

Essential oil of lavender in anxiety disorders: Ready for prime time?

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How to cite: Malcolm BJ, Tallian K. Essential oil of lavender in anxiety disorders: Ready for prime time? Ment Health Clin [Internet]. 2017;7(4):147-55. DOI: 10.9740/mhc.2017.07.147.

Abstract

Anxiety disorders are some of the most common psychiatric disorders, with potentially debilitating consequences on individual function. Existing pharmacotherapies for anxiety disorders are limited by delay to therapeutic effect, dependence, tolerance, withdrawal, and abuse potential. Therefore, safe and evidence-based complementary or alternative therapies may be important allies in the care of patients with anxiety disorders. Essential oils are lipophilic and concentrated botanical extracts that exhibit many properties of drugs, although they are not Food and Drug Administration approved and have limitations characteristic of herbal preparations. Lavender essential oil has an extensive anecdotal history of anxiolytic benefit that has recently been supported by clinical efficacy studies. The 2 primary terpenoid constituents of lavender essential oil, linalool and linalyl acetate, may produce an anxiolytic effect in combination via inhibition of voltage-gated calcium channels, reduction of 5HT_{1A} receptor activity, and increased parasympathetic tone. The objectives of this article are to provide a brief overview of lavender oil in aromatherapy, explore variability in the constituents of lavender oil, summarize its pharmacology and safety profile, as well as describe its body of research that has been conducted for anxiety.

Keywords: lavender, essential oil, linalool, linalyl acetate, Silexan, anxiety, stress, complementary and alternative medicine

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Disclosures: B.J.M. has no relevant conflicts of interest or financial relationships to disclose. K.T. has no relevant conflicts of interest or financial relationships to disclose.

Background

Anxiety disorders are prevalent psychiatric conditions that can be debilitating in many patients and include phobia, panic, general anxiety (GAD), and separation anxiety disorders.¹ It is estimated that the 12-month prevalence of anxiety disorders is about 10% in the adult population and that females are twice as likely to have an anxiety disorder

in comparison with males.^{2,3} Afflicted individuals typically exhibit both psychiatric and somatic symptoms, with depression, sleep disturbance, and substance use disorders being common comorbidities.⁴⁻⁶ Current anxiolytic treatment options have limitations in efficacy, such as delay to onset (eg, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, buspirone) as well as habituation, tolerance, and abuse potential (eg, benzodiazepines, pregabalin). Other limiting factors include side effects, like sedation (eg, hydroxyzine, benzodiazepines) and withdrawal syndromes (eg, benzodiazepines, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors).⁷ Even when used appropriately, anxiolytic agents may lack efficacy or only be partially effective in controlling symptoms, warranting the consideration of complementary or alternative treatment options.

Essential oil (EO) of lavender (LEO; *Lavandula angustifolia*) is purported to be antibacterial, antifungal, anxiolytic,



antidepressant, analgesic, carminative (smooth-muscle relaxant), as well as to have beneficial immunomodulatory effects on wound healing.⁸⁻¹⁰ Folkloric claims of benefit in anxiety have been supported recently by clinical data, while other studies have produced inconclusive or equivocal results. Although whole-plant formulations may not provide adequate concentrations of active ingredients for effect, EOs are concentrated lipophilic extracts of aromatic terpenoid constituents. They are able to traverse cell membranes and exhibit pharmacologic effects at nanomolar concentrations, making them *drug-like* and increasing suitability for potential pharmaceutical application.¹¹ The objectives of this article are to provide a brief overview of lavender oil in aromatherapy, explore variability in the constituents of lavender oil, summarize its pharmacology and safety profile, and describe its body of research that has been conducted for anxiety.

Lavender Oil and Aromatherapy

Historically, EOs have been delivered as aromatherapy via inhalation or topical routes. Essential oils delivered via inhalation route may exert psychologic effects, because the olfactory bulb has limbic inputs in the amygdala and hippocampus that are associated with emotion and memory.¹² It is hypothesized that smell-triggered emotional memory may be the etiologic root of situational anxiety in some circumstances. This form of emotional memory is exemplified by state anxiety associated with the characteristic smell of the dentist's office, which has been reduced with LEO.¹³ Conversely, particular smells may be associated with positive emotions and mood, which is a core tenet of hypothesized benefits in aromatherapy.

Studies of aromatherapy pose significant challenges to highly rigorous research because of the inability to blind investigators and participants from the scent of the EO or control topical massage, confounding any observed benefit. Many small, randomized trials of aromatherapy have been performed in medical settings that may provoke anxiety, although the participants who were included had not received a diagnosis of an anxiety disorder at baseline. Reduction of state anxiety in such situations as preoperative anxiety, chest tube removal, cosmetic procedures, and intensive care unit stays, were reported.¹⁴⁻¹⁸ However, other similarly designed studies¹⁹⁻²² in similar settings have failed to show benefit or have not demonstrated clear benefit. A single observational pilot study²³ in postpartum women with anxiety demonstrated reduced anxiety levels using a rose/lavender oil blend for 15 minutes twice weekly during the course of 4 weeks. One study²⁴ concluded that participant expectation of relaxation was a greater factor than LEO itself,

highlighting the expectation bias to which aromatherapy studies may be subject to despite blinding.

Variability in Lavender Oil Constituents

Essential oils, including LEO, are complex compositions of compounds that may contain up to several hundred distinct chemical entities. They vary in constituents in a manner similar to that of herbal products, because the aromatic compounds produced are a function of the botanical products' genetics, growth conditions, and oil extraction process. Gas chromatography–mass spectrometry has aided in untangling which constituents occur most frequently, allowed insight into variability among LEOs, and given clues about which constituents may be primarily active. For example, one analytic study found varying concentrations of linalool (26.73%-57.48%) and linalyl acetate (4.01%-35.39%) among 9 different LEO samples.²⁵ This concentration variability leads to significant heterogeneity in products used in different studies and adds to the difficulty in delineating results.

In Germany, a standardized essential oil extract of *Lavandula angustifolia* (SLO) for oral administration has been developed and approved for use in subsyndromal anxiety. The SLO product (Silexan, W. Spitzner Arzneimittelfabrik GmbH, Ettlingen, Germany), contains the 2 primary constituents of lavender oil—linalool and linalyl acetate—at concentrations of 36.8% and 34.2%, respectively.¹¹ Although SLO has consistent amounts of linalool and linalyl acetate, they comprise only 71% of the oils' overall composition, leaving room for variation in constituents that occur in lower concentrations. The SLO product is available in 80-mg gel capsules for once- or twice-daily administration and is marketed as an over-the-counter dietary supplement called Calm Aid in the United States. The use of a standardized oral formulation in SLO has greatly increased the ability to study lavender oil with a high degree of methodologic rigor, including through randomized, double-blinded, placebo-controlled studies. Although not the intended focus of this article, SLO provides the highest-quality clinical evidence currently available for LEO.^{26,27}

Although SLO is standardized to 80 mg, a similar dose size can be calculated readily using a nonstandardized LEO. The density of lavender oil has been estimated to be around 0.88 g/mL at 20°C.²⁸ Therefore, 0.1 mL of oil would weigh approximately 88 to 89 mg. Assuming 20 drops per milliliter, this would equate to around 2 drops of LEO for a dose of 88 mg, although variability is to be expected given the imprecise nature of this calculation, and it may be more accurate to measure a volume or directly weigh the oil.

Mechanism of Action

A few lines of inquiry have helped to elucidate potential mechanism(s) of action of LEO in anxiety-related conditions, which appears to be related to inhibition of voltage-gated calcium channels (VGCCs), reduction of 5HT_{1A} receptor activity, and increased parasympathetic tone. A purely psychologic mechanism has been refuted in the case of LEO's anxiolytic effects because anosmic mice display inhibition of marble burying after lavender oil inhalation.²⁹ Pharmacokinetic data after topical application in healthy human volunteers also demonstrated the ability of LEO's constituents linalool and linalyl acetate to rapidly penetrate cell membranes and reach serum concentrations in excess of 100 ng/mL, corroborating pharmacodynamic action.³⁰

In mice, SLO was used along with diazepam, pregabalin, and other essential oil-based terpenes as active controls to investigate pharmacodynamic properties. The SLO lacked appreciable affinity for serotonin, norepinephrine, or dopamine reuptake transporters, as well as monoamine oxidase-A or γ -aminobutyric acid-A receptors, suggesting a novel mechanism compared with traditional anxiolytic therapies. Linalool and linalyl acetate displayed inhibitory activity on Ca²⁺ influx mediated by VGCCs in murine synaptosomes as well as primary hippocampal neurons with an estimated IC₅₀ of 37 nM for linalool. In contrast to pregabalin, which exerts inhibition of Ca²⁺ influx via interaction with α 2 δ -1 and α 2 δ -2 subunits of P/Q type VGCCs, SLO did not bind with these subunits, although it did produce a nonspecific decrease in Ca²⁺ influx across N, T, and P/Q type VGCCs, suggesting a truly unique mechanism.¹¹

A randomized, blinded, placebo-controlled crossover trial³¹ in 17 healthy human volunteers investigated brain changes detectable by positron emission tomography and magnetic resonance imaging scanning after administering 8 weeks of SLO at 160 mg/d. The investigators focused on the inhibitory 5HT_{1A} receptor because of increases in activity of this receptor being highlighted in the pathophysiology of anxiety in previous neuroimaging studies.³² They found reduced binding potential at the 5HT_{1A} receptor in the hippocampus and the anterior cingulate cortex in the SLO group compared with placebo, which has also been demonstrated after administration of escitalopram or electroconvulsive therapy in patients with anxiety.^{31,33} The authors postulate that reductions in 5HT_{1A} receptor activity may be a commonality in the anxiolytic efficacy of various interventions, and that SLO also acts via this mechanism.

Additional to central effects, lavender oil appears to have peripheral effects that may be important to its mechanism of action. Lavender oil has displayed increased parasympathetic activity as well as decreased hemodynamic parameters in rats, dogs, and humans.³⁴⁻³⁸ These effects may help alleviate somatic symptoms of anxiety characterized by autonomic arousal, although they may introduce pharmacodynamic interaction potential with antihypertensive or central nervous system depressant agents.

pathetic activity as well as decreased hemodynamic parameters in rats, dogs, and humans.³⁴⁻³⁸ These effects may help alleviate somatic symptoms of anxiety characterized by autonomic arousal, although they may introduce pharmacodynamic interaction potential with antihypertensive or central nervous system depressant agents.

Pharmacokinetics

Linalyl acetate is a carboxylated ester and metabolized to linalool by β -esterases, which are mostly found in hepatocytes but are also found in the periphery. Linalool is metabolized primarily through conjugation with glucuronic acid and is oxidized by cytochrome P450 enzymes (CYP450). Linalool is excreted primarily in urine but is also excreted via feces and in expired air.³⁹

Two clinical drug interaction studies^{40,41} have been conducted using SLO. One was conducted in 16 healthy volunteers who were administered SLO 160 mg/d for 11 days in a double-blind, randomized, placebo-controlled, crossover fashion.⁴⁰ Various drugs were used for phenotyping effects on CYP enzymes, with no clinically relevant inhibition or induction found on CYP 1A2, 2C9, 2C19, 2D6, and 3A4 enzymes. The second was a double-blind, randomized, placebo-controlled, crossover trial conducted in 24 women taking oral contraceptives during two menstrual cycles.⁴¹ No changes in area under the curve or maximum serum concentration (C_{max}) values of ethinyl estradiol or levonorgestrel were discovered, and there were no changes in secondary outcomes that may indicate impairment of oral contraceptive efficacy. However, the time to maximum concentration (T_{max}) for levonorgestrel was slightly delayed. Although this may not be clinically significant in the use of daily oral contraceptives, efficacy of emergency contraceptives in which efficacy is critically time dependent could be impacted.⁴¹ Effects on glucuronosyltransferase have not been described.

Safety and Tolerability

Lavender essential oil has been granted Generally Recognized as Safe status by the Food and Drug Administration (21CFR182.20 2015), which means that it is safe when used for its intended purpose as a food additive.⁴² Many EOs are inappropriate for oral administration in their undiluted form because of irritant, inflammatory, or cytotoxic effects on skin and especially mucous membranes, warranting dilution or avoidance. LEO is seemingly well-tolerated in this regard and is often applied topically or administered orally in an undiluted form. Reports of in vivo contact dermatitis and in vitro

cytotoxicity, however, exist, warranting caution.^{43,44} Long-term studies demonstrating safety are lacking.

Reports of prepubertal gynecomastia in boys exposed to LEO have been reported, although these are far from conclusive.⁴⁵ LEO displayed very weak estrogenic and antiandrogenic activity in vitro, raising doubt as to whether the effects could actually induce gynecomastia.⁴⁶

Poisoning by lavender is uncommon. In the late 1960s and early 1970s, the LD₅₀ values for lavender taken orally and applied topically were determined. In mice, the oral LD₅₀ was 13.5 ± 0.9 g/kg, where central nervous system depression occurred 10 to 15 minutes following ingestion and death occurred 1 to 3 days later.^{47,48} Similar results were observed in rats.⁴⁷ For dermal applications, the LD₅₀ was greater than 5 g/kg, with no systemic symptoms or deaths in rabbits observed up to 14 days.⁴⁸ In humans, an 18-month-old boy ingested homemade lavandin (*Lavandula x intermedia*) extract. Three hours following the ingestion, the child developed confusion and deep drowsiness, with adaptive motor response to painful stimuli indicative of moderate brain injury (Glasgow Coma Score = 9). His neurologic status normalized within 6 hours of hospitalization, and a follow-up electroencephalogram was normal at 24 hours. Comparative toxicology analysis between the boy's blood, urine, and pure lavandin extract showed linalyl acetate, linalyl formate, and acetone were detected in all samples. Acetone, which was a confounding factor for coma in the poisoning, was found to be slightly higher than normal in healthy adults and was concluded not to be the cause of the central nervous system depression.⁴⁹

Efficacy in Anxiety Disorders

Medline and EMBASE searches were conducted between database inception and September 15, 2016. Search terms included *linalool or linalyl acetate or lavender oil or Lavandula angustifolia or Silexan* and *anxiety or stress*. Searches were conducted independently by one of the study authors (B.J.M.) as well as a medical librarian. Articles reviewed were randomized studies that enrolled at least 10 human participants with an anxiety disorder, featured an end point that measured anxiety, and were written in English. Review articles were screened for additional references.

Five double-blinded and randomized controlled trials using either placebo or active controls were identified that are summarized in the Table.⁵⁰⁻⁵⁴ All trials were conducted in Germany, had a duration of 6 to 10 weeks, and used the oral standardized lavender oil preparation SLO. Studies were conducted in an outpatient setting and were generally mixed between psychiatric and primary

care practices. Some major strengths of the studies were adequate power to detect differences in treatments, use of both intention-to-treat and per protocol analysis sets, and prohibition of concomitant anxiolytic medications or psychotherapy during the study period. Participants were predominantly female (66%-77%), an average age of 45 to 49 years, white, and had a moderate to severe anxiety according to baseline Hamilton Anxiety Rating Scale (HAMA) scores. Psychiatric and neurologic comorbidities were generally excluded, including personality disorders, substance use disorders, and suicidality. Varying degrees of depressive symptoms were allowed, although this was study dependent. In all trials SLO was found to be efficacious in reducing HAMA scores (Table) and was well tolerated, with gastrointestinal side effects being the most commonly reported side effect.

Three of the studies^{50,51,53} compared SLO 80 mg daily to placebo. One study⁵³ (n = 318) included patients with Mixed Anxiety and Depressive Disorder and measured both anxiolytic and antidepressant effects. Mixed Anxiety and Depressive Disorder is a World Health Organization International Classification of Diseases (ICD) diagnosis pertaining to patients suffering from anxiety with autonomic features and depressive symptoms of equal intensity without anxious or depressive symptoms being predominant. SLO was found to be efficacious in reducing HAMA scores (Table) as well as Montgomery-Asberg Depression Rating Scale Scores. Montgomery-Asberg Depression Rating Scale scores decreased from 22.0 at baseline to 12.8 ± 8.7 with SLO, compared with 22.1 ± 6.1 to 16.0 ± 9.8 with placebo, which corresponded with a mean difference of 3.53 (95% confidence interval: 1.36, 4.14; *P* < .001) in favor of SLO. The other two studies^{50,51} evaluated the effect of SLO on HAMA along with sleep by measuring the Pittsburgh Sleep Quality Index (PSQI) at baseline and scheduled visits in patients with subsyndromal anxiety disorder, and anxiety and restlessness with disturbed sleep. Subsyndromal anxiety disorder includes patients with pronounced anxiety or phobic avoidance who do not meet criteria for a more specific anxiety disorder. It is a World Health Organization ICD diagnosis, although it was paralleled in *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, as anxiety not otherwise specified. Restlessness and agitation with disturbed sleep is an ICD-10 diagnosis falling under an umbrella of disorders involving signs and symptoms associated with a negative emotional state that is not well defined. It is often used when signs and symptoms do not conform to traditional anxiety diagnoses. Patients treated with SLO compared with placebo for subsyndromal anxiety disorder (n = 216) had significant overall improvements in HAMA (Table) and PSQI scores (*P* = .002), with perceived sleep latency (*P* = .034), sleep duration (*P* = .001), and sleep quality (*P* = .003) most improved.⁵¹ In patients with anxiety-related restlessness

and disturbed sleep ($n=170$), there was no significant improvement in PSQI scores observed ($P=.091$), despite significant reductions in HAMA scores (Table).⁵⁰ Baseline PSQI scores were similar in patients between the two studies; thus, it appears that observed benefits on sleep were limited to patients with subsyndromal anxiety disorder. Although further studies are required to fully characterize SLO's effect on sleep architecture in different patient populations, PSQI and HAMA scores along with reported adverse effects suggest that SLO has an anxiolytic effect while lacking sedative or hypnotic properties.

Two other studies^{52,54} used active comparators and studied patients with GAD. The first study⁵⁴ ($n=77$) compared a single daily dose of lorazepam 0.5 mg to SLO 80 mg and found SLO to be noninferior. Although 0.5 mg of lorazepam may be an adequate dose for some patients, it may be subtherapeutic in others. The second and largest study to date⁵² ($n=536$) featured both an active (paroxetine) and placebo control and compared them to SLO at both 80- and 160-mg daily dosages. The study found SLO in doses of 80 or 160 mg (administered as 80 mg orally twice a day) to be better than placebo in reducing HAMA scores, whereas the comparator paroxetine 20 mg did not separate significantly from placebo (Table). Paroxetine was administered in a fixed dose of 20 mg without titration, and although this may be a sufficient dose for some patients, others require higher doses to achieve response.⁵⁵ Patients were monitored for the week after discontinuation of the study period for withdrawal symptoms, which were not observed in participants randomized to SLO. Additional secondary outcomes, including patient self-rating SF-36 Health Survey Questionnaire and clinician-rated Clinical Global Impressions scale, were assessed in both studies. SLO and paroxetine showed improvement over placebo, whereas positive comparable results were seen between SLO and lorazepam with GAD for both the SF-36 and Clinical Global Impressions.

Discussion

Available trials support the short-term efficacy of the standardized lavender oil extract SLO in the treatment of anxiety disorders, including subsyndromal anxiety disorder (anxiety not otherwise specified), GAD, restlessness and agitation with disturbed sleep, and Mixed Anxiety and Depressive Disorder. Many treatment guidelines in anxiety disorders predate the publication of most of the randomized controlled trials featured in the Table. The British Association for Psychopharmacology (2014) and National Institute for Health and Clinical Excellence (2011) guidelines for GAD acknowledge evidence for SLO based on the single trial they examined⁵⁴; however, sufficient

data to make a definitive recommendation for use were not available at that time.^{7,56}

The SLO appears to have a calming effect without producing sedation, which is advantageous compared with benzodiazepines or pregabalin. SLO also lacks a withdrawal syndrome and is not thought to have abuse potential.⁵² Pharmacokinetic drug interaction potential appears minimal, and adverse effects observed in studies were mild. Onset of efficacy occurs within 2 weeks in patients who respond, in contrast to the 4 to 6 weeks it takes for monoamine reuptake-inhibiting antidepressants to have a therapeutic effect. Additionally, monoamine reuptake-inhibiting antidepressants often produce transient side effects upon initiation, including increased anxiety, often necessitating a short course of benzodiazepines for effective management.

There are many unanswered questions regarding the use of LEO in the treatment of anxiety, as well as limitations to the current body of evidence. Essential oil of lavender lacks evidence in many types of anxiety, such as panic and phobic disorders. Moreover, with the exception of GAD, the anxiety-related disorders studied tended to be nonspecific diagnoses given in the context of prominent symptoms that lacked criteria for a better defined anxiety disorder. Long-term safety studies are lacking, which is concerning, given that anxiety disorders may be chronic conditions and LEO has displayed cytotoxic properties.⁴⁴ Given the variability in LEO preparations, it is also unclear if results observed in trials using SLO are reproducible using LEO from other sources or if constituents that are less well characterized are playing an important role in the oil's effect. Trials conducted have used SLO as monotherapy, so it is unknown if it is appropriate or effective to use adjunctively with traditional anxiolytic medications. When active comparators were used, doses were fixed and potentially subtherapeutic. All trials of SLO have been conducted in Germany and include mostly middle-aged white women, which reduces the ability to generalize results to other populations, such as children, adolescents, the elderly, or other ethnic groups. Psychiatric comorbidity is common with anxiety disorders, although many were excluded from clinical trials, which lowers the external validity of observed findings. Eructation (belching) was a commonly reported side effect in clinical trials, raising the question as to whether blinding may be compromised because patients could potentially taste lavender oil upon eructation.

Conclusions

The SLO product exhibits many desirable properties of an anxiolytic agent, including a calming effect without sedation, as well as a lack of dependence, tolerance, or

TABLE: Randomized controlled trials conducted with lavender essential oil in patients with anxiety disorders

Study	Study Design	Sample	Intervention	Primary Outcome	Main Result	Adverse Effects
Kasper et al ⁵¹ (2010)	DB with 2 parallel groups 27 General and psychiatric primary care centers in Germany	<ul style="list-style-type: none"> Anxiety disorder NOS (DSM-IV) <i>subsyndromal anxiety disorder</i> 216 Participants (SLO, 107; placebo, 109) Baseline HAMA total score ≥ 18 points; PSQI > 5 	Capsules containing 80 mg of SLO or matching placebo: 1 PO daily $\times 10$ wk	HAMA: score change from baseline to wk 10	HAMA: <ul style="list-style-type: none"> Baseline: 26.8 ± 5.4 SLO; 27.1 ± 5.3 placebo ($P < .755$) SLO decrease: 16.0 ± 8.3; placebo decrease: 9.5 ± 9.1 ($P < .001$) 	GI-related side effects
Woelk and Schläfke ⁵⁴ (2010)	DB with 2 parallel groups Outpatient general practitioners in Germany	<ul style="list-style-type: none"> Patients with GAD (DSM-IV) Average duration of illness: 4.5 ± 5.0 y Baseline HAMA total score ≥ 18 points 77 Participants (SLO, 40; lorazepam, 37) 	Capsules containing 80 mg of SLO or lorazepam 0.5 mg: 1 PO daily $\times 6$ wk	HAMA: score change from baseline to wk 6	HAMA: <ul style="list-style-type: none"> SLO: baseline, 25.0 ± 4.0; week 6, 11.3 ± 6.7 Lorazepam: baseline, 25.0 ± 4.0; week 6, 11.6 ± 6.6 	SLO: eructation, dyspepsia, nausea Lorazepam: nausea, fatigue
Kasper et al ⁵² (2014)	DB with 4 parallel groups 57 Psychiatric and general practices in Germany	<ul style="list-style-type: none"> Patients with GAD (DSM-5) Average duration of illness 2.5 y, current episode 1 y 536 Participants (SLO, 160 mg/d, 128; 80 mg/d, 135; paroxetine, 137; placebo, 136) Baseline HAMA total score ≥ 18 points 	Capsules containing 80 mg of SLO, matching placebo, or paroxetine: SLO 80 mg; 160 mg; paroxetine 20 mg; placebo PO daily $\times 10$ wk	HAMA: score change from baseline to wk 10	HAMA: decreased <ul style="list-style-type: none"> SLO 160 mg/d ($P < .001$), 14.1 ± 9.3 SLO 160 mg/d ($P < .001$), 12.8 ± 8.7 SLO 80 mg/d ($P = .002$), 11.3 ± 8.0 paroxetine ($P = .096$), and 9.5 ± 9.0 placebo 	No withdrawal-related symptoms measured in posttrial observation week

TABLE: Randomized controlled trials conducted with lavender essential oil in patients with anxiety disorders (continued)

Study	Study Design	Sample	Intervention	Primary Outcome	Main Result	Adverse Effects
Kasper et al ⁵⁰ (2015)	DB with 2 parallel groups 17 General and psychiatric practices in Germany	<ul style="list-style-type: none"> Patients with restlessness, disturbed sleep, and subthreshold anxiety disorder (R45.1 ICD-10) 170 Participants (SLO, 86; placebo, 84) Baseline HAMA total score ≥ 18 points; PSQI ≥ 6; VAS ≥ 5 for agitation and restlessness 	Capsules containing 80 mg of SLO or matching placebo: 1 PO daily \times 10 wk	HAMA: score change from baseline to wk 10	<ul style="list-style-type: none"> HAMA: Baseline: 25.5 ± 6.0; wk 10: 13.7 ± 7.0 SLO decrease -12.5; placebo decrease -9 ($P = .01$) 	Eructation, diarrhea, oral discomfort, gastritis (10.5%)
Kasper et al ⁵³ (2016)	DB with 2 parallel groups 35 Psychiatric practices in Germany	<ul style="list-style-type: none"> Patients with MADD (ICD-10 F41.2) 318 Participants (SLO, 160; placebo, 158) Baseline HAMA total score ≥ 18 points 	Capsules containing 80 mg of SLO or matching placebo: 1 PO daily \times 10 wk	HAMA: score change from baseline to wk 10	<ul style="list-style-type: none"> HAMA: Baseline: 25.7 ± 5.6; week 10: 14.9 ± 9.3 2.47-Point difference between SLO and placebo (95% CI: 0.48, 4.47; $P = .008$) 	Eructation, nausea

CI = confidence interval; DB = double blind; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition; GAD = generalized anxiety and depressive disorder; GI = gastrointestinal; HAMA = Hamilton Anxiety Rating Scale; ICD = International Classification of Diseases; MADD = mixed anxiety and depressive disorder; NOS = not otherwise specified; PO = orally; PSQI = Pittsburgh Sleep Quality Index; SLO = standardized essential oil extract of *Lavandula angustifolia*; VAS = visual analog scale.

withdrawal. SLO has a relatively benign side effect profile in short-term studies, and its onset of efficacy is more rapid than current first-line agents. Evidence from multiple high-quality randomized trials suggests a role for SLO in the treatment of anxiety disorders. The favorable safety and efficacy profile of SLO makes it a reasonable alternative to consider in patients with anxiety disorders. Clinicians should exercise caution given limitations of the current evidence base and lack of Food and Drug Administration endorsement in the management of anxiety disorders.

References

- American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. Arlington (VA): American Psychiatric Association; 2013.
- Kessler RC, Aguilar-Gaxiola S, Alonso J, Chatterji S, Lee S, Ormel J, et al. The global burden of mental disorders: an update from the WHO World Mental Health (WMH) Surveys. *Epidemiol Psychiatr Soc*. 2009;18(1):23-33. DOI: [10.1017/S1121189X00001421](https://doi.org/10.1017/S1121189X00001421). PubMed PMID: [19378696](https://pubmed.ncbi.nlm.nih.gov/19378696/).
- McLean CP, Asnaani A, Litz BT, Hofmann SG. Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. *J Psychiatr Res*. 2011;45(8):1027-35. DOI: [10.1016/j.jpsychires.2011.03.006](https://doi.org/10.1016/j.jpsychires.2011.03.006). PubMed PMID: [21439576](https://pubmed.ncbi.nlm.nih.gov/21439576/).
- Kushner MG, Sher KJ, Beitman BD. The relation between alcohol problems and the anxiety disorders. *Am J Psychiatry*. 1990;147(6):685-95. DOI: [10.1176/ajp.147.6.685](https://doi.org/10.1176/ajp.147.6.685). PubMed PMID: [2188513](https://pubmed.ncbi.nlm.nih.gov/2188513/).
- Wittchen HU. DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1994;51(5):355-64. DOI: [10.1001/archpsyc.1994.03950050015002](https://doi.org/10.1001/archpsyc.1994.03950050015002). PubMed PMID: [8179459](https://pubmed.ncbi.nlm.nih.gov/8179459/).
- Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol*. 2011;21(9):655-79. DOI: [10.1016/j.euroneuro.2011.07.018](https://doi.org/10.1016/j.euroneuro.2011.07.018). PubMed PMID: [21896369](https://pubmed.ncbi.nlm.nih.gov/21896369/).
- National Collaborating Centre for Mental Health. Generalised anxiety disorder in adults: management in primary, secondary

- and community care. Leicester (UK): The British Psychological Society & The Royal College of Psychiatrists; 2011.
8. Cavanagh HMA, Wilkinson JM. Biological activities of Lavender essential oil. *Phytother Res.* 2002;16(4):301-8. DOI: [10.1002/ptr.1103](https://doi.org/10.1002/ptr.1103). PubMed PMID: [12112282](https://pubmed.ncbi.nlm.nih.gov/12112282/).
 9. Jones C. The efficacy of lavender oil on perineal trauma: a review of the evidence. *Complement Ther Clin Pract.* 2011;17(4):215-20. DOI: [10.1016/j.ctcp.2011.01.003](https://doi.org/10.1016/j.ctcp.2011.01.003). PubMed PMID: [21982136](https://pubmed.ncbi.nlm.nih.gov/21982136/).
 10. Nagai K, Nijima A, Horii Y, Shen J, Tanida M. Olfactory stimulatory with grapefruit and lavender oils change autonomic nerve activity and physiological function. *Auton Neurosci.* 2014;185:29-35. DOI: [10.1016/j.autneu.2014.06.005](https://doi.org/10.1016/j.autneu.2014.06.005). PubMed PMID: [25002406](https://pubmed.ncbi.nlm.nih.gov/25002406/).
 11. Schuwald AM, Nöldner M, Wilmes T, Klugbauer N, Leuner K, Müller WE. Lavender oil-potent anxiolytic properties via modulating voltage dependent calcium channels. *PLoS One.* 2013;8(4):e59998. DOI: [10.1371/journal.pone.0059998](https://doi.org/10.1371/journal.pone.0059998). PubMed PMID: [23637742](https://pubmed.ncbi.nlm.nih.gov/23637742/).
 12. Gottfried JA. *Neurobiology of sensation and reward.* Boca Raton (FL): CRC Press/Taylor & Francis; 2011.
 13. Kritsidima M, Newton T, Asimakopoulou K. The effects of lavender scent on dental patient anxiety levels: a cluster randomised-controlled trial. *Community Dent Oral Epidemiol.* 2010;38(1):83-7. DOI: [10.1111/j.1600-0528.2009.00511.x](https://doi.org/10.1111/j.1600-0528.2009.00511.x). PubMed PMID: [19968674](https://pubmed.ncbi.nlm.nih.gov/19968674/).
 14. Braden R, Reichow S, Halm MA. The use of the essential oil lavender to reduce preoperative anxiety in surgical patients. *J Perianesth Nurs.* 2009;24(6):348-55. DOI: [10.1016/j.jopan.2009.10.002](https://doi.org/10.1016/j.jopan.2009.10.002). PubMed PMID: [19962101](https://pubmed.ncbi.nlm.nih.gov/19962101/).
 15. Cho MY, Min ES, Hur MH, Lee MS. Effects of aromatherapy on the anxiety, vital signs, and sleep quality of percutaneous coronary intervention patients in intensive care units. *Evid Based Complement Alternat Med.* 2013;2013:381381. DOI: [10.1155/2013/381381](https://doi.org/10.1155/2013/381381). PubMed PMID: [23476690](https://pubmed.ncbi.nlm.nih.gov/23476690/).
 16. Franco L, Blanck TJJ, Dugan K, Kline R, Shanmugam G, Galotti A, et al. Both lavender fleur oil and unscented oil aromatherapy reduce preoperative anxiety in breast surgery patients: a randomized trial. *J Clin Anesth.* 2016;33:243-9. DOI: [10.1016/j.jclinane.2016.02.032](https://doi.org/10.1016/j.jclinane.2016.02.032). PubMed PMID: [27555173](https://pubmed.ncbi.nlm.nih.gov/27555173/).
 17. Grunebaum LD, Murdock J, Castaneda-Tardan MP, Baumann LS. Effects of lavender olfactory input on cosmetic procedures. *J Cosmet Dermatol.* 2011;10(2):89-93. DOI: [10.1111/j.1473-2165.2011.00554.x](https://doi.org/10.1111/j.1473-2165.2011.00554.x). PubMed PMID: [21649812](https://pubmed.ncbi.nlm.nih.gov/21649812/).
 18. Hasanzadeh F, Kashouk NM, Amini S, et al. The effect of cold application and lavender oil inhalation in cardiac surgery patients undergoing chest tube removal. *EXCLI J.* 2016;15:64-74. DOI: [10.17179/excli2015-748](https://doi.org/10.17179/excli2015-748). PubMed PMID: [27047319](https://pubmed.ncbi.nlm.nih.gov/27047319/).
 19. Bikmoradi A, Seifi Z, Poorolajal J, Aragchian M, Safiaryan R, Oshvandi K. Effect of inhalation aromatherapy with lavender essential oil on stress and vital signs in patients undergoing coronary artery bypass surgery: a single-blinded randomized clinical trial. *Complement Ther Med.* 2015;23(3):331-8. DOI: [10.1016/j.ctim.2014.12.001](https://doi.org/10.1016/j.ctim.2014.12.001). PubMed PMID: [26051567](https://pubmed.ncbi.nlm.nih.gov/26051567/).
 20. Dunn C, Sleep J, Collett D. Sensing an improvement: an experimental study to evaluate the use of aromatherapy, massage and periods of rest in an intensive care unit. *J Adv Nurs.* 2008;21(1):34-40. DOI: [10.1046/j.1365-2648.1995.21010034.x](https://doi.org/10.1046/j.1365-2648.1995.21010034.x). PubMed PMID: [7897075](https://pubmed.ncbi.nlm.nih.gov/7897075/).
 21. Graham PH, Browne L, Cox H, Graham J. Inhalation aromatherapy during radiotherapy: results of a placebo-controlled double-blind randomized trial. *J Clin Oncol.* 2003;21(12):2372-6. DOI: [10.1200/JCO.2003.10.126](https://doi.org/10.1200/JCO.2003.10.126). PubMed PMID: [12805340](https://pubmed.ncbi.nlm.nih.gov/12805340/).
 22. Muzzarelli L, Force M, Sebold M. Aromatherapy and reducing preprocedural anxiety: a controlled prospective study. *Gastroenterol Nurs.* 2006;29(6):466-71. DOI: [10.1097/00001610-200611000-00005](https://doi.org/10.1097/00001610-200611000-00005). PubMed PMID: [17273013](https://pubmed.ncbi.nlm.nih.gov/17273013/).
 23. Conrad P, Adams C. The effects of clinical aromatherapy for anxiety and depression in the high risk postpartum woman—a pilot study. *Complement Ther Clin Pract.* 2012;18(3):164-8. DOI: [10.1016/j.ctcp.2012.05.002](https://doi.org/10.1016/j.ctcp.2012.05.002). PubMed PMID: [22789792](https://pubmed.ncbi.nlm.nih.gov/22789792/).
 24. Howard S, Hughes BM. Expectancies, not aroma, explain impact of lavender aromatherapy on psychophysiological indices of relaxation in young healthy women. *Br J Health Psychol.* 2010;13(Pt 4):603-17. DOI: [10.1348/135910707X238734](https://doi.org/10.1348/135910707X238734). PubMed PMID: [17845737](https://pubmed.ncbi.nlm.nih.gov/17845737/).
 25. Shellie R, Mondello L, Marriott P, Dugo G. Characterisation of lavender essential oils by using gas chromatography-mass spectrometry with correlation of linear retention indices and comparison with comprehensive two-dimensional gas chromatography. *J Chromatogr A.* 2002;970(1-2):225-34. DOI: [10.1016/S0021-9673\(02\)00653-2](https://doi.org/10.1016/S0021-9673(02)00653-2). PubMed PMID: [12350096](https://pubmed.ncbi.nlm.nih.gov/12350096/).
 26. Kasper S. An orally administered lavandula oil preparation (Silexan) for anxiety disorder and related conditions: an evidence based review. *Int J Psychiatry Clin Pract.* 2013;17 Suppl 1:15-22. DOI: [10.3109/13651501.2013.813555](https://doi.org/10.3109/13651501.2013.813555). PubMed PMID: [23808618](https://pubmed.ncbi.nlm.nih.gov/23808618/).
 27. Perry R, Terry R, Watson LK, Ernst E. Is lavender an anxiolytic drug?: a systematic review of randomised clinical trials. *Phytomedicine.* 2012;19(8-9):825-35. DOI: [10.1016/j.phymed.2012.02.013](https://doi.org/10.1016/j.phymed.2012.02.013). PubMed PMID: [22464012](https://pubmed.ncbi.nlm.nih.gov/22464012/).
 28. Lavender essential oil material safety data sheet. Oldham (UK): Essential Oils Direct [2015; cited 2016 Sep 1]. Available from: https://www.essentialoilsdirect.co.uk/lavender-lavandula_angustifolia-essential_oil.html
 29. Chioca LR, Antunes VDC, Ferro MM, Losso EM, Andreatini R. Anosmia does not impair the anxiolytic-like effect of lavender essential oil inhalation in mice. *Life Sci.* 2013;92(20-21):971-5. DOI: [10.1016/j.lfs.2013.03.012](https://doi.org/10.1016/j.lfs.2013.03.012). PubMed PMID: [23567808](https://pubmed.ncbi.nlm.nih.gov/23567808/).
 30. Jäger WGB, Jirovetz L, Fritzer M. Percutaneous absorption of lavender oil from a massage oil. *J Soc Cosmet Chemists.* 1992;43:49-54.
 31. Baldinger P, Hoflich AS, Mitterhauser M, Hahn A, Rami-Mark C, Spies M, et al. Effects of Silexan on the serotonin-1A receptor and microstructure of the human brain: a randomized, placebo-controlled, double-blind, cross-over study with molecular and structural neuroimaging. *Int J Neuropsychopharmacol.* 2015;18(4):pyuo63. DOI: [10.1093/ijnp/pyuo63](https://doi.org/10.1093/ijnp/pyuo63). PubMed PMID: [25522403](https://pubmed.ncbi.nlm.nih.gov/25522403/).
 32. Akimova E, Lanzenberger R, Kasper S. The serotonin-1A receptor in anxiety disorders. 2009;66(7):627-35. DOI: [10.1016/j.biopsych.2009.03.012](https://doi.org/10.1016/j.biopsych.2009.03.012). PMID: [19423077](https://pubmed.ncbi.nlm.nih.gov/19423077/).
 33. Spindelegger C, Lanzenberger R, Wadsak W, Mien LK, Stein P, Mitterhauser M, et al. Influence of escitalopram treatment on 5-HT 1A receptor binding in limbic regions in patients with anxiety disorders. *Mol Psychiatry.* 2009;14(11):1040-50. DOI: [10.1038/mp.2008.35](https://doi.org/10.1038/mp.2008.35). PubMed PMID: [18362913](https://pubmed.ncbi.nlm.nih.gov/18362913/).
 34. Cha JH, Lee SH, Yoo YS. Effects of aromatherapy on changes in the autonomic nervous system, aortic pulse wave velocity and aortic augmentation index in patients with essential hypertension. *J Korean Acad Nurs.* 2010;40(5):705-13. DOI: [10.4040/jkan.2010.40.5.705](https://doi.org/10.4040/jkan.2010.40.5.705). PubMed PMID: [21157172](https://pubmed.ncbi.nlm.nih.gov/21157172/).
 35. Hur MH, Oh H, Lee MS, Kim C, Choi AN, Shin GR. Effects of aromatherapy massage on blood pressure and lipid profile in Korean climacteric women. *Int J Neurosci.* 2007;117(9):1281-7. DOI: [10.1080/00207450600936650](https://doi.org/10.1080/00207450600936650). PubMed PMID: [17654092](https://pubmed.ncbi.nlm.nih.gov/17654092/).
 36. Komiya M, Sugiyama A, Tanabe K, Uchino T, Takeuchi T. Evaluation of the effect of topical application of lavender oil on autonomic nerve activity in dogs. *Am J Vet Res.* 2009;70(6):764-9. DOI: [10.2460/ajvr.70.6.764](https://doi.org/10.2460/ajvr.70.6.764). PubMed PMID: [19496667](https://pubmed.ncbi.nlm.nih.gov/19496667/).
 37. Sayorwan W, Siripornpanich V, Piriyaunyaporn T, Hongratana-worakit T, Kotchabhakdi N, Ruangrunsi N. The effects of lavender oil inhalation on emotional states, autonomic nervous system, and brain electrical activity. *J Med Assoc Thai.* 2012;95(4):598-606. PubMed PMID: [22612017](https://pubmed.ncbi.nlm.nih.gov/22612017/).

38. Shen J, Nijima A, Tanida M, Horii Y, Maeda K, Nagai K. Olfactory stimulation with scent of lavender oil affects autonomic nerves, lipolysis and appetite in rats. *Neurosci Lett*. 2005;383(1-2):188-93. DOI: [10.1016/j.neulet.2005.04.010](https://doi.org/10.1016/j.neulet.2005.04.010). PubMed PMID: [15878236](https://pubmed.ncbi.nlm.nih.gov/15878236/).
39. Bickers D, Calow P, Greim H, Hanifin JM, Rogers AE, Saurat JH, et al. A toxicologic and dermatologic assessment of linalool and related esters when used as fragrance ingredients. *Food Chem Toxicol*. 2003;41(7):919-42. DOI: [10.1016/S0278-6915\(03\)00016-4](https://doi.org/10.1016/S0278-6915(03)00016-4). PubMed PMID: [12804649](https://pubmed.ncbi.nlm.nih.gov/12804649/).
40. Doroshyenko O, Rokitta D, Zadoyan G, Klement S, Schlafke S, Dienel A, et al. Drug cocktail interaction study on the effect of the orally administered lavender oil preparation silexan on cytochrome P450 enzymes in healthy volunteers. *Drug Metab Dispos*. 2013;41(5):987-93. DOI: [10.1124/dmd.112.050203](https://doi.org/10.1124/dmd.112.050203). PubMed PMID: [23401474](https://pubmed.ncbi.nlm.nih.gov/23401474/).
41. Heger-Mahn D, Pabst G, Dienel A, Schlafke S, Klipping C. No interacting influence of lavender oil preparation silexan on oral contraception using an ethinyl estradiol/levonorgestrel combination. *Drugs R D* 2014;14(4):265-72. DOI: [10.1007/s40268-014-0065-5](https://doi.org/10.1007/s40268-014-0065-5). PubMed PMID: [25319228](https://pubmed.ncbi.nlm.nih.gov/25319228/).
42. Food and Drug Administration [Internet]. 21CFR182.20 - Code of Federal Regulations Title 2. Silver Spring (MD): Food and Drug Administration; 2016 [cited 2016 Oct 1]. Available from: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=182.20>
43. Gangemi S, Minciullo PL, Miroddi M, Chinou I, Calapai G, Schmidt RJ. Contact dermatitis as an adverse reaction to some topically used European herbal medicinal products - part 2: *Echinacea purpurea-Lavandula angustifolia*. *Contact Dermatitis*. 2015;72(4):193-205. DOI: [10.1111/cod.12328](https://doi.org/10.1111/cod.12328). PubMed PMID: [25600644](https://pubmed.ncbi.nlm.nih.gov/25600644/).
44. Prashar A, Locke IC, Evans CS. Cytotoxicity of lavender oil and its major components to human skin cells. *Cell Prolif*. 2004;37(3):221-9. DOI: [10.1111/j.1365-2184.2004.00307.x](https://doi.org/10.1111/j.1365-2184.2004.00307.x). PubMed PMID: [15144499](https://pubmed.ncbi.nlm.nih.gov/15144499/).
45. Henley DV, Lipson N, Korach KS, Bloch CA. Prepubertal gynecomastia linked to lavender and tea tree oils. *N Engl J Med*. 2007;356(5):479-85. DOI: [10.1056/NEJMoa064725](https://doi.org/10.1056/NEJMoa064725). PubMed PMID: [17267908](https://pubmed.ncbi.nlm.nih.gov/17267908/).
46. Kalyan S. Prepubertal gynecomastia linked to lavender and tea tree oils. *N Engl J Med*. 2007;356(24):2542; author reply 2543-4. PubMed PMID: [17575592](https://pubmed.ncbi.nlm.nih.gov/17575592/).
47. Jenner PM, Hagan EC, Taylor JM, Cook EL, Fitzhugh OG. Food flavourings and compounds of related structure, I: acute oral toxicity. *Food Cosmet Toxicol*. 1964;2:327-43.
48. Letizia CS, Cocchiara J, Lalko J, Api AM. Fragrance material review on linalyl acetate. *Food Chem Toxicol*. 2003;41(7):965-76. PubMed PMID: [12804651](https://pubmed.ncbi.nlm.nih.gov/12804651/).
49. Landelle C, Francony G, Sam-Lai NF, Gaillard Y, Vincent F, Wroblewski I, et al. Poisoning by lavandin extract in a 18-month-old boy. *Clin Toxicol (Phila)*. 2008;46(4):279-81. DOI: [10.1080/15563650701281098](https://doi.org/10.1080/15563650701281098). PubMed PMID: [18363117](https://pubmed.ncbi.nlm.nih.gov/18363117/).
50. Kasper S, Anghelescu I, Dienel A. Efficacy of orally administered Silexan in patients with anxiety-related restlessness and disturbed sleep—a randomized, placebo-controlled trial. *Eur Neuropsychopharmacol*. 2015;25(11):1960-7. DOI: [10.1016/j.euroneuro.2015.07.024](https://doi.org/10.1016/j.euroneuro.2015.07.024). PubMed PMID: [26293583](https://pubmed.ncbi.nlm.nih.gov/26293583/).
51. Kasper S, Gastpar M, Müller WE, Volz HP, Möller HJ, Dienel A, et al. Silexan, an orally administered *Lavandula* oil preparation, is effective in the treatment of ‘subsyndromal’ anxiety disorder: a randomized, double-blind, placebo controlled trial. *Int Clin Psychopharmacol*. 2010;25(5):277-87. DOI: [10.1097/YIC.0b013e3283b3242](https://doi.org/10.1097/YIC.0b013e3283b3242). PubMed PMID: [20512042](https://pubmed.ncbi.nlm.nih.gov/20512042/).
52. Kasper S, Gastpar M, Müller WE, Volz HP, Möller HJ, Schläfke S, et al. Lavender oil preparation Silexan is effective in generalized anxiety disorder—a randomized, double-blind comparison to placebo and paroxetine. *Int J Neuropsychopharmacol*. 2014;17(6):859-69. DOI: [10.1017/S1461145714000017](https://doi.org/10.1017/S1461145714000017). PubMed PMID: [24456909](https://pubmed.ncbi.nlm.nih.gov/24456909/).
53. Kasper S, Volz HP, Dienel A, Schläfke S. Efficacy of Silexan in mixed anxiety-depression—a randomized, placebo-controlled trial. *Eur Neuropsychopharmacol*. 2016;26(2):331-40. DOI: [10.1016/j.euroneuro.2015.12.002](https://doi.org/10.1016/j.euroneuro.2015.12.002). PubMed PMID: [26718792](https://pubmed.ncbi.nlm.nih.gov/26718792/).
54. Woelk H, Schläfke S. A multi-center, double-blind, randomised study of the lavender oil preparation Silexan in comparison to Lorazepam for generalized anxiety disorder. *Phytomedicine*. 2010;17(2):94-9. DOI: [10.1016/j.phymed.2009.10.006](https://doi.org/10.1016/j.phymed.2009.10.006). PubMed PMID: [19962288](https://pubmed.ncbi.nlm.nih.gov/19962288/).
55. Dunner DL, Dunbar GC. Optimal dose regimen for paroxetine. *J Clin Psychiatry*. 1992;53 Suppl:21-6. PubMed PMID: [1531817](https://pubmed.ncbi.nlm.nih.gov/1531817/).
56. Baldwin DS, Anderson IM, Nutt DJ, Allgulander C, Bandelow B, den Boer JA, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. *J Psychopharmacol*. 2014;28(5):403-39. DOI: [10.1177/0269881114525674](https://doi.org/10.1177/0269881114525674). PubMed PMID: [24713617](https://pubmed.ncbi.nlm.nih.gov/24713617/).