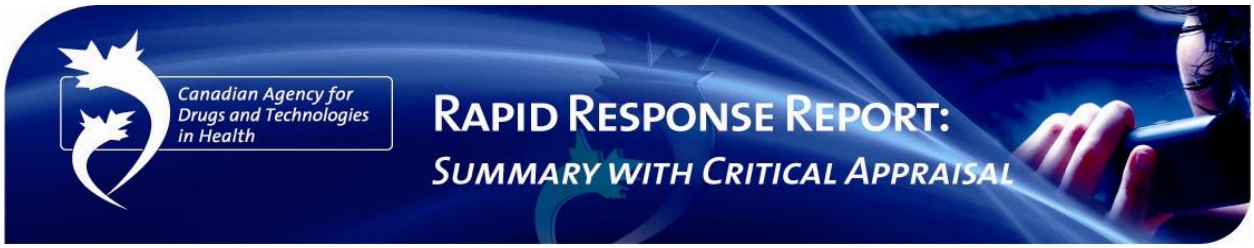

TITLE: Buspirone for the Treatment of Anxiety: A Review of Clinical Effectiveness, Safety, and Cost-Effectiveness

DATE: 03 May 2012

CONTEXT AND POLICY ISSUES

Generalized Anxiety Disorder (GAD) is a chronic anxiety disorder characterized by excessive, pervasive and uncontrollable worry.[1] In the general population, GAD has a lifetime prevalence of 6%.[1] Diagnosed twice as often in women than men, GAD typically presents as somatic illness, pain, fatigue, depression and/or sleep disturbances.[1] Diagnosis can be made using the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Disease 10 (ICD-10) as GAD can be mistaken for hypochondriasis or major depression.[1] Illness severity and response to therapy are assessed using the Hamilton Anxiety Rating Scale (HARS).[1] In clinical trials, response is often defined as a Clinical Global Impression Score (CGI) of less than 2% or a 50% reduction in HARS score. Pharmacological treatments for GAD include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, anticonvulsants, benzodiazepines (BZD), buspirone, and other therapies.[1] First-line agents include excitalopram, paroxetine, sertraline, or venlafaxine extended release (XR). Patients who have inadequate response to first-line agents after eight to twelve weeks of treatment should be considered for second-line medication.[1] If an SSRI was chosen initially and was ineffective, a switch to another SSRI or an SNRI should be considered.[1] Second-line therapies include BZD, buspirone, imipramine and pregabalin.[1] While BZD are second-line treatment, they may be used at any time if agitation or anxiety is severe.[1]

This review evaluates the comparative effectiveness, safety and cost-effectiveness of buspirone versus BZD, SSRIs, and SNRIs.

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of buspirone versus benzodiazepines, serotonin reuptake inhibitors, or serotonin-norepinephrine reuptake inhibitors for the treatment of anxiety?

2. What is the comparative safety of buspirone versus benzodiazepines, serotonin reuptake inhibitors, or serotonin-norepinephrine reuptake inhibitors for the treatment of anxiety?

3. What is the cost-effectiveness of buspirone versus benzodiazepines, serotonin reuptake inhibitors, or serotonin-norepinephrine reuptake inhibitors for the treatment of anxiety?

KEY MESSAGE

There is no conclusive evidence to suggest that buspirone is more effective than BZD, SSRIs, or SNRIs. Buspirone was associated with less drowsiness, fatigue, nervousness, depression and sleep disturbance than BZD.[2] SSRIs and SNRIs can cause sedation, dizziness, falls, nausea, and sexual dysfunction.[2] No evidence was found regarding the cost-effectiveness of buspirone versus BZD, SSRIs or SNRIs for the treatment of GAD.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, CINAHL, The Cochrane Library (2012, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated lists of major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2002 and April 5, 2012.

Selection Criteria and Methods

One reviewer screened citations to identify health technology assessments, systematic reviews, meta-analyses, randomized and non-randomized studies, and economic evaluations on the use of buspirone for the treatment of anxiety. Potentially relevant articles were ordered based on titles and abstracts, where available. One reviewer considered full-text articles for inclusion according to the selection criteria listed in Table 1.

Population	Adults with generalized anxiety disorder (GAD)
Intervention	Buspirone
Comparator	Benzodiazepines (BZD) Selective Serotonin Reuptake Inhibitor (SSI) Serotonin-Norepinephrine Reuptake Inhibitor (SNRI)
Outcomes	Clinical effectiveness Safety: overuse, dependency, sedation/sleepiness Cost-effectiveness
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCT), non-randomized studies, and economic evaluations

Exclusion Criteria

Articles were excluded if they did not satisfy the selection criteria, if they had incomplete methods, were included in a selected systematic review, or were narrative reviews or case reports.

Critical Appraisal of Individual Studies

Critical appraisal of the included studies was performed based on study design. Systematic reviews were assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) criteria.[3] Randomized studies were assessed for quality using the Down's and Black instrument.[4] Instead of calculating numeric scores, the strengths and limitations of each study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 102 citations. Upon screening titles and abstracts, 10 potentially relevant articles were retrieved for full-text review. Two potentially relevant reports were retrieved from grey literature and hand searching. Of the 12 potentially relevant reports, one contained an irrelevant population, two contained an irrelevant intervention, one was a duplicate and three were narrative reviews. Five publications were included in this review. The process of study selection is outlined in the PRISMA flowchart (Appendix 1).

1. Comparative Clinical Effectiveness and Safety of Buspirone for Anxiety

Summary of Study Characteristics

The comparative clinical effectiveness of buspirone was reported in four systematic reviews and meta-analyses[2,5-7] and one RCT.[8] The New Zealand systematic review reported on the effectiveness and safety of abecarnil, antidepressants, antipsychotics, applied relaxation, BZD, buspirone, cognitive behavioural therapy, hydroxyzine, and pregabalin for the treatment of GAD in adults.[2] A United States Cochrane review reported on the comparative effectiveness and safety of azapirones, placebo, BZD, antidepressants, psychotherapy or kava kava for the treatment of GAD in adults.[5] Another review from the United States reported on the comparative effectiveness of pharmacologic treatments for GAD in adults and children.[6] A German systematic review compared the effectiveness of BZD and azapirones for treating GAD in adults.[7] A randomized, single-blind study compared the effectiveness of sertraline and buspirone for the treatment of GAD in elderly patients.[8] Studies were conducted in New Zealand,[2] the United States,[5,6] Germany[7] and Iran[8] between 2005[7] and 2011.[2] Summaries of study characteristics, critical appraisal and study findings can be found in Appendices 2, 3, and 4, respectively. A summary of the clinical evidence on the comparative effectiveness and safety of buspirone for anxiety can be found in Table 2.

Systematic reviews and meta-analyses

Systematic reviews contained as few as eight[2] and as many as 48 studies.[7] While all systematic reviews included adults with GAD based on criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases 10

(ICD-10), one review contained two studies that included children.[6] Three systematic reviews compared the effectiveness of pharmacologic treatments including SSRIs, SNRIs, antipsychotics, BZD, buspirone, cognitive behavioural therapy, hydroxyzine, pregabalin, kava kava, complementary alternative therapies, and placebo.[2,5,6] The German review compared the drug classes BZD and azapirones for the treatment of GAD in adults.[7] Overall, the reviews reported on symptom severity using the Hamilton Rating Scale for Anxiety (HAM-A)[2,5-7] or the Clinical Global Impression Scale (CGIS),[5] compliance based on the number of drop outs,[5,7] quality of life (QoL),[2] and adverse events (AEs).[2,5]

RCTs

An eight-week randomized, single-blinded study compared buspirone (10-15 mg/day) versus sertraline (50-100 mg) for the treatment of GAD in elderly patients.[8] The study was conducted from February 2002 to December 2005 in an outpatient psychiatry clinic in Iran. Forty-six patients who met DSM-IV criteria for GAD and were older than 60 years of age were recruited for study. The mean age was 67 years and 57% of participants were female and demographic and clinical characteristics were comparable between groups after randomization.[7] The study reported on symptom severity at zero, two, four, and eight weeks using the Hamilton Rating Scale for Anxiety (HRSA), compliance and AEs.

Summary of Critical Appraisal

Systematic reviews and meta-analyses

All systematic reviews with meta-analyses[2,5-7] were based on a comprehensive literature search using pre-defined criteria. Three reviews reported restricting searches to English[2,6,7] or German[7] language articles. One[5] of four reviews reported that study selection was performed by two reviewers. Two reviews[2,5] listed both included and excluded studies, while two only reported included studies.[6,7] Two reviews reported extracting data in duplicate.[5,5] All reviews used appropriate methods to pool studies and assessed publication bias.[2,5-7] The German review conducted a random effects analysis and a sensitivity analysis excluding all studies that did not provide means and standard deviations to evaluate the stability of their results.[7] The systematic review from the United States assessed the robustness of their analysis by computing the number of studies with negative findings that would need to be combined with the studies reviewed in order to lead to non-significant results.[6] Three of four reviews provided conflict of interest statements.[2,6,7]

RCTs

The single-blind RCT had explicitly described the research question, eligibility criteria, interventions, outcomes, and patient characteristics.[7] While patients were randomized to treatment, the method of randomization was not reported.[7] Single-blinding was unclear and may have led to potential information bias. The study was sponsored by the university.[8]

Summary of Findings

Systematic reviews and meta-analyses

<u>Comparative Clinical Effectiveness of Buspirone versus BZD, SSRIs, and SNRIs</u>

The New Zealand review reported the effectiveness and safety of SSRIs, SNRIs, BZDs and buspirone in adults with GAD based on two systematic reviews and an RCT.[2] Compared with BZD, it is unclear whether buspirone is more effective for improving symptoms at six weeks.[2] The p value was not reported for an RCT that showed 54% of buspirone recipients and 61% of diazepam recipients had a 40% reduction in HAM-A at six weeks.[2] A systematic review reported that alprazolam was more effective than buspirone in reducing HAM-A Weighted Mean Difference (WMD: 1.1; 95% confidence interval [CI] 0.28, 1.92).[2] Another systematic review reported that lorazepam was more effective than buspirone in reducing HAM-A scores in 60 people (WMD: 1.1; 95% CI 0.29, 1.91).[2] Re-analysis of pooled drug company data suggested that recent use of BZD limited the effectiveness of buspirone in patients with GAD.[2]

The Cochrane review reported that azapirones, including buspirone, were superior to placebo for treating GAD. The number needed to treat using the CGI scale was 4.4 (95% CI 2.16, 15.4).[5] It was unclear whether zazpirones were more clinically effective than benzodiazepines according to a meta-analysis of three trials.[5] Lorazepam (WMD: 1.1; 95% CI 0.29, 1.91, p=0.009) and alprazolam (WMD: 1.1; 95% CI 0.28, 1.92, p=0.009) were superior to buspirone but buspirone showed inconclusive results compared with diazepam (WMD: -0.20, 95% CI -7.45, 7.05, p=0.96).[5] One study showed inconclusive results comparing venlafaxine to buspirone (venlafaxine XR 75 mg: relative risk [RR]: 0.74; 95% CI 0.41, 1.34; 150 mg RR: 1.24; 95% CI 0.69, 2.21, p=0.47).[5]

A systematic review conducted in the United States reported that based on a meta-analysis of RCTs, medications for GAD varied in the magnitude of their effect size (ES), ranging from moderate to poor.[6] Buspirone had a low ES.[6] The difference in ES between pairs of drugs was small (venlafaxine XR versus buspirone, [ES difference between pairs of active drugs] 0.20; venlafaxine XR versus diazepam, 0.07).[6]

A German systematic review suggests that azapirones and BZD are equally effective in treating GAD.[7] For treating anxiety, the mean ES for BZD versus azapirones was effect size g=0.32 random effects variance (τ^2=0.002, χ^2=51.3, n=37) versus g=0.30 (τ^2=0.04, χ^2=25.1, n=21).[7]

<u>Comparative Safety of Buspirone versus BZD, SSRIs and SNRIs</u>

A systematic review contained in the New Zealand report showed that buspirone resulted in less drowsiness, fatigue, nervousness, depression, insomnia, and sleep problems than BZD [2] BZD, however, resulted in less nausea and dizziness than buspirone.[2]

A Cochrane review showed that dropout rates were significantly in favour of BZD over buspirone (RR: 1.24, 95% CI 1.01, 1.52, p=0.04).[5] No significant differences were found between the number that dropped out on buspirone versus venlafaxine XR 75 mg or 150 mg.[5] Patients on buspirone reported less fatigue, depression, sleepiness, sleep problems and dry mouth compared with BZD recipients. BZD users reported less nausea and dizziness compared with buspirone users.[5]

According to a German systematic review, 21% of BZD users and 31% of buspirone users dropped out of treatment (τ(51)=-2.2, p<0.05).[7] The results suggest that BZD are preferred when the duration of treatment is short as BZD pose increased risk of dependence and withdrawal after long-term treatment.[7]

Randomized controlled trials (RCTs)

Buspirone versus Sertraline for GAD in Elderly Patients

A single-blind, randomized trial comparing sertraline (50-100 mg/day) versus buspirone (10-15 mg/day) reported that buspirone was significantly superior to sertraline after two and four weeks ($p<0.001$).[8] However, at the end of the eight week study period, this difference did not reach statistical significance ($p=0.016$). After eight weeks, the mean HRSA score significantly decreased in both sertraline ($p<0.001$) and buspirone ($p<0.001$) treated patients.[8] No clinically adverse events (AE) were reported.

Table 2. Summary of the Comparative Effectiveness and Safety of Buspirone for GAD

Intervention	Evidence	Results
Comparative Effectiveness and Safety of Buspirone for GAD		
Azapirones (buspirone)	4 systematic reviews,[2,5-7] single-blind RCT[8]	**Effectiveness** • Buspirone had a low ES: 0.17[6] • Azapirones may be less effective than BZD[2,5] • Azapirones are as effective as BZD[7] • Buspirone may be less effective in recent BZD users[2,5] • Unable to conclude whether azapirones are superior to SSRIs[5] • Buspirone was significantly superior to sertraline for relieving GAD in elderly patients at 2 and 4 weeks, but this did not reach statistical significance at 8 weeks.[8] **AE** • Buspirone can have unpleasant AE[2] • Side effects were mild and non serious[5]
BZD	4 systematic reviews[2,5-7]	**Effectiveness** • ES: 0.38[6] • BZD may reduce symptoms of GAD[2] • BZD are as effective as azapirones[7] **AE** • BZD increase risk of dependence, sedation and can cause AE in neonates during pregnancy • Fewer participants stopped taking BZD than azapriones[5,7]
SSRIs (imipramine, paroxetine, sertraline, escitalopram)	2 systematic reviews,[2,6] single-blind RCT[8]	**Effectiveness** • ES: 0.36[6] • SSRIs reduce GAD symptoms compared with PLC[2] • Buspirone was significantly superior to sertraline for relieving GAD in elderly patients at 2 and 4 weeks, but this did not reach statistical significance at 8 weeks.[8] • After 8 weeks, the mean HRSA score significantly decreased in both groups.[8] **AE** • SSRIs can cause sedation, dizziness, falls, nausea, and sexual dysfunction[2] • No clinically AE were observed.[8]
SNRIs (venlaflaxine)	2 systematic reviews[2,6]	**Effectiveness** • ES: 0.42[6] • Venlafaxine reduces GAD symptoms compared with PLC[2]

Intervention	Evidence	Results
Comparative Effectiveness and Safety of Buspirone for GAD		
		AE • Venlafaxine can cause sedation, dizziness, falls, nausea and sexual dysfunction[2]

AE: adverse event; BZD: benzodiazepines; ES: effect estimate; GAD: Generalized Anxiety Disorder; HRSA: Hamilton Rating Scale for Anxiety; PLC: placebo; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

2. Cost-Effectiveness of Buspirone for GAD

No evidence was found regarding the cost-effectiveness of buspirone compared with BZD, SSRIs, or SNRIs for the treatment of GAD.

Limitations

The evidence included in this review has inherent limitations that limit its usefulness in drawing conclusions about the comparative clinical effectiveness, safety and cost effectiveness of buspirone for GAD. While four systematic reviews compared the effectiveness of buspirone versus BZD, SSRIs and SNRIs, and an RCT compared buspirone versus sertraline, there was uncertainty regarding the number of included RCTs and patients in one review.[2] The studies included in the review reported on two, four, six, or eight week safety and efficacy.[2,7,8] While buspirone was more effective than sertraline for reducing GAD in elderly patients in one RCT, no significant difference in HRSA scores was found at eight weeks.[8] GAD is a chronic long-term illness and longer term studies are needed to provide more complete information regarding comparative safety and effectiveness. There may be some uncertainty regarding the accuracy of diagnosis of patients in the included studies as some patient characteristics were not reported[2,6] and diagnosing GAD can be difficult as most patients have other health problems.[2] No evidence was found regarding the cost-effectiveness of buspirone compared with BZD, SSRIs, or SNRIs for treating GAD.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Four systematic reviews suggest that buspirone may be as[5,7,7] or less[6] effective than BZD and that buspirone may be less effective in recent BZD users.[2,5] One systematic review was unable to conclude whether azapirones, as a class, was superior to SSRIs for reducing GAD symptoms.[5] While buspirone was significantly superior to sertraline for relieving GAD in elderly patients at two and four weeks, no significant difference was found between groups at eight weeks.[8] While fewer patients stopped taking BZD than azapirones, BZD have an increased risk of dependency.[5,7] Buspirone was associated with less drowsiness, fatigue, nervousness, depression, and sleep disturbance than BZD.[2] SSRIs and SNRIs can cause sedation, dizziness, falls, nausea, and sexual dysfunction.[2] There is no conclusive evidence to suggest that buspirone is more effective than BZD, SSRIs, or SNRIs. No evidence was found regarding the cost-effectiveness of buspirone versus BZD, SSRIs or SNRIs for the treatment of GAD.

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REFERENCES

1. Swinson RP, Antony MM, Bleau P, Chokka P, Craven M, Fallu A, et al. Management of anxiety disorders. Can J Psychiatry [Internet]. 2006 [cited 2012 Apr 20];51(Suppl 2):1S-92S. Available from: http://ww1.cpa-apc.org:8080/Publications/CJP/supplements/july2006/anxiety_guidelines_2006.pdf

2. Gale CK, Millichamp J. Generalised anxiety disorder. Clin Evid (Online) [Internet]. 2011 [cited 2012 Apr 12];pii:1002. Available from: http://www.clinicalevidence.bmj.com/x/pdf/clinical-evidence/en-gb/systematic-review/1002.pdf

3. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2012 May 2];7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

4. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2012 May 2];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

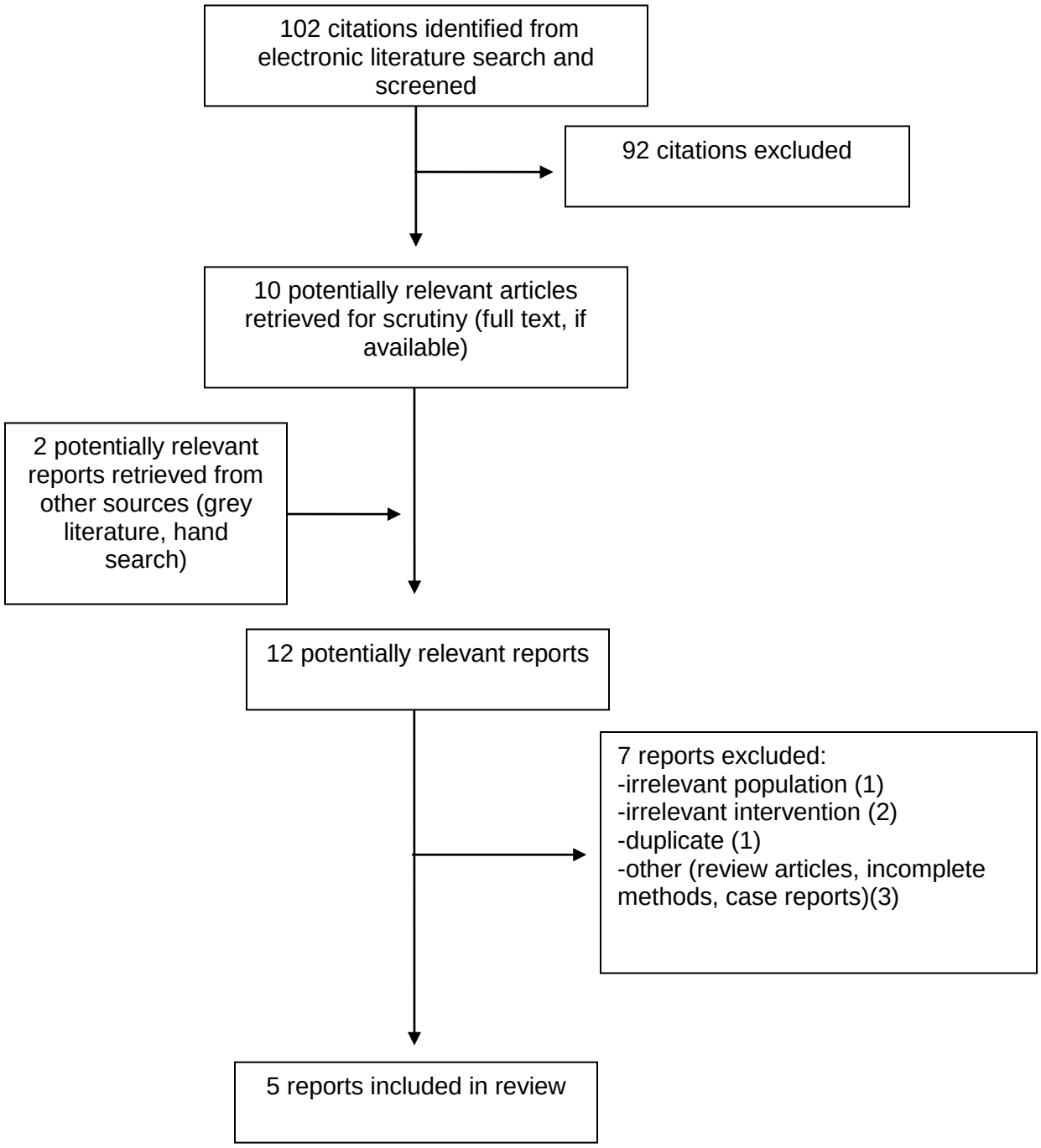
5. Chessick CA, Allen MH, Thase M, Batista Miralha da Cunha AB, Kapczinski FF, de Lima MS, et al. Azapirones for generalized anxiety disorder. Cochrane Database Syst Rev. 2006;3:CD006115.

6. Hidalgo RB, Tupler LA, Davidson JR. An effect-size analysis of pharmacologic treatments for generalized anxiety disorder. J Psychopharmacol. 2007 Nov;21(8):864-72.

7. Mitte K, Noack P, Steil R, Hautzinger M. A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. J Clin Psychopharmacol. 2005 Apr;25(2):141-50.

8. Mokhber N, Azarpazhooh MR, Khajehdaluee M, Velayati A, Hopwood M. Randomized, single-blind, trial of sertraline and buspirone for treatment of elderly patients with generalized anxiety disorder. Psychiatry Clin Neurosci [Internet]. 2010 Apr [cited 2012 Apr 9];64(2):128-33. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1440-1819.2009.02055.x/pdf

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Summary of Study Characteristics

First Author, Publication Year Country	Study Design	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
Comparative Clinical Effectiveness and Safety of Buspirone for GAD					
Systematic Reviews and Meta-analyses					
Gale[2] 2011 New Zealand	SR of 2 SR (8 RCTs, 300 participants)	Adults with GAD (DSM, ICD-10); age NR	Buspirone, abecarnil, SSRIs, SNRIs, antipsychotics, applied relaxation, BZD, CBT, hydroxyzine, PGB	Active comparator or PLC	Symptom severity at 6 wk (HAM-A), QoL, AE,
Chessick[5] 2009 United States	Systematic review, meta-analysis (36 studies, 5908 participants; duration 4-9 wk)	Adults with GAD (ICD-10, DSM-III, DSM-III-R, or DSM-IV); aged 18-74 yr.	Azapirones, (buspirone alone or in combination with other drugs and/or psychological treatment)	BZD/ antidepressant, different azapirone, psychological treatment, kava kava or PLC	Symptom severity (HAM-A, CGI), compliance (drop outs, AE)
Hidalgo[6] 2007 United States	Systematic review, meta-analysis (21 DB RCTs, 8 SSRI, 5 venlafaxine, 3 AH, 2 PGB, 2 buspirone arms, 4 BZD arms, 2 CAM); participants and age NR,	Adults and children with GAD (DSM-III-R, DSM-IV, or ICD-10); age NR 2 studies assessed children	SSRIs (paroxetine, sertraline, fluvoxamine, escitalopram), SNRIs (venlafaxine), BZD (alprazolam, diazepam, lorazepam), azapirones (buspirone), AH, PGB, CAM	Active comparator or PLC	Symptom severity (HAM-A)
Mitte[7] 2005 Germany	Systematic review, meta-analysis (48 studies)	Adults with GAD (DSM or exact description of the disorder); mean age 39 years; 57% F	Azapirone	BZD or PLC	Symptom severity (HAM-A), compliance (drop outs)
Randomized Controlled Trials (RCTs)					
Mokhber[8] 2010 Iran	RCT, single blind, 8 wks (n=46)	Adults with GAD (DSM-IV) aged > 60 yr, mean age: 67, 57% F	Buspirone (10-15 mg/day) (n=25)	Sertraline (50-100 mg/day) (n=21)	Symptom severity at 0, 2, 4, 8 wk (HRSA), compliance, AE

AE: adverse events; AH: antihistamines; BZD: benzodiazepines; CAM: complementary/alternative medicine; CBT: cognitive behavioural therapy; CGI: Clinical Global Impression Scale; DB: double blind; DSM: Diagnostic and Statistical Manual of Mental Disorders; GAD: generalized anxiety disorder; HAM-A: Hamilton Anxiety Scale; HRSA: Hamilton Rating Scale for Anxiety; NR: not reported; PGB: pregabalin; PLC: placebo, QoL: quality of life; RCT: randomized controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitor; SR: systematic review; SSRI: selective serotonin reuptake inhibitor; wks: weeks

APPENDIX 3: Summary of Critical Appraisal

First Author, Publication Year	Strengths	Limitations
Comparative Clinical Effectiveness and Safety of Buspirone for GAD		
Systematic Reviews and Meta-Analyses		
Gale[2] 2011 New Zealand	• Comprehensive literature search based on pre-defined criteria • Study selection was performed using well defined criteria • A list of included and excluded studies was provided • Trial quality assessed based on predefined criteria (GRADE). • Publication bias assessed. • Conflict of interest statement was included	• Search restricted to English language articles • Unclear if study selection and data extraction was in duplicate • The number of people or RCTs included in a SR was unclear for the reporting of AE
Chessick[5] 2009 United States	• Comprehensive literature search based on pre-defined criteria • Study selection was performed by two independent reviewers • A list of included and excluded studies was provided • Data extraction was performed in duplicate by two reviewers • Characteristics of included studies were explicit • Methods of pooling studies were appropriate and publication bias was assessed • None of the authors declared any conflicts of interest	
Hidalgo[6] 2007 United States	• Comprehensive literature search based on pre-defined criteria • Study selection was performed using well defined criteria • A list of included studies was provided • Characteristics of included studies were explicit • Methods of pooling studies were appropriate and publication bias was assessed • Conflict of interest statement was included	• Language restrictions were imposed; English language articles were included • Excluded studies were not listed
Mitte[7] 2005 Germany	• Comprehensive literature search based on pre-defined criteria • A list of included studies was provided • Data extraction was performed in duplicate by two reviewers	• Language restrictions were imposed; English and German language articles were included • Excluded studies were not listed • It is unclear whether study selection was performed by 2 reviewers

First Author, Publication Year	Strengths	Limitations
Comparative Clinical Effectiveness and Safety of Buspirone for GAD		
	• Characteristics of included studies were explicit • Methods of pooling studies were appropriate and publication bias was assessed • Conflicts of interest were stated	• No conflict of interest statement provided
Randomized Controlled Trials (RCTs)		
Mokhber[8] 2010 Iran	• Clearly described research question, eligibility criteria, intervention and outcomes • Patients were randomized to treatment • University sponsored	• Method of randomization NR • Single blinding unclear, potential for bias

AE: adverse event; GRADE: Grading of Recommendations Assessment, Development and Evaluation; NR: not reported; RCT: randomized controlled trials

APPENDIX 4: Summary of Findings

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Comparative Clinical Effectiveness and Safety of Buspirone for GAD		
Systematic Reviews and Meta-Analyses		
Gale[2] 2011 New Zealand	• It remains uncertain if buspirone is more effective than BZD for improving symptoms at 6 weeks (very low quality evidence). **Comparative Clinical Effectiveness** • RCT of 240 people reported that 54% of buspirone recipients and 61% of diazepam recipients responded with at least a 40% reduction in HAM-A score at 6 weeks (p: NR).[2] • Alprazolam recipients had lower HAM-A than buspirone recipients in a SR of one RCT (n=60) [WMD: 1.1; 95% CI 0.28, 1.92].[2] • Lorazepam recipients had lower HAM-A than buspirone recipients in a SR of one RCT (n=60) [WMD: 1.1; 95% CI 0.29, 1.91].[2] **QoL** (no data) **Adverse Effects** • According to an RCT of 240 patients, diazepam was associated with more fatigue and weakness compared with buspirone but less headache and dizziness (p: NR).[2] • Buspirone was associated with less drowsiness, fatigue, nervousness, depression, insomnia, and sleep problems than BZD according to a SR of an unclear number of people or RCTs [RR: 0.29; 95% CI 0.21, 0.41; RR: 0.24; 95% CI 0.13, 0.45); RR: 0.17; 95% CI 0.06, 0.47; RR: 0.22; 95% CI 0.12, 0.39; RR: 0.14; 95% CI 0.03, 0.63; RR: 0.25, 95% CI 0.08, 0.81].[2] • BZD were associated with less nausea and dizziness than buspirone [RR: 2.84; 95% CI 1.14, 7.09; RR: 2.28; 95% CI 1.15, 4.54].[2] • Reanalysis of pooled drug company data from 8 RCTs comparing BZD versus placebo or buspirone suggest recent BZD use limits the buspirone effectiveness.[2]	• "Various treatments, such as BZD, buspirone, hydroxyzine, antidepressants, and pregabalin may all reduce symptoms of anxiety in people with GAD but they all have unpleasant AE and most trials were short term (page 2)."[2] • "BZD increase risk of dependence, sedation, and accidents, and cause AE in neonates if used during pregnancy (page 2)."[2] • "Buspirone may be less effective if used in people who recently took BZD (page 2)."[2] • "Antidepressants have been shown to reduce symptoms compared to placebo but antidepressants can cause AE including sedation, dizziness, falls, nausea, and sexual dysfunction (page 2)."[2]
Chessick[5] 2009 United States	• Thirty-six trials reported on 5906 participants randomly allocated to azapirones and/or placebo, BZD, antidepressants, psychotherapy or kava kava. Three trials compared azapriones versus BZD.	• "Azapirones appear to be useful in treating GAD, particularly for those who have not been on BZD. Azapirones may not be superior to BZD and do not

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	Comparative Clinical Effectiveness • It is unclear whether azapirones were better than BZD; in some cases BZD are better [Lorazepam (n=40) WMD: 1.1; 95% CI 0.29, 1.91 (p=0.008) and alprazolam (n=39) WMD: 1.1; 95% CI 0.28, 1.92 (p=0.009) were superior to buspirone but buspirone versus diazepam results were inconclusive (n=19) WMD: -0.20; 95% CI -7.45, 7.05 (p=0.96).[5] • One study showed non-conclusive results between buspirone and venlafaxine XR using CGI venlafaxine XR, 75 mg, (n=182) RR: 0.74; 95% CI 0.41, 1.34 and venlafaxine XR, 150 mg (n=184) RR: 1.24; 95% CI 0.69, 2.21 (p=0.47) but 150 mg may be superior to 75 mg.[5] • Fewer participants stopped taking BZD compared with azapirones. **Drop outs** • A significant difference was found favouring BZD over buspirone [RR:1.24; 95% CI 1.01, 1.52 (p=0.04).[5] • NSD was found comparing buspirone and venlafaxine XR [RR: 0.98 95% CI 0.6, 1.6 (p=0.92) and RR: 0.7; 95% CI 0.45, 1.09 (p=0.12) for 75 mg and 150 mg venlafaxine XR, respectively.[5] **Adverse Effects** • Buspirone users reported less drowsiness, fatigue, nervousness, depression, insomnia, and sleep problems compared to BZD, while those on BZD reported less nausea and dizziness compared with buspirone.[5] • In a trial that discontinued diazepam or buspirone at 6 wk, those on diazepam showed withdrawal symptoms compared with buspirone users (p<0.001).[5] • Buspirone users reported less dry mouth compared to venlafaxine while venlafaxine users reported less dizziness compared with buspirone.[5]	appear as acceptable as BZD. Side effects appear mild and non serious. Longer term studies are needed to show azapirones are effective in treating GAD, a chronic long-term illness (Page 2)."[5]
Hidalgo[6] 2007 United States	Mean ES for each drug from highest to lowest were PGB, hydroxyzine, venlafaxine XR, BZD, SSRI, buspirone and CAM. Buspirone (ES: 0.17 ± 0.21, NS) was as effective as PLC and CAM was worse than PLC.[6] **Comparative Clinical Effectiveness** • Venlafaxine XR versus buspirone ES: 0.20 • Venlafaxine XR versus diazepam ES: 0.07	"Medications investigated in DB randomized clinical trials included in our meta-analysis varied in the magnitude of their ES, ranging from moderate to poor. On the higher end, the anticonvulsant PGB and AH hydroxyzine, followed in

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	• Hydroxyzine versus buspirone ES: 0.26 • Pregabalin versus lorazepam ES: -0.16 • Pregabalin versus lorazepam ES: 0.22 • Opipramol versus alprazolam ES: -0.07 **Adverse Effects** (NR)	order by venlafaxine XR, BZD, Buspirone had a low ES, and CAM performed worse than placebo (page 871).[6]
Mitte[7] 2005 Germany	72 ES were included in the analysis for anxiety, involving BZD (diazepam, alprazolam, lorazepam) and azapirones (buspirone). Four studies investigated drugs less than 4 wks but ES were comparable with those studied longer.[7] **Comparative Clinical Effectiveness** • BZD ES: 0.32 (τ^2=0.02, χ^2=51.32, n=37) • Azapirones ES: 0.3 (τ^2=0.04, χ^2=25.14, n=21) • Multiple regression analysis controlling for diagnostic criteria, drug dose, subjects, dropouts, and sample size showed NSD between classes (β=0.05, NSD, n=49)[7] **Mean ES (>5 studies)** • Alprazolam ES: 0.33 (τ^2=0.0, χ^2=4.26, n=6) • Buspirone ES: 0.34 (τ^2=0.02, χ^2=14.59, n=12) • Diazepam ES: 0.30 (τ^2=0.0, χ^2=3.25, n=12) • Lorazepam ES: 0.17 (τ^2=0.0, χ^2=3.73, n=6) • Venlafaxine ES: 0.33 (τ^2=0.0, χ^2=3.72, n=5) • Number of trails too low for statistical comparison[7] **Drop Outs** • Mean un-weighted drop out: 24.4% (SD=16, n=65) • BZD: 20.5% (SD=14, n=35); azapirones: 30.7% (SD=18, n=18); significant difference [τ(51)=-2.25, p<0.05].[7]	"Azapirones and BZD were equally effective. Compliance (dropout rate) was higher for BZD. Pharmacotherapy, especially BZD and azapirones is effective in the short-term treatment of patients with GAD. There is no superiority of one drug class in reducing symptomatology (page 141).[7]
Randomized Controlled Trials (RCTs)		
Mokhber[8] 2010 Iran	Both sertraline and buspirone had an anxiolytic effect based on a steady decrease in total HRSA scores for both groups throughout study. **Comparative Clinical Effectiveness** • 2 wk HRSA: 19.0 $\pm$ 5.8 for buspirone versus 28.5 $\pm$ 4.9 for sertraline • 4 wk HRSA: 15.6 $\pm$ 5.5 for buspirone versus 21.5 $\pm$ 4.6 for sertraline • (p<0.001) for buspirone • 8 wk mean HRSA: 15.5 $\pm$ 6.7 versus 12.8 $\pm$ 6.0 for buspirone versus sertraline (p=0.16, NSD) • Mean HRSA after 8 wk significantly decreased in the sertraline group (f=643.6, p<0.001) and the	"Both sertraline and buspirone appear to be efficacious and well tolerated in the treatment of GAD in elderly patients. Further studies with larger sample size, evaluating the effect of medical illness, cognitive impairment, depression, and combined therapy with support and psychotherapy are needed (page 128).[8]

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	buspirone group (f=667.0, P<0.001) using repeated measures. • HRSA0 – HRSA 8 was greater for buspirone but NSD (15.7 ± 7.5 versus 13.1 ± 7.5; t=-1.07, p=0.29)[8] **Drop outs** • No one withdrew from study [8] **AE** • No clinically significant serious AE[8]	

AE: adverse event; BZD: benzodiazepines; CAM: complementary/alternative medicine; CI: confidence interval; ES: effect size; HAM-A: Hamilton Anxiety Scale; NSD: no significant difference; NR: not reported; PLC: placebo; RCT: randomized controlled trials; SR: systematic review; XR: extended release; WMD: weighted mean difference