

The Official Academic Journal of the European Association of Clinical Psychology and Psychological Treatment



# CLINICAL PSYCHOLOGY IN EUROPE

The Official Academic Journal of the European Association of Clinical Psychology and Psychological Treatment

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# Overcoming Barriers and Limitations – Why This New Journal Is Needed

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# Highlights

- Introducing the new journal *Clinical Psychology in Europe* (CPE).
- Overcoming artificial barriers by focusing on evidence instead of traditions.
- Bridging the gap from basic experimental to treatment-related research.
- Supporting open science recommendations.
- Covering a broad variety of research efforts.
- Full open access but no publication fees.

We warmly welcome you to the reading of our newly founded journal *Clinical Psychology in Europe* – CPE!

Most of us receive requests to submit a manuscript to some obscure new journal just about every day. And today you are holding another new journal in your hands and may – with good reason – be wondering whether it is really necessary to launch a new journal given the numerous existing options for submissions.

Our resounding answer is: Yes, we need this journal "Clinical Psychology in Europe" (CPE). Not because we feel the need to add another obscure new journal to the field, but because we are keen to have a journal that is committed to encouraging a modern and self-critical discussion in the scientific community, to have a journal that is open-minded about topics considered for publication, to have a journal that increases the visibility of our field of research and to have a journal that provides innovative ideas for future research in clinical psychology.



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CPE aims to face several challenges in the field of clinical psychology:

A first challenge stems from the past, when clinical psychology limited its power and potential to influence society with tensions and artificial barriers between traditions, especially between traditions of psychotherapy ("schools").

To face this challenge, CPE is clearly committed to evidence-based treatments, independent of their traditional roots. We encourage all innovations that attempt to overcome these kinds of barriers, we aim to integrate different approaches, and to find a common language in clinical psychology. Although science thrives on critical debates, we should aim to have these constructive debates inside our community – while acting as one powerful group for societal aims.

Secondly, it is all too often forgotten that clinical psychology is not limited to treatment. The fruitful exchange between basic approaches, mechanistic and experimental research, diagnostics and classification, epidemiology and interventional research is the basic motor of our science. Interventions without links to basic sciences are isolated applications, but not serious fields of research. Relating the different fields of clinical psychology to each other, but also with the progress of other areas such as neuroscience, emotion regulation, learning, social interaction, and many others, creates the cross-links that characterize top scientific fields.

Accordingly, in CPE we aim to provide a balanced ratio of articles reporting on basic, mechanistic, and experimental research in clinical psychology, research from associated areas, such as neuroscience, behavioral medicine, or health psychology and articles presenting treatment-related issues. Our goal is to stimulate interdisciplinary exchange and understanding.

A third critical challenge (not only for clinical psychology, but for science in general) is the risk of disseminating false positive results. Clinical psychology, and in particular intervention research, is particularly prone to this threat. Many psychotherapy researchers are strongly identified with their favorite approaches and theories, and sometimes tend to disrespect one major rule of "Good Research Practice": Distrust your own research, and cross-check every result critically before you attempt to publish it. This disrespect is problematic as the dissemination of false positive results misleads other researchers, deceives society, and leads to misallocation of resources.

To face this challenge, CPE supports open science endeavors. We do not consider current proposals for open science as the final result of these discussions, but as a process during which we should try and evaluate different approaches to continuously improve the validity of published results. Our supporting publisher "Leibniz Institute for Psychology Information (ZPID)" provides several tools to improve open science, for example literature databases, archives for data-sharing, repositories, support for study planning or pre-registration (https://www.leibniz-psychology.org/en/).

Fourth, it is our impression that there is extensive knowledge around, but this knowledge does not always reach the scientific community. Given the pressure to 'publish or



perish', many researchers focus on submitting empirical research articles. Journals welcome these manuscripts and only rarely allow for updates or general overviews. Accordingly, there are limited opportunities for experts to share knowledge they have accumulated over several years of work in a specific field.

To reflect the broad variety of research efforts, CPE provides the opportunity to submit different types of articles. For empirical research, the typical *Research Articles* can be submitted. However, we also encourage submitting *Scientific Updates* on the current knowledge of a field in which experts can share their current summaries with all of us. The same holds true for the publication of other expertise or events, such as inaugural speeches or keynote lectures, which are characterized by thorough preparation. CPE can help to further disseminate this knowledge using the format of *State-of-the-Art Overviews*. To meet our goal of providing a platform of exchange, CPE further encourages authors to report *Latest Developments* (such as new technical applications or recently developed questionnaires) as well as topics related to *Politics and Education* in the field of clinical psychology. For example, the description of different legal regulations for clinical psychology and psychological interventions might inform and stimulate the development of such regulations in different countries.

And finally, we face a challenge in meeting the major societal aim of research: Disseminate it for the benefit of others and let others make use of it. This is why journals exist and why we meet at conferences. However, many journals have developed a life of their own with financial benefit becoming more and more relevant. As we are convinced that the decision about publication should not depend on whether authors can afford to pay substantial article processing charges we are delighted that – thanks to the support of Leibniz Institute for Psychology Information – our aim of not charging any publication costs for articles has become reality!

We welcome your submissions at https://cpe.psychopen.eu and we are looking forward to collaborating with you! Now enjoy reading the first issue of CPE and get inspired.

Winfried Rief, Editor in Chief, and Cornelia Weise, Managing Editor





Editorial



Check for updates

# The European Association of Clinical Psychology and Psychological Treatment (EACLIPT): A New Organization for the Future!

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The European Association of Clinical Psychology and Psychological Treatment (EACLIPT) was founded in 2017 with representatives of many European countries. At its launch, many people were surprised to hear that such an organization did not already exist given the role of clinical psychology both as a branch of psychology and psychological research, but also as a renowned profession.

We knew several national organizations existed for clinical psychologist practitioners and researchers across Europe, as well as European and international organizations for various subdisciplines of psychology and forms of psychotherapy. But we regarded the absence of a targeted organization for Europe as a serious omission. Thus, the EACLIPT aims to strengthen science, practice and political representation in relation to clinical psychology.

In this editorial we will briefly describe the aims of the EACLIPT and also our achievements to date. Finally, we will outline our wishes for the future.

The EACLIPT's aims are broad. We want to foster research, education and dissemination of scientifically evaluated findings, and address the following topics:

- Diagnostics and classification of mental health conditions
- Psychological and psychobiological mechanisms of health and disease
- Psychological treatments, psychotherapy
- Prevention and rehabilitation
- Healthcare issues in mental health conditions



- · Dissemination and implementation of evidence-based psychological treatments
- Education in clinical psychology
- Representation of clinical psychology in politics across Europe.

Although the EACLIPT focuses on clinical psychology, we are also dedicated to both research and practice. It is, however, by no means an organization exclusively for clinicians, since we also have a strong interest in the status of clinical psychology as a research area and as an important profession from a policy perspective. Thus, policy and research are regarded as more urgent areas for EACLIPT to focus on than the actual practice of clinical psychology. The latter has many national and international organizations and, when it comes to psychotherapy brands, also several psychotherapy organizations.

The EACLIPT is needed right now for several reasons. First, we believe that clinical psychology is more than psychotherapy. Second, the world, and indeed Europe, is shrinking as practitioners and patients move across borders. This requires European-wide standards both in research and in clinical practice, and also cross-border collaboration. The profession of clinical psychology is also expanding into medicine and healthcare in general. This necessitates research into disorders and health problems that have often been regarded as extraneous to psychology. Good practice in research and clinical tasks demand that we define quality criteria for training in and provision of clinical psycholog-ical healthcare, and that we improve comparability of training programs in European countries.

What have we done so far? Following our initial gathering in Amsterdam, the Netherlands, in 2017, we arranged a small closed inaugural conference in Linköping, Sweden, in 2018. In between those two meetings we formed a board which then convened in Amsterdam. We also had regular monthly board meetings by phone and developed a website www.eaclipt.org. And, as you can see, the journal was initiated and launched its first issue in 2019.

The board has also actively sought to recruit members, find national representatives and attend important meetings at EU-level (e.g., parliament). We have also had to deal with numerous practical matters that accompany an organization's launch. We have also initiated a newsletter. Although the exact number of our members is unknown at this editorial's publication, membership topped 400 at the time of writing. We have also began planning for our first conference. The first European congress of the EACLIPT will be held in Germany, Dresden, 31 Oct - 02 Nov 2019, under the topic: "No health without mental health: European clinical psychology takes responsibility".

Finally we should mention our expectations. We hope that the EACLIPT will help advancing the field of clinical psychology and all connected academic and clinical fields in Europe. We expect clinical psychology to be even more relevant in the future than it is today. Clinical psychology has already had a favourable impact on the treatment of mental health conditions and, increasingly, other health problems too. This has been driven



by progress in research. But it is not enough just to know what works when it comes to clinical problems (including both assessment and treatment procedures). We also need to make an effort to disseminate that knowledge, not least at policy level. Finally, we hope that the profession of both researchers and clinicians (sometimes the same person serving in both functions) will benefit from the EACLIPT and that we will manage to develop policy documents and research collaborations across Europe.

#### Gerhard Andersson, president EACLIPT

Further Board members: Claudi Bockting, Roman Cieślak, Céline Douillez, Thomas Ehring, Andreas Maercker, Winfried Rief







Scientific Update and Overview

#### Check for updates

# An Overview of the Evidence for Psychological Interventions for Psychosis: Results From Meta-Analyses

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# Abstract

**Background:** There are numerous psychological approaches to psychosis that differ in focus, specificity and formats. These include psychodynamic, humanistic, cognitive-behavioural and third-wave-approaches, psychoeducation, various types of training-based approaches and family interventions.

**Method:** We briefly describe the main aims and focus of each of these approaches, followed by a review of their evidence-base in regard to improvement in symptoms, relapse and functioning. We conducted a systematic search for meta-analyses dating to 2017 for each of the approaches reviewed. Where numerous meta-analyses for an approach were available, we selected the most recent, comprehensive and methodologically sound ones.

**Results:** We found convincing short- and long-term evidence for cognitive behavioural approaches if the main aim is to reduce symptom distress. Evidence is also strong for psychoeducative family interventions that include skills training if the main aim is to reduce relapse and rehospitalisation. Acceptance and commitment therapy, mindfulness-based approaches, meta-cognitive and social skills training, as well as systemic family interventions, were also found to be efficacious, depending on the outcome of interest, but meta-analyses for these approaches were based on a comparatively lower number of outcome studies and a narrower selection of outcome measures. We found no convincing evidence for psychodynamic approaches, humanistic approaches or patient-directed psychoeducation (without including the family).

**Conclusions:** An array of evidence-based psychological therapies is available for psychotic disorders from which clinicians and patients can choose, guided by the strength of the evidence and depending on the outcome area focused on. Increased effort is needed in terms of dissemination and implementation of these therapies into clinical practice.



## Keywords

psychosis, schizophrenia, psychological therapy, intervention, evidence

## Highlights

- Meta-analyses show convincing evidence for CBT if the main target is psychotic symptoms.
- Meta-analyses show convincing evidence for family interventions if the main target is relapse.
- Effects are promising for ACT, mindfulness-based and systemic approaches, but more research is needed.
- The array of effective approaches allows clinicians and patients to select the most appropriate one.

Patients with psychotic disorders often face a diverse and complex set of problems. One part of these problems are the symptoms as such. These include persecutory delusions, hearing voices and feeling driven, or negative symptoms, such as the loss of drive. Not only do these symptoms tend to cause severe distress (Lincoln, 2007; Woodward et al., 2014), they can also be accompanied by an array of interpersonal problems or social withdrawal (Depp et al., 2016; Mondrup & Rosenbaum, 2009). Accordingly, relatives and other people involved also often report difficulties in communication or feeling helpless (Treanor, Lobban, & Barrowclough, 2013). Moreover, an acute episode that might have involved voluntary or involuntary hospitalisation can be traumatizing (Paksarian et al., 2014) and many patients and relatives report continuous worry about possible relapse (Gumley et al., 2015; Lal et al., 2019). Unsurprisingly, therefore, many patients and their relatives seek professional help.

Since the discovery of antipsychotic drugs in the early 1950s, this help has been primarily pharmacological in nature. Although medication is valuable in the acute phase, the effect sizes in randomised trials for medication alone are only small to moderate (Leucht et al., 2012) and may come at the cost of disadvantageous long-term side effects (Murray et al., 2016). Also, medication is not well accepted by many patients (Wade, Tai, Awenat, & Haddock, 2017). Based on the requirement to inform evidence-based additions and alternatives to antipsychotic medication (Morrison, Hutton, Shiers, & Turkington, 2012), and an increasingly better understanding of the psychological mechanisms that cause and maintain psychotic symptoms (for a comprehensive and service-user oriented overview of this research see Cooke, 2014) different psychological approaches have been developed over the past decades. These differ in their focus and formats, but ultimately all aim to help patients to either overcome or to cope better with symptoms and to improve functioning and well-being.



## Methods of the Review

The scope of the present review covers the efficacy of different psychological approaches for psychosis offered in combination with pharmacotherapy as reflected in meta-analyses.

A systematic search for methodologically sound meta-analyses via Web of Science, PsycINFO, PSYNDEX, and Medline was conducted to establish a German guideline for the psychological treatment of schizophrenia and psychotic disorders (Lincoln, Pedersen, Hahlweg, Wiedl, & Frantz, 2019). This guideline was initiated by the German Society for Clinical Psychology and Psychotherapy as an adjunct to the S-3 German guideline, which has a broader focus. Considering recommendations by the Association of the Scientific Medical Societies in Germany (AWMF), evidence derived for the different psychological approaches is based on recent meta-analyses including well-conducted randomised controlled trials (RCTs). Starting out from the comprehensive meta-analysis on the treatment and management of psychosis and schizophrenia in adults (National Collaborating Centre for Mental Health [NCCMH], 2014 [Update]) conducted for the NICE-guidelines (National Institute for Health and Care Excellence) in 2009 we searched the literature from 2010 to 2017 for additional meta-analyses (Note. The guideline covered research until 2016. For the present overview we updated this search to cover meta-analyses published up to the end of 2017). When a psychological approach was not covered in the NICEguidelines (NCCMH, 2014), we additionally searched for meta-analyses published before 2010. The identified meta-analyses were critically appraised for methodological quality as well as overlap and we selected the most recent, comprehensive and methodologically sound analyses (e.g. conducted by the Cochrane Collaboration or other independent researchers). A complete list of the reviewed and selected meta-analyses is added in the Appendix. Meta-analyses were included if they focused on schizophrenia, delusional disorders, schizoaffective disorders and acute and transient psychotic disorders following DSM-III-R, DSM-IV or DSM-5 criteria.

The outcome measures covered include improvement in symptoms (overall symptoms, positive symptoms and negative symptoms), relapse rates and rehospitalisations as well as psychosocial functioning.

Psychological approaches reviewed covered individual and group interventions conducted within in- and out-patient settings. We report the effectiveness of each approach on the basis of randomised-controlled trials that compared the approach either to the usual treatment (TAU; e.g. pharmacotherapy and consultation) condition alone or to a TAU plus an active control condition (e.g. supportive therapy or psychoeducation) at post-treatment and/or at follow-up (ranging from weeks to years). In order to be able to compare the effectiveness of these approaches we focus on comparisons to "any control", because meta-analyses on approaches which have not been comprehensively investigated often do not differentiate between comparisons to TAU versus active controls. Only effect sizes based on at least two independent original studies were considered.



# Description of the Reviewed Approaches and Their Respective Evidence Basis

#### **Cognitive Behavioural Therapy for Psychosis**

#### Description

Cognitive behavioural interventions for psychosis (CBTp) build on the assumption that psychotic symptoms lie on a continuum with normal experiences. They are also informed by research suggesting that psychotic experiences result from normal, though exaggerated, mechanisms of perception and reasoning. This understanding has formed the basis for cognitive models of psychosis. As one of the most influential of these models, Garety, Kuipers, Fowler, Freeman, & Bebbington (2001) postulate that psychotic symptoms develop when stressors overload a person, causing them to have unusual experiences. According to this model, not the unusual experience itself is crucial but its appraisal. A variety of approaches within the CBTp-framework have been described (Fowler, Garety, & Kuipers, 1995; Morrison, Renton, Dunn, Williams, & Bentall, 2004). Most descriptions converge in stressing the importance of building a stable therapeutic relationship through the process of listening and validating, of taking a collaborative approach and of working with an individual case formulation. The use of cognitive and behavioural interventions for working with psychotic symptoms as well as for changing dysfunctional beliefs and interventions to prevent relapse are also essential elements.

#### **Evidence Base**

Beyond the NICE-Meta-Analysis conducted in 2009 our review is based on seven further meta-analyses (Burns, Erickson, & Brenner, 2014; Jauhar et al., 2014; Jones, Hacker, Cormac, Meaden, & Irving, 2012; Lutgens, Gariepy, & Malla, 2017; Turner, van der Gaag, Karyotaki, & Cuijpers, 2014; van der Gaag, Valmaggia, & Smit, 2014; Velthorst et al., 2015) selected from a larger pool of 13 meta-analyses.

As can be seen in Table 1, with the exception of the Cochrane-analysis by Jones et al., (2012), the meta-analyses consistently detected small effects on *overall symptoms* at post-treatment and at various follow-up periods favouring CBTp over TAU. The findings were less consistent, however, when CBTp was compared to active control. The picture is similar for *positive symptoms*, with Jones et al. (2012) reporting mixed findings, while the other meta-analyses consistently revealed effects in favour of CBTp compared to TAU, both at post-treatment and at follow-ups. Again, the comparisons to active control groups were less consistent. For *negative symptoms* there were small post-therapy effects (Jauhar et al., 2014; Lutgens et al., 2017) and small follow-up effects (NCCMH, 2014), overall, however, the non-significant findings outweighed the significant ones. *Relapse rates, rehospitalisations* and *functioning* were only investigated in two meta-analyses (Jones et al., 2012; NCCMH, 2014), and are based on a smaller number of studies. Neither meta-analy-



sis showed an effect on relapse and the effects for rehospitalisations and functioning were mixed.

#### **Third-Wave-Approaches to Psychosis**

#### Description

Third-wave-approaches are new developments in CBT which emphasise the relevance of acceptance, mindfulness and emotions, the relationship, values, goals, and meta-cognition (Hayes & Hofmann, 2017). In psychosis, adaptations of mindfulness-based therapy, acceptance and commitment therapy (ACT) and compassion focused therapy (CFT) have been studied most. In order to ease distress and achieve acceptance as well as to support the regaining of control, mindfulness-based interventions for psychosis guide patients to notice sensations and their own emotional and cognitive reactions to them with awareness (Chadwick, 2014). In meditation-based practices, patients learn to observe their thoughts, feelings and symptoms in an accepting and non-judgmental way. Mindfulness interventions for psychosis have been implemented as single treatments (e.g. Chadwick, 2014) or combined with CBT (e.g. Wright et al., 2014).

In ACT (Hayes, Strosahl, & Wilson, 1999) experiential avoidance and cognitive fusion are suggested to be the core processes of suffering. In order to increase psychological flexibility and reduce distress associated with psychotic symptoms, patients are guided to develop a balance between committed value-guided action when solving actual problems and acceptance when control of thoughts and feelings is limited (e.g. in the case of hallucinations). ACT has been adapted for the treatment of psychosis (O'Donoghue, Morris, Oliver, Johns, & Hayes, 2018; combined with CBT, Wright et al., 2014).

Compassion-focused therapy (CFT, Gilbert & Procter, 2006) encourages patients to be more compassionate towards themselves and others while reducing shame and self-criticism. Compassionate mind training includes appreciation and imagery exercises as well as aspects of mindfulness and aids the patient to experience different aspects of compassion in order to promote mental wellbeing. CFT has been adapted for the treatment of psychosis (Brähler, Harper, & Gilbert, 2013).

#### **Evidence Base**

We selected two (Cramer, Lauche, Haller, Langhorst, & Dobos, 2016; Louise, Fitzpatrick, Strauss, Rossell, & Thomas, 2018) from an identified pool of four meta-analyses. No metaanalysis reported effects-sizes for CFT based on more than one original study, hence, only mindfulness-based interventions and ACT are reviewed.

Both meta-analyses revealed no significant effect of ACT, but a significant small effect of mindfulness-based interventions on *overall symptoms* at post-treatment (Cramer et al., 2016; Louise et al., 2018). One meta-analysis analysed the effect at follow-up and reported an even increased effect (Cramer et al., 2016).



ACT showed a significant moderate effect on *positive symptoms*, but not on *negative symptoms* at post-treatment (Cramer et al., 2016).

The number of *rehospitalisations* was only investigated for ACT, revealing a significant small effect (based on two studies; Cramer et al., 2016). *Relapse* and *functioning* were not analysed.

#### **Psychodynamic Therapy for Psychosis**

#### Description

Early psychoanalytic conceptions of psychosis understand psychotic symptoms as a manifestation of the mind being invaded by the unconscious and by dreams (Federn, 1928/1952). More contemporary approaches underline the importance of early relationship patterns (e.g. Bion, 1962; Winnicott, 1991). Internal representations of experiences with significant others and current relationships are assumed to result in tension and psychotic symptoms are considered as a "constructive" way of dealing with this tension (von Haebler & Freyberger, 2013). Psychodynamic therapy focuses on these processes and helps the patient to gain self-awareness and understanding of the influence of the past on present behaviour and it fosters new positive relationship experiences. An empathic, respectful and supportive attitude allows re-enactment of internalised relational patterns in the therapist-patient interaction (Lempa, Montag, & von Haebler, 2013).

#### **Evidence Base**

We identified two meta-analyses. However, both the meta-analysis conducted for the NICE-guidelines (NCCMH, 2014) and the one of the Cochrane Collaboration (Malmberg, Fenton, & Rathbone, 2001) were based on four original studies only. The aggregated data of the two analyses did not indicate significant improvement in overall symptoms, functioning (NCCMH, 2014) or rehospitalisations (Malmberg et al., 2001) in patients treated with psychodynamic therapy compared to any control. The inclusion criteria for the present review were not fulfilled as none of the relevant outcome measures were covered by more than one original study; hence, psychodynamic therapies are not included in Table 1.

#### Humanistic or Client-Centred Approaches

#### Description

In client-centred or humanistic therapy, unconditional positive regard, accurate empathy and genuineness are assumed to help a patient to increase the congruence between the real self and the ideal self (Rogers, Gendlin, Kiesler, & Truax, 1967). Rogers and colleagues' concept of "actualizing tendency" points to an inherent tendency to achieve personal growth and reach one's full potential. In this framework psychotic symptoms are understood as a distortion of this actualising tendency. Client-centred therapy focuses on



personal experiences, whereas relieving specific symptoms is secondary. Thus, no specific therapeutic strategies have been established for psychosis. However, therapists are recommended to pay particular attention to understanding the client's perspective, ensuring that the patient is being heard and emphasising the personal relationship (Gendlin, 1962).

#### **Evidence Base**

Client-centred or humanistic therapy for psychosis has not been covered in a meta-analysis and the only known RCT dates back to 1967 (Rogers) and did not reveal convincing effects.

#### **Psychoeducation for Patients**

#### Description

To enhance knowledge and understanding of psychosis and to improve coping skills psycho-educational interventions are routinely offered in the treatment of psychosis. Mainly in group format, patients receive systematic and structured information on psychosis and its consequences, early warning signs, triggering and maintaining factors, relapse prevention, and modalities of treatment. Psychoeducation aims to help patients to increasingly take personal responsibility and improve coping skills.

#### **Evidence Base**

Two comprehensive meta–analyses (NCCMH, 2014; Turner et al., 2014) that provided sub-analyses on the effect of psychoeducation for patients without involving family members did not show any significant effect of psychoeducation on overall symptoms, positive or negative symptoms (Turner et al., 2014), relapse rates or rehospitalisations (NCCMH, 2014).

#### **Training-Based Approaches**

#### Description

From the range of different training-based approaches that cannot be fully covered within the scope of this review, we exemplarily focus on two widely used training-based interventions – one targeting positive symptoms (Metacognitive training) and one primarily addressing negative symptoms (Social skills training).

Metacognitive training (MCT; Moritz & Woodward, 2007) was designed to address positive symptoms in patients with schizophrenia. As cognitive biases have been related to positive symptoms (e.g. jumping to conclusions or externalizing attributional bias, see Garety & Freeman, 1999), MCT aims to extent patient's knowledge of cognitive biases and to provide corrective experiences. Implementing a wide range of examples and exercises, patients participating in a MCT group training are encouraged to identify and gain



insight into these cognitive biases and reduce conviction in delusional ideas. MCT is mainly administered in group format.

*Social skills trainings* (SST) build on the observation that patients with psychotic disorders tend to show impaired social skills. SST involve therapist modelling and instructing socially confident behaviour in specific situations combined with role-plays. Patients receive supportive feedback from the therapist and video feedback can also be used. During the end of the training that usually takes place in group-format patients are encouraged to practice the newly learnt skills in daily life. A frequently used treatment manual was published by Bellack, Mueser, Gingerich, and Agresta (2013).

#### **Evidence Base for MCT**

A significant small effect on *positive symptoms* was reported in two of three identified meta-analyses on the effect of MCT in psychosis (Eichner & Berna, 2016; Jiang, Zhang, Zhu, Li, & Li, 2015), whereas one did not reveal a significant effect at post-treatment (van Oosterhout et al., 2016). Regarding overall and negative symptoms, relapse / rehospitali-sations and functioning no aggregated effect sizes were reported.

#### **Evidence Base for Social Skill Trainings**

We identified and included three meta-analyses: the NICE meta-analysis (NCCMH, 2014), the Cochrane meta-analysis (Almerie et al., 2015) and the meta-analysis by Turner et al. (2014). There was no effect of SST on overall symptoms compared to control conditions at post-therapy in any of the meta-analyses, follow-up effects were not reported. There was also no effect in favour of SST for positive symptoms (Turner et al., 2014). For negative symptoms there were significant post-therapy effects (NCCMH, 2014; Turner et al., 2014). A significant follow-up effect for SST versus TAU was found in one meta-analysis (Almerie et al., 2015). For relapse and rehospitalisation, the findings were mixed. There was no significant effect for functioning, neither at post-assessment nor at follow-up.

#### **Family Interventions**

#### Description

Interventions that include the family are subsumed under the term "family intervention". The patient may be included in all, some, or – in some programmes – no sessions. Depending on the approach, a family intervention will involve 12 to 25 treatment sessions during the course of a year or longer and accompany the family through the remission phase. The diverse approaches can be broadly subdivided into psycho-educative family interventions, comprehensive interventions that combine information with problemsolving, social and communication skills, and systemic family interventions.

The *psychoeducational approach* builds on the observation that patients with psychosis often rely on relatives for support (Dixon, Adams, & Lucksted, 2000) and the assump-



tion that involved family members thus require information and assistance to cope with the challenges posed to the family system. It thus conveys basic knowledge about psychosis, building on the vulnerability-stress models. It sees psychosis as mental illness and enlists family members as therapeutic agents, taking care not to make the relatives feel blamed (Lucksted, McFarlane, Downing, & Dixon, 2012). It aims to convey the relevance of medical and psychosocial treatment, reduce misconceptions and provide a basis on which to promote the self-management skills, improve family coping and reduce relapse.

The *skill-training approach* builds on findings showing higher rates of relapse if a patient's family displays a communication style characterised by high levels of criticism, hostility, or emotional over-involvement ("high expressed emotion", Butzlaff & Hooley, 1998). It builds on the assumption that problems that arise from caring for a mentally ill family member can be solved if the family develops good problem solving strategies and a supportive way of communicating. The therapist models the verbal and non-verbal communication rules and assists the family to use the communication skills in a series of role-plays. The improved skills are then used to solve practical problems within the family context, using a problem solving approach. A well-established program of this type is described by Falloon, Boyd, and McGill, (1984).

*Systemic approaches* assume that relationships within the family (or other relevant social systems) influence the feelings, beliefs and behaviour of the "index patient" and vice versa and therefore, that psychotic symptoms may have arisen from specific interaction patterns within the family. The therapy aims to identify and change these patterns in order to reduce symptoms. If, for example, family members have stopped communicating about relevant issues with the patient, the therapist would attempt to re-include the patient in the communication processes. Changes in interactions are promoted by specific systemic questioning and reframing (e.g. Retzer, 2004).

#### **Evidence Base for Family Interventions in General**

We selected three meta-analyses (Claxton, Onwumere, & Fornells-Ambrojo, 2017; NCCMH, 2014; Pharoah, Mari, Rathbone, & Wong, 2010) from a pool of four available ones. These did not differentiate between different types of family interventions and thus report omnibus effects, with the bulk of the interventions covered in these analyses being psychoeducational in nature, with or without additional skill training.

As can be seen in Table 1, short-term benefits were mixed, but family interventions demonstrated significant long-term benefits over any control conditions on *overall symptoms in any of the three meta-analyses.* The effects on positive and negative symptoms were short-term in nature (NCCMH, 2014). For *relapse and rehospitalisation* the majority of the effects were significant and in the moderate to large range, both at post therapy and at follow-ups, although the long-term effects were non-consistent. Small to moderate effects were also found for short- (Claxton et al., 2017; NCCMH, 2014) and long-term *functioning* (NCCMH, 2014; Pharoah et al., 2010).



In order to provide a picture on differential effectiveness, we reviewed three additional meta-analyses each focusing on one of the three specific subtypes, psychoeducative family interventions (Lincoln, Wilhelm, & Nestoriuc, 2007), comprehensive programs including skilltraining (Pfammatter, Junghan, & Brenner, 2006) and systemic approaches (Pinquart, Oslejsek, & Teubert, 2016). Moreover, the NICE meta-analysis (NCCMH, 2014) provided a sub-analysis for psychoeducative interventions that included the family.

As can be seen in Table 1, psychoeducative family interventions demonstrated no significant effect on any of the symptom measures (Lincoln et al., 2007; NCCMH, 2014), but a significant small follow-up effect on relapse and rehospitalisation (combined) in one meta-analysis (ES = 0.48; Lincoln et al., 2007) but not in the other (NCCMH, 2014).

For comprehensive programmes including skill-trainings, one meta-analysis (Pfammatter et al., 2006) demonstrated a small follow-up effect on general psychopathology, relapse and rehospitalisation and a short-term benefit on functioning.

For systemic family approaches there was an overall significant effect on all outcome measures combined, without differentiating between the different outcomes (Pinquart et al., 2016).



	Gener	General psycho- pathology (ES)	Positive symptor	Positive symptoms (ES)	Negative symptom	Negative symptoms (ES)		Relapse (RR)	Rehospitali sation (RR)	Rehospitali- sation (RR)	Funct	Functioning (ES)
Meta-analysis	Post	Follow-ups Post	Post	Follow-ups Post	Post	Follow-ups	Post	Follow-ups	Post	Follow-ups	Post	Follow-ups
		Cog	nitive-ł	Cognitive-behavioural therapy (CBTp)	l thera	py (CBTp)						
NCCMH, 2014 (NICE, k = 19)	$0.27^{*}$	$0.23^{*}$	$0.17^{*}$	$0.15^{*}$	n.s.	$0.16^{*}$		n.s.	n.s.	$0.76^{*}$	n.s.	$0.20^{*}$
Comparison: TAU		$0.40^{*}$		$0.51^{*}$		$0.38^{*}$				*	n.s.	n.s.
		$0.19^{*}$								n.s.		
NCCMH, $2014$ (NICE, k = 14)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.		n.s.	$0.50^{*}$	n.s.
Comparison: active treatments		n.s.		n.s.		n.s.						
Jones et al., $2012$ (Cochrane, $k = 20$ )	n.s.	*	n.s.	n.s.	n.s.	n.s.		n.s.	n.s.	n.s.	* 9	n.s
Comparison: any control	n.s.	n.s.		*	n.s.	n.s.				n.s.		n.s.
	*					n.s.						
						n.s.						
Burns et al., $2014 (k = 12)$	$0.52^{*}$	$0.40^{*}$	$0.47^{*}$	$0.41^{*}$								
Comparison: any control												
Jauhar et al., $2014 (k = 50)$	$0.33^{*}$		$0.25^{*}$		$0.13^{*}$							
Comparison: any control												
van der Gaag et al., 2014 ( <b>k</b> = 18)			$0.44^{*}$									
Comparison: any control			$0.36^{*}$									
Velthorst et al., $2015 (k = 30)$					n.s.	n.s.						
Comparison: any control						n.s.						
Turner et al., 2014 ( <b>k</b> = 22)	$0.16^{*}$		$0.16^{*}$		n.s.							
Comparison: active treatments												
Lutgens et al. (2017)					$0.34^{*}$							
Comparison: TAU												

Results From Meta-Analyses on the Efficacy of Psychological Approaches to Psychosis

Table 1

	Gener	General psycho- Positive	Positive		Negative	ve			Rehospitali-	pitali-		
	patho	nology (ES)	symptoms (ES)	ms (ES)	sympte	symptoms (ES)	Relapse (RR)	e (RR)	sation (RR)	(RR)	Funct	Functioning (ES)
Meta-analysis	Post	Follow-ups Post		Follow-ups	Post	Follow-ups	Post	Follow-ups	Post	Follow-ups	Post	Follow-ups
		N	lindfuln	Mindfulness-based interventions	interve	ntions						
Cramer et al., $2016 (k = 4)$	$0.62^{*}$	$1.27^{*}$								$1.40^{*}$		
Comparison: TAU												
Louise et al., $2017 (k = 4)$	$0.46^{*}$											
Comparison: any control												
		Accept	ance and	l commitr	nent th	Acceptance and commitment therapy (ACT)						
Cramer et al., $2016 (k = 4)$	n.s.		$0.63^{*}$		n.s.				$0.41^{*}$			
Comparison: TAU												
Louise et al., $2017 (\mathbf{k} = 4)$	n.s.											
Comparison: any control												
			Psycł	<b>Psychodynamic therapy</b>	c theral	y						
				I								
			Hum	Humanistic approaches	proach	SS						
				I								
		Psychoed	lucation	not invol	ving faı	Psychoeducation not involving family members	ers					
NCCMH, 2014 (NICE, sub-analyses, $k = 12$ )	n.s							n.s.		n.s.		
Comparison: any control												
Turner et al., $2014 (k = 8)$	n.s.		n.s.		n.s.							
Comparison: active treatments												



	Gene	General psycho-	Positive	je j	Negative	ive			Rehos	Rehospitali-		
	patho	pathology (ES)		symptoms (ES)	sympt	symptoms (ES)	Relapse (RR)	e (RR)	sation (RR)	(RR)	Functi	Functioning (ES)
Meta-analysis	Post	Follow-ups	Post	Follow-ups	Post	Follow-ups	Post	Follow-ups	Post	Follow-ups	Post	Follow-ups
			Met	Metacognitive training	trainiı	ß						
Jiang et al., $2015 (k = 4)$			*									
Comparison: any control												
Eichner & Berna, 2016 ( $k = 15$ )			$0.34^{*}$									
Comparison: any control												
van Oosterhout et al., 2016 ( $k = 11$ )			n.s.									
Comparison: any control												
			So	Social skills training	training	50						
NCCMH, 2014 (NICE, $k = 20$ )	n.s.				0.37		n.s	n.s.		n.s.	n.s.	
Comparison: any control							post n.s	post n.s.; follow-up n.s. <sup>b</sup>	n.s. <sup>b</sup>			
Almerie et al., 2015 (Cochrane, $k = 10$ )						*		$0.52^{*}$				
Comparison: TAU												
Almerie et al., $2015$ (Cochrane, $k = 3$ )	n.s.				n.s.							
Comparison: active treatments												
Turner et al., 2014 (k = 16)	n.s.		n.s.		$0.27^{*}$							
Comparison: active treatments												
		Ι	amily i	Family interventions OVERALL	ns OVI	ERALL						
NCCMH, $2014$ (NICE, $k = 32$ )	$0.36^{*}$	$0.30^{*}$	$0.46^{*}$	n.s.	$0.26^{*}$	n.s.	$0.55^{*}$	$0.62^{*}$	$0.53^{*}$	*	n.s.	$0.38^{*}$
Comparison: any controls							$0.66^{*}$	$0.80^{*}$	$0.57^{*}$	n.s.	$0.22^{*}$	$0.58^{*}$
									*	n.s.		n.s.
									n.s.			
Pharoah et al., $2010$ (Cochrane, k = 53)		*						n.s.	n.s.	$0.78^{*}$		*
Comparison: any controls								0.55*		$0.46^{*}$		*
								$0.64^{*}$		n.s.		*
								$0.64^{*}$				



		.							,			
	Gener	General psycho- pathology (ES)		Positive symptoms (ES)	Negative sympton	Negative symptoms (ES)	Relaps	Relapse (RR)	Rehospitali- sation (RR)	pitali- (RR)	Functi	Functioning (ES)
Meta-analysis	Post	Follow-ups	Post	Follow-ups	Post	Follow-ups	Post	Follow-ups	Post	Follow-ups	Post	Follow-ups
Claxton et al., 2017 (k = 14) Comparison: any controls	n.s.	0.85					Combii rehospi n.s.	Combined analysis of relapse and rehospitalisation: post: *; follow-up: n.s.	of relap: ost: *; fo	se and llow-up:	0.74	
			Fan	Family psychoeducation	seducati	ion						
Lincoln et al., 2007 (k = 6) Comparison: any controls	n.s.						Combi rehosp	Combined analysis of relapse and rehospitalisation at follow-up: 0.48*	of relap: follow-1	se and up: 0.48*		
NCCMH, $2014$ (NICE, k = 2)										n.s.		
Comparison: any controls												
		F	amily (	Family comprehensive programs	ısive pro	ograms						
Pfammatter et al., 2006 ( $k = 31$ )		$0.40^{*}$						$0.42^{*}$		$0.22^{*}$	$0.38^{*}$	
Comparison: any controls										$0.51^{*}$		
			System	Systemic family interventions	interver	ıtions						
Pinquart et al., 2016 (k = 7) Comparison: TAU	Analys	sis of differe	nt outco	ome measur	es combi	ined at post:	0.69* an	Analysis of different outcome measures combined at post: 0.69 $^{*}$ and follow-up: 0.69 $^{*}$	0.69*			
Note. Effect sizes based on at least two independent original studies are reported. Comparable effect sizes (Cohen's d, Hedge's g, and standardised mean differences) are denoted as ES (effect size) without reporting confidence intervals. If only odds ratio, risk ratios, partial et a squared and not-standardised mean differences were	endent o ing confi	riginal studi idence inter	es are rí vals. If o	eported. Co	mparable tio, risk	e effect sizes ratios, partie	(Cohen ıl eta sqı	's d, Hedge's 1ared and no	g, and s t-standa	standardised rdised mear	l mean c n differe	ifferences) nces were
reported in a meta-analysis we only indicated if the effect was statistically significant at $p < 0.05$ (*) vs non-significant (n.s.). If available, effects compared to "any controls" are reported, if these data were not available effects compared to treatment as usual ("TAU") or "active treatments" (for instance other psychological approaches for psychosis or unspecified treatments) are reported, post = post-treatment; follow-up = all follow-up time-points combined; k = number of studies re-	l if the e available ents) are	ffect was stê e effects con reported. p	ttisticall apared t ost = po	ly significan to treatment st-treatmen	tt at $p < 0$ as usua t; follow	0.05 (*) vs no 1 ("TAU") or -up = all foll	n-signif "active 1 ow-up t	icant (n.s.). Il treatments" ( ime-points c	availab (for insta ombined	le, effects co ance other p 1; k = numb	ompared sycholo er of stu	to "any gical ap- dies re-
viewed in the meta-analysis of sub-analysis, <sup>a</sup> any control" was superior to the treatment. <sup>b</sup> effect sizes based on studies reporting combined analysis of relapse and rehospitalisation only.	<sup>b</sup> effect s	izes based o	n studie	s reporting	combine	ed analysis o	f relapse	and rehospi	italisatio	n only.		



## Discussion

As has become apparent from this review, there are now a variety of different psychological interventions available, of which the majority have a good evidence base for the outcomes that they focus on primarily. If the aim is to reduce general psychopathology or positive symptoms, CBT has the strongest evidence-base both in terms of the number of studies conducted and in regard to the robustness of effects over follow-up periods. Other approaches, such as acceptance and commitment therapy, mindfulness-based approaches, and meta-cognitive training are also promising for these outcomes. Negative symptoms, however, appear to respond better to social skills trainings.

Family interventions are also well-researched and appear to be effective for a broader array of outcomes, including relapse and rehospitalisation as well as functioning. Within family interventions, the strongest effects are found for a combination of psychoeducative and skill-training with families, although it needs noting that this specific combination was only the focus in one meta-analysis. Systemic approaches are also promising, but more high-quality randomised controlled trials are necessary to ascertain their effectiveness for different types of outcomes. There was no convincing evidence for patientdirected psychoeducation (without family involvement) despite the fact that this approach is widespread. However, it may be more difficult to construct a fair evaluation of this approach in RCTs because any control condition is likely to involve psychoeducation to a certain extent. Psychodynamic therapies and humanistic approaches were also not found to be effective, but more RCTs are required in order to draw definite conclusions in this regard.

No approach has a consistently good evidence-base for the entire range of outcomes investigated. This may be partly due to the fact that different types of interventions have focused on different types of outcomes. For example, family interventions have a traditional focus on relapse, whereas CBT focusses on the positive symptoms. Thus, studies investigating these approaches did not consistently include a wider spectrum of outcome measures. More RCTs focusing on the full spectrum of outcome areas are required in order to understand whether different approaches are truly differentially effective. Also, with the exception of a few large effect sizes for family interventions, the effect sizes were largely in the small to marginally moderate range - and thus no higher than those found for pharmacotherapy. However, all original studies in the meta-analyses included here are based on designs that compare psychological interventions combined with medication to medication alone or to medication combined with an additional control condition. Thus, the effects need to be interpreted as "add-on" effects to medication and cannot be directly compared with the effect sizes for medication. So far, it is unclear whether psychological therapy would fare better or worse without the combination with medication as this question has not been investigated.



#### **Limitations of This Analysis**

The wide scope of interventions reviewed comes at the price of detail. For reasons of space, we did not include the specific search-terms or provide a full account of each of the meta-analyses excluded along with the reasons for in- or exclusion. Also, we did not report the evidence available for questions regarding specific subgroups, formats (e.g. group versus individual, short versus long) or settings (e.g. is family intervention more effective when delivered to individual families versus in groups of families). In Table 1, we focused on the comparison to all control conditions for reasons of brevity and in order to be able to compare different approaches for which such distinctions were not always available. Naturally, differentiating between comparisons to TAU versus active controls is more conclusive and therefore these distinctions were made in the section on CBT for which they are consistently available. Moreover, we abstained from detail in the reporting of effect-sizes (e.g., we did not report standard-deviations, the type of effects, or the number of studies for each comparison). Finally, we disregarded any reported effect-size based on one original study only. Readers seeking more detailed evidence reports are referred to the British or German guidelines (Lincoln et al., 2019; NCCMH, 2014), and to the original meta-analyses cited.

The method as such, a summary of meta-analyses, also has its limitations due to the overlap between meta-analyses. Moreover, the differences in methodological rigour, the inclusion criteria, and the classification of therapy approaches (e.g. inconsistency in what is counted as CBT) result in high levels of heterogeneity in the findings and make it difficult to directly compare different meta-analyses. We attempted to control this bias to a certain extent by disregarding meta-analyses with strong overlap or questionable quality. Another limitation is that the focus on meta-analyses does not provide information on psychological approaches, that are not represented well in the meta-analyses and reviews outdated at an increasing speed and several new ones have been published since finalizing the selection for this overview.

In this context, it is also worth mentioning a recent meta-analysis that also approached the question of the effectiveness of different psychological approaches to psychosis (Bighelli et al., 2018). This network meta-analysis aggregated data on the level of individual trials on CBT, metacognitive training, mindfulness and acceptance and commitment therapy among other approaches. Similar to our findings, CBT was the most represented among the included treatments and was found to have significant efficacy in comparison with treatment as usual for positive, overall and negative symptoms and functioning. It also showed higher efficacy in comparison with inactive control conditions for positive symptoms whereas there was no convincing proof of efficacy of other treatments. Thus, CBT fared slightly better, even, than in our approach, while third-wave approaches and meta-cognitive therapy were less well supported. Family interventions were not included.



## **Final Conclusions**

The variety of efficacious interventions available for psychotic disorders is reassuring. Unfortunately, however, efficacy studies and clinical guidelines alone do not guarantee the implementation of evidence-based interventions, in routine clinical practice (Pilling & Price, 2006). For example, despite the NICE guideline recommendation to offer CBT to all patients with psychosis, only a minority of eligible patients with psychosis are being offered CBT in the UK (Prytys, Garety, Jolley, Onwumere, & Craig, 2011). In Germany, studies indicate that only a minority of psychosis patients have access to evidence-based psychotherapy (Schlier & Lincoln, 2016). To our knowledge, this serious implementation problem of evidence-based interventions is not restricted to Germany and the UK. Thus, although further high quality RCTs focusing on the full spectrum of outcomes are needed, the most relevant challenge to date is that of implementation.

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Scientific Update and Overview

#### Check for updates

# Third Wave Treatments for Functional Somatic Syndromes and Health Anxiety Across the Age Span: A Narrative Review

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# Abstract

**Background:** Functional disorders (FD) are present across the age span and are commonly encountered in somatic health care. Psychological therapies have proven effective, but mostly the effects are slight to moderate. The advent of third wave cognitive behavioural therapies launched an opportunity to potentially improve treatments for FD.

**Method:** A narrative review of the literature on the application of mindfulness-based therapies (MBT) and Acceptance & Commitment Therapy (ACT) in children and adult populations with FD.

**Results:** There were very few and mainly preliminary feasibility studies in children and adolescents. For adults there were relatively few trials of moderate to high methodological quality. Ten MBT randomised trials and 15 ACT randomised trials of which 8 were internet-delivered were identified for more detailed descriptive analysis. There was no evidence to suggest higher effects of third wave treatments as compared to CBT. For MBT, there seemed to be minor effects comparable to active control conditions. A few interventions combining second and third wave techniques found larger effects, but differences in outcomes, formats and dosage hamper comparability.

**Conclusions:** Third wave treatments are getting established in treatment delivery and may contribute to existing treatments for FD. Future developments could further integrate second and third wave treatments across the age span. Elements unambiguously targeting specific illness beliefs and exposure should be included. The benefit of actively engaging close relatives in the treatment not only among younger age groups but also in adults, as well as the effect of more multimodal treatment programmes including active rehabilitation, needs to be further explored.



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## Keywords

functional disorders, functional somatic syndromes, health anxiety, somatic symptom disorder, third wave treatments, mindfulness, acceptance and commitment therapy, narrative review

# Highlights

- The methodological quality of third wave interventions for FD should be improved, especially in younger age groups.
- The effect of ACT interventions may be comparable to CBT in adults with FD.
- The evidence for third wave interventions in young people with FD is still very limited.
- Newer studies combining second and third wave treatments show some promise.
- Agreement on, and for child populations further development of, core outcomes, could help determine effect across studies.

Functional disorders (FD) can be defined as conditions where the individual's experiences of physical symptoms cause excessive discomfort and/or worry and where no adequate organ pathology in terms of conventional medical disease can be determined to explain the symptoms (Fink & Rosendal, 2015). FD are a burden for sufferers and their families, they are difficult to treat and costly as they incur a high health expenditure and derived societal costs (Henningsen, Zipfel, Sattel, & Creed, 2018).

#### **Diagnostic Classification**

Functional disorders can clinically be split into two overall categories (see Table 1).

The first category refers to conditions characterised by bodily distress, a now wellaccepted term to describe the phenomenon of clusters of disabling unspecific bodily symptoms often designated as functional somatic syndromes (FSS); the best known being chronic fatigue syndrome (CFS), fibromyalgia/chronic pain (FM/CP) and irritable bowel syndrome (IBS) (Fink & Schröder, 2010). The second category refers to conditions dominated by health anxiety (HA), i.e. impairing illness worry and persisting ruminations about harbouring or getting serious illness (Fink et al., 2004). Although the two categories overlap in their clinical presentations and can be comorbid, the primary problem differs which has implications for the treatment focus.

In the psychiatric classifications ICD-10 (WHO, 1992) and DSM-IV (American Psychiatric Association, 1994), FD are mainly categorised under somatoform and related disorders. However, the terminology of these diagnoses has been criticised for being too exclusive in their diagnostic criteria as well as over-emphasising a mind-body dualism in contrast to the prevailing understanding of these disorders within an integrated biopsy-



#### Table 1

#### Two Main Categories of Functional Disorders

	Disorders	dominated by
Characteristics	Bodily distress (FSS)	Health anxiety (HA)
Primary problem	Experience of disabling physical symptoms	Experience of worries and anxiety related to physical sensations
Functional impairment	Severe physical disability (e.g. sick leave, bedridden. In children and adolescents often long-term school absence)	Less severe physical disability (e.g. going to work serves as a distraction from distressing thoughts. In children and adolescents it will often be going to school or playing computer games)
Typical initial treatment	Body can be fixed and the symptoms	Wish for 100% reassurance that they do
expectations	disappear	not harbour a severe or deadly illness.

*Note.* FSS = Functional Somatic Syndromes; HA = Health Anxiety.

chosocial framework (Dimsdale, Sharma, & Sharpe, 2011; Henningsen, Zipfel, & Herzog, 2007). In the more recent DSM-5 (American Psychiatric Association, 2013), FD are classified primarily as somatic symptom disorders (SSD) with an added category of illness anxiety disorder designated to conditions with HA but without concurrent distressing bodily symptoms (in which case SSD is used). In contrast to ICD-10, developmental aspects are to some degree incorporated in DSM-5 as it specifies that in children, a single prominent symptom such as recurrent abdominal pain, headache, fatigue or nausea is more common than in adults. It also emphasises that parents' response to the symptoms is crucial as this may determine levels of associated distress and the extent to which medical help is sought.

In daily clinical practice, the psychiatric classifications are rarely used, as FD are primarily diagnosed in primary and specialised somatic health care. Thus, each medical specialty has developed its own classification leading to the use of a vast number of both unspecific symptom diagnoses as well as the previously mentioned FSS diagnoses. As a consequence, management in both the paediatric and adult health care settings is very heterogeneous, often formed by biomedical practices in each medical specialty and often not evidence-based. In addition, it is well-established that excessive biomedical treatment efforts cause iatrogenic harm in these conditions (Henningsen et al., 2007; Lindley, Glaser, & Milla, 2005).

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#### **Developmental Aspects of FD**

Young children usually present a single prominent symptom (Domènech-Llaberia et al., 2004; Rask et al., 2009) such as abdominal pain, headaches, fatigue or muscle pains rather than the varied symptom presentation often seen in adults. The long-term prognosis varies from complete recovery to persistent symptoms into adulthood. With increasing age, full recovery seems to become more and more unlikely (Joyce, Hotopf, & Wessely, 1997; Norris et al., 2017).

With respect to HA, key features such as symptom preoccupation and medical help seeking predominate mostly with the parents, although HA-like symptoms may present already in preschool children (Rask, Elberling, Skovgaard, Thomsen, & Fink, 2012; Schulte & Petermann, 2011). Also, preadolescents can report excessive illness worries with fears, beliefs and attitudes very similar to the cognitive and behavioural features of HA in adults (Eminson, Benjamin, Shortall, Woods, & Faragher, 1996; Rask et al., 2016; van Geelen, Rydelius, & Hagquist, 2015; Wright & Asmundson, 2003). However, HA is still sparsely examined as a distinct concept in youth.

#### Epidemiology

Across the age span, the severity of both FSS and HA varies on a spectrum from mild and moderate to severely disabling conditions. New studies suggest that FSS affect 15% of the adult population, whereas approximately 2% of the population has very disabling conditions (Eliasen et al., 2018). In comparison, 4-10% of the general child and adolescent population experiences daily or high levels of impairing functional symptoms persisting for months or years (Hoftun, Romundstad, Zwart, & Rygg, 2011; Janssens, Klis, Kingma, Oldehinkel, & Rosmalen, 2014; Rask et al., 2009). The prevalence estimates for HA vary considerably across studies, but a recent study reported a prevalence of 3.4% (Sunderland, Newby, & Andrews, 2013) in the general population. Around 8-9% of the prevalence estimates for HA as a disorder are not available in young age groups.

#### **Cognitive Behavioural Therapies for FD**

Chronicity, severity and multiplicity of symptoms are all predictors of poor prognosis (Rosendal et al., 2017). Therefore, timely and evidence-based treatment is essential for improving the long-term physical, psychosocial and financial consequences. Across age groups, patient-activating therapies are the most promising treatments, and cognitive behavioural therapy (CBT) has so far been the most prevailing in intervention studies (Abbott et al., 2018; Bonvanie et al., 2017; Henningsen et al., 2018). While moderate to large effect sizes (ES) have been reported for CBT-based treatment for HA (Hedman et al., 2011; Newby et al., 2018; Thomson & Page, 2007; Weck, Neng, Schwind, & Hofling,



2015), improvements are only small to moderate for FSS in adults (Henningsen et al., 2018; van Dessel et al., 2014).

In children and adolescents, the use of CBT for HA has only been reported in a single case study (Roberts-Collins, 2016). With regard to FSS, existing studies have almost exclusively focused on CBT-based treatments for single symptoms or syndromes; primarily functional abdominal symptoms, chronic fatigue, tension-type headache, fibromyalgia or mixed pain complaints in children as young as 6 years of age (Abbott et al., 2018; Bonvanie et al., 2017). Overall, the ES are found to be somewhat larger than the corresponding estimates in adult studies (Bonvanie et al., 2017). This may indicate that children and adolescents are more susceptible to psychological treatments than adults or that young people present less chronic and/or severe FSS. However, the results should be interpreted with caution as the majority of these studies are quite small and heterogeneous with regard to e.g. inclusion criteria, setting, dose and type of delivered treatment and therapist experience (Abbott et al., 2018; Bonvanie et al., 2017).

Overall, these results, especially as to FSS, suggest that the efficacy of existing psychological treatments for FD could be improved. This has spurred interest in studies exploring the potential of the newer third wave behavioural therapies for these disorders.

#### Treatment With Third Wave Psychological Therapies for FD

#### Mindfulness-Based Therapies (MBT)

MBT translate meditation from Buddhism and other spiritual practices into clinical interventions. While classical CBT approaches tend to prioritise changing the content of private experiences like thoughts, MBT emphasise the awareness of thoughts, feelings and sensations as transient events that can potentially be problematic but do not have to be. Thus, compared to CBT, there is no explicit focus on behavioural activation or modification. In most interventions, mindfulness is taught in groups emphasising an experiential format with sharing of experiences in the enquiry phase after formal meditations. The most well-known MBT programmes are Mindfulness Based Stress Reduction (MBSR) and Mindfulness Based Cognitive Therapy (MBCT). The primary homework in most MBT is daily mindfulness practice.

MBT are proposed to work through at least four processes: 1) attention regulation, 2) body awareness, 3) emotion regulation and 4) change in self-perspective (Hölzel et al., 2011) (see Figure 1).



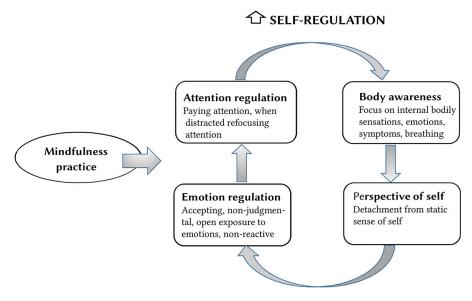


Figure 1. A model of proposed processes in mindfulness-based therapies.

Note. Adapted from Hölzel et al., 2011.

MBT could potentially change the perception of bodily symptoms through changes in interoception at a subconscious level and carry reductions in negative appraisal of symptoms. Furthermore, MBT might improve emotion regulation, which is proposed to play a prominent role in FSS (Dahlke, Sable, & Andrasik, 2017) and as a by-product reduce comorbid anxiety and depression. In HA especially, one may hypothesise that mindfulness exercises can function as a direct exposure to anxiety-provoking bodily sensations and that the development of a more non-judgmental and accepting stance towards these bodily sensations may alleviate the symptom experience.

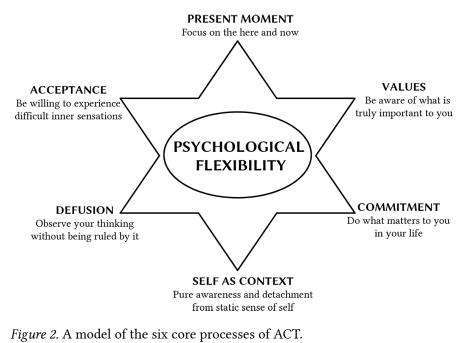
#### Acceptance and Commitment Therapy

The overarching goal of ACT is to increase psychological flexibility, defined as the ability to stay in contact with the present moment regardless of unpleasant thoughts, feelings and bodily sensations, while choosing one's behaviours based on the situation and personal values. In ACT, there are specific assumptions regarding the role of language for how human beings tend to handle 'the universal experience of pain' (loss, illness, conflict, and trauma) with avoidance of inner experience (Hayes, Luoma, Bond, Masuda, & Lillis, 2006).

ACT proposes six core therapeutic processes which interact to promote psychological flexibility (see Figure 2). Experiential techniques such as mindfulness, defusion, meta-phors and self-as-context exercises are used to illustrate and teach these processes. Compared to MBT, the kinship with second wave cognitive behavioural therapies is more obvious both in terms of format and content, e.g. the use of functional analyses, in which



behaviours are analysed in terms of short- and long-term consequences (Hayes, 2016) and the focus on commitment to behaviour change.



Note. Adapted from Hayes et al., 2006.

Specifically for FSS, a main treatment focus in ACT is on a behavioural shift from control and avoidance behaviours to choosing values-based actions even when aversive symptoms are present. Acceptance of bodily symptoms might both increase the engagement in behaviour change and lead to a reduction in symptom experience. In HA, where ruminations about bodily sensations are prominent (see Table 1), the focus on defusion from distressing illness-related thoughts could be helpful in alleviating the anxiety attached to illness labels such as cancer or sclerosis. Functional analysis may help foster a clearer understanding of the negative long-term effects of control and avoidance behaviours typical for HA (e.g. bodily checking and seeking information on symptoms on the internet).

## The Evidence-Base for MBT and ACT for HA and FSS

An overview of the search methods and criteria for selection of studies for the current paper is provided in Table 2.



Table 2

Search Methods and Criteria for Selection of Studies

- Publications on treatment outcome using Acceptance & Commitment Therapy or mindfulness-based therapies for health anxiety and various functional somatic syndromes were identified in searches performed in September 2018 on PubMed by the help of a research librarian.
- The database was searched for English language studies using the terms 'Third wave' or 'Mindfulness-based stress reduction' or 'Mindfulness-based cognitive therapy' or 'MBCT' or 'MBSR' or 'Acceptance and Commitment Therapy' or 'Mindfulness' combined with 'Chronic Pain' or 'Fibromyalgia' or 'Fatigue Syndrome' or 'Irritable Bowel Syndrome' or 'Abdominal Pain' or 'Functional Gastrointestinal Disorders' or 'Somatoform Disorders' or 'Health anxiety' or 'Hypochondriasis' or 'Illness anxiety disorder' or 'Somatic symptom disorder'.
- For studies on adult populations, the search was restricted to systematic reviews and the reference lists of
  included studies were examined for additional eligible studies. The Web of Science was used for forward
  citation to identify additional papers. Only studies which randomised ≥50 patients were included<sup>a</sup>. With
  regard to chronic pain populations, studies were excluded if a substantial part of the population did not have
  an idiopathic or functional pain condition. Pure online self-help programmes with no therapist contact were
  not included.
- For child and adolescent papers the search terms were further combined with the terms 'child' or 'adolescent' or 'youth or 'paediatrics' or 'minor' or 'juvenile' or 'teen'. Based on the overall small number of studies no restriction was here applied with regard to study type.
- The methodological quality of the studies, including randomised controlled trials were rated using the psychotherapy outcome study rating scale (Öst, 2008).

<sup>a</sup>This cut-off was set in order to exclude studies which would better be classified as pilot trials (Bell, Whitehead, & Julious, 2018).

#### **Evidence for HA in Adults and Children**

#### **MBT** for HA

The first preliminary results on the use of MBT in adults with HA were encouraging as a pilot study found significant improvements of MBCT on disease-related thoughts and somatic symptoms at 3-month follow-up (Lovas & Barsky, 2010), and a qualitative study reported MBCT adapted to HA to be acceptable for the patients (McManus, Surawy, Muse, Vazquez-Montes, & Williams, 2012; Williams, McManus, Muse, & Williams, 2011). In the following RCT (McManus et al., 2012), 74 patients were randomised to either MBCT in addition to usual unrestricted service or usual unrestricted services alone (Table 3).

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	Quality score (0-42)		30		24			20		16		25		19
	1 Main outcomes <sup>b</sup>		FU (12 mo): HA composite (combination of self- report and clinician rated): + (ES: 0.48)		FU (10 mo): Illness worry: + (ES: 0.89)			FU (2 mo): Tender point count (myalgic score): = Pain and functioning: = Depression: = Medical care: =		FU (3 mo): IBS severity: +(ES: nr) HR-QOL: + (ES: nr)		FU (2 mo): FM impact: = HR-QOL: =		FU (9 mo): General health status (VAS): = SF36 PCS: = SF36 MCS: =
	No of subjects randomised (dropout at latest FU) IG CG		3 36 38 (4) (2)		(11)(8)			99 64 64 (total: 63)		100 36 39 (2) $ (7)$		100 59 59 59 (12) (10) (3)		74 64 61 (15) (12)
	8 Diagnosed 전ge, y (SD) <sup>a</sup> 년 comorbidity <sup>a</sup> Age, y (SD) <sup>a</sup> 년		41.3 (12.0) 78 43.9 (11.0)		37.0 (9.9)  71 35.5 (7.6)			47.7 (10.6) 99		$\frac{44.7}{41.0} (12.5)   10$		52.5 (9.6) 10		47.6 (11)  74 46.5 (12)
			50% 47%		60% 52%			No of other diagnoses: 2.2 (1.6)  2.0 (2.0)		nr		nr		81% ≥ one physical disease 35% anxiety and/or depression
	Duration of symptoms/ disorder (SD) <sup>a</sup>	tudies	8.8 y (10.2)		10.0 y (10.3) 11.0 y (10.5)	lt studies		4.9 y (4.2) 5.2 y (7.3)		л		14.3 y (10.2) 5		H H
	Exclusion criteria	HA adult studies	Substance abuse • Severe psychiatric comorbidity • Unstable psychotropic medication		Severe HA according Severe psychiatric comorbidity to criteria by Fink et • Other somatic/psychiatric al. (2004)) condition primary • Pregnancy	MBT: FSS adult studies		Substance abuse • Severe psychiatric comorbidity • Impending litigation/judgment for disability compensation • Severe chronic medical condition • Pregnancy		Major psychiatric disorder • Severe gastrointestinal well- defined illness • Pregnancy		Participation in other clinical trial • Life-threatening disease • Supressed immune functioning		Symptoms fully explained by medical condition • Substance abuse • Major psychiatric disorder • Cognitive impairment • Prior MBCT treatment
	Main inclusion criteria		Diagnosis of hypochondriasis according to DSM- IV-TR		Severe HA according to criteria by Fink et al. (2004))			Clinical diagnosis of FM		Physician diagnosis according to ROME- II criteria		Diagnosis according to ACR criteria		mptom
	Condition		НА		НА			FM		IBS		y FM		Frequent >6 mo sy attendance duration in GP for persistent MUS
T Studies	Setting		University setting	urk	Specialised clinic for functional disorders, university hospital			University setting		л	ų	Interdisciplinary FM pain unit, university medical center	<b>Jetherlands</b>	University setting
Overview of Included RCT Studies	Comparison	l. (2012); UK	TAU	Eilenberg et al. (2016); Denmark	TM		03); USA	Education support group	(2011); USA	Social support group	Schmidt et al. (2011); Germany	MBSR Active control Interdiscip 8 group to control pain unit, sessions plus 7 for non-specific university In workshop factors, or WL medical ce	Van Ravesteijn et al. (2012); Netherlands	Combined EUC University and WL setting
Overview of	Treatment format & dose	McManus et al. (2012); UK	MBCT 1 individual session plus 8 group sessions	Eilenberg et al	ACT 10 group sessions		Astin et al. (2003); USA	MBSR/Qigong Education 8 group support gr sessions	Gaylord et al. (2011); USA	MBSR 8 group sessions plus one half-day retreat	Schmidt et al.	MBSR 8 group sessions plus 7 f hr workshop	Van Ravesteijı	MBSR 8 group sessions plus 6 hr silent day

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Table 3



9

Third Wave Treatments for Fu	inctional Disorders
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Quality score (0-42)	16	28	13	14	58	19	18
d t Main outcomes <sup>b</sup>	FU (6 mo): BS-severity: = BS-QOL: =	FU (12 mo): SF36 PCS: = HR-QOL: =	FU (2 mo): FM Impact Questionnaire, Physical fmtioning (PP): = FM Impact Questionnaire, Pain severity (PS): + (ES: 0.62)	PT (no FU for comparison): SF36 vitality score: + (ES: 0.39) Pain severity (PS): =	FU (6 mo): Brief Pain Inventory Short Form (BPI), interference scale: = SF12: =	FU (3 mo): Disability: + (ES: 0.37) SF36 physical functioning: = Depression: = Pain intensity: =	PT (no FU for comparison): Chronic Pain Acceptance Questionnaire (CPAQ): + (ES: 0.41) Pain interference: + (ES: 0.56)
No of subjects subjects randomised d (dropout at latest FU) Le IG CG	90 43 47 (23) (13)	80 59/60 (13) (16)	$\frac{10051 40}{(10) (13)}$	72 54 55 (14) (22)	51 57 57 (6)(8)	69 37 36 (9)(8)	59 38 38 (6) (6)
Diagnosed comorbidity <sup>a</sup> Age, y ( <i>SD</i> ) <sup>a</sup>	45.0 y (12.4) 44.0 y (12.6)	38.0 (9.0)  40.0 (8)	Peri- menopausal (age mr)	46.5 (12.4)  48.8 (12.2)	55.0 (12.5)	58.0 (12.8)	49.1 (10.3)
	nr	22% 20% major depression 24% 23% anxiety	73% medical comorbidity including chronic fatigue syndrome	nr	54% current psychiatric disorder	81% ≥ one comorbid disorder (somatic or psychiatric)	57% medical condition 58% psychiatric problem
Duration of symptoms/ disorder (SD) <sup>a</sup>	ä	12.0 y (10.6) y 15.0 y (12.6)	и	e 7.8 y (5.2) 11.8 y (11.1)	llt studies 15.0 y (13.5)	10.0 y (nr)	s 15.3 y (11.7) e
Exclusion criteria	medication Self-reported diagnoses of mood, anxiety, or psychotic disorders • Use of psychotics • Prior participation in MBSR	Substance abuse • Major 12.0 y (10.6) psychiatric disorder • Pregnancy 15.0 y (12.6)	H	Unstable medication • Cognitive 7.8 y (5.2) impairment 11.8 y (11.1)	ACT: FSS adult studies Pain interference and Substance abuse or major severity ≥ 5 on 10 psychiatric disorder within point scale medical conditions • Currently in psychotherapy for pain	If GP judged further medical tests and procedures necessary • Conditions interfering with participation in treatment	Medical investigation Ongoing medical investigations 15.3 y (11.7) within past year or treatment which could • Impairment caused interfere with treatment • Acute by pain conditions
Main inclusion criteria	On stable medication	Multi- Diagnosis according organ BDS to research criteria (i.e., for BDS (Fink & multiple Schröder, 2010) FSS)	Physician-verified diagnosis • Able to attend sessions	и	Chronic Pain interference and non- severity ≥ 5 on 10 maligmant point scale months	≥ 3 mo pain	Medical investigation within past year • Impairment caused by pain
Condition	IBS	Multi- organ BDS (i.e., multiple FSS)	FM	Non- specific chronic pain conditions	Chronic non- malignant pain ≥ 6 months	Mixed chronic pain conditions	Chronic pain
Setting	university setting	rk Specialised clinic for functional disorders, university hospital	University setting	k Specialised pain Non- clinic, speci university chror hospital pain condi	Primary care setting	Primary care setting	n Pain Centre, nuniversity hospital
Comparison	Zernicke et al. (2013); Canada MBSR WL 8 group sessions plus 3 hr workshop	Fjorback et al. (2013); Denmark MBSR EUC Sy Sgroup EUC ch sessions plus 3 fu tr follow-up u session u	WL WL	a Cour et al. (2015); Denmark MBSR WL Broup essions plus 192 hr follow- 192 sesion	l. (2011); CBT Primar 8 group sessions setting	al. (2013); UK TAU	Buhrman et al. (2013); Sweden       ACT     Online       ACT     Online       Pain Centr       7 guided     discussion forum university       online     and WL       modules plus 2     phone calls
Treatment format & dose	Zernicke et al. MBSR 8 group sessions plus 3 hr workshop	Fjorback et al. MBSR 8 group 8 group 8 essions plus 3 hr follow-up session	Cash et al. (2015); USA MBSR WL 8 group sessions plus half-day meditation retreat	la Cour et al. ( MBSR 9 group sessions plus 4½ hr follow- up session	eta	McCracken et al. (2013); UK ACT TAU 4 group sessions	Buhrman et al ACT 7 guided online modules plus 2 phone calls



Quality score (0-42)		27		24		31		22		25		18
Main outcomes <sup>b</sup>		FU (6 mo): Am Inpact Cuestionnaire: + - ACT 's medication: (ES: 1.43) - ACT 's WU: (ES: 2.11) Pain catastrophizing: + PACT vs. WU: (ES: 0.69) - ACT vs. WU: (ES: 0.72)		<ul> <li>76 82/79/77 FU (6 mo):</li> <li>(29))((29))(13) Pain interference:</li> <li>(29))(29)(13) Pain interference:</li> <li>Guided ACT vs. Expressive writing: + (ES: 0.47)</li> <li>(ES: 0.47)</li> <li>Guided ACT vs. WL: =</li> </ul>		FU (6 mo): Pain Disability: + (ES: 0.63) HR-QOL: =		FU (6 mo): Pain interference: o Cuided ACT vs WL: + (ES: 0.58) • Guided vs m-guided ACT := Physical functioning: =		FU (14 mo): Self-rated global health improvement (CGI): + SF36 PCS: =		FU (3 mo): FM Impact Questionnaire revised (FIQ- R): + (ES: 1.59) 6-minute walk test: =
No of subjects randomised (dropout at latest FU) IG CG		51 52 53 (6) (8) (6)		82 79 77 (29) (29) (13)		30 30 (11) (12)		$\begin{array}{c} 84 & 100   101   101 \\ (46)   (45)   (26) \end{array}$		82 59 61 60 (15) (11) (14)		33 34 (8) (9)
a Remales %		96		76		73		84		82		95
<sup>a</sup> Age, y ( <i>SD</i> )		$\begin{array}{c} 49 \ (6.0) \\ 47.8 \ (5.9) \\ 48.3 \ (5.7) \end{array}$		52.9 (13.3) 52.3 (11.8) 53.2 (12.0)		40.3 (11.4)		51.7 (13.1) 1		$\begin{array}{c} 38.8 & (8.0) \\ 38.7 & (8.6) \\ 40.1 & (8.5) \end{array}$		39.7 (9.4)
Diagnosed comorbidity <sup>a</sup> Age, y (SD) <sup>a</sup>		25% depression		Rheumatic disease: 10%  8% 12%		20% major depression • 20% general anxiety • 18% social phobia • 18% panic disorder		57.3% medical 51.7 (13.1) conditions • 39.4% mental conditions		22%		nr
Duration of symptoms/ disorder (SD) <sup>a</sup>		13.0 y		≥5 y duration: Rheumatic 59% 70% 61% disease: 10% 8% 12%		0.9 y (7.5)		114.5 mo (121)				10.2 y (7.8)
Exclusion criteria		Severe psychiatric or medical disorders, drug/alcohol abuse		Low psychological inflexibility • Low psychological distress & severe psychological distress • Major depressive disorder • Concurrent CBT-based treatment		Concurrent CBT-based treatment • Major psychiatric disorder • Not able to fill in questionnaires		Tumor-related pain • Ongoing or planned psychological pain intervention • Elevated suicide risk		Substance abuse • Major 9.8 y (8.8) psychiatric disorder • Pregnancy 9.9 y (7.3) 9.3 y (6.7)		Diagnosis according Major psychiatric disorder to ACR criteria • Severe somatic disease • Chronic fatigue syndrome
Main inclusion criteria		No pharmacological treatment • No psychological treatment during previous year		Pain intensity $\geq 4$ • Pain $\geq 3$ days per week for $\geq 6$ mo				≥ 6 mo plus interference Computer literacy		Multi Diagnosis according organ BDS to research criteria (i.e., for BDS (Fink & multiple Schröder, 2010) FSS)		Diagnosis according to ACR criteria
Condition		FM		Chronic pain		n Mixed pain conditions		Chronic pain		Multi organ BDS (i.e., multiple FSS)		FM • Self- reported pain >3 (0-10)
Setting		Primary care setting	pue	University setting		Specialised pain Mixed pain ≥ 6 mo pain clinic, conditions university hospital		Health insurance provider	rk	Specialised oclinic for functional disorders, university hospital		University setting
Comparison	(2014); Spain	Pregabalin plus Primar, duloxetine/other setting medications, or WL	Trompetter et al. (2015); Holland	Expressive writing, or WL	2015); Sweden	Applied relaxation	); Germany	Non-guided online ACT, or WL	Pedersen et al. (2018); Denmark	Brief ACT Specialise (group workshop clinic for (group workshop clinic for plus 1 individual functional consultation), or disorders, EUC hospital hospital	(2018); Canada	TAU
Treatment format & dose	Luciano et al. (2014); Spain	ACT F 8 group c sessions r	Trompetter et	ACT E 9 guided v online N modules	Kemani et al. (2015); Sweden	ACT 12 group r sessions	Lin et al. (2017); Germany	ACT Cuided online Contropues 7 Number 2010	Pedersen et al.	ACT E 9 group ( sessions F F	Simister et al. (2018); Canada	ACT 7 online modules

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Think wave freatments for Functional Disorders	Third Wave	e Treatments	for Functional	Disorders
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Quality score (0-42)		20			53		28		58		35
d t Main outcomes <sup>b</sup>		FU (9 mo): Feasibility: + Fasibility i + Arient global impression of change (PCIG): = Pain interference: + (ES: 0.4)			PT (no FU for comparison): BS symptom severity (GSRS-IBS) : + (5: 1.21) BS total pain: + (ES: 0.64) BS-QOL: + (ES: 0.93)		FU (6 mo): BS symptom severity (GSRS-IBS): + (E.S. 0.44) BS-QOL: (E.S. 0.31)		FU (6 mo): Ba symptom severity (GSRS-IBS): + (E3: 0.48) IBS-QOL: (E3: 0.26)		FU (6 mo): Symptom severity: = Disability: =
No of No of subjects adomised dropout at latest FU) L		65 31 32 (8) (6)			85 43 43 (5)(0)		79 98 97 (11) (15)		80 156 153 (21) (19)		64 127 128 (38) (36)
Age, y (SD) <sup>a</sup>		45.5 (14) 6	es		34.6 (9.4) 8		38.9 (11.1) 7		42.4 (14.5) 8		43.4 (12.9) 6
Diagnosed comorbidity <sup>a</sup>		nr	adult studi		'n		n		Ĩ		50.4%
Duration of symptoms/ disorder (SD) <sup>a</sup>		Median 6.8 y (range 0.8-47.5)	wave: FSS a		6.3 y (7.3)		14.9 y (11.2)		15.9 y (12.4)		14.6 y (2.9)
Exclusion criteria		Previous ACT or CBT for pain • Other current psychological treatment • Severe psychiatric disorder	Combined second and third wave: FSS adult studies		Prior diagnosed with Displaying "alarm symptoms" BS by physician for organic gastroenterological - Fulfil ROME-III BS disease - Ourent or previous inflammatory bowel disease - Lactose or gluten intolerance not proper corrected with diet - Substance abuse • Major psychiatric disorder • < 2 y of BS symptoms		Prior diagnosed with Displaying "alarm symptoms" IBS by physician for organic gastroenterological - Pulfil ROME-III BS disease - Ourrent or previous inflammatory bowel disease - Lactose or gutten intolerance not proper corrected with diet - Substance abuse • Major psychiatric disorder • < 2 y of IBS symptoms		Prior diagnosed with Displaying "alarm symptoms" IBS by Physiciam for organic gastroenterological Fulfii ROME-III IBS disease - Current or previous criteria - Lactose or gluten intolerance to proper corrected with diet Substance abuse - Major psychiatric disorder psychiatric disorder - Insufficient language or computer skills		Substance abuse • Major psychiatric disorder • Specific types of psychopharmacological treatment
Main inclusion criteria		>3 mo plus distress and disability	Comb		Prior diagnosed with BS by physician • Fulfi ROME-III IBS criteria		Prior diagnosed with IBS by physician • Fulfil ROME-III IBS criteria		Prior diagnosed with IBS by physician endifi ROME-III IBS criteria criteria		Diagnosis according to DSM-5
Condition		Complex chronic pain			IBS		IBS		IBS		SSD
Setting		Pain management centre, university hospital			University 1 hospital setting		University hospital setting		University hospital setting	Germany	7 university mental health outpatient clinics
Comparison	18); UK	TAU		Ljótsson et al. (2010); Sweden	Online University discussion forum hospital setting	Ljótsson et al. (2011); Sweden	Internet- delivered stress management	Ljótsson et al. (2014); Sweden	ICBT without exposure component	Kleinstauber et al. (in press); Germany	Conventional CBT
Treatment format & dose	Scott et al. (2018); UK	ACT 45 min individual session plus 8 online modules plus 45 min individual session		Ljótsson et al.	CBT based on exposure and mindfulness exercises (ICBT), 5 online modules	Ljótsson et al.	ICBT 5 online modules	Ljótsson et al.	5 modules	Kleinstauber (	CBT with emotion regulation training (ENCERT), individual 20-25 sessions



Quality score (0-42)		20	
Main outcomes <sup>b</sup>		FU (4.7 mo): Disability (FDI: parent & child version): = Pain-related fear (PAIRS): + (ES: 0.29) Pain interference: = SF36 PCS: = SF36 MCS: =	Note. ACR = American College of Rheumatology; ACT = Acceptance and Commitment Therapy; BDS = Bodily Distress Syndrome; CBT = Cognitive Behavioural Therapy; CG = Control Group; BS = Effect Size; BCC = Enhanced Usual Care; PDI = Functional Disability Inventory; FM = Fibrouryalgia; FSS = Functional Somatic Syndromes; FU = Follow-Up; GP = General Practice; HA = Health Axiety; HR-QCL = Health-Effect Quartic Provention Group; MBCT = Mindfulness Based Cognitive Therapy; MSR = Mindfulness Based Stress Related Quality of Life; ISS = Irritable Bowed Syndrome; IG = Inter- vention Group; MBCT = Mindfulness Based Cognitive Therapy; MBSR = Mindfulness Based Stress Related Quality of Life; ISS = Irritable Bowed Syndrome; IG = Inter- vention Group; MBCT = Mindfulness Based Cognitive Therapy; MBSR = Mindfulness Based Stress Related Quality of Life; SSD = Somatic Symptom Disorder; TAU = Treatment Component Summary; MUS = Medically Unexplained Symptoms; nr = not reported; PAISE = Pain and Impairment Relationship Scale; PCS = Physical Component Summary; PT = Post Treatment; ST36(12 = 36-Item/12-Item Short Form Health Survey; QUL = Quality of Life; SSD = Somatic Symptom Disorder; TAU = Treatment as Usual; VAS = Visual Analogue Scale; WL = Wait List. "Numbers either shown for the total study sample or for each treatment am. <sup>10</sup> Plus sign (+) indicates improvement in favour of the intervention group, equal sign (=) indicates no effect. If several follow-ups the latest time-point is reported.
No of subjects randomised (dropout at latest FU) IG CG		78 16 16 H (3)(5) 11 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	drome; CBT ibromyalgia Irritable Bo fulness-base iship Scale; J ic Symptom r of the inter r of the inter
Age, y ( <i>SD</i> ) <sup>a</sup> Females %		14.8 (2.4) 78	Distress Syn ttory; FM = F af Life; IBS = MBT = Mind: tent Relation SSD = Somat ent in favou
Diagnosed <sup>a</sup> Age, y (SD) <sup>a</sup>		nr 1	DS = Bodily ability Inven ted Quality of Reduction; N and Impairm lity of Life; S s improvem ss improvem
Duration of symptoms/ disorder (SD) <sup>a</sup>	study	/ 32 mo (nr)	t Therapy; B inctional Dis Health-Rela Based Stress AIRS = Pain ; QOL = Qua n (+) indicate n (+) indicate
Exclusion criteria	FSS child study	Explained by organic pathology 32 mo (mr) • Major psychosocial or psychiatric issues • Major cognitive dysfunctions • Already CBT treatment • Previous amitriptyline treatment	atance and Commitment ed Usual Care; FDI = Fu lth Anxiety; HR-QOL = /; MBSR = Mindfulness ] ms; nr = not reported; P. ort Form Health Survey; ort Form Health Survey; reatment arm. <sup>b</sup> Plus sig reported.
Main inclusion criteria		: 3 mo pain	<i>Note.</i> American College of Rheumatology; ACT = Acceptance and Therapy; CG = Control Group; ES = Effect Size; EUC = Enhanced Usual ( Syndromes; FU = Follow-Up; GP = General Practice; HA = Health Anxie vention Group; MBCT = Mindfulness Based Cognitive Therapy; MBSR = Component Summary; MUS = Medically Unexplained Symptoms; nr = n Summary; PT = Post Treatment; SF36/12 = 36-Item/12-Item Short Form I as Usual; VAS = Visual Analogue Scale; WL = Wait List. <sup>a</sup> Numbers either shown for the total study sample or for each treatment indicates no effect. If several follow-ups the latest time-point is reported
Condition		un Mixed pain z syndromes	heumatolog = Effect Size General Pra General Pra s:s Based Cc ically Unexy 36/12 = 36-1 36/12 = 36-1 ul study sam -ups the lat -ups the lat
Setting		Multidisciplinary Specialised pain Mixed pain ≥ 3 mo pain treatment clinic, syndromes university hospital	College of F Group; ES : Group; ES : w-Up; GP = = Mindfulnc MUS = Med reatment; SF Analogue S i for the totz :veral follow
Comparison	Wicksell et al. (2009); Sweden	Multidisciplina treatment	<i>Note.</i> ACR = American College of Rheumatology; ACT Therapy; CG = Control Group; ES = Effect Size; EUC = Syndromes; FU = Follow-Up; GP = General Practice; HL vention Group; MBCT = Mindfulness Based Cognitive <sup>4</sup> Component Summary; MUS = Medically Unexplained S summary; PT = Post Treatment; SF36/12 = 36-Item/12-1 as Usual; VAS = Visual Analogue Scale; WL = Wait List "Numbers either shown for the total study sample or fo indicates no effect. If several follow-ups the latest time- indicates no effect. If several follow-ups the latest time-
Treatment format & dose	Wicksell et al.	ACT 10 individual sessions, 1-2 parental sessions	Note. ACR : Therapy; C Syndromes vention Gru Component Summary; J as Usual; V, "Numbers e indicates no

A medium ES of 0.48 was reported at one-year follow-up, which is at the lower end compared to existing CBT approaches. However, the drop-out rate was only 3%, which is noticeably lower than rates reported in some of the CBT-based treatments for HA (e.g. 25% from CBT in Greeven et al. (Greeven et al., 2007) and 35% from CBT in Visser & Bouman (Visser & Bouman, 2001)).

#### ACT for HA

Only one RCT study using ACT for HA has been reported (Eilenberg, Fink, Jensen, Rief, & Frostholm, 2016) (Table 3). The RCT was preceded by an uncontrolled pilot study suggesting that ACT group therapy may be an effective and acceptable treatment of HA (Eilenberg, Kronstrand, Fink, & Frostholm, 2013). For the larger controlled study, the between-group effect sizes were large (ES = 0.89), and the treatment programme was well accepted by the patients. Thus, only 9 out of 135 eligible participants declined participation, and the drop-out rate in the ACT treatment was low as only 4 (6%) out of 63 patients discontinued and one never attended the treatment. The programme was recently translated into an internet-based format, iACT for HA, with promising feasibility and efficacy reported in a pilot study (Hoffmann, Rask, Hedman-Lagerlof, Ljótsson, & Frostholm, 2018). The results from a subsequent larger RCT with inclusion of 101 patients randomized to either iACT or an active control condition with an internet-delivered discussion forum are pending (Hoffmann, 2018). The literature search revealed no published treatment studies using any of the above approaches for children and adolescents with HA.

#### **Evidence for FSS in Adults**

#### **MBT for FSS**

Eight studies were located (Table 3). Three were on FM (Astin et al., 2003; Cash et al., 2015; Schmidt et al., 2011). One study focused on chronic pain (la Cour & Petersen, 2015), 2 on IBS (Gaylord et al., 2011; Zernicke et al., 2013), 1 on persistent MUS (van Ravesteijn, Lucassen, Bor, van Weel, & Speckens, 2013) and 1 on multi-organ BDS (Fjorback et al., 2013).

The smaller study on FM population found a potentially clinically relevant effect on symptom severity (Cash et al., 2015) of the MBSR program compared to treatment as usual (TAU). The two larger studies on FM (Astin et al., 2003; Schmidt et al., 2011) which both included an active control condition, an education support group and an education support including stretching and relaxation training, found no differences in their main outcomes (Table 3). Schmidt et al. thus concluded that MBSR cannot be recommended as a treatment for FM (Schmidt et al., 2011).

The study on chronic pain (la Cour & Petersen, 2015) used an MBSR programme on top of usual care in a hospital-based pain clinic and found moderate effects on the main



outcome of vitality, symptoms of anxiety and depression and control over pain immediately post-treatment but did not include long-term outcomes.

The two studies on IBS (Gaylord et al., 2011; Zernicke et al., 2013) both used MBSR and randomised 75 and 90 patients respectively. Both studies found clinically relevant within-group changes on the IBS symptom severity and other outcome measures. However, in the Zernicke study (Zernicke et al., 2013), which had a 6-month follow-up as opposed to 3 months in the Gaylord study (Gaylord et al., 2011), there was no significant difference between the MBSR and the waitlist at this final follow-up.

A Dutch study on high utilizers with persistent medically unexplained symptoms in primary care employed MBCT and found no effect on their primary outcome of general health status nine months after end of treatment. This also applied for the secondary outcomes except for the mindfulness skills of observing and describing (van Ravesteijn et al., 2013). The other study in the more severe spectrum (Fjorback et al., 2013) was also negative as there was no difference between the two groups even though the MBSR group had improved more on the main outcome of SF-36 Physical Component Summary towards the end of the active treatment period, whereas the enhanced treatment as usual caught up during the 1-year follow-up.

#### ACT for FSS

The majority of ACT studies in FSS have been conducted in chronic pain populations including FM, and the number of participants is surprisingly small. In the two most recent reviews on ACT for chronic pain, only five of 11 studies (Veehof, Trompetter, Bohlmeijer, & Schreurs, 2016) and six of 10 studies (Hughes, Clark, Colclough, Dale, & McMillan, 2017) respectively randomised at least 50 participants.

When including these larger trials, seven ACT studies were located for chronic pain, three of which were face-to-face (Kemani et al., 2015; McCracken, Sato, & Taylor, 2013; Wetherell et al., 2011) and four of which were guided internet-delivered studies (Buhrman et al., 2013; Lin et al., 2017; Scott, Chilcot, Guildford, Daly-Eichenhardt, & McCracken, 2018; Trompetter, Bohlmeijer, Veehof, & Schreurs, 2015). Two studies were specifically on FM of which one was face-to-face (Luciano et al., 2014) and one guided internet-delivered (Simister et al., 2018). For multiple FSS, one study was located (Pedersen et al., 2018). That is, all in all 10 studies on FSS of which five were internet-delivered.

On top of the above distinct ACT interventions, one very recent study examined CBT with or without added acceptance-based emotion-regulation strategies for multiple medically unexplained symptoms (Kleinstauber et al., in press). Finally, three consecutive studies from one research group examined internet-delivered acceptance-based exposure therapy for IBS (Ljótsson et al., 2010; Ljótsson et al., 2011; Ljótsson et al., 2014).

Kemani and colleagues (Kemani et al., 2015) randomised 60 patients with chronic pain to either 12 90-minute weekly group sessions of ACT or applied relaxation (AR) but only



obtained 6-month follow-up data on 37 participants. They found significantly larger effects of the ACT intervention immediately post-treatment on pain disability, but the AR group caught up in the follow-up period. A pilot RCT of a 4x4-hour primary care based ACT group intervention for chronic pain found only small effects compared to treatment as usual (McCracken et al., 2013). Wetherell (Wetherell et al., 2011) compared group CBT to the same amount of group ACT, all in all 12 hours, and overall found small and comparable effects of the two conditions on all outcomes (Wetherell et al., 2011). Interestingly, they found that participants assigned to CBT rated this as more credible after the first session, whereas ACT participants reported more satisfaction at the end of treatment.

Four studies examined the effect of guided internet-delivered ACT for chronic pain randomising 76, 238, 302, and 63 participants, respectively (Buhrman et al., 2013; Lin et al., 2017; Scott et al., 2018; Trompetter et al., 2015). The two largest trials were threearmed (Lin et al., 2017; Trompetter et al., 2015) (Table 3). Both of these studies found clinically relevant improvements of small to moderate effect of the ACT intervention compared to the control conditions, although the Trompetter study found unexpected improvements in the waitlist control (ibid). The results from these two larger internet-based studies were generally supported by the two smaller studies (Buhrman et al., 2013; Scott et al., 2018), even though the Buhrman study (Buhrman et al., 2013) included a large number of outcome measures given the small sample size.

The two studies on FM both found promising effects (Luciano et al., 2014; Simister et al., 2018). A group-based intervention carried out at primary health care centres in Spain was found superior on most outcome measures at 6-month follow-up compared to both recommended pharmacological treatment and to a waitlist control with large effects on fibromyalgia impact (Luciano et al., 2014). This finding was generally supported by the smaller study randomising 67 participants to either online ACT or treatment as usual (Simister et al., 2018).

Pedersen et al. (Pedersen et al., 2018) conducted a tree-armed intervention study examining group-based ACT with a brief ACT intervention (group workshop + individual session) and enhanced care (Pedersen et al., 2018) for patients with multiple FSS. They found effect of extended ACT on the primary outcome of patient-rated overall health improvement 14 months after randomisation but failed to replicate this finding on any of the secondary outcomes such as illness, worry, emotional distress and health-related quality of life.

A German multicentre study included patients with multiple medically unexplained symptoms (Kleinstauber et al., in press) and compared two active treatments, namely conventional CBT for FSS, which mainly focused on causing and maintaining factors and ENCERT: ENCERT was CBT with a primary focus on negative emotions as cause and consequence of FSS. This treatment arm included emotion regulation strategies such as acceptance and mindfulness-based strategies and cognitive reappraisal (ibid). They found medium to high effects on most outcomes in both conditions but also superior outcomes



of ENCERT on a number of secondary outcomes such as health anxiety, symptom distress and emotion regulation skills.

Finally, a series of three studies on the same treatment programme for IBS (Ljótsson et al., 2010; Ljótsson et al., 2011; Ljótsson et al., 2014) combined acceptance strategies with mindfulness training and exposure. In the first modules of the treatment, they introduced mindfulness training and acceptance of symptoms together with a psychological model of IBS with the core message that behaviours which serve to avoid or control symptoms often increase the intensity of, and attention given to, symptoms (Ljótsson et al., 2010). The last phase of the treatment introduced exposure such as attending contexts where symptoms normally occur, exercises to provoke symptoms and abolishment of behaviours to control the occurrence of symptoms (ibid.). They found high effects of this treatment compared to an online discussion forum (Ljótsson et al., 2010). In a subsequent study, the treatment was found superior with medium effect sizes on several outcomes compared to stress management, which emphasised symptom control through relaxation, dietary changes and problem-solving skills (Ljótsson et al., 2011). Finally, in a disentanglement study, they examined the effect of the intervention with and without the final exposure phase of the treatment programme and found a medium effect size in favour of the inclusion of systematic exposure (Ljótsson et al., 2014).

#### **Evidence for FSS in Children and Adolescents**

#### **MBT for FSS**

Our search identified 8 studies on MBT for FSS in children; the first study published in 2013 (Jastrowski Mano et al., 2013). The studies were generally small (*N*, range 6-21). Most used pilot designs and mainly examined a developmentally adapted version of the MBSR programme in tertiary care settings on children and adolescents in the age range from 12 to 18 years with mixed chronic pain conditions. Only one smaller study has been on young patients with various FSS including chronic fatigue (Ali et al., 2017).

Attrition and recruitment problems were described in five of the studies (Hesse, Holmes, Kennedy-Overfelt, Kerr, & Giles, 2015; Jastrowski Mano et al., 2013; Lovas et al., 2017; Ruskin, Gagnon, Kohut, Stinson, & Walker, 2017; Ruskin, Kohut, & Stinson, 2015) as well as problems with obtaining sufficient post test data to draw valid conclusion about outcome (Ruskin, Gagnon, Kohut, Stinson, & Walker, 2017). However, three other recent studies indicate better feasibility results with low attrition and high acceptability but heterogeneous results when it comes to potential efficacy (Ali et al., 2017; Chadi et al., 2016; Waelde et al., 2017). Ali et al. (Ali et al., 2017) conducted an open trial on 18 adolescents with various FSS and found preliminary evidence for the MBSR programme with regard to improvement of functional disability, symptom impact and anxiety with consistency between parent and child measures. Chadi et al. (Chadi et al., 2016) evaluated a combination of MBSR and MBCT on 20 female adolescents who were randomised to either an intervention group or a waitlist control group. They reported no improvements in psycho-



logical or pain symptoms but did find significant reductions in pre and post-mindfulness session salivary cortisol levels. Waelde et al. (Waelde et al., 2017) conducted an open trial on 20 adolescents with chronic pain who received a six-week group intervention based on an adult programme named 'Inner Resources for Stress' combining meditation practices, breath-focused cue word repetition and visualisation. Functional disability and frequency of pain complaints improved with small effect sizes (d = 0.2-0.3). Though parents in the study did not receive any specific interventions, their worry about their child's pain decreased with a large effect size (d = 0.75).

#### ACT for FSS

Also with regard to ACT, the evidence is still sparse in younger age groups. We identified 6 ACT studies (Gauntlett-Gilbert, Connell, Clinch, & McCracken, 2013; Kanstrup et al., 2016; Kemani, Kanstrup, Jordan, Caes, & Gauntlett-Gilbert, 2018; Wicksell, Dahl, Magnusson, & Olsson, 2005; Wicksell, Melin, Lekander, & Olsson, 2009; Wicksell, Melin, & Olsson, 2007) including only one smaller RCT (Wicksell et al., 2009) (Table 3). A seventh study included several modalities, i.e. CBT, ACT and multi-family therapy (Huestis et al., 2017). All studies relate primarily to adolescents diagnosed with various types of chronic idiopathic pain and four were performed at the same research centre.

Wicksell et al. were the first to describe an ACT-oriented outpatient intervention in young patients with high levels of pain-related disability; first in a case study (Wicksell et al., 2005), next in a case series on 14 adolescents (Wicksell et al., 2007) and subsequently in an RCT on 32 adolescents (mean age 14.8 yrs). The RCT compared 10 sessions of ACT and one to two parent sessions with a multidisciplinary treatment including amitriptyline medication (Wicksell et al., 2009). Overall significant improvements with decreased disability were observed in all three studies, and specifically in the RCT, effects in favour of ACT were seen post-treatment in pain-related fear, pain interference and in quality of life. However, prolonged treatment in the control group complicated comparisons between the groups at follow-up assessments where all primary outcomes except pain-related fear became comparable (Table 3). The same research group later compared different formats of an extended version of this ACT programme, provided either individually (n =18) or as group-based treatment (n = 12). Medium to large effects post-treatment were reported in both formats on pain interference, depression, pain reactivity and psychological flexibility as well as in parent pain reactivity and psychological flexibility post-treatment (Kanstrup et al., 2016).

In an uncontrolled trial (Gauntlett-Gilbert et al., 2013), 98 adolescents (mean age 15.6 yrs) with non-malignant pain underwent a 3-week residential multidisciplinary ACT treatment (approx. 90 hrs) in a specialised setting. The programme comprised physical conditioning, activity management and psychotherapy with promotion of acceptance of pain and related distress as well as engagement in values-consistent behaviour. Parent involvement was included in most sessions. The adolescents improved in self-reported



functioning and objective physical performance at a 3-month follow-up. They were less anxious and catastrophic, attended school more regularly and used health care facilities less often. The programme was re-evaluated on another 164 patients as regards both adolescent and parental variables and the relationship between parental psychological flexibility and adolescent pain acceptance (Kemani et al., 2018). As in the former study, results indicated positive effects on the adolescents' functioning and pain acceptance but also a significant positive relationship between changes in parental psychological flexibility and adolescent pain acceptance.

A last study from 2017 describes the utility and outcomes of a multimodal intervention (CAPTIVES) including CBT, ACT and multi-family therapy in 17 youth (aged 13-17 years) with chronic pain and their parents (Huestis et al., 2017). The programme included weekly concurrent 60 min. youth and parent groups, concluded with an additional 30 min. multi-family group session. The families found the programme engaging and constructive and large effects were reported on pain catastrophising, acceptance and protective parenting. Similar effects were found for functional disability, pain interference, fatigue, anxiety and depression.

Recently, a study protocol describing the design of a large RCT comparing groupbased ACT with enhanced usual care for adolescents with various FSS was published (Kallesøe et al., 2016). However, the results are still pending (personal communication).

#### Discussion

Even though third wave treatments are employed increasingly, there are still relatively few intervention studies in adults of moderate to high methodological quality in FD. Thus, in the updated 2016 review (Veehof et al., 2016) of a 2011 review (Veehof, Oskam, Schreurs, & Bohlmeijer, 2011) on acceptance and mindfulness-based interventions, the authors concluded that the study quality had not improved in the five years since the first review, a finding supported by Öst's review on ACT for a broad range of conditions (Öst, 2014). As is the case with many emerging treatments, most studies in children and adolescents are small and uncontrolled in design.

#### **Evidence for Third Wave Treatment in HA**

For HA, the only two third wave RCTs on adults found a medium effect of MBCT tailored to HA (McManus et al., 2012) and high effect of ACT (Eilenberg et al., 2016). There were no studies in children or adolescents. Again, more studies are needed to replicate the findings from the above studies, especially the promising results of the ACT study, which reported high ES on the primary outcome and medium to high effect on most secondary outcomes and high retention of patients. It is worth noting that this study did, together with the vast majority of ACT interventions, include elements from second wave CBT



such as psychoeducation using the vicious circle of anxiety and interoceptive exposure http://funktionellelidelser.dk/fileadmin/www.funktionellelidelser.au.dk/Publikationer/ ACT\_Manual.pdf

With regard to younger age groups, HA is an emerging topic in the scientific literature. Integrating potential early childhood and family risk factors can help inform the development of specialised third wave therapies in children and adolescents (Thorgaard, Frostholm, & Rask, 2018) as well as for parents with so-called health anxiety by proxy (Thorgaard et al., 2017), i.e. parents who present with excessive and seemingly unreasonable concern about their child's symptoms.

#### **Evidence for Third Wave Treatment in FSS**

Overall, there seems to be only minor effects of MBT in FSS. These findings are in line with the conclusions from a meta-analytic review that ES were higher for ACT therapies compared to MBT for the majority of the examined outcomes (Veehof et al., 2016). Some of the MBT studies in both adults and younger age groups are hampered by attrition, which may also suggest that MBT does not offer an alternative to second wave treatments in terms of retention. The two studies on MBT for IBS in adults (Gaylord et al., 2011; Zernicke et al., 2013) might suggest a bigger potential for this subgroup of patients given the clinically relevant change on the main outcome, but the effects may be transient. In children, there may be recruitment and retention problems for MBT programmes if the intervention is not properly modified and tailored according to developmental aspects. Children and adolescents in general require more explanation and rationale, shorter formal exercises (e.g. around 3-5 min compared to 20-45 min in adults) as well as a greater variety of practices if they are to engage fully (Perry-Parrish, Copeland-Linder, Webb, & Sibinga, 2016; Thompson & Gauntlett-Gilbert, 2008). From a clinical viewpoint, quite a few patients seem to benefit from MBT formats, and some of the target processes such as body awareness and emotional regulation could have promise. However, the mindfulness training may need to be embedded with other methods to prevent attrition and to increase effect.

There is no evidence to suggest that ACT is superior to CBT in FSS. More high quality studies are needed to conclude whether ACT is just as effective as CBT since the smaller studies, which have been included in many reviews, inherently have an increased risk of bias. There seems to be a potential in ACT-based therapist-guided internet-delivered interventions with a number of studies in chronic pain conditions reporting effects comparable to that of face-to-face interventions. Especially noteworthy here are the studies on acceptance-based exposure-based therapy for IBS (Ljótsson et al., 2010; Ljótsson et al., 2011), where acceptance-based techniques, mindfulness training and strict exposure training are combined to produce consistently large effects, and where the exposure element has been shown to add considerable effect (Ljótsson et al., 2014). Further studies



could potentially benefit from tailoring symptom-specific exposure in the context of acceptance methods.

For conditions characterised by multiple symptoms from several organ systems, it was likewise the study which combined conventional CBT with third wave methods that had more convincing results (Kleinstauber et al., in press). Worth noting here is the dosage of treatment with 20-25 individual sessions as compared to e.g. 9 group sessions in the other trial on multiple symptoms (Pedersen et al., 2018). A secondary analysis of a group-based CBT intervention for multiple FSS (Schröder, Sharpe, & Fink, 2015b) found higher effect in the subgroup of patients with fewest symptoms. This suggests that illness severity should be taken into account when designing interventions, and more extensive interventions may be needed in the severe spectrum of FSS.

With regard to children, the evidence is surprisingly low with small and mostly uncontrolled studies on paediatric chronic pain conditions. Therefore, it remains unclear whether observed effects reflect differences in samples, designs, instruments used, method of analysis or actual effects of different treatment modalities. However, the emphasis on experiential exercises and metaphors in ACT may render this approach particularly appropriate for children. Concepts that would normally be too abstract for children can become accessible through experience and metaphorical language (Coyne, McHugh, & Martinez, 2011; Murrell, Coyne, & Wilson, 2004). Still, larger and well-designed trials are needed to compare ACT to CBT interventions to examine the potential superiority of this approach in youth with FSS.

#### Involvement of Family and Close Relatives in Third Wave Treatment

The paediatric studies specifically emphasised inclusion of caregivers in treatment. This is supported by a number of studies reporting that parents may inadvertently reinforce maladaptive illness perceptions and illness behaviours in their child (Chow, Otis, & Simons, 2016; Guite, McCue, Sherker, Sherry, & Rose, 2011; Palermo, Valrie, & Karlson, 2014; Simons, Smith, Kaczynski, & Basch, 2015). Engaging parents may both help them ameliorate their own concerns and teach them how to reinforce and model adaptive behaviours. Recent studies have shown improvements in parental psychological flexibility of an 8-week ACT group programme (Wallace, Woodford, & Connelly, 2016) and a one-session MBT workshop (Ruskin, Campbell, Stinson, & Ahola Kohut, 2018) in parents of children with chronic pain, i.e. parents' abilities to accept their distress about their child's suffering and to focus on broader goals rather than being absorbed by worries about whether their child's pain improved.

In adult patients with FSS (CFS), their illness also seems to have a negative impact on the family (Higgins et al., 2015; Leonard & Cano, 2006), and partners' responses may even influence the course of the disorder (Schmaling, Smith, & Buchwald, 2000). Dynamic management involving family systems and close relatives to promote adaptive function-



ing, quality of life and resilience may therefore also be an interesting focus for future studies on adults.

#### **Potential Challenges With Third Wave Treatment**

For FD, there is agreement that illness beliefs play a prominent role and that changes in beliefs such as perceived control (Christensen, Frostholm, Ornbol, & Schröder, 2015) and fear-avoidance beliefs (Chalder, Goldsmith, White, Sharpe, & Pickles, 2015) have been found to mediate the effect of CBT. One may speculate that there is a risk that the third wave meta-cognitive processes aimed at a general shift in perspective on inner experience and the self may not sufficiently address the specific cognitive beliefs that may perpetuate the symptoms for each individual patient. This risk may be further enhanced by the fact that all the included ACT studies, which were not internet-based, were groupbased (Kemani et al., 2015; Luciano et al., 2014; McCracken et al., 2013; Pedersen et al., 2018; Wetherell et al., 2011). Group-based therapy may have advantages in terms of providing support, promoting social skills and mirroring processes etc. but may also have risks in terms of not properly addressing the specific needs of each patient.

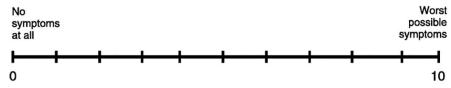
Large differences exist in use of outcome domains making it difficult to compare studies. Some ACT studies have used pain interference and pain acceptance as primary outcomes taking the point of departure that greater acceptance of symptoms and less interference of the pain in daily life are essential goals in ACT. Even though that may ring true from a theoretical perspective, we need more knowledge of the clinical importance of such changes. Other studies use syndrome-specific outcomes, hampering the comparability between syndromes. Including as a minimum the two numeric analog scale items on symptom intensity and symptom interference recommended by the European Network on Somatic Symptom Disorders in future adult trials (Rief et al., 2017) could have a major impact on the interpretation and comparability of studies. These scales encompass both the third wave focus on decreasing interference of symptoms as well as symptom reduction (see Figure 3).

For children and adolescent populations, the availability of validated questionnaires is extremely scant, and much more work is needed to develop and test such measures.



#### Symptom Intensity:

During the last 7 days, the overall intensity of my bodily symptoms was:



#### Symptom Interference:

During the last 7 days, my bodily symptoms interfered with daily life activities

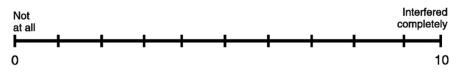


Figure 3. Two numeric rating scales recommended in future trials for FD.

Note. The scales are available at http://links.lww.com/PSYMED/A408 in more than 20 languages.

#### **Conclusion and Perspectives**

In sum, the evidence for third wave behavioural approaches for FD are still limited when it comes to larger controlled studies and very sparse and almost non-existing in younger age groups. There may have been hype surrounding the advent of third wave treatments which have hampered the ability among researchers and clinicians to communicate accurately about the advantages and disadvantages of these methods (Van Dam et al., 2018). Especially for children and adolescents, much progress remains to be made in empirically evaluating the effectiveness of third wave treatment. Thus, CBT-based programs still have much better evidence for this age group (Bonvanie et al., 2017).

There is often an unfortunate division between researchers and clinicians who study and treat adults with FD and those who work with children and adolescents with the same disorders. Joint efforts with mutual exchange of experiences and results could pave the way for further development of existing programmes such as the involvement of the family system in adult programmes.

Even though the field of FD will continue to be challenged by problems with diagnostic classification, agreement on joint outcomes across syndrome diagnoses and possibly more dismantling studies using e.g. single-case designs and/or experimental studies could also be a way forward to further explore which patient characteristics are compatible with certain approaches and techniques, both when it comes to children, adolescents and adults.

Finally, more studies explicitly combining methods from second and third wave approaches may be a promising avenue for patients across the age span.



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Scientific Update and Overview

# **Revisiting the Cognitive Model of Depression: The Role of Expectations**

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#### Abstract

**Background:** The cognitive model of depression was highly stimulating for a better understanding and development of treatment for depression. However, the concept of "cognition" is rather broad and unspecific, and we suggest to focus on the cognitive subset of expectation. **Method:** We conducted a narrative review on the role of expectations, and present an expectationfocused model of explaining why depression tends to persist despite the occurrence of positive

events.

**Results:** Several results from basic neuroscience to effects in clinical interventions indicate that expectations play a special role not only for the understanding of the development of mental disorders and the effects of treatment approaches, but especially for an improved understanding of the persistence of mental disorders. If expectations are a major mechanism of depression, the treatment of depression must maximize the violation of dysfunctional expectations. We also introduce the concept of immunization that describes any cognitive or behavioral strategies to reduce the effect of expectation violation experiences, and hereby contributing to expectation maintenance despite expectation contradicting events. We postulate that the development of immunization strategies could help to better understand the transition from episodic to chronic depression.

**Conclusion:** While in early periods of depression development, a focus on expectation change might be sufficient in treatment, the treatment of patients with chronic depression requires addressing these cognitive and behavioral immunization strategies more intensively. Further implications for treatment and research are outlined that are derived from this balance between expectation violation and cognitive immunization in depression.



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#### Keywords

depression, persistence, expectation, expectation violation, cognitive immunization

#### Highlights

- A focus on "expectations" helps to better understand the maintenance of depression
- We offer a model that explains why depression persists even in the presence of positive experiences.
- Many psychological treatments focus on the violation of negative expectations, but cognitive immunization can hinder treatment success
- We suggest strategies on how to improve psychological treatments for depression by maximizing expectation violation, and minimizing cognitive immunization

#### **Expectations as Subsets of Cognitions**

The cognitive model of depression has had tremendous impact on our understanding of cognition as an underlying mechanism of psychopathology and on the development of successful treatment approaches. Cognition as a construct, however, is extremely broad, starting from perceptions, automatic thoughts, intermediate beliefs, up to schemas, self-concepts, existential life goals and more generalized concepts (Beck & Haigh, 2014). Moreover, the cognitive model does not differentiate among cognitions concerning the past, present, and future. In this manuscript, we will focus on the role of expectations. We will argue that expectations play a specific role in our understanding of depression and other forms of psychopathology and we will discuss advantages of an in-depth perspective of this specific construct for understanding and treating depression.

The importance of expectations as specific subsets of cognition are obvious in the definition of this construct. Expectations are estimations of the likelihood of future events, and they are triggered by internal or external events ("priors"). Expectations are by definition cognitions that deal with the future, and impact future well-being. Most people have impressive abilities to cope with momentary unpleasant feelings, pain, earache and social rejection, as long as they do not expect these aversive experiences to last forever, or to be frequently repeated in the future. Thus, expectations regarding the stability of these experiences may have considerable impact on the emotions they elicit. Considering that psychological interventions are not able to change the past, and that addressing issues of the present is only of relevance if it impacts on the future, one major goal of psychological interventions should focus on improving the quality of life in the future of patients. Expectations offer the link between present state and future well-being.



Other observations support the special role of expectations. Placebo- and nocebo-research has shown that a patient's expectations determine the success of various medical interventions, ranging from antidepressant pills to heart surgery (Enck, Bingel, Schedlowski, & Rief, 2013; Rief, Bingel, Schedlowski, & Enck, 2011). Therefore, expectations can be considered the most frequently investigated mechanism of treatment success in health care systems because this mechanism has been shown to play a role in nearly all fields of medicine (Schedlowski, Enck, Rief, & Bingel, 2015). A meta-analysis of the association between treatment expectations and treatment outcome for psychological treatments confirmed the special role of patients' treatment outcome expectations (Constantino, Arnkoff, Glass, Ametrano, & Smith, 2011), a result that was also found for psychological treatments of mental disorders or chronic pain (Cormier, Lavigne, Choiniere, & Rainville, 2016; Delgadillo, Moreea, & Lutz, 2016). Expectations predict the transition from acute pain to chronic pain, and the persistence of pain symptoms (Gehrt et al., 2015; Holm, Carroll, Cassidy, Skillgate, & Ahlbom, 2008).

Modern neuroscience further supports the importance of focusing on predictions/ expectations. Whereas former models of the brain mainly considered its function as passively waiting for sensory input before processing it, modern models consider the brain a "prediction coding machine", continuously creating predictions about what will happen next (Seth, Suzuki, & Critchley, 2012). "Prediction errors" trigger selective attention, and they are able to stimulate learning processes. Thus, the brain's predictions steer perception, attention, and information processing in general. The parallel between the neuroscientific concepts of prediction and prediction error versus the more applied concepts of expectation and expectation violation is obvious (D'Astolfo & Rief, 2017). Of further relevance is the blunted reward processing in depression (Pizzagalli, 2014; Wilson et al., 2018), which could help to understand why depressed patients do not update negative expectations. The "Bayesian brain" offers a computational perspective on mood as creating and updating "priors" over uncertainty (Clark, Watson, & Friston, 2018). Finally, expectations also offer a link between mind and body: they trigger anticipatory physiological reactions. The anticipation of threat triggers physiological fight-flight-reactions. The anticipation of pain activates the somatosensory fields that are responsible for pain perception (Koyama, McHaffie, Laurienti, & Coghill, 2005), but also brain functions that are responsible for pain control (Wager, Scott, & Zubieta, 2007).

Whereas expectations as mechanisms of treatment success are frequently investigated, the specific role of expectations as a mechanism of disorders and in the maintenance of mental problems is a less frequently studied topic. However, expectations can play a special role in improving our understanding of transdiagnostic processes, hereby offering a link to the RDoC-approach (Insel, 2014). Anxiety disorders and phobias are by definition expectation disorders, and also for associated fields such as OCD-associated disorders, expectations can be considered a core feature contributing to the persistence of



clinical problems (Rief & Glombiewski, 2017). However, the role of expectations in depression is less obvious, and this will be discussed in the next section.

#### The Cognitive Model and the Specific Role of Expectations in Depression

The cognitive model of mental disorders goes back to formulations of ancient Greek philosophers, such as Epiktet (born about 50 A.D.). It postulates that negative affective states develop not because of direct external influences (e.g., social rejection), but because of the interpretation of these external and internal events. It was the merit of A.T. Beck to translate this approach to improve our understanding of depression. Beck's original formulation of the cognitive triad in depression can be easily transformed to expectations: negative expectations for outcomes relevant to the self, negative expectations about other's behavior, and finally negative expectations about future events. The cognitive model was supported by various experimental studies, summarized elsewhere (Gotlib & Joormann, 2010; Joormann & Quinn, 2014).

The standard assessment of dysfunctional attitudes (Dysfunctional Attitudes Scale DAS; Oliver & Baumgart, 1985) targets various expectations, but also covers other cognitions considered to be specific to depression. However, the question arises whether other cognitions have explanatory value for depression beyond the value of depression-specific expectations. To investigate this question, we developed a self-rating scale to assess depression-specific expectations. Using a path analytical approach, we analyzed whether other cognitive aspects of depression explain additional variance, if the role of depression-specific expectations was controlled (Kube et al., 2018c). In this study, depression-specific expectations had a clear association with depression, while other cognitions did not significantly add to this association. This confirms the special illness-relevant role of expectations as an important subgroup of cognitions.

Kube and colleagues (Kube, D'Astolfo, Glombiewski, Doering, & Rief, 2017) developed a depressive expectations scale that allows to assess situation-specific expectations in major depression.

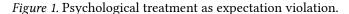
This scale includes 25 items. The depression-specific expectations can be clustered into four subgroups: Expectation of social rejection, expectation of (lack of) social support, expectation of ability to regulate mood, and expectations about the ability to perform cognitive tasks and about the likelihood of professional achievements. The advantage of this scale is that all its specific items can be directly translated into behavioral experiments, which offer the opportunity to assess expectations in depressed patients, to motivate them to test them, and to modify expectations after expectation violation experiences. Thus treatment of depression can be reformulated as an intervention to change dysfunctional expectations, mainly via the exposure to expectation violating situations (see Figure 1).



While typical CBT approaches also cover some of these strategies, our plea is to better focus on expectation change not only in anxiety treatment (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014), but also in depression treatments. One future gain of focusing on expectation could be the development of more effective and economic interventions for depression.



Prediction of this model: The more intensive the exposure to expectation violation is, the more effective is the resulting expectation change



Depression has been also linked to reward expectancy (Greenberg et al., 2015). Not expecting reward and not expecting positive events is closely associated with depressive states. Moreover, it has been postulated that depression is mainly characterized by a lack of positive expectations (instead of increased negative expectations); a concept that was also confirmed using longitudinal designs (Horwitz, Berona, Czyz, Yeguez, & King, 2017).

## The Role of Cognitive Immunization in Depression

If negative expectations are a core part of depression, the crucial question is why these negative expectations persist, even after new positive experiences ("expectation violating situations"). Whereas difficult life conditions or critical life events can lead to the development of negative expectations, and thereby contribute to the development of episodes of depression (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; McLaughlin et al., 2017; Nelson, Klumparendt, Doebler, & Ehring, 2017), the process of persistence of these negative expectations is still poorly understood. Even patients with depression experience positive life events, positive interactions, successful performances, but most of these events do not lead to a change in negative expectations, and development of positive expectations. Therefore, we introduced another construct in our depression model that helps to understand the persistence of negative expectations even if positive experiences occur. This concept is "(cognitive) immunization". It describes all cognitive (and sometimes also behavioral) processes to invalidate the effect of positive, expectation violating experiences. While we will focus on cognitive immunization processes, behavioral strategies can also contribute to immunization: avoiding expectation-violating situations, selective attention and ignoring stimuli that transport the contradicting information are just a few examples.



These processes can also be observed in psychological interventions. It happens when psychotherapists try to induce positive, disconfirming experiences, but patients continuously invalidate them. Typical invalidation strategies are declaring these experiences as exceptions to the rule ("if someone is friendly with me, this is only the exception to the rule that people dislike me"; "you, as a psychotherapist, are only friendly with me because you are getting paid for it"), or invalidation of a positive situation in general ("although I succeeded in this exam, in other, much more important exams, I will fail").

Many psychological interventions aim to violate negative expectations of patients. They can be even optimized in optimizing expectation violation experiences. However, as shown in Figure 2, cognitive immunization can contribute to the invalidation of expectation violation effects. Thus treatment aims should be reformulated to maximize expectation violation effects, and to minimize (cognitive) immunization processes.



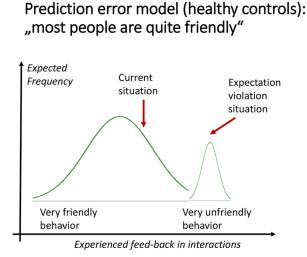
Figure 2. Expectation violation and cognitive immunization.

## A Stochastic Understanding of Expectation Change

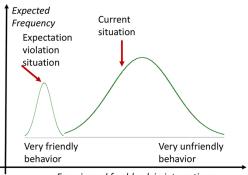
The neuroscientific prediction error paradigms have been extended by stochastic approaches, and this extension is also helpful to better understand expectation maintenance versus expectation change in depressed patients. If healthy people develop the expectation that most people are quite friendly, they interpret a broad variety of the behavior of the person with whom they're interacting as confirmation of their expectations (see Figure 3, top). Even neutral events (see arrow) confirm the positive expectations about the behavior and intentions of others. This is a potential explanation for the reported optimism bias of healthy people to memorize neutral events as being positive, and to expect positive outcomes even without any information supporting this expectation (Sharot, Riccardi, Raio, & Phelps, 2007). Expectations form an interpretation bias towards their confirmation, and this sticking to expectations can be postulated to have an evolutionary meaning, providing stability in humans' life. Moreover, expectation confirmation can be postulated to be a typical automatic process, not requiring much cognitive resources, while the revision of expectations can be more demanding. To really challenge long-held expectations, other highly discrepant and powerful experiences are necessary. In healthy



people, this means that only very harsh social rejection or traumatizing events really challenge their positive expectations about future events.



#### Prediction error model (depressed patients): "most people are quite unfriendly"



Experienced feed-back in interactions

Figure 3. A stochastic model of expectation maintenance.

When developing depression, the curve of expectations appears to move to the more negative part (see Figure 3, bottom). Most events are interpreted as confirmation of a negative view of the world. Even neutral experiences may be considered as confirmation of negative expectations (see arrow). In other words: The very same experience that confirms positive expectations in healthy persons can confirm negative expectations in depressed patients. Again, to change negative expectations of depressed patients, very powerful, clearly distinguishable positive experiences are necessary. This example highlights why normal experiences and their attribution (e.g. in cognitive work) sometimes do not lead to any changes of negative expectations; effortful cognitive evaluations do not auto-



matically lead to changing automatic processes of confirmations of negative expectations.

# Experimental Studies Investigating Expectation and Cognitive Immunization in Depression

Kube et al. (Kube, Rief, Gollwitzer, & Glombiewski, 2018b) investigated the interplay of expectation manifestation and expectation change in depression quite elegantly using an experimental paradigm. Participants received a negative performance expectation ("the following test on emotional intelligence is hard to succeed"). Afterwards, participants received different tasks on emotional intelligence that are difficult to evaluate which answers are correct. During the first trials, participants received the feedback that they were not successful, as expected. Both healthy controls and depressed patients developed similar negative expectations after these experiences (Kube, Rief, Gollwitzer, Gärtner, & Glombiewski, 2018a). However, after several failures, performance feedback switched to more frequent positive results ("expectation violation"). In accordance with the depression model mentioned above, healthy controls changed their negative expectation to positive, while negative expectations of depressed patients persisted despite positive feedback.

In a second experiment, the same authors introduced either instructions that supported cognitive immunization strategies ("the following test is not really valid, but just a weak indicator of performance"), while others received strategies aimed to inhibit cognitive immunization ("this is a really powerful and valid test"). If depressed patients received strategies that inhibited cognitive immunization, the change to positive feedback resulted also in a change of negative expectations to positive expectations (Kube et al., 2018a). In other words: if cognitive immunizations are blocked in depressed patients, patients can benefit from positive experiences. This offers new foci for treatment planning and prevention of treatment failures in depression.

These effects are in line with other studies investigating cognitive adaptation processes in depression. Depressed persons have less favorable success expectations, and show a tendency to self-confirmation of negative attitudes (Morris, 1997). Further evidence comes from a study of Everaert and others (Everaert, Bronstein, Cannon, & Joormann, 2018) who found that depressed patients do not only have a negative interpretation bias, but also showed a reduced revision of negative interpretations by disconfirmatory positive information. Liknaitzky and colleagues confirmed that patients with depression have a reduced ability to update interpretations after receiving expectation violating information (Liknaitzky, Smillie, & Allen, 2017). Of note, this effect was independent of the direction of expectation violations.



# Treatment Implications of the Expectation Model of Depression

The implications for psychological treatments can be reduced to two main strategies: amplifying the effect of expectation violations if positive experiences occur, and reducing the effect of cognitive immunization. First experiences with these foci in the work with patients were quite encouraging: patients can easily adapt this expectation model, and understand what is meant by cognitive immunization. After such a psychoeducational period, both typical expectations associated with the depressive disorder, but also cognitive immunization strategies that occur in everyday experiences when positive events occur, can be collected. Instead of continuing with cognitive dispute techniques like in cognitive therapy, patients are informed that humans often maintain negative expectations even if positive experiences occur. Therefore, they are encouraged to develop more openness for experiences that are not in accordance with current expectations. Considering the reduced motivation for complex and effortful cognitive processes in many patients with depression, we are working on developing more and more attention-based strategies that do not require complex cognitive reasoning.

Patients must be sensitized for the perception of relevant information, before starting with behavioral experiments. What would be the first stimuli indicating that expectations could be wrong? What kind of immunization strategies can be expected by this patient, if expectation violation occurs? What could be possible strategies to avoid the negative effect of cognitive immunization? Only after such a cognitive preparation period, are behavioral experiments testing negative expectations executed.

This strategy can easily be extended with a behavioral component. What kind of patient's behavior would maximize the likelihood of confirmations of negative expectations (e.g., avoiding eye contact although you hope for positive interaction with others; not preparing for an exam because expecting to fail anyway; ...). After collecting behavioral patterns that serve to confirm negative expectations, the question can be reversed: What would be behavior patterns that minimize the likelihood of fulfillment of negative expectations? Not surprisingly, these kinds of behaviors should be shown during subsequent behavioral experiments. Table 1 shows a structure of such an expectation focused psychological intervention; further details can be found elsewhere (Rief & Glombiewski, 2016, 2017).

This brief guideline shows that expectation-focused psychotherapy is not a completely new approach, but more like an improved focus on most relevant cognitive and behavioral aspects in depression. While full evaluation trials in depression are lacking, we have positive evidence for expectation-focused approaches from other clinical fields. Exposure therapy in anxiety disorders has been reformulated as a therapy to disconfirm negative expectations, and to increase inhibition of avoidance behavior (Craske, 2015; Craske et al., 2014). In pain disorder, many patients report "fear avoidance" behavior which can be considered as a special expectation pattern of chronic pain. If these patients were treated



#### Table 1

#### The Steps of Expectation-Focused Psychological Interventions

#### Why are expectations maintained despite contradicting information? Examples of queries and patients' reflections as part of the psychoeducation

# What are my specific expectations?

Others don't like me.
How can I check whether my expectations are valid?
Go to a party and check whether people talk to me.
What are signals, perceptions, observations, that would show me that my expectations are disconfirmed?
Others talk to me; others initiate eye contact
What kind of immunization strategies do I typically use in such a situation?
Thought: "They only look at me because they have negative thoughts about me"; I look away; If somebody talks to me, this is just on account of being polite – $s/he$ has no special interest in me.
How can I deal with my immunization strategies?
Accept negative thoughts, but be open for contradicting experiences; don't look away
Results of behavioral test
People came and talked to me
What are further situations to test my expectations? At work during coffee breaks
How should I behave to make my negative expectations come true?
Avoid eye contact; stand away from others, facial expression of bad mood
How should I behave to make my negative expectations not come true?
Stand closer []; search eye contact; don't walk away []
Results of reality checks
I was concerned that others don't like me. However, I made it quite difficult for them to show me some

sympathy. And I use a lot of "immunization strategies" if positive events occur.

with a highly focused expectation-based exposure intervention, they showed the most impressive improvements even in treatment arms with less treatment sessions than comparative treatments (Glombiewski et al., 2018). Obviously, the improved focusing in pain patients led to more effective, but also more economic interventions.

An expectation-focused approach was also used for a better preparation of patients undergoing heart surgery. Pre-operatively, patients received an optimization of expectations about how life can continue after successful heart surgery. Such an expectation-focused intervention was compared to an emotionally-supportive intervention, and to standard medical care. Although the expectation-focused intervention was just two sessions in person, two phone calls (before surgery) and one booster phone call after sur-



gery, patients in this arm showed the lowest disability scores six month after surgery (Rief et al., 2017). It is most impressive that such a low dose intervention achieved these striking effects. With more than 120 patients in this trial, it can be postulated that many risk factors and life problems were prevalent in these patients that were not addressed at all during the psychological interventions (e.g., marital conflicts, adverse early life experiences); however, quality of life improved substantially just by improving expectations. This is a further argument to better focus on crucial mechanisms that maintain mental, behavioral and even physical disorders (Holmes et al., 2018). Current depression treatments should be optimized to change dysfunctional expectations according to the principles outline above, and these treatments should be subject to further evaluation.

### Implications for Research

Several hypotheses can be derived from the expectation model of depression that should be a further subject of investigation. First, it is postulated that healthy individuals show more immunization strategies to prevent them from the effects of negative experiences than depressed patients. If healthy individuals are repeatedly exposed to positive events, and subsequently negative experiences occur, we expect them to stick to positive expectations, and to activate immunization strategies. This is in line with some studies indicating that depressed patients are sometimes more "realistic" than healthy individuals, because healthy individuals show an optimism bias (Sharot, Korn, & Dolan, 2011). This can be also considered as a resilience mechanism of healthy people (Brown, 2012).

With the first depressive episodes, the expectation curve is hypothesized to move to a more negative level. This change could be induced by negative experiences that trigger the first depressive episode, but also the depressive episode itself is associated with a change of expectations. If the expectation curve has been moved to the more negative side, this could receive a self-maintaining functionality and is resistant to change. After this move has happened, depressed patients could tend to interpret neutral events as confirmation of their negative expectations, while healthy controls interpret the same neutral experiences as confirmation of their positive view of the world. Again this dynamic can be subject to experimental, cross-sectional and longitudinal studies, to better understand and confirm ongoing mechanisms.

Another hypothesis is that only very salient positive information is able to modify negative expectations in depressed patients. This could be studied with experimental designs to investigate the effects of expectation development, expectation persistence and change to the positive or to the negative direction.

The above described expectation model may also be a model to better understand the process of persistence of depressive episodes. We hypothesize that patients with persistent depression show more immunization strategies than patients with episodic depression, in particular to invalidate the effects of positive experiences. This sticking to nega-



tive expectations is further supported by automatic information processes, while expectation change is frequently associated with effortful cognitive processes. Again, this has implications for treatment planning. The more chronic the depressive state is, the more relevant it might be to address cognitive immunization strategies in patients.

To summarize, several hypotheses of the expectation model of depression can be extracted that can be subject to further evaluation. It not only invites observational studies, but also more mechanistic research using experimental designs. Further paradigms should be developed to establish and modify expectation processes that should have special ecological validity for affective disorders.

# Linking the Expectation Model of Depression With Other Psychological Concepts

The suggested expectation model of depression focuses on aspects of how negative expectations develop, how they contribute to depression-specific symptoms and disability, and why negative expectations are maintained even if contradicting positive events occur. Such a focus offers various links to other prominent depression concepts, and a few of them will be addressed.

Neuroscience has shown that the expectation of negative emotions (e.g. pain) activates brain areas that are responsible for this emotion, and hereby facilitates the expected perception of the corresponding negative experience (Atlas & Wager, 2012; Keltner et al., 2006; Koyama et al., 2005; Wager et al., 2004). This implies that the manifestation of expectations supports the persistence of negative mood that is associated with the expected negative experience. For the development of expectations, associative learning processes (Rheker, Winkler, Doering, & Rief, 2017), observational learning (Vögtle, Barke, & Köner-Herwig, 2013) or instructional learning can contribute.

To overcome negative expectations, powerful expectation-violating positive experiences are necessary. However, this requires an individual to attend to this new information, to react to its positive content, and to modify and memorize the revised version of expectations. For this process, reward sensitivity, a concept that is closely linked to neurophysiological processes in depression, can be crucial (Alloy, Olino, Freed, & Nusslock, 2016). Blunted reward sensitivity was also found in relatives of depressed patients (Liu et al., 2016). The postulated role of reward insensitivity is in line with recent findings that patients with depression show reduced revision of negative interpretations by disconfirmatory positive information (Everaert, Bronstein, Cannon, & Joormann, 2018).

A revision of negative expectations requires a detailed perception and memorization of expectation-violating experiences. However, many patients with depression suffer from unspecific autobiographical memory reports (Kim, Yoon, & Joormann, 2018; Sumner, Griffith, & Mineka, 2010). According to the ViolEx-model of revising expectations (Rief et al., 2015), a revision of expectations requires a very specific definition of



specific expectations a priori, and a clear comparison of expected versus experienced specific outcomes. If experiences are memorized only vaguely, their potential power to stimulate expectation violations is only low. This notion is in accordance with the fact that abstract ruminations lead to more regrets about past decisions than concrete ruminations (Dey, Joormann, Moulds, & Newell, 2018).

Repetitive negative thinking, ruminations and worrying are also major features of depression (Gotlib & Joormann, 2010; McEvoy et al., 2018). These strategies can be considered as preventing the change of negative expectations, even when positive events occur. Therefore, a close link between these cognitive processes and immunization strategies exists.

Persistent depressive disorder is frequently associated with negative early life experiences and the development of insecure attachment styles. While negative life events can trigger the establishment of various negative expectations directly, insecure attachment styles can be also reformulated as negative relationship expectations. An association between attachment and depression was frequently shown; this association is mediated via social anxieties (Manes et al., 2016). Social anxieties (like all anxiety disorders) can be mainly understood as expectation disorders. Several psychological interventions try to address these relationship expectations, and the active formulation of a "transference hypothesis" in CBASP is a typical example (McCullough, 2000; McCullough et al., 2011). Obviously, many psychological interventions include explicit or implicit interventions attempting to change relationship expectations, although an even more focused and explicit work with relationship expectations seems promising.

With this subchapter, we wanted to highlight that the expectation model of depression is able to integrate other evidence-based approaches of depression research, and it invites to link this concept with others. While these are just a few examples, further conceptual work is possible and needed.

## **Closing Remarks**

While the cognitive model of depression was highly stimulating for a better understanding, improved conceptualization and development of treatment for depression, we suggest that it is time to better specify this approach. Several results from basic neuroscience regarding effects in clinical interventions indicate that expectations can play a special role not only for the understanding of the development of mental disorders and effects of treatment approaches, but especially for an improved understanding of persistence of mental disorders. Therefore, we also introduced the concept of immunization to describe any cognitive or behavioral strategies to reduce the effect of expectation violation experiences, and hereby contributing to expectation maintenance despite expectation contradicting events. We postulate that the development of immunization strategies could, in particular, be of relevance for the transition from episodic to chronic depression. While in



early periods of depression development, a focus on expectation change might be sufficient in treatment approaches as long as it respects some of the principles mentioned above, the treatment of patients with persistent depressive disorder requires more and more to address these cognitive and behavioral immunization strategies.

We understand our manuscript mainly as stimulating further research and using this conceptual framework, instead of presenting a final model. First experimental results confirm its usability, and first clinical experiences encourage this approach as something that is easily explained to patients who found it very helpful. However, the model of the interplay between expectation processes and immunization strategies should be subject to further evaluation.

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Scientific Update and Overview

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# Developments in Psychotraumatology: A Conceptual, Biological, and Cultural Update

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## Abstract

**Background:** This report discusses recent developments of psychotraumatology mainly related to the recently published ICD-11, but also from a societal point of view.

**Methods:** The selected aspects of the development of this field will be presented as a scoping review.

**Results:** In the first section, the new concept of disorders specifically associated with stress and its relevant diagnostic groups (posttraumatic stress disorder [PTSD], complex PTSD, prolonged grief disorder, and adjustment disorder) are presented, with an emphasis on PTSD. The second section embeds these diagnostic concepts within a broader context. In particular, the concept of psychotraumatology is applied to the impact of adverse childhood experiences. More specifically, recent scientific developments are discussed with respect to biological stress research. In a third section, a global perspective is applied that reflects psychotraumatology as embedded in culturally-specific concepts. Lastly, societal developments are taken into consideration. This section focusses on recent processes of victim acknowledgement and compensation taking place in Europe and beyond. Examples are provided for how traumatic stress is perceived and processed in society. Concepts such as continuous stress and historical trauma are also discussed.

**Conclusion:** Demands and opportunities of basic research and psychological interventions with a global focus are outlined.

# Keywords

psychotraumatology, ICD-11, Posttraumatic Stress Disorder (PTSD), adverse childhood experiences, child abuse, acknowledgment of victims, cultural background, survivor status, compensation



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# Highlights

- Psychotraumatology is an expanding field including both basic research and intervention-related research.
- Starting points of this new research area are not only potential traumatic events but also adverse childhood experiences.
- In a globalized world, cultural and societal factors play an increasingly important role in psychotraumatology.

In the early 1980s, the scientific field of *psychotraumatology* arose with the first description of posttraumatic stress disorder (PTSD) as a new diagnostic category in DSM-III (American Psychiatric Association, 1987). Today, this research area has been internationally recognized and well-accepted despite prevailing critical concerns and controversies (Rosen, Spitzer, & McHugh, 2008). From its initial description in the 1980s, concepts of psychotraumatology have continuously developed. This is also reflected by the growing number of scientific publications, the founding of thematically relevant journals, as well as increasing public awareness and perception (Maercker & Augsburger, 2017).

In the following sections, recent developments in psychotraumatology will be described. First, we will focus on new diagnostic concepts and changes in stress-related disorders associated with the launch of ICD-11. Since ICD is a major classification system used in clinical practice in many European countries, we will only briefly refer to alternative concepts as presented in DSM. A more detailed and explicit comparison of ICD-11 and DSM-5 extends beyond the scope of this review.

Second, we will describe recent developments in areas closely related to PTSD, mainly adverse childhood experiences (ACEs) and their biological impact. We focus on this specific topic for two reasons: First, in clinical practice, ACEs remain an often-neglected area despite their frequent occurrence and large burden. Second, technical advancements have resulted in a vast increase in recent years in studies focusing on biological markers associated with ACEs.

In a third section, culturally-specific models of mental disorders will be discussed with a focus on global challenges. And, lastly, aspects of public discourses are considered.

The aim of this report is to give a summarized overview of selective topics and concepts associated with recent developments in the field of psychotraumatology and in light of ICD-11. Thus, core areas were selected according to the authors' personal research foci.



# New Conceptualizations of Stress-Related Disorders in ICD-11

The updated 11<sup>th</sup> version of the International Classification of Disorders (ICD-11) of the World Health Organization (WHO, 2018) brought about a number of significant changes in the conceptualization of stress-related mental disorders. These changes are a marked contrast to the other major classification system, the Diagnostic and Statistical Manual, version 5 (DSM-5), released by the American Psychiatric Association (APA, 2013). With ICD-11, PTSD and two additional stress-related mental disorders can now be adequately diagnosed: a complex form of PTSD and prolonged grief disorder. Moreover, a completely new symptom formulation was also grouped in this category, for adjustment disorder occurring after severe non-traumatic stressors (First, Reed, Hyman, & Saxena, 2015; Maercker et al., 2013). Some years previously, these changes were discussed for DSM-5. But at this time the committee declared that sufficient evidence was not provided for an empirically valid distinction between PTSD and complex PTSD. As a consequence, the current PTSD diagnosis in DSM-5 also incorporates symptoms that are specified as complex PTSD in ICD-11. In addition, prolonged grief disorder cannot be diagnosed as a "full disorder" in DSM-5, but exists as a provisional diagnostic concept in the appendix (under the term "Persistent complex bereavement disorder"). Concerning adjustment disorder, the concept has remained largely the same in its transition from DSM-IV to DSM-5.

In the following sections, the four diagnoses (PTSD, complex PTSD, prolonged grief disorder, adjustment disorder) will be introduced and discussed. All criteria are based on the online version of the ICD-11 (WHO, 2018).

#### PTSD

PTSD manifests itself after exposure to an extremely threatening adverse event or series of events. It is characterized by the following three symptom clusters: 1) Re-experiencing of the traumatic event(s). This occurs in the form of vivid intrusive memories, such as flashbacks or nightmares. 2) Avoidance of thoughts or reminders of the traumatic event(s) or avoidance of activities, situations, or persons that elicit memories. 3) Persistent perception of heightened current threat, as characterized by an enhanced startle reaction or alertness. For a diagnosis of PTSD, all symptom clusters must persist for several weeks and lead to significant impairment in psychosocial functioning (WHO, 2018).

In contrast to both DSM-5 and ICD-10, the intrusion criterion of ICD-11 is stricter and not only requires aversive memories of the traumatic event(s), but also stronger feelings of vivid re-experiencing. In addition, the definition of hyperarousal focuses on increased perception of threat. ICD-11 prevalence rates of PTSD are lower than those for ICD-10 and are also reduced in comparison to DSM-5 (Brewin et al., 2017). Results from the World Mental Health survey indicate a lifetime prevalence from 3.0-3.4% worldwide (Stein et al., 2014).



#### **Complex PTSD (CPTSD)**

CPTSD can develop after exposure to an extreme and threatening event or a sequence of events, from which escape or flight is difficult or impossible. In order to give a diagnosis of CPTSD, individuals first need to fulfill all symptoms of PTSD. In addition, difficulties in three further areas must be reported: 1) Severe problems with affect regulation; 2) perception of oneself as diminished, worthless, or defective; and 3) persistent difficulties in establishing or maintaining relationships and the feeling of being close to others. As with PTSD, all symptoms need to lead to significant impairment in psychosocial functioning (WHO, 2018). This diagnosis is the successor of ICD-10 personality disorder F62.0 (*Enduring Personality Change After Catastrophic Experience*), but with an entirely new conceptualization. To date, limited information on prevalence rates is available for the US, Denmark, and Germany. In these countries, the rates range between 0.5-1.0%, across 1-12 months (Brewin et al., 2017; Maercker, Hecker, Augsburger, & Kliem, 2018).

### **Prolonged Grief Disorder (PGD)**

PGD can develop after the loss of a loved one. It is marked by a persistent and intense longing for the deceased, accompanied by a strong cognitive attachment. In addition, intense emotional suffering occurs, such as sadness, feelings of guilt, anger, denial, or difficulties in accepting the death (WHO, 2018). It is important to note that all these symptoms can fall within the normal range of grieving. They may only be considered as pathological if they persistently occur over an atypically long period of time, in relation to what is considered as normative in the respective social, cultural, and religious setting. This aspect is important as it allows a broad range of culturally-related variability. For instance, in traditional Western or European cultures, symptoms that present within one year of mourning may be perceived as acceptable within this setting.

Regarding prevalence rates, studies are still lacking with respect to the new ICD-11 criteria. A recent meta-analysis on a preliminary concept of PGD reported a prevalence rate of 9.8% following the violent loss of a close person (Lundorff, Holmgren, Zachariae, Farver-Vestergaard, & O'Connor, 2017). In general, lower rates are expected for ICD-11 (e.g., Kersting, Brahler, Glaesmer, & Wagner, 2011).

#### Adjustment Disorder

Adjustment disorder manifests itself as an intense reaction towards a clearly identifiable psychosocial stressor. Typically, it occurs within one month following the starting point of the stressor. A main symptom is the cognitive attachment towards the stressor or its consequences. This can be expressed as excessive worrying, persistent burdensome thoughts about the stressor, and constant rumination. For a diagnosis of adjustment disorder, these symptoms must lead to significant impairment in psychosocial functioning.



Improved functioning should only be possible with considerable effort. Over the course of time, a symptom remission can occur within six months (WHO, 2018). In contrast to both ICD-10 and DSM-5, this new concept of adjustment disorder brings significant changes: First, the core symptoms of preoccupation and failure to adapt are now clearly described and must be present for a diagnosis. And second, in the current formulation, the subtypes of adjustment disorder (e.g., depressive or anxious) were omitted, as previous studies showed a high degree of overlap between the subtypes (Maercker & Lorenz, 2018). Regarding prevalence rates, a recent study reported a one-year prevalence of 2% in a representative German sample (Glaesmer, Romppel, Brahler, Hinz, & Maercker, 2015). However, rates are much higher in risk samples. For instance, rates ranged between 13.8-17.2% in a sample of individuals who had experienced involuntary job loss in Switzerland (Perkonigg, Lorenz, & Maercker, 2018).

The above four stress-related diagnoses not only emphasize the considerable improvements in clinical utility (Maercker et al., 2013), but also reflect the fact that therapeutic interventions for specific disorders have been developed and evaluated in recent years (Schnyder & Cloitre, 2015). For PTSD, trauma-focused specific psychotherapeutic interventions that incorporate a variant of exposure show the best evidence for treatment efficacy (e.g., narrative exposure therapy, trauma-focused cognitive-behavioral therapy). For complex PTSD, a phase-based intervention was developed and is currently being evaluated (e.g., Cloitre, Koenen, Cohen, & Han, 2002). For prolonged grief disorder, different treatment manuals are available (Rosner et al., 2014). Lastly, adjustment disorder is also benefitting from new interventions on a low-threshold level (Maercker, Lorenz, Perkonigg, & Kapfhammer, 2016).

A remaining issue is the different conceptualizations of the disorders, specifically PTSD with respect to DSM-5 and ICD-11. Recent studies point to the fact that different subgroups of patients are being identified depending on the classification system used (e.g., Barbano et al., 2019). However, these discrepancies also offer the opportunity for further scientific discourse.

# Expanding the Concept of Psychotraumatology

Today, it is well recognized that traumatic experiences during childhood, such as sexual abuse or physical violence, can have a long-lasting and devastating impact on later life. More recently, less severe types of traumatic experiences, such as verbal abuse, have also gained awareness as a similarly potent form of maltreatment (Teicher, Samson, Polcari, & McGreenery, 2006). The term Adverse Childhood Experiences (ACE) incorporates a much broader range of these exposure types, including emotional or physical neglect, or peer violence. It is evident that some of these maltreatment types extend beyond the definition of a traumatic event, according to the classification of DSM or ICD.



#### **Consequences of Adverse Childhood Experiences**

The first systematic investigation of adverse childhood experiences (the so-called ACE - studies) incorporated a huge sample of 17,300 study participants and were a milestone for later research (Anda et al., 2006; Dube et al., 2001). For the first time, not only the long-term consequences of exposure to physical or sexual abuse were assessed, but also the impact of a broad range of other experiences, such as emotional abuse, physical or emotional neglect, and other risk factors in the child's environment. The ACE-studies resulted in overwhelming evidence for the significant negative impact of these experiences in later life: up to a 3.6-fold increased risk for depressive disorders, 2.4-fold increased risk for anxiety disorders, 2.7-fold increased risk for occurrence of hallucinations, 2.1-fold increase for sleeping disorders, and 7.2-fold increased risk for alcohol abuse. In addition, risk for somatic complaints was increased by 2.7-fold, and severe obesity showed up to a 1.9-fold increased risk (Anda et al., 2006).

These ACE-studies not only led to the general acknowledgement of the detrimental effects of adverse childhood experiences, but also resulted in the development of standardized and validated measures to assess ACEs. Today, the Childhood Trauma Questionnaire is one such questionnaire investigating adverse and traumatic childhood experiences, and has thus far been used in more than 500 studies (Viola et al., 2016).

Several meta-analyses have provided further evidence and confirmed the risk for the development of mental and somatic diseases and behavioral problems as a result of adverse experiences (e.g., Augsburger, Basler, & Maercker, in press; Hughes et al., 2017; Norman et al., 2012). Additionally, a meta-review (summarizing previous reviews) on sexual abuse, demonstrated the devastating impact of sexual abuse on later life, showing an increased risk for a broad range of severe disorders and symptoms (e.g., personality disorders, eating disorders, psychotic symptoms, sexual dysfunction, and also somatic complaints, such as pelvic pain or non-epileptic seizures); as well as impairment in social interactions, and an increased risk for future exposure to sexual violence, but also involvement in aggressive acts (Maniglio, 2009). This last aspect is particularly relevant for the field of pediatric and adolescent psychiatry (Anda et al., 2006; Augsburger, Meyer-Parlapanis, Bambonyé, Elbert, & Crombach, 2015). However, the sequela of ACEs also expand to geronto-psychiatry, evident in an increased risk for cognitive deficits in older age (Burri, Maercker, Krammer, & Simmen-Janevska, 2013).

#### **Modulation of the Biological Stress Response**

As mentioned above, adverse childhood experiences present an unspecific risk factor for increased vulnerability to later (psycho)pathology. They are assumed to have an impact on biological regulatory mechanisms in the human body. More specifically, exposure to ACEs may result in a cascade of neuro-endocrine and immunologic alterations that are associated with changes in the brain (Nemeroff, 2016; Teicher & Samson, 2013, 2016).



These processes refer to disturbed regulation of the human stress reaction, and the hypothalamic-pituitary-adrenal axis (HPA axis). Accordingly, structural changes are likely to occur in stress-sensitive brain regions with a high density of glucocorticoid receptors, to which the stress hormone cortisol binds (Nemeroff, 2016). Most evident is an increase in volume of the Amygdala, as well as a reduction of the Hippocampus, but structural changes in prefrontal regions have also been reported (Nemeroff, 2016; Teicher & Samson, 2016). More recent studies investigating connectivity have demonstrated a strong connection between these brain regions. Accordingly, the inhibition of brain regions, such as the amygdala, that are involved in the processing of fear stimuli, can act in a hyperactive manner. However, different types of adverse experiences can lead to differential effects (see Norman et al., 2012; Teicher & Samson, 2016). Similarly, brain regions are likely to have sensitive phases during a specific age period, in which they are particularly vulnerable to the effect of adverse experiences. In addition, there may be a genderspecific component. For instance, the hippocampus of girls appears to be more stress-resistant than the hippocampus of boys (Teicher & Samson, 2016).

All these aspects can be subsumed under the term "type-and-timing" as they relate to differential effects during specific age periods and for various types of ACEs (Nemeroff, 2016; Teicher & Samson, 2016). These new developments complement the cumulative effects of ACEs with a dose-response relationship that was reported in the initial ACE-studies (Anda et al., 2006). Teicher and Samson (2013) even argue in favor of two biologically distinct groups of patients with mental disorders that can be differentiated based on their specific neuro-biological alterations: those with exposure to ACEs and those without. This assumption has been taken up by other scientists (cf. Nemeroff, 2016) and, if proven valid, would result in huge implications for diagnostic procedures as well as the treatment of disorders.

Whilst findings of altered biological circuits offer a powerful explanation for the longterm impact of ACEs, many studies rely on cross-sectional data, thus compromising causality. However, a limited number of studies also provide evidence from a longitudinal perspective. For instance, Trickett, Noll, Susman, Shenk, and Putnam (2010) investigated long-term HPA axis activity by assessing cortisol levels in two cohorts of young women with or without exposure to sexual violence, who were followed up from a mean age of 11 until the age of 24. In accordance with previous findings, cortisol levels and trajectories between the two cohorts significantly differed. However, the sample size was rather small and potential confounders were not taken into account.

#### **Epigenetic Alterations**

The field of epigenetics investigates the direct impact of the environment on transcription of the human DNA through the process of methylation, without changing the original DNA-sequence (Marinova et al., 2017; Turecki & Meaney, 2016). Due to its involvement in the stress reaction, focus is placed on methylation in glucocorticoid receptor



genes (Nemeroff, 2016). Here, a large number of experimental studies with animals demonstrate increased methylation to be associated with a lack of maternal care (Nemeroff, 2016; Turecki & Meaney, 2016). Regarding humans, similar results have been reported with respect to adverse childhood experiences (Nemeroff, 2016). A systematic review incorporating 27 studies with humans supported the assumption of increased methylation, despite different methodological approaches (Turecki & Meaney, 2016).

Some researchers argue that alterations in methylation are not specifically induced by ACEs, but are rather a general effect associated with a broad range of mental disorders. However, previous research has provided evidence that patients with PTSD and additional exposure to ACEs showed increased rates of methylation compared to PTSD patients without exposure to ACEs (Pape & Binder, 2014). These results are in favor of effects specifically induced by ACEs and support the previously discussed theory of a biologically distinct subtype (cf. Teicher & Samson, 2016).

#### **Outlook on ACEs**

Overall, these findings demonstrate the future potential of research involving biomarkers and epigenetic approaches. Epigenetic processes can also aid in the identification of mechanisms involved in the trans-generational transmission of adverse experiences, as indicated by previous studies (Yehuda et al., 2016). Despite these significant findings, premature conclusions should be avoided: Many relevant studies did not incorporate potential confounding variables, thus weakening causal explanations (Nemeroff, 2016). Furthermore, the majority of studies apply cross-sectional research designs, with retrospective self-reports of ACEs (see Hughes et al., 2017). Regarding type and timing of ACEs, the heterogeneity of assessments (e.g., different scales, frequency versus severity of events) and restricted sample types further limit generalizability.

Additionally, epigenetic research itself suffers from methodological constraints: Different extraction methods (e.g., saliva versus serum), as well as non-standardized procedures for pre-processing, weaken empirical evidence. Moreover, the previously mentioned shortcomings in study designs, such as cross-sectional studies and the failure to include mediators, require a cautious interpretation of causality.

Finally, the implications of these findings for clinical practice remain less clear. Nemeroff (2016) highlights two important aspects: First, can these biological alterations be prevented by psychotherapy or pharmacotherapy, if detected early? And second, it needs to be investigated, if these biological alterations are reversible following interventions. While preliminary studies with animals and also studies with war veterans support this view, evidence is far from conclusive (Nemeroff, 2016).

In sum, the majority of findings are consistent and provide strong evidence for increased later vulnerability towards mental disorders, with relative effects for specific types of events. Further research is required in order to disentangle potential methodological constraints and draw final conclusions.



# Modeling of Culturally-Specific Trauma Concepts

Focusing on European, US-American, and Australian PTSD researchers (the so-called "Global North"), one aspect that is often neglected concerns the cultural background of patients. Thus, it is basically assumed that psychological processes and their social implications work in a universal manner across all cultures. However, both clinical practice and (cross)-cultural clinical research still have to demonstrate if these assumptions are valid (Hinton & Good, 2016; Maercker, Heim, & Kirmayer, 2019). This aspect is particularly relevant, as many patients with PTSD symptoms grow up in cultures other than the "Global North". Examples include individuals from war-affected regions (e.g., Afghanistan, Iraq, Syria), those who have experienced political prosecution (e.g., in the case of the Rohingya communities in Myanmar in 2017), or natural catastrophes (e.g., Banda Aceh tsunami in 2004).

Within the context of the migration and refugee movement affecting Europe in 2015, many countries began to tailor their psychological and psychotherapeutic interventions towards these groups (Silove, Ventevogel, & Rees, 2017). However, there is still too little work on culturally-specific adaptations. This may lead to an over-simplification, which may account for the fact that many interventions developed in Western communities show less efficacy in other samples, as a recent meta-analysis indicated (Thompson, Vidgen, & Roberts, 2018). Consequently, an extension of theoretical models is required, to help explain the development and maintenance of PTSD in a culturally-sensitive manner. Thus far, the existence of these models is rather limited (Bernardi, Engelbrecht, & Jobson, 2018; Hinton, Ojserkis, Jalal, Peou, & Hofmann, 2013; Maercker & Horn, 2013). In our working group, the socio-interpersonal model of PTSD was developed, which explicitly takes cultural aspects into account (Maercker & Hecker, 2016; Maercker & Horn, 2013). More specifically, it works on three levels (cf. Filipp & Aymanns, 2018):

1. The traumatized individual is an *interdependent* self in relation to other human beings. This stands in contrast to the independent self – a traditional differentiation in cultural psychology. It is indisputable that the self is never completely independent from its social relations, but is always interdependent, also in individualized societies from the Global North. This is mainly relevant with respect to exposure to traumatic events and the frequent arising of specific social emotions, such as guilt and shame, but also anger, rage, and thoughts of revenge. All these emotions reflect the interdependency between the self and others. Moreover, the individual's perception and self-labelling of the traumatic event and its sequela (e.g., *"I am traumatized"*, *"I am diagnosed with PTSD"*), relates to the interaction with and comparison to other persons. For example, as a result of this comparison, members



from disadvantaged communities frequently argue that their own personal experiences are not relevant as the whole community is suffering. As a consequence, they do not perceive themselves as individuals seeking help (Rechsteiner, Maercker, & Tol, 2019).

- 2. The maintenance of trauma-related symptoms is embedded in a *dialogical* or *communicative* process. To date, research has mainly focused on procedures of service utilization in order to identify person-related internal and external barriers. Here, a shift is needed towards the exploration of possibilities for individuals to self-disclose their traumatic experiences, as well as the investigation of reactions from other persons towards this disclosure (Pielmaier & Maercker, 2011). As speechlessness and the inability to verbalize what happened is a significant facet of trauma-related disorders, this dialogue between individuals is essential. The tremendous value of relationships between two people or within a community is therefore reflected by the opportunity for individuals with similar experiences can additionally provide non-verbal support, resulting in feelings of emotional connection. These aspects fit well with the rationale of Narrative Exposure Therapy, which has been successfully applied in diverse international settings (cf., Schauer, Neuner, & Elbert, 2011).
- 3. From a broader perspective, the societal and cultural context play a significant role in relation to the impact of traumatic experiences. Here the model becomes a sociocultural one, referring to cultural value orientation and religious or traditional cultural beliefs. For instance, cross-cultural studies indicate an association between traditional norms in the society (e.g., conformity, obedience, or benevolence) and increased rates of PTSD after exposure to interpersonal violence (Maercker et al., 2009). This leads to the essential question, with great relevance for the respective health care system, if the status of a victim or survivor is ascribed to these affected individuals in their respective society. A refusal of this societal acknowledgement of the survivor status can result in feelings of being left alone, and may lead to increased helplessness, embitterment, and fatalism. This may also contribute to a cycle of ongoing violence in fragile regions, perpetuated by inter-generational transmission (Elbert, Rockstroh, Kolassa, Schauer, & Neuner, 2006). Inevitably, these contextual factors require a culturally-sensitive or even culturally-adapted treatment approach for patients from the "Global South" (previously termed "non-Western countries") (Dickerson et al., 2018; Von Lersner & Kizilhan, 2017; Whealin et al.,



2017). This cultural adaptation is visible when certain parameters are considered, such as setting, delivery mode, translation, treatment goals, local conceptualizations of disorders, the use of metaphors, and particularities of relationships (Bernal & Sáez-Santiago, 2006). Currently, there are limited studies that consider the treatment of PTSD or complex PTSD, whilst also taking these aspects into account. However, a recent meta-analysis was published concerning E-mental health of common mental disorders and the so-called scalable psychosocial interventions. It demonstrates that treatment efficacy is linearly and positively associated with the number of culturally-adapted parameters (Harper Shehadeh, Heim, Chowdhary, Maercker, & Albanese, 2016). Nevertheless, further research is needed, for instance, concerning culturally appropriate metaphors of adverse events (Meili, Heim, & Maercker, 2018).

Following this socio-interpersonal model of PTSD, trauma-focused interventions also need to incorporate interventions on a group or community level (Maercker & Hecker, 2016). This corresponds to the WHO's demand for new theoretically derived, empirically verifiable interventions for the international arena (Tol et al., 2011).

# **Public Discussions**

Nowadays, the field of psychotraumatology is not only limited to clinical psychology and psychiatry, but extends to the overall society: It is discussed among legal experts, historians, anthropologists, politicians, the media, cultural scientists, as well as artists. In the public media, traumatic experiences and its sequela are present on a level similar to depression and substance abuse. In this section, public aspects of psychotraumatology will be discussed (cf. Maercker, 2017, p. 70 et seq.).

### Acknowledgement and Compensation of Survivors

The general public has started to acknowledge the immense damage that traumatic experiences can cause to individuals' mental and physical health. This is an important step in order to remedy past failures, for instance, with respect to institutional abuse. In Germany, Austria, and Switzerland, round table discussions were initiated and commissioners were implemented for specific topics, in order to collectively process these dark chapters of the past. An example in Germany is the round table *Sexual child abuse in dependent relationships and power relations in private and public institutions and in the family*, and the round table *Residential care in the 50s and 60s*. In Austria, the position of an *Independent Commissioner for Victims of the Catholic Church* was implemented in 2010. Finally, in Switzerland, there is the *Independent Commission of Experts on Institutional Care* at the Swiss Federal Parliament. The work of these institutions is based on state-of-the-art sci-



entific findings, which also incorporates the recent findings concerning the impact of ACEs. For instance, an investigation at the University of Ulm in Germany assessed the current health status of victims of sexual abuse, who were involved in the round table *Sexual Child Abuse*. They reported a high rate of mental disorders, with 40% depressive disorders, 19% PTSD, and 18% anxiety disorders (Spröber et al., 2014).

As previously described, it is a political and societal necessity to acknowledge the suffering of survivor groups that have been previously neglected. However, it is not appropriate to exclusively focus on the high incidence of trauma-related disorders in these groups. It is similarly important to investigate and emphasize results related to resilience, that is, reasons for overcoming traumatic stress. Increased public awareness is needed for this second aspect. Certainly, this must not imply that financial compensation is only accessible for survivors suffering from their traumatic experiences, but must be offered to all survivors. Thus, discussions about the criteria that need to be fulfilled in order to gain access to compensation need to continue (Maercker & Augsburger, 2017).

#### **Continuous Stress and Historical Aspects of Traumatic Experiences**

In the process of re-formulating the ICD-11 grouping of disorders specifically associated with stress, a new diagnostic category was discussed: continuous trauma disorder. In many countries and regions, there is no clear onset and end of a traumatic event, but rather a constant and ongoing threat for human life (e.g. Somasundaram, 2014). Accordingly, the term "post-traumatic" is not feasible for these regions and the diagnosis of PTSD does not apply, if taken literally. From a biological viewpoint, in these circumstances the body is in a state of constant high physiological alertness in order to survive – resulting in impaired body function and significant distress. Currently, best-practice suggestions are available for dealing with these aspects (World Health Organization, 2016). However, in the relevant ICD-11 working group, the incorporation of an entirely new diagnostic concept was rejected, and was instead referred to the areas of emergency psychology and medicine.

Related to this is the term "historical trauma", which describes the experiences of systematic violent discrimination, persecution, and extermination of ethnic or religious groups. It is often called "historical" if public acknowledgment is not provided and if an "atonement" is not yet sufficient (Kirmayer, Gone, & Moses, 2014). Examples include collective traumatic experiences of the First Nations and African-Americans in the US, or the Holocaust in Europe. More recently, the term has also been used to describe nonman-made mass catastrophes, such as the tsunami in 2004, or the 2011 Fukushima nuclear disaster in Japan. Some researchers suggest that collective perceptions and pathological alterations in thoughts and behavior emerge following these events, which can be differentiated from symptoms associated with PTSD or similar diagnoses. For instance, Somasundaram (2014) reported the following changes, among others, in response to



these experiences: general mistrust, suspicion, brutalization, a drop in morals and values, passivity, and negativism.

#### **Processing of Trauma in Other Public Areas**

Perceptions and explanations related to traumatic stress also expand beyond the previously discussed aspects and permeate into several other public areas. This is not only reflected by topics such as cultures of memory, and the occurrence of several Truth and Reconciliation Commissions following political violence; but also, art exhibitions featuring artists that try to process and integrate their biographical experiences and wounds into their artistic work. Examples for the latter include the internationally renowned conceptual artists Joseph Beuys or Marina Abramović (see Maercker, 2017). Not surprisingly, within these settings, the conceptualizations of traumatic stress and psychotraumatology can differ from a scientific point of view. Also, in this area, recent developments may not be sustainable. Nevertheless, they have the potential to aid and support individuals in overcoming their personal experiences.

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Research Article



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# Evidence of a Media-Induced Nocebo Response Following a Nationwide Antidepressant Drug Switch

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# Abstract

**Background:** In 2017, patients on a generic or branded antidepressant venlafaxine were switched to a new generic formulation (Enlafax). In February and April 2018, two major NZ media outlets ran stories about the new generic being less effective and causing specific side effects. This study aimed to examine the effect of the media coverage on drug side effects reported to the national Centre for Adverse Reactions Monitoring (CARM) and whether the specific symptoms reported in the media increased compared to side effects not reported in the media.

**Method:** We analysed monthly adverse reaction reports for Enlafax to CARM from October 2017 to June 2018 and compared adverse reports, complaints of decreased therapeutic effect and specific symptom reports before and after the media coverage using an interrupted time series analysis.

**Results:** We found the number of side effects and complaints of reduced therapeutic effect increased significantly following the media stories (interruption effect = 41.83, 95% CI [25.25, 58.41], p = .003; interruption effect = 15.49, 95% CI [7.01, 23.98], p = .012, respectively). The specific side effects mentioned in the media coverage, including suicidal thoughts, also increased significantly compared to other side effects not mentioned in the media.

**Conclusions:** In the context of a drug switch, media reports of side effects appear to cause a strong nocebo response by increasing both the overall rate of side effect reporting and an increase in the specific side effects mentioned in the media coverage, including reduced drug efficacy and heightened suicidal thoughts.

# Keywords

media, nocebo effect, venlafaxine, side effects, generic medicines



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# Highlights

- The study provides further evidence that media coverage of side effects can induce a nocebo effect.
- This is the first study to look at media coverage of an antidepressant brand switch.
- The increase in reported adverse events was higher for those symptoms mentioned in the media reports.

Switches from branded to generic medicine formulations have become more frequent in recent times as health funders seek to reduce costs. These switches to generic medical and psychotropic medications have from time to time caused an increase in reported adverse events (Desmarais, Beauclair, & Margolese, 2011; Leclerc et al., 2017), and this is likely to be due to negative attitudes towards generic medicines rather than pharmacological differences between the branded and generic versions of the medication (Colgan et al., 2015).

This phenomenon is known as the nocebo effect and research using inert medicines has shown that people report a reduced therapeutic effect and more side effects from a generic-labelled placebo compared to a branded placebo (Faasse, Martin, Grey, Gamble, & Petrie, 2016). Similarly, the process of switching from one placebo tablet to another is associated with reports of side effects and reduced drug efficacy (Faasse, Cundy, Gamble, & Petrie, 2013). The nocebo effect can also occur in active medications and there is recent evidence that media coverage about drug side effects can create a nocebo response by highlighting negative reactions to a particular medication and prompting an increase in symptom complaints and drug discontinuation (Faasse & Petrie, 2013).

In 2017, 45,000 New Zealand patients prescribed the antidepressant venlafaxine were switched to a new funded generic (Enlafax XR) from either the branded originator or a different generic version. In February 2018, two major print and online media outlets in New Zealand ran stories on patients' complaints that the new generic was less effective and causing an increase in various symptoms, including heightened suicidal thoughts. A few months later, another media report was released, again discussing patients' reports of ineffectiveness and side effects from Enlafax. Based on previous research, we tested two hypotheses: firstly, that media coverage of the complaints following the venlafaxine switch would be associated with an increase in adverse drug reactions reported to the New Zealand Centre for Adverse Reactions Monitoring (CARM); and secondly, that the specific side effects reported in the media would increase compared to other side effects not reported in the coverage.



# Method

#### **Newspaper Articles**

On February 28 2018, two leading New Zealand media outlets, The New Zealand Herald (NZME) and Stuff (Fairfax Media), published newspaper and online articles on the venlafaxine brand switch. The New Zealand Herald ran a story titled "Patients say generic Pharmac-funded version of antidepressant venlafaxine left them depressed, anxious" (Henry, 2018), while Stuff's article was titled "Anti-depressant swap: Sufferers claim generic drug is harming their condition" (Maude, 2018). These articles described the personal experience of two patients when they switched from their original brand Efexor to Enlafax. The reports stated that the new, cheaper generic version was not as efficacious in managing the patients' depression and they were also experiencing side effects. The New Zealand Herald article specifically mentioned that patients were reporting suicidal thoughts, nausea, fatigue, headaches and anxiety.

In April, Stuff released another online article, which continued on the subject of the previous media coverage. This media report, "Fight over Pharmac's switch to generic anti-depressant brand continues" (Steele, 2018), again stated that the new generic was not as effective and noted that various adverse events had been reported - specifically headaches, anxiety and suicidal thoughts. Of the two websites, Stuff is the most viewed with approximately 161,600 unique views per day, while The New Zealand Herald has 94,800 views (https://www.siteprice.org). Neither of these stories suggested patients report side effects to their doctor or to CARM.

#### Adverse Drug Reactions

A report of all adverse reactions to venlafaxine was obtained from CARM through Medsafe, New Zealand's medicines monitoring agency. The CARM database collects adverse reactions to medicines and vaccines, the majority of which are submitted by healthcare professionals. Reporting is usually made online and CARM reporting forms can be accessed on the website https://nzphvc.otago.ac.nz. Reports were obtained from October 2017 to July 2018 and included the month the report was received, the patients' age and gender, and up to five symptoms attributed to the medicine. As the data was anonymous and publicly available, the study did not require ethical approval.

#### Measures

The number of reports of decreased therapeutic response was calculated for each month. Decreased therapeutic response is an adverse reaction category on the CARM database equivalent to a reduced efficacy of the medicine.



The total number of side effects reported each month was also calculated as was the number of times the five specific side effects mentioned in the New Zealand Herald article were reported. The side effects were matched to the corresponding adverse reactions in the CARM database with headaches, nausea and anxiety being matched exactly. Two of the media-mentioned side effects were considered broad enough to cover a range of CARM adverse reactions. As such, reports of fatigue, lethargy and tiredness were grouped under the broader side effect of fatigue, while suicidal thoughts were matched with reports of suicidal tendencies, suicidal ideation and impulses to self-harm. The five most common adverse reactions not mentioned in the media reports were identified from the CARM database and used as control symptoms. These were dizziness, drug withdrawal syndrome, irritability, sleep disturbance and a fuzzy head.

#### **Statistical Analyses**

Interrupted time series analyses were conducted to investigate whether the February and April media reports on the venlafaxine brand switch were associated with an increase in the CARM reporting of decreased therapeutic response, total number of side effects and the specifically mentioned side effects in the months directly after the media reports compared to the five months before. An autoregressive integrated moving average (ARI-MA) model with an autoregression term of 1 and moving average term of 1 was used for all analyses. As the three media reports were a one-off interruption to the normal time series, a binary independent variable was created to indicate their presence by month. March and May were given the value of 1 as these were the periods directly after the February and April media reports and all other months were coded 0. The analysis produces an estimated interruption effect, which is the change in the rate of adverse event reporting from the months coded 0 and 1, and indicates whether this change is significantly different. This is a more conservative analysis as the adverse event reports in March and May are averaged together to calculate the general effect of the three media stories rather than both months being compared separately to the pre-media rate. Analyses were conducted in SAS (v9.4 SAS Institute Inc., Cary, NC) using the SAS PROC ARIMA procedure. An alpha level of .05 was considered significant.

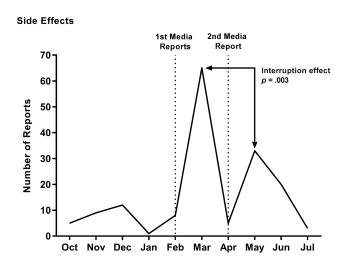
### Results

In total, there were 100 adverse event reports from October 2017 to July 2018. The average age of reporters was 43.7 years old and 70.0% were female. In the five months prior to the first newspaper articles, the average number of adverse event reports to CARM was 6.00 (SD = 1.23) per month. In March and May, the two months directly after the release of the articles, the average number of CARM reports significantly increased to 25.50

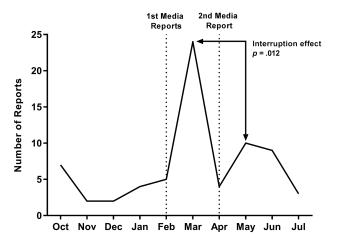


(SD = 12.02; interruption effect i.e. difference between the pre-media average and March + May average = 19.45, 95% confidence interval (CI) [10.77, 28.13], p = .005).

The newspaper articles also had a significant effect on side effect reporting with the pre-media average of 7.00 reports (SD = 4.18) a month increasing to 49.00 (SD = 26.63) in March and May, see Figure 1. Similarly, the rate of decreased therapeutic response reporting significantly increased from 4.00 (SD = 2.12) during the previous months to an average of 17.00 (SD = 9.90) over March and May. The interruption effect of the media on side effect reporting = 41.83, 95% CI [25.25, 58.41], p = .003. Interruption effect for decreased therapeutic response reports = 15.49, 95% CI [7.01, 23.98], p = .012.



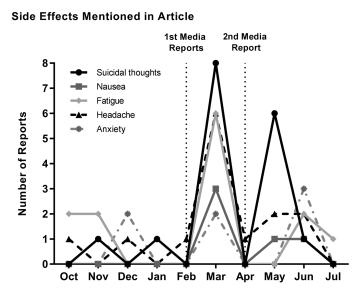
**Decreased Therapeutic Response** 



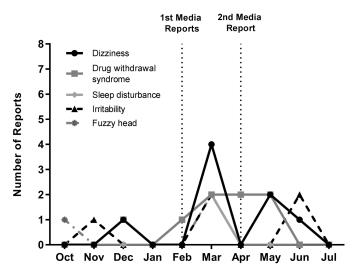
*Figure 1.* Number of reports of side effects and decreased therapeutic response before and after the media reports.



A further analysis investigated whether the reports to CARM of the specific side effects mentioned in the February New Zealand Herald article increased in March and May compared to the five previous months. Figure 2 shows the rate of reporting for the media-mentioned side effects and Table 1 shows the interruption effects and corresponding p values.



Side Effects Not Mentioned in Article



*Figure 2.* Numbers before and after media reports for the specific side effects reported in the media and control symptoms not in media reports.



Table 1

Variable	Interruption effect	95% CI	p
Side effects mentioned in article			
Suicidal thoughts	6.64	[4.60, 8.68]	< .001
Nausea	1.95	[0.62, 3.28]	.029
Fatigue	1.63	[-1.45, 4.71]	.339
Headache	3.62	[1.05, 6.19]	.034
Anxiety	0.39	[-2.34, 3.11]	.791
Side effects not mentioned in article			
Dizziness	2.70	[1.72, 4.60]	.002
Drug withdrawal syndrome	2.96	[0.53, 5.39]	.055
Sleep disturbance	0.75	[0.20, 1.30]	.036
Irritability	0.50	[-0.91, 1.91]	.507
Fuzzy head	0.88	[-0.30, 2.06]	.190

Estimated Interruption Effects of the Newspaper Articles on CARM Reports for Specifically Mentioned Side Effects and Control Side Effects

Prior to the media coverage, suicidal thoughts were reported an average of 0.40 times (SD = 0.55) per month but following the media report this significantly increased to 7.00 (SD = 1.41) across March and May. There were no adverse event reports of nausea before the media coverage, but reporting significantly increased to 2.00 (SD = 1.41) during the post-media months. The average rate of reporting per month of headache was 0.60 (SD = 0.55) before the media focus, which significantly increased to 4.00 (SD = 2.83) reports in March and May. Fatigue was reported 0.80 times (SD = 1.10) over the five pre-media months but this did not change significantly after the media coverage (M = 4.00, SD = 4.24). Similarly, the reporting of anxiety did not change, going from an average of 0.40 (SD = 0.89) before the media coverage to 1.00 (SD = 1.41) after the focus.

The side effects most frequently reported to CARM that were not mentioned in the newspaper article were investigated to determine the effect on other adverse events. Dizziness, sleep disturbance, irritability and fuzzy head were all reported an average of 0.20 times (SD = 0.45) per month before the media focus. Following the coverage, there was a significant increase in the reporting of dizziness (M = 3.00, SD = 1.41) and sleep disturbance (M = 1.00, SD = 1.41). There was no change in the post-media rate of reporting for irritability and fuzzy head (both M = 1.00, SD = 1.41). Before the media articles, drug withdrawal syndrome was reported an average of 0.40 times (SD = 0.55) a month, which did not change after the media coverage (M = 2.00, SD = 0).



# Discussion

### Main Findings

This study found that reports by the two largest New Zealand media outlets highlighting the side effects and lack of efficacy of a new generic antidepressant were followed by a significant increase in reports to CARM of similar side effects. The increase in reported adverse events was largely limited to those mentioned in the media reports. While two of the control symptoms, dizziness and sleep disturbance, did also increase, this was at a lower rate than the symptoms mentioned in the media stories. The results are consistent with a nocebo response driven by the media coverage, whereby patients' expectations of particular side effects result in an increase in those specific symptoms. A pharmacological explanation for this effect is very unlikely as the side effects highlighted in the media stories and the control side effects were mentioned at a similar rate *prior* to the media coverage. Following the media coverage, it was those symptoms mentioned in the media stories that were mostly affected.

A particular concern in the findings is the mirroring of reports of decreased therapeutic efficacy, which could potentially drive non-persistence with antidepressant therapy. Also of public health relevance is the increase in reports of suicidal ideation which is likely due to the highlighting of suicidal thoughts and behaviour by patients discussed in the media stories in February and again in April.

### **Comparison With Other Studies**

Previous studies have shown that information about likely side effects from medication can result in a significant increase in reports of those specific effects. Patients who were told about sexual side effects when starting finasteride or beta-blocker medication were significantly more likely to report these symptoms than patients who were not told of these side effects (Cocco, 2009; Mondaini et al., 2007). Similarly, in the context of a clinical trial, those patients warned of gastrointestinal side effects in one research site were more likely to complain of this as a side effect and withdraw from the study due to these complaints (Myers, Cairns, & Singer, 1987).

Seeing another person in a media story report side effects from a medication can also increase the expectations of a similar response (Faasse & Petrie, 2016). In an earlier study by our group, media reporting on a change in the formulation and appearance of thyroxine replacement therapy that led to a dramatic increase in adverse reaction reports (Faasse, Cundy, & Petrie, 2009), found side effect complaints increased significantly after television news stories. The largest increases concerned symptoms mentioned in the media reports. This was strongest for the initial coverage and weakened with successive stories (Faasse, Gamble, Cundy, & Petrie, 2012). This occurred in the current study, as the May adverse event reporting was not as large as in March. Research on side effects from



electromagnetic fields has also shown that alarmist media reports, which emphasise adverse effects, exacerbate the nocebo effect and lead to greater symptom reporting and a perceived sensitivity to the supposedly harmful substance (Verrender, Loughran, Dalecki, Freudenstein, & Croft, 2018; Witthöft & Rubin, 2013).

Switches to generic medicine provide potential for a nocebo response to be strongly influenced by negative media coverage as non-adherence, patient reports of decreased efficacy and increased side effects are more common following switches (Boone et al., 2018; Weissenfeld, Stock, Lüngen, & Gerber, 2010). A nocebo response induced through media reports can have a detrimental effect. Recent work has shown that negative stories in the media about statins have led to an increase in the rate of patients discontinuing statins in the United Kingdom (Matthews et al., 2016) and this early discontinuation has been linked to an increase in myocardial infarction and death from cardiovascular disease in Denmark (Nielsen & Nordestgaard, 2016).

The likely mechanisms of the nocebo response found in this study are social transmission and the misattribution of common symptoms to the effects of the new medication (Petrie & Rief, 2019). Previous research has found that seeing another person report side effects after receiving a treatment increases the likelihood of side effects' complaints after receiving the same treatment, especially if the observer can empathise with the person reporting the side effects (Faasse, Parkes, Kearney, & Petrie, 2018). Studies have also found that individuals with higher levels of psychological distress also report a greater number of physical symptoms (Watson & Pennebaker, 1989). This is likely to be of more relevance in this group of patients taking an antidepressant and thus allowing more symptoms to be misattributed to the effects of the new generic medicine. While generic switches are now commonplace in New Zealand, a recent general population survey found 38% still preferred taking branded medication compared to a generic or no preference (Kleinstäuber, MacKrill, & Petrie, 2018). Following a switch to a generic medicine more side effects are reported by patients who are older, female and by those who have been on their previous branded medicine longer (MacKrill & Petrie, 2018).

### Strengths and Limitations

While this study drew on adverse reports to a national database, it is likely that the rates are a substantively low estimate of the true effect of the nocebo effect caused by the media coverage. Studies estimate that reports to a national adverse database represent less than 10% of detected adverse drug reactions (McGettigan, Golden, Conroy, Arthur, & Feely, 1997; Smith et al., 1996). It is further likely that many patients would not have sought medical assistance for symptoms due to the perception that there was little that could be done by their GP.

The study is limited by the non-experimental design and restricted in outcomes to the specific side effect categories recorded by CARM. As such, it is possible that patients may have experienced other side effects that the CARM database does not measure. Although



patients can make direct reports using online forms this makes up only a small percentage of CARM reports. The behavioural outcomes of the adverse event reporting are also unknown. It is not known whether there was an increase in suicidal behaviour following the stories or whether patients stopped venlafaxine or changed to another medication.

In conclusion, we found media coverage of reports of a lack of efficacy and side effects following a switch to a generic version of venlafaxine were likely responsible for an increase in similar reports to a national centre for adverse drug reactions. Of particular concern is how media reports of increases in suicidal thoughts and loss of drug efficacy following a drug switch can be readily converted in similar complaints across the wider community. More research is also required on how such media reports are associated with increases in non-adherence and non-persistence with medication, as well as possible increases in suicidal behaviour. Future work may also be needed to develop guidelines for media reporting on generic switches with a view to avoiding these adverse outcomes.

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Politics and Education



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# **The Heterogeneity of National Regulations in Clinical Psychology and Psychological Treatment in Europe** Where Are We Coming From, Where Are We Now, and Where Are We Going?

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# Abstract

**Background:** The Bologna Process was initiated to harmonize study processes and contents throughout Europe in order to facilitate communication and cross-border study exchange. However, when it comes to postgraduate education and practical work in clinical psychology, no such harmonization exists - there is still significant heterogeneity between European countries.

**Method:** To initiate the section Politics and Education, we analysed the current situation in Europe with regard to national regulations on education, training and practice in clinical psychology and psychological treatment and give a brief summary on the status quo.

**Results:** There are extensive differences across Europe regarding governmental and national regulations for psychologists in general, and clinical psychologists in particular. Whereas some countries have very detailed regulations including a description of reserved activities for clinical psychologists, others leave the profession widely unregulated. When it comes to psychological treatment, some countries define it as an independent activity allowed to be applied by different professions, others clearly restrict access to the profession of psychotherapists.

**Conclusion:** A great diversity in national regulations and practical issues related to clinical psychology and psychological treatment exists across Europe. Our results underline the importance of the Politics and Education section in the journal Clinical Psychology in Europe in order to strengthen the development of an international perspective on clinical psychology.



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## Keywords

Clinical Psychology, psychological treatment, education, national regulations, Europe

## Highlights

- National regulations for clinical psychologists differ significantly between European countries.
- Structure and contents of postgraduate training in clinical psychology vary widely across Europe.
- In some countries, treatment is reserved to psychologists, in others it's open for further professions.
- The Politics and Education section shall foster understanding, communication and cooperation.

The section "Politics and Education" has been included in *Clinical Psychology in Europe* (CPE) to inform our readers about national regulations for training and practice in clinical psychology and psychological treatment. To describe the current political and educational situation of clinical psychology in Europe, the Bologna Process is an important starting point: As an intergovernmental cooperation of 48 European countries, the Bologna Process aims to improve the internationalization of higher education throughout Europe. Its aim is to not only harmonize study processes and, in part, study contents across Europe, but also to facilitate an easier comparison of qualifications in order to facilitate exchange and cross-cultural communication. However, postgraduate education and practical work in various health professions have been unaffected by the Bologna Process (Baeten, 2017). This is of particular importance for clinical psychology, which is still a rather young and emerging profession. Currently, legal regulations for clinical psychologists (e.g. requirements for the admission to postgraduate training, structure and contents of postgraduate training, or prerequisites for work permission as a health care provider in a clinical practice) vary substantially throughout Europe (European Commission [EC], 2016; Hokkanen et al., 2019). Accordingly, clinical psychology in Europe is characterized by diversification rather than by convergence and agreement. Even neighboring countries, such as the Nordic countries or German-speaking ones, which in some cases cooperate very closely at university level, differ significantly in postgraduate education and their respective professional status (EC, 2016; Karayianni, 2018; Kryspin-Exner, Kothgassner, & Felnhofer, 2017). Further substantial differences can be found in the relationship and differentiation between clinical psychology and psychological treatment (Van Broeck & Lietaer, 2008).

Although the pan-European heterogeneity in clinical psychology is obvious, details about conditions in various countries are not well known. This applies both to countries and their bilateral communication, but also for multinational initiatives or the superordi-



nate administration (e.g. the European Union, EU) (EC, 2016). Even professionals are often unaware of the regulations in their respective countries, not to mention the differences between countries. As a European journal of clinical psychology, it is an essential goal of CPE to shed light on this important issue.

The following article introduces this section of the journal and starts with an overview of different structures of governmental regulations for clinical psychology in Europe. In addition, we specify the tasks and objectives of this section and goals for possible contributions. We aim not only to provide information on differences between countries, but also to present strengths and limitations of various national regulations, and to provide examples that could be helpful for countries who are currently in the process of establishing national regulations for clinical psychology. Finally, knowledge about the heterogeneity of national regulations in clinical psychology is also essential for investigators of European projects including psychological treatments.

# Starting Points: Clinical Psychology in Academia and Clinical Practice

Clinical psychology has different roots and traditions in Europe (Routh, 2014). Whereas more psychodynamically oriented approaches have been developed in Central Europe and influenced the German-speaking and Romano-phone countries, the empirically oriented Anglo-American tradition has had a substantial impact on the current state of clinical psychology in Europe (Routh, 2014). Although the understanding of clinical psychology as an empirical science with a strong neuro-scientific component has prevailed in academia in almost all European countries, the transfer of this conception into clinical practice varies widely (Cheshire & Pilgrim, 2004; Plante, 2011). However, basic psychological and neuroscientific theories and empirical findings should be applied with the goal of improving the understanding as well as the classification, prevention and treatment of mental disorders and relevant psychological aspects of medical conditions. Instead, applied clinical psychology has been strongly influenced by the strong identification of psychologists, associations, and sometimes even societies with a specific approach to psychotherapy (e.g. psychodynamic, cognitive-behavioral, humanistic, or systemic approaches; Plante, 2011). It should be noted that this runs contrary to the primary goal of an academic profession: Practical work should not be based on selected belief systems, but on scientific evidence relevant to its field, along with clinical expertise.

# **Governmental Regulations for Psychologists**

According to the EU, more than 6,000 professions are subject to state or supranational (EU) regulations, 42% of which are in the health and social care sector (Baeten, 2017). The



professions of psychology and clinical psychology are, in most European countries, regulated by the relevant Member State, but are not subject to supranational EU regulations (EC, 2016). This adds to the understanding of the diversity of clinical psychology throughout Europe. Europe-wide analyses of the professional state of psychology and clinical psychology in the 28 EU- and four of the non-EU states (i.e. Iceland, Liechtenstein, Norway and Switzerland) revealed the following picture (EC, 2016; Hokkanen et al., 2019): Only five states (15.6%) had no legal or state regulation of any kind for psychology in general or health care in particular (EC, 2016, pp. 8ff.). Hokkanen et al. (2019) analyzed a slightly different sample and found state regulations in 25 out of 29 examined countries (86%). Countries without any general psychology regulations are Bulgaria, Germany, and the three Baltic states, with Germany having regulations for psychological psychotherapists and child/adolescent psychotherapists, and Bulgaria stipulating minimal educational requirements for working as a psychologist in health care facilities. In 17 of the above mentioned 32 countries, there are regulations for the profession "psychologists" in general, some of which also include clinical-psychological activities. Twelve states have specific regulations for "clinical psychologists" and nine for "psychologists in health care" (health psychology). In 11 of these countries, there are separate regulations for other specialized psychologists and activities in various fields, for example forensic, counseling, school, traffic, occupational, or neuropsychologists (for further details see EC, 2016). In addition, some states have specific regulations for the treatment of children and adolescents (e.g. Czech Republic, Hungary, Lithuania and the United Kingdom [UK]). This brief overview clearly demonstrates how diversely the profession is regulated throughout Europe.

# Specific Regulations for Clinical Psychologists

As reported above, 12 European countries have specific regulations for clinical psychologists, including Austria, Cyprus, the Czech Republic, Hungary, Iceland, Ireland, Malta, the Netherlands, Slovakia, Slovenia, Spain, and the UK (EC, 2016). Still, clinical psychologists are trained very differently; they have a differing range of reserved activities and work in diverse areas (e.g. public health care services vs. private sector). In some countries, clinical psychology is narrowly defined as a singular profession (e.g. Austria, Hungary and Czech Republic) whereas in others it is conceptualized as a clinically focused specialization of health psychology (e.g. Malta, Netherlands, Spain and the UK). In general, there is no consistent distinction between health psychology and clinical psychology: In some states, both professions are separated by their range of activities (e.g. prevention and health promotion vs. treatment and rehabilitation in Cyprus or the UK), in others by the severity of the mental disorder (e.g. health psychology for mild cases, and clinical psychology for severe cases in the Czech Republic or the Netherlands). Similarly, there are differing understandings of clinical psychology, clinical psychological treatment, and



psychotherapy: In some countries, psychotherapy is a sub-specialization of clinical-psychology and thereby reserved for clinical psychologists (e.g. Slovakia, Hungary), in others, psychotherapy is a distinct profession with separate regulations and may also be open to holders of qualifications from related fields (e.g. medicine or pedagogy). As mentioned above, in some states clinical psychology is affiliated to other specialties, e.g. forensic psychology (Malta, Cyprus and the UK), neuropsychology (Netherlands and Hungary), or counseling psychology (Ireland, Malta, Slovakia, Czech Republic, UK and Cyprus) (see EC, 2016) which implies a specific appearance of clinical psychological work in these countries.

Differences across Europe are also evidenced by whether the title "Clinical Psychologist" is protected by a specific (psychology) law, or if the profession and its activities are only generally mentioned in another law, e.g. a health law. The former is the case in about 50% of European countries (Hokkanen et al., 2019), the latter in about one third (e.g. Denmark, Ireland and Spain). In some countries, both a title protection and a reference in specific health acts can be found (e.g. Iceland and Lithuania). Further differences pertain to the reservation of activities for clinical psychologists: According to the EC overview (EC, 2016, p. 19 ff.), two states have pure title protection without any reserved activities (Netherlands and the UK), three others have reserved activities without title protection (Ireland, Slovakia and Cyprus), and seven have both (Iceland, Malta, Austria, Slovenia, Spain, Czech Republic and Hungary).

And finally, the core competencies of clinical psychologists in Europe are defined to a differing degree. Competencies include in most European countries clinical-psychological diagnostics and assessment and psychological treatment. Additionally, clinical psychologists in various countries are enabled to carry out activities such as counseling, crisis intervention, education and training, as well as research and evaluation. In some countries these competencies are very clearly defined (e.g. Austria), in many others they are vaguely specified and are difficult to separate from activities of other professions in the health care system (EC, 2016).

### **Education and Training in Clinical Psychology**

The situation of education and training for clinical psychologists is an important topic for the profession, and also for this journal. And again, there are tremendous differences between various European states regarding the structure, extent, and contents of training. In the majority of European countries, training in clinical psychology requires university studies (Bachelor and Master) followed by postgraduate training. Only in a few countries is training in clinical psychology already included during graduate studies (e.g. Norway). Postgraduate training varies between two to 12 years (EC, 2016) and contains a broad range of subjects, e.g. training in diagnostics and (clinical) psychological testing, training in counseling, specific treatment methods and crisis intervention as well as



training in research methods and evaluation. In most curricula, specific obligatory courses are integrated into internships or trainee programs and are accompanied by continuous supervision. Moreover, in some countries the training is accompanied by personal and professional self-reflection (e.g. Austria), and is completed by a state examination (e.g. Austria or Spain) (EC, 2016). The most comprehensive training in clinical psychology can be found in the Czech Republic, Hungary, the Netherlands, Slovenia, and Spain (EC, 2016), where it is usually based on training in health psychology. Austria has the shortest training - of between 1.5 and 2 years.

# Differentiation Between Clinical Psychology and Psychological Treatment

Significant differences between the European countries can also be found in the relationship between clinical psychology and psychological treatment (BPtK, 2011; EC, 2016; Van Broeck & Lietaer, 2008). Of the 28 EU states, 13 separately regulate the profession of psychotherapists via governmental law (Austria, Belgium, Finland, France, Germany, Hungary, Italy, Lithuania, Luxembourg, the Netherlands, Romania, Slovakia and Sweden), a further three states regulate psychotherapists in a health-related law (Croatia, Latvia and Malta), and Bulgaria regulates the educational requirements for psychotherapists (Master's degree in psychology). Ireland and Cyprus are planning to issue laws for psychological treatment and two non-EU countries (Liechtenstein and Switzerland) already have them. However, the regulations of the different countries are very heterogeneous and differ significantly regarding their understanding of psychological treatment in general, criteria for theoretical and practical training, as well as the number of approved methods (Van Broeck & Lietaer, 2008).

In Austria, Finland and Sweden, psychotherapy is defined as an independent occupation that can be learnt and practiced by different professions (almost 40 in Austria, eight to ten in Finland and Sweden). In most other countries, access to the profession of psychotherapists is restricted, mostly to psychologists and physicians/psychiatrists (e.g. France, Italy, Liechtenstein, Switzerland, Slovakia and Hungary). In Belgium, Germany and the Netherlands, pedagogues (general, clinical, or social pedagogues for children and adolescents) are additionally admitted to practice psychological treatment. Accordingly, in most European countries, non-medical psychological treatment is reserved to psychologists; in Hungary, psychotherapy is a reserved activity for clinical psychologists, an approach which is also planned in Ireland (EC, 2016).

In most countries, only the titles "psychotherapy" and "psychotherapist" are protected, but not the activity itself. Hence psychological treatment can also be carried out by other professions (e.g. physicians, clinical psychologists, and clinical pedagogues) in the context of their respective professional activities, although it is not permitted to be called



"psychotherapy". In some countries, further specific activities (e.g. family therapy) are reserved for psychotherapists, (e.g. Germany, Hungary, Italy, Slovakia, and Switzerland).

There is also a great difference in the number of psychotherapeutic methods approved for training and practice. The numbers vary between four (Finland) and 23 (Austria), with five to seven approved methods in the majority of countries. The generally accepted methods are cognitive behavioral therapy (incl. 3rd wave methods), psychoanalysis, psychodynamically-oriented approaches (e.g. Analytic Psychotherapy following C.G. Jung, or Individual Psychology according to A. Adler), client centered psychotherapy according to Rogers, systemic (family) therapy, Gestalt therapy following Perls, existential psychotherapies (e.g. according to Frankl). Occasionally, hypnosis, integrative, or feminist therapies are also accepted (BPtK, 2011).

### **Conclusion and Consequences**

In conclusion, we find a great diversity in regulations of clinical and health-related psychology and psychological treatment as well as in the relation of clinical psychology and psychological treatment on all levels of analysis. Psychological treatment is, in a few countries, reserved exclusively for clinical psychologists, whereas in others it can also be applied by other psychologists and/or other professions. In most cases, however, clinical psychology and psychological treatment are two independent professional fields. In Germany, for example, clinical psychology represents an academic-scientific subject and (psychological) psychotherapy is its application in practice (Kryspin-Exner et al., 2017). The great diversity and heterogeneity demonstrated in this overview underlines the importance of the goal of CPE's section "Politics and Education": Accomplishing transparency and clarity about the political and educational situation regarding clinical psychology and psychological treatment in Europe. This will be a necessary precondition for improving communication between different countries and different professions, for improving the field of clinical psychology as a whole, as well as for being able to coordinate European or multinational initiatives regarding research, structural changes, and psychological treatment.

### Tasks and Objectives of the "Politics and Education" Section

It is the aim of the journal *Clinical Psychology in Europe* and its various sections to develop and strengthen an international perspective on clinical psychology and psychological treatment (https://cpe.psychopen.eu/about#AimsandScope). Accordingly, for the section "Politics and Education", the main purpose is to publish articles dealing with various aspects of the political and legal situation and recent developments in Europe regarding training in clinical psychology and clinical psychological practice. The primary goal is to increase knowledge about different regulations and training modalities in Europe in or-



der to foster understanding, communication and cooperation between professionals in the field of clinical psychology.

A central topic of European integration is promoting mobility and exchange of professions, which also applies for clinical psychology. On the one hand, clinical psychologists planning to move to another EU country or a country outside the EU should be kept fully informed about regulations as well as opportunities to perform their job in the respective country. On the other hand, comprehensive information is important for crossnational initiatives (e.g. on education and training in clinical psychology and psychological treatment), scientific projects, and the promotion of evidence-based practical applications of clinical psychology. It is, however, not planned to compile a legal encyclopedia in this section. Rather, papers should deal with the topics of interest in an introductory manner, provide an overview, and refer to further readings.

#### Papers to Be Submitted to This Section

Manuscripts submitted to this section should address one of the following topics: (1) legal regulations on education, training, and practice in clinical psychology and psychological treatment in health care; (2) specific aspects related to politics and education, e.g. prerequisites for, and contents of, training in various psychological treatments, or the relationship between clinical psychology and psychological treatment in a certain country; (3) commentaries on university studies (e.g. Master's or Doctorate level), European harmonization, or pan-European regulations (e.g. by the European Federation of Psychologists' Associations or other organizations) are also welcome. The focus of the papers should be on clinical psychology, or on psychological treatment as an area of the application of clinical psychology.

All contributions will be reviewed by the editors and must meet the requirements of the journal (for details please see https://cpe.psychopen.eu/about#Author-Guidelines). Manuscripts should not exceed a maximum of 2,500 words (excluding references, author description and cover page). Papers can be submitted to the journal at any time. However, one of the editors should be contacted beforehand to agree upon the planned topic. In addition, the editors will actively invite experts to submit manuscripts on various topics of interest.

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Letter to the Editor | Commentary

#### Check for updates

# No Health Without Mental Health – European Clinical Psychology Takes Responsibility

1st European Congress on Clinical Psychology and Psychological Treatment in Dresden, Germany, October 31 – November 2, 2019

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The European Association of Clinical Psychology and Psychological Treatment (EACLPT) was founded in 2017 with the goal of promoting European collaborations on research and education about mental health problems as well as their treatment. In 2019, the association's first congress will take place to foster such collaborations from October 31<sup>st</sup> to November 2<sup>nd</sup> in Dresden, Germany. It will be the first international meeting in the field of clinical psychology at a European level.

The conference theme "No Health without Mental Health - European Clinical Psychology Takes Responsibility" expresses our goal of moving mental health into societal focus. Mental disorders are among the most debilitating conditions and clinical psychology offers a wide range of preventive and therapeutic interventions. The discussion of these, as well as underlying etiological models, will be at the heart of the conference. Keynote speakers include Claudi Bockting, Susan Bögels (University of Amsterdam), David Clark (University of Oxford), Stefan Hofmann (Boston University) and Maria Karekla (University of Cyprus).

We invite submissions for symposia and poster presentations on the full range of clinical psychological research: diagnostics and classification, psychological and psychobiological mechanisms, psychological treatments, prevention and rehabilitation. We particularly encourage early career researchers to join the conference. Targeted pre-conference workshops, mentoring and financial support can be offered.



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The conference will be a unique chance to discuss current challenges for mental health in Europe and initiate collaborations and joint projects with colleagues from all over the continent. We look forward to seeing you in Dresden!

#### For details on the conference and registration visit:

www.clinicalpsychologycongress2019.eu



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