Toward a paradigm shift in treatment and research of mental disorders

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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, reviewer 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; Eckstain 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 (≥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).
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 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 (Glazsiou et al., 2014; Hoffmann et al., 2017). Incomplete reporting contributes to an avoidable waste in research (Chalmers et al., 2014; Glazsiou et al., 2014). Poor reporting of interventions was found for pharmacological interventions and even more so for non-pharmacological interventions (Glazsiou 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 comorbid 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
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; Sakuluk 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; Munafó 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
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; Steiner 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 ‘burn-out 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.

Acknowledgements. We thank Juergen Matzat for reviewing and approving this article. Juergen Matzat is an official patient representative of the The Federal Joint Committee (http://www.english.g-ba.de), the highest decision-making body of the joint self-government of physicians, dentists, hospitals, and health insurance funds in Germany.

Author contributions. All authors have contributed to this article and concurred on its content.


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