Gabapentin and pregabalin in bipolar disorder, anxiety states and insomnia: Systematic review, meta-analysis and rationale

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Declaration:

I, James Hong, confirm that the work presented in this thesis is my own. Where the work was done with input from collaborators, I have indicated this in relevant parts of the thesis. Where information has been derived from external sources, I confirm that this has also been indicated in the thesis.

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Acronyms

BD - Bipolar disorder

CENTRAL - Cochrane Central Register of Controlled Trials

CGI-BP - Clinical Global Impression modified for use in Bipolar Disorder

CGI-I - Clinical Global Impression-Improvement

CGI-S - Clinical Global Impression-Severity

CI - Confidence interval

CNS - Central nervous system

CSF - Cerebrospinal fluid

DB - Double-blind

DG – Dentate gyrus

DSM - Diagnostic and Statistical Manual of Mental Disorders

E-I balance - Excitatory-inhibitory balance

ESS - Epworth Sleepiness Scale

FDA - US Food and Drug Administration

GABA - Gamma-aminobutyric acid

GAD - Generalised anxiety disorder

GC – Granule cell

GRADE - Grading of Recommendations, Assessment, Development and Evaluation

HAM-A - Hamilton Anxiety Rating Scale

HAM-D - Hamilton Depressing Rating Scale

ICD - International Classification of Diseases

ICTRP - the International Clinical Trials Registry Platform

InsP3 - Inositol triphosphate

IPD - Individual patient data

IQR - Interquartile range

ISI - Insomnia Severity Index

ISS - Insomnia Severity Scale

KSD - Karolinska sleep diary

LA - Lateral amygdala

LAT1 - L-type amino acid transporter 1

LC - Locus coeruleus

LOCF - Last observation carried forward

LSAS - Liebowitz Social Anxiety Scale

LTP - Long-term potentiation

MAR – Missing at random

MD - Mean difference

MDD - Major depressive disorder

MMPI-2 - Minnesota Multiphasic Personality Inventory-2

MOS-SS - Medical Outcomes Study Sleep Scale

NRS - Numeric rating scale

OCD - Obsessive compulsive disorder

PAS - Panic and Agoraphobia scale

PCL-M - PTSD Checklist-Military version

PD - Panic disorder

PNS - Peripheral nervous system

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PSG - Polysomnography

PSQI - Pittsburgh Sleep Quality Index

PTSD - Post-traumatic stress disorder

RCT - Randomised controlled trial

RDoC - Research Domain Criteria

RR - Risk ratio

SAD - Social anxiety disorder

SD - Standard deviation

SMD - Standardised mean difference

STAI-S - State-Trait Anxiety Inventory (State anxiety scale)

SUD - Substance use disorder

VAS - Visual analogue scale

VGCC - Voltage-gated calcium channel

VRS - Verbal rating scale

WASO - Wake after sleep onset

Y-BOCS - Yale-Brown Obsessive Compulsive Scale

YMRS - Young Mania Rating Scale

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Abstract

The gabapentinoids, gabapentin and pregabalin, target the $\alpha_2\delta$ subunits of voltage-gated calcium channels. Initially licensed for pain and seizures, they have become widely prescribed drugs. Many of these uses are off-label for psychiatric indications, and there is increasing concern about their safety, so it is particularly important to have good evidence to justify this usage. A systematic review and meta-analysis of the evidence for three of their common psychiatric uses – bipolar disorder, anxiety disorders/states, and insomnia – was carried out. Published and unpublished literature were searched and a random-effects pairwise meta-analysis was performed for each outcome where possible. Efficacy and acceptability were assessed using only double-blind randomised controlled trials. Assessment of tolerability also included single blind or open-label trials and non-randomised evidence. Where a quantitative synthesis could not be conducted, results were presented narratively. Fifty-five double-blind randomised controlled trials (RCTs) and 15 open-label studies were identified. For bipolar disorder, four double-blind RCTs investigating gabapentin, and no double-blind RCTs investigating pregabalin, were identified. A quantitative synthesis could not be performed due to heterogeneity in study population, design and outcome measures. Across the anxiety spectrum, a consistent but not universal effect in favour of gabapentinoids compared to placebo was seen (standardised mean difference [SMD] ranging between -2.25 and -0.25). Notably, pregabalin (SMD -0.55, 95% CI -0.92 to -0.18) and gabapentin (SMD -0.92, 95% CI -1.32 to -0.52) were more effective than placebo in reducing preoperative state anxiety, with gabapentin showing a dose effect. In insomnia, results were inconclusive. There is moderate evidence of efficacy of gabapentinoids in state

anxiety and anxiety disorders, but minimal evidence in bipolar disorder and insomnia and they should be used for these disorders only with strong justification. This recommendation applies despite the attractive pharmacological and genetic rationale for targeting voltage-gated calcium channels. It may be possible to develop modified $\alpha_2\delta$ ligands, targeting particular subtypes or isoforms, with a more beneficial therapeutic profile. A future direction for clinical research would be to explore the targeted treatment of comorbid anxiety in bipolar disorder using gabapentinoids or modified $\alpha_2\delta$ ligands.

Thesis summary

The aims of this thesis are:

1. to assess the efficacy, acceptability and tolerability of gabapentin and pregabalin in three psychiatric disorders in which they are commonly used – bipolar disorder, anxiety disorders/states, and insomnia – and,
2. to discuss the rationale for the further investigation and use of these gabapentinoids, and $\alpha_2\delta$ ligands more generally, in psychiatry.

The thesis begins with a background to the work, including gabapentinoid use in psychiatry, their mechanisms of action and relation to voltage-gated calcium channels more broadly. It explains the clinical importance of and motivation for evidence synthesis of gabapentinoids in bipolar disorder, anxiety disorders/states and insomnia. It then describes the method of the systematic review, which collects and critically appraises both published and unpublished evidence on gabapentin and pregabalin from clinical trials (double-blind randomised controlled trials only for efficacy). Where appropriate, quantitative synthesis is conducted by a random effects pair-wise meta-analysis. Finally, the interpretation of findings and strengths and limitations of the study are discussed. To complement this, the rationale for the use and development of $\alpha_2\delta$ ligands is explored. Future directions for research in relation to the literature and findings of the current work are outlined.

Learning points and reflection

In carrying out the work for this thesis, I gained critical insights into the following: (i) the elements of a methodologically robust systematic review and meta-analysis, (ii) the rationale for targeting voltage-gated calcium channels in psychiatric disorders, (iii) traditional conceptual underpinnings and their weaknesses in psychiatric research and practice; the potential of novel psychiatric constructs, based on the neurosciences, to pave the way for transdiagnostic research, (iv) limitations of standard pair-wise meta-analyses and constraints of existing clinical studies, particularly of gabapentinoids in psychiatric disorders, (v) opportunities and challenges in the dissemination of academic work, (vi) important 'human factors' involved in the execution of high-quality work in evidence synthesis and in research more generally, and (vii) the potential for evidence-based mental health research to impact clinical practice and generate new insights and hypotheses.

It was a privilege to be immersed in the work and collaborate with colleagues and experts in such a way as to gain a deeper view of psychiatry, which otherwise may not have been possible. Conducting this work has equipped me with both theoretical knowledge and practical mechanisms by which to meaningfully interpret and feasibly address gaps in psychiatric research and practice. These include approaches to investigate and modulate psychiatrically relevant biological processes in a nuanced way, more sophisticated methods of evidence synthesis that may involve individual patient data and opportunities for clinical research in the targeted treatment of 'bipolar anxiety' using gabapentinoids or modified $\alpha_2\delta$ ligands.

Chapter 1: Introduction

1.1 Summary

This chapter introduces the context and motivation for my thesis. It starts by describing the use of gabapentinoids in clinical practice, the existing evidence for their use and potential harms. It also outlines the known mechanisms of gabapentin and pregabalin, which are modulators of voltage-gated calcium channels, and potential therapeutic mechanisms of action. It then provides an overview of voltage-gated calcium channels and the $\alpha_2\delta$ subunit, the molecular target of gabapentinoids. Finally, it briefly describes what a systematic review/meta-analysis is, and its importance in the evidence synthesis of interventions. The chapter ends with the objectives of this thesis, in relation to the literature that is described.

1.2 Gabapentinoids in clinical psychiatry

Initially developed as gamma-aminobutyric acid (GABA) analogues for treatment of epilepsy, the gabapentinoids – gabapentin and pregabalin – are used in a range of disorders. Gabapentin is licensed for use in the USA for the treatment of focal seizures and post-herpetic neuralgia (Goodman and Brett 2019a) and in the UK for focal seizures and peripheral neuropathic pain (Joint Formulary Committee). Pregabalin has similar indications, as well as for fibromyalgia in the USA and generalised anxiety disorder (GAD) in the UK (Goodman and Brett 2019a; Joint Formulary Committee). Since their introduction in 1993, these drugs have become two of the most commonly prescribed medications (Goodman and Brett 2017), with a significant proportion likely to have been off-label. An early study of 105 Medicaid

patients showed that 95% of prescriptions for gabapentin were for off-label indications, at least 10% of which were for psychiatric disorders (Hamer et al. 2002). In the UK, at least half of all gabapentinoid prescriptions are off-label, and one in five are co-prescribed with opioids (Montastruc, Loo, and Renoux 2018). A recent survey using the US-based TriNetX electronic health records network (Taquet et al. 2021) showed that gabapentin had been prescribed at least once in 13.6% of patients with bipolar disorder (BD), 11.5% with anxiety disorders, and 12.7% with insomnia disorder; for pregabalin, the figures were 2.9%, 2.6%, 3.0% respectively (PJH, *unpublished observations*).

1.2.1 Evidence for use of gabapentinoids in bipolar disorder, anxiety disorders/states and insomnia

Despite the widespread off-label use of gabapentin in BD, the evidence for its efficacy is unclear (Houghton et al. 2017). Gabapentin was not found to be effective over placebo in a comprehensive network meta-analysis of pharmacologic treatments in acute mania (Cipriani et al. 2011). Systematic reviews of gabapentin treatment in psychiatric and/or substance use disorders showed inconclusive evidence for efficacy in BD, but possible efficacy for some anxiety disorders (Berlin, Butler, and Perloff 2015; Ahmed et al. 2019). These studies did not examine pregabalin, did not attempt a quantitative synthesis, and only included published studies.

Beyond its licensed use for GAD in the UK, pregabalin has been used in the management of other anxiety disorders (Blanco et al. 2013) and acute anxiety states

such as preoperative state anxiety (Nutt, Mandel, and Baldinetti 2009). The efficacy of pregabalin is well established in GAD (Slee et al. 2019) but is unclear in other anxiety disorders such as social anxiety disorder (Williams et al. 2020). A review of pregabalin for preoperative anxiolysis did not attempt a quantitative synthesis (Torres-González et al. 2020). Gabapentinoids may also be of benefit in the treatment of insomnia in some conditions (Atkin, Comai, and Gobbi 2018), but again the evidence is unclear. Overall, these studies show that there is limited evidence for the efficacy of gabapentinoids in several of the disorders for which they are used.

1.2.2Potential harms of gabapentinoid use

Gabapentinoids have potential harms, including a range of serious side-effects, and evidence of misuse and addiction potential (Bonnet and Scherbaum 2017; Morrison, Sandilands, and Webb 2017; Goodman and Brett 2019b; Molero et al. 2019), leading to their re-categorisation as controlled drugs in the UK in 2019. In the United States, pregabalin (but not gabapentin) has been a federally controlled drug since market availability because of its potential for dependence and abuse (Schjerning et al. 2016). Previous reports (Goodman and Brett 2019b) suggest that gabapentinoids cause several side effects associated with central nervous system depression, such as drowsiness, dizziness, and gait instability, which may be associated with increased risk of accidental physical injuries (Molero et al. 2019). The addictive potential of gabapentinoids is reportedly higher in patients with substance use disorders; this effect is reported to be associated with augmentation of euphoria (Evoy, Morrison, and Saklad 2017). Importantly, concurrent use of opioids and gabapentin is associated with increased risk of opioid-related death (Gomes et al.

2017). Gabapentinoids have also been associated with an increased risk of suicidal behaviour and road traffic accidents (Molero et al. 2019).

Yet, rates of prescribing have at least tripled in the US and UK since the mid-2000s (Goodman and Brett 2019a; Mahase 2020). In the US, gabapentin is often used in pregabalin-approved FDA indications as the former is significantly cheaper (Goodman and Brett 2019a). Physicians turn to off-label use of gabapentinoids as they are a quick and potentially safer alternative to opioids in chronic pain management (Goodman and Brett 2017). Prescribing behaviour may also be driven by potential clinical benefits in some psychiatric disorders including BD (Sokolski et al. 1999) and insomnia (Lo et al. 2010), but the evidence for their use has not been rigorously assessed. Efficacy has been reported but often in the form of case reports and open-label studies (Egashira et al. 2011; Soutullo, Casuto, and Keck Jr 1998; Erfurth et al. 1998).

1.2.3 Gabapentin and pregabalin: pharmacodynamics and pharmacokinetics

Gabapentin and pregabalin are high-affinity ligands of the $\alpha_2\delta$ subunit of voltage-gated calcium channels (VGCCs; see **section 1.3)** in the central nervous system (CNS) (Chincholkar 2018). Gabapentin, taken orally, is absorbed in the intestines via the L-type amino acid transporter 1 (LAT1) (Dickens et al. 2013). Absorption of gabapentin exhibits non-linear kinetics (Bockbrader 2010), and is dose-limited due to a saturable transport mechanism in intestinal absorption (Stewart et al. 1993) as well as the blood-brain barrier (BBB) (Luer et al. 1999). As dose increases from 900 to

3600 mg per day, gabapentin bioavailability decreases from ~60% to 33% (Wesche and Bockbrader 2005). Compared to gabapentin, pregabalin has better oral bioavailability across the range of clinically used doses (>90%), three-fold greater maximum rate of absorption, and linear pharmacokinetics (Bockbrader 2010). Cerebrospinal fluid (CSF) concentrations of the drugs increase with time and with multiple doses; mean CSF concentrations peak at least six hours after peak plasma concentrations and decrease at a slower rate than in plasma (Bockbrader 2010). Autoradiographic studies in animals suggest that gabapentin and pregabalin exhibit proportionally similar distribution into the CSF (Bockbrader 2010). Gabapentin and pregabalin are not bound to plasma proteins and undergo renal excretion with an elimination half-life of six hours. Pregabalin displays higher affinity for $\alpha_2\delta$ subunits than gabapentin (Alles, Cain, and Snutch 2020), and pregabalin is approximately 2.5 times more potent than gabapentin (Wesche and Bockbrader 2005). Whilst there are differences in dose-related efficacy, both drugs show dose effects in licensed indications including post-herpetic neuralgia, focal seizures and GAD (Bockbrader 2010).

1.2.4 Therapeutic mechanisms of action of gabapentinoids

Despite the nomenclature, gabapentin and pregabalin do not directly affect GABAergic systems. The therapeutic actions of gabapentinoids are instead mediated by their binding to the $\alpha_2\delta$-1/$\alpha_2\delta$-2 subunits of VGCCs (Dolphin 2016) (see **section 1.3**). Hendrich and colleagues showed that mutations of $\alpha_2\delta$-1 and $\alpha_2\delta$-2, but not $\alpha_2\delta$-3, block the neuronal actions of gabapentin (Hendrich et al. 2008). The $\alpha_2\delta$-1

and $\alpha_2\delta$-2 isoforms are widely expressed in the CNS and have been shown to modulate the function of VGCCs (see **section 1.3.2**) (Dolphin 2016).

In an autoradiographic study of R217A mutant mice (arginine-to-alanine mutation at amino acid 217 of the $\alpha_2\delta$-1 protein), $\alpha_2\delta$-1-binding of pregabalin was selectively reduced in the neocortex, CA1/CA2/CA3 and dentate gyrus of the hippocampus, entorhinal cortex, basolateral amygdala and the spinal cord, suggesting that the $\alpha_2\delta$-1 is the major binding protein in these sites (Bian et al. 2006). Consistent qualitative findings were reported for the neuroanatomical localisation gabapentin in wild-type mice (Hill, Suman-Chauhan, and Woodruff 1993).

Gabapentin and pregabalin inhibit neuronal calcium currents, an effect most prominently observed after chronic, rather than acute, administration (Dolphin 2016; Hendrich et al. 2008). Gabapentin prevents Rab11-dependent recycling of $\alpha_2\delta$ subunits to the plasma membrane, associated with a corresponding reduction in trafficking of α-1 subunits (Tran-Van-Minh and Dolphin 2010) which may be responsible for its effect on calcium currents. The results are mixed, however, as in some cases there are no acute changes on gabapentin administration (Moore, Baba, and Woolf 2002). The effects appear to be dependent on the baseline level of $\alpha_2\delta$-1 expression (Dolphin 2016), as well as on the cell type, method of drug delivery, drug concentrations, and assays used (Alles, Cain, and Snutch 2020).

The gabapentinoids affect multiple neurotransmitter systems, including glutamatergic, cholinergic and monoaminergic systems, and various neuronal

populations through several mechanisms, including its effects on VGCC-mediated calcium currents and channel trafficking (Stahl et al. 2013). Both gabapentin and pregabalin reduce the amplitude and paired-pulse ratio of excitatory postsynaptic currents, an effect attributable to reduced presynaptic glutamate release from neurons in the entorhinal cortex (Cunningham et al. 2004). Gabapentin has been shown to decrease electrically-evoked dopamine release from the caudate nucleus in vitro (Reimann 1983). It has also been shown to inhibit biogenic synthesis and release of dopamine, serotonin and noradrenaline in rat hippocampal and mesolimbic regions, but not basal amine synthesis (Pugsley, Whetzel, and Dooley 1998). Pregabalin increases dopamine release in the nucleus accumbens in the early phase of a neuropathic pain model in rats (Kato, Ide, and Minami 2016), whilst reducing K+-evoked release of serotonin and noradrenaline in human neocortical slices (Brawek et al. 2008). The effect of gabapentinoids on neurotransmitter release is therefore cell type- and region-specific (Yoshizumi et al. 2012), dependent on the experimental conditions, and can also be $\alpha_2\delta$-independent. In the locus coeruleus (LC), gabapentin induces glutamate release from astrocytes via an $\alpha_2\delta$-independent mechanism (Suto et al. 2014) and also inhibits GABA release (Yoshizumi et al. 2012) – both enhancing noradrenergic descending inhibition and suppressing neuropathic pain. This apparent increase in LC noradrenergic activity is an effect classically associated with anxiogenesis (Dell'Osso et al. 2010). However, gabapentin has been shown to increase tonic inhibitory conductance in the hippocampus by increasing δ-containing GABA-A receptor expression (Yu et al. 2019a), which along with $\alpha_2\delta$-1-dependent mechanisms (Lotarski et al. 2011), may contribute to the overall anxiolytic effect. Interestingly, some stereoisomeric analogues of gabapentin with high affinity

for $\alpha_2\delta$ do not have the same therapeutic effects (Urban et al. 2005). Such findings suggest that mere binding to the $\alpha_2\delta$ subunit is not sufficient for the therapeutic actions of the gabapentinoids, which may also affect $\alpha_2\delta$ subunit interaction with other proteins in roles related and unrelated to VGCC function (Dolphin 2018a).

1.3 Voltage-gated calcium channels and the $\alpha_2\delta$ subunit

A priori, gabapentinoids represent attractive candidate molecules for psychiatric indications because of their mode of action. As described previously, they act via VGCCs, binding to the $\alpha_2\delta$ auxiliary subunit that regulates channel trafficking and function (Dolphin 2018a). Though genes encoding $\alpha_2\delta$ subunits have not thus far been associated with psychiatric phenotypes, other VGCC genes – particularly *CACNA1C*, which encodes the α-1 subunit of the $Ca_V1.2$ L-type VGCC subtype – show robust, transdiagnostic associations with multiple disorders, including BD (Heyes et al. 2015; Cross-Disorder Group of the Psychiatric Genomics Consortium 2019). Furthermore, prescription of calcium channel blockers, which block the α-1 subunit of L-type VGCCs, is associated with reduced hospitalisations in patients with severe mental illness (Hayes et al. 2019). More broadly, dysregulation of cellular calcium is observed in patients with BD and some other psychiatric disorders (Harrison et al. 2016).

1.3.1 Voltage-gated calcium channels

VGCCs are multi-subunit protein complexes which open on depolarisation of the membrane potential, following which calcium moves across the membrane down its electrochemical gradient (Catterall 2011). The influx of calcium, and resulting

increase in intracellular calcium concentration, affects downstream cellular processes including neurotransmitter release, calcium-dependent gene expression, hormone secretion and pacemaker activity (Nanou and Catterall 2018). VGCCs have four subunits: the α1 subunit (the transmembrane calcium-selective pore), γ subunit (modulates biophysical properties of the channels) and the β and α2δ subunits (trafficking of the α1 subunit to the cell membrane and modulates biophysical properties of the channels) (Catterall 2011). VGCCs are comprised of three families, determined by the sequence homology of ten different α-1 subunits (Catterall 2011).

$Ca_v1.1$ to $Ca_v1.4$, or the L-type VGCCs, are the main target of calcium channel blockers used in clinical practice and of greatest therapeutic interest in psychiatric disorders (Harrison et al. 2020). The L-type VGCCs are involved in a variety of functions including hormone secretion, local calcium signalling and gene transcription (Nanou and Catterall 2018). The other families, including Ca_v2 and Ca_v3 VGCCs, have diverse functions including initiation of synaptic transmission, calcium signalling, rhythmic action potential generation in sleep rhythms (Nanou and Catterall 2018). The Ca_v1 and Ca_v2 families associate with the α2δ subunit, the molecular target of gabapentinoids (Dolphin 2016). Importantly, calcium channel diversity is increased by alternative splicing of VGCC mRNAs (Lipscombe, Pan, and Gray 2002) and the combination and stoichiometry of the auxiliary (α2δ, β and γ) subunits (Catterall 2011).

In particular, $Ca_v1.2$ is strongly implicated in NMDA-dependent hippocampal long-term potentiation (LTP) (Kabir, Martinez-Rivera, and Rajadhyaksha 2017). $Ca_v1.2$ -

mediated calcium influx activates downstream signalling pathways, including protein kinase ERK and CREB-dependent transcription (Moosmang et al. 2005) which are associated with several forms of learning and memory. Notably, $Ca_v1.2$ has been shown to be responsible for most of L-type current in lateral amygdala (LA) neurons, and pharmacologic inhibition prevents thalamo-LA LTP and fear conditioning (Striessnig et al. 2014).

1.3.2$\alpha_2\delta$ subunits

α2δ proteins – comprising α2δ-1, α2δ-2, α2δ-3 and α2δ-4 – are extracellular subunits of VGCCs encoded by four genes in the mammal: *CACNA2D1*, *CACNA2D2*, *CACNA2D3* and *CACNA2D4* (Ablinger et al. 2020). The genes for the respective α2δ subunits encode a precursor protein which is post-translationally modified. Within the series of post-translational processing steps, the proteolytic cleavage between the α2 and δ moieties is essential to the mature function of the α2δ protein (Dolphin 2018a); also see **section 4.4.6**. The α2δ-1, α2δ-2, and α2δ-3 isoforms are widely expressed in the CNS and peripheral nervous system (PNS) (Davies et al. 2007). More specifically, the α2δ-1 subunit is found in many neuronal types, primarily in pre-synaptic terminals of excitatory neurons but also to a lesser extent in dendrites and somata (Dolphin 2016).

The $\alpha_2\delta$ subunits are significant modulators of presynaptic VGCC density and probability of neurotransmitter release (Hoppa et al. 2012); a function that is critically dependent on the proteolytic maturation of the $\alpha_2\delta$ proteins (Ferron, Kadurin, and Dolphin 2018). In general, α2δ subunits increase the cell surface expression of Ca_v1

and Ca_v2 channels and increase calcium current density (Cassidy et al. 2014). The perfect MIDAS motif is required for α2δ-mediated increase in calcium current (Hoppa et al. 2012), and calcium current density is partly associated with increased forward trafficking of channels (Bauer et al. 2009).

The diverse roles of α2δ subunits extend to altering voltage-dependent and kinetic properties of the calcium currents, such as by increasing the kinetics of inactivation for VGCCs (Dolphin 2016). α2δ expression is associated with a negative shift in the voltage-dependence of steady-state inactivation and hyperpolarisation of voltage-dependence of activation (Dolphin 2018a). Correspondingly, the level of α2δ expression influences action potential waveforms (Hoppa et al. 2014; Margas et al. 2016), and the association of α2δ-1 with α-1c ($Ca_v1.2$ VGCC pore) allows the channel to operate at physiological membrane potentials (Savalli et al. 2016).

Finally, the α2δ subunits appear to be important in synapse formation. Knockout mouse models of α2δ show aberrant changes in synaptic morphology in several systems (Pirone et al. 2014; Brodbeck et al. 2002), indicating a role for maintenance of synapse structure. In particular, the α2δ-1 isoform is critically involved in synaptogenesis by interacting with astrocyte-derived thrombospondin (TSP) to induce excitatory synaptogenesis (Eroglu et al. 2009).

1.4 Evidence synthesis

Whereas neurobiological considerations guide further investigations of therapeutic targets, justification for the clinical use of interventions comes from rigorous systematic reviews and meta-analyses of all available evidence. Previous studies have assessed the evidence for use of gabapentinoids in a range of conditions (**section 1.2.1**), but these reviews require updating using robust methods of evidence synthesis in psychiatric disorders in which gabapentinoids are widely used: BD, anxiety disorders/states and insomnia/sleep disturbance.

1.4.1 Systematic review

A systematic review addresses defined questions, with *a priori* methods of literature search, screening, and analysis strategies described in a review protocol prior to undertaking the work (Cipriani and Barbui 2006a). In this sense, a systematic review is distinct to a narrative review, which does not use explicit methods and instead relies on implicit criteria to select studies. Narrative reviews analyse the data using a purely qualitative approach, relying on the experiential and subjective knowledge of the investigator (Cipriani and Barbui 2006a). A key advantage of a systematic review is its use of explicit methodology, which helps to avoid systematic errors and enhance reproducibility (Siddaway, Wood, and Hedges 2019). The quality and nature of a systematic review will be highly dependent on these pre-defined methods. Good systematic reviews use transparent, replicable methods to retrieve and critically appraise all available evidence, that are appropriate for the types of studies being synthesized (Higgins et al. 2021).

1.4.2Meta-analysis

A meta-analysis is the statistical pooling of the results of individual studies, in which each study is given a weight proportional to its sample size and inversely proportional to the variance (Cipriani and Barbui 2006b). The decision to conduct such a quantitative synthesis ultimately rests with the investigators, but there are generally accepted criteria which should be met. Individual studies must report quantitative data, examine similar constructs, employ similar experimental designs, and provide results that can be converted into standardised effect sizes (Siddaway, Wood, and Hedges 2019). Whilst a properly conducted meta-analysis always involves a systematic review, not every systematic review is followed by a meta-analysis (Cipriani and Barbui 2006a). The validity and interpretation of meta-analytical results will depend on the nature and quality of the essential elements of a systematic review, including the review question, eligibility criteria, identification and selection of studies, collection of relevant data, risk of bias assessment, comparisons and method of meta-analysis (Higgins et al. 2021).

In mental health research, the most commonly used standardised effect sizes of continuous outcomes are Cohen's *d* (Schäfer and Schwarz 2019) and Hedge's *g* (Hedges and Olkin 1985), which indicate the difference between two groups based on standard deviations. The outcome of a meta-analysis is influenced by the chosen statistical model, such as the fixed-effects and random-effects models (Nikolakopoulou, Mavridis, and Salanti 2014). The fixed-effects model assumes that all effect sizes of the included studies are from a homogeneous population; hence

any deviation from the overall treatment effect is assumed to be due to sampling error (Borenstein et al. 2010). In contrast, the random-effects model addresses the concern, and real-world situation, that the population from which studies are conducted are not homogeneous; true differences may exist between effect sizes of individual studies (Borenstein et al. 2010). In the random-effects model, it is assumed that individual studies deviate not only due to sampling error but also other sources of variance. Hence, the pooled result from a random-effects meta-analysis reflects the mean of the distribution of true effects (Borenstein et al. 2010).

Between-study heterogeneity is often assumed to exist *a priori*, particularly in meta-analyses of mental health interventions. Clinical heterogeneity may exist due to differences in participant characteristics, interventions and outcomes (Gagnier et al. 2013). Methodological heterogeneity refers to variability in trial design or execution (Gagnier et al. 2013). Finally, statistical heterogeneity is variability in summary effect estimates (Gagnier et al. 2013). Statistical heterogeneity is a quantifiable property reflecting the variability in effect sizes. The I^2 statistic, directly based on the Cochran's Q (a classical test of heterogeneity), is a statistical measure of heterogeneity that describes the percentage of variability in effect sizes not due to sampling error (von Hippel 2015). By convention, I^2 of 50% and 75% are interpreted as moderate and substantial heterogeneity, respectively (Higgins and Thompson 2002). Whilst various methods exist to explore sources of significant heterogeneity, including subgroup and metaregression analyses (Gagnier et al. 2013), these should where possible be specified prior to undertaking a systematic review.

1.4.3Risk of bias

Bias is defined as a form of systematic error (Higgins et al. 2021), which can lead to under- or over-estimation of the true intervention effect. Biases can vary in magnitude and direction across studies included in a systematic review, and can exist in the meta-analysis of findings from the included studies (Higgins et al. 2021). Assessing the internal validity of studies is a key part of considering their potential limitations and those of the conclusions drawn from a systematic review. The Cochrane Risk of Bias (RoB) Tool is a widely-used tool that facilitates the assessment of the RoB in randomised trials (i.e. the risk that a randomised trial would under- or over-estimate the true effect). The 2011 version of the Cochrane RoB Tool, used in this thesis, specifies six domains to be assessed independently by at least two systematic reviewers (Higgins et al. 2011):

(i) selection bias: systematic differences between baseline characteristics of groups compared in a trial. Sources of selection bias include inadequate random sequence generation and/or inadequate allocation concealment.

(ii) performance bias: systematic differences between groups in care provided, or exposure to factors other than the intervention being studied. Sources of performance bias include inadequate blinding of study personnel and/or participants, or factors associated with un-blinding.

(iii) detection bias: systematic differences between groups in how outcomes are determined. Sources of detection bias include inadequate blinding of outcome assessors, or factors associated with un-blinding.

(iv) attrition bias: systematic differences between groups in withdrawal from a study, associated with incomplete outcome data. Sources of attrition bias

include variations in the amount, nature or handling of incomplete outcome data.

(v) reporting bias: systematic differences between reported and unreported findings. Reporting bias arises from selective reporting of outcomes.

(vi) other bias: biases that are not covered in the above five domains and are relevant to specific clinical settings or trial designs. For instance, recruitment bias may occur in cluster-randomised trials when the cluster type (intervention or control) is known. In crossover trials, carryover (residual) effects may bias responses to subsequent treatments.

1.5 Objectives

Given the potential harms of gabapentinoids and their widespread off-label prescribing, it is important to assess rigorously the evidence base for their use.

The objectives of this thesis are to:

1) Conduct a systematic review all available published and unpublished evidence on gabapentin and pregabalin in bipolar disorder, anxiety disorders/states and insomnia
2) Assess the efficacy and acceptability of gabapentin and pregabalin in these disorders using random-effects pairwise meta-analyses where appropriate, or narrative descriptions where a quantitative synthesis is not possible, of double-blind randomised controlled studies only
3) Assess the tolerability of gabapentin and pregabalin from double-blind, single-blind or open-label trials, as well as non-randomised evidence
4) Explore and discuss in depth the rationale for the use of gabapentinoids and development of modified $\alpha_2\delta$ ligands in psychiatric disorders, and outline future directions for research.

Chapter 2: Methods

2.1 Summary

This chapter outlines the methods of the systematic review and meta-analysis, any post-hoc adjustments (i.e. changes to the protocol made after its initial registration) and the rationale for these changes. The strengths and limitations of the methods are discussed more generally in **Chapter 4**.

2.1.1 Acknowledgments

The study was conceived by the authors of the protocol paper published in *BMJ Open* (Houghton et al. 2017), registered prior to the start of my work on data extraction, analysis, interpretation, drafting and revising of the manuscript produced as a result. For work conducted in relation to this thesis (also see section 5.2, p.92 on Dissemination), the following contributors are acknowledged. **Data extraction/analyses**: Dr Lauren Z Atkinson (LZA), Dr Noura Al-Juffali, Dr Amine Award, Prof Andrea Cipriani (AC). **Additional input and interpretation**: Prof John R Geddes (JRG), Prof Elizabeth M Tunbridge (EMT).

2.2 Search strategy

To identify published studies, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, MEDLINE In-Process and PsycINFO were searched from their inception to 4th August 2020 (see published protocol (Houghton et al. 2017) for details). For unpublished studies, international trial registries

(ClinicalTrials.gov; the International Clinical Trials Registry Platform [ICTRP], www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal) and the websites of the following regulatory agencies were searched: the European Medicines Agency, the United States Food and Drug Administration in the US, the Medicines and Healthcare Products Regulatory Agency in the UK, the Medicines Evaluation Board, The Medical Products Agency, the Pharmaceuticals and Medical Devices Agency, and the Therapeutic Goods Administration in Australia. Reference lists of included studies were hand checked for relevant papers and systematic reviews.

2.3 Search terms

The following phrase was used in literature searches (Houghton et al. 2017):

> ((((‘bipolar disorder’ OR ‘cyclothymic disorder’) OR ‘sleep initiation and maintenance disorders’ OR (‘anxiety’ OR ‘anxiety disorders’ OR ‘agoraphobia’ OR ‘anxiety, separation’ OR ‘combat disorders’ OR ‘neurotic disorders’ OR ‘obsessive-compulsive disorder’ OR ‘panic disorder’ OR ‘phobic disorders’ OR ‘stress disorders, traumatic’ OR ‘stress disorders, post-traumatic’ OR ‘psychological trauma’ OR ‘stress disorders, traumatic, acute’)) AND (‘gamma-aminobutyric acid’ OR ‘pregabalin’)) combined with terms for randomised controlled trials (efficacy) OR adverse effects (tolerability))*, †
>
> **Subject (MeSH) entries sourced from MEDLINE*
>
> †*The search terms did not include ‘phobia’. To ensure that ‘social phobia’ was included in the systematic review, a further search was done; this search did not generate additional papers.*

2.4 Selection criteria

To assess efficacy and acceptability (dropout rate), double-blind, randomised controlled trials (DB-RCT) comparing gabapentin or pregabalin, in any dose, frequency, route of administration or setting, with placebo or any other active pharmacological treatment, were included. RCTs investigating adjunctive gabapentin/pregabalin to pre-existing treatment and trials allowing rescue medications were included if pre-existing treatments or rescue medications were evenly distributed in the experimental and comparator intervention arms. To assess tolerability (adverse effects), randomised and non-randomised studies, irrespective of blinding, were included. Crossover trials were only included if data from the first period, prior to crossover, were available. Cluster randomised trials were excluded. Patients of any age, sex, ethnicity, and clinical setting were included, but studies with patients with serious medical illness were excluded.

For BD, studies that assessed both acute treatment (follow-up of 3 weeks for manic and mixed episodes; 8 weeks for depression) and long-term treatment (>12 weeks) were included. Studies with patients of any BD subtype based on standardised diagnostic criteria, i.e. the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) were included. Studies were excluded if a diagnosis of BD was defined using cut-off scores on screening questionnaires, or if patients reported a concurrent Axis I disorder (excluding comorbid anxiety or insomnia). For anxiety, studies of any anxiety disorder as defined in ICD or DSM were included. We also included studies investigating preoperative state anxiety. Studies were excluded if patients reported a concurrent

Axis I disorder (excluding BD or insomnia). For insomnia, studies investigating sleep or insomnia, including healthy populations and those with a defined sleep disorder, were included. Three authors (JSWH, LZA, AA) independently screened titles and abstracts generated by the search strategies. Full-text articles were reviewed for inclusion and the relevant information was extracted from included trials.

2.5 Outcomes

2.5.1 Primary outcome

For the **acute treatment of BD**, the primary outcome was efficacy of gabapentin or pregabalin as measured by the following:

(i) number of hospital admissions during the study period

(ii) length of hospital admission

(iii) change on validated manic or depressive symptom rating scales from baseline

(iv) change on validated psychotic symptom rating scales from baseline

(v) response to treatment (i.e. at least 50% improvement on any validated rating scale)

(vi) time to cessation of additional treatment for manic/depressive symptoms.

For the **long-term treatment of BD**, the primary outcome was efficacy measured by the following:

(i) time to recurrence of any mood episodes

(ii) number of recurrences of any mood episodes during the trial period

(iii) number of recurrences of manic, mixed, or depressive episodes.

For the **acute and long-term treatment of anxiety states or disorders**, the primary outcome was efficacy as measured by change in validated and standardised anxiety rating scales.

For the **acute and long-term treatment of insomnia**, the primary outcome was efficacy measured by the following:

(i) objectively measured or self-reported sleep time

(ii) self-reported sleep quality

(iii) sleep onset latency.

2.5.2Secondary outcomes

Secondary outcomes included acceptability and tolerability of gabapentin or pregabalin in acute/long-term treatment of BD, anxiety states/disorders, and insomnia.

Acceptability was measured as follows:

(i) participants dropping out of treatment due to any cause

(ii) participants dropping out of treatment due to adverse events

(iii) participants dropping out of treatment due to inefficacy.

Tolerability was measured as follows:

(i) the number of participants experiencing at least one adverse event

(ii) the number of participants experiencing a pre-specified list of side effects in the British National Formulary (Joint Formulary Committee).

2.6 Data extraction

The following data were extracted from studies meeting the inclusion criteria:

- Study characteristics (blinding, randomisation, sponsorship, crossover/parallel group design).
- Participant characteristics (age, sex, ethnicity, study setting, primary diagnosis according to DSM or ICD classification, comorbidity, severity, treatment history for the index episode).
- Intervention details (intervention treatment, comparator treatment, dosage, frequency of administration, route of administration, duration of therapy, co-interventions).
- Outcome measures of interest in terms of efficacy, tolerability and adverse events (see **section 2.5** of this chapter).

Where both published and unpublished data were available, data from unpublished sources were prioritised in the case of any discrepancies. Authors were contacted for additional data if necessary. Graphical data were extracted using WebPlotDigitizer version 4.4 (https://automeris.io/WebPlotDigitizer). Risk of bias for each study was independently assessed by four investigators (JSWH, LZA, NA, AA) using the Cochrane Risk of Bias tool (Higgins et al. 2021). Any disagreements were resolved by consensus with another team member.

2.7 Data analysis

Continuous outcomes were calculated as mean differences (MDs) or standardised MDs (SMDs) with 95% confidence intervals (CI). For studies where the continuous outcome of interest was reported in median/interquartile range (IQR)/range, the method by Wan and colleagues (Wan et al. 2014) was used to convert values to mean/standard deviation (SD). To deal with multiplicity of continuous outcome measures, the most relevant outcome was selected based on previous literature relevant to the diagnostic category, e.g. in GAD, we used baseline-to-endpoint change in the Hamilton Anxiety Rating Scale (HAM-A) where possible (Slee et al. 2019). In preoperative state anxiety studies, the primary outcome measure recorded at 1-2 hours post-drug administration and closest to the time of the induction of anaesthesia was used. For dichotomous outcomes, risk ratios (RRs) were calculated with 95% CI. For studies with multiple treatment arms of the same type of interventional drug, the mean/SDs were combined following methods described in the Cochrane Handbook (Higgins et al. 2021). In subgroup analyses where arms were allocated to different subgroups based on intervention-related factors (e.g. dose), the number of patients in the placebo arm was split across the intervention arms being meta-analysed (Rucker, Cates, and Schwarzer 2017).

Random effects meta-analyses were conducted, as appropriate, within each disorder (Houghton et al. 2017) as well as across the spectrum of anxiety disorders or states. The grouping of this ‘anxiety spectrum’ was decided post-hoc to include any disorder classified as an ‘anxiety disorder’ under DSM or ICD classifications, as well as acute anxiety states. Heterogeneity between studies was assessed by visual inspection of

forest plots and I^2 statistic. Cases of significant heterogeneity were investigated through subgroup analyses of dose.

The following sensitivity analyses were undertaken:

(i) excluding trials of gabapentin/pregabalin as adjunctive treatment

(ii) excluding trials involving patients with psychiatric comorbidities

(iii) excluding trials allowing rescue medications

(iv) excluding trials where the outcome measure of interest was originally reported in median/IQR/range.

Funnel plots were visually inspected for asymmetry (small study effect) in meta-analyses containing at least 10 studies. Statistical analyses were conducted using Review Manager (The Cochrane Collaboration 2020) and R (Balduzzi, Rücker, and Schwarzer 2019). Data that could not be meta-analysed are presented narratively in a table. The certainty of evidence was estimated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework (Guyatt et al. 2013). This study is registered with PROSPERO (registration number CRD42016041802), and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al. 2009).

Chapter 3: Results

3.1 Selection process

Out of 4268 records initially identified, 70 studies were selected for inclusion; 55 DB-RCTs and 15 open-label studies (Figure 1, p.37). One open-label study (Schaffer et al. 2013) included an observational component. A high-level overview of all included DB-RCTs by diagnostic group is provided in Table 1 (p.38). Characteristics of individual DB-RCTs are available in Table 2 (p.40). Most domains of risk of bias (Higgins et al. 2021) were rated as unclear risk (Figure 2A, p.52) due to lack of sufficient details to warrant a judgment of either low or high risk of bias. Notably, studies investigating BD and GAD rated mostly as high risk of bias in the 'incomplete outcome data' domain (Figure 2B, p.53), due to high rates of drop-out and the use of simple imputation methods (i.e. Last Observation Carried Forward, LOCF) for missing data.

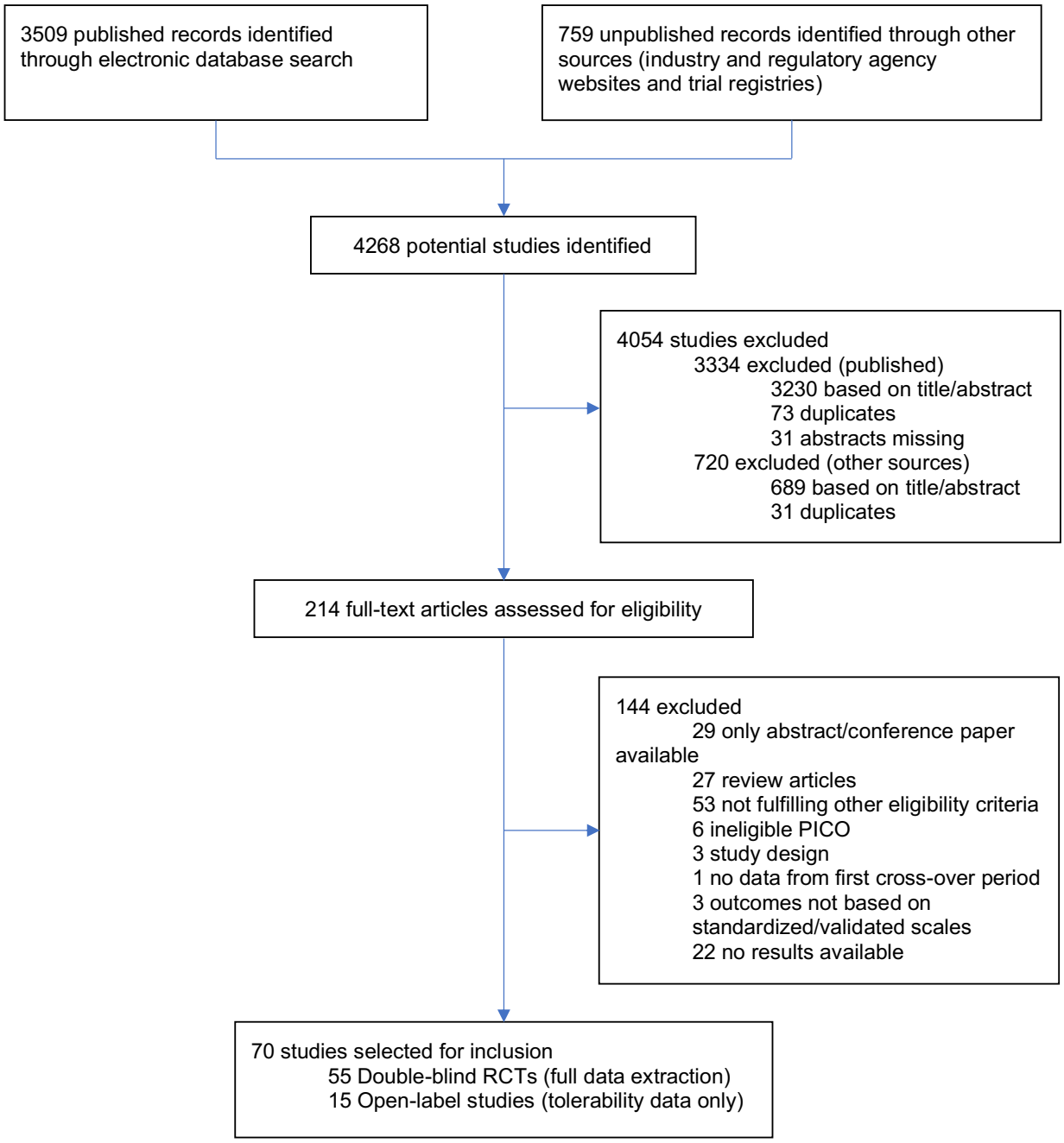


Figure 1. PRISMA flowchart of included and excluded studies

Table 1. Characteristics of all diagnostic groups

Total DB-RCT studies, k = 55
Total participants randomized, n = 9012

	Total num. of studies			**Num. of randomised patients**	**Range of publication dates**	**Range of duration of double-blind intervention**	**Primary outcome measures**	**Mean age, years**	**Mean % female**	**% DSM / % ICD**
		Num. >1 type of active investigational drug	***Num. placebo controlled***							
Bipolar disorder (BD)	4	3	2	231	2000 - 2006	6 – 52 weeks	MMPI-2 (Mokhber 2008) YMRS, HAM-D (Pande 2000) CGI-BP (Frye 2000) CGI-BP-M (Vieta 2006)	37.5	64.1%	100% DSM-IV
Insomnia (all)	9	7	1	1460	2007 - 2015	Single dose – 12 weeks	ESS, PSQI, ISS, PSG-WASO, sleep diaries	42.0	58.9%	66.7% DSM-IV / 0% ICD
Insomnia (gabapentin)	8	6	0	1086	2007 - 2015	Single dose – 12 weeks		42.5	58.2	62.5% DSM-IV / 0% ICD
Insomnia (pregabalin)	1	1	1	374	2010	8 weeks		40.8	60.7%	100% DSM-IV-TR, GAD and related sleep disturbance
Anxiety studies (all)	42	40	12	7321	1999 - 2020	Single dose – 26 weeks		43.0	60.4%	100% DSM-IV or DSM-V, for all studies (excluding pre-op studies)
Generalized anxiety disorder (pregabalin)	11	10	5	3825	2003 - 2014	4 – 24 weeks	HAM-A	43.1	62.7%	100% DSM-IV
Pre-operative state anxiety (gabapentin)	13	12	5	1062	2004 - 2015	*	VAS 0-100, VAS 0-10, NRS 0-10, STAI-S	48.9	70.3%	*
Pre-operative state anxiety (pregabalin)	10	10	1	1463	2009 - 2019	*	VAS 0-100, VAS 0-10, NRS 0-10, VRS 0-10	42.5	55.6%	*
Pre-operative state anxiety (gabapentin	1	1	1	90	2012	*	VAS 0-10	44.7	100%	*

and pregabalin)										
Social anxiety disorder (all)	4	4	0	685	1999 - 2011	10 – 26 weeks	LSAS	36.0	40.9%	100% DSM-IV
Posttraumatic Stress Disorder (pregabalin)	1	1	0	37	2014	6 weeks	PCL-M	48.2	0	100% DSM-IV-TR
Panic disorder (gabapentin)	1	1	0	103	2000	8 weeks	PAS	35.0	63.4%	100% DSM-IV
Obsessive Compulsive Disorder (pregabalin)	1	1	0	56	2020	12 weeks	Y-BOCS	32.4	66.2%	100% DSM-V

CGI-BP/CGI-BP-M, Clinical Global Impression modified for use in Bipolar Disorder; **ESS,** Epworth Sleepiness Scale; **HAM-A,** Hamilton Anxiety Rating Scale; **HAM-D,** Hamilton Depressing Rating Scale; **ISS,** Insomnia Severity Scale; **LSAS,** Liebowitz Social Anxiety Scale; **MMPI-2,** Minnesota Multiphasic Personality Inventory-2; **NRS,** Numeric rating scale; **PAS,** Panic and Agoraphobia scale; **PCL-M,** PTSD Checklist-Military version; **PSG-WASO,** Polysomnography-derived Wake after sleep onset; **PSQI,** Pittsburgh Sleep Quality Index; **STAI-S,** State-Trait Anxiety Inventory (State anxiety scale); **VAS,** Visual analogue scale; **VRS,** Verbal rating scale; **Y-BOCS,** Yale-Brown Obsessive Compulsive Scale; **YMRS,** Young Mania Rating Scale

Table 2. Characteristics of included double-blind randomised controlled studies

Study name	No. of arms	Drug	No. patients randomised	Mean age (SD)	% Female	Dose (min-max)	Dosing Schedule	Mean dose delivered	Baseline severity scale, threshold	Diagnosis/Procedure	Study type	Patient status	Length of intervention	Rescue medication ***	Industry Sponsored
Bipolar Disorder															
Gabapentin															
Frye (2000) (NCT00001482)	3	Gabapentin	9	*	*	900-4800 (mg/day)	Flexible	*	*	DSM-IV, Refractory bipolar and unipolar affective illness (including BP I and BP II; rapid cycling and non-rapid cycling; and unipolar patients)	DB Randomized Cross-over Monotherapy	Inpatients	6 weeks	Unclear	No
		Lamotrigine	10	*	*	25-500 (mg/day)	Flexible	*	*						
		Placebo	11	*	*	0-0	Flexible	0	*						
Mokhber (2008)	3	Gabapentin	20	28.9 (10.6)	50	900 (mg/day)	Fixed	*	*	Bipolar DSM-IV Dysphoric mania. History of BP I.	DB Randomized Parallel Monotherapy Placebo run-in	Outpatients	8 weeks	Yes	Unclear
		Carbamazepine	19	28.9 (9.6)	62	600 (mg/day)	Fixed	*	*						
		Lamotrigine	20	27.8 (7.7)	55	100 (mg/day)	Fixed	*	*						
Pande (2000) (945-209)	2	Gabapentin (+ Lithium, valproate, or combination)	59	40.7 (9.4)	50	600-3600 (mg/day)	Flexible	*	YMRS, >/=12	DSM-IV BP I, with manic/hypomanic or mixed symptoms	DB Randomized Parallel Adjunctive	Outpatients	10 weeks	Unclear	Yes
		Placebo (+ Lithium, valproate, or combination)	58	38.2 (10.5)	46	0-0	Flexible	0	YMRS, >/=12						
Vieta (2006) (945-291)	2	Gabapentin + TAU	13	46.2 (14.3)	76.9	1200-2400 (mg/day)	Flexible	*	HAM-D, <8	DSM-IV Bipolar Depression	DB Randomized Parallel Adjunctive	Outpatients	52 weeks	Unclear	Yes
		Placebo + TAU	12	47.6 (15.8)	66.7	0-0	Flexible	0	HAM-D, <8						

Insomnia/Sleep Disturbance														
Gabapentin														
Brower (2008)	2	Gabapentin	10	46 (*)	40	1500 (mg/day)	Fixed	*		DSM-IV Alcohol Dependence and comorbid Insomnia	DB Randomized Parallel Monotherapy Placebo run-in	Outpatients	6 weeks	Unclear	Yes
		Placebo	11	44 (*)	54.5	0-0	Fixed	0							
Furey (2014)	2	Gabapentin	128	41.4 (16.7)	56.3	250 (mg/day)	Fixed	250	ESS, <10	Healthy Volunteers with occasional disturbed sleep	DB Randomized Parallel Monotherapy	Outpatients	4 weeks	Unclear	Yes
		Placebo	128	41.5 (16.6)	52.3	0-0	Fixed	0	ESS, <10						
Malcolm (2007)	2	Gabapentin	101[a]	*	*	600-1200 (mg/day)	Fixed	*	CIWA-Ar, >/=10	DSM-IV Alcohol Dependence and Alcohol Withdrawal Syndrome with Sleep Disturbance	DB Randomized Parallel Monotherapy	Outpatients	4 days	Unclear	No
		Lorazepam	101[a]	*	*	6 (mg/day)	Fixed	*	CIWA-Ar, >/=10						
Mason (2014) (NCT00391716)	3	Gabapentin (low dose)	54	41.9 (10.1)	38.9	900 (mg/day)	Fixed	*	*	DSM-IV Alcohol Dependence and related sleep disturbance	DB Randomized Parallel Monotherapy	Outpatients	12 weeks	Unclear	Yes
		Gabapentin (high dose)	47	45.2 (11.3)	34	1800 (mg/day)	Fixed	*	*						
		Placebo	49	46.8 (11.3)	57.1	0-0	Fixed	*	*						
Mowla (2015)	2	Gabapentin + TAU	31	*	*	100-600 (mg/day)	Flexible	400	PSQI, >5, ISI >8	DSM-IV Major Depressive Disorder with sleep problems	DB Randomized Parallel Monotherapy	Inpatients	4 weeks	Unclear	No
		Clonazepam + TAU	32	*	*	0.5-2 (mg/day)	Flexible	1	PSQI, >5 ISI >8						
NCT01014533 (HUM00010947) (1R01AA016117 -01A1)	2	Gabapentin	30	37 (8.9)	23.3	600-1200 (mg/day)	Fixed	*	CIWA-Ar, <8	DSM-IV Alcohol Dependence and related sleep disturbance	DB Randomised Parallel Monotherapy	Outpatients	1 week	Unclear	Yes
		Placebo	29	34.9 (12.5)	20.7	0-0	Fixed	*	CIWA-Ar, <8						
	3	Gabapentin (low dose)	125	42.2 (17.0)	62.4	250 mg	Fixed	250	*		DB Randomised Parallel	Outpatients	Single dose	Unclear	Yes

Rosenberg (2014) (NCT00674752)		Gabapentin (high dose)	125	40.7 (17.1)	68.8	500 mg	Fixed	500	*	Healthy Volunteers with occasional disturbed sleep	Monotherapy				
		Placebo	127	42.0 (15.6)	68.5	0-0	Fixed	0	*						
Yurcheshen (2009)	2	Gabapentin	30	52.7 (3.6)	100	900 (mg/day)	Fixed	900	*	Post-menopausal women experiencing at least seven hot flushes per day	DB Randomized Parallel Monotherapy	Outpatients	12 weeks	No	No
		Placebo	29	53 (3.1)	100	0-0	Fixed	0	*						
						Pregabalin									
Bollu (2010)	3	Pregabalin	121	39.5 (11.9)	63.6	300-600 (mg/day)	Flexible	*	*	DSM-IV-TR Generalized Anxiety Disorder and related sleep disturbance	DB Randomized Parallel Monotherapy Placebo run-in	Outpatients	8 weeks	No	Yes
		Venlafaxine	125	42.6 (11.8)	57.6	75-225 (mg/day)	Flexible	*	*						
		Placebo	128	40.2 (12.1)	60.9	0-0	Flexible	*	*						
						Generalized Anxiety Disorder									
						Pregabalin									
Feltner (2003)	4	Pregabalin (low dose)	70	37.9 (10.9)	51.4	150 (mg/day)	Fixed	150	HAM-A >/= 20	DSM-IV Generalized Anxiety Disorder	DB Randomized Parallel Monotherapy	Outpatient	4 weeks	Unclear	Yes
		Pregabalin (high dose)	66	36.3 (10.9)	50.0	600 (mg/day)	Fixed	600	HAM-A >/= 20						
		Lorazepam	68	39.2 (11.7)	58.8	6 (mg/day)	Fixed	6	HAM-A >/= 20						
		Placebo	67	37.8 (10.8)	50.7	0-0	Fixed	0	HAM-A >/= 20						
Feltner (2008)	2	Pregabalin	168	38.7 (*)	55.4	450 (mg/day)	Fixed	450	HAM-A </= 11	DSM-IV Generalized Anxiety Disorder	DB Randomized Parallel Monotherapy	Outpatient	24 weeks	Unclear	Yes
		Placebo	170	38.8 (*)	58.8	0-0	Fixed	0	HAM-A </= 11						
Hadley (2012) (NCT00368745)	2	Pregabalin	56	40.1 (10.6)	75	150-600 (mg/day)	Flexible	*	*	DSM-IV	DB Randomized Parallel Monotherapy	Outpatient	12 weeks	Yes	Yes

(2006-001347-66)		Placebo	50	43.5 (11.3)	68	0-0	Flexible	0	*	Generalized Anxiety Disorder, on benzodiazepine (BDZ)	BDZ taper for up to 6 weeks from baseline				
Kasper (2009) (NCT00151450) (EUCTR2004-001500-13-IE)	3	Pregabalin	121	39.5 (11.9)	64	300-600 (mg/day)	Fixed	*	HAM-A >/= 20	DSM-IV Generalized Anxiety Disorder	DB Randomized Parallel Monotherapy	Outpatient	8 weeks	Unclear	Yes
		Venlafaxine	125	42.6 (11.8)	58	75-225 (mg/day)	Fixed	*	HAM-A >/= 20						
		Placebo	128	40.2 (12.1)	61	0-0	0		HAM-A >/= 20						
Kasper (2014) (NCT00624780) (EUCTR2007-004768-32-ES)	3	Pregabalin (low dose)	206	40.5 (12.3)	64.6	150-300 (mg/day)	Flexible	*	HAM-A >/= 14	DSM-IV Generalized Anxiety Disorder	DB Randomized Parallel Monotherapy	*	12 weeks	No	Yes
		Pregabalin (high dose)	206	42.4 (11.5)	57.8	450-600 (mg/day)	Flexible	*	HAM-A >/= 14						
		Lorazepam	203	42.6 (11.2)	60.1	3-4 (mg/day)	Flexible	*	HAM-A >/= 14						
Montgomery (2006)	4	Pregabalin (low dose)	97	45.0 (12.0)	59	400 (mg/day)	Fixed	376	HAM-A >/= 20	DSM-IV Generalized Anxiety Disorder	DB Randomized Parallel Monotherapy	Outpatient	6 weeks	Unclear	Yes
		Pregabalin (high dose)	110	42.0 (12.0)	65	600 (mg/day)	Fixed	557	HAM-A >/= 20						
		Venlafaxine	113	46.0 (12.0)	65	75 (mg/day)	Fixed	75	HAM-A >/= 20						
		Placebo	101	43.0 (12.0)	58	0-0	Fixed	0	HAM-A >/= 20						
Montgomery (2008) (EUCTR2004-000955-40-LV)	2	Pregabalin	177	72.4 (5.6)	79	150-600 (mg/day)	Flexible	*	HAM-A >/= 20, MMSE >/= 24	DSM-IV Generalized Anxiety Disorder	DB Randomized Parallel Monotherapy	Outpatient	8 weeks	Unclear	Yes
		Placebo	96	72.2 (6.4)	75	0-0	Flexible	0	HAM-A >/= 20, MMSE >/= 24						
Pande (2003)	4	Pregabalin (low dose)	69	37.9 (11.8)	49.3	150 (mg/day)	Fixed	150	HAM-A >/= 20	DSM-IV Generalized Anxiety Disorder	DB Randomized Parallel Monotherapy	Outpatient	4 weeks	Unclear	Yes
		Pregabalin (high dose)	70	35.5 (11.2)	57.1	600 (mg/day)	Fixed	600	HAM-A >/= 20						

		Lorazepam	68	33.9 (9.7)	63.2	6 (mg/day)	Fixed	6	HAM-A >/= 20						
		Placebo	69	35.7 (11.5)	68.1	0-0	Fixed	0	HAM-A >/= 20						
Pohl (2005)	4	Pregabalin (low dose)	78	*	*	200 (mg/day)	Fixed	200	HAM-A >/= 20	DSM-IV Generalized Anxiety Disorder	DB Randomized Parallel Monotherapy	Outpatient	6 weeks	Unclear	Yes
		Pregabalin (medium dose)	89	*	*	400 (mg/day)	Fixed	385	HAM-A >/= 20						
		Pregabalin (high dose)	88	*	*	450 (mg/day)	Fixed	440	HAM-A >/= 20						
		Placebo	86	*	*	0-0	Fixed	0	HAM-A >/= 20						
Rickels (2005)	5	Pregabalin (low dose)	91	38.0 (10.0)	64	300 (mg/day)	Fixed	300	HAM-A >/= 20	DSM-IV Generalized Anxiety Disorder	DB Randomized Parallel Monotherapy Placebo run-in	Outpatient	4 weeks	Unclear	Yes
		Pregabalin (medium dose)	90	38.0 (12.0)	59	450 (mg/day)	Fixed	450	HAM-A >/= 20						
		Pregabalin (high dose)	89	39.0 (12.0)	67	600 (mg/day)	Fixed	600	HAM-A >/= 20						
		Alprazolam	93	40.0 (12.0)	66	1.5 (mg/day)	Fixed	1.5	HAM-A >/= 20						
		Placebo	91	41.0 (12.0)	63	0-0	Fixed	0	HAM-A >/= 20						
Rickels (2012) (NCT00413010) (EUCTR2006-006339-31-FI)	2	Pregabalin (+ SSRI/SNRI)	180	43.7 (11.5)	71.7	150-600 (mg/day)	Flexible. Fixed in final 2 weeks	431.125	HAM-A >/= 22 (for open-label phase), Responder rate <50% to enter DB phase	DSM-IV Generalized Anxiety Disorder	DB Randomized Parallel Adjunct Preceded by 8-week, open-label phase with SSRI/SNRI	Outpatients	8 weeks	Unclear	Yes
		Placebo (+ SSRI/SNRI)	176	43.5 (12.5)	65.3	0-0	Flexible. Fixed in final 2 weeks	0	HAM-A >/= 22 (for open-label phase), Responder rate <50% to enter DB phase						

Pre-operative State Anxiety														
Gabapentin														
Abdel-Halim (2009)	4	Gabapentin	20	45.0 (14.0)	100	800 mg	Single dose	800 mg	Radical mastectomy	DB Randomized Parallel	Pre-operative, elective, GA	Single dose	Midazolam IV 2-4mg	Unclear
		Dexamethasone IV	20	48.0 (15.0)	100	16 mg	Single dose	16 mg						
		Gabapentin + Dexamethasone IV	20	46.0 (10.0)	100	800 mg 16 mg	Single dose	800 mg 16 mg						
		No intervention	20	46.0 (16.0)	100	0-0	Single dose	0						
Adam (2012)	2	Gabapentin	32	36.0 (12.0)	43	1200 mg	Single dose	1200 mg	Orthopedic Surgery/Open Inguinal Hernia Repair	DB Randomized Parallel	Pre-operative, elective, GA	Single dose	No	No
		Placebo	32	39.0 (14.0)	34	0-0	Single dose	0						
Bakry (2012)	2	Gabapentin	30	63.2 (4.8)	27	1200 mg	Single dose	1200 mg	Cataract Surgery	DB Randomized Parallel	Pre-operative, elective, LA	Single dose	No	No
		Placebo	30	61.3 (5.5)	30	0-0	Single dose	0						
Clarke (2010)	2	Gabapentin	22	Med (IQR) 59 (53-69)	43.5	600 mg	Single dose	600 mg	Total hip arthroplasty	DB Randomized Parallel	Pre-operative, elective, GA	Single dose	No	No
		Placebo	48	63.5 (55.5-68.5)	45.8	0-0	Single dose	0						
Clarke (2013)	2	Gabapentin	25	41.6 (6.6)	100	1200 mg	Single dose	1200 mg	Non-Cardiac Surgery	DB Randomized Parallel	Pre-operative, GA	Single dose	No	No
		Placebo	25	41.8 (6.8)	100	0-0	Single dose	0						
Hoseini (2015) (IRCT20140412 17231N1)	4	Gabapentin	22	40.5 (8.38)	*	600 mg	Single dose	600 mg	Laparoscopic Cholecystectomy	DB Randomized Parallel	Pre-operative, GA	Single dose	No	Unclear
		Melatonin	22	39.45 (11.4)	*	6 mg	Single dose	6 mg						

		Clonidine	22	44.14 (8.41)	*	0.2 mg	Single dose	0.2 mg						
		Placebo	22	38.14 (10.8)	*	0-0	Single dose	0						
Joseph (2014) (CTRI/2010/091/002830)	3	Gabapentin	25	43.3 (8.6)	100	600 mg	Single dose	600 mg	Hysterectomy	DB Randomized Parallel	Pre-operative, Elective, GA	Single dose	Unclear	No
		Alprazolam	25	46.1 (9.3)	100	0.5 mg	Single dose	0.5 mg						
		Placebo	25	44.4 (5.6)	100	0-0	Single dose	0						
Khezri (2013) (NCT01200641) (ACTRN12610000727044)	3	Gabapentin	40	75.6 (10.1)	73.9	600 mg	Single dose	600 mg	Cataract Surgery	DB Randomized Parallel	Pre-operative, Elective, LA	Single dose	No	No
		Melatonin	40	73.5 (11.3)	60	6 mg	Single dose	6 mg						
		Placebo	40	72.9 (10.8)	66.6	0-0	Single dose	0						
Ménigaux (2005)	2	Gabapentin	20	31.0 (8.0)	30	1200 mg	Single dose	1200 mg	Knee Arthroscopy	DB Randomized Parallel	Pre-operative, Elective, GA	Single dose	No	No
		Placebo	20	31.0 (8.0)	35	0-0	Single dose	0						
Pathak (2014)	2	Gabapentin	40	41.5 (11.6)	82.5	1200 mg	Single dose	1200 mg	Open Cholecystectomy	DB Randomized Parallel	Pre-operative, Elective, GA	Single dose	No	Unclear
		Placebo	40	37.4 (11.1)	90	0-0	Single dose	0						
Rorarius (2004)	2	Gabapentin	38	Med (IQR) 47 (44.8-50)	100	1200 mg	Single dose	1200 mg	Vaginal hysterectomy	DB Randomized Parallel	Pre-operative, Elective, GA	Single dose	No	No
		Oxazepam	37	45 (42-50.5)	100	15 mg	Single dose	15 mg						
Sava (2009)	2	Gabapentin	25	*	*	800 mg	Single dose	800 mg	Rectocolic surgery	DB Randomized Parallel	Pre-operative, Elective, GA	Single dose	No	Unclear
		Placebo	25	*	*	0-0	Single dose	0						
Tirault (2010)	3	Gabapentin	70	46.0 (12.0)	71	1200 mg	Single dose	1200 mg	Various elective surgeries requiring GA	DB Randomized Parallel		Single dose	Unclear	Unclear

		Hydroxyzine	70	47.0 (12.0)	62	75 mg	Single dose	75 mg			Pre-operative, Elective, GA			
		Placebo	70	44.0 (13.0)	58	0-0	Single dose	0						
Pregabalin														
Gonano (2011)	2	Pregabalin	20	45.1 (10.2)	40	300 mg	Single dose	300 mg	Knee arthroscopic meniscectomy	DB Randomized Parallel	Pre-operative, Elective, GA	Single dose	No	No
		Placebo	20	41.8 (11.2)	30	0-0	Single dose	0						
Moreau-Bussiere (2013) (NCT01158859)	2	Pregabalin	25	Med (IQR) 36 (31-38)	100	150 mg	Single dose	150 mg	Laparoscopic Gynecologic Procedures	DB Randomized Parallel	Pre-operative, Elective, GA	Single dose	No	No
		Placebo	25	33 (29-36)	100	0-0	Single dose	0						
Nasr (2014)	2	Pregabalin	20	31.0 (5.0)	100	150 mg	Single dose	150 mg	Laparoscopic Adhesiolysis	DB Randomized Parallel	Pre-operative, Elective, GA	Single dose	No	No
		Melatonin	20	32.5 (4.0)	100	6 mg	Single dose	6 mg						
NCT00468845	3	Pregabalin	162	Range 25-70	100	150 mg	Single dose	150 mg	Hysterectomy	DB Randomized Parallel	Pre-operative, GA	Single dose	Yes	Yes
		Pregabalin	170	Range 25-71	100	300 mg	Single dose	300 mg						
		Placebo	169	Range 25-72	100	0-0	Single dose	0						
NCT00551135	4	Pregabalin (low dose)	108	*	0	50 mg	Multiple dosing	**	Inguinal Hernia Repair	DB Randomized Parallel	Pre-operative, Multi center, GA	Multiple dosing**	No	Yes
		Pregabalin (medium dose)	106	*	0	150 mg	Multiple dosing	**						
		Pregabalin (high dose)	103	*	0	300 mg	Multiple dosing	**						
		Placebo	108	*	0	0-0	Multiple dosing	0						
Nutt (2009)	3	Pregabalin	27	35.1 (12.2)	70.4	150 mg	Single dose	150 mg	Dental Procedure,	DB Randomized Parallel	Pre-operative,	Single dose	No	Yes

(EUCTR2005-003006-29-GB)		Alprazolam	31	41.8 (12.4)	51.6	0.5 mg	Single dose	0.5 mg	with Dental Anxiety Total Score >/= 12 at the screen visit and at baseline on day of procedure		Multi center, Outpatients			
		Placebo	31	36.8 (12.7)	64.5	0-0	Single dose	0						
Shimony (2016) (NCT01612832)	2	Pregabalin	50	52.6 (15.5)	48	150 mg	Single dose	150 mg	Craniotomy	DB Randomized Parallel	Pre-operative, Elective, GA	Single dose	No	No
		Placebo	50	51.6 (16.8)	45	0-0	Single dose	0						
Singh (2019)	2	Pregabalin	30	40.9 (12.2)	50	150 mg	Single dose	150 mg	Laparoscopic Cholecystectomy	DB Randomized Parallel	Pre-operative, Elective, GA	Single dose	No	No
		Placebo	30	36.3 (11.9)	50	0-0	Single dose	0						
Spreng (2011) (NCT00353704)	2	Pregabalin	25	44.1 (10.8)	50	150 mg	Single dose	150 mg	Discectomy	DB Randomized Parallel	Pre-operative, Elective, GA	Single dose	Unclear	No
		Placebo	25	42.9 (7.6)	46	0-0	Single dose	0						
White (2009)	4	Pregabalin (low dose)	27	43.0 (14.0)	55.6	75 mg	Single dose	75 mg	Elective ambulatory and short-stay (<24h) procedures, including ENT, General surgery, Plastics, Urologic	DB Randomized Parallel	Pre-operative, Elective	Single dose	No	Yes
		Pregabalin (medium dose)	27	48.0 (16.0)	55.6	150 mg	Single dose	150 mg						
		Pregabalin (high dose)	27	46.0 (13.0)	29.6	300 mg	Single dose	300 mg						
		Placebo	27	48.0 (15.0)	55.6	0-0	Single dose	0						
Gabapentin & Pregabalin														
Ghai (2012)	3	Gabapentin	30	45.6 (5.9)	100	900 mg	Single dose	900 mg	Hysterectomy	DB Randomized Parallel	Pre-operative, Elective, GA	Single dose	No	No
		Pregabalin	30	45.1 (6.5)	100	300 mg	Single dose	300 mg						
		Placebo	30	43.4 (5.7)	100	0-0	Single dose	0						

Posttraumatic Stress Disorder															
Pregabalin															
Baniasadi (2014)	2	Pregabalin	18	47.7 (3.3)	0	300 (mg/day)	Fixed	*	*	DSM-IV-TR Chronic Posttraumatic Stress Disorder	DB Randomized Parallel Adjunct	Inpatients	6 weeks	Unclear	No
		Placebo	19	48.6 (3.8)	0	0-0	Fixed	0	*						
Social Anxiety Disorder (Social Phobia)															
Pregabalin															
Feltner (2011)	4	Pregabalin (low dose)	78	36.8 (10.1)	41	300 (mg/day)	Fixed	*	LSAS >/= 50	DSM-IV Social Anxiety Disorder (Social Phobia), Generalized Subtype	DB Randomized Parallel Monotherapy	Outpatients	11 weeks	Unclear	Yes
		Pregabalin (medium dose)	86	35.1 (12.1)	41.9	450 (mg/day)	Fixed	*	LSAS >/= 50						
		Pregabalin (high dose)	82	35.1 (11.7)	31.7	600 (mg/day)	Fixed	*	LSAS >/= 50						
		Placebo	82	34.6 (11.2)	47.6	0-0	Fixed	0	LSAS >/= 50						
Greist (2011)	2	Pregabalin	80	34.4 (*)	42.5	450 (mg/day)	Fixed	*	CGI-I </=2 & >/=25% reduction in LSAS from open-label baseline	DSM-IV Social Anxiety Disorder (Social Phobia), Generalized Subtype	DB Randomized Parallel Monotherapy, 10 week open-label phase (LSAS >/= 50 for open-label), before 26-week DB phase.	Outpatients	26 weeks	Unclear	Yes
		Placebo	73	36.5 (*)	39.7	0-0	Fixed	0	Same as above						
Pande (2004)	3	Pregabalin	42	36.3 (10.4)	31	150 (mg/day)	Fixed	*	LSAS >/= 50	DSM-IV Social Anxiety Disorder (Social Phobia), Generalized Subtype	DB Randomized Parallel Monotherapy, Placebo lead-in	Outpatients	10 weeks	Unclear	Yes

		Pregabalin	47	37.9 (12.4)	48.9	600 (mg/day)	Fixed	*	LSAS >/= 50						
		Placebo	46	41 (11.2)	43.5	0-0	Fixed	0	LSAS >/= 50						
							Gabapentin								
Pande (1999)	2	Gabapentin	34	35.6 (9.6)	*	900-3600 (mg/day)	Flexible	*	LSAS >/= 50	DSM-IV Social Anxiety Disorder (Social Phobia)	DB Randomized Parallel Monotherapy, Placebo lead-in	Outpatients	14 weeks	Unclear	Yes
		Placebo	35	35.6 (9.6)	*	0-0	Flexible	0	LSAS >/= 50						
							Panic Disorder								
							Gabapentin								
Pande (2000)	2	Gabapentin	52	34.0 (10.6)	58	600-3600 (mg/day)	Flexible	*	*	DSM-IV Panic Disorder, with or without agoraphobia, With at least one panic attack per week for the 3 weeks before screening	DB Randomized Parallel Monotherapy, Placebo lead-in	*	8 weeks	No	Yes
		Placebo	51	36.0 (9.4)	69	0-0	Flexible	0	*						
							Obsessive-Compulsive Disorder								
							Pregabalin								
Mowla (2020)	2	Pregabalin (+ sertraline)	28	33.6 (11.3)	65.3	75-225 (mg/day)	Flexible	185.9	*	DSM-V Obsessive-Compulsive Disorder, All patients had failed to respond to at least 12 weeks of treatment with an adequate and stable dose of sertraline. Concurrent sertraline continued throughout the trial. Mean dose of Sertraline 256.5 mg/day; dosage range 100-300mg/day	DB Randomized Parallel Adjunct	Outpatients	12 weeks	Unclear	No
		Placebo (+ sertraline)	28	31.1 (12.2)	67.1	0-0	Flexible	0	*						

Legend. BP I, bipolar I disorder, BP II, bipolar II disorder; CGI-I, Clinical Global Impression-Improvement scale; CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol-Revised; DB, double-blind; TAU, treatment as usual; DSM-IV, Diagnostic and Statistical Manual for Mental Disorders, 4th edition; ESS, Epworth Sleepiness Scale; GA, General anesthesia; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D, Hamilton Depression Rating Scale; IQR, Interquartile range; ISI, Insomnia Severity Index; LA, Local anesthesia; LSAS, Liebowitz Social Anxiety Scale; Med, Median; mg, milligrams; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; YMRS, Young Mania Rating Scale

[a] Malcolm 2007, number randomized patients total 101 combining both arms of the study. Authors were contacted, without success, for breakdown of numbers randomized across the arms.
* Missing
** NCT00551135: 50mg arm dosing: 25mg night before; 25mg 2+/-1 hour before surgery; then 25mg BD for 7 days; 150mg arm dosing: 75mg night before; 75mg 2+/-1 hour before surgery; then 75mg BD for 7 days; 300mg arm dosing: 150mg night before; 150mg 2+/-1 hour before surgery; then 150mg BD for 7 days
*** Rescue medications in pre-operative studies: Standard post-operative medications (e.g. analgesia, antiemetics, etc.) were not considered rescue medications when assessing pre-operative anxiety studies. Rescue medications were considered if they could plausibly confound patient anxiety

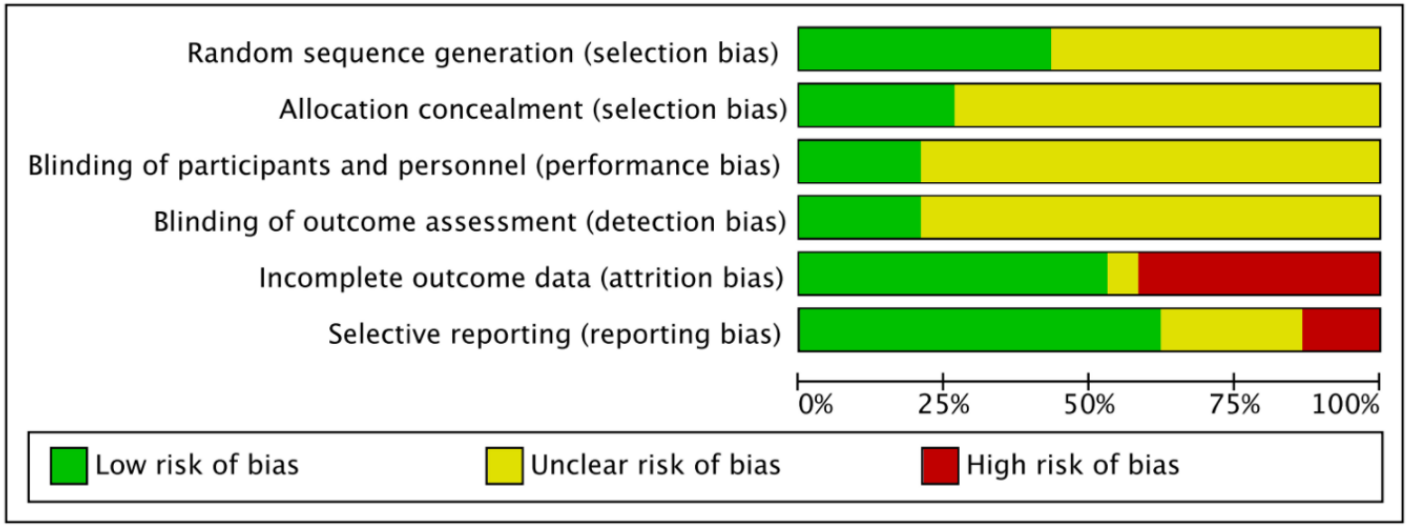


***Figure 2A. Risk of bias (RoB) summary**. The RoB assessment was done for all included DB-RCTs using the 2011 Cochrane RoB tool. Most domains were rated as unclear risk of bias due to lack of sufficient details to warrant either a low or high risk of bias judgment. Nearly half of all studies were rated as high RoB for attrition bias. Legend: RoB, risk of bias; DB-RCT, double-blind randomised controlled trial.*

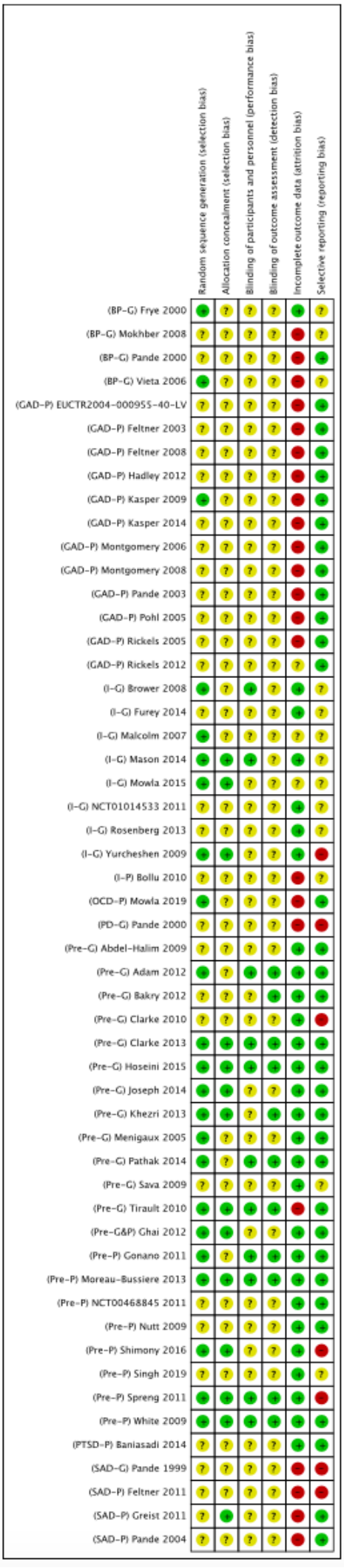


Figure 2B. Risk of bias by individual study.
Legend: *BP-G, gabapentin in bipolar disorder; GAD-P, pregabalin in generalized anxiety disorder; I-G/I-P, gabapentin/pregabalin in insomnia; OCD-P, pregabalin in obsessive compulsive disorder; PD-G, gabapentin in panic disorder; Pre-G/Pre-P, gabapentin/pregabalin in preoperative state anxiety; Pre-G&P, gabapentin and pregabalin in preoperative state anxiety; PTSD-P, pregabalin in posttraumatic stress disorder; SAD-G/SAD-P, gabapentin/pregabalin in social anxiety disorder.*

3.2 Bipolar disorder

Four DB-RCTs investigating the efficacy of gabapentin in BD were identified. 101 patients were randomised to receive gabapentin, 81 to placebo, 30 to lamotrigine and 19 to carbamazepine. The mean age of all randomised patients was 37.5 years and 64.1% were female (Table 1, p.38).

3.2.1 Acute treatment

Three studies compared gabapentin with three different comparators for the acute treatment of BD across heterogeneous patient groups with manic/hypomanic, depressed and/or mixed symptoms (Mokhber et al. 2008; Frye et al. 2000; Pande, Crockatt, et al. 2000) (Table 3, p.56). Each study assessed efficacy of gabapentin using a different outcome measure. Quantitative analysis was not performed due to clinical and methodological heterogeneity.

Gabapentin was significantly more effective than lamotrigine and carbamazepine in reducing depressive symptoms on the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) depression subscale (50%, 33.5% and 13.6% reduction, respectively), but there were no group differences in improvements on the MMPI-2 mania subscale (Mokhber et al. 2008). A cross-over study (Frye et al. 2000) observed response rates of 50% for lamotrigine, 33% for gabapentin and 18% for placebo on the Clinical Global Impressions-Bipolar Version (CGI-BP) during the first phase, but without clear statistical significance. A third study, testing adjunctive gabapentin versus placebo, reported a significantly greater improvement in the total Young Mania Rating Scale

(YMRS) score in the placebo group but no significant between-group difference in the Hamilton Rating Scale for Depression (HAM-D) change score (Pande, Crockatt, et al. 2000).

3.2.2Long-term treatment

One long-term treatment study of 25 patients with BD in clinical remission (13 on gabapentin, 12 on placebo) (Vieta et al. 2006) showed a significant benefit of gabapentin versus placebo on CGI-BP change scores (gabapentin: -2.1, placebo: -0.6) (Table 3, p.56). Further details of the studies are available in Table 1 (p.38) and Table 2 (p.40).

Table 3. Double-blind randomised controlled trials of gabapentin in bipolar disorder (BD).

Study ID	Design	Population	Intervention and Comparator(s)	Placebo control?	Duration of intervention	Primary outcome measure	Key results
Acute treatment of BD							
Mokhber 2008	Parallel	DSM-IV dysphoric mania	Fixed dose gabapentin 900mg/day (n=18), carbamazepine 600mg/day (n=13) and lamotrigine 100mg/day (n=20)	No	8 weeks	MMPI-2	All treatment groups showed a significant within-group improvement in the mania and depression subscales of the MMPI-2 at 8 weeks. Gabapentin showed a significantly greater improvement on the depression symptoms subscale (50%) compared to lamotrigine (33.5%) and carbamazepine (13.6%). There were no significant between-group differences in improvement on the mania symptom subscale. The authors included only study completers in the efficacy analyses.
Frye 2000	Cross-over	DSM-IV refractory bipolar disorder (BD-I=11; BD-II=14) and unipolar depression (UP=6)	Flexibly dosed gabapentin (mean dose phase 1=3,987mg), lamotrigine (274mg), and placebo	Yes	6 weeks (per phase)	CGI-BP	Response rates (CGI-BP score of much or very much improved) observed during phase 1 were 50% for lamotrigine, 33% for gabapentin and 18% for placebo. Similar clinical response rates were seen across all three phases of the study. Only participants completing all three phases of the study were included in the analysis.

Pande 2000	Parallel	DSM-IV BD-I with manic/hypomanic (n=82), or mixed symptoms (n=35)	Flexible dose adjunctive gabapentin (n=58) or placebo (n=59) alongside adjunctive treatment with valproate (n=57), lithium (n=39), or both (n=21).	Yes	10 weeks	YMRS and HAM-D	The placebo group showed a significantly greater improvement in the total YMRS change score compared to gabapentin. There was no significant between-group difference in the HAM-D change score. Secondary outcomes showed no significant differences in CGIC response rate or HAM-A change scores between gabapentin and placebo groups, demonstrating no evidence in favor of gabapentin as an adjunctive treatment in BD.
Long-term treatment of BD							
Vieta 2006	Parallel	DSM-IV BD-I or BD-II in clinical remission (HAM-D ≤ 8 and YMRS ≤ 4)	Flexibly dosed adjunctive gabapentin (n=13) or placebo (n=12)	Yes	1 year	CGI-BP	There was a significant difference in favor of gabapentin in baseline-to-endpoint (1 year) change in CGI-BP score (gabapentin -2.1, placebo -0.6) and in use of sleeping medication (PSQI-item 6, gabapentin -1.1 vs placebo -0.6). There were no significant differences in YMRS, HAM-D, HAM-A, PSQI change scores, or time to recurrence of new mood episode between gabapentin and placebo groups.
Tolerability							
To further examine the tolerability of gabapentin and pregabalin in BD, 11 open-label studies were included, 8 of which reported outcome data. Among reported side effects, gabapentin was commonly associated with sedation, movement disorders, dyspepsia, drowsiness, dizziness, headache, sleep problems, fatigue and cognitive side effects. Pregabalin was associated with thought overactivation, weight gain and increased appetite. All adverse event data are presented in Appendix, Table 4.							
BD-I, bipolar disorder type 1; BD-II, bipolar disorder type 2; CGI-BP, Clinical Global Impressions-Bipolar Version; CGIC, Clinical Global Impression of Change; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D, Hamilton Rating Scale for Depression; MMPI-2, Minnesota Multiphasic Personality Inventory-2; PSQI, Pittsburgh Sleep Quality Index; YMRS, Young Mania Rating Scale.							

3.3 Anxiety disorders or states

3.3.1 Anxiety spectrum

42 DB-RCTs investigating anxiety disorders or states (GAD; social anxiety disorder, SAD; preoperative state anxiety; post-traumatic stress disorder, PTSD; obsessive compulsive disorder, OCD; panic disorder, PD) were selected for inclusion (Table 1, Table 2; p.38 and 40). 3539 patients were randomised to receive pregabalin, 525 to gabapentin, 2280 to placebo, and 937 to active comparators. The mean age of all randomised patients was 43.0 years, and 60.4% were female (Table 1, p.37). 5190 patients from eligible anxiety studies were analysed for efficacy. Gabapentinoids were significantly more effective than placebo across a range of disorders within the anxiety spectrum (SMDs between -2.25 and -0.25) (Figure 3, p.61). Findings for PTSD, OCD and PD are also presented narratively below, as only one DB-RCT was identified for each of these disorders. Meta-analyses were also conducted for pregabalin (only) versus placebo (SMD -0.43, 95% CI -0.57 to -0.30) and gabapentin (only) versus placebo (SMD -0.84, 95% CI -1.19 to -0.49) (Appendix Figures 1 and 2).

3.3.2 Generalised anxiety disorder

Pregabalin was significantly more effective than placebo in treating GAD (SMD -0.37, 95% CI -0.45 to -0.29) (Figure 3, p.61). Sensitivity analyses excluding studies in which pregabalin was used as adjunctive treatment, participants had psychiatric comorbidities, or rescue medications were allowed did not significantly alter the effect estimate or estimate of uncertainty (Appendix Table 1). The RR of all-cause drop-out

was comparable for pregabalin and placebo. Compared to placebo, pregabalin significantly reduced the RR of drop-out due to inefficacy (RR 0.44, 95% CI 0.28 to 0.70), but showed a trend increase in RR of drop-out due to adverse events (RR 1.30, 95% CI 0.99 to 1.71) (Figure 6, p.64). Primary and secondary outcomes relating to the efficacy and acceptability of pregabalin versus lorazepam and venlafaxine are presented in Appendix Figures 3-6. Visual inspection of the funnel plot did not show evidence of small-study effects (Appendix Figure 7).

3.3.3Social anxiety disorder

Acute treatment

Pregabalin was significantly more effective than placebo in the acute treatment of SAD (SMD -0.25, 95% CI -0.45 to -0.04) (Figure 3, p.61). There was no significant difference in the RR of all cause drop-out or drop-out due to adverse events (Figure 7, p.65). Compared to placebo, pregabalin showed a trend reduction in RR of drop-out due to inefficacy (RR 0.39, 95% CI 0.15 to 1.03) (Figure 7).

Long-term treatment

A 14-week study of gabapentin in SAD (Pande et al. 1999) showed significant improvement in symptoms compared to placebo across multiple clinician-evaluated and self-report rating scales. A 26-week study (Greist et al. 2011) investigating pregabalin for relapse prevention found that a fixed dose of 450mg/day significantly reduced overall relapse rate compared to placebo (27.5% vs 43.8%, based on CGI-Improvement/CGI-Severity criteria).

3.3.4Preoperative state anxiety

Compared to placebo, both pregabalin (SMD -0.55, 95% CI -0.92 to -0.18) and gabapentin (SMD -0.92, 95% CI -1.32 to -0.52) were significantly more effective in reducing preoperative state anxiety (Figure 3, p.61). Significant heterogeneity was found between these studies, which was investigated post-hoc through subgroup analyses based on empirically guided dose thresholds of dose-dependent efficacy (Baldwin et al. 2013; Markota and Morgan 2017).

High doses (>600mg) of gabapentin were found to be significantly effective in reducing preoperative state anxiety (SMD -1.30, 95% CI -1.72 to -0.87), but low doses (600mg) were not (Figure 4, p.62). A high degree of heterogeneity across studies in the high dose group remained (I^2 = 81%), hence the validity of the high dose effect estimate is uncertain. Visual inspection of a funnel plot for gabapentin versus placebo in preoperative state anxiety suggested possible small study effects, with greater effect size being observed in high-dose gabapentin studies with smaller samples (Appendix, Figure 8). There was no significant subgroup difference between low (≤150mg) and high (300mg) doses of pregabalin (Figure 5, p.63). Interestingly, low-dose pregabalin was significantly more effective than placebo (SMD -0.29, 95% CI -0.54 to -0.05), whilst the high dose was not.

It is worth noting that the splitting of patients in the placebo arm across the intervention arms, to facilitate dose-related subgroup analysis, resulted in a slightly reduced overall effect estimate (SMD -0.43, 95% CI -0.73 to -0.13) (Figure 5, p.63)

compared to the original analysis (Figure 3, p.61), but the overall effect remained significant.

Sensitivity analyses did not significantly alter the results (Appendix, Table 2 and Table 3). It was not feasible to perform meta-analyses for acceptability of pregabalin and gabapentin in preoperative state anxiety studies. Short outcome assessment times (lasting hours rather than weeks) meant that dropouts occurred in very few studies. In such cases, dropouts were due to practicalities of preoperative procedures and not due to participant decision.

3.3.5Posttraumatic stress disorder, obsessive compulsive disorder and panic disorder

Three DB-RCTs were included, two assessing adjunctive pregabalin for the treatment of PTSD (Baniasadi et al. 2014) and OCD (Mowla and Ghaedsharaf 2020) and one assessing gabapentin for the treatment of PD (Pande, Pollack, et al. 2000) (also see Table 2, p.39). A quantitative synthesis was not conducted due to clinical and methodological heterogeneity. Adjunctive pregabalin was more effective than placebo in combat-related chronic PTSD (significantly reduced severity of symptoms on the PTSD checklist military version at 6 weeks, but not HAM-A, HAM-D or Spitzer Quality of Life Index) and SSRI-resistant OCD (significantly reduced score on the Yale-Brown Obsessive-Compulsive Scale at 12 weeks). However, eight weeks of flexibly dosed gabapentin was not more effective than placebo in patients with PD (comparable baseline-to-endpoint change on the Panic and Agoraphobia Scale).

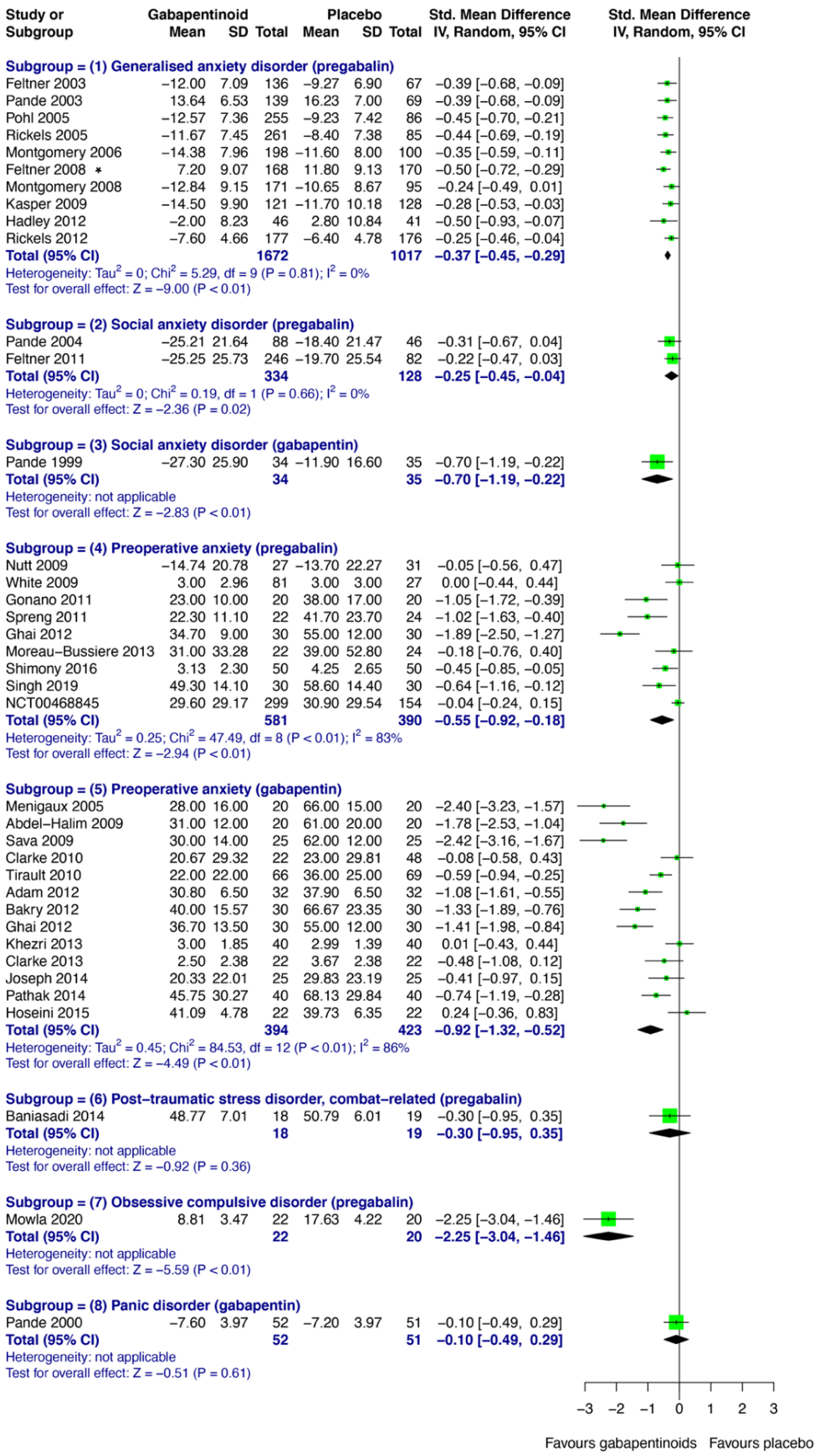


Figure 3. Forest plots showing efficacy of gabapentinoids versus placebo across the anxiety spectrum. CI, confidence interval; SD, standard deviation; IV, inverse variance. *Feltner 2008 is a relapse-prevention trial (pregabalin vs placebo in generalised anxiety disorder). A sensitivity analysis excluding Feltner 2008 (Appendix Figure 9) showed no material difference in the pooled effect size or CI.

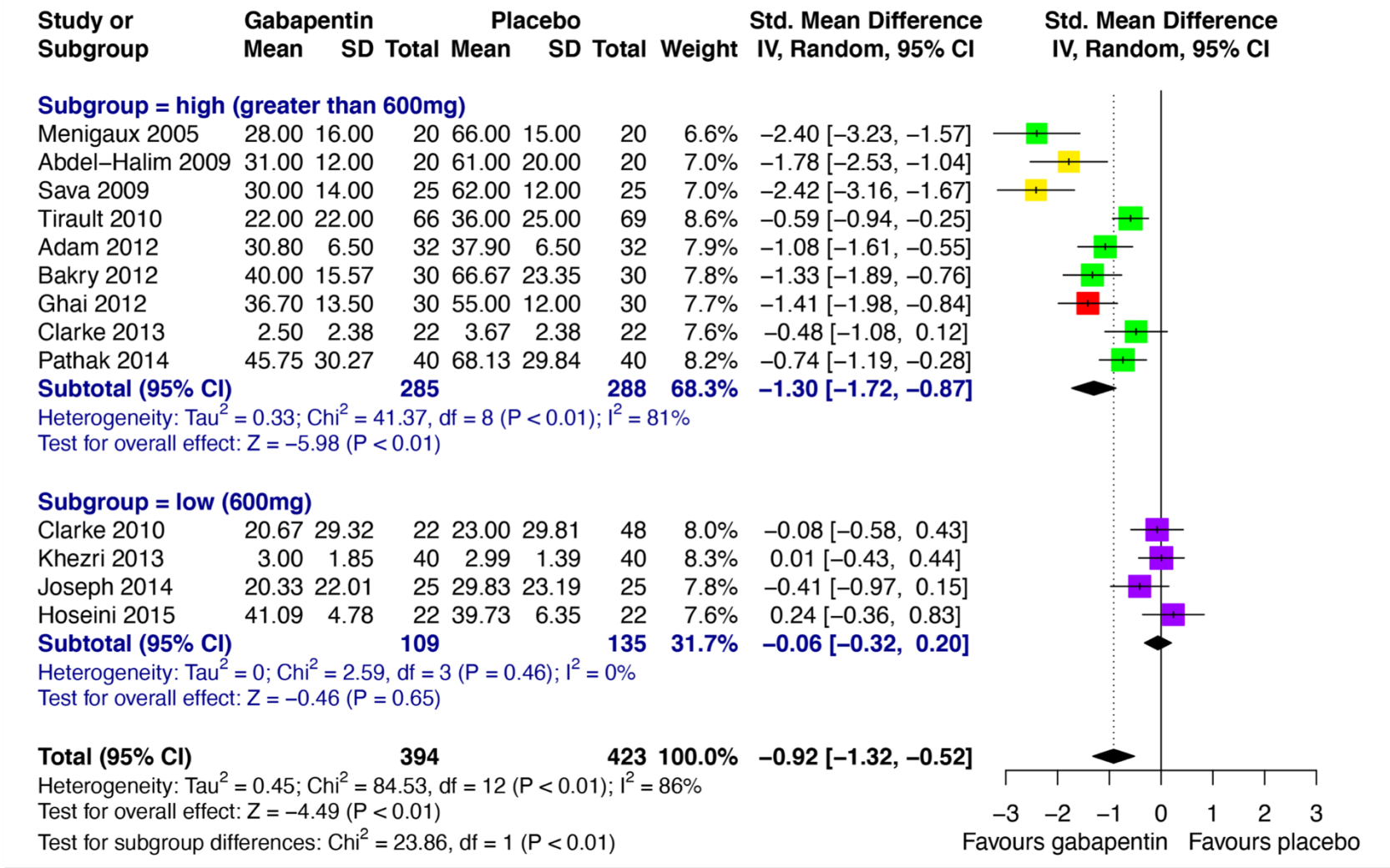


Figure 4. Subgroup analysis of empirically guide high (>600mg; including 1200mg (green), 900mg (red) and 800mg (yellow)) versus low doses (600mg, purple) of gabapentin versus placebo (Markota and Morgan 2017) in preoperative state anxiety. *CI, confidence interval; SD, standard deviation; IV, inverse variance.*

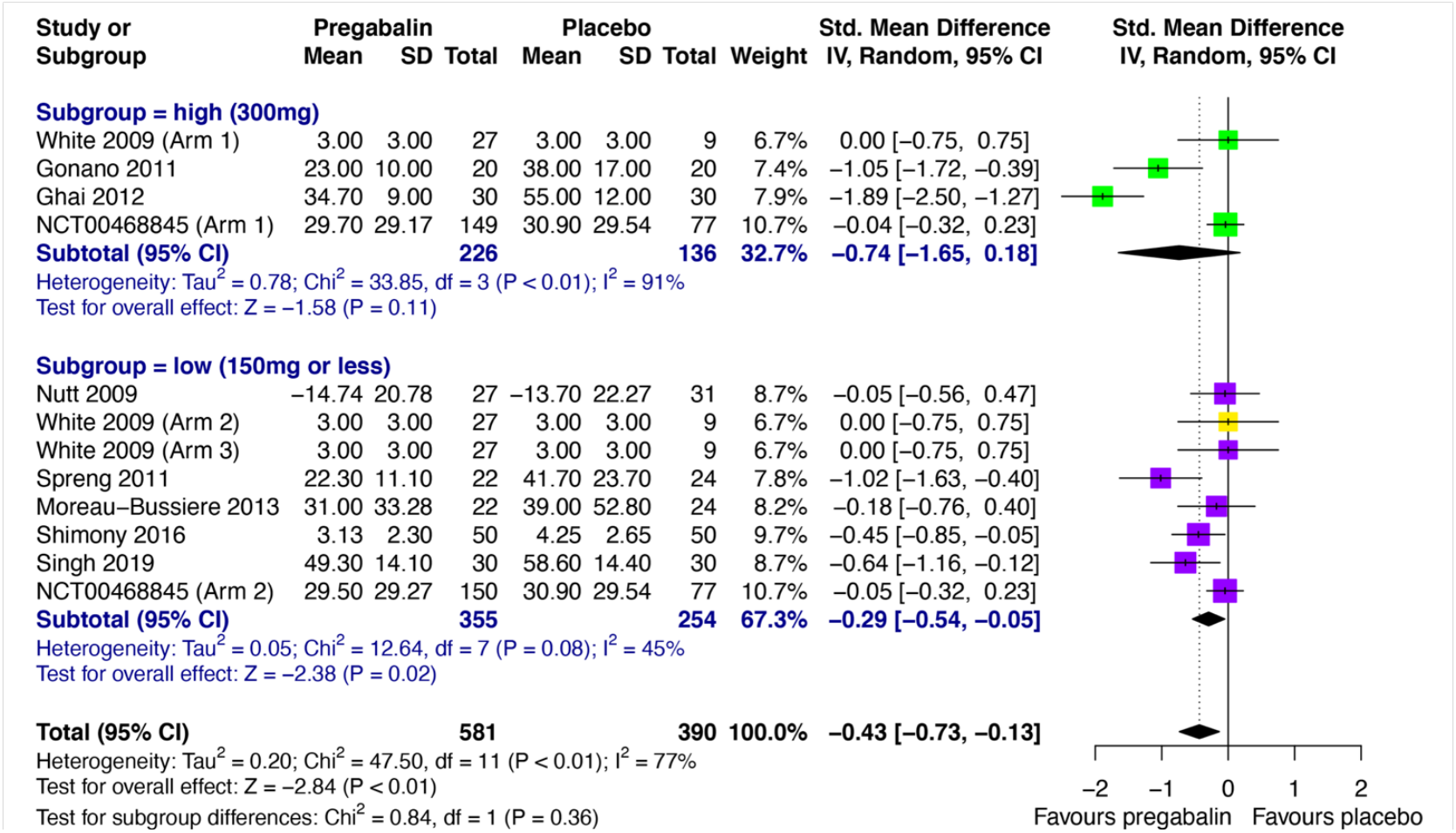
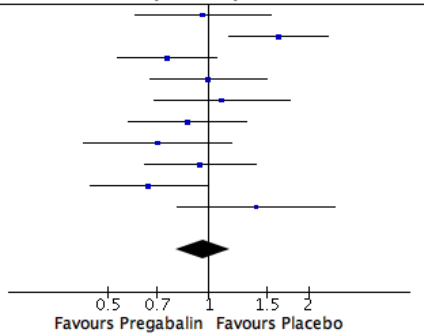


Figure 5. Subgroup analysis of empirically guided high (300mg, green) versus low doses (≤150mg; including 75mg (yellow) and 150mg (purple)) of pregabalin versus placebo (Baldwin et al. 2013) in preoperative state anxiety. *CI, confidence interval; SD standard deviation; IV, inverse variance.*

A. All cause dropout

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
(GAD-P) Feltner 2003	37	136	19	67	9.0%	0.96 [0.60, 1.53]
(GAD-P) Feltner 2008	61	168	38	170	12.1%	1.62 [1.15, 2.29]
(GAD-P) Hadley 2012	27	56	32	50	12.2%	0.75 [0.54, 1.06]
(GAD-P) Kasper 2009	33	121	35	128	10.5%	1.00 [0.66, 1.50]
(GAD-P) Montgomery 2006	45	207	20	101	9.0%	1.10 [0.69, 1.76]
(GAD-P) Montgomery 2008	44	181	27	96	10.3%	0.86 [0.57, 1.30]
(GAD-P) Pande 2003	27	139	19	69	8.1%	0.71 [0.42, 1.18]
(GAD-P) Pohl 2005	70	255	25	86	11.0%	0.94 [0.64, 1.39]
(GAD-P) Rickels 2005	51	270	26	91	10.4%	0.66 [0.44, 0.99]
(GAD-P) Rickels 2012	27	180	19	176	7.5%	1.39 [0.80, 2.41]
Total (95% CI)		**1713**		**1034**	**100.0%**	**0.96 [0.80, 1.16]**
Total events	422		260			

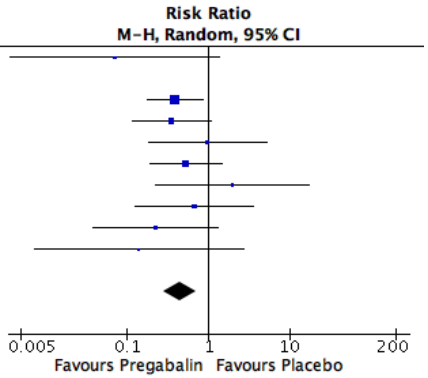
Heterogeneity: Tau² = 0.05; Chi² = 17.98, df = 9 (P = 0.04); I² = 50%
Test for overall effect: Z = 0.41 (P = 0.68)



B. Dropout due to inefficacy

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
(GAD-P) Feltner 2003	0	136	3	67	2.4%	0.07 [0.00, 1.35]
(GAD-P) Feltner 2008	0	168	0	170		Not estimable
(GAD-P) Hadley 2012	7	56	16	50	32.3%	0.39 [0.18, 0.87]
(GAD-P) Kasper 2009	4	121	12	128	17.1%	0.35 [0.12, 1.06]
(GAD-P) Montgomery 2006	4	207	2	101	7.4%	0.98 [0.18, 5.24]
(GAD-P) Montgomery 2008	7	181	7	96	20.1%	0.53 [0.19, 1.47]
(GAD-P) Pande 2003	4	139	1	69	4.4%	1.99 [0.23, 17.43]
(GAD-P) Pohl 2005	4	255	2	86	7.4%	0.67 [0.13, 3.62]
(GAD-P) Rickels 2005	2	270	3	91	6.6%	0.22 [0.04, 1.32]
(GAD-P) Rickels 2012	0	180	3	176	2.4%	0.14 [0.01, 2.68]
Total (95% CI)		**1713**		**1034**	**100.0%**	**0.44 [0.28, 0.70]**
Total events	32		49			

Heterogeneity: Tau² = 0.00; Chi² = 5.94, df = 8 (P = 0.65); I² = 0%
Test for overall effect: Z = 3.52 (P = 0.0004)



C. Dropout due to adverse events

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
(GAD-P) Feltner 2003	18	136	4	67	7.0%	2.22 [0.78, 6.29]
(GAD-P) Feltner 2008	10	168	4	170	5.8%	2.53 [0.81, 7.91]
(GAD-P) Hadley 2012	6	56	6	50	6.7%	0.89 [0.31, 2.59]
(GAD-P) Kasper 2009	15	121	7	128	10.2%	2.27 [0.96, 5.37]
(GAD-P) Montgomery 2006	21	207	10	101	14.8%	1.02 [0.50, 2.09]
(GAD-P) Montgomery 2008	19	181	9	96	13.3%	1.12 [0.53, 2.38]
(GAD-P) Pande 2003	16	139	7	69	10.7%	1.13 [0.49, 2.63]
(GAD-P) Pohl 2005	28	255	7	86	12.1%	1.35 [0.61, 2.98]
(GAD-P) Rickels 2005	22	270	9	91	13.9%	0.82 [0.39, 1.72]
(GAD-P) Rickels 2012	8	180	4	176	5.4%	1.96 [0.60, 6.38]
Total (95% CI)		**1713**		**1034**	**100.0%**	**1.30 [0.99, 1.71]**
Total events	163		67			

Heterogeneity: Tau² = 0.00; Chi² = 7.04, df = 9 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.88 (P = 0.06)

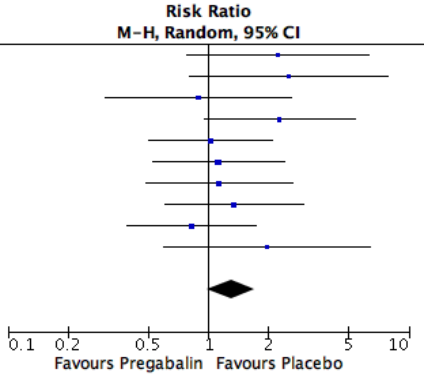
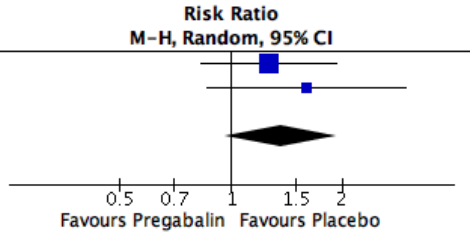


Figure 6. Forest plots of acceptability (dropouts) of pregabalin versus placebo in generalised anxiety disorder. *CI, confidence interval; M-H, Mantel-Haenszel method.*

A. All cause dropout

Study or Subgroup	Pregabalin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
(SAD-P) Feltner 2011	76	246	20	82	67.9%	1.27 [0.83, 1.94]
(SAD-P) Pande 2004	31	89	10	46	32.1%	1.60 [0.86, 2.97]
Total (95% CI)		**335**		**128**	**100.0%**	**1.37 [0.96, 1.94]**
Total events	107		30			

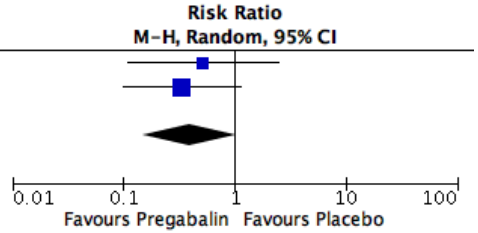
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.38$, df = 1 (P = 0.54); $I^2 = 0\%$
Test for overall effect: Z = 1.75 (P = 0.08)



B. Dropout due to inefficacy

Study or Subgroup	Pregabalin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
(SAD-P) Pande 2004	3	89	3	46	37.7%	0.52 [0.11, 2.46]
(SAD-P) Feltner 2011	5	246	5	82	62.3%	0.33 [0.10, 1.12]
Total (95% CI)		**335**		**128**	**100.0%**	**0.39 [0.15, 1.03]**
Total events	8		8			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.19$, df = 1 (P = 0.66); $I^2 = 0\%$
Test for overall effect: Z = 1.91 (P = 0.06)



C. Dropout due to adverse events

Study or Subgroup	Pregabalin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
(SAD-P) Feltner 2011	42	246	1	82	42.8%	14.00 [1.96, 100.12]
(SAD-P) Pande 2004	15	89	4	46	57.2%	1.94 [0.68, 5.51]
Total (95% CI)		**335**		**128**	**100.0%**	**4.51 [0.52, 39.44]**
Total events	57		5			

Heterogeneity: $Tau^2 = 1.85$; $Chi^2 = 3.87$, df = 1 (P = 0.05); $I^2 = 74\%$
Test for overall effect: Z = 1.36 (P = 0.17)

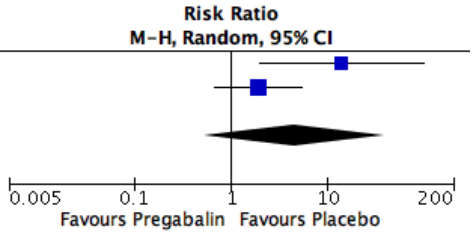


Figure 7. Forest plots of acceptability (dropouts) of pregabalin versus placebo in social anxiety disorder.
CI, confidence interval; M-H, Mantel-Haenszel method.

3.4 Insomnia/Sleep disturbance

Eight DB-RCTs assessed efficacy of gabapentin on sleep related outcomes. Of two trials with sufficient data to conduct a random effects meta-analysis (Brower et al. 2008; Mason et al. 2014), 111 patients were randomised to receive gabapentin and 60 to placebo (mean age 44.8 years; 44.9% female). In participants with alcohol dependence and related sleep disturbance, gabapentin did not demonstrate improvement in sleep scales compared to placebo (Figures 8 and 9, p.70). The RR for all-cause drop-out was comparable for gabapentin and placebo (RR 0.96, 95% CI 0.59 to 1.57) (Figure 10, p.70). Dropouts due to adverse events and due to inefficacy could not be assessed as there was no incidence of dropouts contributing to either outcome. Tolerability (side effect) data are reported in Appendix Table 4 (p.128).

Just one DB-RCT (Bollu et al. 2010) assessed the efficacy of pregabalin (n=121) versus venlafaxine (n=125) and placebo (n=128) on sleep related outcomes (mean age of all randomised patients 40.8 years, 60.7% female) (Table 1, p.37). Pregabalin significantly reduced scores on the Medical Outcomes Study Sleep Scale (MOS-SS) and Sleep Problems Index II compared to placebo at weeks 4 and 8.

3.4.1 Alcohol-related insomnia

Self-reported sleep quality

As described above, the meta-analyses did not reveal a significant effect in favour of gabapentin (Figures 8 and 9, p.70). Brower et al randomised participants to gabapentin (n=10) or placebo (n=11) for 6 weeks (Brower et al. 2008). Gabapentin was titrated up to 1,500mg over 10 days, for a total intervention duration of 6 weeks

in participants with alcohol dependence and comorbid insomnia. Gabapentin was not significantly better than placebo in improving subjective sleep outcomes. Mason et al tested gabapentin (two doses: 900mg/day and 1800mg/day) versus placebo over 12 weeks in participants with alcohol dependence (Mason et al. 2014). The study showed a significant linear dose effect on the Pittsburgh Sleep Quality Index (PSQI), along with the Alcohol Craving Questionnaire and Beck Depression Inventory II, between treatment and placebo groups.

Objectively measured or self-reported sleep time

The study by Brower and colleagues was the only placebo-controlled study of gabapentin in participants with alcohol dependence to report objective or self-reported sleep time (Brower et al. 2008). There were no significant differences between treatment and placebo groups in subjective or polysomnography (PSG)-derived total sleep time.

Sleep onset latency

The study by Brower and colleagues was the only placebo-controlled study of gabapentin in participants with alcohol dependence to report sleep onset latency (Brower et al. 2008). There were no significant differences between treatment and placebo groups in subjective sleep onset latency or PSG-derived sleep onset latency.

3.4.2Healthy participants with occasional sleep disturbance

Two studies (Rosenberg et al. 2014; Furey et al. 2014) tested gabapentin versus placebo in adults with occasional disturbed sleep. Rosenberg et al found that a single dose of gabapentin (250mg or 500mg) performed significantly better in improving the following: PSG-derived wake after sleep onset (WASO) and PSG-derived total sleep time (Rosenberg et al. 2014). Only the higher dose (500mg) was significantly better than placebo in improving sleep quality (Karolinska sleep diary (KSD) sleep quality index) and self-reported total sleep time. Furey et al also reported improvements after 28 days of follow-up on 250mg gabapentin versus placebo (on the KSD sleep quality index, subjective and objective WASO/total sleep time) (Furey et al. 2014). Both studies reported no significant difference between gabapentin and placebo in sleep onset latency.

3.4.3Sleep disturbance associated with major depressive disorder

Mowla and colleagues tested flexible dose gabapentin versus clonazepam in patients with major depressive disorder (MDD) currently taking SSRI (Mowla et al. 2015). There were significant within-group but not between-group improvements on the PSQI or Insomnia Severity Index (ISI). Gabapentin and clonazepam were comparable in effectiveness for the management of MDD-associated insomnia, with a better side effect profile for gabapentin.

3.4.4Sleep disturbance associated with generalized anxiety disorder

Bollu and colleagues performed a post-hoc analysis of a previously published DB-RCT (Kasper et al. 2009) testing 8-week flexible dose gabapentin versus venlafaxine versus placebo in patients with GAD (Bollu et al. 2010). Subjective sleep assessment was done using MOS-SS. Compared to placebo, pregabalin significantly reduced the sleep disturbance subscale of MOS-SS at both 4 and 8 weeks.

3.4.5Sleep disturbance associated with menopause

Yurcheshen and colleagues conducted a post-hoc analysis (Yurcheshen et al. 2009) of a published DB-RCT (Guttuso et al. 2003) testing gabapentin's effects on hot flashes in postmenopausal women. Gabapentin of 900mg/day was compared against placebo. There were statistically significant improvements on the PSQI global score at 4 weeks. Improvement was seen also at 12 weeks but this did not reach statistical significance (p=0.07). The global improvement was reflected in the sleep quality and sleep efficiency factors of the PSQI.

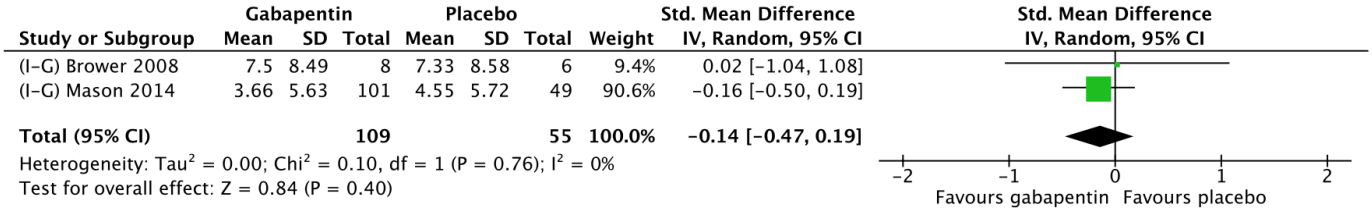


Figure 8. Forest plot of efficacy of gabapentin versus placebo in alcohol dependence-related insomnia, at week 6 from baseline. *CI, confidence interval; IV, inverse variance; SD, standard deviation.*

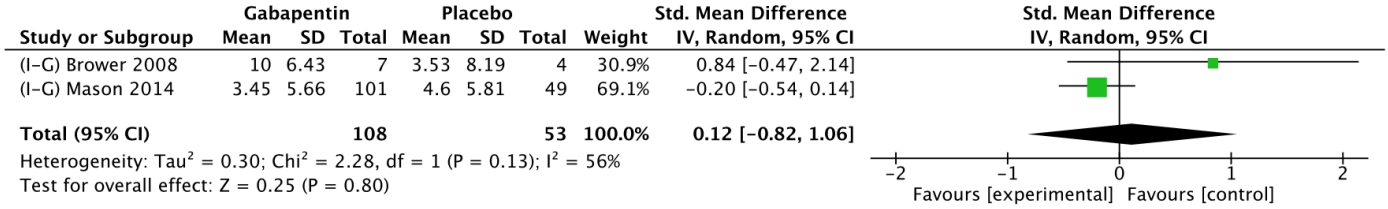


Figure 9. Forest plot of efficacy of gabapentin versus placebo in alcohol dependence-related insomnia, at week 12 from baseline. *CI, confidence interval; IV, inverse variance; SD, standard deviation.*

All cause dropout

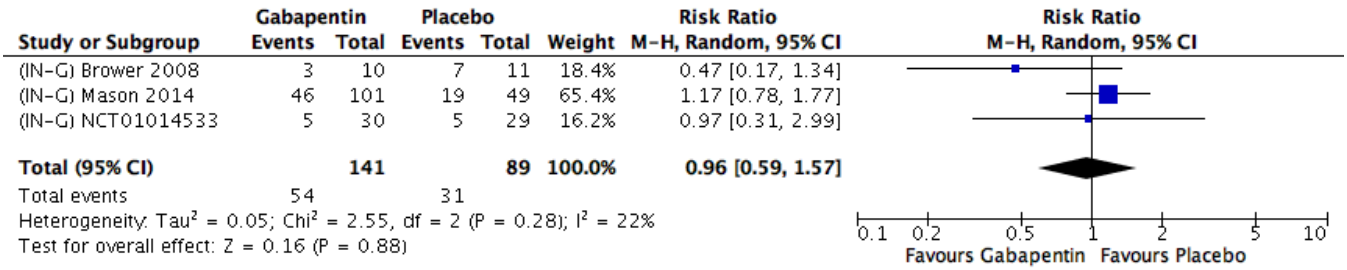


Figure 10. Forest plot of acceptability (dropouts) of gabapentin versus placebo in alcohol dependence-related insomnia. *CI, confidence interval; M-H, Mantel-Haenszel method.*

3.5 Tolerability

3.5.1 Bipolar disorder

In addition to double-blind RCTs, 11 open-label studies were included for analysis of tolerability, 8 of which reported outcome data (Appendix Table 4, p.128; also see Appendix for reference list of included studies). The following seven open-label studies assessed gabapentin as an adjunct to mood stabiliser or benzodiazepine treatment (total patients *n*=144): Altshuler et al., 1999; Knoll et al., 1998; McElroy et al., 1997; Perugi et al., 1999; Wang et al., 2002; Young et al., 1997; Young et al., 1999.

Gabapentin was most commonly associated with sedation (39/144, 27%), movement disorders (ataxia/tremor) (17/144, 12%) and gastrointestinal upset (17/144, 12%). In addition, sleep problems, drowsiness, fatigue and cognitive side-effects (forgetfulness/memory loss, impaired cognition) were reported across studies. One study assessed pregabalin as an adjunct to standard treatments for BD (*n*=58, Schaffer et al., 2012). This study reported adverse events including thought overactivation (12/58, 21%), weight gain (8/58, 14%) and increased appetite (8/58, 14%).

3.5.2 Anxiety disorders/states

The side effect profile of gabapentinoids was comparable across the studies of anxiety disorders/states. Nineteen studies were included to examine the tolerability of pregabalin in GAD, SAD, PTSD, OCD and PD of which 17 reported side-effect

outcomes (Appendix Table 4, p.128). Two DB-RCTs reported side-effect outcomes of gabapentin in SAD and PD (Appendix Table 4). For studies of preoperative state anxiety, assessment of tolerability was limited due to inconsistent reporting of preoperative side effects across trials. Common side effects of gabapentin and pregabalin included drowsiness, dry mouth, dizziness, headache, fatigue and visual disturbance (Appendix Table 4).

Generalised anxiety disorder and Social anxiety disorder

12 monotherapy DB-RCTs (Feltner et al., 2003; Feltner et al., 2008; Feltner et al., 2011; Greist et al., 2011; Hadley et al., 2012; Kasper et al., 2009; Montgomery et al., 2006; Montgomery et al., 2008; Pande et al., 2003; Pande et al., 2004; Pohl et al., 2005; Rickels et al., 2005), 1 DB-RCT adjunctive to SSRI/SNRI treatment (Rickels et al., 2012), 1 open-label, randomised study (Cvjetkovic-Bosnjak et al., 2015) and 1 open-label non-randomised study (Montgomery et al., 2013). Refer to Appendix Table 4 (p.128) and reference list of included studies.

Of 2,703 patients treated with pregabalin across these studies, 631 (23.3%) reported experiencing dizziness, 541 (20%) drowsiness, 235 (8.7%) headache, 223 (8.3%) dry mouth, 204 (7.5%) infection, 187 (6.9%) nausea, 135 (5%) fatigue, 94 (3.5%) visual disturbance, 81 (3%) thinking abnormally, 78 (2.9%) insomnia, 68 (2.5%) weight gain, 52 (1.9%) constipation and 48 (1.8%) diarrhoea. Other less commonly reported side-effects included vertigo, movement disorders, vomiting and incoordination. In studies with multiple dose arms, it was observed that more side-effects were reported with increasing pregabalin dose, as might be expected (e.g. Feltner et al., 2003;

Feltner et al., 2011, Montgomery et al., 2006; Pande et al., 2003; Pande et al., 2004; Rickels et al., 2005). Only one DB-RCT study assessed gabapentin in SAD (Pande et al., 1999), with tolerability data showing that side effects included infection, dizziness, headache, drowsiness and fatigue.

Preoperative state anxiety

Gabapentin was associated with drowsiness in 3 DB-RCTs in preoperative state anxiety (23/148, 16% patients randomised to gabapentin arms) (Abdel-Halim et al., 2009; Rorarius et al., 2004; Tirault et al., 2010). Rorarius et al., (2004) further reported side effects of dry mouth (21/38, 55%), dizziness (6/38, 16%), headache (5/38, 13%) and visual disturbance (2/38, 5%) in gabapentin treated patients, although similar incidence of side-effects was experienced in the comparison oxazepam arm of the study. Only 1 DB-RCT of pregabalin in preoperative state anxiety reported tolerability data (Nutt et al., 2009), with reported side effects including fatigue (7/27, 26%) dizziness (6/27, 22%), disturbances in attention (3/27, 11%) and drowsiness (3/27, 11%).

3.5.3Insomnia/sleep disturbance

Nine studies were included to examine the tolerability of gabapentin in insomnia/sleep disturbance, of which 7 reported side-effect outcomes; 6 DB-RCTs (Brower et al., 2008; Furey et al., 2014; Mason et al., 2014; NCT01014533, Rosenburg et al., 2013; Yurchesen et al., 2009) and 1 open-label, non-randomised study (NCT02040532) (Appendix Table 4, p.128; Appendix, reference list of included studies).

Of 575 patients treated with gabapentin across these studies, 66 (11%) reported experiencing at least 1 side effect. The most commonly reported across studies were headache (32/66, 48% of patients), fatigue (27/66, 41%), drowsiness (21/66, 32%), dizziness (8/66, 12%) and nausea (5/66, 8%) although it is unclear whether these could be attributed to the condition being studied. Tolerability of pregabalin in insomnia/sleep disturbance could not be examined due to side-effect data not being reported.

Chapter 4: Discussion

4.1 Summary of key findings

This thesis presents the findings of a systematic review on the efficacy, acceptability and tolerability of gabapentinoids in BD, anxiety disorders/states and insomnia/sleep disturbance. By comparison with prior studies, this systematic review covered more disorders and databases, considered only DB-RCTs for evidence synthesis on efficacy, included unpublished literature, and, as far as possible, conducted quantitative syntheses. The study shows that there is minimal evidence to support the use of gabapentinoids in BD and insomnia. A moderate effect size was seen across the anxiety spectrum; this was also significant for several individual anxiety disorders and showed a dose effect of gabapentin in preoperative anxiolysis.

4.1.1 Bipolar disorder

In BD, the small number of DB-RCTs investigating gabapentin, and absence of studies investigating pregabalin, highlight the sparse evidence base on which to evaluate the efficacy of gabapentinoids in the treatment of BD. A quantitative synthesis was not performed due to heterogeneity in study population, design and outcome measures. The evidence is inconclusive and does not support the current use of gabapentinoids in the management of BD.

4.1.2Anxiety spectrum

The analysis of all anxiety-related studies showed statistically significant low to large effect sizes favouring gabapentinoid use, compared to placebo, across the spectrum of anxiety disorders/states. This transdiagnostic effect is supported by the fact that state, trait and pathological anxiety are mediated by a common brain network (Spampinato et al. 2009; Takagi et al. 2018) and by the common neural phenotypes observed across anxiety disorders (Etkin and Wager 2007; see **section 4.3** for further discussion). The approach necessitated the inclusion of baseline-to-endpoint change scores as well as post-intervention scores, but a study of 21 meta-analyses found that combining post-intervention and change scores produces valid meta-analytical results (da Costa et al. 2013).

The results suggest a dose-dependent effect of preoperative gabapentin, with >600mg being required for significant acute anxiolysis. These analyses were performed post-hoc to investigate the large between-study heterogeneity and therefore should be considered as hypothesis-generating to guide future studies. The choice of dose thresholds was based on empirical reports of dose-dependent effects in GAD. For gabapentin, a dose-response pattern has been observed in GAD with remission/mild anxiety symptoms on total daily doses of gabapentin ≥900mg/day and recurrence of severe anxiety symptoms, suggesting ineffectiveness, at <600mg/day (Markota and Morgan 2017). For pregabalin, we used a similar approach based on a reported difference in efficacy between 150mg/day versus 200-600mg/day in GAD (Baldwin et al. 2013).

4.1.2.1 Gabapentinoids and mechanism of anxiolysis

The anxiolytic effect of gabapentinoids is at least partly mediated by their action on the $\alpha_2\delta$-1 subunit (Lotarski et al. 2011). $\alpha_2\delta$-1 is the major binding protein for gabapentinoids in the amygdala (Bian et al. 2006), and overexpression of $\alpha_2\delta$-1 in the amygdala of rats results in an 'anxiety phenotype' reversed by pregabalin (Nasca et al. 2013). However, the mechanisms underlying acute versus chronic effects of gabapentinoids on symptoms of anxiety require further investigation. Gabapentin has been shown to cause only small effects on calcium currents with acute treatment, whereas longer incubation significantly reduces calcium currents (Dolphin 2018a). One possibility is that gabapentinoids selectively target calcium channel populations of rapid turnover, such that they would have varying effects on currents depending on subcellular region, e.g. presynaptic terminals compared to cell bodies (Dolphin 2016). Genotype-dependent effects on efficacy and speed of onset of action of gabapentinoids have also been reported (Chesler et al. 2003).

Chronic pregabalin treatment has been shown to reduce the intrinsic excitability of dentate gyrus (DG) granule cells (GC) and accelerate the maturation of adult-born DGCCs (Lempel et al. 2017). Neurogenesis in the ventral, rather than the dorsal, part of the DG is increased by chronic antidepressant treatment; an effect that may be associated with the modulation of mood and behaviour (Santarelli et al. 2003; Kheirbek and Hen 2011). Moreover, optogenetic studies suggest a functional dissociation between the ventral and dorsal DG (Kheirbek et al. 2013). Activation of dorsal DGGCs impairs encoding of contextual fear memories with little effect on anxiety-related behaviours, but activation of ventral DGGCs suppresses innate

anxiety-related behaviours (Kheirbek et al. 2013), identifying the ventral DG as a potential target for therapeutic modulation in anxiety disorders. The DG is also implicated in gabapentin-induced increase in cell surface expression of hippocampal δ-$GABA_A$ receptors, which are highly expressed in the DG, and resulting increase in tonic inhibitory conductance in the hippocampus (Yu et al. 2019b). In the same study, gabapentin-induced acute anxiolysis was dependent on the presence of δ-$GABA_A$ receptors (Yu et al. 2019b).

Given these diverse but converging mechanisms of gabapentinoid action, it would be interesting to investigate the effects of differential VGCC, $\alpha_2\delta$ subunit as well as δ-$GABA_A$ receptor expression and functional diversity on neuronal excitability and network plasticity along the dorsoventral axis of the DG and its projection areas. This may clarify therapeutically relevant mechanisms of mood and anxiety-regulation in regions which receive extensive input from the ventral hippocampus and are strongly associated with behavioural responses to emotional stimuli (prefrontal cortex, amygdala, hypothalamus) (Kheirbek et al. 2013).

4.1.3Insomnia

The meta-analysis of studies of alcohol-related insomnia found that gabapentin was not significantly better than placebo in improving self-reported sleep quality. One relevant study of alcohol-related insomnia (Brower et al. 2008) reported total sleep time and sleep onset latency but did not show a significant benefit of gabapentin over placebo on these outcome measures. Two studies of gabapentin versus placebo in healthy adults with occasional sleep disturbance (Furey et al. 2014; Rosenberg et al.

2014) suggest a limited benefit in this population for sleep quality and total sleep time.

Gabapentinoids may improve sleep in patients with a range of clinical conditions, such as GAD- and neuropathic pain-associated insomnia (Roth et al. 2014), but the extent to which sleep parameters are affected by direct or indirect effects in these conditions is unclear (Stahl et al. 2013). Whilst studies of pregabalin versus placebo in GAD included in our review reported improvements in insomnia subscales of HAM-A, these were not meta-analysed due to concerns regarding confounding and the validity of HAM-A subscales in insomnia.

4.1.3.1 Gabapentinoids and sleep regulation

Gabapentin has been shown to increase the duration of slow-wave sleep (SWS), a significant marker of homeostatic sleep regulation (Bellesi et al. 2014), in healthy human adults (Foldvary-Schaefer et al. 2002). Enhanced SWS is associated with improved sleep-dependent memory consolidation and cognitive performance (Bellesi et al. 2014), whereas impaired slow-wave activity is associated with multiple neuropsychiatric disorders including BD, depression, and Alzheimer's disease (Lee et al. 2020; Scholes et al. 2020).

Fast and slow calcium-dependent-hyperpolarisation pathways in neurons are pivotal in the regulation of SWS and sleep homeostasis (Tatsuki et al. 2016). Moreover, a hyperactive inositol triphosphate (InsP3) receptor/calcium signaling pathway is associated with disturbed sleep patterns in BD (Schlecker et al. 2006). Abnormal

sleep regulation is a well-established BD phenotype, and sleep deprivation can induce hypomania in people with BD and healthy subjects (Hensch et al. 2019). Genome-wide studies have found significant associations between BD-related sleep phenotypes and known circadian genes (Shi et al. 2008). Notably, variants of the *CACNA1C* gene are associated with altered sleep parameters (Kantojärvi et al. 2017); this gene is also significantly implicated in the pathogenesis of BD (Harrison et al. 2016).

4.2 Harms, side effects, potential for misuse

The limited evidence for efficacy of gabapentinoids in several of the conditions studied here is complemented by good evidence of their side-effects and potential harms. Consistent with previous reports (Goodman and Brett 2019a), the findings show that gabapentinoids commonly cause side effects associated with central nervous system depression, such as drowsiness and dizziness, which may be associated with increased risk of accidental physical injuries and road traffic incidents (Molero et al. 2019). At a neurobiological level, blockade of the $\alpha_2\delta$-1 isoform can abolish corticostriatal LTP; high doses of gabapentinoids may have dose- and duration-dependent effects on neuronal processes underlying memory and learning (Zhou et al. 2018).

The prescription of gabapentinoids has risen significantly in the UK (Montastruc, Loo, and Renoux 2018) and US (Goodman and Brett 2017). In a pharmacoepidemiologic study of ambulatory care in the US, there was no clear FDA-approved indication in >95% of gabapentinoid-related healthcare visits (Zhou et al. 2019). Primary care

doctors comprised the largest proportion of gabapentinoid prescribers, but psychiatrists were in the top four highest-prescribing specialties (Zhou et al. 2019). Moreover, it is clear that a significant proportion of gabapentinoid prescriptions in the UK and US are off-label and co-prescribed with opioids (Zhou et al. 2019; Montastruc, Loo, and Renoux 2018). Whilst the prevalence of gabapentinoid abuse is 1% in the general population, the rate is 40-65% in patients with prescriptions and 15-22% in those with substance use disorders (SUD) (Hägg, Jönsson, and Ahlner 2020). The association is strongest in those with opioid addiction, a pattern observed in countries including the US, Germany and Italy (Hägg, Jönsson, and Ahlner 2020). This is of particular concern given the harms when used concurrently with opioids (Gomes et al. 2017). Against this background, the extensive off-label usage of gabapentinoids appears unwarranted and requires closer scrutiny.

4.2.1 Potential mechanisms of addiction

The biological mechanism for gabapentinoid abuse is not established but there are clues. Using the conditioned place preference paradigm in mice, Althobaiti and colleagues showed that gabapentin has a dose-dependent effect on the development of drug-seeking behaviour, which was significantly attenuated with a dopamine 1 receptor antagonist (Althobaiti et al. 2020). Interestingly, pregabalin attenuates the reinforcing and withdrawal effects of opioids in mice when administered prior to morphine, but potentiates the rewarding effects when given shortly after a low dose of morphine (Vashchinkina et al. 2018). In the nucleus accumbens, $\alpha_2\delta$-1 is upregulated after cocaine administration, and gabapentin reduces cocaine-induced, but not sucrose-induced, reinstatement (Spencer et al. 2014). These studies suggest

that the effect of gabapentinoids on addiction-related behaviour is dependent on dose and timing of co-consumed substances of abuse, as well as implicating the $\alpha_2\delta$ subunit as a potential target for addiction therapy. Indeed, it has been suggested that opioid abusers may be using $\alpha_2\delta$ ligands in order to reduce withdrawal symptoms (McAnally, Bonnet, and Kaye 2020).

4.3 Limitations

This study is based on aggregate-level data. Aggregate-level systematic reviews are inherently dependent on the quality of the primary studies and summary data provided (Broeze et al. 2010). Furthermore, subgroup-specific effects are particularly difficult to explore at the aggregate level, and most subgroup analyses of aggregate data have poor replicability (Ioannidis 2008). Whilst these limitations would be overcome by conducting an individual patient data (IPD) meta-analysis (Ioannidis 2008), this is often weighed against the practical constraints of IPD availability and access, as well as the value added of treatment effect sizes obtained from IPD meta-analyses versus aggregate meta-analyses (Tierney et al. 2020).

Subgroup analyses conducted in the current work were post-hoc in nature and therefore are hypothesis-generating. The empirical dose thresholds used to guide subgroup analysis of preoperative state anxiety studies were based on dose-dependent efficacy reports in GAD, and there was no formal check of the evenness of covariate distribution. Additionally, the method by Wan et al (Wan et al. 2014) was used to convert median/IQR/range to mean/SD to facilitate meta-analysis of preoperative state anxiety studies, which had high between-study heterogeneity. It is

unclear whether this method has been sufficiently validated, but a sensitivity analysis of studies originally reporting median/IQR/range data did not significantly alter the results. Moderate-to-high heterogeneity remained in some subgroups, hence limiting conclusions that may be drawn regarding the treatment effect size in some diagnostic groups (Imrey 2020). Meta-analyses could not be conducted in some disorders, but this is reflective of the heterogeneous nature of the individual studies which precluded quantitative synthesis. Finally, the risk of bias was high in many domains resulting in high levels of uncertainty in the treatment effect estimates based on GRADE assessments (Appendix Tables 5A-F, p.146). The prominent side-effect profiles of gabapentinoids (Zaccara et al. 2012) may be associated with difficulties in maintaining the blinding of patients and participants, and this may have led to the overestimation of effect sizes based on subjective outcomes (Savovic et al. 2018). Therefore, trial results suggesting gabapentinoid efficacy should be interpreted with caution, particularly when such findings form the basis for their use in unlicenced indications.

Where imputation was performed on missing data, LOCF was the most common method in the included studies. The validity of the LOCF method depends on the assumption that participant outcomes remain stable after they have dropped out, but this approach is particularly prone to bias in mental health trials due to the progressive and fluctuating nature of psychiatric disorders (Mavridis et al. 2014). Simple imputation methods, such as LOCF and mean value imputation, do not appropriately account for imputation uncertainty and lead to underestimations of the standard error (Little et al. 2012). Unsurprisingly, LOCF analysis has been shown to

introduce positive or negative biases that significantly affect statistical test results (Lachin 2016). Most psychiatric trials report dropout rates of greater than 20%; this is important because, depending on the mechanisms of missing-ness, missing data may increase the risk of bias of studies and lead to invalid conclusions (Potkin and Siu 2009). Alternative, more statistically sophisticated methods to deal with missing data exist, including maximum likelihood-based methods (Li and Stuart 2019), inverse probability weighting (Mansournia and Altman 2016) and multiple imputation (Sterne et al. 2009). However, the potential for such methods to correct for biases relies on the assumption that data are missing at random (MAR), in which the probability of a missing outcome is not related to the outcome itself; participant characteristics could explain the propensity for missing data (Little et al. 2012; Mavridis et al. 2014). Systematic reviewers typically cannot ascertain the reason(s) for missing data and the MAR assumption is difficult to empirically test (Mavridis et al. 2014). Therefore, sensitivity analyses should ideally be conducted to evaluate different scenarios for mechanism(s) of data missing-ness (Mavridis et al. 2014), as should also be done using a principled, systematic approach for dealing with missing data in individual clinical studies (Carpenter and Smuk 2021).

Whilst the focus of this work was on anxiety- and other disorder-specific rating scales in accordance with the protocol (Houghton et al. 2017), the CGI rating scales could have been further analysed to facilitate interpretation of the HAM-A findings. The CGI-I and CGI-S scales have indeed been shown to have good correlation with HAM-A and LSAS (Bandelow et al. 2006), though the former are relative measures as opposed to HAM-A and LSAS which measure progress in more absolute terms

(Bandelow et al. 2006). Additional analysis could provide an opportunity to validate the correlation between HAM-A and CGI outcomes in studies investigating the comparative efficacy of gabapentinoids. Given the face validity and broad applicability of CGI to different disorders (Busner and Targum 2007), it would also be interesting to explore its implementation in the routine clinical setting for better real world evidence monitoring and analysis (Berk et al. 2008).

The historically DSM/ICD-based clinical studies make it challenging to interpret and compare treatment effect sizes with respect to transdiagnostic constructs being affected by the intervention. As previously mentioned, there is empirical support for the shared neurobiological basis of anxiety disorders (Etkin and Wager 2007), hence one would hypothesize that a drug affecting an implicated neural circuit in one disorder would improve the same or related circuits in another anxiety disorder. Furthermore, proof of principle studies show that spatiotemporally precise manipulation of neural circuits and behaviour can be achieved in freely moving mice by the use of optogenetic techniques (Covington et al. 2010; Allsop et al. 2014; Tye et al. 2011). As clinical studies increasingly adopt neurobiological frameworks, notably the Research Domain Criteria (RDoC) (Insel et al. 2010), gold standard methods in evidence synthesis (e.g. IPD meta-analyses) based on treatment effects directly relevant to measurable RDoC constructs will likely lead to future insights across psychiatric disorders. Standardised treatment effect sizes, for instance, would no longer simply involve statistical pooling of effects in current diagnostic categories. Rather, pooling across transdiagnostic domains correlated to improvement in specific symptom clusters, would result in domain-specific standardised effect sizes in

addition to the current disorder-specific standardised effect sizes. Already, meta-analyses use established methods to assess evidence for interventions, hypothesized causal associations, and make broader conclusions (Gurevitch et al. 2018) on topics ranging from drug efficacy (Cipriani et al. 2011) and disease mechanisms (Litchfield et al. 2021; Harrison et al. 2019) to neural circuits (Etkin and Wager 2007) and genetic association studies (Munafo and Flint 2004). The success of future evidence synthesis studies for RDoC-guided trials would be dependent on the validity of the constructs. It is not certain, for instance, whether existing RDoC domains are empirically valid (Markowitz and Friedman 2020) and the suitability of these constructs in mapping symptoms to circuits will require continual evaluation. However, it may become possible to obtain more specific insights into how a specific pharmacologic intervention relates to various circuit-based domains within individuals (if individual patient data meta-analyses are conducted). It may also help to further validate, or invalidate, a preconceived mapping of symptoms to circuits based on an existing hypothesis on the therapeutic mechanism of action (Williams 2016).

Of course, even where common neural phenotypes exist, there may also be differences in neural circuit involvement that challenge traditional diagnostic boundaries. It has long been appreciated that there are overlapping as well as distinct neural activation patterns within the ‘anxiety and stress disorders’ (PD, SP, SAD, PTSD, GAD, OCD) (Etkin and Wager 2007; Duval, Javanbakht, and Liberzon 2015). For instance, all involve hyperactivation of the amygdala and most involve hyperactivation of the insula, whereas on balance PTSD features significant hypoactivation of the prefrontal cortex (Duval, Javanbakht, and Liberzon 2015).

Furthermore, the reverse activation pattern has also been found in patients with PTSD experiencing dissociative symptoms (Friedman et al. 2011). The neural circuitry profile of OCD also includes amygdala and insular hyperresponsivity, but is distinguished from other 'anxiety and stress disorders' by a pattern of fronto-striatal hyperactivity (Stein et al. 2010). This is accompanied by comparatively stronger evidence of cognitive deficits in executive functioning (Stein et al. 2010).

The most recent DSM and ICD classification systems depart from previous editions by placing PTSD and OCD within separate diagnostic categories (Pai, Suris, and North 2017; Stein et al. 2019; Fenske and Petersen 2015). PTSD and OCD are no longer within the broad category of anxiety disorders; the rationale for this change goes beyond empirical findings of activation and connectivity patterns (Friedman et al. 2011). Psychiatric nosology is a continually evolving, as well as highly debated and controversial, field (Aftab and Ryznar 2021). However, at least in the context of research, a more practical, though technically challenging, approach would be to characterise the evolution of neural connectivity and activation patterns, correlate these to the clusters of symptoms an individual exhibits, and target these neural dysfunctions (i.e. precision medicine) (McTeague et al. 2020; Ressler and Mayberg 2007; Goldstein-Piekarski et al. 2021). In principle, this would bypass the need to categorise a disorder as an 'anxiety disorder' or 'traumatic stress disorder' and could translate findings of intra-individual variability to therapeutic discoveries. On this basis, a stronger argument could be made that the development of precision psychiatry must be accompanied by the refinement or deconstruction of our linguistic

as well as empirical reasoning in the classification of phenomena (Pierre and Frances 2016; Rosenman and Nasti 2012).

4.4 Rationale for $\alpha_2\delta$ ligands in psychiatry

Neurobiological and pharmacological considerations supporting the candidacy of a drug target should never trump the empirical clinical evidence regarding efficacy and safety. Nevertheless, they may be useful when evaluating the potential for further investigations of the target where evidence is limited.

4.4.1 Voltage-gated calcium channels and psychiatric disorders

As outlined earlier, a role for VGCCs in psychiatric disorders is supported by genomic data. The evidence includes both common and rare variants and is most robust for schizophrenia (Ripke, Walters, and O'Donovan 2020) and BD (Mullins et al. 2021), but VGCC associations are observed across a range of psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics et al. 2013), albeit not yet for anxiety disorders (Levey et al. 2020). However, the genetic associations to VGCCs are primarily with α-1 and β subunits; it has not been established whether there are robust associations directly implicating genes for the VGCC $\alpha_2\delta$ subunit that is the target of gabapentinoids.

4.4.2 Calcium pathophysiology

In support of genomic findings, pathway analyses show replicable association of calcium signaling, glutamate signaling and second messengers, with BD (Nurnberger

et al. 2014; Harrison, Geddes, and Tunbridge 2018). Postsynaptic calcium signaling processes control synaptic plasticity and gene expression that influence neural circuit function, and these processes appear to be a common target of psychiatric risk genotypes (Harrison, Geddes, and Tunbridge 2018). On balance, intracellular calcium signaling is increased in BD, and this increase appears to be primarily state-independent (Harrison, Geddes, and Tunbridge 2018). A meta-analysis of cellular calcium concentrations in BD showed a robust, moderate effect size increase in both basal and stimulated free intracellular calcium (Harrison et al. 2019).

Abnormally elevated calcium could increase membrane excitability and activate transcription through several pathways (Berridge 2013), for instance CREB-BDNF signaling (Finkbeiner et al. 1997). BDNF influences temporally precise cortical development (Shieh et al. 1998) by triggering biochemical pathways regulating glutamatergic synapse-selective structure and function (Rauti et al. 2020). Furthermore, the BNDF/MAPK pathway has been shown to regulate affective behaviours (Ninan 2014), and BDNF infusions into the hippocampus of BDNF-deficient mice reverses abnormal psychiatric phenotypes (Sakata et al. 2013). Notably, lithium, the mainstay of mood stabilisation, enhances CREB activity by inhibiting GSK-3beta (a negative modulator of CREB) (Berridge 2013). Interestingly, a de novo loss of function mutation in CAMKK2, a central component of neuronal calcium signaling pathways, was identified in an exome sequencing study of BD (Kataoka et al. 2016) with significant functional effects on cell viability (Xy Ling et al. 2020).

4.4.3CACNA1C gene association with psychiatric phenotypes

The *CACNA1C* gene, which encodes the α-1 subunit of the L-type VGCC Cav1.2 (Nanou and Catterall 2018), is strongly associated with BD, schizophrenia and major depression (Harrison, Geddes, and Tunbridge 2018). The well-established intronic risk SNP rs1006737 within the CACNA1C gene correlates with higher levels of CACNA1C mRNA and increased density of Cav1.2-mediated currents in induced human neurons (Yoshimizu et al. 2015). Furthermore, the rs1006737 haplotype is associated with morphologic effects e.g. grey matter volume, and cognitive domains involving spatial memory and attention (Yoshimizu et al. 2015). The risk genotype, and altered effects on VGCC function, affects mediotemporal emotional processing and prefrontal working memory processing, neural circuit dysfunctions associated with both BD and schizophrenia (Bigos et al. 2010; Harrison et al. 2016). However, there is temporal and spatial specificity in the association between the risk genotype, direction of effect on *CACNA1C* mRNA expression and psychiatric phenotype (Gershon et al. 2014; Harrison 2016). For instance, embryonic deletion of *Cacna1c* in forebrain glutamatergic neurons is associated with an anxiety-like phenotype in mice, whilst inactivation during adulthood is associated with an opposite, potentially cognitively beneficial, effect (Dedic et al. 2018). More broadly, VGCCs are critically involved in neuronal development and network connectivity during development and adulthood (Kamijo et al. 2018). The spatiotemporally dependent effects of VGCCs on psychiatric phenotypes highlight the neurodevelopmental nature of these conditions (Morris-Rosendahl and Crocq 2020).

4.4.4$\alpha_2\delta$-1 and excitatory synaptogenesis

As previously mentioned, the $\alpha_2\delta$-1 protein promotes excitatory synapse formation (Eroglu et al. 2009). This effect is prominent in later development, and increased $\alpha_2\delta$-1 correlates with enhanced glutamatergic neurotransmission (Bikbaev et al. 2020). Conversely, loss of $\alpha_2\delta$-1 causes profound deficits in the number, structure and activity of excitatory synapses in the mouse cortex (Risher et al. 2018). In addition to promoting glutamatergic synaptogenesis, presynaptic $\alpha_2\delta$ subunits regulate the alignment of presynaptic active zones with the postsynaptic density (Schöpf et al. 2021). The $\alpha_2\delta$ subunits are therefore critical for both the formation of and signaling across excitatory networks. Interestingly, BDNF deficiency has been shown to reduce cell surface expression of $\alpha_2\delta$-1 and excitatory drive in the mouse ventromedial hypothalamus, a region associated with satiety, leading to hyperphagia, weight gain and metabolic disturbances (Cordeira et al. 2014). Given the critical role of $\alpha_2\delta$ subunits in excitatory synapse formation, altered levels of relative expression of $\alpha_2\delta$ isoforms during critical neurodevelopmental periods may impact excitatory-inhibitory (E-I) balance in neuronal networks. E-I imbalance in various neural circuits is associated with multiple psychiatric disorders including autism (Lee, Lee, and Kim 2017), schizophrenia (Kehrer et al. 2008) and BD (Lee et al. 2018).

4.4.5Direction of modulation of voltage-gated calcium channels

The desired nature and direction of manipulation required for therapeutic benefit remains to be determined. Whilst the existing VGCC data are based on antagonism

[25, 61], alternative, more nuanced and spatiotemporally precise approaches are likely to be important.

Structural changes caused by alternative splicing generates functionally distinct neuronal VGCCs in terms of voltage-gating properties, density and coupling with downstream signalling pathways (Gray, Raingo, and Lipscombe 2007). The multiple isoforms encoded by VGCC genes (Clark et al. 2020) affect pharmacologically relevant properties, including sensitivity to the existing channel blockers (Hofmann et al. 2014) and are differentially expressed between tissues (Striessnig et al. 2014). Alternatively spliced variants of $Ca_v2.1$, which underlie much of fast synaptic transmission in the CNS, have differential effects on neurotransmitter release and synaptic plasticity (Thalhammer et al. 2017). Furthermore, the presynaptic balance of $Ca_v2.1$ splice variants is homeostatically regulated to maintain normal network function by controlling synaptic efficacy (Thalhammer et al. 2017). Alternative splicing of *Cacna1b* ($Ca_v2.2$) pre-mRNA alters neurotransmitter release probability, e.g. glutamatergic medial perforant path-dentate gyrus synapses, and is associated with differential behavioural responses of mice in aversive environments (Bunda et al. 2019).

The impact of rare mutations also hints at the need to modulate, rather than simply block, VGCC function in psychiatric disorders. In the case of *CACNA1C*, for example, gain-of-function mutations cause Timothy Syndrome, in which autism is a cardinal feature (Splawski et al. 2004), but autism has also been reported as a feature with loss-of-function mutations (Endres et al. 2020). The latter findings are consistent with

the presence of psychiatry-relevant phenotypes in *Cacna1c* heterozygous rats (Moon et al. 2018), which have reduced gene dosage. Taken together, these findings highlight the need for therapeutic agents that are capable of fine-tuning function, perhaps by targeting specific isoforms, or acting homeostatically, in order to maximise clinical benefit and minimise side effects.

4.4.6$\alpha_2\delta$ subunits: targets for nuanced modulation

Targetting the $\alpha_2\delta$ subunits, as the gabapentinoids do, provides a potential means to achieve nuanced modulation of VGCC function. $\alpha_2\delta$ subunits increase the density of VGCCs on the plasma membrane, direct trafficking of these channels to subcellular sites, and enhance function by altering their biophysical properties (Dolphin 2016). Conversely, gabapentin decreases the number of $\alpha_2\delta$ and α-1 subunits on the cell surface (Tran-Van-Minh and Dolphin 2010) and reduces VGCC currents (Martin et al. 2002), suggesting an inhibitory role. The precise effect of gabapentin on calcium currents depends on the stoichiometry of VGCC auxiliary subunits (Martin et al. 2002) which, like the other VGCC subunits, differ in abundance between tissues, raising the possibility that gabapentinoids may differentially affect VGCC currents in different cell types. Furthermore, it is possible that the gabapentinoids' effects on anxiety are mediated by $\alpha_2\delta$-dependent, but VGCC-independent, mechanisms (Dolphin 2018b). Notably, $\alpha_2\delta$-1 promotes dendritic spine maturation by interacting with NMDA receptors (NMDARs) and promoting NMDAR trafficking to synaptic sites (Chen et al. 2018). Thus, as well as clarifying the clinical effects of the gabapentinoids, it will be of interest to establish the molecular mechanisms that underlie their psychiatric effects to illuminate pathophysiology and identify novel

therapeutic strategies. Ultimately, a personalised medicine approach may well be appropriate (Tomlinson et al. 2020), given the genomic and other contributions to VGCC function and involvement in psychiatric disorders (Rees and Owen 2020).

4.4.7Future directions for clinical research: targeted treatment of anxiety in bipolar disorder

Gabapentinoids, as shown here, are broadly efficacious across the anxiety spectrum, and it is likely that this reflects a pharmacologic effect on transdiagnostic anxiety phenotypes mediated by $\alpha_2\delta$-dependent mechanisms. Anxiety is the most common co-morbidity in patients with BD (Spoorthy, Chakrabarti, and Grover 2019), reflecting in part a dual genetic burden (Lopes et al. 2020). Comorbid anxiety may drive mood instability via an amplifying effect of anxiety-associated mental imagery in patients with BD (Holmes et al. 2008). It is also associated with greater symptom burden, rapid mood cycles, increased suicidality and worse treatment response (Goodwin et al. 2016; Pavlova et al. 2015). However, there are to date no clinical trials investigating the efficacy of gabapentinoids in the treatment of anxiety in BD. Antidepressants may be used in bipolar anxiety but there is a risk of mood destabilisation and antidepressant-induced mania (Goodwin et al. 2016). An advantage of gabapentinoids would be its distinct $\alpha_2\delta$-mechanism of action which has not been shown to be associated with an increased risk of mania (Goodwin et al. 2016). Therefore, a future area of research would be to explore the targeted treatment of ‘bipolar anxiety’ using gabapentinoids or modified $\alpha_2\delta$ ligands.

Chapter 5: Conclusion

5.1 Concluding remarks

The aim of this thesis was to comprehensively assess the efficacy, acceptability and tolerability of gabapentin and pregabalin in BD, anxiety disorders/states and insomnia. The results of the systematic review and meta-analysis show that the widespread and often off-label psychiatric prescribing of gabapentinoids is not supported by robust evidence except for some anxiety disorders/states. Thus, despite the attractive genetic and pharmacological rationale for their use, caution is indicated, and further evidence of efficacy and safety is required. It may also be possible to develop modified $\alpha_2\delta$ ligands, targeting particular subtypes or isoforms, with a more beneficial therapeutic profile. A future direction for clinical research would be to explore the targeted treatment of comorbid anxiety – a highly prevalent and under-treated condition in BD – using gabapentinoids or modified $\alpha_2\delta$ ligands.

5.2 Dissemination

Aspects of this work have been modified and included in a manuscript under review with *Molecular Psychiatry* at the time of thesis completion. A statement of authorship has been included in the manuscript submission.

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Appendix

Reference list of included studies

DB-RCT (k = 55)

Bipolar disorder

Frye 2000 (NCT00001482)

Frye MA, Ketter TA, Kimbrell TA, Dunn RT, Speer AM, Osuch EA et al. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. *J Clin Psychopharmacol* 2000; 20(6): 607-14. doi: 10.1097/00004714-200012000-00004.

Mokhber 2008

Mokhber N, Lane CJ, Azarpazhooh MR, Salari E, Fayazi R, Shakeri MT et al. Anticonvulsant treatments of dysphoric mania: a trial of gabapentin, lamotrigine and carbamazepine in Iran. *Neuropsychiatr Dis Treat* 2008; 4(1): 227-34. doi: 10.2147/ndt.s2316.

Pande 2000a (945-209)

Pande AC, Crockatt JG, Janney CA, Werth JL, Tsaroucha G. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Gabapentin Bipolar Disorder Study Group. *Bipolar Disord* 2000; 2(3 Pt 2): 249-55. doi: 10.1034/j.1399-5618.2000.20305.x.

Vieta 2006 (945-291)

Vieta E, Manuel Goikolea J, Martínez-Arán A, Comes M, Verger K, Masramon X et al. A double-blind, randomized, placebo-controlled, prophylaxis study of adjunctive gabapentin for bipolar disorder. *J Clin Psychiatry* 2006; 67(3): 473-7. doi: 10.4088/jcp.v67n0320.

Pre-operative studies

Abdel-Halim 2009

Abdel-Halim JMK, ElAwady GA, ElShaikh SM, Azer MS. Gabapentin and dexamethasone as adjuvants for intraoperative and postoperative pain management. *Eg J Anaesth* 2009; 25(4): 347-354.

Adam 2012

Adam F, Bordenave L, Sessler DI, Chauvin M. Effects of a single 1200-mg preoperative dose of gabapentin on anxiety and memory. *Ann Fr Anesth Reanim* 2012; 31(10): e223-7. doi: 10.1016/j.annfar.2012.05.006.

Bakry 2012

Bakry AEAE, Marey H. The effect of gabapentin premedication on pain and anxiety during cataract surgery under peribulbar block. *Egyptian Journal of Anaesthesia* 2012; 28(1): 13-47. doi: 10.1016/j.egja.2011.10.001.

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Clarke H, Kay J, Orser BA, Gollish J, Mitsakakis N, Katz J. Gabapentin does not reduce preoperative anxiety when given prior to total hip arthroplasty. *Pain Med* 2010; 11(6): 966-71. doi: 10.1111/j.1526-4637.2010.00826.x.

Clarke 2013

Clarke H, Kirkham KR, Orser BA, Katznelson R, Mitsakakis N, Ko R et al. Gabapentin reduces preoperative anxiety and pain catastrophizing in highly anxious patients prior to major surgery: a blinded randomized placebo-controlled trial. *Can J Anaesth* 2013; 60(5): 432-43. doi: 10.1007/s12630-013-9890-1.

Ghai 2012

Ghai A, Gupta M, Rana N, Wadhera R. The effect of pregabalin and gabapentin on preoperative anxiety and sedation: a double blind study. *Anaesth Pain & Intensive Care* 2012; 16(3): 257-261.

Gonano 2011

Gonano C, Latzke D, Sabeti-Aschraf M, Kettner SC, Chiari A, Gustorff. The anxiolytic effect of pregabalin in outpatients undergoing minor orthopaedic surgery. *J Psychopharmacol* 2011; 25(2): 249-253. doi: 10.1177/0269881109106928.

Hoseini 2015 (IRCT2014041217231N1)

Hoseini VS, Yekta RA, Marashi S, Marashi SM. The efficacy of melatonin, clonidine and gabapentin in reducing preoperative anxiety and postoperative pain in patients undergoing laparoscopic cholecystectomy: a randomized clinical trial. *Arch Anesth & Critical Care* 2015; 1(4): 120-125.

Joseph 2014 (CTRI/2010/091/002830)

Joseph TT, Krishna HM, Kamath S. Premedication with gabapentin, alprazolam or a placebo for abdominal hysterectomy: Effect on pre-operative anxiety, post-operative pain and morphine consumption. *Indian J Anaesth* 2014; 58(6): 693-9. doi: 10.4103/0019-5049.147134.

Khezri 2013 (ACTRN12610000727044, NCT01200641)

Khezri MB, Oladi MR, Atlasbaf A. Effect of melatonin and gabapentin on anxiety and pain associated with retrobulbar eye block for cataract surgery: a randomized double-blind study. *Indian J Pharmacol*. 2013; 45(6): 581-6. doi: 10.4103/0253-7613.121368.

Menigaux 2005

Ménigaux C, Adam F, Guignard B, Sessler DI, Chauvin M. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. *Anesth Analg* 2005; 100(5): 1394-9. doi: 10.1213/01.ANE.0000152010.74739.B8.

Moreau-Bussière 2013 (NCT01158859)

Moreau-Bussière F, Gaulin J, Gagnon V, Sansoucy Y, de Médicis E. Preoperative pregabalin does not reduce propofol ED(50): a randomized controlled trial. *Can J Anaesth* 2013; 60(4): 364-9. doi: 10.1007/s12630-013-9885-y.

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Nasr DA, Abdellatif AA. Efficacy of preoperative melatonin versus pregabalin on perioperative anxiety and postoperative pain in gynecological surgeries. *Egypt J Anaesth* 2014; 30(1): 89-93.

NCT00468845

NCT00468845. Study of the efficacy and safety of pregabalin compared to placebo for treatment of post-surgical pain from hysterectomy. https://clinicaltrials.gov/ct2/show/NCT00468845 (first received 3 May 2007).

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Nutt 2009

Nutt D, Mandel F, Baldinetti F. Early onset anxiolytic efficacy after a single dose of pregabalin: double-blind, placebo- and active-comparator controlled evaluation using a dental anxiety model. *J Psychopharmacol* 2009; 23(8): 867-73. doi: 10.1177/0269881108094722.

Pathak 2014

Pathak L, Chaturvedi A. Effect of gabapentin premedication on preoperative anxiety and postoperative pain. *Health Renaissance* 2014; 11(3): 254-259. https://doi.org/10.3126/hren.v11i3.9642

Rorarius 2004

Rorarius MG, Mennander S, Suominen P, Rintala S, Puura A, Pirhonen R et al. Gabapentin for the prevention of postoperative pain after vaginal hysterectomy. *Pain* 2004; 110(1-2): 175-81. doi: 10.1016/j.pain.2004.03.023.

Sava 2009

Sava M, Rusu N. Effects of gabapentin on preoperative anxiety and postoperative analgesia with morphine in rectocolic surgery. *Jurnalul Roman de Anestezie Terapie Intensiva/Romanian Journal of Anaesthesia and Intensive Care* 2009; 16(1): 10-16.

Shimony 2016 (NCT01612832)

Shimony N, Amit U, Minz B, Grossman R, Dany MA, Gonen L et al. Perioperative pregabalin for reducing pain, analgesic consumption, and anxiety and enhancing sleep quality in elective neurosurgical patients: a prospective, randomized, double-blind, and controlled clinical study. *J Neurosurg* 2016; 125(6): 1513-1522. doi: 10.3171/2015.10.JNS151516.

Singh 2019

Singh D, Yadav JS, Jamuda BK, Singh P. Oral Pregabalin as Premedication on Anxiolysis and Stress Response to Laryngoscopy and Endotracheal Intubation in Patients Undergoing Laparoscopic Cholecystectomy: A Randomized Double-Blind Study. *Anesth Essays Res* 2019; 13(1): 97-104. doi: 10.4103/aer.AER_12_19.

Spreng 2011 (NCT00353704)

Spreng UJ, Dahl V, Raeder J. Effect of a single dose of pregabalin on post-operative pain and pre-operative anxiety in patients undergoing discectomy. *Acta Anaesthesiol Scand* 2011; 55(5): 571-6. doi: 10.1111/j.1399-6576.2011.02410.x.

Tirault 2010

Tirault M, Foucan L, Debaene B, Frasca D, Lebrun T, Bernard JC et al. Gabapentin premedication: assessment of preoperative anxiolysis and postoperative patient satisfaction. *Acta Anaesthesiol Belg* 2010; 61(4): 203-9.

White 2009

White PF, Tufanogullari B, Taylor J, Klein K. The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. *Anesth Analg* 2009; 108(4): 1140-5. doi: 10.1213/ane.0b013e31818d40ce.

Generalised anxiety disorder (GAD)

Feltner 2003

Feltner DE, Crockatt JG, Dubovsky SJ, Cohn CK, Shrivastava RK, Targum SD et al. A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. *J Clin Psychopharmacol* 2003; 23(3): 240-9. doi: 10.1097/01.jcp.0000084032.22282.ff.

Feltner 2008

Feltner D, Wittchen HU, Kavoussi R, Brock J, Baldinetti F, Pande AC. Long-term efficacy of pregabalin in generalized anxiety disorder. *Int Clin Psychopharmacol* 2008; 23(1): 18-28. doi: 10.1097/YIC.0b013e3282f0f0d7.

Hadley 2012 (NCT00368745, 2006-001347-66)

Hadley SJ, Mandel FS, Schweizer E. Switching from long-term benzodiazepine therapy to pregabalin in patients with generalized anxiety disorder: a double-blind, placebo-controlled trial. *J Psychopharmacol* 2012; 26(4): 461-70. doi: 10.1177/0269881111405360.

Kasper 2009 (NCT00151450, EUCTR2004-001500-13-IE)

Kasper S, Herman B, Nivoli G, Van Ameringen M, Petralia A, Mandel FS et al. Efficacy of pregabalin and venlafaxine-XR in generalized anxiety disorder: results of a double-blind, placebo-controlled 8-week trial. *Int Clin Psychopharmacol* 2009; 24(2): 87-96. doi: 10.1097/yic.0b013e32831d7980.

Kasper 2014 (NCT00624780, EUCTR2007-004768-32-ES)

Kasper S, Iglesias-García C, Schweizer E, Wilson J, DuBrava S, Prieto R et al. Pregabalin long-term treatment and assessment of discontinuation in patients with generalized anxiety disorder. *Int J Neuropsychopharmacol* 2014; 17(5): 685-95. doi: 10.1017/S1461145713001557.

Montgomery 2006

Montgomery SA, Tobias K, Zornberg GL, Kasper S, Pande AC. Efficacy and safety of pregabalin in the treatment of generalized anxiety disorder: a 6-week, multicenter, randomized, double-blind, placebo-controlled comparison of pregabalin and venlafaxine. *J Clin Psychiatry* 2006; 67(5): 771-82. doi: 10.4088/jcp.v67n0511.

Montgomery 2008 (EUCTR2004-000955-40-LV)

Montgomery S, Chatamra K, Pauer L, Whalen E, Baldinetti F. Efficacy and safety of pregabalin in elderly people with generalised anxiety disorder. *Br J Psychiatry* 2008; 193(5): 389-94. doi: 10.1192/bjp.bp.107.037788.

Pande 2003

Pande AC, Crockatt JG, Feltner DE, Janney CA, Smith WT, Weisler R et al. Pregabalin in generalized anxiety disorder: a placebo-controlled trial. *Am J Psychiatry* 2003; 160(3): 533-40. doi: 10.1176/appi.ajp.160.3.533.

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Pohl RB, Feltner DE, Fieve RR, Pande AC. Efficacy of pregabalin in the treatment of generalized anxiety disorder: double-blind, placebo-controlled

comparison of BID versus TID dosing. *J Clin Psychopharmacol* 2005; 25(2): 151-8. doi: 10.1097/01.jcp.0000155820.74832.b0.

Rickels 2005

Rickels K, Pollack MH, Feltner DE, Lydiard RB, Zimbroff DL, Bielski RJ et al. Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. *Arch Gen Psychiatry* 2005; 62(9): 1022-30. doi: 10.1001/archpsyc.62.9.1022.

Rickels 2012 (NCT00413010, EUCTR2006-006339-31-FI)

Rickels K, Shiovitz TM, Ramey TS, Weaver JJ, Knapp LE, Miceli JJ. Adjunctive therapy with pregabalin in generalized anxiety disorder patients with partial response to SSRI or SNRI treatment. *Int Clin Psychopharmacol* 2012; 27(3): 142-50. doi: 10.1097/YIC.0b013e328350b133.

Social anxiety disorder/Social phobia

Feltner 2011

Feltner DE, Liu-Dumaw M, Schweizer E, Bielski R. Efficacy of pregabalin in generalized social anxiety disorder: results of a double-blind, placebo-controlled, fixed-dose study. *Int Clin Psychopharmacol* 2011; 26(4): 213-20. doi: 10.1097/YIC.0b013e32834519bd.

Greist 2011

Greist JH, Liu-Dumaw M, Schweizer E, Feltner D. Efficacy of pregabalin in preventing relapse in patients with generalized social anxiety disorder: results of a double-blind, placebo-controlled 26-week study. *Int Clin Psychopharmacol* 2011; 26(5): 243-51. doi: 10.1097/YIC.0b013e3283491fd5.

Pande 1999

Pande AC, Davidson JR, Jefferson JW, Janney CA, Katzelnick DJ, Weisler RH et al. Treatment of social phobia with gabapentin: a placebo-controlled study. *J Clin Psychopharmacol* 1999; 19(4): 341-8. doi: 10.1097/00004714-199908000-00010.

Pande 2004

Pande AC, Feltner DE, Jefferson JW, Davidson JR, Pollack M, Stein MB et al. Efficacy of the novel anxiolytic pregabalin in social anxiety disorder: a placebo-controlled, multicenter study. *J Clin Psychopharmacol* 2004; 24(2): 141-9. doi: 10.1097/01.jcp.0000117423.05703.e7.

Panic disorder

Pande 2000b

Pande AC, Pollack MH, Crockatt J, Greiner M, Chouinard G, Lydiard RB et al. Placebo-controlled study of gabapentin treatment of panic disorder. *J Clin Psychopharmacol* 2000; 20(4): 467-71. doi: 10.1097/00004714-200008000-00011.

PTSD

Baniasadi 2014

Baniasadi M, Hosseini G, Fayyazi Bordbar MR, Rezaei Ardani A, Mostafavi Toroghi H. Effect of pregabalin augmentation in treatment of patients with combat-related chronic posttraumatic stress disorder: a randomized controlled trial. J *Psychiatr Pract* 2014; 20(6): 419-27. doi: 10.1097/01.pra.0000456590.12998.41.

OCD

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Bollu 2010

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Furey SA, Hull SG, Leibowitz MT, Jayawardena S, Roth T. A randomized, double-blind, placebo-controlled, multicenter, 28-day, polysomnographic study of gabapentin in transient insomnia induced by sleep phase advance. *J Clin Sleep Med* 2014; 10(10): 1101-9. doi: 10.5664/jcsm.4110.

Malcolm 2007

Malcolm R, Myrick LH, Veatch LM, Boyle E, Randall PK. Self-reported sleep, sleepiness, and repeated alcohol withdrawals: a randomized, double blind, controlled comparison of lorazepam vs gabapentin. *J Clin Sleep Med* 2007; 3(1):24-32.

Mason 2014

Mason BJ, Quello S, Goodell V, Shadan F, Kyle M, Begovic A. Gabapentin treatment for alcohol dependence: a randomized clinical trial. *JAMA Intern Med* 2014; 174(1): 70-7. doi: 10.1001/jamainternmed.2013.11950.

Mowla 2015

Mowla A, Ahmadzadeh L, Razeghian Jahromi L, Dastgheib SA. Comparing Gabapentin with Clonazepam for Residual Sleeping Problems following Antidepressant Therapy in Patients with Major Depressive Disorder: A Randomized Clinical Trial. *Clin Drug Investig* 2015; 35(8): 513-7. doi: 10.1007/s40261-015-0304-8.

NCT01014533

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Rosenberg RP, Hull SG, Lankford DA, Mayleben DW, Seiden DJ, Furey SA et al. A randomized, double-blind, single-dose, placebo-controlled, multicenter, polysomnographic study of gabapentin in transient insomnia induced by sleep phase advance. *J Clin Sleep Med* 2014; 10(10): 1093-100. doi: 10.5664/jcsm.4108.

Yurcheshen 2009

Yurcheshen ME, Guttuso T Jr, McDermott M, Holloway RG, Perlis M. Effects of gabapentin on sleep in menopausal women with hot flashes as measured by a Pittsburgh Sleep Quality Index factor scoring model. *J Womens Health (Larchmt)* 2009; 18(9): 1355-60. doi: 10.1089/jwh.2008.1257.

Open label studies (k = 15)

Bipolar disorder

Altshuler 1999

Altshuler LL, Keck PE, McElroy SL, Suppes T, Brown ES, Denicoff K et al. Gabapentin in the acute treatment of refractory bipolar disorder. *Bipolar Disord* 1999; 1: 61-65. doi:10.1034/j.1399-5618.1999.10113.x.

Astaneh 2012

Astaneh AN, Rezaei O. Adjunctive treatment with gabapentin in bipolar patients during acute mania. *Int J Psychiatry Med* 2012; 43(3): 261-271. https://doi.org/10.2190/PM.43.3.e.

Erfurth 1998

Erfurth A, Kammerer C, Grunze H, Normann C, Walden J. An open label study of gabapentin in the treatment of acute mania. *J Psychiatr Res* 1998; 32(5): 261-264. https://doi.org/10.1016/S0022-3956(98)00010-7.

Knoll 1998

Knoll J, Stegman K, Suppes T. Clinical experience using gabapentin adjunctively in patients with a history of mania or hypomania. *J Affect Disord* 1998; 49(3): 229-233. https://doi.org/10.1016/S0165-0327(98)00027-5.

Mauri 2001

Mauri MC, Laini V, Scalvini ME, Omboni A, Ferrari VMS, Clemente A, et al. Gabapentin and the prophylaxis of bipolar disorders in patients intolerant to lithium. *Clin Drug Investig* 2001; 21(3): 169-174. https://doi.org/10.2165/00044011-200121030-00002.

McElroy 1997

McElroy SL, Soutullo CA, Keck PE, Kmetz GF. A pilot trial of adjunctive gabapentin in the treatment of bipolar disorder. *Ann Clin Psychiatry* 1997; 9: 99-103. https://doi.org/10.1023/A:1026257303275.

Perugi 1999

Perugi G, Toni C, Ruffolo G, Sartini S, Simonini E, Akiskal H. Clinical experience using adjunctive gabapentin in treatment-resistant bipolar mixed states. *Pharmacopsychiatry* 1999; 32(4): 136-141. https://doi.org/10.1055/s-2007-979219.

Schaffer 2012

Schaffer LC, Schaffer CB, Miller AR, Manley JL, Piekut JA, Nordahl TE. An open trial of pregabalin as an acute and maintenance adjunctive treatment for outpatients with treatment resistant bipolar disorder. *J Affect Disord* 2013; 147: 407-410. https://doi.org/10.1016/j.jad.2012.09.005.

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Wang PW, Santosa C, Schumacher M, Winsberg ME, Strong C, Ketter TA. Gabapentin augmentation therapy in bipolar depression. *Bipolar Disord* 2002; 4: 296–301. https://doi.org/10.1034/j.1399-5618.2002.01211.x.

Young 1997

Young LT, Robb JC, Patelis-Siotis I, MacDonald C, Joffe RT. Acute treatment of bipolar depression with gabapentin. Biol Psychiatry 1997; 42(9): 851-853. https://doi.org/10.1016/S0006-3223(97)00305-3.

Young 1999

Young LT, Robb JC, Hasey GM, MacQueen GM, Siotis IP, Marriott M, et al. Gabapentin as an adjunctive treatment in bipolar disorder. *J Affect Disord* 1999; 55(1): 73-77. https://doi.org/10.1016/S0165-0327(98)00192-X.

Generalised anxiety disorder (GAD)

Cvjetkovic-Bosnjak 2015

Cvjetkovic-Bosnjak M, Soldatovic-Stajic B, Babovic SS, Boskovic K, Jovicevic M. Pregabalin versus sertraline in generalized anxiety disorder. An open label study. *Eur Rev Med Pharmacol Sci* 2015; 19(11): 2120–2124.

Generalised anxiety disorder, social anxiety disorder and panic disorder

Montgomery 2013

Montgomery S, Emir B, Haswell H, Prieto R. Long-term treatment of anxiety disorders with pregabalin: A 1 year open-label study of safety and tolerability. *Curr Med Res Opin* 2013; 29(10): 1223-1230. https://doi.org/10.1185/03007995.2013.820694.

OCD

Oulis 2011

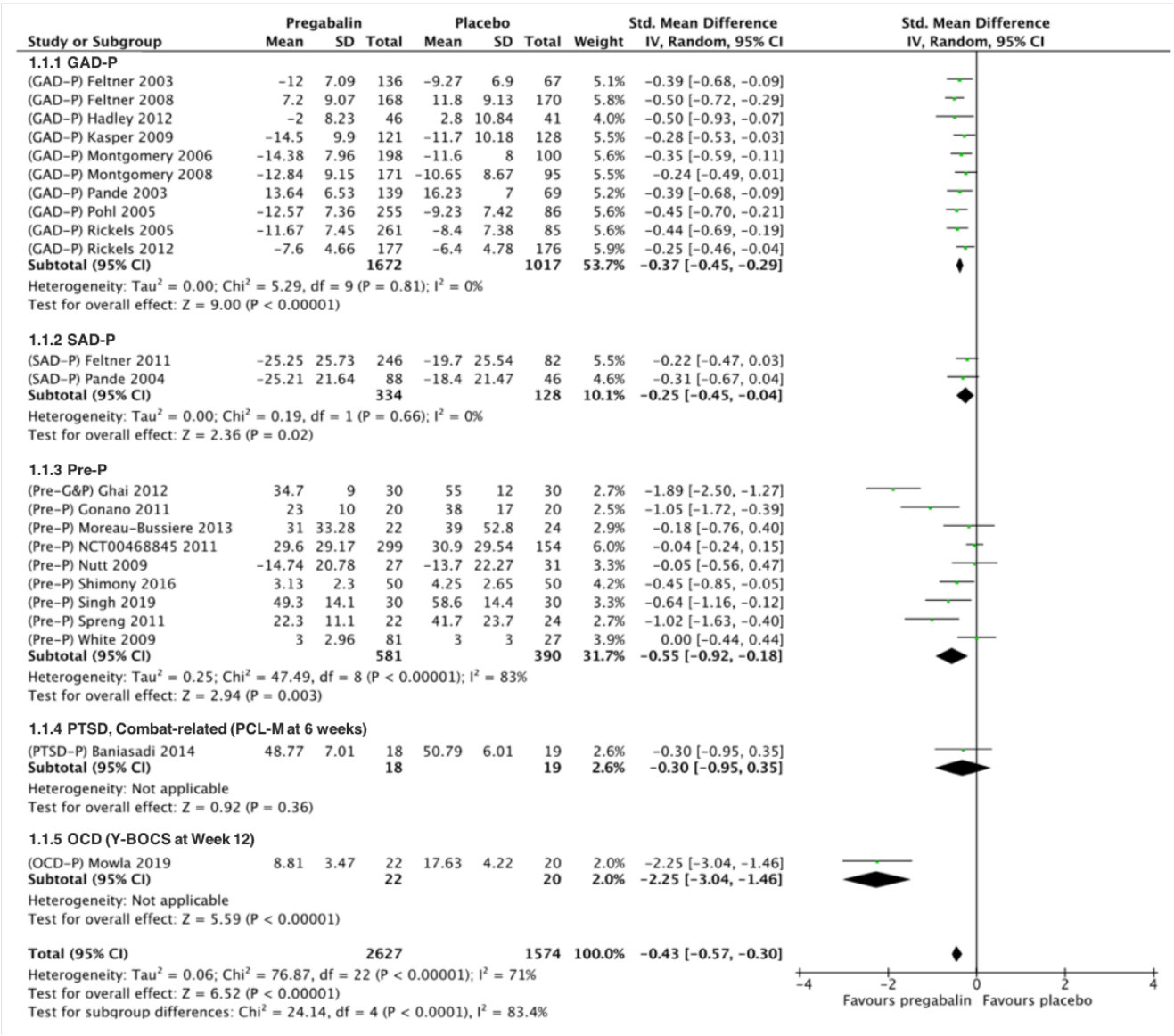
Oulis P, Mourikis I, Konstantakopoulos G. Pregabalin augmentation in treatment-resistant obsessive-compulsive disorder. *Int Clin Psychopharmacol* 2011; 26(4): 221-224. https://doi.org/10.1097/YIC.0b013e3283466657.

Insomnia

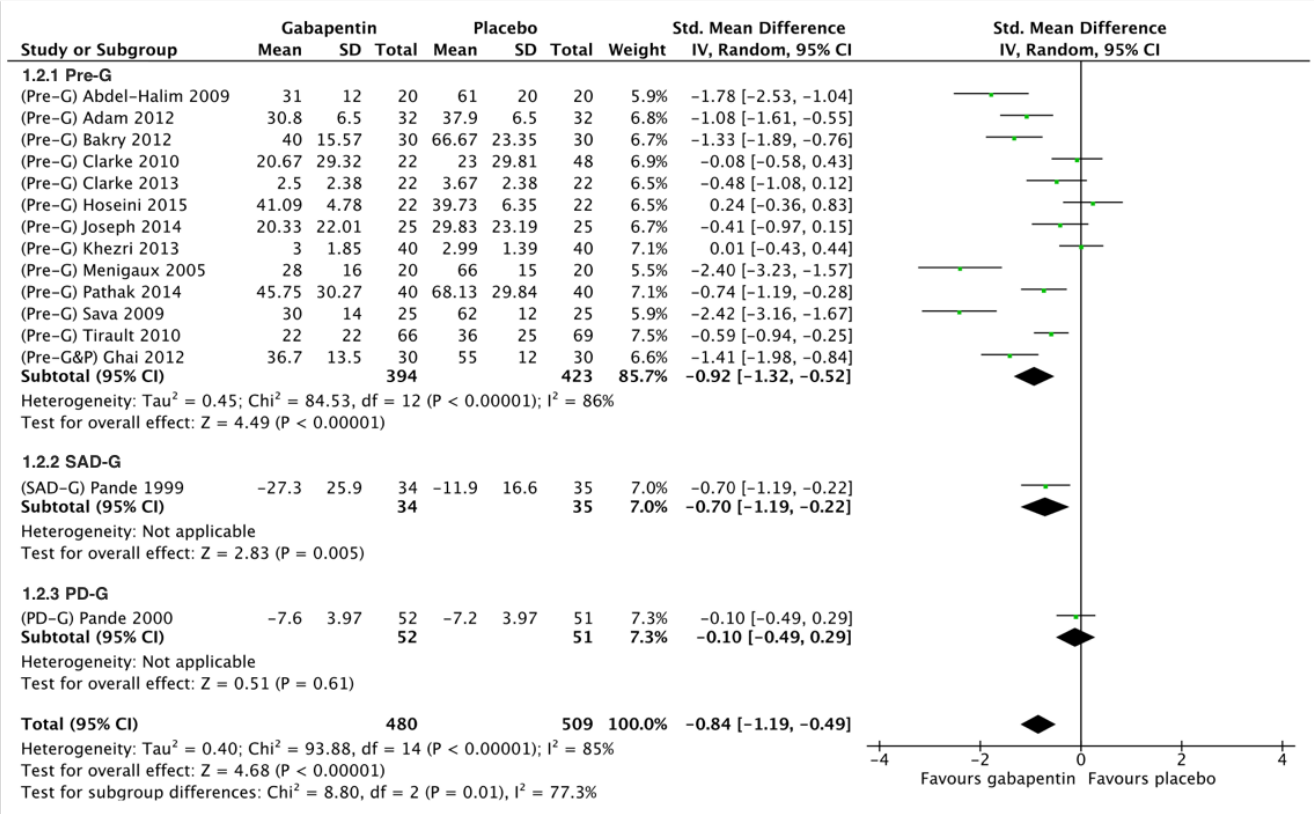
NCT02040532

NCT02040532. Gabapentin for Insomnia Symptoms and Nighttime Vasomotor Symptoms (VMS) in Peri- and Postmenopausal Women. https://clinicaltrials.gov/ct2/show/NCT02040532 (first received 20 January 2014).

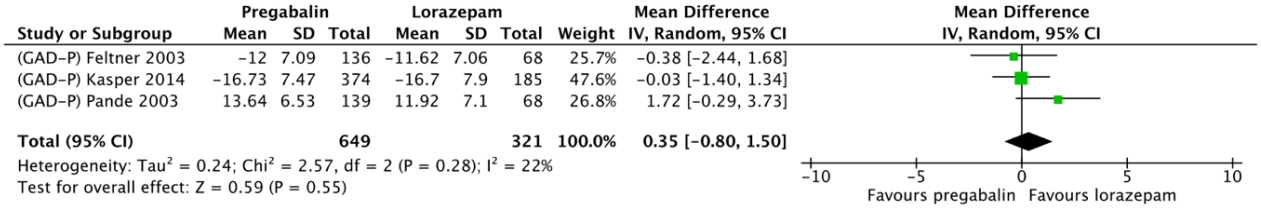
Figures



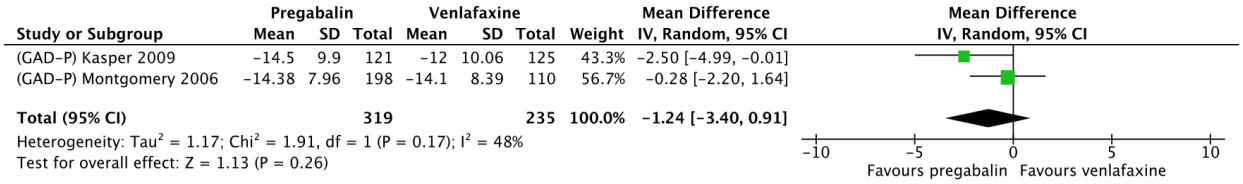
Appendix Figure 1. Forest plots of efficacy of pregabalin versus placebo in anxiety studies (GAD, generalised anxiety disorder; SAD, social anxiety disorder; preooperative anxiety; PTSD, posttraumatic stress disorder; OCD, obsessive compulsive disorder). *CI, confidence interval; IV, inverse variance; SD, standard deviation.*



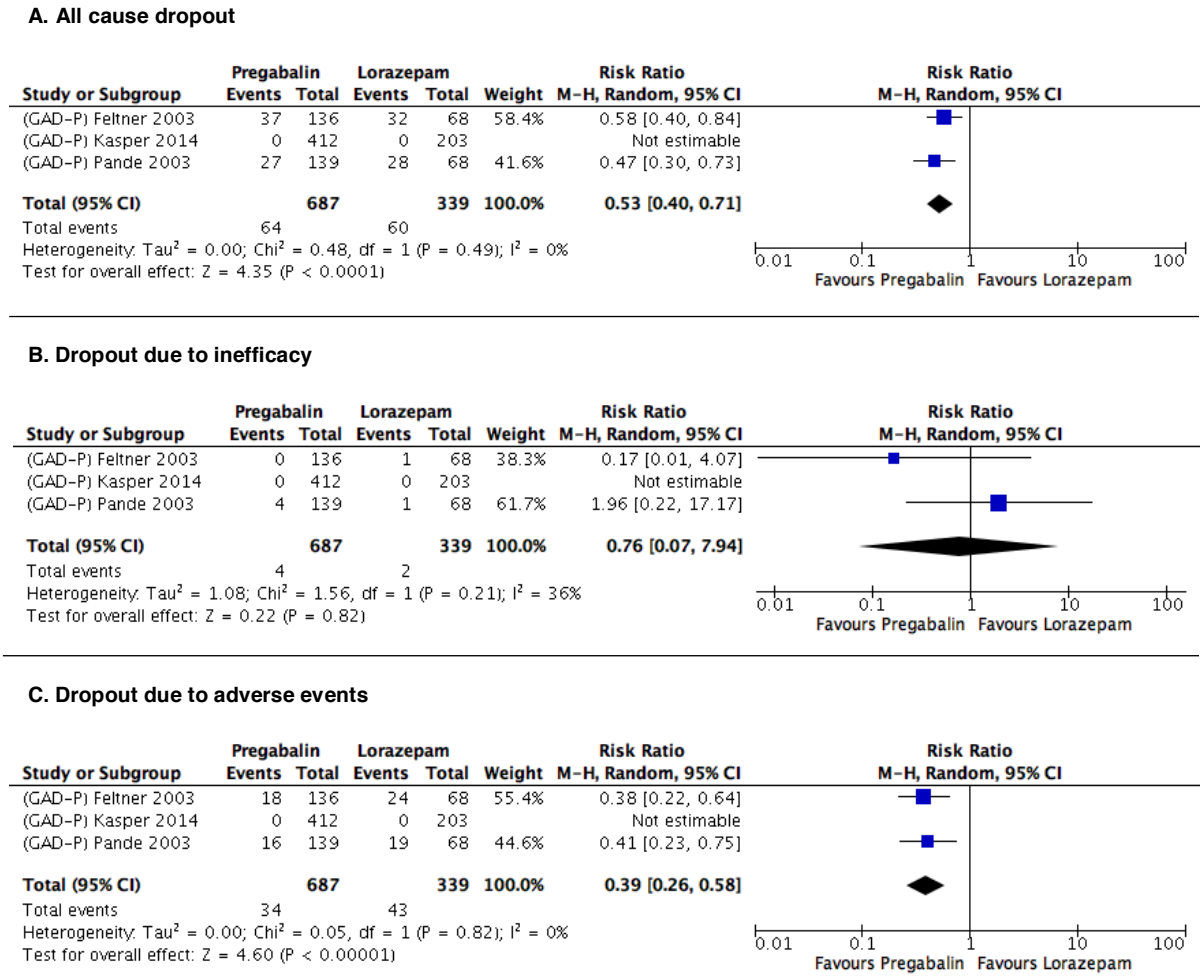
Appendix Figure 2. Forest plots of efficacy of gabapentin versus placebo in anxiety studies (Preoperative anxiety; SAD, social anxiety disorder; PD, panic disorder). *CI, confidence interval; IV, inverse variance; SD, standard deviation.*



Appendix Figure 3. Forest plot of efficacy of pregabalin versus lorazepam in GAD based on mean difference in in HAM-A. *CI, confidence interval; IV, inverse variance; SD, standard deviation; GAD, generalised anxiety disorder, HAM-A, Hamilton anxiety scale.*



Appendix Figure 4. Forest plot of efficacy of pregabalin versus venlafaxine in GAD based on mean difference in in HAM-A. *CI, confidence interval; IV, inverse variance; SD, standard deviation; GAD, generalised anxiety disorder, HAM-A, Hamilton anxiety scale.*

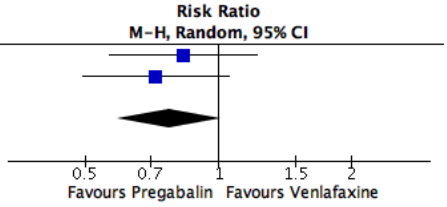


Appendix Figure 5. Forest plot of acceptability (dropouts) of pregabalin versus lorazepam in GAD. *CI, confidence interval; M-H, Mantel-Haenszel method; SD, standard deviation; GAD, generalised anxiety disorder.*

A. All cause dropout

Study or Subgroup	Pregabalin Events	Total	Venlafaxine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
(GAD-P) Kasper 2009	33	121	41	125	49.7%	0.83 [0.57, 1.22]
(GAD-P) Montgomery 2006	45	207	34	113	50.3%	0.72 [0.49, 1.06]
Total (95% CI)		**328**		**238**	**100.0%**	**0.77 [0.59, 1.02]**
Total events	78		75			

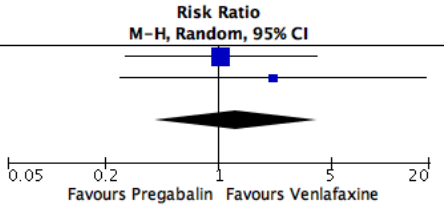
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.85 (P = 0.06)



B. Dropout due to inefficacy

Study or Subgroup	Pregabalin Events	Total	Venlafaxine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
(GAD-P) Kasper 2009	4	121	4	125	71.9%	1.03 [0.26, 4.04]
(GAD-P) Montgomery 2006	4	207	1	113	28.1%	2.18 [0.25, 19.30]
Total (95% CI)		**328**		**238**	**100.0%**	**1.28 [0.40, 4.05]**
Total events	8		5			

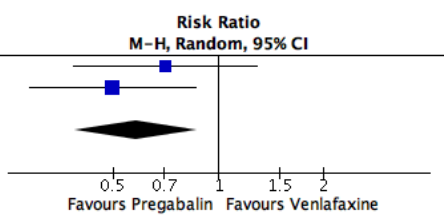
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.41 (P = 0.68)



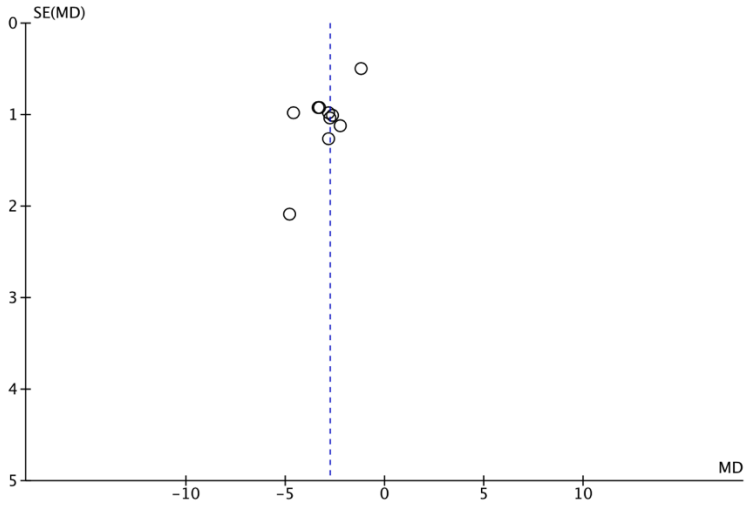
C. Dropout due to adverse events

Study or Subgroup	Pregabalin Events	Total	Venlafaxine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
(GAD-P) Kasper 2009	15	121	22	125	44.7%	0.70 [0.38, 1.29]
(GAD-P) Montgomery 2006	21	207	23	113	55.3%	0.50 [0.29, 0.86]
Total (95% CI)		**328**		**238**	**100.0%**	**0.58 [0.39, 0.87]**
Total events	36		45			

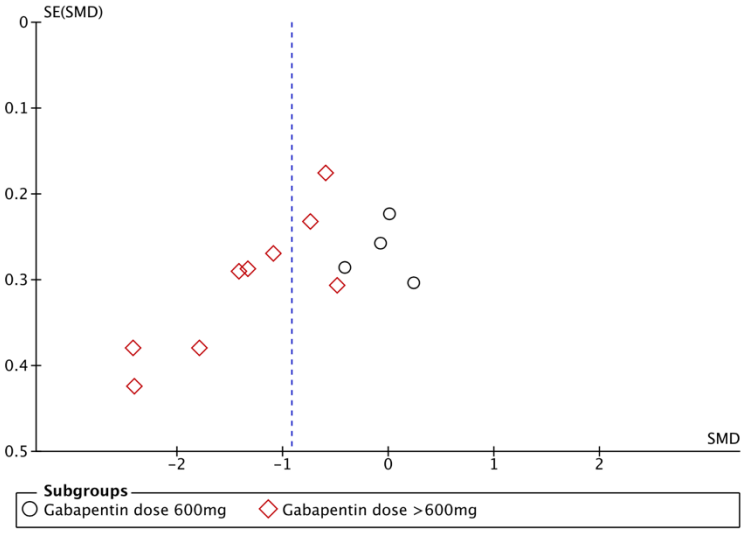
Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 2.62 (P = 0.009)



Appendix Figure 6. Forest plot of acceptability (dropouts) of pregabalin versus venlafaxine in GAD. *CI, confidence interval; M-H, Mantel-Haenszel method; SD, standard deviation; GAD, generalised anxiety disorder.*

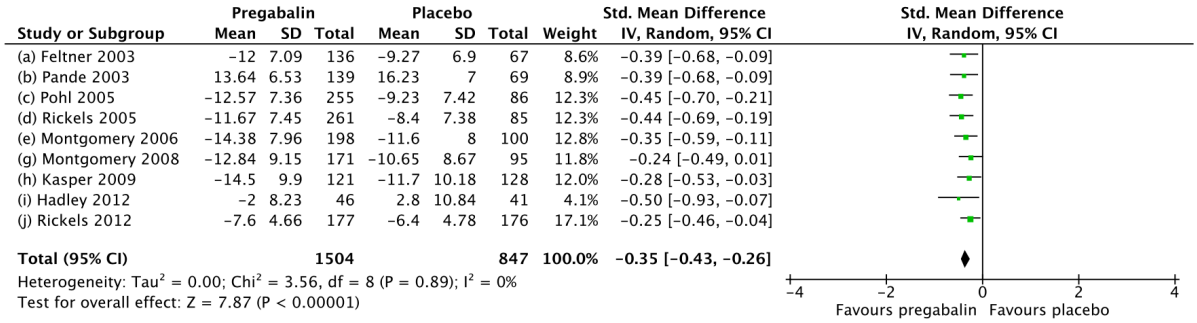


Appendix Figure 7. Funnel plot of studies investigating the efficacy of pregabalin versus placebo in GAD. There is no obvious funnel plot asymmetry. X-axis: Effect estimate (MD) in HAM-A. Y-axis: SE(MD). Each dot represents a single study. *GAD, generalised anxiety disorder; HAM-A, Hamilton Anxiety Rating Scale; MD, mean difference; SE(MD), standard error of the MD.*

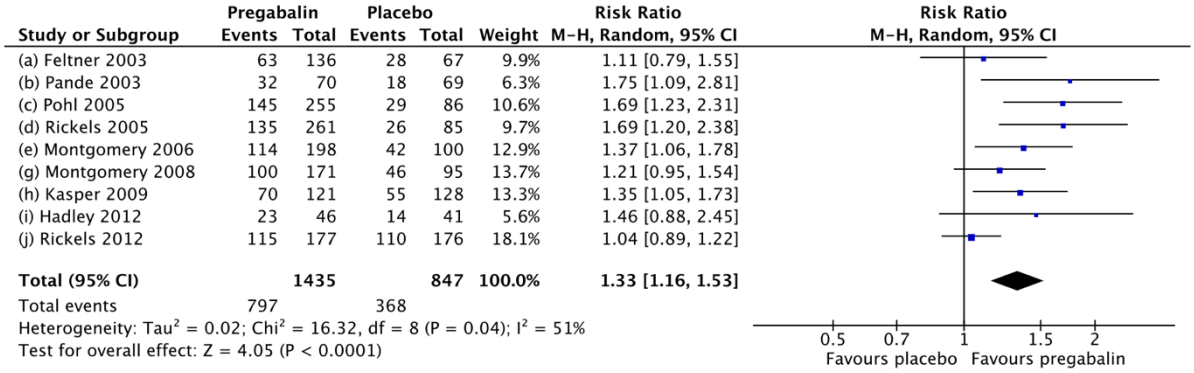


Appendix Figure 8. Funnel plot of studies investigating the efficacy of gabapentin versus placebo in preoperative anxiety. The funnel plot suggests possible small study effects, with greater effect size being observed in high-dose gabapentin studies with smaller samples. This should be interpreted with caution due to potential confounding by the high degree of I^2 heterogeneity that was observed in the high-dose group and lack of formal statistical assessment*. X-axis: treatment effect estimate in SMD. Y-axis: SE(SMD). Each dot represents a single study, with red square representing studies investigating gabapentin at a dose above 600mg (k=9 studies), and black circles representing studies investigating gabapentin dose of 600mg (k=4). SMD, standardised mean difference; SE(SMD), standard error of the SMD.*

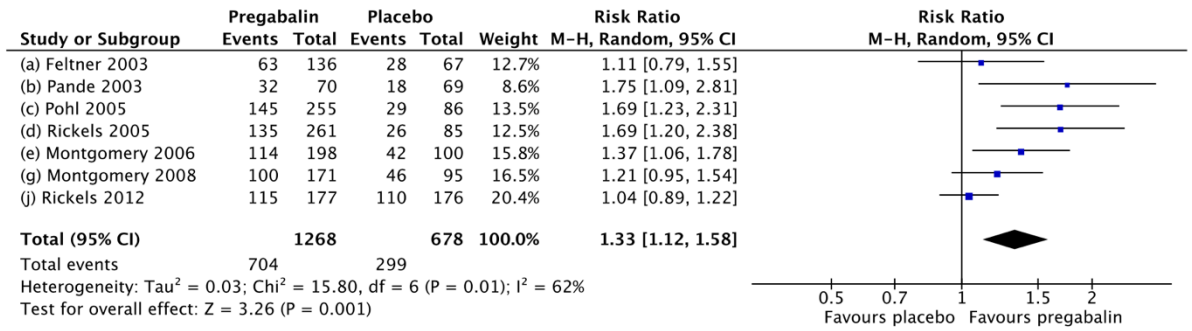
Appendix Figure 9. Forest plot of efficacy of pregabalin versus placebo in GAD – Sensitivity analysis excluding Feltner 2008 (relapse prevention study). *CI, confidence interval; IV, inverse variance; SD, standard deviation; GAD, generalised anxiety disorder.*



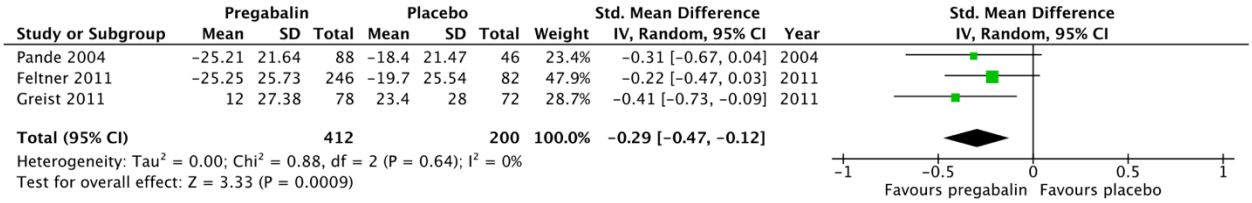
Appendix Figure 10. Forest plot of CGI-I response of pregabalin versus placebo in GAD. *Events = number of responders based on CGI-I response criteria (Score of 1 'very much improved' or 2 'much improved'). CGI-I, Clinical Global Impressions-Improvement scale; CI, confidence interval; M-H, Mantel-Haenszel method; SD, standard deviation; GAD, generalised anxiety disorder.*



Appendix Figure 11. Forest plot of CGI-I response of pregabalin versus placebo in GAD – Sensitivity analysis excluding Kasper 2009 and Hadley 2012 (studies where CGI responder count was imputed using the method from (Siafis et al. 2021)). *CGI-I, Clinical Global Impressions-Improvement scale; CI, confidence interval; M-H, Mantel-Haenszel method; SD, standard deviation; GAD, generalised anxiety disorder.*



Appendix Figure 12. Forest plot of efficacy of pregabalin versus placebo in SAD including Greist 2011 (relapse prevention study). *CI, confidence interval; IV, inverse variance; SD, standard deviation; SAD, social anxiety disorder.*



Tables

Appendix Table 1. Sensitivity analyses of meta-analysis of pregabalin vs placebo in GAD.
CI, confidence interval; GAD, generalised anxiety disorder; HAM-A, Hamilton anxiety rating scale; MD, mean difference.

Pregabalin vs placebo in GAD	**Reason for sensitivity analysis A-C**	**No. of studies**	**No. patients randomised**	**Effect estimate, MD in HAM-A**	**95% CI** ***Lower limit, Upper limit***	**Heterogeneity (I^2)**
Random effects	Refer to Figure 3 in main text (p.58).	10	2689	-2.76	-3.53, -2.00	37%
A	Exclusion of studies of pregabalin as add-on therapy.	9	2336	-3.14	-3.84, -2.45	0%
B	Exclusion of studies with psychiatric comorbidities.	6	1642	-2.52	-3.55, -1.48	42%
C	Exclusion of studies with rescue medications.	9	2602	-2.69	-3.47, -1.92	38%
Fixed effects	Fixed effects analysis	10	2689	-2.50	-3.06, -1.93	37%

Appendix Table 2. Sensitivity analyses of meta-analysis of gabapentin vs placebo in preoperative anxiety by dose subgroups. *CI, confidence interval; IQR, interquartile range; SD, standard deviation; SMD, standardised mean difference.*

Gabapentin vs placebo in preoperative anxiety	**Reason for sensitivity analyses A-C**	**Subgroup (Low dose: 600mg; High dose: >600mg)**	**No. of studies**	**No. patients randomized**	**Effect estimate, SMD**	**95% CI** *Lower limit, Upper limit*	**Heterogeneity (I^2)**
Random effects	Refer to Figure 4 in main text (p.59)	All doses	13	817	-0.92	-1.32, -0.52	86%
		Low dose	4	244	-0.06	-0.32, 0.20	0%
		High dose	9	573	-1.30	-1.72, -0.87	81%
A	Sensitivity analysis – exclusion of studies that did not report baseline measures *or* reported group differences in baseline measures	All doses	8	593	-0.70	-1.05, -0.34	76%
		Low dose	2	150	-0.03	-0.36, 0.30	0%
		High dose	6	443	-0.91	-1.21, -0.61	55%
B	Sensitivity analysis – exclusion of studies with high probability of skew (mean/SD <1).	All doses	11	697	-1.04	-1.50, -0.59	87%
		Low dose	2	124	0.09	-0.26, 0.44	0%
		High dose	9	573	-1.30	-1.72, -0.87	81%
C	Sensitivity analysis – exclusion of studies with extracted data reported in median/IQR/range.	All doses	8	513	-1.23	-1.78, -0.67	87%
		Low dose	1	44	0.24	-0.36, 0.83	N/A
		High dose	7	469	-1.42	-1.94, -0.90	84%
Fixed effects	Fixed effects analysis	All doses	13	817	-0.74	-0.89, -0.60	86%
		Low dose	4	244	-0.06	-0.32, 0.20	0%
		High dose	9	573	-1.08	-1.26, -0.90	81%

Appendix Table 3. Sensitivity analyses of meta-analysis of pregabalin vs placebo in preoperative anxiety by dose subgroups.

CI, confidence interval; IQR, interquartile range; SD, standard deviation; SMD, standardised mean difference.

Pregabalin vs placebo in preoperative anxiety	**Reason for sensitivity analysis, A-C**	**Subgroup (Low dose, ≤150mg; High dose, 300mg)**	**No. of studies**	**No. patients randomised**	**Effect estimate, SMD**	**95% CI** ***Lower limit, Upper limit***	**Heterogeneity (I^2)**
Random effects	Refer to Figure 5 in main text (p.60)	All doses	12	971	-0.43	-0.73, -0.13	77%
		Low dose	8	609	-0.29	-0.54, -0.05	45%
		High dose	4	362	-0.74	-1.65, 0.18	91%
A	Sensitivity analysis – exclusion of studies that did not report baseline measures *or* reported group differences in baseline measures	All doses	11	925	-0.38	-0.69, -0.08	76%
		Low dose	7	563	-0.20	-0.38, -0.02	6%
		High dose	4	362	-0.74	-1.65, 0.18	91%
B	Sensitivity analysis – exclusion of studies with high probability of skew (mean/SD <1).	All doses	10	698	-0.51	-0.88, -0.14	79%
		Low dose	6	336	-0.39	-0.70, -0.09	42%
		High dose	4	362	-0.74	-1.65, 0.18	91%
C	Sensitivity analysis – exclusion of studies with extracted data reported in median/IQR/range.	All doses	11	925	-0.46	-0.78, -0.14	79%
		Low dose	7	563	-0.31	-0.59, -0.04	52%
		High dose	4	362	-0.74	-1.65, 0.18	91%
Fixed effects	Fixed effects analysis	All doses	12	971	-0.31	-0.44, -0.17	77%
		Low dose	8	609	-0.25	-0.42, -0.09	45%
		High dose	4	362	-0.40	-0.62, -0.17	91%

Appendix Table 4. Tolerability (table of adverse effects)

Study name	Intervention	N patients	N participants experiencing at least 1 troublesome SE	Amnesia	Anxiety	Convulsion	Depression	Dizziness	Drowsiness	Emotional lability	Euphoria	Insomnia	Leucopoenia	Movement disorder (i.e ataxia & tremor)	Vertigo	Visual disturbance	Weight gain	Other
BIPOLAR DISORDER																		
RANDOMISED DOUBLE-BLIND TRIALS																		
GABAPENTIN																		
Frye (2000) (NCT00001482)	Gabapentin 900-4800 mg/day	9	* (SEs not reported for 1st crossover period)	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	Lamotrigine 25-500 mg/day	10	* (SEs not reported for 1st crossover period)	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	Placebo	11	* (SEs not reported for 1st crossover period)	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Mokhber (2008)	Gabapentin 300-900 mg/day	18	2	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	Carbamazepine 400-600 mg/day	13	6	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	Lamotrigine 25-100 mg/day	20	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*

Pande (2000) (945-209)	Gabapentin 600-3600 mg/day (Adjunctive therapy with Lithium, Valproate or combination)	59	45	6	0	0	1	11	14	0	0	1	0	3	0	4	2	Refer to (a) below this table
	Intervention	**N patients**	**N participants experiencing at least 1 troublesome SE**	**Amnesia**	**Anxiety**	**Convulsion**	**Depression**	**Dizziness**	**Drowsiness**	**Emotional lability**	**Euphoria**	**Insomnia**	**Leucopoenia**	**Movement disorder (i.e ataxia & tremor)**	**Vertigo**	**Visual disturbance**	**Weight gain**	**Other**
Pande (2000) continued	Placebo (Adjunctive therapy with Lithium, Valproate or combination)	59	39	2	0	0	0	3	7	0	0	1	0	7	0	1	4	Refer to (a) below this table
Vieta_2006 (945-291)	Gabapentin 1200-2400 mg/day (Adjunctive therapy with Lithium, Valproate, Carbamazepine or combination)	13	10	*	*	*	*	2	*	*	*	2	*	2	*	*	*	Constipation=4; Headache=3; Nausea=3
	Placebo (Adjunctive therapy with Lithium, Valproate, Carbamazepine or	12	7	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*

combination
)

Study name	Intervention	N patients	N participants experiencing at least 1 troublesome SE	Amnesia	Anxiety	Convulsion	Depression	Dizziness	Drowsiness	Emotional lability	Euphoria	Insomnia	Leucopoenia	Movement disorder (i.e ataxia & tremor)	Vertigo	Visual disturbance	Weight gain	Other
OPEN LABEL TRIALS																		
GABAPENTIN																		
Altshuler 1999	Gabapentin 300-3600 mg/day (Adjunctive therapy to TAU)	28	12	0	0	0	0	1	0	0	0	0	0	2	0	0	0	Gastrointestinal upset=4; Headache=1; Sedation=5
Astaneh 2012	Lithium	30	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	Lithium plus Gabapentin 900 mg/day	30	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Erfurth 1998	Gabapentin (Adjunctive therapy to TAU)	6	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	Gabapentin 1200-3600 mg/day	8	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Knoll 1998	Gabapentin 300-3300 mg/day (Adjunctive	12	11	0	0	0	0	0	0	0	0	0	0	3	0	0	1	Alopecia=1; Fatigue=2; Irritability=3;

	therapy to TAU)																			Nausea=1; Sedation=5
Mauri 2001	Gabapentin 300-2400 mg/day	21		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
McElroy 1997	Gabapentin 300-4800 mg/day (Adjunctive therapy to TAU)	9		7	0	0	0	0	0	0	0	0	0	0	2	0	1	0		Constipation=1; Dark urine=1; Episodic disorientation=1; Forgetfullness=1; Migraine=1; Sedation=7; Memory loss=2
Perugi 1999	Gabapentin 300-2000 mg/day (Adjunctive therapy to TAU)	21		*	*	*	*	*	*	*	*	*	*	*	7	*	*	*		Irritability=5; Nausea=3; Sedation=9
Wang 2002	Gabapentin 600-3300 mg/day (Adjunctive therapy to stable doses of mood stabilisers or typical antipsychotics)	22		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		Hypomanic symptoms=3; Impaired cognition=1; Sedation=7
Young 1997	Gabapentin 300-2400 mg/day (Adjunctive therapy to TAU)	15		*	0	3	0	0	3	0	0	0	0	0	3	0	0	2		Gasrointestinal upset=13; Incoordination=1; Sedation=6
Young 1999	Gabapentin 300-3600 mg/day (Adjunctive	37		*	*	9	*	*	*	8	*	*	*	*	*	*	5	*		Constipation=4; Dry mouth=6; Sexual difficulties=9;

	therapy to TAU)																		Sleep problems=7
PREGABALIN																			
Schaffer 2012	Pregabalin (Adjunctive therapy to TAU)	58		*	*	*	*	*	*	*	*	*	*	*	*	*	*	8	Increased appetite=8; Overactivation=12

Study name	Intervention	N patients	N participants experiencing at least 1 troublesome SE	Amnesia	Anxiety	Convulsion	Depression	Dizziness	Drowsiness	Emotional lability	Euphoria	Insomnia	Leucopoenia	Movement disorder (i.e ataxia & tremor)	Vertigo	Visual disturbance	Weight gain	Other
								INSOMNIA/SLEEP DISTURBANCE										
RANDOMISED DOUBLE-BLIND TRIALS																		
GABAPENTIN																		
Brower 2008	Gabapentin 300-1500 mg/day	10	10	0	0	0	0	2	3	0	0	0	0	1	0	0	0	Abdominal pain=1; Constipation=1; Diarrhea=1; Dry mouth=1; Headache=3; Indigestion=2; Memory disturbance=1; Menstrual cramps=1; Nerve/muscle pain=2; Paleness=1; Twitching/tingling=2
	Placebo	11	10	0	0	0	0	1	1	0	0	0	0	1	0	0	0	Altered mental state=2; Headache=3; Indigestion=4;

																		Memory disturbance=1; Twitching/tingling=1
	Gabapentin 250 mg/day	128	13	0	0	0	0	1	4	0	0	0	0	0	0	0	0	Diarrhea=1; Dry mouth=1; Headache=4; Nausea=1; Sluggishness=1
Furey 2014	Placebo	128	10	0	1	0	0	0	1	0	0	0	0	0	1	1	0	Headache=3; Hypertension=1; Impotence=1; Musculoskeletal stiffness=1; Restlessness=1
INSOMNIA-gabapentin (DB-RCTs) continued	**Intervention**	**N patients**	**N participants experiencing at least 1 troublesome SE**	**Amnesia**	**Anxiety**	**Convulsion**	**Depression**	**Dizziness**	**Drowsiness**	**Emotional lability**	**Euphoria**	**Insomnia**	**Leucopoenia**	**Movement disorder (i.e ataxia & tremor)**	**Vertigo**	**Visual disturbance**	**Weight gain**	**Other**
Malcolm 2007	Gabapentin 600-1200 mg/day	101 total participants randomised †	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	Lorazepam 6 mg/day		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Mason 2014 (NCT00391716)	Gabapentin 1800 mg/day	47	1	*	*	*	*	*	*	*	0	6	*	*	*	*	*	Headache=6; Fatigue=9
	Gabapentin 900 mg/day	54	3	*	*	*	*	*	*	*	0	10	*	*	*	*	*	Headache=7; Fatigue=13
	Placebo	49	1	*	*	*	*	*	*	*	1	11	*	*	*	*	*	Headache=8; Fatigue=12
Mowla 2015	Gabapentin 100-600 mg/day (adjunctive to TAU for MDD)	31	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*

	Clonazepam . 5-2 mg/day (adjunctive to TAU for MDD)	32	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
NCT01014533 (HUM00010947 1R01AA016117-01A1)	Gabapentin 600-1200 mg/day	30	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Cough Increased=2; Flu Syndrome=2
	Placebo	29	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Irritability=2
Rosenburg 2013 (NCT00674752)	Gabapentin 500 mg single dose	125	5	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	Altered mental state=1; Headache=2; Nausea=1
	Gabapentin 250 mg single dose	125	4	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	Headache=1; Hypertension=2; Sinusitis=1
	Placebo	127	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Asthma=1; Headache=1; Nausea=1; Vomiting=1
Yurcheshen 2009	Gabapentin 900 mg/day	30	15	*	*	*	*	4	6	*	*	*	*	*	*	*	*	*	Menses=2; Rash=2
	Placebo	29	8	*	*	*	*	0	0	*	*	*	*	*	*	*	*	*	Menses=3
PREGABALIN																			
Bollu 2010	Pregabalin 300-600 mg/day	121	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	Venlafaxine 75-225 mg/day	125	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	Placebo	128	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
OPEN LABEL TRIALS																			
GABAPENTIN																			
NCT02040532	Gabapentin 100-600 mg/day	26	11	0	0	0	0	0	8	0	0	4	0	0	0	0	4		Abdominal pain=4; Cough Increased =4; Fatigue=6; Flatulence=4; Flu syndrome=6; Headache=9;

																		Hot flushes=7; Increased libido=4; Musculoskeletal stiffness=4; Nausea=3; Rash=1; Sweating=8; Tension=4

Study	Intervention	N patients	N participants experiencing at least 1 troublesome SE	Amnesia	Anxiety	Convulsion	Depression	Dizziness	Drowsiness	Emotional lability	Euphoria	Insomnia	Leucopoenia	Movement disorder (i.e ataxia & tremor)	Vertigo	Visual disturbance	Weight gain	Other
GENERALISED ANXIETY DISORDER																		
RANDOMISED DOUBLE-BLIND TRIALS																		
PREGABALIN																		
Feltner 2003	Pregabalin 150 mg/day	70	51	2	*	*	*	7	20	*	*	*	*	*	*	0	*	Refer to (b) below this table
	Pregabalin 600 mg/day	66	59	2	*	*	*	19	33	*	*	*	*	*	*	5	*	

	Placebo	67	45	0	*	*	*	5	8	*	*	*	*	*	*	0	*	
	Lorazepam 6 mg/day	68	62	4	*	*	*	13	41	*	*	*	*	*	*	1	*	
Feltner 2008	Pregabalin 450 mg/day	168	*	*	*	*	*	7	10	*	0	*	*	*	*	*	8	Refer to (c)
	Placebo	170	*	*	*	*	*	5	0	*	0	*	*	*	*	*	0	
Hadley 2012 (NCT00368745)	Pregabalin 150-600 mg/day	56	33	*	11	*	*	12	3	*	*	4	*	2	*	5	*	Refer to (d)
	Placebo	50	29	*	10	*	*	3	2	*	*	7	*	4	*	2	*	
Kasper 2009 (NCT00151450)	Pregabalin 300-600 mg/day	121	*	*	*	*	*	25	11	*	*	5	*	*	16	*	2	Refer to (e)
	Venlafaxine 75-225 mg/day	125	*	*	*	*	*	12	6	*	*	12	*	*	10	*	1	
	Placebo	128	*	*	*	*	*	8	3	*	*	6	*	*	4	*	1	
Kasper 2014 (NCT00624780)	Pregabalin 450-600 mg/day	206	* (SEs not reported for DB period)	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	Pregabalin 150-300 mg/day	206	* (SEs not reported)	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	Lorazepam 3-4 mg/day	206	* (SEs not reported)	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*

GAD continued	**Intervention**	**N patients**	**N participants experiencing at least 1 troublesome SE**	**Amnesia**	**Anxiety**	**Convulsion**	**Depression**	**Dizziness**	**Drowsiness**	**Emotional lability**	**Euphoria**	**Insomnia**	**Leucopoenia**	**Movement disorder (i.e ataxia & tremor)**	**Vertigo**	**Visual disturbance**	**Weight gain**	**Other**
Montgomery 2006	Pregabalin 400 mg/day	97	*	*	*	*	*	22	13	*	*	1	*	*	*	*	*	Refer to (f)
	Pregabalin 600 mg/day	110	*	*	*	*	*	29	15	*	*	3	*	*	*	*	*	
	Venlafaxine 75 mg/day	113	*	*	*	*	*	14	4	*	*	8	*	*	*	*	*	
	Placebo	101	*	*	*	*	*	7	3	*	*	5	*	*	*	*	*	

Montgomery 2008 (EUCTR2004-000955-40-LV)	Pregabalin 150-600 mg/day	181	127	*	*	*	*	36	23	*	*	5	*	5	4	5	5	Refer to (g)
	Placebo	96	54	*	*	*	*	11	7	*	*	6	*	0	0	1	0	
Pande 2003	Pregabalin 150 mg/day	69	*	1	*	*	*	16	10	*	*	2	*	0	*	4	*	Refer to (h)
	Pregabalin 600 mg/day	70	*	5	*	*	*	27	25	*	*	1	*	7	*	8	*	
	Lorazepam 6 mg/day	68	*	3	*	*	*	9	37	*	*	4	*	8	*	1	*	
	Placebo	69	*	3	*	*	*	4	8	*	*	1	*	0	*	1	*	
Pohl 2005	Pregabalin 200 mg/day	78	*	*	*	*	*	27	24	*	8	*	*	*	*	5	*	Refer to (i)
	Pregabalin 400 mg/day	89	*	*	*	*	*	44	33	*	9	*	*	*	*	10	*	
	Pregabalin 450 mg/day	88	*	*	*	*	*	37	21	*	13	*	*	*	*	12	*	
	Placebo	86	*	*	*	*	*	13	11	*	1	*	*	*	*	3	*	
Rickels 2005	Pregabalin 300 mg/day	91	*	*	*	*	*	37	35	*	*	*	*	*	*	8	*	Refer to (j)
	Pregabalin 300-450 mg/day	90	*	*	*	*	*	34	36	*	*	*	*	*	*	10	*	
	Pregabalin 300-600 mg/day	89	*	*	*	*	*	35	37	*	*	*	*	*	*	8	*	
	Alprazolam 0.5-1.5 mg/day	93	*	*	*	*	*	15	42	*	*	*	*	*	*	4	*	
	Placebo	91	*	*	*	*	*	9	15	*	*	*	*	*	*	3	*	
Rickels 2012 (NCT00413010)	Pregabalin 150-600 mg/day (Adjunctive to SSRI/SNRI)	180	81	*	*	*	*	21	22	*	4	5	*	*	*	8	4	Refer to (k)

	Placebo (Adjunctive to SSRI/SNRI)	176	59	*	*	*	*	10	15	*	0	1	*	*	*	2	0	
OPEN LABEL TRIALS																		
PREGABALIN																		
Cvjetkovic-Bosnjak 2015	Pregabalin 225 mg/day	47	*	*	*	*	*	6	5	*	*	0	*	*	1	*	*	Nausea=2
	Sertraline 150 mg/day	60	*	*	*	*	*	3	0	*	*	2	*	*	1	*	*	Diarrhea=3; Nausea=8

Study	Intervention	N patients	N participants experiencing at least 1 troublesome SE	Amnesia	Anxiety	Convulsion	Depression	Dizziness	Drowsiness	Emotional lability	Euphoria	Insomnia	Leucopoenia	Movement disorder (i.e ataxia & tremor)	Vertigo	Visual disturbance	Weight gain	Other
SOCIAL ANXIETY DISORDER																		
RANDOMISED DOUBLE-BLIND TRIALS																		
GABAPENTIN																		
Pande 1999	Gabapentin 900-3600 mg/day	34	*	*	2	*	*	8	7	*	*	3	*	*	*	2	2	Refer to (m) below this table
	Placebo	35	*	*	0	*	*	2	3	*	*	3	*	*	*	1	4	
PREGABALIN																		
Feltner 2011	Pregabalin 300 mg/day	78	68	8	*	*	*	27	29	*	*	*	*	*	*	*	4	Refer to (n)
	Pregabalin 450 mg/day	86	80	3	*	*	*	34	31	*	*	*	*	*	*	*	6	
	Pregabalin 600 mg/day	82	76	6	*	*	*	30	39	*	*	*	*	*	*	*	10	
	Placebo	82	49	0	*	*	*	5	9	*	*	*	*	*	*	*	0	
Greist 2011	Pregabalin 450 mg/day	80	*	*	*	*	8	9	2	*	*	20	*	*	*	*	*	Refer to (p)
	Placebo	73	*	*	*	*	8	3	1	*	*	21	*	*	*	*	*	
Pande 2004	Pregabalin 150 mg/day	42	34	1	*	*	0	5	4	*	*	3	*	0	*	1	*	Refer to (q)
	Pregabalin 600 mg/day	47	47	5	*	*	3	19	20	*	*	4	*	3	*	5	*	
	Placebo	46	40	2	*	*	1	4	4	*	*	6	*	0	*	0	*	

Study	Intervention	N patients	N participants experiencing at least 1 troublesome SE	Amnesia	Anxiety	Convulsion	Depression	Dizziness	Drowsiness	Emotional lability	Euphoria	Insomnia	Leucopoenia	Movement disorder (i.e ataxia & tremor)	Vertigo	Visual disturbance	Weight gain	Other
PANIC DISORDER																		
RANDOMISED DOUBLE-BLIND TRIALS																		
GABAPENTIN																		
Pande 2000	Gabapentin 600-3600 mg/day	52	*	*	*	*	*	12	16	*	*	*	*	6	*	*	*	Fatigue=9; Headache=14; Indigestion=5; Infection=11; Nausea=6
	Placebo	51	*	*	*	*	*	6	9	*	*	*	*	1	*	*	*	Fatigue=7; Headache=12; Indigestion=7; Infection=7; Nausea=8
GENERALISED ANXIETY DISORDER, SOCIAL ANXIETY DISORDER AND PANIC DISORDER																		
OPEN LABEL TRIALS																		
PREGABALIN																		
Montgomery 2013	Pregabalin 200-600 mg/day	528	404	*	*	*	*	66	40	*	*	25	*	*	*	*	29	Accidental injury=3; Diarrhea=10; Fatigue=21; Headache=28; Nausea=18
OBSESSIVE COMPULSIVE DISORDER																		
RANDOMISED DOUBLE-BLIND TRIALS																		
PREGABALIN																		
Mowla 2020	Pregabalin 75-225 mg/day (Adjunctive to Sertraline)	28	*	0	0	0	0	1	4	0	0	0	0	0	0	0	0	Headache=1

	Placebo (Adjunctive to Sertraline)	28		*	0	0	0	0	0	1	0	0	0	0	0	0	0	0	Headache=1; Nausea=2
OPEN LABEL TRIALS																			
PREGABALIN																			
Oulis 2011	Pregabalin 225-675 mg/day (Adjunctive to TAU)	10		8	0	0	0	0	5	0	0	0	0	0	0	0	0	3	Fatigue=3
POST TRAUMATIC STRESS DISORDER																			
RANDOMISED DOUBLE-BLIND TRIALS																			
PREGABALIN																			
Baniasadi 2014	Pregabalin 300 mg/day	18		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	Placebo	19		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*

Study	Intervention	N patients	N participants experiencing at least 1 troublesome SE	Amnesia	Anxiety	Convulsion	Depression	Dizziness	Drowsiness	Emotional lability	Euphoria	Insomnia	Leucopoenia	Movement disorder (i.e ataxia & tremor)	Vertigo	Visual disturbance	Weight gain	Other
PRE-OPERATIVE ANXIETY																		
RANDOMISED DOUBLE-BLIND TRIALS																		
GABAPENTIN [$]																		
Abdel-Halim 2009	Gabapentin 800 mg single dose	20	*	*	*	*	*	0	2	*	*	*	*	*	*	*	*	Nausea/Vomiting=1
	Dexamethasone IV 16 mg single dose	20	*	*	*	*	*	0	0	*	*	*	*	*	*	*	*	Nausea/Vomiting=1
	Gabapentin 800 mg + Dexamethasone IV 16 mg single dose	20	*	*	*	*	*	0	2	*	*	*	*	*	*	*	*	*
	No intervention	20	*	*	*	*	*	0	1	*	*	*	*	*	*	*	*	Nausea/Vomiting=1
Ménigaux 2005	Gabapentin 1200 mg single dose	20	0	*	*	*	*	*	0	*	*	*	*	*	*	*	*	*
	Placebo	20	0	*	*	*	*	*	0	*	*	*	*	*	*	*	*	*
Tirault 2010	Gabapentin 1200 mg single dose	70	*	*	*	*	*	1	5	*	*	*	*	*	*	0	*	*
	Hydroxyzine 75 mg single dose	70	*	*	*	*	*	1	6	*	*	*	*	*	*	0	*	Headache=1
	Placebo	70	*	*	*	*	*	0	2	*	*	*	*	*	*	1	*	Headache=1; Nausea/Vomiting=1

PREGABALIN‡																		
Gonano 2011	Pregabalin 300 mg single dose	20	0	*	*	*	*	0	0	*	*	*	*	0	*	0	*	*
	Placebo	20	0	*	*	*	*	0	0	*	*	*	*	0	*	0	*	*
Nutt 2009	Pregabalin 150 mg single dose	27	*	*	*	*	*	6	3	*	*	*	*	*	0	*	*	Disturbance in attention=3; Fatigue=7
	Alprazolam 0.5 mg single dose	31	*	*	*	*	*	3	0	*	*	*	*	*	2	*	*	Disturbance in attention=1; Fatigue=7; Feeling abnormal=2
	Placebo	31	*	*	*	*	*	3	0	*	*	*	*	*	0	*	*	Fatigue=3
Roraruis 2004	Gabapentin 1200 mg single dose	38	38	*	*	*	*	6	14	*	*	*	*	*	*	2		Dry mouth=21; Headache=5
	Oxezepam 15 mg single dose	37	37	*	*	*	*	4	12	*	*	*	*	*	*	1		Dry mouth=15; Headache=5
Shimoni 2016	Pregabalin 150 mg single dose	50	*	*	*	*	*	2	1	*	*	*	*	*	*	*	*	*
	Placebo	50	*	*	*	*	*	0	2	*	*	*	*	*	*	*	*	*

* Side effect data is not reported/not reported in full e.g. only most frequent side effects (in more than 5 or 10% of patients) are reported and presence of other side effects are unknown. † Authors contacted for data per arm, but no response.
$ The following preoperative studies (gabapentin) did not report adverse events: Adam 2012, Bakry 2012, Clarke 2010, Clarke 2013, Hoseini 2015, Joseph 2014, Khezri 2013, Pathak 2014, Sava 2009, Ghai 2012. Refer to Table 2 in main text for study characteristics.
ǂ The following preoperative studies (pregabalin) did not report adverse events: Moreau-Bussiere 2013 (NCT01158859), Nasr 2014, NCT00551135 2009, NCT00468845 2011, Spreng 2011, Singh 2019, White 2009, Ghai 2012. Refer to Table 2 in main text for study characteristics.

(a) 'Other adverse events' in bipolar disorder

(a) Pande 2000, Bipolar disorder, Other adverse events

Arm: Gabapentin 600-3600 mg/day (Adjunctive therapy with Lithium, Valproate or combination)
Abdominal pain=2; Acne=2; Abnormal ejaculation=2; Abnormal gait=4; Accidental injury=2; Alopecia=1; Anorexia=1; Arthralgia=1; Asthenia=2; Asthma=1; Back pain=2; Chest pain=2; Chills=1; Confusion=1; Constipation=3; Diarrhea=9; Dry mouth=5; Dry skin=1; Indigestion=1; Dysphagia=1; Dyspnea=2; Flu syndrome=2; Hair Disorder=1; Headache=6; Hypotonia=1; Impotence=1; Incoordination=2; Increased Appetite=5; Infection=1; Manic Reaction=2; Nausea=4; Neck Pain=1; Nervousness=1; Nystagmus=1; Pain=1; Papancolau Smear Susupicious=1; Paranoid reaction=1; Peripheral Edema=4; Pharyngitis=2; Polyurea=2; Postural Hypotension=1; Rhinitis=2; Sinusitis=1; Speech Disorder=2; Thirst=3; Urinary Frequency=1; Urinary Incontinence=2; Urinary Tract Infection=1; Urinary Urgency=2; Vasodilatation=1; Vomiting=1
Arm: Placebo (Adjunctive therapy with Lithium, Valproate or combination)
Abdominal pain=4; Acne=1; Abnormal Dreams=1; Abnormal stools=1; Accidental injury=2; Alopecia=1; Anorexia=1; Arthralgia=1; Asthenia=3; Back pain=3; Balanitis=1; Confusion=2; Constipation=2; Cough Increased=1; Diarrhea=7; Dry mouth=3; Dry skin=1; Indigestion=4; Ecchymosis=1; Face Edema=1; Flu syndrome=3; Generalised Edema=1; Headache=7; Hypothyroidism=1; Impotence=1; Incoordination=2; Increased Appetite=4; Infection=6; Libido Decreased=1; Manic Reaction=5; Nausea=6; Neck Pain=1; Neuropathy=1; Pain=2; Palpitation=1; Parasthesia=1; Pericarditus=1; Peripheral Edema=3; Pharyngitis=1; Photophobia=1; Pleural Disorder=1; Pneumonia=1; Psoriasis=1; Psychosis=1; Pruritis=1; Rash=1; Rhinitis=2; Sinusitis=1; Thinking Abnormal=2; Thirst=1; Tinnitus=1; Tongue Disorder=1; Twitching=1; Urinary Tract Infection=1; Vasodilatation=1; Vomiting=1

(b-q) 'Other adverse events' in GAD and SAD

(b) Feltner 2003, GAD, Other adverse events

Arm: Pregabalin 150 mg/day
Accidental injury=2; Diarrhea=3; Dry mouth=8; Fatigue =5; Headache=7; Infection=6; Nausea=7; Thinking abnormal/confusion=1
Arm: Pregabalin 600 mg/day
Accidental injury=4; Diarrhea=2; Dry mouth=10; Fatigue =1; Headache=12; Infection=4; Incoordination=1; Nausea=4; Thinking abnormal/confusion=1; Rhinitis=4
Arm: Placebo
Accidental injury=2; Diarrhea=5; Dry mouth=7; Fatigue =4; Headache=6; Infection=6; Nausea=5; Thinking abnormal/confusion=1
Arm: Lorazepam 6 mg/day
Accidental injury=1; Dry mouth=5; Fatigue =7; Headache=5; Infection=1; Incoordination=5; Nausea=11; Thinking abnormal/confusion=6; Rhinitis=1

(c) Feltner 2008, GAD, Other adverse events

Arm: Pregabalin 450 mg/day
Dry mouth=6; Headache=17; Infection=25; Incoordination=2; Thinking abnormal/confusion=3
Arm: Placebo
Dry mouth=2; Headache=19; Infection=19

(d) Hadley 2012, GAD, Other adverse events

Arm: Pregabalin 150-600 mg/day
Diarrhea=3; Fatigue=5; Headache=7; Hyperacusis=3; Hyperhidrosis=3; Nausea=5; Pain=3; Paraesthesia=6; Peripheral oedema=5; Vomiting=3
Arm: Placebo
Diarrhea=5; Fatigue=8; Headache=13; Hyperacusis=1; Irritability=4; Nausea=7

(e) Kasper 2009, GAD, Other adverse events
Arm: Pregabalin 300-600 mg/day
Constipation=5; Dry mouth=13; Fatigue=12; Headache=21; Hyperhidrosis=3; Nausea=15
Arm: Venlafaxine 75-225 mg/day
Constipation=7; Dry mouth=15; Fatigue=16; Headache=20; Hyperhidrosis=10; Nausea=32
Arm: Placebo
Constipation=4; Dry mouth=5; Fatigue=5; Headache=15; Hyperhidrosis=7; Nausea=11

(f) Montgomery 2006, GAD, Other adverse events
Arm: Pregabalin 400 mg/day
Constipation=7; Diarrhea=4; Dry mouth=5; Fatigue=5; Headache=7; Infection=9; Nausea=9; Vomiting=4
Arm: Pregabalin 600mg/day
Constipation=7; Diarrhea=5; Dry mouth=5; Fatigue=4; Headache=9; Infection=3; Nausea=14; Vomiting=2
Arm: Venlafaxine 75mg/day
Constipation=7; Diarrhea=5; Dry mouth=8; Fatigue=14; Headache=10; Infection=3; Nausea=31; Vomiting=9
Arm: Placebo
Constipation=2; Diarrhea=6; Dry mouth=2; Fatigue=6; Headache=13; Infection=4; Nausea=8; Vomiting=5

(g) Montgomery 2008, GAD, Other adverse events
Arm: Pregabalin 150-600mg/day
Abdominal pain=7; Accidental injury=7; Back pain=4; Constipation=5; Diarrhea=4; Dry mouth=6; Fatigue=5; Headache=18; Hypertension=7; Infection=10; Incoordination=2; Indigestion=4; Nausea=16; Pain=1; Peripheral Edema=7; Paresthesia=5; Thinking abnormal=1
Arm: Placebo
Abdominal pain=3; Accidental injury=1; Back pain=5; Constipation=2; Diarrhea=5; Dry mouth=2; Fatigue=3; Headache=8; Hypertension=1; Infection=3; Nausea=6; Pain=4; Peripheral Edema=3; Thinking abnormal=2

(h) Pande 2003, GAD, Other adverse events
Arm: Pregabalin 150mg/day
Constipation=1; Depersonalisation=1; Diarrhea=2; Dry mouth=6; Fatigue=4; Headache=13; Infection=8; Nausea=5; Pain=4; Thinking abnormal=2; Vomiting=1
Arm: Pregabalin 600mg/day
Constipation=5; Depersonalisation=6; Diarrhea=8; Dry mouth=11; Fatigue=6; Headache=15; Infection=3; Incoordination=8; Nausea=6; Pain=1; Thinking abnormal=9; Vomiting=2
Arm: Lorazepam 6mg/day
Constipation=3; Depersonalisation=4; Diarrhea=2; Dry mouth=3; Fatigue=11; Headache=6; Infection=2; Incoordination=13; Nausea=6; Thinking abnormal=6; Vomiting=1
Arm: Placebo
Constipation=2; Diarrhea=2; Dry mouth=2; Fatigue=4; Headache=9; Infection=9; Incoordination=2; Nausea=7; Pain=1; Thinking abnormal=1; Vomiting=5

(i) Pohl 2005, GAD, Other adverse events
Arm: Pregabalin 200mg/day
Dry mouth=19; Flatulence=8; Infection=13; Incoordination=3; Thinking abnormal=6
Arm: Pregabalin 400mg/day
Dry mouth=24; Flatulence=2; Infection=11; Incoordination=14; Thinking abnormal=12
Arm: Pregabalin 450mg/day
Dry mouth=15; Flatulence=11; Infection=9; Incoordination=12; Thinking abnormal=5
Arm: Placebo
Dry mouth=9; Flatulence=2; Infection=6; Incoordination=2; Thinking abnormal=2

(j) Rickels 2005, GAD, Other adverse events
Arm: Pregabalin 300mg/day
Constipation=2; Dry mouth=18; Fatigue=7; Infection=10; Incoordination=4; Nausea=10
Arm: Pregabalin 300-450mg/day
Constipation=12; Dry mouth=16; Fatigue=10; Infection=14; Incoordination=11; Nausea=13
Arm: Pregabalin 300-600mg/day
Constipation=3; Dry mouth=21; Fatigue=7; Infection=15; Incoordination=15; Nausea=10
Arm: Alprazolam 0.5-1.5mg/day
Constipation=3; Dry mouth=4; Fatigue=13; Infection=8; Incoordination=3; Nausea=9
Arm: Placebo
Constipation=5; Dry mouth=8; Fatigue=2; Infection=9; Nausea=10

(k) Rickels 2012, GAD, Other adverse events
Arm: Pregabalin 150-600 mg/day (Adjunctive to SSRI/SNRI)
Cold=5; Constipation=5; Cough=2; Diarrhea=7; Dry mouth=4; Fatigue=7; Headache=17; Indigestion=6; Flatulence=4; Infection=3; Joint pain= 5; Nausea=13; Paraesthesia=4; Vomiting=2
Arm: Placebo (Adjunctive to SSRI/SNRI)
Cold=6; Constipation=3; Cough=6; Diarrhea=7; Dry mouth=2; Fatigue=5; Headache=7; Indigestion=1; Infection=6; Joint pain= 1; Nausea=8; Paraesthesia=1; Vomiting=4

(m) Pande 1999, SAD, Other adverse events
Arm: Gabapentin 900-3600mg/day
Decreased libido=3; Diarrhea=4; Dry mouth=4; Fatigue=5; Flatulence=3; Headache=8; Increased appetite=3; Infection=10; Nausea=4; Nervousness=5; Rhinitis/Sinusitis=5; Thinking abnormal=4; Vasodilation=2
Arm: Placebo
Diarrhea=2; Fatigue=3; Headache=9; Infection=8; Increased appetite=2; Nausea=1; Nervousness=4; Rhinitis/Sinusitis=1; Thinking abnormal=2; Vasodilation=1

(n) Feltner 2011, SAD, Other adverse events
Arm: Pregabalin 300mg/day
Dry mouth=7; Fatigue=8; Headache=10; Infection=4; Nausea=4; Thinking abnormal=5
Arm: Pregabalin 450mg/day

Dry mouth=12; Fatigue=3; Headache=12; Infection=10; Nausea=11; Thinking abnormal=9
Arm: Pregabalin 600mg/day
Dry mouth=11; Fatigue=10; Headache=9; Infection=10; Nausea=9; Thinking abnormal=15
Arm: Placebo
Dry mouth=1; Fatigue=1; Headache=11; Infection=10; Nausea=5; Thinking abnormal=1

(p) Greist 2011, SAD, Other adverse events
Arm: Pregabalin 450mg/day
Headache=11; Infection=17; Nausea=9; Thinking abnormal=1
Arm: Placebo
Headache=17; Infection=12; Nausea=7; Thinking abnormal=2

(q) Pande 2004, SAD, Other adverse events
Arm: Pregabalin 150mg/day
Anorgasmia=1; Depersonalisation=2; Dry mouth=3; Fatigue=6; Headache=12; Infection=7; Nausea=3; Pain=4; Thinking abnormal=1
Arm: Pregabalin 600mg/day
Accidental injury=4; Anorgasmia=3; Decreased libido=4 Depersonalisation=4; Dry mouth=3; Fatigue=9; Headache=10; Infection=3; Incoordination=4; Nausea=4; Nervousness=6; Pain=3; Thinking abnormal=10
Arm: Placebo
Dry mouth=1; Fatigue=3; Headache=11; Infection=9; Nausea=2; Nervousness=4; Pain=1; Thinking abnormal=3

Appendix Table 5A-F. GRADE (Grading of Recommendations, Assessment, Development and Evaluation) Summary Tables.

Appendix Table 5A. Gabapentinoids compared to placebo in the acute and long-term treatment of anxiety disorders/states

Patient or population: anxiety spectrum
Setting: any
Intervention: gabapentinoids
Comparison: placebo

Outcomes	№ of participants Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with gabapentinoids
Pregabalin versus placebo in **generalised anxiety disorder**	2689	⊕⊕◯◯ LOW	-	-	SMD **0.37 lower** (0.45 lower to 0.29 lower)
Pregabalin versus placebo in **social anxiety disorder**	462	⊕⊕◯◯ LOW	-	-	SMD **0.25 lower** (0.45 lower to 0.04 lower)
Pregabalin versus placebo in **preoperative anxiety**	971	⊕◯◯◯ VERY LOW	-	-	SMD **0.55 lower** (0.92 lower to 0.18 lower)
Pregabalin versus placebo in **posttraumatic stress disorder**	37 (1 study)	-	-	-	SMD **0.3 lower** (0.95 lower to 0.35 higher)

Appendix Table 5A. Gabapentinoids compared to placebo in the acute and long-term treatment of anxiety disorders/states

Patient or population: anxiety spectrum
Setting: any
Intervention: gabapentinoids
Comparison: placebo

Outcomes	№ of participants Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with gabapentinoids
Pregabalin versus placebo in **obsessive compulsive disorder**	42 (1 study)	-	-	-	SMD **2.25 lower** (3.04 lower to 1.46 lower)
Gabapentin versus placebo in **preoperative anxiety**	817	⊕◯◯◯ VERY LOW	-	-	SMD **0.92 lower** (1.32 lower to 0.52 lower)
Gabapentin versus placebo in **social anxiety disorder**	69 (1 study)	-	-	-	SMD **0.7 lower** (1.19 lower to 0.22 lower)
Gabapentin versus placebo in **panic disorder**	103 (1 study)	-	-	-	SMD **0.1 lower** (0.49 lower to 0.29 higher)

Legend: CI, confidence interval; SMD**,** standardised mean difference.

Appendix Table 5B. Pregabalin compared to placebo or active comparator in the treatment of generalised anxiety disorder

Patient or population: generalised anxiety disorder
Setting: any
Intervention: pregabalin
Comparison: placebo or active comparator

Outcomes	№ of participants Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo or active comparator	Risk difference with pregabalin
Pregabalin vs Placebo assessed with: Hamilton Anxiety Rating Scale, HAM-A	2689	⊕⊕◯◯ LOW	-	The mean pregabalin vs Placebo was **0**	MD **2.76 lower** (3.53 lower to 2 lower)
Pregabalin vs Lorazepam assessed with: Hamilton Anxiety Rating Scale, HAM-A	970	⊕⊕◯◯ LOW	-	The mean pregabalin vs Lorazepam was **0**	MD **0.35 higher** (0.8 lower to 1.5 higher)
Pregabalin vs Venlafaxine assessed with: Hamilton Anxiety Rating Scale, HAM-A	554	⊕⊕◯◯ LOW	-	The mean pregabalin vs Venlafaxine was **0**	MD **1.24 lower** (3.4 lower to 0.91 higher)

Legend: CI, confidence interval; MD**,** mean difference.

Appendix Table 5C. Pregabalin compared to placebo in social anxiety disorder

Patient or population: social anxiety disorder (short-term treatment)
Setting: any
Intervention: pregabalin
Comparison: placebo

Outcomes	№ of participants Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with pregabalin
Liebowitz Social Anxiety Scale (LSAS)	462	⊕⊕◯◯ LOW	-	The mean Leibowitz Social Anxiety Scale, LSAS, at week 10 was **0**	MD **6.07 lower** (10.98 lower to 1.15 lower)
Hamilton Anxiety Rating Scale (HAM-A)	463	⊕⊕◯◯ LOW	-	The mean Hamilton Anxiety Rating Scale, HAM-A, at week 10 was **0**	MD **0.83 lower** (2.08 lower to 0.42 higher)

Legend: CI, confidence interval; SMD**,** standardised mean difference.

Appendix Table 5D. Gabapentin compared to placebo in the management of preoperative anxiety

Patient or population: the management of preoperative anxiety
Setting: preoperative
Intervention: gabapentin
Comparison: placebo

Outcomes	№ of participants Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with gabapentin
Gabapentin vs placebo for **preoperative anxiety** (Low-dose subgroup + High-dose subgroup)	817	⊕◯◯◯ VERY LOW	-	-	SMD **0.92 lower** (1.32 lower to 0.52 lower)
Low-dose subgroup (gabapentin dose of 600mg)	244	⊕⊕◯◯ LOW	-	-	SMD **0.06 lower** (0.32 lower to 0.2 higher)
High-dose subgroup (gabapentin dose >600mg)	573	⊕◯◯◯ VERY LOW	-	-	SMD **1.3 lower** (1.72 lower to 0.87 lower)

Legend: CI, confidence interval; SMD**,** standardised mean difference.

Appendix Table 5E. Pregabalin compared to placebo in the management of preoperative anxiety

Patient or population: the management of preoperative anxiety
Setting: preoperative
Intervention: pregabalin
Comparison: placebo

Outcomes	№ of participants Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with pregabalin
Pregabalin vs placebo for **preoperative anxiety** (Low-dose subgroup + High-dose subgroup)	971	⊕◯◯◯ VERY LOW	-	-	SMD **0.43 lower** (0.73 lower to 0.13 lower)
Low-dose subgroup (pregabalin dose <300mg)	609	⊕⊕◯◯ LOW	-	-	SMD **0.29 lower** (0.54 lower to 0.05 lower)
High-dose subgroup (pregabalin dose of 300mg)	362	⊕◯◯◯ VERY LOW	-	-	SMD **0.74 lower** (1.65 lower to 0.18 higher)

Legend: CI, confidence interval; SMD**,** standardised mean difference.

Appendix Table 5F. Gabapentin compared to placebo in the treatment of insomnia in participants with alcohol dependence

Patient or population: insomnia in participants with alcohol dependence
Setting: any
Intervention: gabapentin
Comparison: placebo

Outcomes	№ of participants Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with gabapentin
Self-reported sleep quality assessed with: SMD (PSQI and SPQ) at week 6	164	-	-	-	SMD **0.14 lower** (0.47 lower to 0.19 higher)
Self-reported sleep quality assessed with: SMD (PSQI and SPQ) at week 12	161	-	-	-	SMD **0.12 higher** (0.82 lower to 1.06 higher)

Legend: CI, confidence interval; PSQI, Pittsburgh Sleep Quality Index; SMD**,** standardised mean difference; SPQ, Sleep Problems Questionnaire

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).