

**PROPOSAL FOR THE INCLUSION IN THE WHO MODEL LIST OF ESSENTIAL
MEDICINES OF A SELECTIVE-SEROTONIN REUPTAKE INHIBITOR FOR
GENERALISED ANXIETY DISORDER**

Corrado Barbui & Andrea Cipriani

Department of Medicine and Public Health,
Section of Psychiatry and Clinical Psychology,
University of Verona, Policlinico "G.B. Rossi",
Piazzale Scuro 10, 37134 Verona, Italy.

WHO Collaborating Centre for Research and Training in Mental Health

Tel +39-045-812.6418

Tel +39-045-812.4900

Fax +39-045-585871

E-mail: corrado.barbui@univr.it

Web page of our Section:

<http://www.psychiatry.univr.it>

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Synopsis

One of the selective serotonin-reuptake inhibitors (SSRIs) is proposed for the inclusion in the World Health Organisation (WHO) Model List of Essential Medicines for the treatment of adult individuals with Generalised Anxiety Disorder.

Currently, according to the WHO Model List of Essential Medicines (WHO EML), essential medicine for GAD is diazepam. In the WHO EML diazepam represents benzodiazepines.

A major problem with the benzodiazepines is that these agents should be prescribed in the short-term only, but the chronic nature of Generalised Anxiety Disorder requires by definition long-term treatment. This paradox prompted research to assess the efficacy of other agents, in particular the SSRIs, in individuals with GAD.

This document reviewed all available randomised evidence comparing escitalopram, paroxetine and sertraline with placebo, benzodiazepines and other antidepressants. We found evidence that escitalopram, paroxetine and sertraline are more effective than placebo in acute treatment. In terms of head-to-head comparisons, there have been few comparator-controlled studies, and most were unpowered to reveal significant differences in efficacy between active compounds. Long-term data are sparse. Placebo-controlled relapse prevention studies in patients who have responded to previous acute treatment revealed a significant advantage for staying on active medication (escitalopram or paroxetine), compared to switching to placebo, for up to six months.

Although no formal cost-effectiveness analyses have been conducted so far, it is notable that some SSRIs are now off-patent, available in generic form and, hence, may have lower acquisition costs in most health care systems. In fact, only one of the SSRIs is still on patent (in the US and in Europe), escitalopram. Taking cost into account, it would therefore seem logical to prefer paroxetine or sertraline over escitalopram because of lower acquisition cost in most countries.

1. Summary statement of the proposal

One of the selective serotonin-reuptake inhibitors (SSRIs) is proposed for the inclusion in the World Health Organisation (WHO) Model List of Essential Medicines for the treatment of adult individuals with Generalised Anxiety Disorder.

1.1 Name of the organization(s) consulted and/or supporting the application

WHO Collaborating Centre for Research and Training in Mental Health, Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Policlinico "G.B. Rossi", Piazzale Scuro 10, 37134 Verona, Italy.

1.2 International Nonproprietary Name (INN, generic name) of the medicine

Paroxetine hydrochloride

Sertraline hydrochloride

Escitalopram oxalate

1.3 Formulation proposed for inclusion

Paroxetine hydrochloride 20 mg tablets

Sertraline hydrochloride 50 mg tablets

Escitalopram oxalate 5 mg tablets

1.4 Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing is requested on the WHO Model List of Essential Medicines as an individual medicine

2. Need for splitting Generalized Anxiety Disorder from Sleep Disorders

Although it is clear that anxiety symptoms and sleep problems may simultaneously be present in the same individual, epidemiological, clinical and therapeutic considerations support the notion that generalised anxiety disorder and insomnia should be considered separate clinical entities.

Anxiety is a condition characterised by the subjective and physiologic manifestations of fear. In anxiety disorders, individuals experience apprehension,

but, in contrast to fear, the source of the danger is unknown. The physiologic manifestations of fear include sweating, shakiness, dizziness, palpitations, mydriasis, tachycardia, tremor, gastrointestinal disturbances, diarrhoea, and urinary urgency and frequency. If anxiety is generalized and persistent over months but not restricted to any particular environmental circumstances, the term generalised anxiety disorder (GAD) is usually used (1;2). The dominant symptoms are variable but include complaints of persistent nervousness, trembling, muscular tensions, sweating, lightheadedness, palpitations, dizziness, and epigastric discomfort. Fears that the patient or a relative will shortly become ill or have an accident are often expressed.

The requirements for the diagnosis of GAD include generalised and persistent excessive anxiety and a combination of various psychological and somatic complaints. These psychological and somatic complaints are given prominence in the WHO's International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) criteria, where at least one symptom of autonomic arousal (palpitations, sweating, trembling, or dry mouth) is essential for the diagnosis, together with up to three other symptoms (chest and abdomen: difficulty breathing, feeling of choking, chest pain, nausea; mental state: dizziness, feelings of unreality [depersonalisation or depression], fear of losing control, fear of dying; general: hot flushes or cold chills, numbness or tingling, muscle tension or aches and pains, restlessness and inability to relax, sensation of lump in throat). Symptoms must be persistent over six months. According to ICD-10 criteria, a diagnosis of GAD cannot be formulated if other anxiety disorders (panic disorder, phobic anxiety disorder, obsessive-compulsive disorder, or hypochondriasis), or physical disorders (hyperthyroidism, an organic mental disorder, or substance-related disorder) are present.

The onset of generalized anxiety is usually before the age of 25 years, and the incidence in men is half that in women. The course is fluctuating, and often quite debilitating (3). In western countries the 12-month prevalence rate is around 3% (4). Anxiety symptoms may be associated with psychiatric or medical disorders. Major depression occurs in almost two third of patients with GAD, panic disorder in a quarter and alcohol abuse in more than one third of patients with GAD (5). Supporters of this diagnosis argue that, despite its overlap with other disorders, the criterion that it has a 6-month duration has created a more homogenous disorder (1).

The term "Sleep disorders" is typically used to indicate a group of conditions characterised by a wide range of sleep abnormalities. According to the *International Classification of Sleep Disorders (6)*, sleep disorders include the following clinical entities:

1. Dyssomnias (disorders of initiating and maintaining sleep and disorders of excessive sleepiness)

A. Intrinsic sleep disorders

1. Psychophysiological insomnia
2. Sleep state misperception
3. Idiopathic insomnia
4. Narcolepsy
5. Recurrent hypersomnia
6. Idiopathic hypersomnia
7. Posttraumatic hypersomnia
8. Obstructive sleep apnea syndrome
9. Central sleep apnea syndrome
10. Central alveolar hypoventilation syndrome
11. Periodic limb movement disorder
12. Restless legs syndrome
13. Intrinsic sleep disorder NOS

B. Extrinsic sleep disorders

1. Inadequate sleep hygiene
2. Environmental sleep disorder
3. Altitude insomnia
4. Adjustment sleep disorder
5. Insufficient sleep syndrome
6. Limit-setting sleep disorder
7. Sleep-onset association disorder
8. Food allergy insomnia
9. Nocturnal eating (drinking) syndrome
10. Hypnotic-dependent sleep disorder
11. Stimulant-dependent sleep disorder
12. Alcohol-dependent sleep disorder
13. Toxin-induced sleep disorder
14. Extrinsic sleep disorder NOS

C. Circadian rhythm sleep disorders

1. Time zone change (jet lag) syndrome
2. Shift work sleep disorder
3. Irregular sleep-wake pattern
4. Delayed sleep phase syndrome
5. Advanced sleep phase syndrome
6. Non-24 hour sleep-wake disorder
7. Circadian rhythm sleep disorder NOS

2. Parasomnias (disorders that primarily do not cause a complaint of insomnia or excessive sleepiness)

A. Arousal disorders

1. Confusional arousals
2. Sleepwalking
3. Sleep terrors

B. Sleep-wake transition disorders

1. Rhythmic movement disorder
2. Sleep starts
3. Sleep talking
4. Nocturnal leg cramps

C. Parasomnias usually associated with REM sleep

1. Nightmares
2. Sleep paralysis
3. Impaired sleep-related penile erections
4. Sleep-related painful erections
5. REM sleep-related sinus arrest
6. REM sleep behavior disorder

D. Other Parasomnias

1. Sleep bruxism
2. Sleep enuresis
3. Sleep-related abnormal swallowing syndrome
4. Nocturnal paroxysmal dystonia
5. Sudden unexplained nocturnal death syndrome
6. Primary snoring
7. Infant sleep apnea
8. Congenital central hypoventilation syndrome
9. Sudden infant death syndrome
10. Benign neonatal sleep myoclonus
11. Other Parasomnia NOS

3. Sleep Disorders Associated with Medical/Psychiatric Disorders

A. Associated with mental disorders

1. Psychoses
2. Mood disorders
3. Anxiety disorders
4. Panic disorder
5. Alcoholism

B. Associated with neurological disorders

1. Cerebral degenerative disorders
2. Dementia
3. Parkinsonism
4. Fatal familial insomnia
5. Sleep-related epilepsy
6. Electrical status epilepticus of sleep
7. Sleep-related headaches

C. Associated with other medical disorders

1. Sleeping sickness
2. Nocturnal cardiac Ischemia
3. Chronic obstructive pulmonary disease
4. Sleep-related asthma
5. Sleep-related gastroesophageo reflux
6. Peptic ulcer disease
7. Fibrositis syndrome

4. Proposed sleep disorders (These are the disorders for which insufficient information is available to confirm their acceptance as definitive sleep disorders)

1. Short sleeper
2. Long sleeper
3. Subwakefulness syndrome

4. Fragmentary Myoclonus
5. Sleep hyperhidrosis
6. Menstruation-associated sleep disorderly
7. Pregnancy-associated sleep disorder
8. Terrifying hypnagogic hallucinations
9. Sleep-related neurogenic tachypnea
10. Sleep-related laryngospasm
11. Sleep choking syndrome

The *International Classification of Sleep Disorders* defines **insomnia** as difficulty with the initiation, maintenance (difficulty with sleep maintenance implies waking after sleep has been initiated but before a desired wake time), duration, or quality of sleep that results in the impairment of daytime functioning, despite adequate opportunity and circumstances for sleep (7). Transient insomnia lasts less than one week, and short-term insomnia one to four weeks. Chronic insomnia lasts more than one month.

Insomnia can be grouped into primary and secondary insomnia (6).

Primary insomnia includes the following clinical entities: (a) idiopathic insomnia (insomnia arising in infancy or childhood with a persistent, unremitting course); (b) psychophysiological insomnia (insomnia due to a maladaptive conditioned response in which the patient learns to associate the bed environment with heightened arousal rather than sleep; onset often associated with an event causing acute insomnia, with the sleep disturbance persisting despite resolution of the precipitating factor); (c) paradoxical insomnia (insomnia characterized by a marked mismatch between the patient's description of sleep duration and objective polysomnographic findings).

Secondary insomnia includes the following clinical entities: (a) adjustment insomnia (insomnia associated with active psychosocial stressors); (b) inadequate sleep hygiene (insomnia associated with lifestyle habits that impair sleep); (c) insomnia due to a psychiatric disorder; (d) insomnia due to a medical condition (insomnia due to a condition such as the restless legs syndrome, chronic pain, nocturnal cough or dyspnea, or hot flashes); (e) insomnia due to a drug or substance (insomnia due to consumption or discontinuation of medication, drugs of abuse, alcohol, or caffeine).

Chronic insomnia has a prevalence of 10 to 15 percent, and occurs more frequently in women, older adults, and patients with chronic medical and psychiatric disorders (8). It may follow episodes of acute insomnia in patients who are predisposed to having the condition and may be perpetuated by behavioral and cognitive factors, such as worrying in bed and holding unreasonable expectations of sleep duration. Consequences include fatigue, mood disturbances, problems with interpersonal relationships, occupational difficulties, and a reduced quality of life (9).

According to the ICD-10, whether a sleep disorder in a given patient is an independent condition or simply one of the features of another disorder should be determined on the basis of its clinical presentation and course as well as on the therapeutic considerations and priorities at the time of the consultation. Generally, if the sleep disorder is one of the major complaints and is perceived as a condition in itself, the code F51 should be used along with other pertinent diagnoses describing the psychopathology and pathophysiology involved in a given case. F51 includes only those sleep disorders in which emotional causes are considered to be a primary factor. The term non-organic insomnia (F51.0) identifies a "condition of unsatisfactory quantity and/or quality of sleep, which persists for a considerable period of time, including difficulty falling asleep, difficulty staying asleep, or early final waking".

In addition to epidemiological and clinical considerations, therapeutic considerations suggest that these two disorders should be considered as separate entities. While it is true that benzodiazepines have had for a long time a key role in the symptomatic treatment of both anxiety and sleep disorders, in recent years these two conditions have been progressively treated with different pharmacological and non-pharmacological interventions (1; 2; 7).

Non-pharmacological treatments for insomnia include education and sleep hygiene, stimulus control, sleep restriction, relaxation training, biofeedback (most commonly electromyography), paradoxical intention, and cognitive therapy, and less commonly used techniques such as autogenic training, guided imagery, self-hypnosis, and meditation. These methods can be used individually or in combinations. Pharmacological treatments of insomnia have focused mainly on symptom management. In addition to benzodiazepines, zolpidem, zaleplon, and zopiclone have been shown to reduce acute insomnia symptoms, although their role in the management of chronic insomnia remains unclear (10). In GAD the most

extensively studied non-pharmacological intervention is cognitive behavioral therapy. This therapy, which teaches patients to substitute positive thoughts for anxiety-provoking ones, usually involves 6 to 12 individual sessions at weekly intervals. Patients record their thoughts and feelings in diaries, noting situations in which they feel anxious and behaviours that relieve the anxiety. They also role-play scenes and rehearse responses to anxiety. An alternative approach to cognitive behavioral therapy is applied relaxation therapy, in which the patient imagines calming situations to induce muscular and mental relaxation. In generalised anxiety disorder, in addition to benzodiazepines, pharmacological interventions backed by scientific evidence include use of antidepressant drugs.

3. Assessment of current use and target population

Benzodiazepines, since the introduction of chlordiazepoxide (approved in 1960) and diazepam (approved in 1961), have rapidly become the treatment of choice for anxiety, replacing the barbiturates and becoming the most frequently used psychiatric class of drugs worldwide. Benzodiazepines are still widely prescribed medications for GAD, although patients with GAD are usually very cautious about drug treatment, fearing problems such as unwanted sedation or the development of physical or psychological dependence.

Recent evidence-based guidelines clearly pointed out that benzodiazepines may be helpful as short-term treatment only, when antidepressants are initiated, since benzodiazepines rapidly relieve symptoms (whereas antidepressants typically take weeks to work) and also help alleviate the restlessness or nervousness sometimes associated with the initiation of antidepressant therapy. The presence of significant coexisting depressive symptoms further suggests to guide treatment choice towards prescription of antidepressant drugs rather than benzodiazepines.

Epidemiological data suggest that the use of SSRIs in patients with GAD is on the increase. Salzman and colleagues, who reported on the pharmacologic treatment of patients diagnosed with GAD in the USA, showed a progressive decrease in benzodiazepine treatment and an increase in antidepressant treatment for GAD patients (11). This increase was not explained by comorbid depressive symptoms (11). Even though use of SSRIs in patients with GAD is on the increase, a relevant proportion of patients with GAD receive no treatment. Vasile and colleagues, who examined medication-prescribing patterns for the treatment of anxiety disorders in

the USA for 12 years, showed that psychotropic treatment patterns seem to have remained relatively stable over 12 years with benzodiazepines the medications most commonly used for GAD (12). Comparatively, SSRI usage as stand-alone medications for these disorders remained low throughout the follow-up period. At the 12-year follow-up, 24% of patients with GAD and 30% of patients with social phobia were utilizing neither an SSRI/ SNRI nor a benzodiazepine. According to these data, treatment recommendations for use of SSRIs in the management of GAD have been having only a modest impact on changes in psychopharmacologic practice (12).

4. Treatment details

4.1 Indications for use

Treatment of adult individuals with Generalised Anxiety Disorder.

4.2 Dosage regimens

Escitalopram dosage is 10 mg orally a day. To minimise early side effects, escitalopram may be started at doses of 5 mg a day. Patients are usually maintained with 10 mg a day for 8-12 weeks. If no signs of clinical improvements are observed, an increase to 20 mg a day may be warranted.

Paroxetine dosage is 20 mg orally a day. To minimise early side effects, paroxetine may be started at doses of 10 mg a day. Patients are usually maintained with 20 mg a day for 8-12 weeks. If no signs of clinical improvements are observed, an increase to 40 mg a day may be warranted.

Sertraline dosage is 50 mg orally a day; dose may be increased if necessary in steps of 50 mg over several weeks; usual dose range is 50–200 mg daily.

4.3 Duration of therapy

Although the concern about benzodiazepines causing dependence has led to recommendations that these drugs should be avoided in the long-term, the alternative of continuous antidepressant therapy is supported by little evidence (13). Despite of this, it is generally recommended that patients who have a response should continue taking the antidepressant for six months to a year (2). According to the NICE guidelines "If the patient is showing improvement on treatment with an antidepressant, the drug should be continued for at least 6

months after the optimal dose is reached, after which the dose can be tapered.”
(<http://www.nice.org.uk/guidance/index.jsp?action=download&o=29642>)

4.4 Reference to existing WHO and other clinical guidelines

In the UK, the National Institute for Clinical Excellence (NICE) issued in April 2007 recommendations for the management of anxiety in adults in primary, secondary and community care (<http://www.nice.org.uk/guidance/index.jsp?action=download&o=29642>). The guideline includes good practice points and evidence-based recommendations for the psychological, pharmacological, service-level and self-help interventions appropriate to each section. According to NICE, “psychological therapy, medication and self-help have all been shown to be effective. The choice of treatment will be a consequence of the assessment process and shared decision-making.” In terms of pharmacological treatment, “Antidepressants should be the only pharmacological intervention used in the longer-term management of generalised anxiety disorder. There is an evidence base for the effectiveness of the SSRIs.” “If one SSRI is not suitable or there is no improvement after a 12-week course, and if a further medication is appropriate, another SSRI should be offered.”

The British Association of Psychiatrists (BAP) issued in 2005 a series of evidence-based guidelines for the use of drugs in anxiety disorders with the emphasis on producing comprehensive but concise and usable guidelines based on a review of the evidence (14). General issues for pharmacotherapy include the following: (a) discuss the benefits and risks of specific drug treatments with patients before treatment; (b) SSRIs are effective across the range of anxiety disorders and are generally suitable for first-line treatment; (c) benzodiazepines are effective in many anxiety disorders but their use should be short term and only considered beyond this in treatment-resistant cases because of problems with side effects and dependence; (d) the use of other drugs such as tricyclic antidepressants, MAOIs, antipsychotics and anticonvulsants needs to be considered in relation to their evidence-base for specific conditions and their individual risks and benefits; (e) with all antidepressants, especially SSRIs and venlafaxine, there should be specific discussion and monitoring of possible adverse effects early in treatment (initial worsening of anxiety/agitation or rarely the emergence of suicidal ideation); (f) with antidepressants and benzodiazepines there should be specific discussion and monitoring of adverse effects on stopping the drugs after a week of treatment

(discontinuation symptoms and, with benzodiazepines, rebound anxiety and withdrawal/dependence) (14).

4.5 Need for special diagnostic or treatment facilities and skills

There is no need for special diagnostic facility per se, but clinical skills in the recognition of GAD, and in the recognition of comorbid psychiatric conditions, is required. SSRI treatment does not require special management skills, although primary health care professionals should consider and monitor possible adverse effects early in treatment (initial worsening of anxiety/agitation or rarely the emergence of suicidal ideation).

5. Need for revising essential medicines in Generalized Anxiety Disorder

According to the WHO Model List of Essential Medicines (WHO EML), 15th List, March 2007, essential medicine for GAD is diazepam (www.who.int/medicines/publications/08_ENGLISH_indexFINAL_EML15.pdf).

Diazepam is included as an “example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources”. Thus, in the WHO EML diazepam represents benzodiazepines.

It has been estimated that up to 75% of patients treated with benzodiazepines show moderate to marked improvement of anxiety symptoms (15). Typically, improvement occurs within the first few weeks of treatment. Despite their efficacy profile, several factors limit the use of benzodiazepines, including adverse events such as sedation, fatigue, impaired psychomotor performance, decreased learning ability, and the potential for abuse (16-18). Benzodiazepines can also aggravate depression, potentiate the effects of alcohol and cause transient global amnesia. Alcohol in combination with benzodiazepines can lead to numerous complications including drug-induced deaths, drug overdoses and traffic accidents (19-21). In the elderly, benzodiazepines can contribute to motor incoordination with increasing potential for falls and other complications (22). Use of benzodiazepines can lead to physical tolerance, and physical and psychological dependence (sometimes in as little as 2 weeks), and discontinuation can be followed by relapse, rebound anxiety

and withdrawal symptoms. These drugs have also been implicated in traffic accidents as a result of impairing reaction time and psychomotor function.

Two types of dependence have been shown to be associated with benzodiazepine use, psychological and physical. Psychological dependence refers to drug craving that can lead to drug-seeking behaviour, and physical dependence occurs when the drug is stopped and symptoms of withdrawal ensue.

For these reasons, at a public health level the use of benzodiazepines is under international control. Medicines under international control are regulated by the Convention on Psychotropic Substances, 1971 (United Nations) (www.incb.org/pdf/e/conv/convention_1971_en.pdf). In addition to international control, in many countries the use of benzodiazepines is strictly controlled by national, regional and local drug regulations. At a clinical level, the use of benzodiazepines is recommended in the short-term only. Clearly, this constitutes a real paradox in the pharmacological treatment of GAD, given that its chronic nature requires by definition long-term treatment.

The epidemiological observation that GAD occurs with other mood disorders in around two third of cases (2;13), in particular depression (23;24), generated the hypothesis that antidepressants may represent a treatment option for both GAD and co-existing depression. It has been observed that many antidepressants were effective in treating symptoms of anxiety at doses similar to those used for treating major depression, and this prompted research to assess the efficacy of antidepressants, in particular the SSRIs, in individuals with GAD.

Currently, several antidepressants have been studied in the treatment of patients with GAD, including some SSRIs (in particular paroxetine, sertraline, escitalopram) and some newer antidepressants (in particular venlafaxine). In many countries one or more of these medicines received marketing authorisation for GAD and represent nowadays the first-line pharmacological treatment of this anxiety disorder. We therefore sought to examine whether the available evidence supporting the use of antidepressants in GAD may prompt the inclusion of one of these medicines in the WHO EML. This document is focused on the evidence supporting paroxetine, sertraline and escitalopram only. We did not include venlafaxine because this medicine has been shown to be associated with acceptability and tolerability problems that limit its use as first-line treatment (25).

6. Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

We first conducted a meta-review of all available systematic reviews of the evidence. This method is not as intensive as a primary systematic review of a specific intervention for a defined clinical disorder, but it has been used to provide a useful overview of large clinical areas, reducing the risk of selective citation and being of help in detecting publication bias. The hierarchy of evidence proposed by the Centre for Evidence Based Medicine (Oxford) was followed, and only reviews that were rated 1A (http://www.cebm.net/levels_of_evidence.asp) were included. Level 1A refers to systematic reviews of RCTs. These provide the most reliable evidence for efficacy and tolerability. In addition, to assess tolerability, we considered observational data when randomized evidence was not available.

We used several sources to identify pertaining evidence. We first searched the National Institute of Health and Clinical Excellence (NICE) guidance website for existing guidelines on the pharmacological treatment of GAD. We then accessed the BMJ Clinical Evidence website, a repository of systematic reviews that summarise the current state of knowledge and uncertainty about the prevention and treatment of clinical conditions, based on thorough searches and appraisal of the literature. It is neither a textbook of medicine nor a set of guidelines. It describes the best available evidence from systematic reviews, randomised trials, and observational studies where appropriate, and if there is no good evidence it says so.

Secondly, we identified relevant systematic reviews by searching the Cochrane Library and the Database of Abstracts of Reviews of Effectiveness (up to September 2008). Cochrane Systematic Reviews are widely recognised as some of the best sources of evidence, being based on rigorous searches including grey and non-English language literature together with electronic and hand searching of medical journals. The Database of Abstracts of Reviews of Effectiveness contains abstracts of quality assessed systematic reviews located by MEDLINE and EMBASE searches from 1994 onwards. There is coverage of earlier reviews but this is not complete. It also contains abstracts of all the systematic reviews included in ACP Journal Club and gives bibliographic details of other reviews identified in searches but not meeting the quality criteria for inclusion in the main database. We additionally searched MEDLINE (1966 to September 2008), EMBASE (1980 to September

2008), PsycINFO (1980 to September 2008) and regional databases (AIM, IMEMR, HELLIS, LILACS, WPRIM) grouped under the general heading of Global Health Index (<http://www.who.int/ghi/medicus/en>) to find evidence and systematic reviews not captured on the Cochrane Library. Additional searches were carried out on the following databases of the NHS Centre for Reviews and Dissemination: Health Technology Assessment and Turning Research into Practice.

If systematic reviews answering each clinical question were found, the search for randomised controlled trials (RCTs) was confined to studies published after the date of the search conducted for the review. If no relevant systematic reviews were found, Cochrane Controlled Clinical Trials Register, MEDLINE, and EMBASE were searched to their origin.

Our search strategy was based on the strategy developed at the UK Cochrane Centre (26) and on the search strategy used for *BMJ Clinical Evidence* (www.clinicalevidence.com).

The results of systematic reviews and clinical trials identified and selected through this review process were used to produce a descriptive summary of study findings, in conjunction with a tabular approach to recording the results.

Bullet points of the search process (update September 2008)

- ✓ Main sources: Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials; Medline; Embase; PsycINFO.
- ✓ Additional sources: Centre for Reviews and Dissemination (website); Database of Abstracts of Reviews of Effects (online database); Health Technology Assessment (online database); National Institute for Health and Clinical Excellence (website); Turning Research into Practice (online database); Global Health Index (website).

7. Summary of available estimates of comparative effectiveness and tolerability

7.1 Efficacy of benzodiazepines versus placebo

The meta-review of all available systematic reviews carried out by Clinical Evidence (27) identified two systematic reviews comparing benzodiazepines with placebo. We additionally found a third systematic review.

Gould and colleagues (28) found that benzodiazepines significantly improved symptoms over 2-9 weeks compared with placebo, and **Mitte** and colleagues (29) similarly showed that benzodiazepines were significantly more effective than placebo at improving anxiety. In 2007, however, a rigorous systematic review and meta-analysis was published by **Martin** and colleagues (30). This review employed as primary outcome measure a "hard" variable, that is withdrawals of subjects before the conclusion of the study. The rationale for this choice was that this pragmatic outcome is an easily applicable measure that has important implications in everyday clinical practice. This review included 12 studies comparing diazepam versus placebo, 7 studies comparing lorazepam versus placebo and 4 studies comparing alprazolam versus placebo. In total, 1189 patients were randomly allocated to benzodiazepines and 1137 to placebo. Participants included were aged from 17 to 70 years, and suffered from GAD according to DSM-IV, DSM-IIIR and DSM-III criteria. 14/23 studies lasted 4 weeks, and only 1/23 lasted more than 8 weeks. In terms of withdrawals for any reason the analysis showed a relative risk of 0.78 (95% CI 0.62 to 1.00, $P = 0.05$), practically on the limit of statistical significance in favour of benzodiazepines. However, in terms of withdrawals due to lack of efficacy the analysis showed a relative risk of 0.29 (95% CI 0.18 to 0.45, $P < 0.0001$), in favour of benzodiazepines. Finally, in terms of withdrawals due to adverse events the analysis showed a relative risk of 1.54 (95% CI 1.17 to 2.03, $P < 0.002$), indicating a risk of over 50% for the benzodiazepine group. The conclusion of the study authors was that this review failed to find convincing evidence of the short-term effectiveness (that is, withdrawals for any reasons) of benzodiazepines in the treatment of GAD. However, robust evidence in favour of benzodiazepines was found in terms of efficacy (that is withdrawals due to lack of efficacy).

The search yielded another meta-analysis that was not included in the present document considering that it aimed at quantifying HAM-A change in score from baseline to endpoint without directly comparing each benzodiazepine with placebo (31).

Summary table of systematic reviews of clinical trials comparing benzodiazepines with placebo in adult individuals with GAD:

Study	Design	Comparison	Sample	Follow-up	Efficacy
Gould 1996	Systematic review of 17 RCTs	BDZ versus PLO	2044	2-9	Benzodiazepines > PLO (anxiety score)
Mitte 2002	Systematic review of 33 RCTs	BDZ versus PLO (diazepam, alprazolam, lorazepam)		Short	Benzodiazepines > PLO (anxiety score)
Martin 2007	Systematic review of 23 RCTs	Diazepam versus PLO (12 trials), lorazepam versus PLO (7 trials), alprazolam versus PLO (4 trials)	1119 (BDZ) 1137 (PLO)	2-24 (only 1 trial lasted more than 8 weeks)	Benzodiazepines = PLO (p = 0.05) (withdrawals for any reason) Benzodiazepines > PLO (p = 0.05) (withdrawals due to lack of efficacy) Benzodiazepines < PLO (withdrawals due to lack adverse effects)

> means "better than"

< means "worse than"

RCT = randomised controlled trials; BDZ = benzodiazepines; PLO = placebo

7.2 Adverse effects of benzodiazepines

Treatment with benzodiazepines is recommended in the short-term only. This recommendation is explained by the lack of evidence that benzodiazepines may be effective in the long-term, and by robust observational evidence that benzodiazepine adverse effects, dependence liability and withdrawal potential is particularly evident in the long-term.

Common adverse effects associated with benzodiazepine use include drowsiness, sedation, muscle weakness, and ataxia. Serious adverse effects include vertigo, headache, confusion, depression, slurred speech or dysarthria, changes in libido, tremor, visual disturbances, urinary retention or incontinence, gastrointestinal disturbances, changes in salivation, and amnesia. Some patients may experience a

paradoxical excitation which may lead to hostility, aggression, and disinhibition. Respiratory depression and hypotension occasionally occur with high dosage and parenteral administration.

Long-term use may induce dependence and withdrawal symptoms, a syndrome characterised by anxiety, depression, impaired concentration, insomnia, headache, dizziness, tinnitus, loss of appetite, tremor, perspiration, irritability, perceptual disturbances such as hypersensitivity to physical, visual, and auditory stimuli and abnormal taste, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia, and orthostatic hypotension.

Use of benzodiazepines during the first trimester of pregnancy has been associated with congenital malformations in the infant. Use in the third trimester may be associated with neonatal withdrawal symptoms (floppy infant syndrome).

Bullet points on benzodiazepine adverse effects

- ✓ Benzodiazepine adverse effects, dependence liability and withdrawal potential is particularly evident in the long-term.
- ✓ Common adverse effects associated with benzodiazepine use include drowsiness, sedation, muscle weakness, and ataxia.
- ✓ Withdrawal symptoms include anxiety, depression, impaired concentration, insomnia, headache, dizziness, tinnitus, loss of appetite, tremor, perspiration, irritability, perceptual disturbances, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia, and orthostatic hypotension.
- ✓ Benzodiazepines during the first trimester of pregnancy may be associated with congenital malformations.

7.3 SSRI's (paroxetine, sertraline and escitalopram) versus placebo

The search yielded three randomised controlled trials that assessed the efficacy of paroxetine versus placebo in patients with GAD (included in Clinical Evidence). One additional RCT compared continued paroxetine treatment versus placebo over 24 weeks, and reported relapse rates. We additionally found two systematic reviews of paroxetine clinical trial data in patients with GAD, and one pooled analysis of paroxetine data.

Pollack and colleagues published in 2001 a double-blind RCT that randomised patients meeting DSM-IV criteria of GAD to flexible dosages of paroxetine versus placebo (32). A total of 331 participants were enrolled and 324 were included in the efficacy analysis, carried out 8 weeks after random allocation. The study included outpatients with a mean age of 40 years, 66% were females and no other axis I disorder was allowed. At follow-up, 61/161 in the paroxetine group and 86/163 in the placebo group failed to meet the study criteria of treatment response. This yielded a RR of 0.72 (95% CI 0.56 to 0.92) and a NNT of 6.72 (95% CI 3.9 to 24.7), both favouring paroxetine over placebo. In terms of dropouts, 34/161 in the paroxetine group and 30/163 in the placebo group failed to complete the study. This yielded a RR of 1.15 (95% CI 0.74 to 1.78).

Rickels and colleagues published in 2003 a double-blind RCT that randomised patients meeting DSM-IV criteria of GAD to 20 or 40 mg of paroxetine versus placebo (33). A total of 566 participants were enrolled and included in the ITT efficacy analysis, carried out 8 weeks after random allocation. The study included outpatients with a mean age of 40 years, 56% were females and no other axis I disorder was allowed. The mean change from baseline in total score on the Hamilton Anxiety Scale was defined as the primary outcome. As reported by the study authors, for the LOCF analysis, 61.7% and 68.0% of the patients in the 20 mg and 40 mg paroxetine group, respectively, fulfilled the defined response criterion at endpoint compared with 45.6% of the placebo patients. Of the paroxetine patients who completed 8 weeks of treatment (observed cases data set), 68% and 80% achieved response in the 20 mg and 40 mg regimens, respectively, compared with 52% of patients given placebo. In this trial completion rates did not differ substantially among patients given placebo (77.8%), 20 mg of paroxetine (76.1%) or 40 mg of paroxetine (72.6%).

Baldwin and colleagues published in 2006 a multi-arm RCT that randomised patients meeting DSM-IV criteria of GAD to escitalopram and paroxetine versus placebo (34). A total of 278 patients were included in the efficacy analysis comparing paroxetine versus placebo. The study included outpatients with a mean age of 40 years, more than 60% were females and no other axis I disorder was allowed. After 12 weeks of follow-up, no significant difference between paroxetine 20 mg and placebo was found in terms of HAM-A scores (HAM-A difference between groups -0.51, 95% CI -2.33 to 1.32, $P = 0.585$). However, in terms of Clinical Global Impression-Improvement (CGI-I) paroxetine was significantly better than

placebo (this result was presented graphically in the primary study report). In this trial withdrawal rates were 15/139 (10.8%) in the placebo group and 26/140 (18.7%) in the paroxetine group. According to study authors, this difference did not reach statistical significance.

Stocchi and colleagues compared continued paroxetine 20-50 mg/day versus placebo in 652 individuals meeting DSM-IV criteria of GAD, and reported the proportion of patients relapsing (an increase in CGI-S score of at least 2 points to a score $<$ or $=$ 4 or withdrawal resulting from lack of efficacy) during the 24-week double-blind treatment (35). It found that significantly fewer paroxetine than placebo patients relapsed during the 24-week double-blind phase (10.9% vs. 39.9%; $P < 0.001$). Placebo patients were almost 5 times more likely to relapse than paroxetine patients (estimated hazard ratio = 0.213, 95% CI = 0.1 to 0.3; $P < 0.001$).

The two systematic reviews of paroxetine data included Pollack 2001 and Rocca 1997 and no meta-analysis was performed (36;37); by contrast, the pooled analysis carried out by Rickels and colleagues identified three published (Pollack 2001, Stocchi 2003, Rickels 2003) and one unpublished RCT (38). The unpublished RCT found a similar mean change from baseline in HAM-A for paroxetine and placebo (paroxetine -12.4, placebo -11.3, $P = 0.171$).

The search yielded two randomised controlled trials that assessed the efficacy of sertraline versus placebo in patients with GAD.

Allgulander and colleagues published in 2004 a double-blind RCT that randomised patients meeting DSM-IV criteria of GAD to sertraline (dose titrated from 25 mg/day in the first week to 50-150 mg/day by week 12) versus placebo (39). A total of 378 patients were randomly assigned to treatment, and 373 were included in the efficacy analysis. The study included outpatients with a mean age of 40 years, 59% in the sertraline group and 51% in the placebo group were females and no other axis I disorder was allowed. After 12 weeks of follow-up, sertraline demonstrated significantly greater efficacy than placebo in terms of HAM-A scores (HAM-A mean change from baseline – 11.7 with sertraline versus -8.0 with placebo, $P < 0.0001$). In this trial completion rates were 147/188 (80%) in the sertraline group and 139/190 (74%) in the placebo group. According to study authors, this

difference did not reach statistical significance. **Dahl** and colleagues published in 2005 a new analysis using the same data set (40).

Brawman-Mintzer and colleagues published in 2006 a double-blind RCT that randomised patients meeting DSM-IV criteria of GAD to sertraline (50-200 mg/day) versus placebo (41). A total of 338 patients were randomly assigned to treatment, and 326 were included in the ITT efficacy analysis. The study included outpatients with a mean age of 40 years, around 55% were females and no other axis I disorder was allowed. After 10 weeks of follow-up, sertraline demonstrated significantly greater efficacy than placebo in terms of HAM-A scores (HAM-A mean difference -2.06, 95% CI -3.90 to -0.21). However, in terms of response rates (at least 50% decrease in HAM-A score) sertraline was not significantly better than placebo (59.2% versus 48.2%, $P = 0.050$). A total of 241 patients completed the study, with 117 subjects (71.3%) in the sertraline group and 124 (76.5%) in the placebo group.

Finally, four randomised controlled trials assessed the efficacy of escitalopram versus placebo in patients with GAD. We additionally identified a pooled analysis of three RCTs.

Davidson and colleagues published in 2004 a RCT that randomised patients meeting DSM-IV criteria of GAD to escitalopram 10-20 mg versus placebo (42). A total of 315 patients were randomly assigned and received at least one dose of double-blind medication, and 307 were included in the efficacy analysis. The study included outpatients with a mean age of 39 years, around 52% were females and no other axis I disorder was allowed. After 8 weeks of follow-up, escitalopram significantly increased rates of remission and response compared with placebo (36% with escitalopram versus 16% with placebo, $P < 0.01$). In this trial 77% of patients (75% of escitalopram-treated patients and 78% of placebo-treated patients) completed the study.

Baldwin and colleagues published in 2006 a multi-arm RCT that randomised patients meeting DSM-IV criteria of GAD to escitalopram and paroxetine versus placebo (34). A total of 681 patients were included in the efficacy analysis comparing three escitalopram arms (5 mg/day; 10 mg/day; 20 mg/day) versus placebo. The study included outpatients with a mean age of 40 years, more than 60% were females and no other axis I disorder was allowed. After 12 weeks of

follow-up, escitalopram at the two higher doses significantly improved mean HAM-A scores compared with placebo (HAM-A mean change: placebo -14.2, escitalopram 10 mg -16.8, $P = 0.006$ versus placebo; escitalopram 20 mg -16.4, $P = 0.022$ versus placebo). In this trial withdrawal rates were 16/139 in the placebo group and 20/136 in the escitalopram 10 mg group, and 25/133 in the escitalopram 20 mg group. As reported by the study authors, compared with 7% in the placebo group, significantly more patients in the escitalopram 20 mg (and paroxetine 20 mg) groups withdrew because of adverse events.

Bose and colleagues published in 2007 a multi-arm RCT that randomised patients meeting DSM-IV criteria of GAD to escitalopram and venlafaxine versus placebo (43). A total of 271 patients were randomly allocated to escitalopram (10-20 mg) and placebo, of whom 206 completed the 8 week trial. The study included outpatients with a mean age of 38 years, more than 60% were females and no other axis I disorder was allowed. After 8 weeks of follow-up, for the primary efficacy outcome, change from baseline at week 8 in HAM-A total score using the LOCF approach, the mean difference for escitalopram versus placebo was -1.52 ($P=0.09$). Using the OC approach, the mean difference for escitalopram versus placebo was -1.92 ($P=0.033$). Double-blind treatment was completed by 104 (76.5%) placebo-treated patients and 102 (80.3%) escitalopram-treated patients.

Allgulander and colleagues compared continued escitalopram 20 mg/day over 24-76 weeks versus placebo in 375 individuals meeting DSM-IV criteria of GAD, and reported time to relapse (HAM-A score 15 or above) (44). It found that significantly fewer escitalopram than placebo patients relapsed during the 24-week double-blind phase (34/187 [18%] with escitalopram vs. 98/188 [52%], $p < 0.001$). Additionally, escitalopram significantly increased time to relapse compared with placebo.

In addition of these RCTs, we identified a pooled analysis of 3 RCTs (Davidson 2004 and two 8-week unpublished trials that compared escitalopram with placebo) (45). It found that escitalopram significantly improved mean HAMA total scores relative to placebo in each RCT. The overall mean change from baseline to week 8 in HAMA total score (LOCF) was -10.1 for escitalopram and -7.6 for placebo ($P < 0.001$).

Summary table of clinical trials comparing paroxetine, sertraline and escitalopram versus placebo in adult individuals with GAD:

Study	Study	Design	Country	Comparison	Sample	Follow-up	Efficacy
Paroxetine	Pollack 2001	RCT	USA and Canada	Paroxetine (flexible dose) versus PLO	324	8	Paroxetine > PLO (HAM-A)
	Rickels 2003	RCT	USA and Canada	Paroxetine 20 mg versus paroxetine 40 mg versus placebo	566	8	Paroxetine > PLO (HAM-A)
	Baldwin 2006	RCT	10 countries	Paroxetine 20 mg versus placebo (versus escitalopram)	278	12	Paroxetine = PLO (HAM-A) Paroxetine > PLO (CGI)
	Stocchi 2003	Prevention of relapse RCT	Italy, Finland, Denmark, Hungary, Greece, Czech Republic	Paroxetine 20-50 mg versus placebo	652	24	Paroxetine > PLO (relapse rate)
Sertraline	Allgulander 2004	RCT	Australia, Canada, Denmark, Norway, Sweden	Sertraline 50-150 mg versus placebo	373	12	Paroxetine > PLO (HAM-A)
	Brawman-Mintzer 2006	RCT	USA	Sertraline 50-200 mg versus placebo	326	10	Paroxetine > PLO (HAM-A) Paroxetine = PLO (response rate)
Escitalopram	Davidson 2004	RCT	USA	Escitalopram 10-20 mg versus PLO	315	8	Escitalopram > PLO (response rate) Escitalopram > PLO (remission rate)
	Baldwin 2006	RCT	10 countries	Escitalopram (5 mg, 10 mg, 20 mg) versus PLO	681	12	Escitalopram 10 mg, 20 mg > PLO (HAM-A)
	Bose 2007	RCT	USA	Escitalopram (10-20 mg) versus placebo	271	8	Escitalopram = PLO (HAM-A)
	Allgulander 2006	Prevention of relapse RCT	Canada, France, Germany, Hungary, Ireland, Poland, Sweden, Switzerland	Escitalopram 20 mg versus PLO	375	24	Escitalopram > PLO (relapse rate)

> means "better than"

< means "worse than"

RCT = randomised controlled trials; PLO = placebo; HAM-A = Hamilton- Anxiety; CGI = clinical global impression

Summary table of systematic reviews comparing paroxetine, sertraline and escitalopram versus placebo in adult individuals with GAD:

Study	Design	Drug	Comparison(s)	Results
Kapczinski 2003	SR	paroxetine	Pollack 2001 (paroxetine versus placebo); Rocca 1997 (paroxetine versus imipramine versus BDZ)	No overall treatment estimates were calculated
Schmitt 2005	SR	paroxetine	Pollack 2001 (paroxetine versus placebo); Rocca 1997 (paroxetine versus imipramine versus BDZ)	No overall treatment estimates were calculated
Rickels 2006	Pooled analysis of 4 RCTs	paroxetine	Pollack 2001 (paroxetine versus placebo); Stocchi 2003 (paroxetine versus placebo); Rickels 2003 (paroxetine 20 mg versus paroxetine 40 mg versus placebo); Unpublished (paroxetine versus placebo, 364 patients, 8 weeks, flexible doses)	Unpublished RCT: no difference paroxetine vs placebo
Goodman 2005	Pooled analysis of 3 RCTs	Escitalopram	Davidson 2004 (escitalopram versus placebo); Unpublished (escitalopram 10-20 mg versus placebo, 8 weeks); Unpublished (escitalopram 10-20 mg versus placebo, 8 weeks). Escitalopram arm (3 RCTs) = 429 patients; placebo arm (3 RCTs) = 427 patients.	Escitalopram > PLO

> means "better than"

< means "worse than"

RCT = randomised controlled trials; SR = systematic review; PLO = placebo

7.4 SSRIs (paroxetine, sertraline and escitalopram) versus other antidepressants

Seven RCTs assessed the comparative efficacy of antidepressants in patients with GAD.

Rocca and colleagues published in 1997 a three parallel group RCT that randomised patients meeting DSM-IV criteria of GAD to paroxetine 20 mg versus imipramine 50-100 mg (the third treatment arm was clordesmethylidiazepam) (46). A total of 81 participants were enrolled and 56 were included in the efficacy analysis, carried out 8 weeks after random allocation. The study included

outpatients with a mean age of around 36 years, 57% were females and no other axis I disorder was allowed. At follow-up, 3/26 in the imipramine group and 2/30 in the paroxetine group failed to meet the study criteria of treatment response. This yielded a RR of 1.73 (95% CI 0.31 to 9.57) suggesting no difference between treatments (although lack of statistical power leaves the possibility of type II error, that is failing to see a difference that may be present). In terms of dropouts, 7/26 in the imipramine group and 5/30 in the paroxetine group failed to complete the study. This yielded a RR of 1.62 (95% CI 0.58 to 4.48).

Ball and colleagues published in 2005 a double-blind RCT that randomised patients meeting DSM-IV criteria of GAD to flexible doses of paroxetine versus flexible doses of sertraline (47). A total of 55 participants were randomly assigned to treatment, but two did not return leaving a ITT population of 53 individuals. The study included outpatients with a mean age of 35 (paroxetine) and 42 (imipramine) years, more than 70% were females. Participants were allowed to have other axis 1 anxiety and depressive disorders, as long as GAD was the primary illness. The mean change from baseline in total score on the HAM-A was defined as the primary outcome. After 8 weeks of follow-up, 17/25 in the paroxetine group and 17/28 in the sertraline group showed a 50% reduction in HAM-A. This yielded a RR of 1.1 (95% CI 0.7 to 1.6). The two treatment groups did not differ in the percentage of subjects who withdrew early (paroxetine 20%, sertraline 20%).

Bielski and colleagues published in 2005 a RCT that randomised patients meeting DSM-IV criteria of GAD to escitalopram and paroxetine (48). A total of 121 patients were included in the efficacy analysis. After 24 weeks of treatment, mean changes in HAMA scores were -15.3 and -13.3 for escitalopram and paroxetine, respectively ($P = 0.13$). This yielded a RR of 1.25 (95% CI 0.99 to 1.59) suggesting no difference between treatments. However, these results should be carefully interpreted, considering that there were differences in withdrawal rates between groups: a total of 64% of escitalopram-treated patients and 53% of paroxetine-treated patients completed all 24 weeks of double-blind treatment.

Baldwin and colleagues published in 2006 a multi-arm RCT that randomised patients meeting DSM-IV criteria of GAD to three fixed doses of escitalopram versus 20 mg paroxetine versus placebo (34). A total of 270 patients were included in the efficacy analysis comparing paroxetine 20 mg versus escitalopram 10 mg. After 12 weeks of follow-up, escitalopram 10 mg significantly improved HAM-A scores

compared with paroxetine 20 mg (HAM-A difference between groups -2.06, 95% CI -3.90 to -0.21). Additionally, in terms of treatment responders, more patients in the escitalopram group showed an improvement of at least 50% in HAM-A compared with the paroxetine group (72% with escitalopram 10 mg versus 60% with paroxetine, $P < 0.05$). These results must however be interpreted with caution, considering that the design (three escitalopram arms versus one paroxetine arm) might have favoured escitalopram, and that sponsorship and/or “wish” bias (49) might have additionally favoured escitalopram.

Tae-Suk Kim and colleagues published in 2006 an open (no masking) RCT that randomised patients meeting DSM-IV criteria of GAD to flexible doses of paroxetine versus flexible doses of venlafaxine Extended Release (XR) (50). A total of 60 patients were randomly assigned, and 46 were included in the efficacy analysis. The study included individuals with a mean age of around 40 years, 56% in the paroxetine group and 66% in the venlafaxine XR group were females and no other axis I disorder was allowed. After 8 weeks of follow-up, no difference in terms of HAM-A mean score was detected. In terms of treatment responders, 23/25 (92%) in the paroxetine group and 19/21 (90%) in the venlafaxine group showed an improvement of at least 50% in HAM-A ($P > 0.05$).

Bose and colleagues published in 2007 a multi-arm RCT that randomised patients meeting DSM-IV criteria of GAD to escitalopram and venlafaxine versus placebo (43). A total of 264 patients were randomly allocated to escitalopram (10-20 mg) and venlafaxine (75-225 mg), and 198 completed the 8 week trial. The study included outpatients with a mean age of 38 years, more than 60% were females and no other axis I disorder was allowed. After 8 weeks of follow-up, for the primary efficacy outcome, similar change from baseline at week 8 in HAM-A total score was calculated for escitalopram and venlafaxine, although no formal comparison was made. In this trial, both active interventions were not statistically better than placebo. Double-blind treatment was completed by 102 (80.3%) escitalopram-treated patients and by 96 (74.4%) venlafaxine-treated patients.

Bystritsky and colleagues published in 2008 a double-blind RCT that randomised 24 patients meeting DSM-IV criteria of GAD to escitalopram 10-20 mg versus bupropion 150-300 mg (51). After 12 weeks of follow-up, similar change from baseline in HAM-A total score was calculated for escitalopram and bupropion.

Summary table of clinical trials comparing paroxetine, sertraline and escitalopram versus other antidepressants in adult individuals with GAD:

Study	Design	Country	Comparison	Sample	Follow-up	Efficacy [notes]
Rocca 1997	RCT	Italy	Paroxetine 20 mg versus imipramine 50-100 mg (versus BDZ)	56	8	No difference (response rate) [low power]
Ball 2005	RCT	USA	Paroxetine (flexible dose) versus sertraline (flexible dose)	53	8	No difference (response rate) [low power]
Bielski 2005	RCT	USA	Escitalopram versus paroxetine	121	24	No difference (response rate) [differences in withdrawal rates]
Baldwin 2006	RCT	10 countries	Escitalopram 10 mg versus paroxetine 20 mg (versus two other doses of escitalopram)	270	12	Escitalopram > paroxetine (HAM-A) Escitalopram > paroxetine (response rate) [design favoured escitalopram; sponsorship bias]
Tae-Suk Kim 2006	RCT	Korea	Paroxetine (flexible dose) versus venlafaxine XR (flexible dose)	46	8	No difference (HAM-A) No difference (response rate) [low power; no masking]
Bose 2007	RCT	USA	Escitalopram (10-20 mg) versus venlafaxine XR (75-225 mg)	264	8	No difference (HAM-A)
Bystritsky 2008	RCT	USA	Escitalopram (10-20 mg) versus bupropion XL (150-300 mg)	24	12	No difference (HAM-A) No difference (CGI-I) [low power]

> means "better than"

< means "worse than"

RCT = randomised controlled trials; BDZ = benzodiazepines; HAM-A = Hamilton- Anxiety; CGI = clinical global impression

7.5 SSRI (paroxetine, sertraline and escitalopram) versus benzodiazepines

Only two RCTs assessed the efficacy of paroxetine in comparison with benzodiazepines. No trials assessed the efficacy of sertraline in comparison with benzodiazepines.

Rocca and colleagues published in 1997 a three parallel group RCT that randomised patients meeting DSM-IV criteria of GAD to paroxetine 20 mg versus clordesmethylidiazepam (mean daily dose 4.2 mg) (the third treatment arm was imipramine 50-100 mg) (46). A total of 55 individuals were included in the efficacy analysis, carried out 8 weeks after random allocation. The study included outpatients with a mean age of around 36 years, 57% were females and no other axis I disorder was allowed. As reported by study authors, among those who completed the study, moderate to marked improvement (CGI-2<3) was reported by 68% of patients treated with paroxetine and 60% of patients treated with 2'-chlordesmethylidiazepam. Interestingly, while during the first 2 weeks of treatment 2'-chlordesmethylidiazepam treatment resulted in the greatest improvement in anxiety ratings, paroxetine treatment resulted in more improvement than 2'-chlordesmethylidiazepam by the fourth week of treatment. In terms of adverse effects, drowsiness was the only significant side-effect experienced by more 2'-chlordesmethylidiazepam treated patients than paroxetine treated patients. However, nausea was observed more frequently in the paroxetine-treated group.

Cui and colleagues published in 2005 a RCT that randomised 80 patients with GAD to paroxetine versus lorazepam (52). After 6 weeks of treatment no significant difference in HAM-A, or rates of recovery (18/40 with paroxetine; 16/40 with lorazepam, $P > 0.05$), was observed between paroxetine and lorazepam.

Summary table of clinical trials comparing paroxetine and sertraline versus benzodiazepines in adult individuals with GAD:

Study	Design	Country	Comparison	Sample	Follow-up	Efficacy [notes]
Rocca 1997	RCT	Italy	Paroxetine 20 mg versus CD (mean dose 4.2 mg) (versus imipramine)	55	8	Paroxetine > CD (HAM-A) No difference (response rates)
Cui 2005	RCT	China	Paroxetine versus lorazepam	80	6	No difference (HAM-A) No difference (response rate) [low power]

> means "better than"

< means "worse than"

RCT = randomised controlled trials; CD = chlor-desmethyl-diazepam; HAM-A = Hamilton- Anxiety

7.6 Adverse effects of antidepressants

It should be noted that the vast majority of information on adverse effects of SSRIs is based on experimental and observational studies conducted in individuals with moderate to severe major depression. Therefore, extrapolation of these data to individuals with GAD may not always be straightforward. By contrast, antidepressant trials conducted in individuals with GAD were mainly focused on efficacy outcomes, and treatment acceptability was very often measured in terms of patients discontinuing the study early. However, in some trials data on the most frequently reported adverse effects were reported.

Adverse effects reported in SSRI epidemiological studies include dry mouth and gastrointestinal disturbances such as nausea, vomiting, dyspepsia, constipation, and diarrhoea. Anorexia and weight loss may also occur. Neurological side-effects include anxiety, restlessness, nervousness, insomnia, but also drowsiness and fatigue. Headache, tremor, dizziness, confusion, agitation, extrapyramidal effects, sexual dysfunction (impotence or ejaculatory problems), and symptoms suggestive of a serotonin syndrome have additionally been described. Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly. SSRIs have occasionally been associated with bleeding disorders and other effects on the blood. SSRIs are generally regarded as being less toxic in overdose than tricyclic antidepressants or MAOIs. Nausea, vomiting, and excitation of the CNS are considered to be prominent features. SSRIs interact with a range of other drugs mainly as a result of their inhibitory activity on hepatic cytochrome P450 isoenzymes. Individual SSRIs do not all exhibit the same degree of inhibition nor do they react with the same

isoenzymes. The range of drugs inhibited by specific SSRIs varies according to which isoenzyme is affected. As SSRIs have occasionally been associated with bleeding disorders and other effects on the blood, caution is advised when they are given with drugs known to affect platelet function. Sequential prescribing of different types of antidepressant may also produce adverse reactions.

Clinical trials comparing SSRIs with placebo consistently reported significantly more asthenia, constipation, dry mouth, abnormal ejaculation, decreased libido, nausea, somnolence, decreased appetite, sweating, yawning and sexual dysfunctions significantly in SSRI users. In the study carried out by Rickels and colleagues, for example, at least one adverse event was reported by 88% of individuals treated with paroxetine 20 mg/day, 86% of individuals treated with paroxetine 40 mg/day versus 74% with placebo (33). In the study carried out by Baldwin and colleagues, which compared escitalopram with paroxetine and placebo, 10% of people exposed to antidepressants complained insomnia, compared with 2% taking placebo (34). Brawman-Mintzer and colleagues found that sertraline was associated with a significant increase in diastolic blood pressure compared with placebo, and with a significant greater weight loss compared with placebo (41).

Abrupt SSRI withdrawal has been associated with adverse effects including dizziness, headache, nausea, vomiting, diarrhoea, movement disorders, insomnia, irritability, visual disturbance, lethargy, anorexia, and lowered mood. A randomised trial that assessed the frequency of withdrawal symptoms associated with use of paroxetine, sertraline and fluoxetine found that significantly more people had adverse effects when discontinuing paroxetine or sertraline compared with people discontinuing fluoxetine (60% with paroxetine ν 66% with sertraline ν 16% with fluoxetine; $P < 0.01$ for paroxetine or sertraline ν fluoxetine). The clinical trial carried out by Baldwin and colleagues, which compared escitalopram and paroxetine with placebo, found a significant increase in scores with paroxetine on the Discontinuation Emergent Signs and Symptoms (DESS) scale at day 7 compared with placebo (4.2 with paroxetine ν 0.4 with placebo, P less than 0.001) (34).

In pregnant women evidence-based guidelines suggest to avoid antidepressants. However, if maternal depression is a major concern, an antidepressant may be prescribed. Current evidence suggests that there is no increased risk of malformations in women exposed to fluoxetine and no evidence of teratogenicity

(53). By contrast, there is some evidence that paroxetine taken in the first trimester may be associated with heart defects (53). Additionally, SSRI exposure after 20 weeks' gestation may be associated with an increased risk of persistent pulmonary hypertension in neonates (54), and all antidepressants carry the risk of withdrawal or toxicity in neonates.

Bullet points on SSRI adverse effects

- ✓ Dry mouth, sexual dysfunction, gastrointestinal disturbances (nausea, vomiting, dyspepsia, constipation, and diarrhoea) and neurological side-effects (anxiety, restlessness, nervousness, insomnia) are frequently reported adverse effects associated with SSRI use.
- ✓ Abrupt SSRI withdrawal has been associated with adverse effects: significantly more people had adverse effects when discontinuing paroxetine or sertraline compared with people discontinuing fluoxetine.
- ✓ Fluoxetine is the SSRI of choice in pregnancy. Paroxetine may be associated with heart defects.
- ✓ The vast majority of information on adverse effects is based on studies conducted in individuals with moderate to severe major depression, and not in individuals with GAD.

7.7 SSRIs and suicidality

There remains uncertainty about the safety of SSRIs, which may cause worsening of suicidal ideas in vulnerable people (55). It should be noted that the majority of information on suicidality and antidepressants is based on systematic reviews of clinical trials conducted in individuals with moderate to severe major depression, and on epidemiological studies similarly conducted in individuals with depressive symptoms. Therefore, extrapolation of these findings to individuals with GAD may not be straightforward.

Regulatory authorities in Europe, the UK, and the USA have issued warnings about the use of SSRIs in children and adolescents. Very recently, after new evidence of a possible increased risk of suicide ideas in young adults, regulatory authorities in the USA expanded these warnings to include adult individuals aged 18-25 (56;57). Two systematic reviews analysed suicidal ideas and completed suicides in randomised trials of AD drugs in individuals with major depression, and a third systematic review, carried out by the FDA, analysed individual patient data from all available

clinical trials of antidepressants conducted in individuals with major depression and other psychiatric and non-psychiatric conditions.

Fergusson and colleagues conducted a systematic review of published RCTs comparing SSRIs with either placebo or other active treatments in patients with depression and other clinical conditions (58). They found an almost two-fold increase in the odds of fatal and non-fatal suicidal attempts in SSRI users compared with users of placebo or other therapeutic interventions (excluding tricyclics). No increase in risk was observed, however, when only fatal suicidal attempts were compared between SSRIs and placebo. Finally, no differences were observed when overall suicide attempts were compared between SSRI and tricyclic users. By contrast, **Gunnell** and colleagues included in their review both published and unpublished RCTs submitted by pharmaceutical companies to the safety review of the Medicine and Healthcare products Regulatory Agency (MHRA) (59). These trials compared SSRIs with placebo in adults with depression and other clinical conditions. Three outcome measures were studied: completed suicide, non-fatal self-harm and suicidal thoughts. No evidence for an increased risk of completed suicide was found, and their analysis found only weak evidence of an increased risk of self-harm, and inconclusive evidence of an increased risk of suicidal thoughts (estimates compatible with a modest protective or adverse effect).

In May 2007 the **Food and Drug Administration** (FDA) ordered that all antidepressant drugs carry an expanded black-box warning incorporating information about an increased risk of suicidal symptoms in young adults aged 18 to 24 years. The new warning was based on the results of a FDA meta-analysis that included 372 placebo-controlled antidepressant trials and nearly 100 000 patients (60). On the basis of this analysis the relationship between antidepressant drug treatment and the incidence of reported suicidal behaviour in clinical trials was strongly related to age: the risk associated with drug treatment relative to placebo was found to be elevated in subjects under age 25, neutral in subjects aged 25 to 64 (reduced if suicidal behaviour and ideation are considered together), and reduced in subjects aged 65 and older. With regards to individual drugs, in terms of suicidal behaviour or ideation, the FDA analysis revealed that, in adults, fluoxetine and sertraline, but not other SSRIs, were associated with a statistically significant protective effect; in terms of suicidal behaviour, sertraline was again associated with a statistically significant protective effect, while paroxetine was associated with a statistically significant increased risk (61). These figures are in line with a growing

body of evidence suggesting that in adults with major depression the frequency of suicidal attempts in adult individuals was higher in patients treated with paroxetine compared with placebo (62-64).

Bullet points on SSRIs and suicidality

- ✓ SSRIs may have two general effects, one promoting suicidality and one preventing it. In older individuals the preventative effect may predominate, while in younger individuals the promoting effect may prevail.
- ✓ In adult individuals, in terms of suicidal behaviour, sertraline was associated with a statistically significant protective effect, while paroxetine was associated with a statistically significant increased risk.
- ✓ The vast majority of information on suicidality and antidepressants is based on re-analyses of clinical trials conducted in individuals with moderate to severe major depression.

8. Summary of available data on comparative cost and cost-effectiveness

No clinical trials, observational studies and database analyses performed an economic evaluation of the cost-effectiveness of antidepressants in individuals with GAD. However, we found one decision-analytic model that compared, from a societal perspective, the cost-effectiveness of escitalopram and paroxetine in the treatment of GAD in the UK (65), and another decision-analytic model that determined the cost-effectiveness of escitalopram for GAD in a Canadian primary care setting (66). A third model assessed, from a health sector perspective, the incremental cost-effectiveness of interventions for generalized anxiety disorder (cognitive behavioural therapy and antidepressants) (67). However, considering the ongoing debate around the role of the decision model approach in the evaluation of psychotropic drugs (68), and considering the general opinion that physicians and policy-makers should be very cautious in basing decisions on economic models, we did not analyse these three models in the present document.

Although no formal cost-effectiveness analyses have been conducted so far, it is notable that some SSRIs are now off-patent, available in generic form and, hence, may have lower acquisition costs in most health care systems. In fact, only one of the SSRIs is still on patent (in the US and in Europe), escitalopram. Taking cost into account, it would therefore seem logical to prefer paroxetine or sertraline over escitalopram because of lower acquisition cost in most countries. According to NICE guidelines “when prescribing an SSRI consideration should be given to using a

product in a generic form" (25). However, in the absence of a full economic analysis, this recommendation cannot be made unequivocally because several other costs may be associated with the use of antidepressants.

9. Summary of regulatory status of the medicine

In the USA (FDA-Labeled indications) escitalopram and paroxetine are indicated in the pharmacological treatment of generalised anxiety disorder. Sertraline does not have this indication yet, although it is currently under development. In the UK paroxetine has marketing authorisation for the treatment of generalised anxiety disorder. In Italy escitalopram and paroxetine are indicated in the pharmacological treatment of generalised anxiety disorder.

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