HHS Public Access

Author manuscript

J Asthma. Author manuscript; available in PMC 2023 February 01.

Published in final edited form as:

J Asthma. 2022 February ; 59(2): 273–287. doi:10.1080/02770903.2020.1847927.

Impact of Interventions Targeting Anxiety and Depression in Adults with Asthma

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Abstract

Objective: High rates of anxiety and depression exist among asthma patient populations. This scoping review will examine the existing interventional therapies that address depression and anxiety symptoms in patients with asthma.

Data Sources: Pubmed, Cochrane, Psychinfo, CINAHL, Google Scholar and EMBASE databases were searched using the following search terms: ‘anxiety asthma’, ‘panic disorder asthma’ and ‘depression asthma’ with a randomized clinical trial filter and additional filters to exclude exclusion criteria.

Study Selections: Study selections included only randomized control trials with anxiety and/or depression and/or panic disorder outcomes as primary or secondary outcomes. Only full-text articles in the English language were included.

Results: This search yielded interventions from pharmacologic (n=3), psychological (n=7), lifestyle medicine (n=10) and complementary and alternative medicine (CAM; n=1) using a range of outcomes from physiologic to psychologic. While the pharmacologic and CAM studies were inconclusive, psychologic and lifestyle interventions showed improvements in asthma (quality of life, symptoms, asthma attacks) and psychological (anxiety, panic fear, depression) outcomes. Variations in selection methods, outcome measures and diagnostic criteria hindered a direct comparison of the studies. Most studies had small sample sizes, high attrition rates and short study durations.

Conclusion: There is limited evidence on best approaches for managing co-morbid anxiety and/or depression in patients with asthma. Psychological and lifestyle medicine interventions are promising with improvements in both asthma and mental health outcomes. Well-designed randomized controlled studies with larger sample sizes, standardized outcomes and longer durations, are needed to better understand the role of depression and anxiety in adults with asthma.

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Declaration of Interest

The project as supported by NHLBI K01 HL 133370. The authors declare that they have no competing interests. The authors alone are responsible for the content and writing of the paper.

Keywords

Asthma; Depression; Anxiety; Antidepressants; Psychotherapy; Cognitive Behavior Therapy; Lifestyle medicine; Panic Disorder; Complementary and alternative medicine

Introduction

Asthma is a complex, multi-faceted disease that affects 334 million people worldwide. It is projected that 100 million additional people will be diagnosed with asthma by 2025 globally (1, 2). Asthma has a high global burden of disability with the disability-adjusted life years (DALYS) estimated at ~15 million per year worldwide (2). According to the World Health Organization, about 250,000 people die prematurely worldwide every year from asthma exacerbations (3).

Depression and anxiety disorders are common in asthma and are major contributors to poor asthma outcomes (4). Approximately 4-20% of the general population will suffer from depression at some point in their life; while there is evidence suggesting that individuals with asthma are twice as likely to develop depressive symptoms compared to their counterparts without asthma (4). Anxiety disorders (i.e. generalized anxiety disorder, panic disorder) are also more prevalent in adults with asthma(5). Panic disorder affects people with asthma at 3 to 10 times the rates observed in the general population(6). Similarly, the prevalence of generalized anxiety disorder in patients with asthma is 9%, which is at least 3 times higher than the rates found in the general population(6, 7). Both depression and anxiety have been associated with poorer asthma outcomes including higher rates of healthcare utilization, poorer asthma control and mortality(8).

Depression has been identified as an independent risk factor for developing asthma (9)The higher rates of depression in adults with asthma suggests that these two conditions may share physiologic mechanisms. A national study in 2016 by Tedner et al showed a significant association between asthma and depression in adult twins after controlling for environmental and genetic factors (10). This association was not found in child participants of the sampled population, which strengthens the argument that asthma and depression share pathogenic elements that go beyond genetic and environmental factors. Existing literature suggests various factors may contribute to the high incidence of depression in asthma and poorer asthma outcomes associated with depression. One possible pathway is through activation of immune inflammatory pathways (4). Depressed individuals have elevated levels of pro-inflammatory cytokines, IL-1, IL-4, IL-6, TNF-alpha which play a critical role in asthma. Cytokines such as IL-1, IL-6 and TNF-α can increase early stages of inflammatory response and cause significant inflammation in asthma (4). Further, depression may play a role in behaviors such as poor medication adherence or lifestyle choices (recreational drug use, sedentary behavior) which can increase the risk for asthma exacerbations (11). The exact pathogenesis of depression in patients with asthma is unclear but with the associated greater morbidity of depression and asthma, it is imperative that it is recognized and treated.

The connection between anxiety disorders (i.e. panic disorder and generalized anxiety disorder) and asthma has long been observed in clinical practice. Del Giacco et al and

others have confirmed this connection in epidemiologic studies. Adults with a lifetime anxiety disorder have a four-fold increased risk of having asthma, especially uncontrolled and more severe asthma(12). While the relationship between asthma and anxiety disorders is bidirectional, either of which can be the cause or consequence of the other, there are some underlying etiopathogenetic mechanisms that explain the association between the two. Anxiety can induce physiological dysregulation of the autonomic nervous system and hypothalamic-pituitary-adrenal axis(13). Chronically elevated levels of anxiety in patients with anxiety disorders may also affect asthma control via increased parasympathetic activity and secretion of proinflammatory cytokines, which are important mediators of asthma exacerbations (14, 15). The dyspnea-fear theory has been proposed to explain panic disorder specifically in asthma which attributes the somatic effect of hyperventilation to abnormally sensitive carbon dioxide receptors in the central nervous system and abnormal “suffocation detectors”(16). There is also evidence to suggest that related measures of anxiety (e.g., anxiety sensitivity) may increase risk for atopy or allergic asthma, which is associated with increased asthma severity (14, 17, 18). Asthma patients with generalized anxiety disorder may have more difficulty making appropriate self-management decisions, which may impact their asthma control and quality of life relative to asthma patients without this disorder. Further the symptoms of both anxiety and asthma include breathlessness, chest tightness, and palpitations, which can lead to misinterpretation of symptoms, overuse of bronchodilators and its’ side effects (20).

Medication and psychological interventions are first-line treatments for mental health disorders (e.g. depression, anxiety). Psychological interventions such as cognitive behavioral therapy guides the patient to challenge the validity of maladaptive thoughts and behaviors and is widely used for depression and anxiety disorders (19, 20). Lifestyle medicine and completementary and alternative medicine may offer potentially safe and low-cost treatment options. Lifestyle medicine can encompass many different areas including the adoption of evidence-based physical activity or exercise, dietary modification, relaxation, breathing exercises, mindfulness-based meditation techniques, spiritual healing and the reduction or cessation of recreational substances (e.g. nicotine, drugs, and alcohol) (21). Complementary and Alternative Medicine can include treatments such as acupuncture and craniosacral therapy which may be attractive to patients wanting a holistic treatment approach. The overall goal of this scoping review is to understand the current evidence in managing depression and/or anxiety symptoms in adults with asthma and identify research gaps in this understudied area.

Methods:

PubMed, Cochrane, PsychInfo, CINAHL and EMBASE were databases utilized to provide relevant articles. The search strategy used the following search terms: ‘anxiety asthma’, ‘panic disorder asthma’ and ‘depression asthma’ and a randomized clinical trial filter to produce maximizing results in literature, pertaining to anxiety, panic disorder and depression in adults with asthma. Filters pretaining to inclusion and exclusion were applied to each database when permitted, to filter relevant out articles that do not meet inclusion criteria. Given the low yield with database results, a search within Google Scholar was conducted with the following term [anxiety and asthma and depression and asthma and panic disorder]

with initial inclusion of a randomized clinical trials. Only full-text articles available in the English language were included. As this is a scoping review, there are no limitations on publication data, with the last search conducted concluding in May 2020. The articles were reviewed by title and abstract for inclusion into the study and excluded based upon irrelevant data in the abstract. Study selections included only randomized control trials with anxiety and/or depression and/or panic disorder as primary or secondary outcomes.

Results:

Our search yielded 371 articles from five databases; PubMed (n=35), Cochrane (n=218), PsychInfo (n=25), CINAHL (n=32) and EMBASE (n=11) and Google Scholar (n=53). For each database, relevant inclusion and exclusion criteria filters were placed in order to filter out article that did not meet the inclusion criteria. After going through the inclusion and exclusion criteria and removing duplicates, we found 19 articles that met our inclusion criteria. Our search was supplemented with a manual search and an examination of the reference lists that met the inclusion criteria, which yielded two additional articles. Overall our search revealed several studies that assessed interventions from pharmacologic (n=3), psychological (n=7), lifestyle medicine (n=10) and complementary and alternative medicine (n=1).

Pharmacologic interventions

We found few studies that investigated pharmacologic therapies in adults with asthma and depression (n=3) and/or anxiety (n=0). Brown et al. has published three randomized controlled studies exploring the effects of anti-depressants on adults with asthma and major depressive disorder (table 1) (22–24). Two of the three studies were placebo-controlled, 12-week trials of escitalopram. In the first proof of concept study (n=26), the authors found no significant between group differences in asthma control, depressive symptoms, or oral prednisone use in those that received treatment with escitalopram vs. placebo (22). When both the placebo and treatment groups were combined, a moderate correlation (r=0.38) in self-reported depressive symptoms as measured by Hamilton Rating Scale for Depression (HRSD) and Inventory of Depressive Symptomatology-Self-Report (IDS-SR) was found. Changes in asthma symptoms correlated significantly with changes in depressive symptoms in the escitalopram, placebo, and combined sample groups (IDS-SR: τ=0.49 – 0.60, P <0.05). A larger scale study, included 139 adults with asthma and compared the effect of escitalopram on differing severities of clinically diagnosed depression (23). They found significant between group differences in asthma control (p=0.04) and a trend to lower use of oral corticosteroids (p=0.07), only in patients with greater depression severity (Hamilton Rating Scale for Depression-HRSD scores ≥ 20) as compared to the placebo group. There were no significant between group differences with the lower depression severity group or combined sample. A similar study examined the effects of a 12-week trial of escitalopram in a sample of 82 adults and found the treatment group had less oral corticosteroid use for asthma exacerbations during the study (p=0.013) (24), yet there were no significant differences in asthma or mood symptoms between treatment group and placebo at trial end.

While these studies had low sample sizes and high attrition rates, they suggest that patients with clinical diagnosed depression, particularly more severe depression, may improve asthma control and reduce oral corticosteroid use with antidepressant therapy. Additionally, asthma symptom severity correlated with depression symptom severity, further demonstrating the association between depressive symptoms reduction and asthma symptom improvements. These studies support the relationship between depression and asthma, but larger clinical trials are needed to establish the clinical efficacy and identify mechanisms involved.

Psychological interventions

Cognitive behavioral therapy (CBT)—CBT has been well-studied in depression and anxiety disorders but less studied in patients with asthma and co-morbid depression and/or anxiety. Seven randomized controlled studies of CBT have been conducted in adults with asthma, with all but two studies included patients with co-morbid depression or anxiety disorders (Table 2) (25–31). In these studies, CBT was administered in a group setting or individually and varied from 3-15 sessions.

Group CBT was tested in two studies compared to usual care or wait list control. York et al conducted a randomized control trial comparing usual care vs. 8 weeks of group CBT provided by trained CBT therapists (25). Participants were anxious or depressed adults (Hospital Anxiety and Depression Score-HADS >8) with severe refractory asthma. The group CBT arm showed significant improvements in the Dyspnea-12 score (d= 0.66; $p<0.05$). Unfortunately, no significant differences were found in asthma control, quality of life, anxiety or depression between groups. Ross et al assessed group-CBT plus asthma education (Group CBT+AE) vs. wait list control in women with asthma and panic disorder (n=48) over 8 weeks (26). Women that received group CBT+AE, had significantly fewer panic attacks ($p=0.03$) and improved anxiety scores ($p\leq0.01$) at 8 weeks and 6 months. An improvement in asthma quality of life ($F(1, 19) = 11.03$, $p \leq .01$) and morning peak expiratory flow ($F(1, 17) = 6.86$, $p \leq .05$) was found at 8 weeks but was not sustained at 6 months. The study had a high drop-out rate (29%) and participants were recruited from a convenience sample of women with asthma and thus the results may lack generalizability.

Five studies studied the role of individual CBT in adults with asthma and anxiety disorders. Parry et al examined adults with asthma and anxiety (HADS anxiety score≥ 8) and found a reduction in self-reported asthma specific fear (Asthma Symptom Checklist panic fear sub-scale) at end of treatment (−2.59 95% CI: −4.39 to −0.79; $p<0.01$) and 6 months (−2.87 95% CI: −5.12 to −0.62; $p<0.01$) in those receiving individual CBT (27). There were also significant improvements to asthma-specific quality of life and depression in the individual CBT group immediately after treatment, but improvements were not maintained at 6-month post treatment. Qualitatively, participants reported greater control over asthma symptoms and were less likely to attribute symptoms to external factors. This study supported the use of individual CBT to decrease fear in patients with asthma and suggested benefit with ongoing treatment for depression. Feldman et al culturally adapted a cognitive behavioral psychophysiological therapy program (CBPT) for Latinos with adults with asthma and panic disorder (28). The study compared CBPT to music and relaxation therapy (MRT).

Participants in the CBPT group had a significant improvement in asthma medication adherence at 8 weeks and 12 weeks. There was no significant between group differences in the psychological outcomes. A major study limitation was 40% drop out rate. Stoop and colleagues examined the effects of psychoeducation and individual CBT on anxious or depressed patients (determined by Mini-International Neuropsychiatric Interview) with asthma/COPD (n=11), or diabetes mellitus (n=12) (29). The study intervention consisted of a 12-month disease management program with stepped up care that started with psychoeducation and advanced to a 10-week course based on the principles of CBT if remission did not occur. The intervention group had a significantly lower level of anxiety (p=0.048) at the end of the program and 6 months post intervention (p=.0007) than the control. Between group differences in depression was clinically significant (Cohen's d=0.61), despite not reaching statistical significance. These results suggest that the combined psychoeducation/CBT intervention may be a potential intervention for treating anxiety and depression in chronic diseases. No disease specific analysis was performed so it is unclear if certain chronic diseases would benefit more from psychoeducation/CBT than others.

Two studies evaluated individual CBT in adults with asthma but no diagnosed anxiety or depressive disorders. Sommaruga et al evaluated the effects of individual CBT in adult inpatients with asthma (30). The intervention consisted of two components: asthma education and individual CBT. The educational sessions focused on asthma management and occurred twice during hospitalization and quarterly in the following year. The indivudal CBT consisted of three meetings with a psychologist over one year to discuss reoccurring themes. At one year, the group that received individual CBT had a significantly lower number of asthma attacks compared to the control group($p<0.05$). No significant differences were found in anxiety or depression symptoms between the two groups. Similar to Sommaruga, Grover and colleagues evaluated the impact of individual CBT (15 sessions over 6-8 weeks) combined with asthma education in adults with asthma (31). An improvement in asthma (symptoms: $p<0.01$, asthma bother: $p<0.05$, asthma quality of life: $p<0.05$) and psychologic outcomes (anxiety and depression: $p<0.01$) were found post-intervention (6-8 weeks) but were not sustained at 12 weeks. A limitation of the study was the small sample size and low retention for 12 week outcome assessments.

These preliminary findings suggest both group and individual CBT may improve asthma outcomes (asthma-related quality of life, symptoms) through mechanisms of reducing depression and anxiety (panic-fear) symptoms in those with underlying depression and/or anxiety disorders. The exisiting studies using CBT have been small, high drop-out rates, and in some cases lacked statistical significance despite reaching clinical significance. Further study in this promising area are needed before implementing into clinical practice of asthma care.

Lifestyle medicine (Table 3)

Physical Activity—Physical activity (PA) has been used in conjunction with typical treatment to help manage depression and anxiety disorders in the general population. The association between PA and improved psychological health is well established, although the

exact mechanism is poorly understood. PA has been proposed as a treatment for depression and anxiety, with meta-analysis in clinical studies showing an effect range of −0.80 and −1.1 in depression and −1.0 to −0.76 in anxiety (32).

There is a dearth of randomized controlled trials exploring the effect of physical activity on depression or anxiety in asthma. Several PA interventions studies examined measures of anxiety and/or depression as secondary outcomes but did not specifically include patients with depression or anxiety disorders(33, 34). Mendes et al. examined the role of an aerobic training intervention on 101 adults with asthma. The participants did not have co-morbid depression and/or anxiety but did present with higher baseline levels of anxiety and depression than a healthy population. They found a significant improvement in health-related quality of life, asthma symptoms ($p<0.05$), state anxiety levels ($p<0.001$) and depression levels ($p<.001$) in those that underwent aerobic training only (33). A moderate linear relationship between baseline anxiety ($r =0.52$; $p< 0.001$) and depression ($r=0.62$; $p< 0.001$) scores was found that improved after aerobic training (i.e., the worse the baseline score, the better the improvement after aerobic training). These results support the role that aerobic training can play on reducing depression or anxiety symptoms in adults with asthma. Coelho and colleagues investigated the effects of a 12-week unsupervised pedometer-based physical activity program in adults with moderate to severe asthma (34). They found no significant improvement in asthma or depression and anxiety symptoms post-intervention. However, this study was limited by a lack of masking of outcome assessors, participant blinding, and lack of participant adherence to the program. Freitas examined the effect of aerobic and resistance training on obese adults (BMI 30-39.9 kg/m^2) with asthma on PA (daily steps), anxiety and depression (HADS score) and asthma symptoms (asthma symptom free days) (35). Those in the intervention group had significantly greater daily step counts (3068α2325 vs. 729α1118; $p=0.019$), asthma symptom free days 14.5α9.6 vs 8.6α11.4 $p<0.05$) and proportion of participants with a decrease in depression symptoms (76.4% vs. 16.6%, $p<0.01$) (23).

Breathing and Relaxation Training—Asthma patients often have dysfunctional breathing with hyperventilation and wheezing, that is often compounded by anxiety and other complex pathophysiologic mechanisms (37). Breathing retraining is a method of relaxation training that includes instruction in pursed lip breathing, reduced respiratory rate, and coordinated breathing and has been shown to improve respiratory parameters as well as reduce anxiety and stress (38). Laurino et al. studied a breathing retraining program held weekly for three months in adults with asthma, and found a within group improvement in agoraphobia and panic disorder ($p<0.05$) but between group differences were not found (39). The study also found a reduction in anxiety symptoms between groups, but these reductions were not statistically significant. Holloway et al. studied the effect of integrated breathing and relaxation techniques in asthma patients (40). They found a significant decrease in depression at 12 months and anxiety at 6 months as measured by HADS in the treatment group compared to the usual care group (control). Their findings were supported by Thomas and colleagues who conducted a randomized clinical trial of breathing modification techniques in adults with asthma and found a reduction in anxiety and depression symptoms at 6 months (41). More recently, Pourdowl et al conducted a study

to test the effectiveness of relaxation training on anxiety and quality of life outcomes in patients with asthma (42). The study consisted of 6 relaxation training program sessions over 6 weeks with specific long- and short-term goals. Outcomes were measured before and after each session showing a significant change in the Spielberger anxiety questionnaire (STAI) after intervention with a reduction from 102.6 to 79.5 ($p<0.001$). Quality of life also increased after relaxation training ($p<0.001$). This study is in line with the findings from Holloway et al in its effective use of the Papworth method of relaxation. Overall, the studies to date that included breathing exercises and retraining therapies show promise in reducing anxiety and depression scores in adults with asthma.

Imagery—One study compared biologically targeted imagery (BTI) and critically thinking asthma management (CTAM) to a waitlist control group. The study included 70 adults with asthma and participants did not have underlying mental health disorder (43). BTI consisted of participants creating imagery that represent health lung functioning twice a week for 6 weeks. CTAM consisted of each individual creating and developing a plan that emphasized the removal of allergy and asthma triggers from the home and work, family support and stress reduction. Improvements in both asthma symptoms (wheezing, $p=0.0062$), psychological symptoms (anxiety, $p=0.0352$; HAT chance, $p=0.0035$) and asthma knowledge ($p=0.027$)/attitude ($p=0.0001$)/self-efficacy ($p<0.0001$) were found in the BTI group compared to the control group. The BTI groups also had a significant improvement in the unsure and confused domains of the POMS-BI when compared to CTAM group. The CTAM group showed improvements in asthma knowledge ($p=0.0075$), attitude ($p=0.0001$) and self-efficacy ($p=0.0011$) domains compared to the control group. No between group changes in psychological outcomes was found in the CTAM vs. control group. Epstein and colleagues conducted a study of mental imagery relaxation exercises in adults with asthma and found no significant effect on anxiety or depression (44).Additional larger studies ursing imagery will need to be performed to test the efficacy of the intervention in adults with asthma.

Spiritual Healing—A single-blind randomized controlled trial of spiritual healing in adults with asthma showed no significant changes with spiritual healing in psychosocial (HADS) or asthma-related quality of life (AQLQ) parameters (45).

Complementary and Alternative Medicine (CAM)—The efficacy of complementary and alternative medicine (CAM) on asthma has limited evidence. A study by Mehl-Madrona et al. examined the role of 12 sessions (over 6 weeks) of acupuncture alone, craniosacral therapy alone or the combination of acupuncture + craniosacral therapy in 89 adults with persistent asthma. They found statistically significant reductions in asthma-related quality of life with acupuncture alone and craniosacral therapy alone at 6 weeks and 3 months (46). The combination of acupuncture and craniosacral treatment was not superior to each therapy alone. Larger scale studies need be conducted to examine if CAM should be used to complement medical management of depression and anxiety in asthma.

Discussion

With an increasing understanding of the association between depression and anxiety with asthma, there is a surprising dearth of investigation of treatments that specifically target depression and anxiety in asthma patients. The field of pharmacologic interventions for depression in asthma is nascent, and there is inadequate evidence to make definitive conclusions about the efficacy of antidepressants in treating asthma-related depression (Table 4). While the reviewed studies found that patients with more severe asthma and depression symptomatology may have a positive response in terms of asthma control with escitalopram, there was little evidence for its effectiveness in improving depressive symptoms. The short duration of these medication trials may have limited the full effect of SSRI treatments, as SSRI may take at least 6 weeks to show effect and even longer to maximize effects. Further studies with larger sample sizes and longer trial duration of antidepressant medications are important to better understand the role of pharmacologic therapies to treat depression in asthma. Furthermore, additional studies are needed to examine outcomes such as hospital utilization, cost effectiveness, and adverse events in depressed individuals with asthma, as well as the relationship between dosing and clinical benefit. Interestingly, we did not find any studies in our search that have assessed pharmacologic therapy for anxiety disorders in asthma.

The papers examining the effect of CBT/CBPT and psychoeducation compared to usual care showed that both individual or group CBT may improve asthma quality of life, anxiety levels, depression and decrease asthma specific panic fear in patients with asthma compared to usual care. However, studies were limited due to the small sample sizes and high attrition. Further, the effects of the interventions were not sustained after the intervention with the exception of two studies(27, 29). Yorke et al showed higher drop-out rates in the group-CBT than control, indicating possible attrition bias (25). Furthermore, the studies lacked attention controls, and participants were aware of the CBT intervention throughout the study. Overall, the evidence in CBT to treat mood disorders, reduce mental health symptoms and improve asthma outcomes is weak and larger and longer studies of CBT are needed. These conclusions were similar to the findings in a 2006 Cochrane review of CBT in asthma (47).

There is growing evidence supporting the relationship between lifestyle medicine and improved asthma outcomes, but more RCTs are required that study these interventions on adults with asthma with depression and anxiety. The studies included in this review showed that physical activity was associated with improvements in psychosocial quality of life and symptom free days in patients with asthma, but there was a lack of studies with primary outcomes with asthma quality of life and depression and anxiety/panic symptoms. The included physical activity intervention studies did not include people with underlying anxiety and depression disorders as seen in the pharmacologic and CBT intervention groups. Though many of the participants had depression and/or anxiety symptoms at baseline. The mechanism between physical activity in asthma and depression/anxiety is unclear, and future work should assess other related and moderating effects. There was weak evidence for spiritual healing and imagery instruction for depression/anxiety and asthma. The included studies for spiritual healing and breathing did not specify inclusion criteria for anxiety or depression disorder, but the studies did show a reduction in anxiety and depression scores.

Studies that address the mechanism of depression and anxiety in asthma are needed as they can provide low-cost and accessible methods of treating asthma.

The overall quality of evidence presented was low due to several factors. Many of the studies did not report patient selection methods which creates a risk of selection bias that is unclear. Furthermore, most of the studies had small sample sizes with high attrition rates, limiting power of the studies. The evidence is also limited on the precise physiological mechanisms of asthma and depression/anxiety. Many of the interventions had a short duration (8 weeks-3 months) with a limited assessment of long-term outcomes and maintenance therapy. This contributes to the low quality of the existing evidence. These weaknesses prevented definitive clinical conclusions to be made about the role of medications and psychological interventions in asthma.

Furthermore, studies lacked uniformity in the diagnostic criteria for asthma, anxiety and depression. Cut-offs for psychological symptom scales determining the recruitment of participants varied from study to study. Many of the studies examined differing disease symptom severities in the population without controlling adequately for them; some studies recruited participants ranging between mild asthma symptoms, and severe refractory asthma. With a lack of uniformity among dignostic criteria and lack of diagnostic tools, undergianosis of comorbidities is often found.They also studied different physiologic and psychologic outcomes, making it difficult to pool data. Most of the studies used validated questionnaires yet these rely on patient self-reports, are often crude, lack sensitivity and do not account for day-to-day variations in mental health symptoms that may mediate physical activity and pulmonary symptoms. Lack of uniformity can be reduced with the addition of precise measurement data that removes variability in day-to-day mental health symptoms.

Limitations of this study are due to the nature of scoping reviews. Due to the scoping review’s broad topic and aim to review available literature, not all relevant articles may be identified. This paper is a review of available literature and does not mean to pose as an evaluation of best research available on a particular hypothesis as seen in an exhaustive systematic review. Variation in study design and sample size would make performing a meta-analysis difficult.

Conclusion

Depression and anxiety are common in asthma and can worsen asthma outcomes.

There is a need for well-designed studies that evaluate the effects of pharmacologic treatment, psychological therapies, lifestyle medicine and CAM interventions on asthma in depressed and anxious adults to better understand their relationship. Our findings mirrored the conclusions in the 2006 Cochrane systematic review on psychological interventions in asthma (47). Future work should assess for potential moderating and mediating effects (i.e. medical adherence) on asthma outcomes as well as psychophysiologic interventions in asthma patients with co-morbid depression and/or anxiety. By developing better treatments for asthma patients with depression and/or anxiety, we can improve patient outcomes as well as reduce morbidity and mortality associated with asthma.

Acknowledgements

We would like to thank Valentin Prieto-Centurion for his assistance in planning the manuscript.

Abbreviations:

ACQ	Asthma Control Questionnaire
AQLQ	Asthma Quality of Life Questionnaire
CAM	Complementary and Alternative Medicine
CBT	Cognitive Behavioral Therapy
COPD	Chronic Obstructive Pulmonary Disease
DALYs	disability-adjusted life years
HADS	Hospital Anxiety and Depression Score
HRDS	Hamilton Rating Scale for Depression
HRQoL	Health Related Quality of Life
IDS-SR	Inventory of Depressive Symptomatology-Self-Report
PA	Physical Activity
RCT	Randomized Control Trial
SSRI	Selective Serotonin Reuptake Inhibitor

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Table 1:

Pharmacologic interventions in asthma

Study	Population	Intervention	Comparator	Outcome	Timing	Setting	Results
Brown 2005[22]	90 adults with asthma and major depressive disorder	12-week double-blind trial of citalopram	Placebo vs citalopram	Primary Outcome: HRSD, IDS-SR Secondary Outcomes[1]: ACQ, AQLQ, corticosteroid use	Intervention: 12 weeks Outcomes Measured: Baseline, weeks 1, 2, 4, 6, 8 and 12	unspecified	**Between group differences:** No significant difference in HRDS, IDS-SR, ACQ at all timepoints measured. Significant difference in oral steroid use F1,273 6.26, (P=0.013) at all lime points measured and follow up assessments.
Brown 2018[23]	139 adults with asthma and major depressive disorder	12-week, double-blind escitalopram (10mg/d) trial	Placebo vs escitalopram; high severity depression (HRSD score ≥ 20) vs low severity depression	Primary Outcomes: ACQ, HRSD, IDS-SR, corticosteroid use	Intervention: 12 weeks Outcomes Measured: Baseline, weeks 1 through 4 and then biweekly for weeks 6, 8, 10, and 12	unspecified	**Between group differences:** No statistically significant in ACQ, HRDS, or IDS-SR. Sub-analysis of higher severity of depression completers: - Change in ACQ between group difference t:t(19)= 2.27; P=.04; d=1.04 - Change in corticosteroid use between group difference: t(19)=2.18; P=0.04; d=1.00 - No statistically significant between group differences in HRSD or ISD-SR observed.
Brown 2012[24]	26 adults with asthma and major depressive disorder	12-week double-blind escitalopram trial	Placebo vs escitalopram	Primary Outcome: ACQ, HAM-D, IDS-SR, oral prednisone use	Intervention: 12 weeks Outcomes Measured: Baseline, weeks 1 through 4 and then biweekly for weeks 6, 8, 10, and 12	unspecified	**Between group differences:** No significant change in HAM-D and IDS-SR. **Combined total sample analysis:** Significant change in HAM-D (t=0.38; P<0.01) and IDS-SR (t=0.49; P<0.01) between baseline and 12 weeks. ACQ correlated with IDS-SR: τ=0.49 – 0.60, P <0.05 in escitalopram, placebo, and combined sample. ACQ correlated with HAM-D in placebo and combined sample only (τ=0.38 – 0.58, P <0.05). No significant difference in oral prednisone use.

1 Secondary Outcomes include only psychosocial, asthma symptoms, and asthma quality of life measures

Hamilton Rating Scale for Depression (HAM-D-17); Hamilton Rating Scale for Anxiety (HAM-A), Hamilton Rating Scale for Depression (HRSD), Inventory of Depressive Symptomatology-Self Report (IDS-SR), Asthma Control Questionnaire (ACQ), Asthma Quality of Life Questionnaire (AQLQ), Dyspnoea-12 (D-12), General Anxiety Disorder questionnaire (GAD-7), Patient Health Questionnaire (PHQ-9), State-Trait Anxiety Inventory (STAI score), Beck's Depression Inventory (BDI), Beck's Anxiety Inventory (BAI)

Table 2:

Psychological interventions in asthma

Study	Population	Intervention	Comparator	Outcome	Timing	Setting	Results
Yorke 2016[25]	51 adults with severe refractory asthma and clinically significant diagnosis of anxiety or depression (HADS>8)	Group-CBT (1.5 hours per session) for 8 weeks delivered by trained clinical psychology therapist	Usual care	Primary Outcome: Psych: HADS, EuroQual5 Asthma: AQLQ, ACQ, Dyspnoea-12	Intervention: 8 weeks Outcomes Measured: Baseline, week 8 and week 16	Unspecified; national specialist severe asthma clinics	**Between group differences:** Significant change in Dyspnea-12 (physical) in group-CBT vs. usual care (d= 0.66; p<0.05). No significant between group difference for AQEQ, ACQ, HADS and EuroQual15.
Ross 2005[26]	48 women with physician diagnosed asthma and panic disorder (based on severity)	CBT + asthma education (CBT-AE) was delivered in small groups (3-5 patients) which received twelve 90-minute treatment sessions over 8 weeks. Sessions 1-8 were conducted twice weekly and sessions 9-12 were spaced 1 week apart. All sessions were conducted by two trained nurse clinicians.	Wait-list control (WLC)	Primary outcomes: (not explicitly stated) Psych: panic attack diary, Sheehan Patient-Rated Anxiety Scale (SPRAS), Anxiety Sensitivity Index (ASI), Agoraphobia subscale of the Fear Questionnaire (FQ-Ago), Beck Depression Inventory (BDI). Asthma: symptoms diary, lung function (peak flow variation-PFV and morning peak expiratory flow- PEF), quality of life (AQEQ)	Intervention: 12 sessions over an 8-week period Outcomes: Treatment group: baseline, 8 weeks and 6 months WFC group: baseline, 8 weeks, 16 weeks, 6 months	Unspecified	**Between group difference:** Statistically significant interaction between total number of panic attacks during 2 weeks, $F(1, 21) = 5.29$, $p = .03$; total SPRAS, $F(1, 22) = 12.75$, $p \leq .01$; and the total ASI, $F(1, 22) = 11.44$, $p \leq .01$ in CBT-AE vs. WLC. Significant difference in AQLQ, $F(1,19) = 11.03$, $p < .01$; and morning PEF, $F(1, 17) = 6.86$, $p \leq .05$ in CBT-AE vs. WLC.
Parry 2012[27]	94 adults with asthma and anxiety (HADS-A>8) or (ASC-PF>28)	Individual CBT intervention to improve self-management of their anxiety 1.5-hour intro 4-6 1-hour sessions +− 2 follow-up sessions	Usual Care	Primary Outcomes: Psych: panic-fear sub-scale of the Asthma Symptom Checklist, a self-report measure of asthma-specific fear Secondary Outcomes: Psych: HAD-D, HAD-A	Intervention: 5-9 sessions Outcomes Measured: Baseline, 1.5-3 months end of treatment, 6 months follow up	Unspecified	**Between group differences:** CBT vs usual care: Significant change in panic fear at end of treatment (−2.59 95% CI: −4.39 to −0.79; p<0.01) and 6 months (−2.87 95% CI: −5.12 to −0.62; p<0.01) in ITT analysis. Significant change in panic fear in complete case analysis at end of treatment (−5.15 95% CI −8.34 to −1.96; p=0.002) only. Significant Change in HAD-Depression (−1 95% CI: −2.0 to −0.1); p=0.04) at end of treatment in ITT analysis. Significant change in asthma-specific quality of life (−1.18 95% CI: −2.26 to −0.10) at end of treatment but not at 6 months.
Feldman[28] 2016	53 Latino adults with physician confirmed asthma, met DSM-IV criteria for current	Individual CBPT weekly for 8 weeks. Available in English or Spanish and delivered by a trained therapist.	Music Relaxation Therapy (MRT) weekly for 8 weeks. Available	Primary outcomes: Psych: PDSS, CGI scale, ASI-3 Asthma: adherence to inhaled corticosteroid use	Intervention: 8 weeks Outcomes measured: Baseline, week 4,	Bronx, NY	**Between group difference:** Significant change in MARS from baseline to post-treatment in CBPT versus MRT (d = 0.76), p =0.017 and baseline to 3-month follow-up

Study	Population	Intervention	Comparator	Outcome	Timing	Setting	Results
	panic disorder and PDSS ≥ 8		in English or Spanish.	(MARS), asthma control (ACQ and pulmonary physician assessment), Secondary outcomes: Psych: AGOR, BSQ, BDI, credibility/expectancy (CEQ) Asthma: quality of life (AQLQ), rescue medication use	week 8 and 3-months		in CBPT versus MRT (d=1.07), p = 0.006. No significant change in PDSS, CGI, ASI-3, ACQ, AGOR, BSQ, BDI, AQLQ, rescue medication use and CEQ.
Stoop 2015[29]	46 adults treated in somatic managed care programs for type 2 diabetes or asthma and COPD who had anxiety or depression (determined by Mini-International Neuropsychiatric Interview)	12-month Disease Management program for Co-morbid Depression and Anxiety which involved stepped care treatment that starts with psychoeducation, then a 10-week course based on CBT principles.	Usual care plus monitoring by questionnaire	Primary Outcome: GAD-7, PHQ-9	Intervention: 12 months Outcomes Measured: Baseline, 12-months intervention and 18 months (six months post intervention)	large primary care organization	**Between group difference:** Intervention vs. Usual care: Significant change in anxiety (GAD-7, fully adjusted)[1] at 12 [f(6, 29)=4.24, p=0.048] and 18 months measured time point [f(6, 28)=8.52, p=0.0007]. Clinically significant change in depression (PHQ-9; fully adjusted) p=0.099, Cohen's d=0.63.
Sommaruga 1995[30]	40 hospitalized adults with asthma	Asthma education occurred twice during admission and quarterly over 1 year. CBT: 3 individual meetings with psychologist over 1 year.	Treated according to International Asthma Guidelines and followed 6 times over 1 year by same physician using examination and spirometry	Primary outcomes (not stated): Psych: Anxiety (STAI X2); depression (QD); psychophysiologic disorders (QPF); Asthma symptom checklist (fear-panic); respiratory illness opinion survey (optimism, negative staff regard, external control, specific internal awareness, psychological stigma, authoritarian attitude); health locus of control scale (internal beliefs, external control, external powerful others); Asthma: missed work/ school; number of asthma attacks, emergency visits and hospitalizations	Intervention: 10±2 (Control Group) day admittance with quarterly asthma lesions and follow up appointments 6 times in the following year	Hospital and home in Italy	**Between group difference:** Number of asthma attacks (p<0.05) at 1 year was lower in the intervention group vs. control group. No significant difference in anxiety depression or psychophysiologic disorders at baseline or post-intervention.
Grover 2007[31]	40 adults (18-45 years old) with asthma diagnosis for at least 2 years and working knowledge of English and Hindi.	CBT consisted of 15 individually tailored 1-hour sessions over 6-8 weeks Other components: asthma self-management program (asthma education, self-management, breathing exercises, behavioral counseling to significant others, self-monitoring)	Self-management (SM) group: asthma self-management program (asthma education, self-management, breathing exercises, behavioral counseling to	Outcomes: Psych: anxiety, HADS Asthma: symptoms (ASC, asthma diary), asthma bother profile (ABP), quality of life (AQLQ), peak expiratory flow rate (PEFR)	Intervention: 6-8 weeks Outcomes: baseline, post-intervention (6-8 weeks), 12-week follow-up in subset of patients	Bangalore, India	**Between group difference:** Significant improvement in asthma symptoms (p<0.01), asthma bother (p<0.05), anxiety, depression (p<0.01) and in asthma quality of life (p<0.05) from baseline to post-intervention in CBT group vs. SM group .

Study	Population	Intervention	Comparator	Outcome	Timing	Setting	Results
			significant others, self-monitoring) 10 1-hour sessions over 6-8 weeks.				

1 Fully adjusted for age, sex and education for (f(6,29) and (f(6,28) Cognitive Behavioral Therapy (CBT); The Agoraphobia Cognitions Questionnaire (AGOR); Mini Asthma Quality of Life Questionnaire (AQLQ); Anxiety Sensitivity Index-3 (ASI-3); The Beck Depression Inventory-II (BDI); The Body Sensations Questionnaire (BSQ); Cognitive behavioral psychophysiologic therapy (CBPT); Clinical Global Impression Scale (CGI); Credibility/Expectancy Questionnaire (CEQ); Generalized Anxiety Disorder 7-item (GAD-7) scale; Hospital Anxiety and Depression Scale (HADS); Panic Disorder Severity Scale (PDSS); Patient Health Questionnaire (PHQ-9)

Table 3:

Lifestyle Medicine Interventions (Physical Activity, Breathing/Relaxation Training, Imagery, Spiritual Healing) and Complementary and Alternative Medicine in Asthma

Study	Population	Intervention	Comparator	Outcome	Timing	Setting	Results[1]
Lifestyle Interventions							
Mendes 2010[33]	101 adults with asthma	Educational program plus breathing exercises (30 min) plus aerobic training (30 min)	Educational program plus breathing exercises	Primary Outcomes: HrQoL Secondary Outcomes[1:] STAI score, BDI score, asthma symptom-free days	Intervention: Twice a week for 3 months Baseline, after treatment	Unspecified	**Between group differences:** No significant difference in HRQoL psychosocial domain, anxiety or depression levels (p<0.001). Moderate linear relationship between baseline anxiety (r=0.52; P <.001) and depression (r=5 0.62; P <.001) scores
Coelho 2017[34]	37 adults with asthma with regular drug therapy	12-week unsupervised pedometer-based physical activity program on daily steps	Usual care	Primary Outcomes: Change in the number of steps Secondary Outcomes: changes in asthma control, health-related quality of life, HAD-A, HAD-B	Intervention: 12 weeks Outcomes Measured: Baseline, 12 weeks, 24-48 weeks	home	**Between group differences:** No significant difference between HAD-A, HAD-D, ACQ, or AQLQ at all timepoints.
Freitas 2018[35]	51 Obese (BMI 30-39.9 kg/m^2) adults with asthma	Weight loss program in addition to exercise (aerobic and resistance) training (WL +E_{group}, n=25)	Weight loss program in addition to Sham (breathing and stretching exercise) (WL+ S_{group}, n=26)	Primary outcomes: daily steps (accelerometer), HADS, asthma symptom free days Secondary outcomes: Berlin Questionnaire	Intervention: 3 months Outcomes measured: baseline and 3 months.	Unspecified	**Between group difference:** Significant change between daily steps (3068±2325 vs. 729±1118; p=0.019). Significant change in proportion of participants with a decrease in depression symptoms (76.4% vs. 16.6%, p<0.01). Significant change in asthma symptom free days (14.5±9.6 vs 8.6±11.4p<0.05) in WL+E group. No between group difference in anxiety (p=0.63)
Laurino 2012[39]	38 adults with asthma who had well-controlled symptoms	A chest physiotherapy group that included a breathing retraining program	Paired control group that included a Subtle Touch	Primary Outcomes: Quality of Life Questionnaire, asthma clinical control Secondary Outcomes: Sheehan Anxiety Scale	Intervention: 3 months weekly Outcomes Measured: Baseline, 12 weeks	clinic	**Between group differences:** No significant difference in asthma outcomes, anxiety, panic or agoraphobia.
Holloway, 2007[40]	85 adults with asthma	An integrated breathing and relaxation technique known as the Papworth method, Five 60min treatments	Usual care	Primary outcome St George's Respiratory Symptoms Questionnaire (SGRQ).	Intervention: 6 months Outcomes Measured: baseline, Post-treatment (6 months after	clinic	**Between group differences:** Significant difference in HADS anxiety scores (p=0.006) 6 months post baseline and

Study	Population	Intervention	Comparator	Outcome	Timing	Setting	Results[1]
		with a respiratory physiotherapist		Secondary Outcomes[1]: HADS	baseline) and at 12 months		depression scores (p=.03) at 12 months post baseline with treatment.
Thomas 2009[41]	Adult with mild to moderate symptomatic asthma	Breathing training (BT) (three sessions of physiotherapist-directed breathing exercises)	Sessions with a health professional (asthma nurse) delivering asthma education	Primary outcome: AQLQ score Secondary Outcomes[1]: ACQ, HAD	Intervention: Outcomes measured: Baseline, 1 month, 6 months	unspecified	**Between group differences:** No significant difference at 1 month for AQLQ, ACQ and HAD scores. Significant between-group differences favoring breathing training in HAD anxiety (1.1, 95% CI 0.2 to 1.9), HAD depression (0.8, 95% CI 0.1 to 1.4) at 6-month outcome. Trends to improved ACQ (0.2, 95% CI 0.0 to 0.4).
Pourdowl 2019[42]	30 adults with asthma	Relaxation training program was conducted in 6 sessions over 6 weeks. Participants were given different short term and long-term goals for each session.	Usual Care	Primary outcomes: STAI, QOL	Intervention: 6 weeks Outcomes measured: Before and after each session and follow up (end of week 6 for control group and weeks 3,5, 12 of follow up for case group)	Unspecified	**Between group differences:** Significant change in STAI after intervention with reduction from 102.6 to 79.5 (P-value <0.001) QOL increased after relaxation training from 308.07 to 546.6 (P<0.001)
Freeman 2005[43]	70 adults with physician diagnosis of asthma	All participants received an asthma education session. Group 1: Biologically targeted imagery (BTI) which consisted of participants creating imagery that represent health lung functioning. Group 2: Critically thinking asthma management (CTAM) where each individual created and developed a CTAM plan that emphasized the removal of allergy and asthma triggers from the home and work, family support and stress reduction. Participants were instructed to devote 30 minutes, 5 days a week outside of class (BTI or CTAM).	Wait-list control (WLC)	Primary outcomes: (not stated) Dependent variables: -Psych: profile of mood states (POMS-BI), health attribution test (HAT), and Revised Asthma Problem Behavior Checklist (RAPBC) scores -Asthma: asthma symptoms, asthma knowledge/self-efficacy (KASE-AQ),	Intervention: Twice a week for 6 weeks Survey outcomes measured pre- and post-intervention or post-waitlist control Asthma symptoms measured twice daily, on a diary. Data were averaged into 3-week periods (weeks 1–3, 4–6, 7–9, and 10–12)and reported as Time 1, 2, 3, and 4.	Alaska Regional Hospital, Anchorage	**Between group difference:** BTI vs. WLC: Significant improvement in wheezing (p=0.0062), anxiety reduction (p=0.0352), HAT chance domain (p=0.0035), KASE-AQ knowledge (p=0.027), attitude (p=0.0001) and self-efficacy (0.0001) domains. BTI vs. CTAM: Significant improvement in POMS-BI domains of unsure (p=0.007) and confused (p=0.046). CTAM vs. WLC: Significant improvement in KASE-AQ knowledge (p=0.0075), attitude (p=0.0001) and self-efficacy (p=0.0011) domain.
Epstein, 2004[44]	68 adults with symptomatic asthma	Individual imagery instruction (week 1) and follow-up (weeks 4, 9,	Usual care	Primary Outcomes: Spirometry (FEV1), medication use,	Intervention: 4 weeks Outcomes measured:	unspecified	**Between group differences:** No statistically significant

Study	Population	Intervention	Comparator	Outcome	Timing	Setting	Results[1]
		15). Participants were given 7 imagery exercises to select from and practice 3 times a day for a total of 15 minutes.		Secondary Outcomes, AQLQ, BDI, Spielberger Anxiety Scales (A-State and A-Trait, Barrett Power as Knowing Participation in Change Tool, Epstein Balloon Test of Ability to Image	Baseline, 4 time points over 17 weeks		differences at all measured outcomes.
Cleland, 2006[45]	88 adults taking pharmacological treatment for asthma	5 sessions of spiritual healing	placebo sessions (delivered by an actor)	Primary outcome: AQLQ Secondary Outcomes[1]: HADS	Intervention: 5 weeks Outcomes measured: Baseline, week 2, week 4 (first weekly treatment), week 12 (follow-up), week 26 (long-term follow-up)	unspecified	**Between group differences:** No statistically significant differences in AQLQ, HADS.
Complementary and Alternative Medicine							
Mehl-Madrona 2007[46]	89 adults with persistent (mild, moderate and severe) asthma	12 sessions of equal length of: (1) acupuncture, (2) craniosacral therapy, (3) combination of craniosacral therapy with acupuncture	Attention control: 6 sessions of sham craniosacral therapy and six one-on-one asthma education classes Standard of care, waitlist control: normal asthma care regimen, offered acupuncture, craniosacral therapy or combination of both at end of study.	Primary Outcomes: pulmonary function, AQLQ Secondary Outcomes[1]: BDI, BAI, Short Form 36: Profile of Mood States	Interventions: 12 sessions over 6 weeks Outcomes measured: Baseline, 6 weeks, 3 months, 6 months	unspecified	**Between group differences:** Significant difference in AQLQ score at: 6 weeks (−3.61, 95% CI: −6.02 to −1.20; p=0.004). 3 months (−2.46, 95% CI: −4.80 to −0.12; p=0.039) No significant difference in depression or anxiety scores between treatment vs control.

[1]Only mood related outcomes and asthma symptoms reported; Beck Anxiety Inventory (BAI), Beck's Depression Inventory (BDI),Hamilton Rating Scale for Depression (HAM-D-17), Hamilton Rating Scale for Anxiety (HAM-A), Health-related quality of life (HRQoL), Inventory of Depressive Symptomatology-Self Report (IDSSR), Asthma Control Questionnaire (ACQ), Asthma Quality of Life (AQLQ), Dyspnoea-12 (D-12), General Anxiety Disorder questionnaire (GAD-7), Patient Health Questionnaire (PHQ-9), State-Trait Anxiety Inventory (STAI score), Beck's Depression Inventory (BDI), Beck's Anxiety Inventory (BAI), Quality of life (QOL), Spielberger Anxiety questionnaire (STAI)

Table 4:

Summary of the state of science and future research considerations of intervention studies

	Pharmacologic	**Psychological**	**Lifestyle Medicine and CAM**
Summary of state of science	Patients with more severe asthma and depression symptomatology may have a positive response in terms of asthma control with escitalopram but show little evidence for its effectiveness in improving depressive symptoms. Changes in asthma symptom severity correlated positively with changes in depression symptom severity. *Caution should be used in any interpretation of these studies, as we only reviewed 3 studies with low sample sizes.	Group and Individual CBT may improve asthma quality of life, anxiety levels, depression and decrease panic fear in patients with asthma compared to usual care. The effects were often short-term and were not usually sustained at long-term follow-up (6-months). Overall quality of evidence on effectiveness of CBT is poor due to differences in study design, type of CBT, and lack of attention control in studies.	Physical activity is associated with improvements in psychosocial quality of life and symptom free days in adults with asthma Breathing relaxation and retraining therapy with a trained physiotherapist improves anxiety scores. Weak evidence for spiritual healing, and imagery instruction for depression/anxiety and asthma.
Future research considerations	Adequately powered RCTs are necessary to verify the efficacy of anti-depressants in asthma, particularly in severely depressed individuals. Longer duration of treatment and period of observation would explore the full impact of SSRIs on asthmatic adults. Researchers should consider studying outcomes such as hospital utilization, cost effectiveness, and adverse events. Researchers should consider further studies that assess the relationship between antidepressant dosing and clinical benefit.	Larger RCTs with adequate power is needed. Researchers should consider including medical adherence as an outcome.	Complementary medicine interventions should be well described and based in strong theoretically background. Researchers should consider exploring interventions in patients with mood disorders and asthma and assessing mood-disorder related primary outcomes in asthma.

CAM (Complementary and Alternative Medicine); RCT (Randomized Control Trials)