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ORIGINAL ARTICLE

Evidence-based treatment of anxiety disorders

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Abstract
Evidence-based medicine combines the best currently available evidence from systematic medical research, together with clinical expertise, in order to provide the best available care for patients. In conjunction with systematic reviews (meta-analyses), a critical review of evidence-based literature forms the basis for the development of clinical treatment guidelines. Current treatment guidelines for generalized anxiety disorder (GAD) advocate the use of selective serotonin reuptake inhibitors (SSRIs) or serotonin–noradrenaline reuptake inhibitors (SNRIs) as the first line of pharmacotherapy. The safety and tolerability profiles of other medications, such as the benzodiazepines, limit their use, especially for long-term treatment. Since data comparing the efficacy in GAD of different SSRIs are limited, selection of one SSRI over another is generally based on consideration of tolerability profiles. Treatment guidelines for patients with social anxiety disorder (SAD) often recommend SSRIs as the first line of medication treatment, as this class has the largest evidence-base in support of efficacy. Less consistent evidence of efficacy exists for other agents, such as reversible inhibitors of monoamine oxidase inhibitor A (RIMAs), and issues of safety are a concern when considering the use of benzodiazepines. Again, there are few head-to-head studies of the SSRIs, and treatment selection is usually made on the basis of tolerability issues. The efficacy and tolerability of the SSRI, escitalopram, has been evaluated in patients with GAD and with SAD. In long-term studies of SAD, escitalopram demonstrated superior efficacy to placebo and paroxetine. It also exhibited a better tolerability profile, as assessed by discontinuation emergent signs and symptoms (DESS), in both patient groups. Furthermore, in relapse prevention trials of SAD, escitalopram conferred a significant benefit relative to placebo.

Key Words: *Anxiety disorders/drug therapy, evidence-based medicine, social phobia, SSRIs*

Introduction

Evidence-based medicine (EBM), or "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" [1], has its origins in concerns about the quality of health care, including excessive variations in individual, institutional and regional diagnostic testing, hospitalization rates, therapeutic interventions, and outcomes. Professional organizations, consumer groups, and government agencies have all advocated for EBM, with the aim of improving the quality of health services. Similarly, there has been growing interest in evidence-based psychiatry in recent decades.

At the same time, clinicians often voice concerns that evidence-based approaches and methods neglect clinical experience and judgment. It is important to emphasize, therefore, that the practice of evidence-based medicine "means integrating individual clinical expertise with the best available external clinical evidence from systematic clinical research" [1]. Without clinical expertise, clinical practice risks being dictated by evidence that may be inappropriate for the individual patient. On the other hand, without evidence, clinical practice rapidly risks becoming out-of-date [1].

In addition, EBM reflects rigorous efforts to retrieve systematically and synthesize clinical data and to make it into a form that is readily available to clinicians, so that it can be incorporated into clinical practice [2]. Clinical practice guidelines, based on a scientific evaluation of the research literature, are "systematically developed statements designed to help clinicians and patients make decisions about appropriate healthcare for specific circumstances" [3]. The aim of such guidelines is to encourage clinical practitioners to use scientific evidence in clinical decision making [4].

Guideline development poses several problems, including effective dissemination and adoption. To be effective, the information within the guideline should be readily available within clinical practice,

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accessible by physicians, and be reviewed and updated regularly [5]. Thus, a useful guideline needs to be simple and user-friendly and to provide a balance between unnecessary detail and excessive generality. The former is unlikely to be evidence-based and the latter is of little help to the clinician in reaching a decision [6].

The three key components of simple user-friendly guidelines identified by Jackson and Feder [7] are:

- identification of the key decisions and their consequences;
- review of the relevant, valid evidence on the benefits, risks and costs of alternative decisions;
- presentation of the evidence required to inform key decisions in a simple, accessible format that is flexible to stakeholder preferences.

Most clinical guidelines regard randomized clinical trials, meta-analyses and systematic reviews as the highest level of evidence to support EBM [8,9]. High-quality meta-analyses can arguably overcome many of the limitations of individual clinical trials and qualitative reviews, by reducing bias and providing sufficient power to demonstrate clear differences in outcomes between treatments. However, the quality of a meta-analysis depends on that of the studies on which it is based, and it is important to bear in mind methodological differences across different trials [10].

An audit of clinical guidelines published over a decade ago counted more than 2000 published in the UK alone, in the years up to 1994 [11]. A visit to the website www.guidelines.gov reveals more than 150 hits for 'anxiety disorders'. Included are guidelines published by the American Psychiatric Association (e.g., on panic disorder [PD] [12]), the American Academy of Child and Adolescent Psychiatry (e.g., on anxiety [13], obsessive compulsive disorder [OCD] [14] and post-traumatic stress disorder [PTSD] [15]), the Expert Consensus Guidelines (e.g., on OCD [16] and PTSD [17]), The World Council on Anxiety guidelines (e.g., on GAD [18], PTSD [19] and PD [20]) and the National Institute for Clinical Excellence [NICE] guidelines on GAD [21] and PTSD [22].

In this presentation, we briefly review some of the issues in deciding on the first line of pharmacotherapy for GAD and SAD, bearing in mind recent data on escitalopram.

Evidence-based guidelines on generalized anxiety disorder (GAD) treatment

Although many treatment options are available for patients with GAD, including non-pharmacological interventions such as cognitive behavioral therapy (CBT), a growing body of evidence, largely from placebo-controlled clinical trials, has confirmed the efficacy of several medications, including the SSRIs and SNRIs in this indication [23]. On the basis of this evidence, most current treatment guidelines for GAD recommend an SSRI or SNRI as the first-line medication treatment option for patients with GAD [18,21,23,24].

There is increasing evidence that antidepressants are effective in GAD, with particular efficacy on the psychic symptoms of anxiety [23]. An important advantage of the SSRIs and SNRIs is their proven efficacy in treating depression and other anxiety disorders that are frequently comorbid with GAD [23]. Furthermore, with the increasing recognition of GAD as a chronic condition, evidence of the long-term safety and efficacy of treatment regimens is mandatory. Importantly, in two recent meta-analyses, the SSRIs and SNRIs clearly demonstrated superiority over placebo in treating patients with GAD [25,26]. Moreover, the demonstrated safety, tolerability and effectiveness of these agents during long-term use support their use as an appropriate maintenance pharmacotherapy treatment for GAD [23,24].

Less consistent evidence of clinical efficacy is available for other agents, such as buspirone and hydroxyzine, and they are ineffective for comorbid depression or anxiety disorders in GAD. These agents are consequently not recommended as a first-line treatment for GAD [23,24]. Similarly, there is a growing consensus that the benzodiazepines are not an optimal first-line medication in GAD [27–29]. Systematic reviews have demonstrated limited evidence for the efficacy of benzodiazepines versus placebo in reducing the symptoms of GAD over 2–9 weeks, and little evidence of their long-term efficacy [30]. In addition, as GAD is frequently comorbid with depressive disorders, or other anxiety disorders, such as panic disorder and SAD, antidepressant agents with broad spectrum effects are favored. The potential for adverse reactions following benzodiazepine withdrawal also limits their use in GAD, although they may be useful short-term in relieving acute exacerbations of GAD.

A variety of psychotherapeutic options have been used to treat GAD. The most consistent results to date have been obtained with CBT. Results from well-conducted trials suggest that CBT is associated with clinically relevant and long-term therapeutic improvements, as compared with controls. Indeed, treatment gains following a 12-week course of CBT may be sustained for up to 1 year [18].

In guidance issued in the UK by NICE [21], the advice for treating patients with GAD is (Figure 1):

- Benzodiazepines should not usually be used beyond 2–4 weeks.
- In the longer-term care of individuals with generalized anxiety disorder, any of the following types of intervention should be offered and the preference of the person with generalized anxiety disorder should be taken into account.

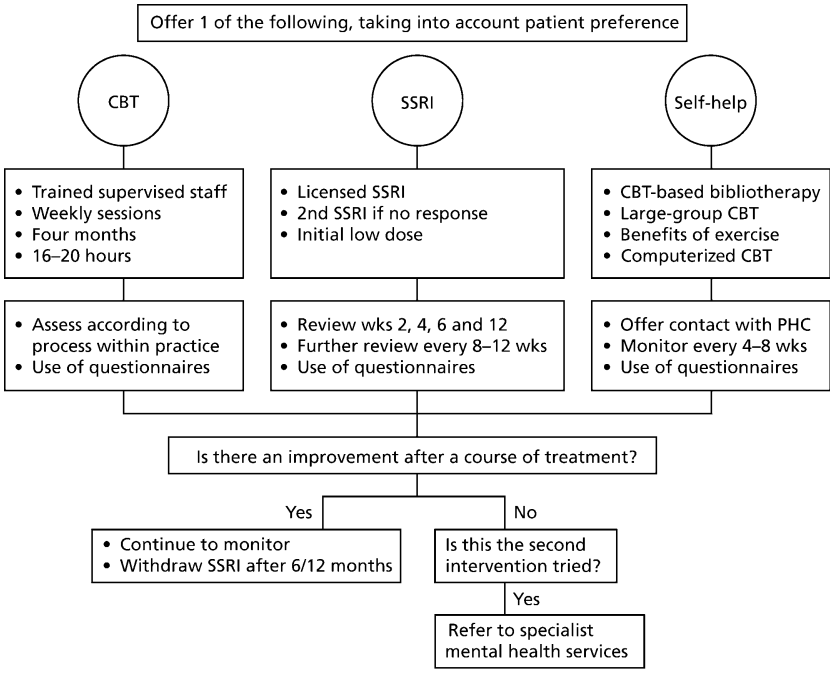

Figure 1. Recommendations for the treatment of GAD in primary care issued by NICE (2004) [21] in the UK.

The interventions that have evidence for the longest duration of effect, in descending order, are:

- psychological therapy (CBT);
- pharmacological therapy (an SSRI);
- self-help (bibliotherapy based on CBT principles).

Although current guidelines recommend the use of SSRIs or SNRIs for the long-term treatment of GAD, evidence comparing the different medications is poor. For this reason, the selection of one particular intervention over another is often based on consideration of tolerability profiles.

Evidence-based guidelines on social anxiety disorder (SAD) treatment

Social anxiety disorder (SAD), or social phobia, is now recognized as a prevalent, chronic, and frequently disabling disorder with onset early in life [31]. The condition is characterized by a persistent fear of negative evaluation or scrutiny by others in social situations, resulting in excessive fear of humiliation or embarrassment, reduced adaptive functioning and clinical distress. Patients with SAD suffer considerable psychiatric comorbidity with other psychiatric disorders, including mood disorders, anxiety disorders and substance abuse or dependence [32].

Epidemiological studies show that SAD is among the most prevalent of all mental disorders. Lifetime prevalence rates are estimated to be in the region of 13–16% [33,34], although more conservative criteria yield lower rates [35]. Nevertheless, the condition often remains undiagnosed and may be completely overlooked among general practitioners. It should also be emphasized that relatively few people with SAD seek professional help for this condition. For example, of 98 patients in a large North American cohort ($n = 1488$) study who met the clinical criteria for SAD, 64% did not seek medical advice, 33% sought help for other psychological problems and only 3% admitted to seeking help for SAD [36].

If untreated, SAD is usually chronic and associated with significant functional impairment. Both pharmacological and cognitive-behavioural approaches to SAD are effective and offer complementary strengths. On the basis of consistent data from randomized controlled trials, present consensus supports the use of SSRIs as the first-line treatment for SAD [24,37,38]. Second-line treatments include monoamine oxidase inhibitors (MAOIs) and reversible inhibitors of monoamine oxidase A (RIMAs). Some benzodiazepines, e.g., clonazepam, may also be of benefit, at least in the short-term.

Evidence in support of the selection of the SSRIs as first line pharmacotherapy for SAD is derived from the results of controlled clinical studies showing statistically significantly improved response rates for the SSRIs, including paroxetine, fluvoxamine, sertraline, citalopram and escitalopram, versus placebo [39]. Furthermore, meta-analyses comparing the efficacy of medications currently used in SAD [40–42] have revealed the greatest evidence of efficacy for the SSRIs.

In a Cochrane review of pharmacotherapy for SAD, Stein and colleagues analyzed data from a total of 36 randomized controlled trials (RCTs), involving 5,264 patients [43]. Of these studies, 17 assessed the

efficacy of SSRIs in this patient group. A variety of other medications were also studied, including MAOIs, RIMAs, benzodiazepines, buspirone, β-blockers, and gabapentin. Twenty-six trials demonstrated that all medication groups showed short-term superiority in treatment response, compared with placebo [43]. The SSRIs were significantly more effective than moclobemide.

Treatment for SAD may need to be continued for several months to strengthen the response and achieve full remission. Although the majority of efficacy studies for SAD have been acute trials, long-term studies demonstrate that for those patients who remain on SSRIs, the treatment response remains superior to those on placebo [44–46]. There is less evidence for other agents over the long term, with regard to both efficacy and tolerability [47]. Furthermore, as differences in efficacy in SAD between the individual SSRIs have not often been evaluated, choice of a specific SSRI for a patient is usually made on the basis of the side effect profile.

The evidence for escitalopram

Escitalopram has demonstrated superiority over other SSRIs in both animal models [48] and in clinical studies of depression [49]. It has been postulated that this is a reflection of the unique mode of action of escitalopram [48].

In patients with GAD, escitalopram (10 and 20 mg) was effective and well-tolerated during 12 weeks of treatment [50]. In a randomized, double-blind, parallel group study in outpatients with GAD, investigating the efficacy and tolerability of escitalopram (5, 10 and 20 mg) in comparison with paroxetine (20 mg/day) and placebo, escitalopram 10 mg was statistically superior to paroxetine 20 mg for the change from baseline to week 12 (LOCF), based on HAM-A and CGI-I. Similarly, in patients with GAD, the mean change in Discontinuation Emergent Signs and Symptoms (DESS) score was statistically significantly lower with escitalopram (10 mg/day) than with paroxetine ($P < 0.001$) [50]. Furthermore, patients who stopped treatment with escitalopram 10 mg had fewer discontinuation effects than those who stopped treatment with paroxetine 20 mg.

In a 24-week, randomized, double-blind, fixed-dose study, escitalopram (5, 10 and 20 mg/day) demonstrated a significantly superior therapeutic effect relative to placebo, in patients with SAD [51]. In this study, enrolled patients (aged 18–65 years) with a primary diagnosis of generalized SAD (DSM-IV criteria, total score of ≥ 70 on the Liebowitz Social Anxiety Scale [LSAS], with fear and avoidance traits in at least four social situations) were randomized to 24 weeks of double-blind treatment with 5 mg/day escitalopram ($n = 167$), 10 mg/day escitalopram ($n = 167$), 20 mg/day escitalopram ($n = 169$), placebo ($n = 170$) or 20 mg/day paroxetine ($n = 169$). Analysis of the therapeutic effect (change in the LSAS from baseline to week 24) showed significant superiority for all doses of escitalopram ($P < 0.05$, $P < 0.01$; $P < 0.001$, respectively) over placebo (Figure 2), while the highest dose of escitalopram was also superior to paroxetine at study endpoint ($P < 0.01$) [51]. Both escitalopram and paroxetine were superior to placebo on the Clinical Global Impression-Improvement scale from baseline to week 24 ($P < 0.001$), with an observed active-treatment difference in favor of escitalopram ($P < 0.05$).

Escitalopram has also demonstrated improved tolerability, as compared with paroxetine, in patients with SAD [51]. In the 24-week study described above, the mean change in the DESS score in patients with SAD ($n = 839$) was significantly lower with escitalopram (10 and 20 mg/day) than with paroxetine (20 mg/day) ($P < 0.001$, $P < 0.05$, respectively) [51,52].

In relapse prevention studies, escitalopram and other pharmacological treatments conferred a significant benefit versus placebo in patients with SAD [44,46,53,54]. For example, in a study comprising a 12-week open-label period with flexible escitalopram doses (10–20 mg/day), followed by a 24-week, randomized, double-blind, fixed-dose comparison of escitalopram (10 or 20 mg/day) and placebo, in patients with SAD ($n = 517$), more than twice as many patients on placebo as on escitalopram suffered relapse (log rank test, $P < 0.001$) [54] (Figure 3). Cox regression analysis showed that the risk of relapse was 2.8 times higher in placebo-treated patients as compared with those on escitalopram ($P < 0.001$; SD 1.20). These findings confirm the superior efficacy of escitalopram, as compared with placebo, in prevention of relapse in patients with SAD.

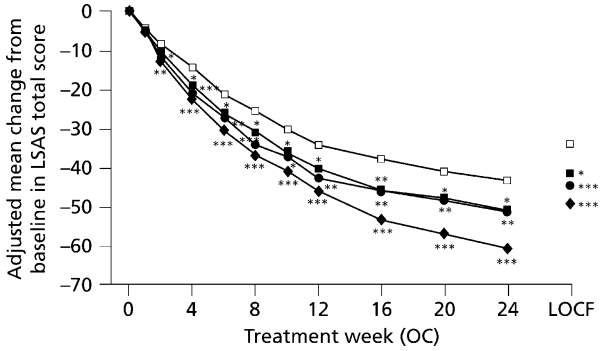

Figure 2. Escitalopram is efficacious in the treatment of social anxiety disorder [51]. (□) Placebo ($n = 164$), (●) escitalopram 5 mg ($n = 166$); (■) escitalopram 10 mg ($n = 162$); (◆) escitalopram 20 mg ($n = 162$). *$P < 0.05$ vs. placebo; **$P < 0.01$ vs. placebo; ***$P < 0.001$ vs. placebo.

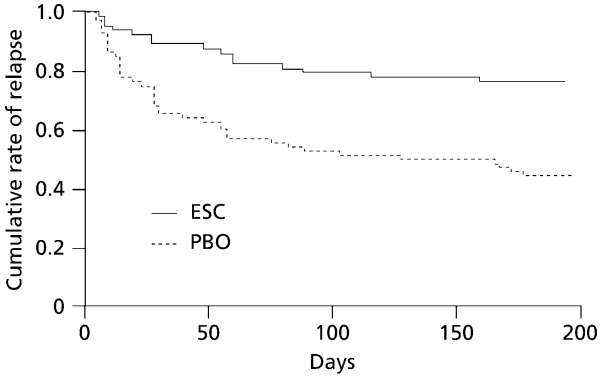

Figure 3. Kaplan–Meier survival analysis of relapse in patients receiving escitalopram (10 or 20 mg/day) ($n=190$) or placebo ($n=181$) during 224 days of treatment. Time to relapse showed a significant advantage for patients treated with escitalopram, compared with patients treated with placebo (log-rank test; $P<0.001$). Relapse criteria were defined as either an increase in LSAS total score of ≥ 10 points over the score at randomization, or withdrawal of the patient from the study, due to an unsatisfactory treatment response (lack of efficacy) as judged by the investigator. Reproduced with permission [54].

Conclusions

The SSRIs and SNRIs are considered the first-line pharmacological treatment for GAD and SAD [23,24]. Stability of the SSRI effect size, in conjunction with other evidence for safety and tolerability and their ability to treat common comorbid disorders, supports the preferential use of these agents in these disorders. Long-term treatment is recommended to reduce rates of relapse.

Compared with benzodiazepines, the SSRIs are more effective for treating comorbid psychiatric disorders. Although the benzodiazepines constitute an effective acute treatment for GAD and SAD, especially when rapid relief from symptoms is required, the associated risks and withdrawal symptoms upon discontinuation, limit their use in routine practice. Accumulating data indicate that the selective SSRI, escitalopram, is effective in both the short- and long-term treatment of GAD and SAD, and has advantages over benzodiazepines and the SSRI, paroxetine.

Key points

- Evidence-based medicine combines information from clinical research and clinical practice to provide the best available care for patients
- Evidence-based literature is used as the basis for clinical treatment guidelines
- Treatment guidelines for patients with generalized anxiety disorder (GAD) recommend use of SSRIs or SNRIs as the first-line pharmacological therapy based on a large body of evidence-based literature
- For patients with social anxiety disorder (SAD), SSRIs are also recommended as the first-line medication of choice due to their large evidence-base in support of efficacy
- Escitalopram, a new type of SSRI, has demonstrated long-term efficacy and tolerability in patients with GAD and SAD and is effective in relapse prevention in patients with SAD

Statement of interest

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