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# Toward a paradigm shift in treatment and research of mental disorders

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## Editorial

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Mental disorders are common and represent a significant and worldwide public health concern (Smith, 2011; Vigo *et al.*, 2016; Patel *et al.*, 2018). The global burden of disease due to mental illness accounts for 21–32% of years lived with disability and 7–13% of disability-adjusted life-years (Vigo *et al.*, 2016). The Lancet commission on global mental health and sustainable development just recently estimated a loss of US$16 trillion to the global economy due to mental disorders in the period 2010–2030 (Patel *et al.*, 2018).

Psychotherapy and pharmacotherapy are the two key available treatments presently offered to millions of subjects with mental disorders around the world. However, recent evidence suggests that their effects are overestimated due to several factors, such as publication bias, researcher allegiance, and other shortcomings in study design (Ioannidis, 2005, 2008; Driessen *et al.*, 2015; Tajika *et al.*, 2015; Cuijpers *et al.*, 2016; Leichsenring *et al.*, 2017; Leucht *et al.*, 2017; Cuijpers *et al.*, 2019; van Os *et al.*, 2019). Thus, the true efficacy of psychotherapy and pharmacotherapy remains contested.

Meta-analyses or systematic reviews of randomized controlled trials (RCTs) are considered to provide the highest level of evidence (1a) (Oxford Centre, 2009). Both meta-analyses and RCTs, however, may differ with regard to the strictness of testing treatment efficacy, depending, for example, on the comparator against which the treatment is tested. Whereas comparisons to waiting list or no-treatment can at best show that a treatment is better than doing nothing, comparisons with treatment as usual (TAU) or placebo show whether treatments have an additional gain compared to TAU or placebo. They also provide information on whether the efforts, costs, and possible side effects of specialized treatments pay off from a health-economic perspective. Thus, these comparisons provide better estimates of the true efficacy of a treatment (Cuijpers *et al.*, 2016).

Recent high-ranking meta-analyses suggest that the efficacy of psychotherapy and pharmacotherapy in comparison to placebo or TAU is limited. For key mental disorders such as depressive disorders (Driessen *et al.*, 2015; Cipriani *et al.*, 2018; Cuijpers *et al.*, 2019), anxiety disorders (Heeren *et al.*, 2015; Curtiss *et al.*, 2017; Li *et al.*, 2017; Liu *et al.*, 2017; Carpenter *et al.*, 2018; Gomez *et al.*, 2018), somatoform disorders (van Dessel *et al.*, 2014), borderline personality disorder (Cristea *et al.*, 2017a), bipolar disorder (Cipriani *et al.*, 2013), schizophrenia spectrum disorders (Jauhar *et al.*, 2014; Leucht *et al.*, 2017), and psychotherapy of children and adolescents (Weisz *et al.*, 2006, 2013, 2017, 2019; Eckshtain *et al.*, 2019), psychotherapy and pharmacotherapy yielded effect sizes in terms of standardized mean differences (SMDs) of about 0.30 or below in comparison with TAU or placebo, especially if effect sizes were adjusted for biases (Leucht *et al.*, 2017; Gomez *et al.*, 2018; Cuijpers *et al.*, 2019). Large effect sizes ($\geqslant$0.80) were only achieved in comparison of psychotherapy to weak comparators such as waiting list conditions (Huhn *et al.*, 2014; Cuijpers *et al.*, 2016; Liu *et al.*, 2017).

Rates for remission and response were found to be limited as well. For depressive and anxiety disorders, meta-analyses reported rates of remission between 37% and 43% (Cuijpers *et al.*, 2014; Li *et al.*, 2017; Springer *et al.*, 2018). For schizophrenia, a recovery rate of 23% was found (Leucht, 2014). Response rates for depressive and anxiety disorders are about 50% (Cuijpers *et al.*, 2014; Loerinc *et al.*, 2015; Barth *et al.*, 2016; Imai *et al.*, 2016; Li *et al.*, 2017; Williams *et al.*, 2017) and 23% for schizophrenia spectrum disorders (Leucht *et al.*, 2017), with response usually defined by a 50% reduction of symptoms (Cuijpers *et al.*, 2014). According to these meta-analyses, presently most patients do not remit and about 50% or more do not respond to the available treatments. Furthermore, success rates of treatments need to be compared to those of placebo or TAU. For depressive and anxiety disorders, placebo response rates range between 35% and 40% (Furukawa *et al.*, 2016; Li *et al.*, 2017; Williams *et al.*, 2017). Thus, the difference in response rates in comparison to placebo is between 10% and 15%, indicating small effect sizes in terms of success rate differences, corresponding to SMDs between 0.20 and <0.30 (Kraemer and Kupfer, 2006).



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In this context, it is of note that TAU is a heterogeneous condition and effect sizes may depend on the type of TAU (Watts *et al.*, 2015). In a meta-analysis testing different forms of TAU psychotherapy (cognitive–behavior therapy) achieved small effect sizes when compared with general practitioner management (0.20) and larger effect sizes (0.71) when compared with minimal contact (Watts *et al.*, 2015). Placebo may be a heterogeneous condition as well when used in trials of psychological interventions. If (psychological) placebos were structurally equivalent to active treatments (e.g. in number and duration of sessions, training of therapists, format of therapy), the differences in outcome were significantly smaller than for structurally inequivalent placebos (SMD = 0.15 *v.* 0.47) (Baskin *et al.*, 2003). Thus, TAU and placebo may be more or less strong comparators, with treatments yielding small effect sizes in comparison to treatments that work or to structurally equivalent placebos and larger effect sizes in comparison to weaker forms of TAU or placebo (Baskin *et al.*, 2003; Watts *et al.*, 2015).

## Further concerns

There are several reasons for further concern.

(1) Even for the above presented estimates of efficacy, it cannot be ruled out that at least some of them are inflated by several biases, such as publication bias, selective reporting of outcomes/analyses, insufficient blinding (psychotherapy studies can *per se* not be fully double-blind), other shortcomings in study design, financial conflicts (e.g. industry funding) and spontaneous remission due to the natural course of mental disorders (Ioannidis, 2005, 2008; Cuijpers *et al.*, 2014, 2016; Huhn *et al., 2014*; Leichsenring *et al.*, 2017; Cipriani *et al.*, 2018).
(2) As another concern which is consistent with the existence of biases, rates of replication among the most highly-cited articles were found to be low for psychotherapy and pharmacotherapy (Tajika *et al.*, 2015; Sakaluk *et al.*, 2019): when large and or better studies were done, the initial highly-cited study was found to have overestimated the treatment benefit by 132% (Tajika *et al.*, 2015).
(3) The description of interventions in publications is often remarkably poor (Hoffmann *et al.*, 2014), in both individual trials and in systematic reviews (Glasziou *et al.*, 2014; Hoffmann *et al.*, 2017). Incomplete reporting contributes to an avoidable waste in research (Chalmers *et al.*, 2014; Glasziou *et al.*, 2014). Poor reporting of interventions was found for pharmacological interventions and even more so for non-pharmacological interventions (Glasziou *et al.*, 2008; Schroter *et al.*, 2012; Hoffmann *et al.*, 2013, 2014, 2015). In a consecutive sample of RCTs testing non-pharmacological interventions published in six leading general medical journals, only 39% of interventions were found to be adequately described (Hoffmann *et al.*, 2013). For psychotherapy, treatment integrity (i.e. the degree to which an intervention is delivered as intended) was only adequately reported in 11% of the analyzed studies published in six high-impact-factor journals (Cox *et al.*, 2019).
(4) Reported effect sizes of psychotherapy for anxiety and depressive disorders seem to have stagnated or even decreased during recent decades (Öst, 2008; Johnsen and Friborg, 2015; Friborg and Johnsen, 2017; Cristea *et al.*, 2017b; Weisz *et al.*, 2019). This is also true for antidepressants in depressive and anxiety disorders and may apply to antipsychotic drugs, too (Schalkwijk *et al.*, 2014; Leucht *et al.*, 2017; Gomez *et al.*, 2018). In the latest meta-analysis of 522 trials on antidepressants, the best efficacy estimates were obtained for an old drug, amitriptyline (Cipriani *et al.*, 2018).
(5) Long-term treatment effects (which may be even smaller than short-term effects) are under-studied (Ioannidis, 2008; Huhn *et al.*, 2014; Steinert *et al.*, 2016; Leichsenring and Leweke, 2017). Especially for pharmacotherapy, only 5% of studies reported more than just short-term follow-up data (compared to 55% of psychotherapy trials) (Huhn *et al.*, 2014).
(6) About 20% of patients drop out of psychotherapy, even more of pharmacotherapy (Swift *et al.*, 2017), with patients apparently experiencing the treatments as not acceptable.
(7) Data on side effects of psychotherapy are scarce (Linden and Schermuly-Haupt, 2014).
(8) It is unclear whether the effect sizes from randomized clinical trials approximate real-world effectiveness (Sherman *et al.*, 2016). Patients seen in clinical practice usually show concomitant disorders but are often excluded from efficacy studies and these patients are more difficult to treat successfully. A large-scale (real-world) effectiveness study, however, recently reported recovery rates of 50% for depressive and anxiety disorders (Clark, 2018). These rates are based on self-report measures (Clark, 2018), whereas in the meta-analyses cited above, remission rates were based on observer-rated measures.
(9) Finally, despite earlier hopes, research on neuroscience and genetics of mental disorders has not been very successful to identify better treatments or useful biomarkers of treatment effects (Insel, 2017). While in daily practice, some patients do respond well and others totally fail, there are no clinically validated biomarkers or other tools to individualize the treatment and to know precisely in advance who will respond best to what treatment (van Os *et al.*, 2019).

Overall, while a certain proportion of patients (who cannot be identified in advance) does benefit from available treatments, most patients do not remit and at least half of the patients do not respond to the available treatments (Cuijpers *et al.*, 2014; Leucht, 2014; Li *et al.*, 2017; Springer *et al.*, 2018). Thus, results for the efficacy of psychotherapy and pharmacotherapy are sobering, indicating only a small incremental gain over TAU or placebo and limited rates for remission and response. As noted above, this (limited) incremental gain needs to be balanced against the efforts, costs, and side effects associated with psychotherapy and pharmacotherapy. The situation is aggravated by the numerous concerns mentioned above (e.g. biases, inflated effect sizes, low rates of replication, lack of long-term studies, stagnating or decreasing effect sizes) raising serious doubts about the available evidence.

## A dead end?

Each mental disorder raises its own host of issues. However, recent evidence across multiple meta-analyses on key mental disorders provides an overarching picture of limited benefits for both psychotherapy and pharmacotherapy. Some differences for specific disorders are not strong enough to weaken the overall impression that a dead end has been reached in the treatment of mental disorders. For this reason, a paradigm shift seems to be required, fostering a new research agenda which has a clearly

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different orientation, with more appropriate study design features, outcomes, processes, and funding mechanisms.

## Suggestions for a research agenda that makes a difference

To overcome this situation, a research agenda is suggested here which encompasses methodological improvements and strategies to discover new treatments, to identify and evaluate new settings for interventions, and to improve available treatments. In addition, a change in funding policy seems to be required. The community of mental health specialists is already becoming receptive to the possibility of major changes in mindset and strategy, as exemplified in the recent deliberations of the Lancet commission on global mental health and sustainable development (Patel *et al.*, 2018). Mental health is seen as a global challenge in a rapidly changing world and with many unmet needs. While many of these needs reflect policy, public health, and social structures, the ability to meet them will require more effective interventions. For developing and implementing more effective interventions, a paradigm shift with improvements on many different fronts is needed, as we discuss below.

## Methodological improvements

As an important first step for further progress, improving study quality is required. The field of mental health interventions needs more reproducible research practices (Tajika *et al.*, 2015; Sakaluk *et al.*, 2019). Independent methodological support with larger studies run without industry control, expansion of team science efforts, adversarial collaboration, study pre-registration, adequate reporting, and data sharing may help avoid biases which often lead to overestimation of effect sizes (Open Science Collaboration, 2015; Leichsenring *et al.*, 2017; Munafò *et al.*, 2017). Furthermore, an adequate description of interventions is required for researchers to build on findings or replicate results and for clinicians and patients to reliably implement interventions (Boutron *et al.*, 2008; Hoffmann *et al.*, 2014). Both the experimental and the control conditions need to be adequately described (Guidi *et al.*, 2017) and researcher allegiance needs to be controlled for (Leichsenring *et al.*, 2017). To improve reporting of interventions, the template for intervention description and replication checklist and guide (TIDieR) was developed (Hoffmann *et al.*, 2014). Whether the quality of reporting has improved needs to be examined over time. Furthermore, active comparators need to be included since waiting list or no-treatment conditions are likely to overestimate effect sizes (Cuijpers *et al.*, 2016; Guidi *et al.*, 2017). While waiting list conditions may be acceptable for a first test of efficacy, active comparators provide more rigorous tests in further steps of research. Long-term follow-ups of RCTs are required capturing major outcomes, including suicide attempts, completed suicides, loss of job, days spent in hospital or on sick leave, overall clinical and social disability, quality of life, side effects, costs, and utilities (Ioannidis, 2008). In addition, trials under real-world conditions are needed to also evaluate pragmatic effectiveness (Sherman *et al.*, 2016).

## Improving available treatments: tailoring the treatment more specifically to the patient

For improving available treatments, a primary focus on the large proportion of patients who do not benefit sufficiently from available treatments or who drop out prematurely is promising (non-responders and drop-outs). Examining, for example, the reasons for prematurely dropping-out allows to identify the limitations of existing treatments (Leichsenring *et al.*, 2019). This type of research will provide important information about patients' needs and for improving treatments. Identifying characteristics of drop-outs and non-responders may allow for both differential and adaptive indication, that is, offering alternative treatments or tailoring a treatment more specifically to the patient, in both psychotherapy and pharmacotherapy. Taking into account relevant factors besides a patient's present state such as response to previous treatments (staging) may be helpful (Fava *et al.*, 2012; Steinert *et al.*, 2016).

Related to non-response and dropping-out, there is a perceived need to apply a more flexible psychotherapeutic approach tailoring the treatment more specifically to the patient – one treatment does not fit all (Cloitre, 2015). This applies to pharmacotherapy as well. Furthermore, since there is evidence to suggest that differences between therapists seem to explain more variance in outcome than differences between treatments, not only in psychotherapy but also in pharmacotherapy (McKay *et al.*, 2006; Wampold and Imel, 2015; van Os *et al.*, 2019), examining patient-treatment matching represents another promising approach (van Os *et al.*, 2019). Focusing on those interactional skills related to better outcome may be helpful in both training and research (van Os *et al.*, 2019). Furthermore, including patients in the evaluation of treatments may help to enhance efficacy and to identify what is helpful, less helpful, or even harmful (Dakin and Arean, 2013). In this way, treatment manuals may be improved on the basis of systematic patient feedback. Similarly, including patient representatives in discussing study design and results may help to build a new generation of pragmatic trials with patient-centered interventions and outcomes.

This kind of patient-centered research needs to take into account what really matters most to patients, which does not only include improvements in specific symptoms but also in trans-syndromal dimensions, social participation, and existential integration (e.g. well-being, social connectedness, occupational integration) (Tolin *et al.*, 2015; van Os *et al.*, 2019). For patients who do not achieve response or remission, strengthening resilience in these social and existential domains may be especially helpful (van Os *et al.*, 2019).

Quality of treatment implementation and delivery may be a crucial issue. New developments in technology-assisted supervision and training are available that need to be systematically studied (Rousmaniere *et al.*, 2014). As a somehow puzzling result, some preliminary data suggest that neither measures of adherence to treatment manuals nor of competence in delivering interventions were associated with outcome (Webb *et al.*, 2010). In routine clinical practice, however, organizational factors of treatment implementation such as problem description, number of treatment sessions, or waiting time before treatment were found to be related to outcome (Clark *et al.*, 2018).

There is evidence that providing feedback on the individual patient's progress may improve the outcome of psychotherapy in patients at risk of non-response (Shimokawa *et al.*, 2010). Feedback may include recommendations to alter the treatment plan, shift intervention strategies, or intensify treatment (Shimokawa *et al.*, 2010). This approach may be applied to pharmacotherapy as well.

In psychotherapy questions of optimal dosing remain open. While some patients benefit from short-term treatments, long-term treatments may be required for others. Most treatments

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included in the meta-analyses mentioned above were short-term, encompassing, for example, 1–28 treatment sessions (Loerinc *et al.*, 2015; Cuijpers *et al.*, 2016). Short-term therapy may be adequate for patients with acute distress (Kopta *et al.*, 1994; Lambert, 2013). For patients with chronic disorders or personality problems, short-term treatment fails most patients (Kopta *et al.*, 1994; Lambert, 2013). It is of note that longer-term treatments do not necessarily imply higher health-care costs. In clinical practice in Germany, for example, therapies of an average of 48 sessions are carried out (Albani *et al.*, 2010) which were shown to save health-care costs (Altmann *et al.*, 2018). These data also reflect the gap between efficacy research and clinical practice with regard to treatment duration. For longer-term psychotherapy benefits, costs and harms need to be assessed – the assumption that long-term psychotherapy is safe by default is naïve. Rigorous data are needed to test the effectiveness, acceptability, and harms of longer-term psychotherapy as well as its combination and/or alteration with drug treatments.

A patient-centered approach also needs to include adaptive strategies of switching from one treatment to another in case of non-response or augmenting one treatment by another, including augmenting psychotherapy by pharmacotherapy or *vice versa* (Thase, 2014; Markowitz and Milrod, 2015). Switching or augmenting is common in pharmacotherapy research (Rush *et al.*, 2006) but such strategies are practically non-existing in psychotherapy research (Markowitz and Milrod, 2015). For psychotherapy, no evidence-based treatment sequence algorithms exist how to proceed if a treatment fails (Markowitz and Milrod, 2015), while designs for such trials are available (Nahum-Shani *et al.*, 2012; Steinert *et al.*, 2016). Switching from one form of psychotherapy to another requires that sufficiently different forms of evidence-based treatments are available, that is, a diversity of treatments. For all these approaches, rigorous trials are required.

## A focus on prevention: identifying (and evaluating) new opportunities and settings for interventions

Considering different approaches to treatment may offer added value, for example, developing interventions for therapy and prevention at the society, community or workplace level to prevent and/or treat mental disorders. Mental problems such as the 'burnout syndrome' may need interventions in occupational and educational or training settings. Some approaches have been shown to be potentially cost-effective (McDaid and Park, 2011) and health care systems are called for to provide effective interventions (Herpertz *et al.*, 2016). Training trainers in the field of health or education in stress prevention, for example, midwives, nurses, teachers, managers in enterprises, pupils, or students, is another promising option (Herpertz *et al.*, 2016). Other settings that have been proposed as targets for interventions include the early years of life, for example, supporting parents, parenting, and the parent–infant relationship to enhance infant and maternal mental health (Barlow *et al.*, 2010) and families with parents suffering from a mental disorder (Taubner *et al.*, 2015). Mothers with a borderline personality disorder, for example, may be supported by enhancing their capacities for mentalization and empathy. This applies to foster families as well (Midgley *et al.*, 2019).

Focusing on healthy aging, at the workplace and in general, is proposed by several stakeholders (McDaid and Park, 2011). In the UK, for example, a Ministry for Loneliness has been established (https://www.nytimes.com/2018/01/17/world/europe/uk-britain-loneliness.html). Depending on its outcome, this could be a model for other countries as well. Finally, early identification and treatment or referral in primary care may prevent chronic developments. For patients who do not have access to face-to-face psychotherapy, Internet-based interventions may be helpful (Andersson and Titov, 2014; Andrews *et al.*, 2018).

Internet-based therapy achieved similar results as face-to-face therapy with comparable effect sizes (0.38) in relation to TAU (Andrews *et al.*, 2018).

All of these possibilities need to be evaluated rigorously as to their effectiveness *v.* potential harms, for example, over-diagnosis and over-treatment. To-date some prevention programs have yielded only small-to-medium effect sizes (Taubner *et al.*, 2015).

## Discovering new treatments

For discovering new treatments, research should allow more exploration of high-risk, out-of-the box ideas and accidental discoveries, for example, by not only reporting adverse events but also large unanticipated beneficial effects, by using online patient forums or by studying the effects of non-prescription recreational drugs (Nutt, 2014).

## A paradigm shift in funding: not more and more of the same

There is no industry funding research in psychotherapy and the industry has largely shifted away from funding pharmacotherapy trials for mental disorders given the limited success to-date (Smith, 2011). Studies addressing the renewed research agenda and the issues listed above need to be properly supported by funding organizations. Decisions on funding from existing public agencies and other funders are often biased toward specific types of inbred research with limited returns, providing just more of the same, for example, funding primarily one form of treatment (Nicholson and Ioannidis, 2012; Lorsch, 2015; MQ, 2015). As advances often spring from unexpected sources, supporting a variety of different (treatment) approaches increases the chance for important discoveries. Initiatives to promote funding of unbiased studies are needed. Payers, insurance companies, and public funders should consider supporting the proposed agenda, given the large burden of disease, accompanying costs and unanswered questions.

## Conclusions

Mental disorders were found to be associated with a 'trillion-dollar brain drain' (Gustavsson *et al.*, 2011; Smith, 2011; Patel *et al.*, 2018) which, as shown above, is presently not effectively addressed by the available treatments and research strategies. Thus, improving treatment strategies for mental disorders can be regarded as a central health challenge of the twenty-first century. To achieve this aim, a paradigm shift in research is required.

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