General practice-based non-pharmacological treatments for anxiety disorders: a systematic review

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GENERAL PRACTICE-BASED NON-PHARMACOLOGICAL TREATMENTS FOR ANXIETY DISORDERS

ABSTRACT

Background – Anxiety disorders (AD) can greatly affect a patient's social and professional life as well as healthcare systems as a whole. Lifetime prevalence rates are as high as 12.5-16% and therefore almost every general practioner is often treating patients with AD. Due to side-effects of classic pharmacological therapy and specific situations as pregnancy and post-partum, non-pharmacological treatment options of AD are more and more considered.

Methods – A narrative systematic review was conducted on every possible science-backed non-pharmacological treatment of AD that is readily applicable in a primary-care setting. Relevant papers published in 2010-2015 were identified by searching the MEDLINE, Embase, PsycINFO and the Cochrane Library databases.

Results – Inclusion criteria were met by 15 articles of which 10 were systematic reviews including a total of 265 separate studies. Data was found supporting the use of face-to-face cognitive behavioral therapy (CBT), internet-based CBT, exercise training and mind-body interventions in the treatment of AD in a general primary care population involving children, adolescents, adults, pregnant women as well as in patients diagnosed with important co-morbidity such as chronic obstructive pulmonary disease (COPD), type II diabetes mellitus (DM) and Parkinson's disease.

Discussion – This systematic review provides clear evidence in favor of the effective use of non-pharmacological therapeutic tools for AD in a general practice setting and as a first line treatment option. Additionally, future use of internet-based CBT and exercise programs for patients with important co-morbidity as COPD and type II DM is very promising but more practical research is necessary.

KEY-WORDS: Anxiety disorders, non-pharmacological, treatment, primary care, general practitioner

INTRODUCTION

Every person feels anxious from time to time and mostly this is a normal physiological response. Sometimes however, feelings of anxiety are out of proportion to the stressful event that induces the anxiety or interfere with and disturb daily social and professional activities. In these cases, a pathological condition such as an anxiety disorder might be present. These two latter elements (out of proportion – interfering with daily life) are common and essential features in the huge group of anxiety disorders according to the worldwide most used classification system for mental illnesses: the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) of the American Psychiatric Association (1). In the DSM-V classification several types of anxiety disorders from the anxiety disorder spectrum are distinguished. These distinct and sometimes overlapping forms include panic disorders (PD) with or without agoraphobia, specific phobias (SP), social phobias (SoP) generalized anxiety disorders (GAD), post-traumatic stress disorders (PTSD) but also anxiety disorders as a consequence of substance abuse or in combination with a chronic physical condition such as diabetes mellitus (DM) or chronic obstructive pulmonary disease (COPD) (1). Anxiety disorders are the most common mental illness in the general population worldwide and are the result of a complex interplay between genetic factors and lifetime events. Numbers estimating lifetime prevalence rates are abundant and fairly consistent and range from 12.5% in Flanders (Belgium) (2) to 13.6% on average in Europe (3) and to approximately 16% in the rest of the world (22).

Anxiety disorders not only greatly affect health-care systems as a whole because of its high prevalence but also have great impact on individual patients suffering from such disorders. The feelings of anxiety patients experience can be so intense and paralyzing that the quality of their social and professional relations decreases to a great extent. Because of this, the sense of general well-being of these patients will further diminish which further potentiates the anxiety disorder and puts these patients in a vicious circle (1; 6; 19). Therefore it is absolutely pivotal that patients seek and receive fast and adequate care. Anxiety disorders are described as being highly-treatable;

nevertheless only one-third up to one-half of all patients receives a treatment. Anxiety disorders are more chronic in nature than other mental disorders and patients tend to relapse in up to 50% of cases (6; 10). Patients suffering from an anxiety disorder are 3-5 time more likely of consulting a physician for reasons not directly related to their mental disorder (1; 3; 6; 22). Anxiety disorders are commonly treated pharmacologically with a combination of antidepressants and minor tranquillizers such as selective serotonin reuptake inhibitors (SSRI's) and benzodiazepines (6; 19). This pharmacological approach should not always be the primary aim of action however. Moreover, in certain cases the use of (extra) medication is highly discouraged: during pregnancy or in the perinatal period, in the elderly who often are already exposed to polypharmacy and who have an increased risk of falling, patients suffering from side-effects induced by use of SSRI's and benzodiazepines,… (23).

Because of all these aforementioned elements of anxiety disorders including its very high prevalence, it is absolutely necessary that primary care physicians are not only well aware of the magnitude of this problem but that they are also able to both diagnose and treat anxiety disorders in an excellent manner (10). Treatment strategies should include non-pharmacological approaches whenever possible and are sometimes even essential. We therefore aimed to perform a systematic review of recent literature to be able to present to primary care physicians a summary of *every* possible effective non-pharmacological treatment option for anxiety disorders for which exists some scientific evidence. In this way we want to maximize the therapeutic arsenal primary care physicians can make use of when working out a customized treatment plan for an individual patient suffering from an anxiety disorder.

METHODS

This narrative systematic review was conducted according to the guidelines of the Cochrane Collaboration and the process and results were noted in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (18; 24).

Search strategy – We electronically searched the MEDLINE (Pubmed), Embase, PsycINFO, and the Cochrane Library databases for recent research papers examining the non-pharmacological treatment of anxiety disorders in primary care settings. Prior to the start of our search, we developed a PICO-question (patient/problem – intervention – comparison – outcome) as follows:

- Patient/problem: patients with an anxiety disorder (non-specified)
- Intervention: non-pharmacological treatments applicable in a primary care setting
- Comparison: no treatment or a pharmacological treatment
- Relief of symptoms and/or improved quality of life

Our final PICO-question therefore was: 'For patients suffering from an anxiety disorder, which effective non-pharmacological treatments exist that are both effective (leading to a relief in symptoms and/or improved quality of life) as well as readily to use in a primary care setting'? Based on this PICO-framework, we used a combination of MeSH search terms and free text to develop a search strategy in Medline for the identification of eligible papers. The final search strategy was applied as follows: (((anxiety[MeSH Terms]) OR anxiety disorder[MeSH Terms]) AND non-pharm*) OR non pharm*. To maximize the amount of possible eligible papers for inclusion in the review, no other search terms were used although our PICO-framework indicated that other search terms should have been included. Therefore inclusion criteria, as outlined further on, were applied very strictly. The same search strategy was used to search all 4 databases mentioned above. In addition, the bibliography of the selected articles were manually screened for other potential relevant papers. Based on the final selection of eligible papers that met the inclusion criteria, a merely narrative

systematic review article was written. Because of the goal of this article (see introduction), a meta-analysis was not performed.

Inclusion criteria

Study design – We included both randomized and non-randomized interventional studies as well as systematic reviews.

Population - Patients suffering from all types of anxiety disorders were looked at if the diagnostic criteria according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) were fulfilled. Patients of both genders and all ages were considered.

Interventions - Only non-pharmacological treatments for anxiety disorders that general practitioners readily can initiate themselves in ambulant care or for which they can easily refer to other primary care providers such as psychologists and psychotherapists were taken into consideration.

Publication date - Only research papers published between January 1st 2010 and December 31th 2015 and written in English were included.

Outcome measures – All effective non-pharmacological treatments presented either in an interventional study or in a systematic review and that are feasible for use in a primary care setting and that were shown to lead to a reduction in anxiety-related symptoms and/or an improvement in the quality of life of the patient(s) were considered.

Data extraction and analysis – The identified papers were screened for eligibility based on title, abstract and full-text. A data extraction worksheet was specifically designed for controlled extraction of the data.

Assessment of study quality – The quality of all selected studies was assessed using the checklist developed by Downs and Black. This checklist is validated to use for the assessment of the methodological quality of both randomized-clinical trials as well as non-randomized experiments and reviews in health care interventions (13). In this way, each study was awarded a quality score

(maximum score = 31). Quality scores of studies included in the present review are represented in table 1. A detailed step-by-step overview of Downs and Black quality scores is also presented in a separate table (see appendix).

Table 1: Study characteristics and quality scores

STUDY	STUDY DESIGN	STUDY POPULATION	ANXIETY DISORDER	QUALITY
Face-to-face CBT				
Marchesi et al. (2015)	Review	Pregnant and postpartum patients (any age)	OCD, PD, SP	20/31
James et al. (2015)	Review	Children and adolescents 4-19 yrs	GAD, OCD, PD, SP	27/31
Gillies et al. (2012)	Review	Children and adolescents 3-18 yrs	PTSD	26/31
Yang et al. (2012)	Review	Parkinson's disease patients (any age)	AD-MC	19/31
Internet-based CBT				
Newman et al. (2013)	RCT	Heterogeneous group primary care patients 18-64 yrs	GAD	19/31
Spence et al. (2011)	RCT	Adolescents 12-18 yrs	GAD, SoP, SAD, SP	20/31
Vigerland et al. (2013)	Pilot study	Children 8-12 yrs	SP	21/31
Berger et al. (2014)	RCT	Heterogeneous group primary care patients > 18 yrs	GAD, PD, SoP	18/31
Mayo et Montgomery (2013)	Review	Heterogeneous group primary care patients > 18 yrs	GAD, OCD, PD, SoP, SP	25/31
Exercise				
Jayakody et al. (2012)	Review	Heterogeneous group primary care patients > 18 yrs	GAD, OCD, PD, SoP, SP	22/31
Van der Heijden et al. (2013)	Review	Type II diabetes mellitus patients > 18 yrs	AD-MC	23/31
Coventry et al. (2013)	Review	Chronic obstructive pulmonary disease patients (any age)	AD-MC	27/31
Mind-body interventions				
Donegan & Dugas (2012)	RCT	Adults 18-64 yrs	GAD	20/31
Marc et al. (2011)	Review	Pregnant patients (any age) at any time point	AD-MC	26/31
Bradt et al. (2013)	Review	Pre-operative patients (any age)	SP	28/31

OCD: obsessive compulsive disorder, PD: panic disorder, SP: specific phobia, PTSD: post-traumatic stress disorder, GAD: generalized anxiety disorder, AD-MC: anxiety disorder due to another medical condition, SoP: social phobia

RESULTS

Search results – The initial search found 286 articles. Every article was screened based on pre-determined inclusion and exclusion criteria. After a careful selection process 15 articles were included in this review (see figure 1).

Characteristics of included studies – Eligibility criteria were met by 15 article consisting of 10 systematic reviews (5; 8; 15; 20; 21; 26-28; 31; 33), 4 RCT's (4; 12; 29; 30) and 1 non-randomized interventional pilot study (32). These articles reported high-quality evidence for the use of face-to-face cognitive behavioral therapy (CBT) (15; 20; 27; 33), internet-based CBT (4; 28-30; 32), exercise therapy (8; 21; 31) and mind-body interventions (5; 12; 26). The studies included in the identified reviews as well as their citation list were manually screened for other potential relevant papers. Individual studies cited in the reviews included in the present review were not once again included as separate studies in this work. The 10 systematic reviews in the present review included 265 separate studies. Overlap between and thus multiple inclusion of the same study in the included reviews did not influence the results of this work as no quantitative or meta-analysis was needed to obtain the main goal of this project. Study subjects included patients diagnosed with an anxiety disorder from both sexes with ages ranging mainly from 3-64yrs with or without an associated medical condition. Characteristics of the included studies are shown in table 1. An overview presenting all non-pharmacological treatments cited in this work sorted by the appropriate target patient population is presented in table 2.

Excluded studies – During the selection process, 123 out of the initially found 286 articles were rejected based on the abstract. Of the remaining 163 articles the full-text was examined and 148 articles were found not be included in this review due to (i) involvement of a pharmacological treatment (26/148), (ii) reporting of a treatment not applicable in primary care (68/123) and (iii)

insufficient scientific quality of the article (no detailed description of included subjects or treatment, no peer-review,…) (54/148).

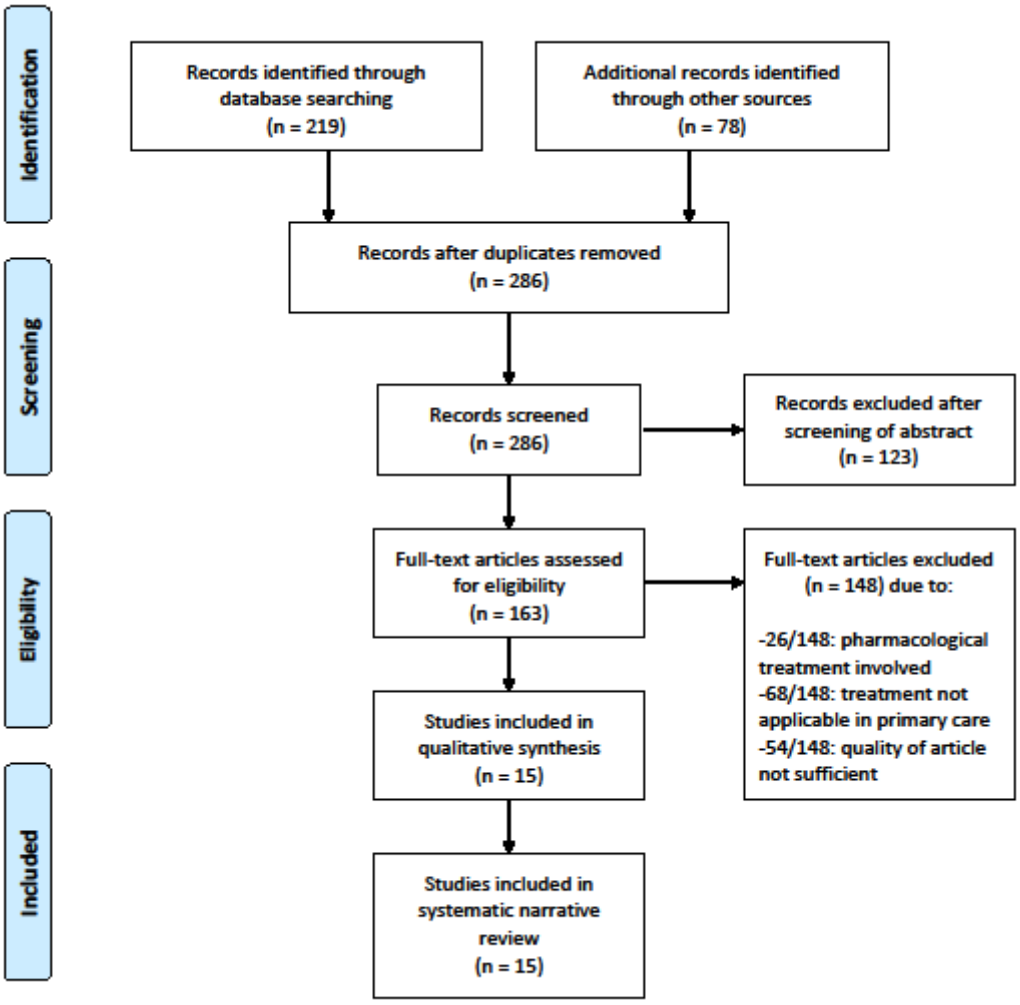


Figure 1: Flow diagram of study selection process

Table 2: Inventory of cited non-pharmacological treatments of anxiety disorders

Patient population	Anxiety disorder	Non-pharmacological treatment applicable?			
		Face-to-face CBT	Online CBT	Exercise	Mind-body interventions
Children and adolescents 3-18 yrs	GAD, OCD, PD, SP, SoP, PTSD	X	X		X
Adults > 18 yrs	GAD, OCD, PD, SP, SoP	X	X	X	X
Pre-operative patients (any age)	SP				X
Pregnant and postpartum patients (any age)	OCD, PD, SP	X			X
COPD patients	AD-MC	X		X	
Type II DM patients	AD-MC	X		X	
Parkinson's disease patients	AD-MC	X			

OCD: obsessive compulsive disorder, PD: panic disorder, SP: specific phobia, PTSD: post-traumatic stress disorder, GAD: generalized anxiety disorder, AD-MC: anxiety disorder due to another medical condition, SoP: social phobia, COPD: chronic obstructive pulmonary disease, DM: diabetes mellitus

Main results

Face-to-face CBT – We identified 4 reviews discussing the effects of face-to-face CBT in primary care: 1 review showing data from studies on OCD, PD and SP in pregnant and postpartum women (27), 2 reviews presenting studies on CBT in children and adolescents (3-18 years) suffering from either GAD, OCD, PD or SP (20) or from PTSD (15) and 1 review on anxiety symptoms in patients diagnosed with Parkinson's disease (33). The review by Marchesi et al. including 18 articles showed that CBT was successful in reducing anxiety levels in women suffering from OCD, PD and SP during pregnancy and postpartum (27). This review also pointed out that administration of SSRI's during late pregnancy exposes the newborn to an increased risk of poor neonatal adaptation syndrome and persistent pulmonary hypertension. The authors therefore advise that CBT should be the first choice in treatment offered to pregnant and breastfeeding women (27). The recent Cochrane systematic review by James and co-workers analyzing 41 studies concluded that CBT is an effective treatment for every different form of childhood and adolescent anxiety disorders but also showed that there is limited and inconclusive evidence that CBT is more effective than pharmacological treatment on the long term (20). Gillies et al. wrote another recent Cochrane systematic review including 14 studies was the first review focusing on psychological therapy for children and adolescents suffering from PTSD after physical or psychological abuse (15). This review showed that CBT is probably the most effective psycho-therapy form in this setting at least up to one month after treatment. The authors indicated that the level of evidence of the review is compromised by substantial heterogeneity in the included studies and that more research investigating the long-term effects of CBT for PTSD is needed. The review by Yang et al. discussed 9 reports on psychosocial interventions including CBT for patients suffering from Parkinson's disease (33) and accompanying anxiety and/or depressive disorder. The review showed that CBT is an effective therapy for the acute management of depression and anxiety in Parkinson's disease but also that effects after treatment are variable on the long-term.

Internet-based CBT – Our search strategy yielded 5 articles on internet-based CBT: 3 RCT's discussing anxiety disorders in either adults (4; 29) or adolescents aged 12-18 years (30), 1 non-randomized interventional trial in 8-12yr old children with specific phobias (32) and 1 review putting together recent evidence on online CBT for adults diagnosed with any form of anxiety disorder (28). Newman and co-workers conducted a RCT including 34 patients suffering from GAD showed that momentary intervention using mobile-technology CBT is a cost-effective and generalizable method to increase efficiency of face-to-face CBT (29). In this RCT it was demonstrated that 6 sessions of internet-based CBT was equally effective as 6 or 12 classical sessions of face-to-face CBT in reducing GAD measures at 6 and 12 months post treatment. Another recent RCT from Spence et al. also compared the effectiveness of 12 weeks of online versus clinic-based CBT in the treatment of adolescent anxiety disorder forms (30). The RCT included 115 adolescents aged 12 to 18 years as well as their parent(s) and showed that both forms of CBT resulted in a ~80% reduction of anxiety measures in both groups at 12 months post treatment indicating that online delivery of CBT is equally effective as conventional CBT in the treatment of anxiety disorders in adolescents. Satisfactory ratings for the online CBT format were also as high as for the clinic-based CBT amongst both the adolescents as their parents. A pilot study by Vigerland and co-workers including 30 children aged 8-12 suffering from a specific phobia showed that 6 weeks of internet-based CBT was able to reduce symptom severity significantly in 35% of the patients immediately post treatment as well as 3 months later (32). Another RCT by Berger et al. showed that in a heterogeneous group of 132 subjects diagnosed with either GAD, PD or SoP 8 weeks of online-guided CBT was more effective in reducing anxiety symptoms in comparison to wait-list controls and that treatment gains were maintained at 6 months post treatment (4). A Cochrane systematic review conducted by Mayo-Wilson and Montgomery and including 92 studies compared several types of mobile-type CBT interventions with no treatment and face-to-face CBT for the treatment of anxiety disorders in adults (28). It was concluded that self-help such as online-guided CBT can be effective in the treatment of anxiety disorder but also that face-to-

face CBT is probably clinically superior. The authors of the review however expressed their concern as inconsistency and risk of bias reduced their confidence in the overall results.

Exercise therapy – We found 3 reviews on exercise therapy in the treatment of anxiety disorders: 1 review on exercise training for anxiety disorders in a general adult primary care population (21) and 2 reviews on anxiety symptoms related to other medical conditions, respectively to type 2 diabetes mellitus (31) and to chronic obstructive pulmonary disease (8). Jayakody and co-workers performed a systematic review including 8 RCT's showing that exercise is an effective adjunctive or augmentation treatment for anxiety disorders in general but also pointed out that it is less effective than antidepressant treatment (21). The authors also concluded that more research is needed to determine which exercise mode (light vs. hard and aerobic vs. anaerobic) is optimal as a treatment for anxiety disorders. The review by van der Heijden et al. including 20 articles evaluated the effects of exercise on symptoms of depression and anxiety and on quality of life in patients suffering from type 2 diabetes mellitus (31). Although only 1 study (25) in this review specifically examined the effect of exercise on anxiety levels, it was shown in this study that exercise significantly improved clinical well-being and reduced anxiety measures. The other studies in this review discussed either the quality of life, emotional well-being or depression symptoms in type II diabetes mellitus patients. Therefore, and in accordance with our search strategy as outlined in the methods section, the entire review was still included in the present work but with focus on the study handling the non-pharmacological treatment of anxiety (25). Coventry and colleagues conducted a review including 29 RCT's on the effect of psychological and lifestyle interventions on anxiety and depression scores in patients diagnosed with COPD (8). Of the 29 RCT's included 16 RCT's focussed on the effect of exercise as stand-alone or in combination with psychological interventions. This review nicely demonstrated that of all examined psychological and lifestyle interventions only multi-component (aerobic and resistance forms) exercise training was effective in significant reducing depression and anxiety scores in patients with COPD (8).

Mind-body interventions – We identified 3 articles on the efficacy of several types of mind-body interventions: 1 RCT examining applied relaxation for treatment of GAD in adults (12), 1 review discussing anxiety disorders in women during pregnancy (26) and 1 review discussing the use of music therapy in reducing anxiety in pre-operative patients (5). Donegan and Dugas performed a RCT in which 57 adults diagnosed with GAD were enrolled and examined if applied relaxation was equally effective as face-to-face CBT (12) in reduction of (i) worrying and (ii) physical anxiety. Applied relaxation consisted of tension awareness training, tension-release training, relaxation by recall, relaxation by counting and conditioned relaxation training involving application of relaxation techniques in everyday situations. The authors concluded that subjects in both treatment groups experienced significant and comparable reductions in physical anxiety symptoms and in time worrying. It was also shown that the reduction in physical anxiety in patients receiving CBT was mainly the result from a reduction in worrying more than in patients treated with applied relaxation (12). A Cochrane systematic review by Marc and co-workers included 8 RCT's examined the effect of mind-body interventions in pregnant women of any age at any time from conception to one month after birth (26). Mind-body interventions included autogenic training, biofeedback, hypnotherapy, imagery, meditation, prayer, auto-suggestion, tai-chi and yoga. The authors concluded that imagery and autogenic training might reduce women's anxiety during pregnancy and labor but strong evidence for the effectiveness of these treatments was lacking. Another Cochrane systematic review by Bradt et al. including 26 trials examined the effectiveness of music therapy in reducing excessive pre-operative anxiety (5). Study participants listened to recorded relaxation music instead of receiving pre-operative anti-anxiety drugs. The review showed that on average music therapy has a beneficial effect on pre-operative anxiety and in 1 large included study music listening was even more effective than administration of midazolam.

DISCUSSION

This systematic review provides a large amount of clear evidence in favor of the effective use of non-pharmacological treatments for anxiety disorders in a general practice setting. Out of the 15 articles discussed in this review, 10 articles (including a total of 265 independent studies) were excellent peer-reviewed systematic reviews indicating that the level of evidence of the data documented in this project is of very high-quality. Several feasible non-pharmacological treatment tools that can be added to the treatment inventory in a general care practice are presented.

The general practitioner's (GP) office is flooded with psychosocial problems, obviously - presented and combined with or without physical illnesses or just as a hidden comorbidity. If the GP can tailor the therapeutic approach of patients suffering from anxiety disorders, treatment adherence and general satisfactory rates will be greatly increased. This is especially true whenever a pharmaceutical treatment is undesirable because of drug-induced side-effects (23) or even not a possibility at all, for example during pregnancy. Indeed, a growing body of evidence claims that the use of antidepressants and anxiolytic medication is not safe during pregnancy and can lead to malformation, poor neonatal adaptation syndrome and persistent pulmonary hypertension in the newborn (7; 27). Anxiety during pregnancy however is a common problem and anxiety and stress can also harm the course of the pregnancy and the development of the unborn child. Therefore CBT (whether face-to-face or internet-based) and mind-body interventions should always be considered as a first choice treatment (7; 26; 27).

Efficacy of non-pharmacological treatments

This review demonstrates that in general, non-pharmacological treatment options of anxiety disorders are effective in reducing anxiety levels and improving quality of life in a varied group of patients. However, we also collected and provide evidence that nor face-to-face or internet-based

CBT, exercise training or mind-relaxation therapies are more effective compared to treatment with SSRI's, SNRI's, TCA's or benzodiazepines. This is especially true for treatment with exercise training: while exercise is an effective first line treatment and more favorable than antidepressants in mild to moderate depressive mood disorders, the appropriate use of exercise training in anxiety disorders is less clear (21; 31). Exercise therapy for anxiety compared to depressive disorders is not as extensively studied yet. The available data however suggest that exercise training is an effective and cost-efficient treatment option but also that it does not reduce anxiety to the level achieved by psychotropic drug therapy (21). More studies are also needed to determine the most efficient mode and duration of exercise training (light vs. hard, aerobic vs. anaerobic and strength training, short vs. prolonged exercise). In the review by Jayakody et al. it was also argued that the beneficial effect of exercise in patients suffering from panic disorder and/or agoraphobia, might not be the resultant of the physiological effects of exercise as such, but that out-of-house exercise is just acting as an exposure technique (21). The Cochrane systematic review by Bradt and co-workers examining the efficacy of music therapy in reducing pre-operative anxiety deserves special attention (5). Anxiety in patients awaiting surgery is very real and patients often suffer from this kind of anxiety not only in the hours before the operative procedure but even days or weeks in advance. Consequences of this type of anxiety are slower wound healing, increased risk of infection and difficulties in induction through anesthesia. The aforementioned review showed that on average music therapy has a beneficial effect on pre-operative anxiety and moreover, in 1 large included study music listening was *even more* effective than administration of midazolam. GP's should therefore routineously address this issue when performing a standard pre-operative examination.

Feasibility of non-pharmacological treatments in primary care

One of the most important factors determining whether or not a GP will consider choosing a non-pharmacological treatment when working with anxious patients is the feasibility of the treatment in a primary care setting. In our view, for a treatment to be feasible in such setting, it should be (i) applicable in the often limited time available during a patient's visit, (ii) ready to perform without a comprehensive education and (iii) face some kind of financial compensation for the health care provider. Because of these reasons, of the non-pharmacological treatment presented in this review, most GP's will only be able to provide exercise training, mind-body relaxation interventions and advise music therapy in selected settings. Assisting patients in internet-based CBT however, might also be an option now or in the nearby future as discussed further on. However, nowadays, a general practice in Western-European and Anglo Saxon countries is often more than just 1 or more GP's. In a modern general practice you can regularly find not only assisting administration personnel but also para-medics as nurses, psychologists, dieticians and midwifes. This opens a whole new perspective as GP's can intensively and even day-to-day informal way collaborate with other health care providers who are more skilled in providing non-pharmacological treatment options to patients. Psychologists are highly trained and experienced in CBT, midwifes are accustomed to using mind-body relaxation techniques in woman during pregnancy, labor as well in the postpartum period. Home care nurses can also be of great importance for patients suffering from anxiety. Indeed, a very recent literature review showed that anxiety is a common symptom in patients with advanced cancer and that nurse-led interventions such as psycho-education, tele-monitoring and complementary care can be of great help in this kind of setting whether it is in hospital or at a patient's home (34). If GP's organize their practice in such way that (i) para-medics are involved in patient care and (ii) follow-up of patients under treatment in their practice is discussed on a regular basis, the quality of health care provided can benefit to a huge extent.

Internet-based CBT and self-assessment tools: the future?

At present, several hundreds of CBT applications can be downloaded from the internet for use on computers and smartphones (4; 29). The use of internet-based and other mobile-technology CBT forms such as email and telephone calls might at first look a little bit odd for health care providers who are used to conventional face-to-face CBT. However, the pilot study as well as every RCT and even the Cochrane systematical review included in this review showed that this modern form of CBT is not less effective than face-to-face CBT (4; 28-30; 32). Internet-based CBT was also shown to be highly effective in reducing anxiety symptoms at 3 months (32) and 6 and 12 months (4; 29; 30) post treatment. It is also noteworthy that the RCT's in the present review proved the use of mobile-technology CBT to be effective and feasible in children and adolescents diagnosed with an anxiety disorder. While the included RCT's demonstrated that online CBT was as effective as conventional CBT, the authors of the review argued that face-to-face CBT might be probably clinically superior (4). The authors of the review however expressed their concern as inconsistency and risk of bias reduced their confidence in the overall results.

The use of internet-based CBT has several advantages. It is a cost-effective, generally applicable and even ecologically favorable therapeutic tool in the treatment of anxiety disorders. It might also encourage patients who would previously have been deprived of therapy to seek for medical help. This can be the case in the financially unfavored, patients with very limited time available but also in those who live in remote areas where depression and anxiety are equally prevalent as in rural communities but also even more undertreated. This is nicely demonstrated in the remote province of Saskatchewan in Canada where implementation of internet-based CBT greatly improved the population's access to psychological services (17). It is also important to note that patients can be treated with computerized and face-to-face CBT jointly together. Internet-based CBT might improve treatment adherence and bridge the 'treatment gap' in between face-to-face appointments with health care providers making very anxious patients feeling more at ease.

Whereas therapeutic guidance in use of internet-based CBT still warrants a thorough educational training, GP's can easily be trained in using and interpreting valid online self-assessment tools. As anxiety disorders remain a heavily underdiagnosed condition, these tools can assist in identifying anxious patients who could benefit from medical help. GP's can then treat these detected patients or redirect them to the appropriate health care provider. Of course, every single mobile application (CBT or diagnostic tool) should be tested separately and validated before being used in clinical practice.

Limitations

In the present review no meta-analysis or calculation of effect sizes was performed because of the large heterogeneity in study protocols, subjects and applied treatments. Inconsistency and risk of bias is an often faced problem in these kinds of reviews. The scope of this review was to provide the GP with an overview of recent literature regarding every possible effective non-pharmacological treatment option for anxiety disorders for which exists sounds scientific evidence. We therefore feel that not implementing more quantitative data does not weaken our findings. However, a clear limitation of this review is that only one researcher has screened the records obtained by the search strategy in the medical databases as described in the methods sections. This flaw increases the likelihood of selection bias to occur as it previously has been shown that article selection by two independent reviewers is recommended in order to increase the reliability of the selection process (14; 18). Since only very recent literature was included, data presented in this review discussing face-to-face CBT for anxiety disorders in adults is sparse. In the past this topic has been discussed however in great detail elsewhere (9; 11; 16).

Implications and future directions

This review will help to raise GP's awareness of their therapeutic possibilities in an extended primary care setting. The presented scientific, effective and safe non-pharmacological treatment options reinforce their treatment inventory for such clinical cases when a treatment without the use of medication is desired or even pivotal. As stated before, this review will also assist primary care providers in tailoring a treatment plan for individual patients.

We want to stress out that further high quality RCT's examining the role of exercise in anxiety reduction in patients with anxiety due to another medical condition such as type II diabetes mellitus and COPD are needed as physical activity as such is primordial in these patients. If achievable but effective exercise training programs can be designed the clinical gains for these patients will be substantial.

Another point that needs special attention is that primary care physicians should be very vigilant for patients with an undiagnosed anxiety disorder. Davidson and colleagues showed that generalized anxiety disorder (GAD), the most common psychiatric disorder to be seen in primary care, was only diagnosed in 34% of actual GAD patients and that only 20% of all GAD patients were treated (10). In the Western-European and Anglo-Saxon countries millions of patients suffer from chronical medical conditions such as type II diabetes mellitus, COPD, Parkinson's disease,… These patients are all at risk of suffering from disabling anxiety due to their medical condition. These data suggest that improved detection of GAD and anxiety disorders in general, leads to more frequent treatment of appropriate patients with a favorable impact not only on individual patients but also on the healthcare system as a whole considering both time and financial resources. Therefore every GP and other primary care healthcare professional should keep a vigilant watch on early detection of a possible anxiety disorder when working with 'everyday' patients. Medical schools training our society's future healthcare providers should also pay extra attention to education in early and efficient diagnosis and treatment of anxiety disorders.

Conclusions

This systematic review provides clear evidence in favor of the effective use of non-pharmacological therapeutic tools for anxiety disorders in a general practice setting. General practitioners can use internet-based or face-to-face CBT, exercise training programs and mind-body interventions as a first line treatment. In this way, the general use of psycho-pharmaceuticals can be diminished and preserved for patients with an unsatisfactory response to non-pharmacological treatments. Further research on exercise programs and internet-based CBT in a primary care setting is needed.

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Appendix - Table: Detailed Downs and Black checklist for measuring study quality

Downs and Black checklist criteria	Included studies							
	Marchesi et al. 2015	**James et al. 2015**	**Gillies et al. 2012**	**Yang et al. 2012**	**Newman et al. 2013**	**Spence et al. 2011**	**Vigerland et al. 2013**	**Berger et al. 2014**
Is the hypothesis/aim/objective of the study clearly described?	1	1	1	1	1	1	1	1
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1	1	1	1	1	1	1	1
Are the characteristics of the patients included in the study clearly described?	1	1	1	1	1	1	1	1
Are the interventions of interest clearly described?	1	1	1	1	1	1	1	1
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	1	2	2	1	1	1	0	0
Are the main findings of the study clearly described?	1	1	1	1	1	1	1	1
Does the study provide estimates of the random variability in the data for the main outcomes?	1	1	1	1	0	1	1	0
Have all important adverse events that may be a consequence of the intervention been reported?	0	1	1	0	1	1	1	1
Have the characteristics of patients lost to follow-up been described?	0	1	1	0	0	1	0	0
Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes?	0	0	1	0	0	0	0	1
Were the subjects asked to participate in the study representative of the entire recruitment-population?	0	1	0	0	0	0	1	0
Were those subjects who were prepared to participate representative of the entire recruitment-population?	1	1	1	0	1	0	0	0
Were the staff, places, and facilities representative of the treatment the majority of patients receive?	1	1	0	1	1	1	1	1
Was an attempt made to blind study subjects to the intervention they have received?	0	0	0	0	0	0	0	0
Was an attempt made to blind those measuring the main outcomes of the intervention?	0	1	1	0	1	1	0	0
If any of the results of the study were based on “data dredging”, was this made clear?	0	1	1	1	0	0	1	1
Do the analyses adjust for different lengths of follow-up of patients?	1	1	1	1	0	0	1	1
Were the statistical tests used to assess the main outcomes appropriate?	1	1	1	1	1	1	1	1
Was compliance with the intervention/s reliable?	1	1	1	1	0	1	1	1
Were the main outcome measures used accurate (valid and reliable)?	1	1	1	1	1	1	1	1
Were the patients in different (intervention) groups recruited from the same population?	1	0	0	1	1	1	1	1
Were study subjects in different (intervention) groups recruited over the same period of time?	1	0	0	0	0	0	1	0
Were study subjects randomized to intervention groups?	0	1	1	0	0	0	0	0
Was the randomized intervention assignment concealed from both patients and health care staff?	0	0	0	0	0	0	0	0
Was there adjustment for confounding in the analyses from which the main findings were drawn?	0	1	1	1	1	1	0	0
Were losses of patients to follow-up taken into account?	0	1	1	0	1	0	0	0
Did the study have sufficient power to detect a clinically important effect?	5	5	5	4	4	4	5	4
Total	**20**	**27**	**26**	**19**	**19**	**20**	**21**	**18**

Downs and Black checklist criteria	Included studies						
	Mayo et al. 2013	**Jayakody et al. 2012**	**Van der Heijden et al. 2013**	**Coventry et al. 2013**	**Donegan et al. 2012**	**Marc et al. 2011**	**Bradt et al. 2013**
Is the hypothesis/aim/objective of the study clearly described?	1	1	1	1	1	1	1
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1	1	1	1	1	1	1
Are the characteristics of the patients included in the study clearly described?	1	1	1	1	1	1	1
Are the interventions of interest clearly described?	1	1	1	1	1	1	1
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	2	1	1	2	1	2	2
Are the main findings of the study clearly described?	1	1	1	1	1	1	1
Does the study provide estimates of the random variability in the data for the main outcomes?	1	1	1	1	1	1	1
Have all important adverse events that may be a consequence of the intervention been reported?	1	1	1	1	1	0	1
Have the characteristics of patients lost to follow-up been described?	1	1	1	0	0	1	1
Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes?	1	0	0	1	1	0	0
Were the subjects asked to participate in the study representative of the entire recruitment-population?	1	1	1	1	0	0	1
Were those subjects who were prepared to participate representative of the entire recruitment-population?	0	0	0	1	0	1	1
Were the staff, places, and facilities representative of the treatment the majority of patients receive?	1	1	1	1	1	1	1
Was an attempt made to blind study subjects to the intervention they have received?	0	0	0	0	0	0	0
Was an attempt made to blind those measuring the main outcomes of the intervention?	1	1	1	1	0	1	1
If any of the results of the study were based on “data dredging”, was this made clear?	0	1	1	1	1	1	1
Do the analyses adjust for different lengths of follow-up of patients?	1	0	1	1	1	1	1
Were the statistical tests used to assess the main outcomes appropriate?	1	1	1	1	1	1	1
Was compliance with the intervention/s reliable?	1	1	1	1	1	1	1
Were the main outcome measures used accurate (valid and reliable)?	1	1	0	1	0	1	1
Were the patients in different (intervention) groups recruited from the same population?	1	1	1	1	1	1	1
Were study subjects in different (intervention) groups recruited over the same period of time?	0	0	0	1	0	1	1
Were study subjects randomized to intervention groups?	1	0	0	0	0	1	0
Was the randomized intervention assignment concealed from both patients and health care staff?	0	0	0	0	0	0	0
Was there adjustment for confounding in the analyses from which the main findings were drawn?	0	0	1	0	0	0	1
Were losses of patients to follow-up taken into account?	0	0	0	1	1	1	1
Did the study have sufficient power to detect a clinically important effect?	5	5	5	5	4	5	5
Total	**25**	**22**	**23**	**27**	**20**	**26**	**28**