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Review Article

Beta-blockers for the treatment of anxiety disorders: A systematic review and meta-analysis

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ABSTRACT

Background: Beta-blocker prescriptions for patients with anxiety increased substantially between 2003 and 2018, yet there is no clinical guidance concerning their use. A previous review of propranolol – a beta-blocker – in the treatment of anxiety concluded there was insufficient evidence to support its use. Additional data have been published in the eight years since that review including some evidence for other beta-blockers. We aimed to synthesise all available data on the effectiveness of beta-blockers in the treatment of anxiety disorders in adults.
Methods: We searched Medline, Embase, PsycINFO, Web of Science, and Trial Registries (September 2023), including randomised controlled trials (RCT), non-randomised control group comparative studies and cross-over trials reporting self- or clinician-reported anxiety symptoms. Study quality was assessed using Cochrane's Risk of Bias tool, with meta-analyses conducted by comparator group using random-effects models.
Results: Searches produced 3068 records, with 10 studies included, of which five were included in meta-analyses (n = 179). There was no evidence for a beneficial effect of beta-blockers compared with either placebo or benzodiazepines in patients with social phobia or panic disorder with/without agoraphobia (p-value for all meta-analyses $\geq$0.54).
Limitations: Many of the included studies had small sample sizes, missing data and high or unclear risk of bias.
Conclusion: Beta-blockers are increasingly prescribed for anxiety, yet there is a lack of robust evidence of effectiveness. There is a need to understand when and why practitioners are using these drugs, and to undertake a large RCT to provide definitive evidence of whether beta-blockers are an effective and safe treatment for anxiety.

1. Introduction

Anxiety disorders are common and are often treated in primary care settings. Patients may present with psychological symptoms such as feeling on 'edge', restlessness, or irritability (Tuma and Maser, 2019). Anxiety is often associated with physical symptoms, such as heart palpitations, excessive sweating, shortness of breath, trembling, or dizziness (Tuma and Maser, 2019), and some individuals will also experience panic attacks (Tuma and Maser, 2019). Psychological interventions are recommended as first-line treatment in several countries, with medication as a second option (NICE, 2011; Katzman et al., 2014; Anxiety and Depression Association of America, 2015). Selective serotonin reuptake inhibitors (SSRIs) are the standard drug prescribed by primary care practitioners to treat anxiety, yet only ~50 % of patients respond to them (Huh et al., 2011). Alternative pharmacological treatment is limited, but includes serotonin and norepinephrine reuptake inhibitors (SNRIs), pregabalin and benzodiazepines, although there are concerns around dependency with the latter (Baldwin et al., 2013; Quagliato et al., 2018).

The beta-blocker propranolol is licensed for treatment of anxiety in the UK (Royal Pharmaceutical Society of Great Britain, 2024), and is prescribed 'off-label' in other countries, such as America (Garakani et al., 2020) and Canada (British Columbia Health Link, 2022). Although beta-blocker prescriptions have increased across all indications in America, Canada, and the UK (Hemmelgarn et al., 2008; Kantor et al., 2015; Rouette et al., 2022), there is no up-to-date evidence available (off-label) for beta-blocker prescriptions for anxiety in America or Canada (Lin et al., 2006). However, recent evidence from UK primary care, indicates that prescriptions for patients with anxiety increased substantially from 3.8/1000 person-years-at-risk (PYAR) in 2003 to 8.7/1000 PYAR in 2018 (Archer et al., 2022).

Propranolol is one of several drugs in the beta-blocker class. Other

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beta-blockers include pindolol, betaxol, nadolol and atenolol. Whilst beta-blockers do not directly treat the psychological symptoms of anxiety, they may help control the physical symptoms, such as palpitations, and this, in turn, may be part of a positive feedback loop that reduces anxiety (Brudkowska et al., 2018). However, beta-blockers do not feature in the UK (NICE, 2011), American (Anxiety and Depression Association of America, 2015) or World Health Organisation (World Health Organisation, 2023) anxiety guidelines and are explicitly not recommended for the treatment of anxiety in Australian, New Zealand and Canadian guidelines (Katzman et al., 2014; Andrews et al., 2018). Thus, there is no clinical guidance concerning when or how they should be used.

A study published in 1987 found that propranolol was more effective than placebo in treating the symptoms of anxiety (severe enough to warrant anxiolytic treatment for one month) after a two week period, but that this was not maintained over time (Meibach et al., 1987). In contrast, a small open-label study with 31 patients examined betaxolol for generalised anxiety disorder (GAD) and found evidence of effectiveness in the short-term (Swartz, 1998). A 2016 review found inconclusive evidence for the benefit of beta-blockers in the treatment of anxiety, with the majority of randomised controlled trials (RCTs) conducted over thirty years ago, with small sample sizes (8 studies; total $N = 202$) (Steenen et al., 2016). The review included research published up to March 2014 and concluded: "the quality of evidence for the efficacy of propranolol at present is insufficient to support routine use of propranolol in the treatment of anxiety" (pg. 128) (Steenen et al., 2016). Additional data have been published in the eight years since the Steenen et al. (2016) systematic review, and whilst Steenen et al. (2016) focussed on propranolol, there is some evidence for the use of other beta-blockers in the treatment of anxiety.

Recent research suggests that atenolol may be beneficial for treating anxiety symptoms, although participants did not necessarily meet the threshold for an anxiety disorder (Armstrong and Kapolowicz, 2020). Another study found that treatment of GAD with sertraline and propranolol combined is superior to sertraline monotherapy (Ríos-Morales et al., 2017). There is further evidence to suggest that propranolol, pindolol, and nadolol may be useful for the short-term treatment of the somatic features of anxiety related to specific situations, such as performance anxiety for musicians (Patston and Loughlan, 2014) or in exam or interview situations (Szeleszczuk and Frączkowski, 2022). Pindolol is a 5-HT1A receptor antagonist, which may have a particular role in ameliorating symptoms of anxiety (Li, 2023). Given the recent trends in increased prescribing for anxiety (Archer et al., 2022), it is therefore timely to conduct a systematic review that is comprehensive and synthesises all available data on the effectiveness of all beta-blockers in the treatment of anxiety disorders in adults.

2. Methods

2.1. Protocol registration

The systematic review protocol was registered in the Prospective Register of Systematic Reviews (PROSPERO) (CRD42022321438; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=321438). The reporting of this study adheres to adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline (Page et al., 2021).

2.2. Search strategy

We searched Medline, Embase, PsycINFO, Web of Science, the ISRCTN Registry, the International Clinical Trials Registry (includes unpublished reports) and the European Union Drug Regulating Authorities Clinical Trials (EudraCT) Database from inception to 29th September 2023. We used database-specific index terms and free text words indicative of anxiety disorders and beta-blockers. The search strategies are provided in Supplement 1. The registries were searched to identify grey literature that met the inclusion criteria. Therefore, searches included papers that had been published, reports from relevant agencies, and unpublished data. The reference lists of all included studies and previous systematic reviews were screened for further eligible studies. Searches were not limited by language to ensure all relevant studies were identified.

2.3. Identification and selection of studies

All identified articles were imported into EndNote version X9 for management. Two reviewers (CA and DC/NW/DK/KT) independently screened titles and abstracts in Rayyan (Ouzzani et al., 2016) using a standardised abstract screening form. An over-inclusive approach was taken in cases of uncertainty, with the full paper obtained along with studies assessed as meeting the inclusion criteria. Two reviewers independently screened the full texts for inclusion. We included studies:

(a) that were randomised controlled trials (RCT) (including cluster RCTs), cross-over design trials, or non-randomised comparative studies with a control group;

(b) examining the effectiveness of beta-blockers (listed in the "Beta-adrenoceptor blocking drugs" section of the British National Formulary (BNF) (Royal Pharmaceutical Society of Great Britain, 2024));

c) as a treatment for adults with an anxiety disorder as defined by Diagnostic and Statistical Manual (DSM) (American Psychiatric Association, 2013); International Classification of Diseases (ICD) (World Health Organisation, 1992), Feighner criteria (Feighner et al., 1972) or Research Diagnostic Criteria (Spitzer et al., 1978) (conditions included were GAD, panic disorder, agoraphobia and social anxiety and excluded Post Traumatic Stress Disorder (PTSD), obsessive-compulsive disorder (OCD) and specific phobias);

(d) for participants aged 18 and over;

(e) with either a placebo or an antidepressant or a benzodiazepine comparator, or a beta-blocker + antidepressant vs antidepressant + placebo comparator;

and (f) outcomes focusing on change in anxiety symptoms (clinician-rated e.g. Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959) or self-report e.g. Generalised Anxiety Disorder Assessment (GAD-7) (Spitzer et al., 2006)) or, for panic disorder, the number of panic attacks).

The opinion of a third reviewer was sought in cases of disagreement. Where more than one article reported results based on the same study data and follow up timepoint, we retained the most comprehensive for inclusion in the review. Additional reports of subsequent follow up periods were also included.

2.4. Data extraction, risk of bias and GRADE assessment

A standardised extraction form was used by two reviewers to record study information including participant characteristics and diagnoses; study design; sample size; control group (and other treatment arms, where relevant); intervention (drug type and dose); all anxiety outcomes and adverse events.

Authors of included studies were contacted to provide outcome data that were not provided in trial reports. For the one study (Ravaris et al., 1991) for which we were unable to contact the authors, we instead contacted the authors of a systematic review (Steenen et al., 2016) that had included the study to establish how they calculated the means and standard deviations (SD). We did not use software to extract data from figures or statistical approaches to impute or estimate missing data.

Two authors independently assessed included studies using Cochrane's 'Risk of Bias 2' (RoB 2.0) tool (Sterne et al., 2019). Studies were rated on the following RoB2 domains: overall bias, randomisation process measurement of the outcome, missing outcome data, selection of the reported results, and deviations from intended interventions. A judgement on the risk of bias was made overall and for each domain

within and across studies, based on: low risk of bias; unclear risk of bias; high risk of bias. Any disagreements in the assessment were resolved through discussions with a third reviewer. We had initially planned to use the RoB1.0 tool but updated this to the more recent RoB 2.0 tool, as recommended in the Cochrane handbook (Higgins et al., 2023).

As a post hoc addition to our PROSPERO registration, we applied the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (Schünemann et al., 2019) to assess the certainty of the evidence from the meta-analyses. GRADE was not used to assess outcomes for which meta-analysis was not possible. Two reviewers (CA and DC) graded the overall certainty of the body of evidence based on five domains (study limitations (risk of bias), indirectness of evidence, inconsistency, imprecision of effect estimates and publication bias). The outcomes assessed were anxiety symptoms and the number of panic attacks.

2.5. Statistical analysis

We used Stata version 17 for statistical analysis. Meta-analyses using the sample size, mean and SD for each study arm were undertaken if trials could be combined, with the same comparator and the same outcome measure, using random-effects models. Continuous outcomes were analysed by calculating the difference in means (MD) between groups, with 95 % confidence intervals (95%CI). We had planned to use standardised mean difference (SMD) for continuous outcomes reported on different scales. However, there were no instances where multiple scales could be standardised due missing data and/or different outcomes measured. For cross-over trials, only results from the first randomised treatment period were included in the analysis. Where studies reported both short-term and long-term outcomes, separate meta-analyses were undertaken for each of these time points. Due to the anticipated variation in follow-up timepoints across included studies, the definition of short-term and long-term was determined by team discussion and consensus after data extraction but prior to conducting meta-analysis. The definition of short-term and long-term outcomes within this review are in line with a similar review (Steenen et al., 2016).

Heterogeneity was assessed using the Chi^2 test and I^2 statistic. Where I^2 values exceeded 50 % we planned to use subgroup analyses to explore between study heterogeneity (Deeks and Altman, 2022) based on the type of beta-blocker (e.g., propranolol, atenolol). We also conducted subgroup analyses based on the type of anxiety disorder (e.g., GAD, Panic disorder) to explore if type of anxiety disorder explained

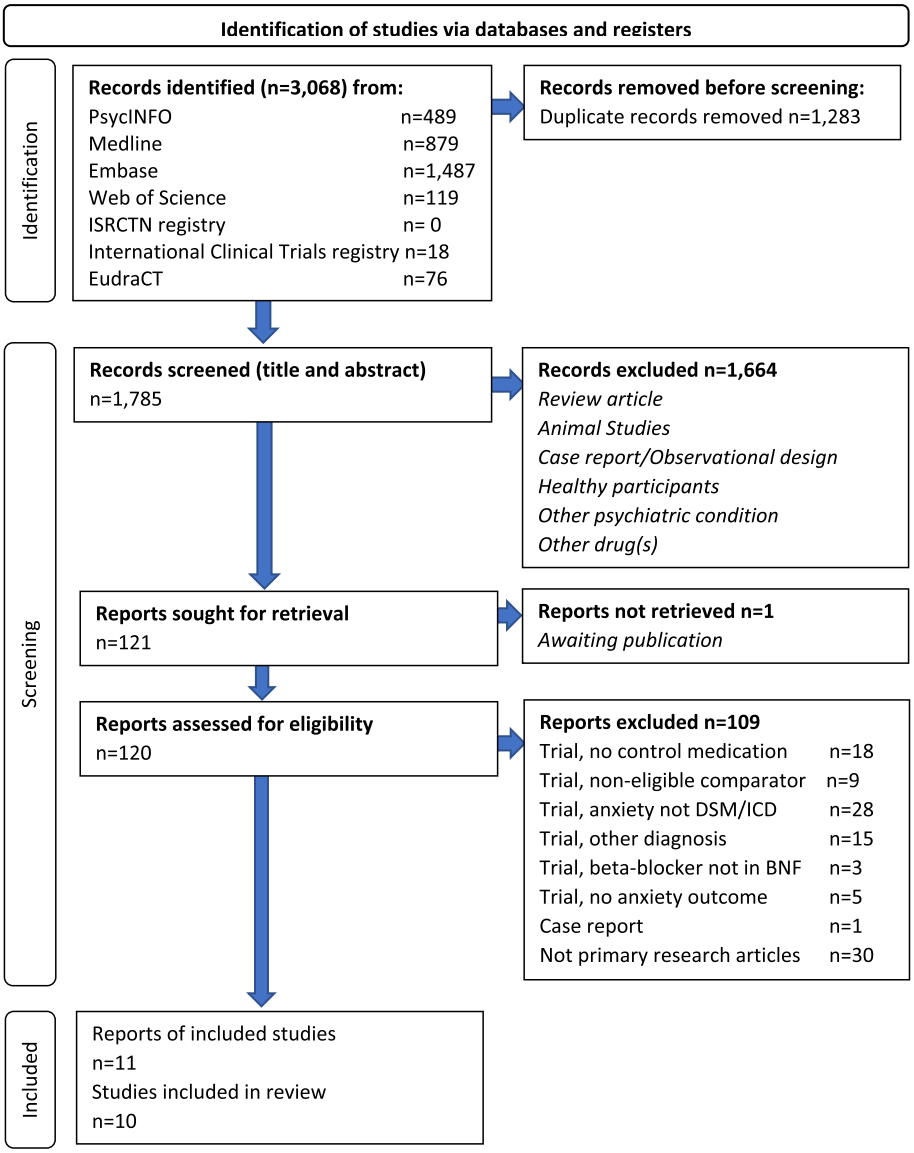

Fig. 1. Flow of information through the systematic review.

differential responses to treatment. We also report tau^2, which is the between-study variance in a random-effects meta-analysis and gives an indication of the spread of underlying intervention effects. We also report the prediction intervals.

2.6. Sensitivity analyses

Sensitivity analyses were conducted by excluding studies with at least one domain rated as high risk of bias, and comparing each of the results with the full analysis which includes all trials.

3. Results

3.1. Inclusion of studies

The flow of information through the review is presented in Fig. 1. Searches produced 3068 citations and after the initial title and abstract screening, 120 articles had full text screening. A total of 11 articles were included, reporting results from 10 studies (two articles report the same trial at different follow up timepoints).

3.2. Study characteristics

The characteristics of the 10 included trials are summarised in Table 1. Two articles report the results of one trial at two follow up points (Liebowitz et al., 1988; Liebowitz et al., 1992). Five studies included placebo as a comparator (Kathol et al., 1980; King et al., 1987; Liebowitz et al., 1988; Munjack et al., 1989; Liebowitz et al., 1992; Turner et al., 1994), although two of these studies included more than one comparator (placebo and benzodiazepine comparators (Munjack et al., 1989); placebo and antidepressant comparators (Liebowitz et al., 1988; Liebowitz et al., 1992)). In addition to the Munjack et al. (1989) study, two other trials used benzodiazepines as the only comparator (Noyes et al., 1984; Ravaris et al., 1991). One study included antidepressants as the only comparator (Munjack et al., 1985). Two studies considered combination therapy (a beta-blocker in addition to an antidepressant) compared with placebo + antidepressant (Hirschmann et al., 2000; Stein et al., 2001).

Five trials included only patients with panic disorder with or without agoraphobia, and three trials included only patients with social phobia. The other two studies included patients with ICD-9 chronic anxiety (King et al., 1987) and mixed DSM-III anxiety disorders ($n = 18$ panic disorder; $n = 5$ agoraphobia with panic; $n = 2$ generalised anxiety; n = 1 social phobia) (Kathol et al., 1980).

3.3. Risk of bias

The risk of bias judgements for the included studies are summarised in Supplement 2. Over half of studies ($n = 6$) had an unclear risk of bias overall, with the remaining four having at least one domain rated as high risk of bias, and therefore were rated as high risk of bias overall. In terms of the specific domains, none of the included studies clearly reported approaches to the randomisation process and therefore were rated as unclear risk of bias. The majority of studies had low risk of bias in deviations from intended interventions ($n = 7$), whilst one study stated "both the patient and the treating physician were aware of the nature of the drug…" (Munjack et al., 1985) and hence was rated as high risk of bias. Many of the studies (n = 7) were rated as having an unclear risk of bias in the measurement of the outcome, however three studies explicitly stated that assessors were blinded (Munjack et al., 1985; Liebowitz et al., 1988; Liebowitz et al., 1992; Turner et al., 1994) and therefore rated as low risk of bias. Six studies were considered as having unclear risk of bias in missing outcome data and seven in selection of the reported results. The study by Ravaris et al. (1991) was rated as high risk of bias on both these domains, as the authors stated that they did not include three randomised patients who dropped out early in the analysis, they excluded one participant's scores due to high score variability, and reported "data from only the most clinically pertinent findings".

3.4. Adverse events

Three studies reported participants dropping out due to "unpleasant" or "very distressing" side effects, but did not explain what these side effects were, or which treatment group the participants were in (i.e the beta-blocker group or the comparator group) (Munjack et al., 1985; Munjack et al., 1989; Stein et al., 2001). One study reported that a "rash and other side effects" were reported by three participants taking atenolol (Liebowitz et al., 1992) and another study reported that one participant dropped out due to the "failure of propranolol to suppress panic attacks" (Ravaris et al., 1991).

Two studies (Kathol et al., 1980; Noyes et al., 1984) provided more detail on adverse events. In the study by Kathol et al. (1980) ($n = 31$), the most frequent side effects reported by participants taking propranolol included dizziness ($n = 5$), fatigue ($n = 2$) and insomnia (n = 3), with three patients withdrawing from the study as they were unable to tolerate the medication. One patient had a mitral valve prolapse. In the study by Noyes et al. (1984) ($n = 21$), the authors state that insomnia was most frequently reported by participants taking propranolol, followed by drowsiness, fatigue, imbalance, trouble thinking, memory difficulty and depressed mood. Two participants dropped out of the study due to heightened anxiety soon after taking propranolol with a further withdrawing due to experiencing a depressive episode during propranolol treatment.

3.5. Meta-analyses

3.5.1. Beta-blockers versus placebo

3.5.1.1. Meta-analysis I. Outcome: Anxiety symptoms (HAM-A) after 2–6 weeks treatment. Five trials compared atenolol (25–100 mg/day) or propranolol (60–240 mg/day) with placebo for adults with social phobia (Liebowitz et al., 1988; Liebowitz et al., 1992; Turner et al., 1994), chronic anxiety (King et al., 1987), panic disorder and/or agoraphobia (Munjack et al., 1989) or included patients with a range of anxiety disorders (GAD, agoraphobia and social anxiety) (Kathol et al., 1980). All five studies reported anxiety symptoms as a mean HAM-A score after 2–6 weeks of treatment. Four trials found no evidence of a difference in anxiety symptoms between beta-blocker (propranolol/atenolol) and placebo treatment groups (King et al., 1987; Liebowitz et al., 1988; Munjack et al., 1989; Liebowitz et al., 1992; Turner et al., 1994). For one study (Kathol et al., 1980), the number of patients who showed a moderate or marked response was greater with propranolol than with placebo, with strong evidence of improvement on several self-rating scales. However, the authors reported that the improvement recorded on the HAM-A scale did not reach 'statistical significance' ($p = 0.15$).

Two trials (Turner et al. (1994); King et al. (1987)) were not included in the meta-analysis because they either did not report the standard deviations for HAM-A scores (Turner et al., 1994) or did not report the data in a way that allowed comparisons between groups during the first cross-over phase (King et al., 1987). Attempts to obtain this data were unsuccessful.

Of the trials included in the meta-analysis (Kathol et al., 1980; Liebowitz et al., 1988; Munjack et al., 1989; Liebowitz et al., 1992), there was no evidence of a difference in anxiety symptoms (measured on HAM-A) between the beta-blocker (atenolol/propranolol) and placebo groups (mean difference = −1.19, 95%CI [−4.99, 2.61], $p = 0.54$) (Fig. 2). Heterogeneity was moderate (three trials, 109 participants in total; $I^2 = 40.0$ %, 95%CI [0.0 %, 83.8 %]; tau$^2 = 4.65$). The overall confidence in the body of evidence for anxiety symptoms was judged to be 'very low'.

Table 1
Included study characteristics.

First author, year	Design	Participants	Intervention	Outcome measures
Kathol et al., 1980	Crossover trial, double-blind	*n* = 31 anxiety disorders (*DSM-III, n = 18 panic disorder; n = 5 agoraphobia with panic disorders; n = 2 GAD; n = 1 social phobia*) Mean age: 36 (range: 17–57) 12/26 completers were women	*Two week treatment period (but at least 7-day washout period beforehand)* Propranolol 160 mg/day vs placebo	HAM-A SCL-90 Severity of symptoms Relief of symptoms
Turner et al., 1994	Parallel groups, double-blind	*n* = 72 Social phobia (DSM-III) Mean age: 35.4 years (range: 18–56) 44/72 were women.	*Twelve week treatment period* Atenolol 25–100 mg/day vs. placebo vs. behavioural 'flooding'	HAM-A CGI Social phobia and anxiety inventory Social avoidance and distress scale Fear of negative evaluation scale Fear questionnaire State Trait anxiety inventory
Liebowitz et al., 1992 and Liebowitz et al., 1988	Parallel groups, double-blind	n = 85 Social phobia (DSM-III) Mean age: 34.3 (range 18 to 50) 23/74 completers were women.	*Eight week treatment period* Placebo given to all in a single-blind fashion for 7 days, only those who do not respond to placebo were randomised to drug therapy. After 8 weeks patients who are "minimally improved" are allowed to continue for another 8 weeks (maintenance phase). Atenolol + placebo 50-100 mg/day vs. Phenelzine + placebo (15-90 mg/day vs. Placebo+ placebo	Clinical and patient global impressions (CGI) scale HAM-A 21-item Hamilton Rating Scale for Depression (HAM—D), Covi Anxiety Scale Raskin Depression Scale Liebowitz Social Phobia Scale Liebowitz Panic and Social Phobic Disorders-Severity Rating form SCL-90, Social Avoidance and Distress Scale (SAD) Fear of Negative Evaluation (FNE) Fear Questionnaire, Willoughby Personality Inventory
Munjack et al., 1989	Parallel groups	*n* = 64 Panic disorder or agoraphobia with panic attacks (DSM-III) Mean age of completers: 31 (range 18–62) 69 % females.	*Five week treatment period* Alprazolam up to 6 mg/day vs. propranolol up to 240 mg/day vs. up to 12 capsules of placebo per day	Trait anxiety HAM-A Sheehan's Panic and Anxiety Scales Marks-Sheehan Phobia Scale Depression HAM-D Side Effects Checklist
Hirschmann et al., 2000	Parallel groups, double-blind	n = 25 panic disorder with or without agoraphobia (DSM-IV) Mean pindolol age: 47.7 ± 6.4 Mean age placebo 37.6 ± 8.3 12/25 were women	For initial *eight weeks n* = 50 patients all received fluoxetine 20 mg/day At end of eight weeks, those with <20 % improvement (*n* = 25) on PSQ and CAS took part in double blind study for *four weeks*: Pindolol 7.5 mg/day plus fluoxetine 20 mg/day vs. placebo plus fluoxetine 20 mg/day	Panic self questionnaire (PSQ) Clinical Anxiety scale (CAS) with Panic attacks HAM-A HAM-D NIMH anxiety scale CGI
Noyes et al., 1984	Crossover trial, double-blind	n = 21 Panic disorder and agoraphobia (DSM-III) Mean age of completers: 34.8y (range 20–61) 62 % were females	*Four week treatment period* Diazepam 5–40 mg/day vs. propranolol 80–320 mg/day for two weeks, followed by a one-week washout period after which treatment allocation was reversed for two weeks	SCL-90 HAM-A Severity of symptom scale Relief of symptoms scale Social impairment scale Panic attack frequency
Ravaris et al., 1991	Parallel groups, double- blind (study psychiatrists were "objective" assessors and aware of allocation)	*n* = 33 Agoraphobia with panic disorder or panic disorder ± phobic avoidance Mean age of alprazolam completers: 37.5 ± 9.0, 93 % female; Mean age of propranolol completers: 33.3 ± 9.0, 93 % female	*Six week treatment period* Alprazolam 5.0 ± 2.3 mg/day (range 1–30) vs. propranolol 182.0 ± 60.5 mg (range 30–300)	HAM-A Marks-Sheehan Phobia Scale; Sheehan's Patient Rated Anxiety Scale Clinician Rated Anxiety Scale Panic and Anxiety Attack Scale Physician's Global Improvement Scale SCL Scale Panic attack frequency
King et al., 1987	Crossover trial, Double-blind	n = 11 chronic anxiety (ICD-9, none were phobic)	*Three week treatment* One week ICI 118551 50 mg tid or propranolol	HAM-A Visual analogue scales for

(*continued on next page*)

Table 1 (*continued*)

First author, year	Design	Participants	Intervention	Outcome measures
		Mean Age: 41.8 (range: 22–51) 7/11 were women	40 mg tid or placebo, given in random order for three weeks	anxiety and tension Symptom emergent checklist
Stein et al., 2001	Crossover trial, double-blind	$N = 14$ generalised social phobia (DSM-IV) Age and sex not reported	*Four week treatment* Pindolol 5 mg tid. or placebo for 4 weeks. Two week taper period, then treatment allocation reversed for four weeks (with another two week taper). Taken alongside usual paroxetine dose throughout (Mean dose before randomisation: 46.4 mg/day (SD = 8.4)).	Liebowitz Social Anxiety Scale Social Phobia Inventory scores
Munjack et al., 1985	Crossover trial, single-blind	$n = 38$ Panic disorder or agoraphobia with panic attacks (DSM-III) Mean age of completers: 36y (range 23–61) 61 % females.	*Six week treatment period* Imipramine up to 300 mg/day vs. propranolol up to 160 mg/day Followed by one week tapering and one week drug-free period Second arm, six week vice-versa drug allocation	Number of panic attacks Avoidance behaviour (ordinal subjective ratings) Secondary outcomes: State and trait anxiety SCL-90 Fear Questionnaire Wolpe-Lang Fear Inventory MMPI (non-self-report measure)

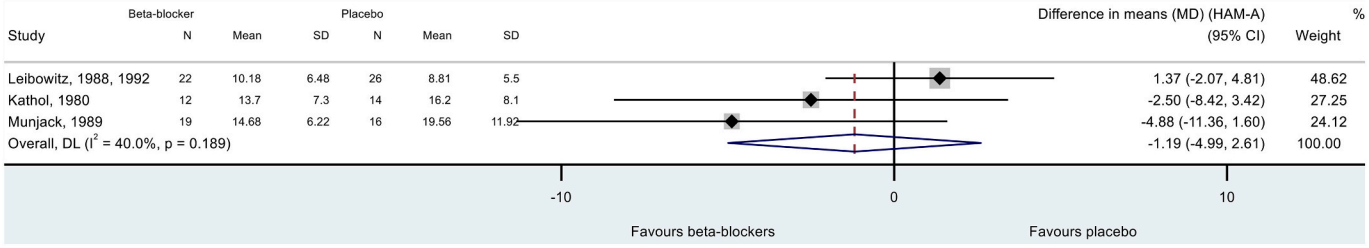

Fig. 2. Meta-analysis *I. beta*-blockers compared to placebo (outcome: anxiety symptoms (HAM-A) after 2–6 weeks treatment).

3.5.2. *Beta-blockers versus benzodiazepines*

3.5.2.1. Meta-analysis 2. Outcome: number of panic attacks after 2 weeks of treatment. Two trials (Noyes et al., 1984; Ravaris et al., 1991) reported on the effectiveness of propranolol (30–320 mg/day) compared with diazepam (5–40 mg/day) or alprazolam (1–30 mg/day) for adults with panic disorder and agoraphobia, expressed as the mean number of panic attacks for the two treatment groups after 2 weeks of treatment.

There was no evidence of a difference in the number of panic attacks after 2 weeks of treatment between those randomised to propranolol or diazepam/alprazolam (mean difference = 1.58, 95%CI [−2.33, 5.50], $p = 0.79$) (Fig. 3A). However, there was substantial statistical heterogeneity (two trials, 50 participants in total; $I^2 = 67.1$ %, 95%CI [0.0 %, 93.5 %]; $tau^2 = 5.37$). The overall confidence in the body of evidence for number of panic attacks was judged to be 'very low'.

3.5.2.2. Meta-analysis 3. Outcome: Anxiety symptoms (HAM-A) after 2 weeks treatment. Two trials (Noyes et al., 1984; Ravaris et al., 1991) reported on the effectiveness of propranolol (30–320 mg/day) compared with a benzodiazepine; diazepam (5–40 mg/day) or alprazolam (1–30 mg/day) for adults with panic disorder and agoraphobia, expressed as mean HAM-A score for the two treatment groups after 2 weeks of treatment.

There was no evidence of a difference in anxiety symptoms (measured on HAM-A) after 2 weeks of treatment between those randomised to propranolol or diazepam/alprazolam (mean difference = 2.81, 95%CI [−16.87, 22.49], $p = 0.78$) (Fig. 3B). However, there was substantial statistical heterogeneity (two trials, 50 participants in total; $I^2 = 85.9$ %, 95%CI [0.0 %, 97.2 %]; $tau^2 = 173.57$). The overall confidence in the body of evidence for anxiety symptoms was judged to be 'very low'.

3.5.2.3. Meta-analysis 4. Outcome: Anxiety symptoms (HAM-A) after 5–6 weeks treatment. Two trials (Munjack et al., 1989; Ravaris et al., 1991) reported on the effectiveness of propranolol (30–320 mg/day) compared with alprazolam (1–30 mg/day) for adults with panic disorder and agoraphobia, expressed as mean HAM-A score for the two treatment groups after 5–6 weeks of treatment.

There was no evidence of a difference in anxiety symptoms between those randomised to propranolol or alprazolam (mean difference = 0.51, 95%CI [−3.39, 4.42], $p = 0.80$) (Fig. 3C). Although the point estimate for I^2 suggests low between study heterogeneity, the confidence intervals indicate this estimate is uncertain (two trials, 50 participants in total; $I^2 = 12.1$ %, 95%CI [0.0 %, 82.5 %]; $tau^2 = 1.06$). The overall confidence in the body of evidence for anxiety symptoms was judged to be 'very low'.

3.5.3. *Beta-blockers versus antidepressants*

Two trials compared beta-blockers (atenolol/propranolol) with antidepressant (phenelzine/imipramine) medication. Meta-analysis was not possible due to missing data in one study (Munjack et al., 1985). Liebowitz et al. (1992) report evidence for phenelzine demonstrating greater effectiveness than atenolol ($X^2 = 5.4$, $p = 0.02$), whilst Munjack et al. (1985) report that there was no evidence of a difference ($X^2 = 0.78$, p = 'not significant') between imipramine and propranolol on ratings of effectiveness.

Beta-blockers + antidepressants versus *antidepressants + placebo.*

The two trials comparing antidepressants plus beta-blockers versus antidepressants plus placebo had contrasting results. Meta-analysis was not possible due to the absence of arm level data in one study (Stein et al. (2001). Hirschmann et al. (2000) found that patients treated with a

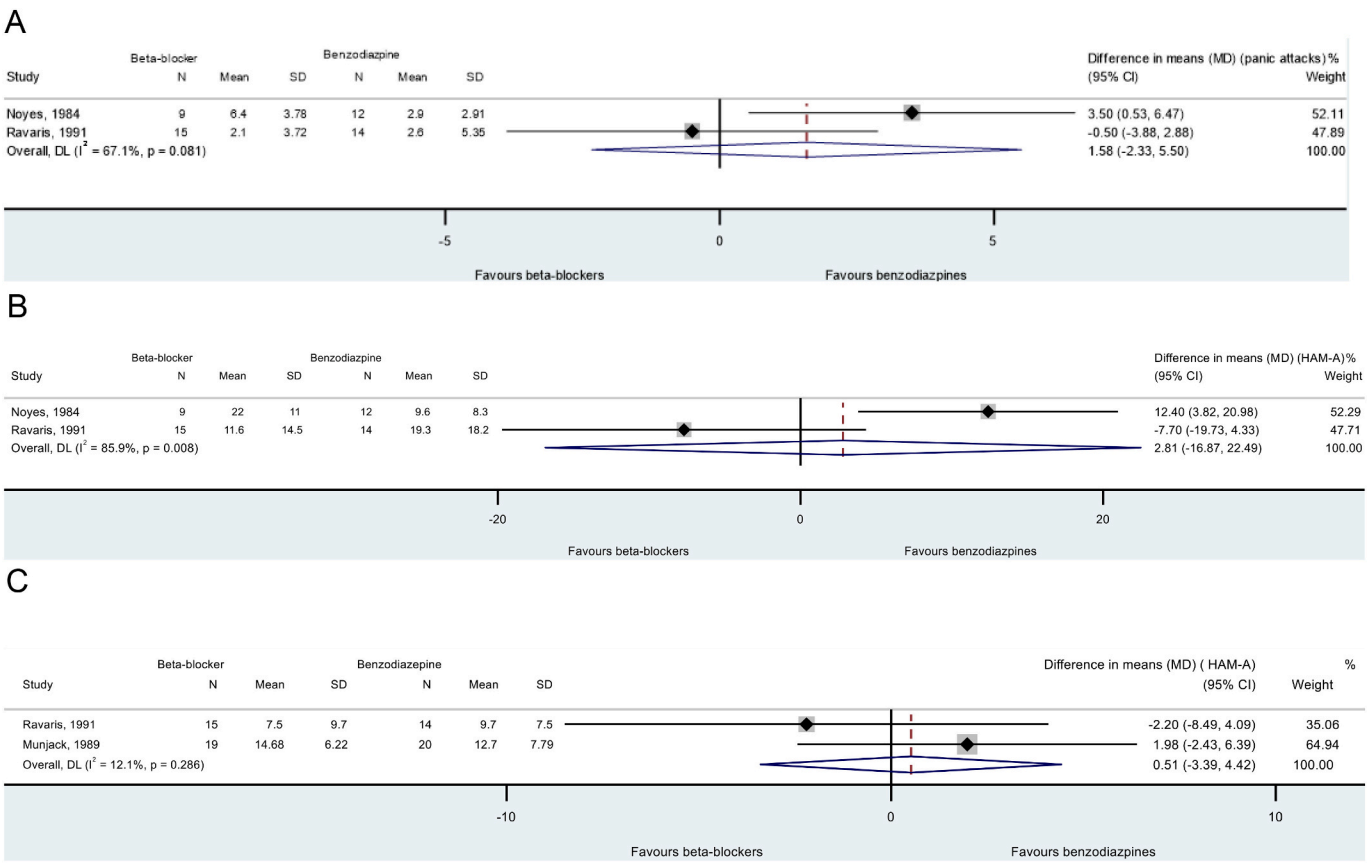

Fig. 3. Meta-analyses 2, 3 & 4: Beta-blockers compared to benzodiazepines
Fig. 3A. Meta-analysis 2. Beta-blockers compared to benzodiazepines (outcome: number of panic attacks after 2 weeks of treatment)
Fig. 3B. Meta-analysis 3. Beta-blockers compared to benzodiazepines (outcome: anxiety symptoms (HAM-A) after 2 weeks treatment.
Fig. 3C. Meta-analysis 4. Beta-blockers compared to benzodiazepines (outcome: anxiety symptoms (HAM-A) after 5–6 weeks treatment).

combination of pindolol and an SSRI demonstrated evidence of improvement over patients treated with an SSRI and placebo ($F = 4.6$, $p < 0.015$), whilst Stein et al. (2001) found that pindolol as an adjunct to paroxetine had no evidence ($F = 1.75$, $p > 0.21$) of effectiveness over placebo in augmenting the effects of SSRI treatment.

3.5.4. Subgroup analyses

3.5.4.1. Beta-blockers versus placebo – for patients with panic disorder with or without agoraphobia only. Two trials (Kathol et al., 1980; Munjack et al., 1989) reported the effectiveness of propranolol (60–240 mg/day) versus placebo for adults with panic disorder and/or agoraphobia, expressed as mean HAM-A score for the two treatment groups after 2 weeks of treatment (for Kathol et al. (1980), 23/26 participants had panic disorder and/or agoraphobia). For participants with a diagnosis of panic disorder, there was only very weak evidence of a difference in the anxiety symptoms (measured on HAM-A) after 2 weeks of treatment between those randomised to propranolol or placebo (mean difference = −3.58, 95%CI [−7.95, 0.79], $p = 0.11$, $I^2 = 0.0$ %, 95%CI [0.0 %, 29.6 %]; $tau^2 = 0.00$) (Supplement 4).

3.5.5. Sensitivity analyses

After excluding the two studies with at least one domain rated as high risk of bias (Kathol et al., 1980; Ravaris et al., 1991) the results were consistent with the results of the main analyses. Of the trials included in the sensitivity analysis of beta-blockers (atenolol/propranolol) compared with placebo for adults with social phobia, panic disorder and/or agoraphobia (Munjack et al., 1989; Liebowitz et al., 1992), there was no evidence of a difference in anxiety symptoms (measured on HAM-A) after 4–5 weeks of treatment between treatment groups (mean difference = −1.13, 95%CI [−7.13, 4.87], Z = −0.37, $p = 0.71$). Heterogeneity was substantial (two trials, 83 participants in total; I2 = 64.2 %, 95%CI [0.0 %, 92.9 %]; $tau^2 = 12.54$).

3.5.6. GRADE

The domain-specific and overall GRADE assessments are presented in Supplement 3. The overall certainty of evidence for each of the primary meta-analyses was rated as very low. This was driven by the study limitations and imprecision domains, whereby each meta-analysis included studies that had a high risk of bias and wide confidence intervals crossing the null value.

4. Discussion

4.1. Summary and interpretation of results

This review found no evidence of a beneficial effect of beta-blockers compared with either placebo or benzodiazepines in patients with social phobia or panic disorder with or without agoraphobia, in terms of either anxiety symptoms or number of panic attacks. This finding was replicated when analyses were repeated according to subtype of anxiety (panic disorder with/without agoraphobia only) and when studies with a high risk of bias were excluded. However, only a small number of trials were included in this review, and many of those were of small sample size (included in review: total $N = 293$ (range: $n = 11$ to $n = 85$); included in meta-analyses: total $N = 179$) and at high (or unclear) risk of bias. The results from the primary meta-analysis were all graded as low certainty of evidence.

Although beta-blockers may help control the physical symptoms of anxiety, they do not act directly on the psychological symptoms. There is some suggestion that beta-blockers may enable a positive feedback loop that can help to reduce anxiety, whereby decreases in somatic symptoms can facilitate a reduction in anxious thoughts related to those somatic symptoms (Brudkowska et al., 2018; MacCormack et al., 2021). However, beta-blockers are either not featured or explicitly not recommended in current clinical guidelines (NICE, 2011; Katzman et al., 2014; Anxiety and Depression Association of America, 2015; Andrews et al., 2018; World Health Organisation, 2023), and it is likely that this is, at least in part, due to the inconclusive evidence for the benefit of this drug in the treatment of anxiety found in an earlier review (Steenen et al., 2016). Although the present updated review provides no further evidence to support the use of beta-blockers for treating anxiety, we note that beta-blocker prescribing for anxiety has increased considerably over the past two decades in UK primary care (Archer et al., 2022). In particular, the increase in young adults starting prescriptions for beta-blocker medication has been substantial, with around half of patients taking it for over six months (Archer et al., 2022).

Against this backdrop of rising prescriptions, there is a clear need to understand when and the reasons why health care practitioners are prescribing beta-blockers for anxiety, and their views on their appropriateness as a first-line treatment. Whilst primary care practitioners do not have any formal clinical guidance concerning when and how they should be use beta-blockers for treating anxiety (NICE, 2011; Anxiety and Depression Association of America, 2015; World Health Organisation, 2023), it is possible that practitioners are prescribing these drugs as a safer, less-addictive, well tolerated, quick-acting alternative to benzodiazepines (Noyes Jr, 1982; Dooley, 2015). Qualitative evidence suggests that beta-blockers may also be preferred by patients who do not want to take conventional psychotropic medication, or who are concerned about the long-term effects of taking antidepressant medication (Archer et al., 2024).

Finally, there is also evidence that beta-blockers are increasingly being prescribed alongside antidepressants as a combination therapy (Archer, 2020), as they are thought to enhance the effects of co-administered antidepressants (Dooley, 2015). However, the two studies included in the present review that examined combination treatment had conflicting results (Hirschmann et al., 2000; Stein et al., 2001). In addition, a recently published report in the UK highlighted a potential under-recognised risk of harm in the use of propranolol alongside antidepressants for patients with depression or anxiety, recommending that BNF and NICE guidance should be updated (Healthcare Safety Investigation Branch, 2020).

4.2. Strength and limitations

This review applied stringent criteria for the systematic review and meta-analysis, in keeping with Cochrane guidelines, and therefore only included studies that were clearly investigating the treatment of DSM or ICD diagnosed anxiety, rather than just anxiety symptoms. We also included all beta-blockers, and did not limit our screening to studies published in English.

We identified a small number of eligible studies ($n = 10$), of which only 5 were included in the meta-analysis. As such, the effect estimates, confidence intervals and prediction intervals may not be reliably interpreted. Moreover, many of the studies identified for inclusion in the present review had small sample sizes and were therefore likely to be underpowered to detect a meaningful difference in outcomes between groups. Many of the studies were conducted over thirty years ago and this may limit the applicability of the findings to the present day given that clinical practice has changed over time. The quality of the included studies was poor with nearly all included studies having a high (or unclear) risk of bias across multiple domains. Missing data was a common problem. We were not able to include 5 studies in the meta-analyses due to unsuccessful attempts to obtain missing data from 4 trials that were conducted between 23 and 39 years ago. As a consequence, it was not possible to meta-analyse data comparing beta-blockers with antidepressants, either as monotherapy or when combined with beta-blockers. However, these studies were described narratively and author reported statistical summaries were described. When conducting the analysis according to subtype of anxiety (panic disorder with/without agoraphobia only), we were not able to separate the outcomes in the patients with this subtype of anxiety ($n = 23$) and those with another subtype (social phobia, GAD; $n = 3$). Thus 3 participants were included in this analysis that did not have the subtype of interest.

Definitions and categorisations of anxiety disorders have changed over the last 50 years and anxiety disorders frequently co-occur with other conditions (Park and Kim, 2020). To minimise between study heterogeneity and improve generalisability of findings to patients in primary care settings, we restricted inclusion criteria to studies of generalised anxiety and related disorders and excluded specific phobias. Although specific phobias are considered as an anxiety disorder by DSM-5, a different treatment approach is required (Bandelow et al., 2014). Conversely, having a broader population inclusion criterion may have facilitated the inclusion of more studies and it is of interest that we did not identify any eligible RCTs that had examined the effectiveness of beta-blockers in the treatment of generalised anxiety disorder.

5. Conclusions

There is a lack of robust evidence of the effectiveness of beta-blockers for the treatment of anxiety. However, beta-blockers are increasingly prescribed routinely for the treatment of anxiety in primary care, despite some safety concerns. Therefore, there is a need to understand firstly, when and why primary care practitioners are using this drug for anxiety, and secondly, to conduct a large multi-centre RCT to assess whether beta-blockers are an effective and safe first-line treatment for anxiety. This would inform treatment guidelines for the large number of patients with anxiety in primary care.

CRediT authorship contribution statement

Charlotte Archer: Writing – review & editing, Writing – original draft, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Nicola Wiles:** Writing – review & editing, Supervision, Formal analysis, Conceptualization. **David Kessler:** Writing – review & editing, Supervision, Formal analysis, Conceptualization. **Katrina Turner:** Writing – review & editing, Supervision, Formal analysis, Conceptualization. **Deborah M. Caldwell:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare no competing interests.

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Availability of data and material

The data that support the findings of this study were derived from the databases and registries available in the public domain. Data to replicate the meta-analysis are included in the figures. Template data collection forms and Stata code are available from the corresponding author on reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.09.068.

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