symptoms is FAS(T).[14] The F stands for 'Face'. Patients may have a drooping face. The A stands for 'Arms': the patient may have paralysis in an arm or leg. The S stands for 'Speech': the patient's speech may be slurred.

In addition to the distinction between ischaemic and haemorrhagic CVA, a distinction can be made between different phases of a CVA, such as preventive, acute, semi-acute, and rehabilitation phase. These phases have their own treatment routes.

1. Description of the need for drug development for stroke

— Preventive phase - the phase prior to a stroke

The experts indicate that in terms of societal needs, the greatest gains can be made in prevention. Prevention includes both pharmacological and non-pharmacological interventions. Various risk factors have been defined for stroke, which result in a low degree of suffering of the patient. It is therefore important for pharmacological treatment that the side effects are minimal in order to still achieve good adherence to the therapy. A lot of research is currently being done into anticoagulants categorised as factor XI inhibitors. These are expected to have less bleeding as a side effect.

— Acute phase: first few hours after stroke onset

Both an ischaemic and a haemorrhagic CVA lead to brain tissue death. In the acute phase, it is therefore important to restore blood vessel patency as soon as possible in the event of an ischaemic CVA, or to stop and/or relieve the bleeding in the event of a haemorrhagic CVA. Some of the patients who develop an ischaemic CVA use anticoagulants as prophylaxis. The treatment of an ischaemic CVA in the acute phase may consist of administering a powerful anticoagulant to dissolve the blockage (thrombolysis). To qualify for this treatment, the effect of the anticoagulants taken as prophylaxis must first be reversed, because the combination of prophylactic anticoagulation and thrombolysis together gives too great a risk of bleeding. In recent years, many new anticoagulants have become available with associated reversal agents. There is currently no need for new or different drugs in this area.

— Semi-acute phase: the period in which the stroke has already started, but there is still room to limit the brain damage caused by the stroke as much as possible

Not every patient can be treated in the acute phase. And brain damage may occur despite prompt treatment in the acute phase. There is a need for medication that can limit brain tissue damage caused by a stroke; these are called neuroprotective drugs. This treatment inhibits the local inflammatory process and swelling. Other targets for treatment are glucose metabolism in the brain and influencing calcium influx.

To date, despite a great deal of research, there are no routinely used neuroprotective drugs. There is a need for new drugs in this respect.

There may be drugs that are used for other conditions that can also have a neuroprotective effect. GLP-1 agonists have been mentioned as an example. These are used in the treatment of diabetes mellitus type II, but may also influence glucose metabolism in the brain. This could be a promising form of drug repurposing.

Source:

11. Wat is een CVA? (beroerte) – Hersenletsel
12. Beroerte | Volksgezondheid en Zorg (vzinfo.nl)
13. Wat is een beroerte? - Hersenstichting
14. Stroke - NHS (www.nhs.uk

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Stroke: In order to reduce the burden of disease as a result of stroke, there is a particular need for prevention (2/2)

— Late phase: the period focused on symptom control, rehabilitation and secondary prevention

Improving quality of life is an important outcome measure in the late phase after stroke. One in three patients develops a depression. There is a need to recognise these patients so that treatment can be started in a timely manner. There is only sporadic research into which antidepressants specifically work for this target group. There is a need for drug repurposing alongside a possible improvement in R&D activity.

2. Possibilities/impossibilities of drug development for stroke

At the moment, regenerating brain tissue is not possible, and this does not seem possible in the short term either. The greatest breakthrough is therefore expected from drugs that can prevent or limit brain damage. In the past, a lot of research has been done into neuroprotective drugs, but this has not yet led to a solution. The timely administration of medication and getting the right dose to the brain (blood-brain barrier) seem to be the biggest challenges. A breakthrough requires more understanding of the underlying pathophysiology.

3. Suggestions for improvement in R&D activity for stroke

— To reduce the burden of disease at a population level, the risk group must be recognised

The experts indicate that when looking at the greatest possible reduction in the burden of disease, the main focus should be on prevention. Prevention can be more effective by better recognising the risk group. Several risk factors have already been identified for this. One possibility that was mentioned was recognition based on data in the Electronic Patient Dossier (EPD) and General Practitioner Information System (HIS). Research in this area will not be coordinated by the industry, but will have to be stimulated by the government.

— Accepting other forms of research for populations in which research is difficult to conduct

Starting treatment of stroke as soon as possible influences the outcome. This means that there is little time in the acute phase of a stroke to inform patients and their families about participation in scientific research. When conducting research, informing patients and obtaining their consent (informed consent) is mandatory. In addition, patients are not always responsive when they arrive at the hospital, which complicates the informed consent procedure. These factors make it difficult to conduct research within this population, and it sometimes takes years before a sufficient number of patients is included in a study. In order to speed up research, other forms of research should be considered, in addition to randomised trials, to demonstrate the effectiveness of medicines. This could include research with smaller groups of patients, or accepting a different informed consent procedure for this population.

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COPD: For effective treatment, a change in thinking towards treatable traits is desirable (1/2)

In the Netherlands, more than 600,000 people suffer from COPD. This leads to approximately 200,000 COPD-related hospital admission days every year.[15] Although COPD is often seen as a disease related to smoking, the incidence is expected to increase in the coming years, mainly as a result of air pollution. It is also possible that COPD will occur in a different, younger population as a result of trends such as electronic cigarettes and vaping.

Subindications

COPD is a collective name for chronic bronchitis and pulmonary emphysema.[16] COPD can be accompanied by all kinds of symptoms, the main ones being tightness of the chest, coughing, coughing up mucus, shortness of breath, fatigue, low muscle strength and weight change.[17]

In practice, the distinction between chronic bronchitis and pulmonary emphysema is often no longer made. More important is recognising the treatable traits, such as bronchoconstriction or inflammation.[18] The distinction according to subindications has not been made for COPD in the identification of gaps in drug development.

1. Description of the need for drug development for COPD

— Further development of existing medication

The current treatment of COPD consists of symptom control. Medication is often administered as a combination preparation to treat bronchoconstriction and inflammation. In the event of a lung attack, patients are instructed to take additional medication if necessary. The combination of drugs increases the dosage of both, while only the dosage of the drug used to treat bronchoconstriction needs to be increased. There is a need for the possibility of more targeted treatment.

An important pillar of the treatment of COPD are anti-inflammatory drugs in the form of corticosteroids. Corticosteroids do not work in all patients. There is a need for other anti-inflammatory drugs that are effective in this group of patients. Moreover, corticosteroids have an overall immunosuppressive effect, so that instead of having an anti-inflammatory effect, they can actually encourage the development of pneumonia. There is a need for anti-inflammatory drugs that have a local and specific action.

— Development of new medication

Timely treatment can prevent progression of the disease and thus the loss of lung capacity. However, the experts indicate that when patients come with complaints, the disease is already advanced. A great need therefore lies in the prevention of COPD and its early detection. Another need exists for disease-modifying treatment that helps prevent the loss of alveoli. A next step is medicinal regeneration of lung tissue.

In the treatment of asthma, some biologicals have a disease-modifying effect. It is possible that these drugs can also be used in the right subgroup of patients with COPD. This form of drug repurposing is considered promising.

2. Possibilities/impossibilities of drug development for COPD

— Thinking in terms of treatable traits is important for precision treatment

Current treatment focuses heavily on bronchoconstriction and inflammation. However, research has identified twelve treatable traits. More effective treatment requires a change in thinking. Only treat with an anti-inflammatory if there is actually an inflammatory component. To stimulate precision treatment, other clinical readout parameters must also be defined.

— Successful drug development and drug repurposing require patient stratification

There are different phenotypes within the group of patients suffering from COPD. A treatment to regenerate lung tissue that works for all of them seems impossible. To demonstrate the effectiveness of such drugs, it is necessary to be able to predict which patients will respond to which type of drug. It is expected that biologicals can play a role in the treatment of COPD, for which better patient stratification is a prerequisite.

Source:
15. Van wens naar werkelijkheid: 25% minder ziekenhuisopnamedagen voor COPD-patiënten | Activiteit | Zorginstituut Nederland
16. Wat is COPD? | Longfonds
17. Symptomen van COPD | Longfonds
18. Treatable traits: toward precision medicine of chronic airway diseases - PubMed (nih.gov)

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COPD: For effective treatment, a change in thinking towards treatable traits is desirable (2/2)

3. Suggestions for improvement in R&D activity for COPD

— Intensification of cooperation with primary care

Many COPD patients are treated by their GP. In order to reach and treat the largest group of patients, it is important to involve GPs in drug development research.

— COPD higher on the public agenda

Because patients have often already lost lung capacity at the time of their diagnosis, early recognition is important. In order to improve recognition, more attention must be generated for COPD, which is why, according to the experts, the condition should be placed higher on the public agenda.

— Encouraging the synergistic effect in public-private partnerships

The experts emphasise that many good ideas originate in academia. Encouraging public-private partnerships increases the chances that these ideas can be realised. Optimising this synergistic effect requires close collaboration between public and private, but also between different research bodies.

— Early involvement of patients

In order to respond to societal needs, it is emphasised that it is necessary to involve patients in all stages of drug development. Patients are in an ideal position to indicate which new medicines are needed. In addition, patients can indicate what are clinically relevant outcome measures for them in follow-up research.

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Dementia: Drug development at a tipping point, scaling up and investing are important right now (1/2)

In the Netherlands, a total of approximately 290,000 people suffer from dementia. 800,000 Dutch people provide informal care to someone with dementia.[19] The incidence of dementia is only expected to increase further in the coming years.

Subindications

Dementia is a collective name for over 50 different brain diseases. Most common in the Netherlands are Alzheimer's disease, vascular dementia, frontotemporal dementia and Lewy Body dementia.[20]The forgetfulness often referred to as dementia is in fact a symptom of all of these brain diseases. In addition, patients suffering from dementia may experience problems with daily activities, confuse time or place, develop language problems, lose things, have poor judgement, withdraw from social activities, and show changes in behaviour and character.[21]

1. Description of the need for drug development for dementia

— Further development of existing medication

At the moment, no preventive or curative pharmacological treatment is possible. A limited number of drugs have been registered that can have a short-term disease-modifying effect in Alzheimer's disease and Lewy Body Dementia. In the field of prevention, cure and disease modification, there is therefore a particular need for the development of new medication.

In addition to the treatment of the condition itself, it is important that the quality of life in patients with dementia is as good as possible. That is why there is a need for the further development of medicines to combat clinical features that arise as a result of dementia, such as anxiety or depression. Now, medicines are often borrowed from other conditions. There is a need for the possibility of treating these secondary manifestations of disease specifically aimed at patients with dementia.

— Development of new medication

Prevention, cure or disease modification are not possible. Much is clear about the pathophysiology of the different forms of dementia; the need now consists of translating the pathophysiology into pharmacological treatment options.

2. Possibilities/impossibilities of drug development for dementia

Dementia is already a collective name for various brain diseases, but different subtypes can also be defined within, for example, Alzheimer's disease. It is impossible to treat dementia as a single condition and diagnosing the different subtypes is an important precondition for successful treatment. New diagnostic methods can increasingly facilitate patient stratification.

In the past, a lot has been invested in the development of pharmacological treatment of dementia in general. These drugs proved ineffective in this context. It is possible that these drugs, when used in the right subgroup of patients, will still prove to be effective. This form of drug repurposing is considered promising.

There are several trials with positive results, as well as a few approved medicines that appear to have a disease-modifying effect. These are Lecanemab, Aducanumab and Donanemab. However, their effect appears to be limited, the costs are high and the drugs have side effects.[22] There are a relatively large number of trials on new disease-modifying treatments from which positive results are expected. The experts emphasise that this can act as a catalyst for the development of other treatment options.

The experts indicate that there are different views as to what dementia actually is. Some see it as a disease of old age, others as a deadly brain disease, the so-called disease paradigm. When you see dementia as a deadly brain disease, you are prepared to accept different or more side effects than when you see dementia as a disease of old age in a vulnerable target group.

In view of the ageing population, there is a need for the prevention of dementia. This requires identifying patients who will develop dementia, or diagnosing dementia early on in the disease process.

This does not seem promising at the moment due to ethical concerns. Because although people can know through screening that they may develop the condition, no effective treatment is available yet. As such, this knowledge can have a negative effect on the quality of life, making early diagnosis undesirable.

Source:

19. Factsheet cijfers en feiten over dementie | Alzheimer Nederland (alzheimer-nederland.nl)
20. Soorten dementie | Alzheimer Nederland (alzheimer-nederland.nl)
21. Herkennen en symptomen van dementie | Alzheimer Nederland (alzheimer-nederland.nl)
22. Nieuw medicijn remt verloop van alzheimer klein beetje af - NRC

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Dementia: Drug development at a tipping point, scaling up and investing are important right now (2/2)

3. Suggestions for improvement in R&D activity for dementia

— Improving public-private partnership

The experts indicate that better public-private partnership is needed. Many good ideas originate in academia, but due to complex regulations regarding, for example, intellectual property, it is not always possible to follow up on these ideas. Researchers at universities often leave for the industry.

A more entrepreneurial climate could attract new investors and contribute to the retention of researchers.

— Simplifying the regulatory framework

The Netherlands has a solid but complex research infrastructure. The safety of participants in studies is guaranteed by Medical Ethical Review Committees (MRECs) and the Central Committee on Research Involving Human Subjects (CCMO). The downside of this is that it hinders foreign organisations from conducting research in the Netherlands. The experts indicate that it is precisely this type of collaboration that can accelerate research.

— Scaling up

Lecanemab is the first disease-modifying agent in the treatment of Alzheimer's disease approved in the United States. The experts indicate that with the first positive results from trials, drug development for Alzheimer's may be at a tipping point. That is why scaling up and investing are essential right now.

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Mood disorders: Effectiveness of treatment may be increased by patient stratification

Every year, about 10% of the Dutch population suffers from some form of a mood disorder.[23] These include both patients who are being treated by their general practitioner and those who receive mental health care.

Subindications

Mood disorders include both depressive disorders, which represent by far the largest group with approximately 1.1 million Dutch people, and bipolar disorders, which affect approximately 150,000 Dutch people annually.[a]

The experts indicate that the greatest burden of disease for patients is caused by *depressive* episodes. Mania and depression are treated differently. The results described here therefore focus on the drug requirement in bipolar and unipolar depression.

1. Description of the need for drug development in mood disorders

— Further development of existing medication

Several pharmacological options are available for the treatment of mood disorders. Various areas are mentioned in which there is a need to improve the current pharmacological treatment. For example, current drugs affect glucose metabolism and have cardiovascular side effects. There is a need for drugs with fewer side effects. In addition, it sometimes takes several weeks for drugs to reach their maximum therapeutic effect and even longer before they also achieve their maximum prophylactic effect. There is a need for quicker acting drugs.

— Development of new medication

Psychedelics can give quick results in both bipolar and unipolar depression. Although psychedelics were not developed for this purpose, they can play a role in the treatment of depression. Drug repurposing with psychedelics for the treatment of depression is considered promising.

The focus group only discussed the treatment of mood disorders in adults. However, the experts indicate that there is a great need within child and adolescent psychiatry for targeted treatment, as opposed to treatment with the same drugs as for adults in adjusted doses.

2. Possibilities/impossibilities of drug development for mood disorders

The experts indicate that there are subgroups within the large group of patients with mood disorders. For effective drug treatment, it is important to be able to recognise these subgroups. However, recognising subgroups based on pathophysiological characteristics is difficult, which is why it is argued to reverse the process: setting up large databases that enable pattern recognition. Based on these patterns, it would be easier to predict how certain subgroups of patients will respond to treatment. The experts indicate that patients with both bipolar and unipolar depression should be included in the same database.

3. Suggestions for improvement in R&D activity for mood disorders

— Encouraging public-private partnerships

The experts indicate that research can be accelerated by collaborating more. The United States is mentioned as an example, where the government drives medicine research more.

— Investing in networks

Patient stratification is mentioned several times as an important precondition for more effective treatment, which requires the creation of a national database that enables pattern recognition. In the past, many studies have been done into the treatment of mood disorders in general, but the drugs studied often turned out to be ineffective. This makes it difficult to secure investment for large-scale studies. When the effectiveness of new medicines can be demonstrated in a subgroup, this can give a new impetus to the necessary investments.

— Need for better treatment monitoring

The experts indicate that we still do not know much about the optimal duration of treatment and the prevention of side effects. Patients sometimes use drug treatment for prolonged periods of time, without this treatment being monitored. To gain more knowledge about optimal treatment duration and side effects, it is necessary to continue to monitor patients after their successful initial treatment.

Source: 23. Depressie en andere stemmingsstoornissen | Leeftijd en geslacht | Volksgezondheid en Zorg (vzinfo.nl)

Note: a. In addition to mood disorders, anxiety disorders also cause a high burden of disease. Anxiety disorders were on the longlist of conditions. The experts who participated in the focus group on mood disorders were also asked about the similarities and differences in drug development gaps with respect to anxiety disorders. The findings are included in Appendix C.

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Overview of possibilities/impossibilities in R&D activity for conditions that were analysed in more depth

The focus groups discussed three main themes: the need for medicines for each condition, the possibilities/impossibilities of drug development for the condition and an exploration of the possible solutions to fill the gap in drug development for the condition in question. The table below provides an overview of the most important findings for the pharmacological need and the possibilities/impossibilities of drug development.

For the conditions for which a qualitative in-depth analysis was carried out, there is a particular need for new medicines. For arthrosis, COPD and mood disorders, it is indicated that the development of new medicines by means of drug repurposing is considered promising.
Some general solutions to fill gaps in drug development are discussed on page 40.

Condition	Need		Possibilities/impossibilities in R&D activity
	Improvement of existing medicines	New medicines	
Arthrosis	—	✓	Patient stratification necessary Proof of concept
Stroke	—	✓	Largest gains in disease burden reduction can be achieved with prevention (recognition of patients with a risk profile)
COPD	✓ a	✓	Patient stratification necessary Treatable traits
Dementia	—	✓	Patient stratification necessary Proof of concept Wish for upscaling following first promising results
Mood disorders	✓ b	✓	National networks for recognition of subgroups

Note:
a. Fewer side effects of anti-inflammatory drugs and precision treatment.
b. Faster effects

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The focus groups have revealed four general suggestions for encouraging drug development (1/2)

The focus groups mentioned several possible solutions to fill the gaps in drug development for each condition. In addition to the condition-specific solutions, there are a number of general solutions that were a recurrent theme in all focus groups. Below is an overview of the possible solutions mentioned:

— Improving public-private partnership

For all conditions, it was indicated that improving public-private partnerships would benefit drug development. It must become easier for universities and industry to jointly develop an idea into a registered medicine. Agreements on intellectual property are mentioned as facilitators.

When public-private partnerships become more common, it will be easier to retain talented researchers for universities. The collaboration can also contribute to greater continuity of research funding. If researchers are less dependent on short-term grants, they will need to spend less time securing funding for their research. This would allow them to bring more focus to their work, which could lead to an acceleration of research.

— Simplifying the regulatory framework

It is indicated that a lot of high-quality research is being done in the Netherlands. However, the complex regulations make it difficult for foreign organisations to participate in Dutch research. In the Netherlands, the rights and safety of participants in scientific research are guaranteed by regulations implemented by the METC and the CCMO. Research must meet strict requirements before participants can be recruited, which is at the expense of rapid research progress. International collaborations can increase the sample size, with which research can be accelerated.

The experts also indicate that due to the complexity of the regulations, drug research often has a long lead time. As a result, promising drugs take a long time to become available to patients. This process can be accelerated by simplifying the regulatory framework for the approval of experimental drugs. The experts have suggested a system in which experimental treatment with a lower threshold is possible under controlled conditions.

— More national and international control

The study expressed a need for national and international steering in various areas:

- For various condition, it is indicated that better patient stratification is a precondition for the further development of pharmacological treatment. This requires new diagnostic studies, or databases of patients with which different subgroups can be recognised based on patterns. As such initiatives will not be coordinated from within the industry, there is a desire to manage them centrally.
- It has also been mentioned that an acceleration in drug development can be achieved through access to larger patient samples. This can be achieved through international cooperation.
- International guidance is preferred for both points, because the Netherlands alone has such a small scale that it is not attractive for research and industry. Joining forces at European level is therefore crucial in this respect.
- Finally, it is indicated that in addition to pharmacological treatment, there is a great need for prevention and early recognition of conditions. This requires close cooperation with primary care. Due to the existing pressure on primary care, this is only possible if these conditions are also high on the public agenda. This at any rate applies to COPD and stroke.

— Improving the infrastructure

It has been mentioned several times that facilitating a good infrastructure contributes to drug development. An example mentioned in this study are the biobanks. To facilitate research, access to research material such as tissues from biobanks must be guaranteed. This requires improvement of the infrastructure.

The experts indicated that research is often fragmented in terms of both conditions and research bodies. Close collaboration between universities, government, primary care and patients is necessary to fill the gaps in drug development.

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5.

Answers to research questions and conclusions

There are gaps in the development of drugs for several conditions, including arthrosis, stroke, COPD, dementia and mood disorders

For 33 conditions with the highest annual burden of disease, this study provided answers to three research questions by means of a funnel approach. The answers to each research question are described below, followed by the resulting conclusions.

Answers to research questions

Research question 1: For which conditions is R&D activity in imbalance with the societal need? Can the need for medicines for these conditions be categorised?

A longlist of conditions with improvement potential has been drawn up on the basis of a conceptual model populated through desk research and surveys. This longlist was validated in interviews with experts, after which five conditions were selected for further qualitative in-depth analysis. These are arthrosis, stroke, COPD, dementia and mood disorders.

The need for drug development for each condition was analysed in more depth in focus groups. These focus groups led to a specific need for each conditions. This need cannot be categorised.

For the conditions arthrosis, COPD and dementia, almost exclusively symptom control is currently available. There is a need for disease-modifying treatments. A second key finding that emerged for all selected conditions is the need for patient stratification. The selected conditions consist of heterogeneous subgroups of patients. With patient stratification, the different subgroups can be identified and a specific treatment can be developed, which is expected to improve the effectiveness of the treatment.

Following on from the need for patient stratification, the possibilities for drug repurposing are also mentioned. Drug repurposing is considered promising for arthrosis, COPD and dementia. In the past, drug repurposing has been studied for the patient population as a whole, which often proved ineffective. These drugs may have potential if they are prescribed to specific subgroups of patients, which can be identified with patient stratification.

Research question 2: Can these conditions be broken down into subindications?

In all focus groups a distinction was made according to possible subindications, in order to subsequently validate with the experts whether this classification was correct and whether it contributed to identifying the need for medicines. The subindications, if any, for each of the conditions are shown below.

— **Arthrosis**

There are different manifestations. Patients can have multiple manifestations of arthrosis at the same time, and the manifestation of arthrosis in a patient can change over time. It is important to recognise that these manifestations exist and that there is a need for patient stratification in the treatment of arthrosis. There is currently no distinction between subindications.

— **Stroke**

Ischaemic and haemorrhagic CVA differ in terms of pathophysiology. This subindication is needed to describe the need for medicines.

— **COPD**

COPD is the official collective name for chronic bronchitis and pulmonary emphysema. However, the distinction between these subindications is no longer made in practice. More important for the treatment of COPD is to distinguish between treatable traits (such as bronchoconstriction). A total of 12 treatable traits have been defined.

— **Dementia**

There are various subindications of dementia. In this study, the most common subindications of dementia in the Netherlands have been examined in depth: Alzheimer's disease, vascular dementia, frontotemporal dementia and Lewy Body dementia.

No other subindications can be distinguished within Alzheimer's disease, but the experts indicate that Alzheimer's disease concerns a heterogeneous group of patients, where there is a need for patient stratification.

— **Mood disorders**

Mood disorders include the subindications bipolar disorder and major depressive disorder. Bipolar disorder can be a depressive disorder or a manic disorder. This study analysed the subindications bipolar depressive disorder and unipolar depressive disorder in more depth.

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The lagging behind of R&D activity has different causes for each condition

Research question 3: What are the causes of limited R&D activity and what can the government do to encourage R&D activity for these conditions?

For the conditions for which a qualitative in-depth analysis was made, the focus groups identified causes why R&D activity is lagging behind, with associated specific solution options.

— **Arthrosis**

The disappointing research results from the past, when a single drug was sought for the entire patient population, are cited as the cause of lagging R&D activity. As a possible solution, more focus on research that encourages patient stratification is requested.

— **Stroke**

In the past, many studies of neuroprotective drugs proved unsuccessful. The experts indicate that the greatest need lies in the prevention of strokes. This requires better recognition of patients with risk factors, which in turn requires close cooperation between primary and secondary care.

— **COPD**

For COPD, it is indicated that research into disease-modifying treatments is taking place, but lags behind the R&D activity for asthma. No clear explanation can be given for this. Collaboration with general practitioners and patient participation is necessary to ensure that drug development for COPD meets the need. The experts are calling on the government to put COPD high on the public agenda.

— **Dementia**

The experts indicate that R&D activity in itself does not lag behind, it is rather that the results of this activity are not forthcoming. Many studies are currently under way into new disease-modifying treatments from which positive results are expected, and an appeal is being made to invest in scaling up right now.

— **Mood disorders**

A large proportion of patients with mood disorders are treated in primary care. Due to the pressure on mental health care, it is virtually impossible for primary care providers to participate in scientific research. This hinders scientific research among a representative patient population. There is an appeal to facilitate setting up large research networks.

Conclusion

This study used a funnel approach to identify conditions for which gaps in drug development may occur. From these, five conditions were then selected for further qualitative in-depth analysis. This qualitative in-depth analysis concerned arthrosis, stroke, COPD, dementia and mood disorders. This qualitative in-depth analysis shows that the emergence of gaps in drug development is more complex than simply the lack of commercial potential of drugs.

Previous research concluded that commercial potential is the main driver for drug research. Other contributing factors described are the state of knowledge, access to research populations and an infrastructure for collaboration. This study confirms that the emergence of gaps in drug development is more complex than just commercial potential. For five selected conditions, the extent to which each of the factors applies has been examined in more detail. The role of other factors differs for each condition, is difficult to determine exactly and is, moreover, subjective.

There are specific needs for medicines for arthrosis, stroke, COPD, dementia and mood disorders. However, what all selected conditions have in common is the need for patient stratification. In the past, drugs for many conditions were developed for the patient group as a whole. However, based on the current knowledge, it is clear that different conditions comprise different subgroups that respond differently to treatments. There is a need to better recognise these groups and develop treatments that target specific subgroups.

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6. Appendices

Appendix A: Overview of organisations that were asked to participate in surveys (1/3)

Condition	Patient associations	Scientific associations
1. Anxiety disorders	Angst, Dwang en Fobie Stichting	Nederlandse Vereniging voor Psychiatrie (Dutch Association for Psychiatry)
2. Arthrosis	ReumaNederland	Nederlandse Vereniging voor Reumatologie (Dutch Rheumatology Association)
	Vereniging Reumazorg Nederland	Nederlandse Orthopaedische Vereniging (Dutch Orthopaedic Association)
		Vereniging Fysiotherapie & Wetenschap (Physical Therapy & Science Association)
3. Asthma	Longfonds	Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (Dutch Society of Physicians for Pulmonary Diseases and Tuberculosis)
4. Stroke	Hersenletsel.nl	Nederlandse Vereniging voor Neurologie (Dutch Association for Neurology)
5. Breast cancer	Harteraad	Nederlandse Vereniging voor Medische Oncologie (Dutch Association for Medical Oncology)
	Borstkankervereniging Nederland	
6. Contact eczema	Vereniging voor mensen met Constitutioneel Eczeem	Nederlandse Vereniging voor Dermatologie en Venereologie (Dutch Society for Dermatology and Venereology)
7. COPD	Longfonds	Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (Dutch Society of Physicians for Pulmonary Diseases and Tuberculosis)
8. Coronary heart disease	Harteraad	Nederlandse Vereniging voor Cardiologie (Dutch Society of Cardiology)
9. Dementia	Alzheimer Nederland	Nederlandse Vereniging voor Neurologie (Dutch Association for Neurology)
		Verenso
10. Diabetes Mellitus	Diabetesvereniging Nederland	Nederlandse Internisten Vereniging (Netherlands Association of Internal Medicine)
11. Colon cancer	Stichting Darmkanker	Nederlandse Vereniging voor Medische Oncologie (Dutch Association for Medical Oncology)
12. Hearing disorders	Stichting Hoormij	KNO-vereniging
13. Eye disorders	Oogvereniging	Nederlandse Oogheelkundig Gezelschap (Netherlands Ophthalmological Society)
14. Heart failure	Harteraad	Nederlandse Vereniging voor Cardiologie (Dutch Society of Cardiology)

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Appendix A: Overview of organisations that were asked to participate in surveys (2/3)

Condition	Patient associations	Scientific associations
15. Cardiac arrhythmias	Harteraad	Nederlandse Vereniging voor Cardiologie (Dutch Society of Cardiology)
16. Brain cancer	Brain tumour contact group	Nederlandse Vereniging voor Medische Oncologie (Dutch Association for Medical Oncology)
17. HIV infections	Hiv Vereniging	Nederlandse Vereniging voor Neurologie (Dutch Association for Neurology)
		Nederlandse Vereniging voor Internist-infectiologen
18. Skin cancer	Stichting Melanoom	Nederlandse Vereniging voor Medische Oncologie (Dutch Association for Medical Oncology)
19. Hypertension	Harteraad	Nederlandse Vereniging voor Cardiologie (Dutch Society of Cardiology)
20. Upper respiratory infections	Longfonds	Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (Dutch Society of Physicians for Pulmonary Diseases and Tuberculosis)
21. Lower respiratory infections	Longfonds	Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (Dutch Society of Physicians for Pulmonary Diseases and Tuberculosis)
22. Leukaemia	Hematon	Nederlandse Vereniging voor Medische Oncologie (Dutch Association for Medical Oncology)
		Nederlandse Vereniging voor Hematologie
23. Lung cancer	Longkanker Nederland	Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (Dutch Society of Physicians for Pulmonary Diseases and Tuberculosis)
		Nederlandse Vereniging voor Medische Oncologie (Dutch Association for Medical Oncology)
24. Multiple myeloma	Hematon	Nederlandse Vereniging voor Medische Oncologie (Dutch Association for Medical Oncology)
		Nederlandse Vereniging voor Hematologie
25. Multiple sclerosis	Multiple Sclerose Vereniging	Nederlandse Vereniging voor Neurologie (Dutch Association for Neurology)
26. Non-Hodgkin lymphoma	Hematon	Nederlandse Vereniging voor Medische Oncologie (Dutch Association for Medical Oncology)
		Nederlandse Vereniging voor Hematologie

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Appendix A: Overview of organisations that were asked to participate in surveys (3/3)

Condition	Patient associations	Scientific associations
27. Pancreatic cancer	Living With Hope	Nederlandse Vereniging voor Heelkunde (Association of Surgeons of the Netherlands)
		Nederlandse Vereniging voor Medische Oncologie (Dutch Association for Medical Oncology)
28. Prostate cancer	Prostaatkankerstichting	Nederlandse Vereniging voor Urologie (Dutch Urological Association)
		Nederlandse Vereniging voor Medische Oncologie (Dutch Association for Medical Oncology)
29. Rheumatoid arthritis	ReumaNederland	Nederlandse Vereniging voor Reumatologie (Dutch Rheumatology Association)
30. Schizophrenia	Ypsilon	Nederlandse Vereniging voor Psychiatrie (Dutch Association for Psychiatry)
31. Oesophageal cancer	Stichting SPKS Leven met maag- of slokdarmkanker	Nederlandse Vereniging voor Medische Oncologie (Dutch Association for Medical Oncology)
		Nederlandse Vereniging voor Heelkunde (Association of Surgeons of the Netherlands)
32. Mood disorders	Depressie Vereniging	Nederlandse Vereniging voor Psychiatrie (Dutch Association for Psychiatry)
33. Parkinson's disease	Parkinson Vereniging	Nederlandse Vereniging voor Neurologie (Dutch Association for Neurology)

General Scientific associations
Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (Royal Dutch Society for the Advancement of Pharmacy, KNMP)
Nederlandse Vereniging van Ziekenhuisapothekers (Dutch Hospital Pharmacists' Association, NVZa)
Nederlands Huisartsen Genootschap (Dutch College of General Practitioners, NHG)
Nederlandse Vereniging voor Klinische Geriatrie (Dutch Geriatrics Society, NVKG)

Professors of pharmacology
Professors of pharmacology were personally invited to participate in the survey. Professors from all UMCs were asked to participate.

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Appendix B: Questionnaire of condition-specific survey[a]

1a. How would you describe the situation with respect to medicines on the market for this condition?

- ○ Pharmacological treatment is not preferred (other interventions such as lifestyle, surgery, etc. are more applicable)
- ○ Better pharmacological treatment is available in other markets (e.g. Japan, China or Russia), but not available in the Netherlands
- ○ No medication available, while medication could be a treatment option
- ○ Pharmacological treatment available, but need for better drug (e.g. simpler administration, fewer interactions, fewer side effects, greater effectiveness, etc.)
- ○ Good, all or almost all patients with this condition can be treated properly with existing medicines

1b. Please explain your answer to the previous question here.

[Space for free text]

2a. What proportion of the patients in the Netherlands with this condition can – in your estimation – be treated with the medicines currently on the international market?

- ○ <20%
- ○ 20-40%
- ○ 40-60%
- ○ 60-80%
- ○ >80%

2b. In what proportion of these patients – in your estimation – is the pharmacological treatment effective?

- ○ <20%
- ○ 20-40%
- ○ 40-60%
- ○ 60-80%
- ○ >80%

3a. How would you describe the R&D activity of biotech and pharmaceutical companies on new drugs for this condition?

- ○ No or limited research is being done into new drugs, but that is understandable given the current state of knowledge, since the chance of success is small
- ○ No or too limited research is being done into pharmacological treatment, while the current state of knowledge would give rise to more R&D activity, since research is promising
- ○ Research into pharmacological treatment is being done, but no suitable remedy has yet emerged
- ○ Other, i.e.: … [Space for free text]

3b. Please explain your answer to the previous question here.

[Space for free text]

4. If you think that pharmacological treatment can be further optimised, can you please explain where you think this potential improvement can be achieved and where the greatest need for improvement lies?

[Space for free text]

5. Are there (sub)indications for this condition that differ in terms of (1) the possibility of pharmacological treatment, (2) the availability of pharmacological treatment and/or (3) the degree of R&D activity for new drugs? If so, please indicate here which (sub)indications this concerns and provide an explanation of any differences.

[Space for free text]

Note a. The condition-specific survey was conducted among members of scientific associations and patient associations.

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Appendix B: Questionnaire of general survey[a]

1. How would you describe the situation with respect to medicines on the market for this condition?

- ○ Pharmacological treatment is not preferred (other interventions such as lifestyle, surgery, etc. are more applicable)
- ○ Better pharmacological treatment is available in other markets (e.g. Japan, China or Russia), but not available in the Netherlands
- ○ No medication available, while medication could be a treatment option
- ○ Pharmacological treatment available, but need for better drug (e.g. simpler administration, fewer interactions, fewer side effects, greater effectiveness, etc.)
- ○ Good, all or almost all patients with this condition can be treated properly with existing medicines.

2. Please explain your answer to the previous question here.

[Space for free text]

3. How would you describe the R&D activity of biotech and pharmaceutical companies on new drugs for this condition?

- ○ No or limited research is being done into new drugs, but that is understandable given the current state of knowledge, since the chance of success is small
- ○ No or too limited research is being done into pharmacological treatment, while the current state of knowledge would give rise to more R&D activity, since research is promising
- ○ Research into pharmacological treatment is being done, but no suitable remedy has yet emerged.
- ○ Other, i.e.: … [Space for free text]

4. Please explain your answer to the previous question here.

[Space for free text]

5. If you think that pharmacological treatment can be further optimised, can you please explain where you think this potential improvement can be achieved and where the greatest need for improvement lies?

[Space for free text]

6. Are there (sub)indications for this condition that differ in terms of (1) the possibility of pharmacological treatment, (2) the availability of pharmacological treatment and/or (3) the degree of R&D activity for new drugs? If so, please indicate here which (sub)indications this concerns and provide an explanation of any differences.

[Space for free text]

Note: a. The general survey was conducted among members of coordinating scientific associations and professors of pharmacology.

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Appendix C: Gaps in drug development for anxiety disorders

In the Netherlands, 15% of adults develop some form of anxiety disorder every year.[24] This concerns all adults aged 18 to 75 who have had one or more anxiety disorders in the past 12 months.

The anxiety disorders can be subdivided into generalised anxiety disorder, panic disorder, specific phobia, social phobia and agoraphobia.[25]

Anxiety disorders and mood disorders share many similarities in pharmacological treatment. The disorders themselves are closely related and may cross over. Two key needs for drug development have been identified:

— Need for patient stratification

The experts indicate that there is a need for better patient stratification for anxiety disorders. As it concerns a heterogeneous group of conditions, there is a need to be able to treat subgroups of patients more specifically. Again, the identification of subgroups based on pathophysiology is difficult. That is why there is a need for large databases that enable pattern recognition. Based on these patterns, it is easier to predict which subgroups of patients will respond to a particular treatment. Due to the close relationship between mood disorders and anxiety disorders, it is indicated that it is preferable to include patients suffering from either condition in the same database.

— Need for drugs with fewer side effects

Anxiety disorders are often treated using drugs that are effective, but can also have an addictive effect, such as benzodiazepines. There is a need for medication with the same effectiveness, but less addictive effect. In addition, as current treatment often has side effects such as glucose intolerance and cardiovascular side effects, there is a need for drugs that do not have these side effects or have them to a lesser extent.

Source:

24. Angststoornissen | Volksgezondheid en Zorg (vzinfo.nl)
25. Angststoornissen | Leeftijd en geslacht | Volksgezondheid en Zorg (vzinfo.nl)

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