The Lancet Psychiatry

# Treatment outcomes for depression: Ten key percentages that highlight the challenge ahead

--Manuscript Draft--

| | |
|---|---|
| **Manuscript Number:** | thelancetpsych-D-19-01174R1 |
| **Article Type:** | Comment |
| **Keywords:** | depression; Psychotherapy; pharmacotherapy; treatment outcome; relapse |
| **Corresponding Author:** | Pim Cuijpers, PhD<br>VU University Amsterdam<br>Amsterdam, NETHERLANDS |
| **First Author:** | Pim Cuijpers, PhD |
| **Order of Authors:** | Pim Cuijpers, PhD |
| | Argyris Stringaris, MD, PhD, FRCPsych |
| | Miranda Wolpert |
| **Manuscript Region of Origin:** | NETHERLANDS |

# Treatment outcomes for depression: challenges and opportunities

Depressive disorders are common, costly, have a strong impact on quality of life, and are associated with considerable morbidity and mortality. Effective treatments are available and antidepressant medication, and talking therapies are included in most guidelines as first-line treatments. These treatments have changed the lives of countless patients worldwide for the better and will continue to do so in the coming decades. However, although treatments are effective for some people, there is great room for improvement. This Comment highlights ten key statistics relating to the limitations of depression treatment outcomes that we feel warrant greater attention.

A considerable proportion of, particularly child and adolescent, patients show improvement without treatment,[1] whilst a substantial number do not show improvement with treatment (table).[2] This means that several people are taking treatments with the risk of negative side effects, who either might have recovered without treatment (whether medication or psychotherapies) or might not improve with treatment.[3] Moreover, all types of recovery without treatment were generally lumped together as "spontaneous improvement". The multitude of ways in which people may recover have as yet been largely under-studied, such as exercise, community engagement, and engagement with nature.[5]

Although many new refinements on treatments have been developed in the past decades, their efficacy has not improved over time.[6] Moreover, it is currently not possible to predict who is most likely to benefit from which interventions or approaches. People are often exposed to different forms of help before they find one that works for them. We also still largely do not understand the underlying mechanisms of how different interventions work.[7] Some of this is due to lack of clarity about what depression is, its boundaries and possible heterogeneity.

Our lack of knowledge cannot be put down only to lack of research in existing treatments. In the past decades more than 500 randomized trials have examined the effects of antidepressant medications, and more than 600 trials have examined the effects of psychotherapies for depression, (although comparatively few are conducted for early-onset depression). However, less than 20% of drug trials and less than 30% of therapy trials have low risk of bias, making the outcomes uncertain. Typically, such

trials do not have sufficient statistical power to examine for whom a treatment is effective, resulting in no reliable evidence on who benefits most from which treatment. Also, many different outcome measures are used in treatment research, making it impossible to merge the results of trials without interfering noise. In addition, longer-term effects are not examined in most trials. Despite these more than 1000 trials, very basic questions of real-life importance to those with depression and those trying to help them have not been answered. For example, should adolescents with depression be treated differently to young adults? Should people experiencing a first-ever episode be treated differently from patients who had a depressive disorder in the past? What is the best next treatment when an individual does not respond to the first treatment? What sort or approaches or interventions outside current treatments may be helpful for which people and in what contexts?

There is much still to learn in relation to effective approaches to prevent or treat depression. In part to address this problem, the Wellcome Trust has launched its new priority mental health programme which focuses on both depression and anxiety in youth (14-24 year olds) (https://wellcome.ac.uk/what-we-do/our-work/mental-health-transforming-research-and-treatments/strategy). The strategy is to create a more integrated and inclusive field of mental health science that can capitalize more effectively on existing siloed knowledge and agree new ways forward, including shared metrics with a greater focus on what might be the core-components of effective interventions, defined to include the widest possible range of approaches. The hope is that over the next ten years we have the potential to find and promote the next generation of approaches and treatments for prevention, intervention, relapse-prevention and ongoing management for depression.

Pim Cuijpers, PhD [a,] Argyris Stringaris, MD, PhD, FRCPsych [b], Miranda Wolpert, PsychD [c,d]

[a] Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health Research Institute, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

[b] Mood Brain and Development Unit, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA

[c] Evidence Based Practice Unit, Faculty of Brain Sciences, UCL, London, United Kingdom
[d] Wellcome Trust, London, United Kingdom
Corresponding author: Miranda Wolpert, Wellcome Trust, 215 Euston Road, London NW1 2BE, United Kingdom; email: m.wolpert@wellcome.ac.uk

Competing interests

Miranda Wolpert leads the Mental Health Priority Area at the Wellcome Trust referred to in the article. The authors report no other competing interests.

References

1. Whiteford HA, Harris MG, McKeon G, Baxter A, Pennell C, Barendregt JJ, et al. Estimating remission from untreated major depression: a systematic review and meta-analysis. Psychol Med 2013;43:1569-85.
2. Bear HA, Edbrooke-Childs J, Norton S, Krause KR, Wolpert M. Systematic review and meta-analysis: Outcomes of routine specialist mental health care for young people with depression and/or anxiety. J Am Acad Child Adol Psychiatry, in press
3. Cuijpers P, Karyotaki E, Weitz E, Andersson G, Hollon SD, van Straten A. The effects of psychotherapies for major depression in adults on remission, recovery and improvement: A meta-analysis. J Affect Dis 2014; 159: 118-26.
4. Wolpert M, Dalzell K, Ullman R, Garland L, Cortina M, Hayes D, et al. Strategies not accompanied by a mental health professional to address anxiety and depression in children and young people: a scoping review of range and a systematic review of effectiveness. Lancet Psychiatry 2019; 1: 46-60.
5. Eckshtain D, Kuppens S, Ugueto A, Ng MY, Vaughn-Coaxum R, Corteselli K, et al. Meta-analysis: 13-year follow-up of psychotherapy effects on youth depression. J Am Acad Child Adol Psychiatry, epub ahead of print
6. Holmes EA, Ghaderi A, Harmer CJ, Ramchandani PG, Cuijpers P, Morrison AP, et al. Psychological Treatments Research in Tomorrow's Science: Seeing Further. Lancet Psychiatry 2018; 5: 237–86.

7. Furukawa TA, Cipriani A, Atkinson LZ, Leucht S, Ogawa Y, et al. Placebo response rates in antidepressant trials: a systematic review of published and unpublished double-blind randomised controlled studies. Lancet Psychiatry 2016;3:1059–66
8. Levkovitz Y, Tedeschini E, Papakostas GI. Efficacy of antidepressants for dysthymia: A meta-analysis of placebo-controlled randomized trials. J Clin Psychiatry 2011; 72: 509-14.
9. Monroe SM, Harkness KL. Is depression a chronic mental illness? Psychol Med 2012; 42: 899-902.
10. Richards D. Prevalence and clinical course of depression: a review. Clin Psychol Rev 2011; 31: 1117–25.

Ten percentages to remember about treatments of depression [a)]

| | *Percentage* | *Definition* | *Source* | *Reference* |
|---|---|---|---|---|
| 1 | 54% of adults show improvement after antidepressant medication. | 50% reduction in symptoms | Meta-analysis of 165 placebo-controlled trials | Levkovitz, 2011 [8] |
| 2 | 35-40% of adults show improvement after a pill placebo in randomized trials. | 50% reduction in symptoms | Meta-analysis of 252 placebo-controlled trials of 1st and 2nd generation antidepressants | Furukawa, 2016 [7] |
| 3 | 62% of adults show improvement after psychotherapy (66% in CBT) | Not meeting MDD criteria in diag-nostic interview | Meta-analysis of 35 randomized trials | Cuijpers, 2014 [3] |
| 4 | 43% of adults show improvement in care-as-usual control groups of psychotherapy trials. | Not meeting MDD criteria in diag-nostic interview | Meta-analysis of 11 randomized trials | Cuijpers, 2014 [3] |
| 5 | 33% of children and young people with anxiety or depression show improvement in treatment-as-usual conditions. | Recovery (scoring below a pre-defined cut-off) | Meta-analysis of 38 trials presenting pre-post differences | Bear, 2020 [2] |
| 6 | 53% of adults with untreated depression show improvement in 12 months. | Study-defined remission rates | Meta-analysis of 19 waitlist control groups and observational studies | Whiteford, 2013 [1] |
| 7 | There is a 60% likelihood that a randomly selected youth receiving psychotherapy would be better off after treatment than a randomly selected youth in a control condition. | Range of outcome metrics | Meta-analysis of 655 randomized trials | Eckshtain et al 2019, [5] |
| 8 | Estimated 50% of people who experience a depression only have it once in their lives | Recovery | Narrative review | Monroe & Harkness 2012 [9] |
| 9 | 25-40% of patients who achieve recovery after treatment will have another depressive episode within two years, 60% after 5 years, and 85% after 15 years. | Recurrence defined as new episodes of MDD | Narrative review | Richards, 2011 [10] |
| 10 | Less than 10% of all interventions not involving a professional that have been suggested to address depression or anxiety in young people have been scientifically researched | Interventions | Scoping and systematic review | Wolpert, 2019 [4] |

[a)] Please note that percentages come from different studies and samples, and that direct comparisons between any given points above may not be warranted. MDD, major depressive disorder.

# Treatment outcomes for depression: challenges and opportunities

Depressive disorders are common, costly, have a strong impact on quality of life, and are associated with considerable morbidity and mortality. Effective treatments are available and antidepressant medication,~~[1]~~ and talking therapies~~[2]~~ are included in most guidelines as first-line treatments. These treatments have changed the lives of countless patients worldwide for the better and will continue to do so in the coming decades. However, although treatments are effective for some people, there is great room for improvement. This Comment highlights ten key ~~percentages~~ statistics relating to the limitations of depression treatment outcomes that we feel warrant greater attention.

A considerable proportion of, particularly ~~young~~**~~[A: give age range]~~**child and adolescent, patients show improvement without treatment,[1~~3~~] whilst a substantial number do not show improvement with treatment (table).[~~4 9~~2] This means that several people are taking treatments with the risk of negative side effects, who either might have recovered without treatment (whether medication or psychotherapies) or might not improve with treatment.[3~~4~~] Moreover, all types of recovery without treatment were generally lumped together as "spontaneous improvement". ~~It is only more recently~~**~~[A: please give year]~~** ~~that there is interest in examining t~~The multitude of ways in which people may recover ~~that~~ have as yet been largely under-studied, such as exercise, community engagement, and engagement with nature.[5~~9~~]

~~On a population level, a modeling study suggested that current treatments can only take away one third of the disease burden of depression, and only under optimal conditions where everyone with a depressive disorder gets an effective evidence-based treatment~~**~~[A: this study was published in 2004 and would be based on studies published considerably before that. Please make it clear here. You hint at it in the next sentence but it needs to be explicit – see my comment in the email]~~**~~.[10]~~ Although many new refinements on treatments have been developed in the past decades, their efficacy has not improved over time.[~~1,2,8~~6] Moreover, it is currently not possible to predict who is most likely to benefit from which interventions or approaches~~treatment~~. ~~Patients~~ People are often exposed to different forms of help ~~multiple treatments~~ before they find one that works for them. We also still largely do

not understand the underlying mechanisms of how different interventions ~~treatments~~ work.[~~11~~7] Some of this is due to lack of clarity about what depression is, its boundaries and possible heterogeneity.~~[12]~~

Our lack of knowledge cannot be put down only to lack of research in existing treatments. In the past decades more than 500 randomized trials have examined the effects of antidepressant medications,~~[1]~~ and more than 600 trials have examined the effects of psychotherapies for depression~~,~~ (although comparatively few are conducted for early-onset depression). However, less than 20% of drug trials and less than 30% of therapy trials have low risk of bias, making the outcomes uncertain.~~[1,2]~~ Typically, such trials do not have sufficient statistical power to examine for whom a treatment is effective, resulting in no reliable evidence on who benefits most from which treatment. Also, many different outcome measures are used in treatment research, making it impossible to merge the results of trials without interfering noise. In addition, longer-term effects are not examined in most trials. Despite these more than 1000 trials, very basic questions of real-life importance to those with depression and those trying to help them have not been answered. For example, should adolescents with depression be treated differently to young adults? Should people experiencing a first-ever episode be treated differently from patients who had a depressive disorder in the past? What is the best next treatment when an individual does not respond to the first treatment? What sort or approaches or interventions outside current treatments may be helpful for which people and in what contexts?

There is much still to learn in relation to effective approaches to prevent or treat depression. In part to address this problem, the Wellcome Trust has launched its new priority mental health programme which focuses on both depression and anxiety in youth (14-24 year olds) (https://wellcome.ac.uk/what-we-do/our-work/mental-health-transforming-research-and-treatments/strategy). The strategy is to create a more integrated and inclusive field of mental health science that can capitalize more effectively on existing siloed knowledge and agree new ways forward, including shared metrics with a greater focus on what might be the core-components of effective interventions, defined to include the widest possible range of approaches. The hope is that over the next ten years we have the potential to find and promote the next

generation of approaches and treatments for prevention, intervention, relapse-prevention and ongoing management for depression.

Pim Cuijpers, PhD [a,] Argyris Stringaris, MD, PhD, FRCPsych [b], Miranda Wolpert, PsychD [c,d]

[a] Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health Research Institute, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

[b] Mood Brain and Development Unit, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA

[c] Evidence Based Practice Unit, Faculty of Brain Sciences, UCL, London, United Kingdom

[d] Wellcome Trust, London, United Kingdom

Corresponding author: Miranda Wolpert, Wellcome Trust, 215 Euston Road, London NW1 2BE, United Kingdom; email: m.wolpert@wellcome.ac.uk

Competing interests

Miranda Wolpert leads the Mental Health Priority Area at the Wellcome Trust referred to in the article. The authors report no other competing interests.

Formatted: Underline

References

~~1. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 2018; 391:1357-66.~~

~~2. Barth J, Munder T, Gerger H, Nuesch E, Trelle S, Znoj H, Juni P, Cuijpers P. Comparative efficacy of seven psychotherapeutic interventions for depressed patients: A network meta-analysis. Plos Med 2013;10: e1001454.~~

~~3~~1. Whiteford HA, Harris MG, McKeon G, Baxter A, Pennell C, Barendregt JJ, et al. Estimating remission from untreated major depression: a systematic review and meta-analysis. Psychol Med 2013;43:1569-85.

24. ~~7.~~ ~~Bear HA, Edbrooke-Childs J, Norton S, Krause KR, Wolpert M. Systematic review and meta-analysis: Outcomes of routine specialist mental health care for young people with depression and/or anxiety. J Am Acad Child Adol Psychiatry, in press~~

3. Cuijpers P, Karyotaki E, Weitz E, Andersson G, Hollon SD, van Straten A. The effects of psychotherapies for major depression in adults on remission, recovery and improvement: A meta-analysis. J Affect Dis 2014; 159: 118-26.

49. Wolpert M, Dalzell K, Ullman R, Garland L, Cortina M, Hayes D, et al. Strategies not accompanied by a mental health professional to address anxiety and depression in children and young people: a scoping review of range and a systematic review of effectiveness. Lancet Psychiatry 2019; 1: 46-60.

58. Eckshtain D, Kuppens S, Ugueto A, Ng MY, Vaughn-Coaxum R, Corteselli K, et al. Meta-analysis: 13-year follow-up of psychotherapy effects on youth depression. J Am Acad Child Adol Psychiatry, epub ahead of print

611. Holmes EA, Ghaderi A, Harmer CJ, Ramchandani PG, Cuijpers P, Morrison AP, et al. Psychological Treatments Research in Tomorrow's Science: Seeing Further. Lancet Psychiatry 2018; 5: 237–86.

713. Furukawa TA, Cipriani A, Atkinson LZ, Leucht S, Ogawa Y, et al. Placebo response rates in antidepressant trials: a systematic review of published and unpublished double-blind randomised controlled studies. Lancet Psychiatry 2016;3:1059–66

86. Levkovitz Y, Tedeschini E, Papakostas GI. Efficacy of antidepressants for dysthymia: A meta-analysis of placebo-controlled randomized trials. J Clin Psychiatry 2011; 72: 509-14.

9. Monroe SM, Harkness KL. Is depression a chronic mental illness? Psychol Med 2012; 42: 899-902.

510. Richards D. Prevalence and clinical course of depression: a review. Clin Psychol Rev 2011; 31: 1117–25.

~~6. Levkovitz Y, Tedeschini E, Papakostas GI. Efficacy of antidepressants for dysthymia: A meta-analysis of placebo-controlled randomized trials. J Clin Psychiatry 2011; 72: 509-14.~~

Formatted: Dutch (Netherlands)

7. Bear HA, Edbrooke-Childs J, Norton S, Krause KR, Wolpert M. Systematic review and meta-analysis: Outcomes of routine specialist mental health care for young people with depression and/or anxiety. J Am Acad Child Adol Psychiatry, in press
8. Eckshtain D, Kuppens S, Ugueto A, Ng MY, Vaughn-Coaxum R, Corteselli K, et al. Meta-analysis: 13-year follow-up of psychotherapy effects on youth depression. J Am Acad Child Adol Psychiatry, epub ahead of print
9. Wolpert M, Dalzell K, Ullman R, Garland L, Cortina M, Hayes D, et al. Strategies not accompanied by a mental health professional to address anxiety and depression in children and young people: a scoping review of range and a systematic review of effectiveness. Lancet Psychiatry 2019; 1: 46-60.
10. Andrews G, Issikadis C, Sanderson K, Corry J, Lapsley H. Utilising survey data to inform public policy: comparison of the cost-effectiveness of treatment of ten mental disorders. Br J Psychiatry 2004;184:526-33.
11. Holmes EA, Ghaderi A, Harmer CJ, Ramchandani PG, Cuijpers P, Morrison AP, et al. Psychological Treatments Research in Tomorrow's Science: Seeing Further. Lancet Psychiatry 2018; 5: 237-86.
12. Stringaris A. What is depression? J Child Psychol Psychiatry 2017;58:1287-9.
13. Furukawa TA, Cipriani A, Atkinson LZ, Leucht S, Ogawa Y, et al. Placebo response rates in antidepressant trials: a systematic review of published and unpublished double-blind randomised controlled studies. Lancet Psychiatry 2016;3:1059-66

Ten percentages to remember about treatments of depression [a)]

| | *Percentage* | *Definition* | *Source* | *Reference* |
|---|---|---|---|---|
| 1. | 54% of adults show improvement after antidepressant medication. | 50% reduction in symptoms | Meta-analysis of 165 placebo-controlled trials | Levkovitz, 2011 [8] |
| 2~~1~~. | 35-40% of adults show improvement after a pill placebo in randomized trials. | 50% reduction in symptoms | Meta-analysis of 252 placebo-controlled trials of 1st and 2nd generation antidepressants | Furukawa, 2016 [7~~12~~] |
| ~~2.~~ | ~~54% of adults show improvement after antidepressant medication.~~ | ~~(50% reduction in symptoms~~ | ~~Meta-analysis of 165 placebo-controlled trials~~ | ~~Levkovitz, 2011 [86]~~ |
| 3 | 62% of adults show improvement after psychotherapy (66% in CBT) | Not meeting MDD criteria in diagnostic interview | Meta-analysis of 35 randomized trials | Cuijpers, 2014 [34] |
| 4 | 43% of adults show improvement in care-as-usual control groups of psychotherapy trials. | Not meeting MDD criteria in diagnostic interview | Meta-analysis of 11 randomized trials | Cuijpers, 2014 [34] |
| 5 | 33% of children and young people with anxiety or depression show improvement in treatment-as-usual conditions. | Recovery (scoring below a pre-defined cut-off) | Meta-analysis of 38 trials presenting pre-post differences | Bear, 2020 [27] |
| 6 | 53% of adults with untreated depression show improvement in 12 months~~, with some evidence of a higher probability of improvement without treatment for children and adolescents~~. | Study-defined remission rates | Meta-analysis of 19 waitlist control groups and observational studies | Whiteford, 2013 [13] |
| ~~7~~ | ~~33% of the disease burden of depression is estimated to be preventable with current best treatments.~~ | ~~Years lived with disability~~ | ~~Modeling study, based on Australian data~~ | ~~Andrews, 2004 [10]~~ |
| 7~~8~~ | There is a 60% likelihood that a randomly selected youth receiving psychotherapy would be better off after treatment than a randomly selected youth in a control condition. | Range of outcome metrics | Meta-analysis of 655 randomized trials | Eckshtain et al 2019, [58] |
| 8. | Estimated 50% of people who experience a depression only have it once in their lives | Recovery | Narrative review | Monroe & Harkness 2012 [9] |
| 9 | 25-40% of patients who achieve recovery after treatment will have another depressive episode after [A: within?] two years, 60% after 5 years, and 85% after 15 years. | Recurrence defined as new episodes of MDD | Narrative review | Richards, 2011 [10~~5~~] |
| 10 | Less than 10% of all interventions not involving a professional that have been suggested to address depression or anxiety in young people have been scientifically researched | Interventions | Scoping and systematic review | Wolpert, 2019 [49] |

[a)] Please note that percentages come from different studies and samples, and that direct comparisons between any given points above may not be warranted. MDD, major depressive disorder.

**Commented [A1]:** This seems just to confuse and weaken the impact. Delete?

**Commented [A2]:** See comment in text about date of this study

**Commented [A3]:** I've reworded thist to make it consistent in format with the other points . Please check that I haven't changed the meaning and edit as necessary.

**Revision of the paper *"Treatment outcomes for depression: challenges and opportunities"* (manuscript thelancetpsych-D-19-01174) according to the points raised by the Editor**

Thank you for the positive comments on our Comment. We have accepted the edits you made in the text and then changed the text according to your other comments. In addition, we also made some more textual edits that we think improve the text further.

Comment: I'm not happy with the title. It feels like the headline for a promotional campaign, which is fine for the campaign, but not for a Lancet Psychiatry comment. Could this be changed to something more bland, such as 'challenges and opportunties'?
Reply: We have changed the title into: *"Treatment outcomes for depression: challenges and opportunities"*

Comment: Table: For psychotherapy, you put the treatment outcome first, then the usual care: I think you should do this for pharmacotherapy as well, so point 2 should come before point 1.
Reply: We have changed the order of the first two points.

Comment: Point 7 doesn't seem to fit with the others. If 54% of adults improve with antidepressants and over 60% with psychotherapy, surely we should be able to manage more than 33% of the burden?
Reply: This point has been removed from the Table and from the text. It is not essential to make the points of the paper clear.

Comment: Comments should have not more than 10 references. Can you edit to remove three?
Reply: We have removed some references, so that the final number is 10.