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(54) Title: NOVEL USES FOR ESREBOXETINE AND RACEMIC REBOXETINE

(57) Abstract: A norepinephrine reuptake inhibitor, or a pharmaceutically acceptable salt thereof, preferably esreboxetine or racemic reboxetine, more preferably esreboxetine, to improve cognitive function, in particular to improve in cognitive function in patients with fibromyalgia is provided. Also provided are methods of treatment of the same.



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NOVEL USES FOR ESREBOXETINE AND RACEMIC REBOXETINE

Field of invention

The invention relates to a number of novel uses for norepinephrine reuptake inhibitors, particularly esreboxetine and racemic reboxetine. In particular this invention relates to a norepinephrine reuptake inhibitor for use to improve cognitive function, and more particularly to a norepinephrine reuptake inhibitor for use to improve cognitive function in patients with fibromyalgia.

Background

Fibromyalgia is a chronic condition characterised by wide spread muscle and joint pain; profound fatigue and sleep disturbance. In 1990 the American College of Rheumatology published criteria for the diagnosis of fibromyalgia as a history of widespread pain and pain in 11 of 18 pre-defined tender points (Wolfe et al. *Arthritis Rheum* 1995, 38(1), pp19-28). The etiology of the disease remains unclear. However individuals diagnosed with fibromyalgia often suffer from comorbid conditions including depressive disorders, bipolar disorders, and anxiety disorders as well as other pain syndromes. These further complicate the treatment strategy. To date the only marketed pharmacological treatment for fibromyalgia is pregabalin (LyricaTM, Pfizer Inc), although others are in development.

Patients suffering from several different diseases, including Alzheimer's disease, major depressive disorder and schizophrenia, are known to experience concomitant or comorbid cognitive dysfunction or impairment. Reports have indicated that, in at least some cases, the cognitive dysfunction or impairment may be associated with malfunction of noradrenergic functioning (Friedman et al, *Biol Psychiatry*, 1999, 46, pp1243-1252). Recent findings have also reported that some fibromyalgia patients, in addition to the core symptoms of the disease, suffer from comorbid cognitive dysfunction or impairment (Glass, *J. Clin. Psychiatry* 2008, 69 (suppl 2), pp20-24). This has become commonly known as "fibro fog". Interestingly, objective tests demonstrate that not all of the different cognitive domains appear to be

affected in fibromyalgia sufferers. Those cognitive domains which have been shown to be particularly impaired in fibromyalgia sufferers include working memory, episodic memory and verbal fluency. For these three cognitive domains specifically objective clinical tests have demonstrated that fibromyalgia sufferers tend to perform similarly to control patients who are 20 years older than themselves (Glass & Park, Current Rheumatology Reports, 2001, 3, pp123-127). By contrast fibromyalgia patients do not appear to demonstrate impaired abilities for other cognitive tasks such as those related to information processing speed. With respect to these aspects of cognitive function, fibromyalgia patients have been shown to perform just as well as their age-matched controls. These results appear to differentiate the cognitive dysfunction of fibromyalgia sufferers from that experienced by sufferers of other disease states, for example depressed patients. This is because depressed patients are typically slow on measures such as information processing speed. In addition, no significant correlations have been found between depression or anxiety disorders comorbid with fibromyalgia and the cognitive dysfunction experienced by fibromyalgia sufferers. Again this indicates that "fibro fog" likely can not be solely attributed to factors such as depression or anxiety which are sometimes also experienced by the fibromyalgia sufferers. By contrast some correlation has been demonstrated between cognitive impairment of fibromyalgia sufferers and their pain and, to a lesser extent, their fatigue (Glass, Current Rheumatology Reports, 2006, 8, pp425-429). This indicates that it is possibly these aspects of fibromyalgia that have at least some impact in driving the negative cognitive effects.

The cognitive dysfunction of fibromyalgia sufferers can negatively impact their ability to function in everyday life, especially in the work place. For example working memory is critical for accurate performance in demanding cognitive situations and it underlies successful performance in many other cognitive tasks. A deficit in working memory ability has repercussive effects on other aspects of cognition, so that a small deficit in working memory can have a large impact. Episodic memory or remembering recently presented information or events is an important aspect of everyday cognitive function and disruption seriously impacts one's ability to perform in the workplace.

Finally deficits in verbal fluency impact a patient's ability to think quickly and come up with the right word for a given situation – again problematic in work place situations which require thinking on our feet. Furthermore fibromyalgia sufferers have been shown to have attention difficulties and in particular find it difficult to pay attention to things which are of importance while ignoring distracting items. These results are consistent with the reduced ability in working memory function because attention tests require people to store information for a short period and also process distracting information. Anecdotally some fibromyalgia patients find the cognitive impairment more troubling than the other symptoms such as pain. Indeed certain sub-populations of fibromyalgia patients for whom cognitive dysfunction or impairment presents a particular concern may benefit from therapies able to target these symptoms specifically. As such there is a need to improve the cognitive function of patients with fibromyalgia, and particularly those who experience difficulties due to cognitive dysfunction or impairment.

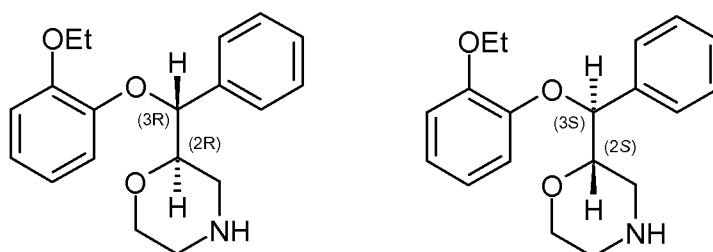
Recently milnacipram, the dual serotonin and norepinephrine reuptake inhibitor (SNRI), was disclosed as being useful for the treatment of cognitive dysfunction associated with fibromyalgia (US patent application US 2008/0058318). However, there remains a need to develop further effective therapies to improve cognitive function in fibromyalgia patients.

Chronic fatigue syndrome is a debilitating disorder characterised by profound tiredness or fatigue (Schluederberg et al, Ann Intern Med 1992, 117, pp325-331). Patients with chronic fatigue syndrome may become exhausted with only light physical exertion, and most often function at a level of activity substantially lower than their capacity before the onset of illness. In addition to the key defining characteristic of fatigue, patients with chronic fatigue syndrome generally report various non-specific symptoms including weakness, muscle aches and pains, excessive sleep, malaise, fever, sore throat, tender lymph nodes, insomnia and depression. As with fibromyalgia, some patients also suffer from comorbid cognitive dysfunction or impairment, usually manifested as impaired memory or mental concentration (Glass, Current Rheumatology Reports, 2006, 8, pp425-429). Therefore there is also

a need to develop effective therapies to improve cognitive function of patients with chronic fatigue syndrome.

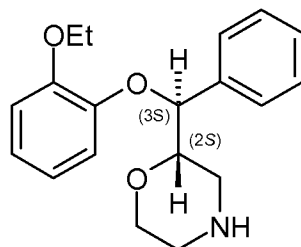
Schizophrenia is a psychotic disorder characterised by abnormalities in perception or expression of reality. Schizophrenia is usually described in terms of positive and negative symptoms. The positive symptoms include delusions, auditory hallucinations and thought disorder. The negative symptoms are so named because they are considered to be the loss or absence of normal traits including cognitive functioning. There is also a need to develop effective therapies to improve cognitive function of patients with schizophrenia.

United States Patent US 4229449 discloses racemic reboxetine, a 50:50 mixture of the two enantiomers of (2RS,3RS)-2-[α -(2-ethoxyphenoxy)benzyl] morpholine



and pharmaceutically acceptable salts thereof. It also discloses several processes for the manufacture of reboxetine. Racemic reboxetine is commercially sold under the trade names of EDRONAX™, PROLIFT™, VESTRA™, and NOREBOX™ for the treatment of depression.

It is now known (see WO 01/01973) that the (2S,3S)-enantiomer of reboxetine, otherwise referred to as (S,S)-reboxetine, or esreboxetine,



possesses greatly improved selectivity for norepinephrine reuptake over serotonin reuptake. Several methods have been disclosed in the art for preparing esreboxetine including those disclosed in WO 03/106441 and WO 2005/082869. Several novel uses of racemic reboxetine and esreboxetine have also been disclosed in the art (WO 01/01973), including the use of racemic reboxetine and esreboxetine for the treatment of fibromyalgia and other somatoform disorders, chronic fatigue syndrome and psychotic disorders including schizophrenia.

Racemic reboxetine has been generally associated with cognitive functioning in some prior art documents. For example Kerr et al (Br J Clin Pharmacol, 1996, 42, pp239-241) have reported a study assessing whether or not racemic reboxetine affects the cognitive and psychomotor skills necessary for optimum function in everyday life. The results demonstrated that racemic reboxetine at doses of 4mg or less does not disrupt cognitive function. In another example Ferguson et al (Int Clinical Psychopharmacology 2003, vol 18 pp 9-14) have reported a study comparing racemic reboxetine with paroxetine on the effect of cognitive functioning in depressed patients. The results provide data to support the possibility that reboxetine favourably affects cognitive processes in depressed patients, in particular with respect to attention and speed of cognitive functioning. In yet another example Schutz and Berk (International Clinical Psychopharmacology, 2001, 16, pp275-278) have reported a study comparing the add on effect of racemic reboxetine to haloperidol in the treatment of the negative symptoms of schizophrenia but no significant difference was seen compared to placebo. Esreboxetine is also known for treating some aspects of cognitive functioning. For example, prior art document WO 01/01973 discloses the use of both racemic reboxetine and esreboxetine to treat attention deficit disorders due to general medical

conditions and prior art document WO 2006/000903 discloses the use of racemic reboxetine and esreboxetine as a mental performance enhancer.

It has now been found that norepinephrine reuptake inhibitors, in particular esreboxetine and racemic reboxetine and more particularly esreboxetine, can be usefully used to improve cognitive function in patients with fibromyalgia. Without wishing to be bound by theory it is believed that these advantageous effects are as a result of the interaction of the norepinephrine reuptake inhibitor with the noradrenergic system which may in turn enhance cognitive processing. It is thought that this occurs because the central adrenergic system is closely associated with areas of the brain, in particular the prefrontal cortex, which may be associated with cognitive deficits. Again, without wishing to be bound by theory, in the case of esreboxetine it is believed that the particularly beneficial effects are due to the greatly improved selectivity of esreboxetine for norepinephrine reuptake over serotonin reuptake. Furthermore, and again without wishing to be bound by theory, it is believed that norepinephrine reuptake inhibitors, in particular esreboxetine and racemic reboxetine and more particularly esreboxetine, can be usefully used to improve cognitive function in patients with chronic fatigue syndrome for similar reasons. Yet further it is believed that norepinephrine reuptake inhibitors, in particular esreboxetine and racemic reboxetine and more particularly esreboxetine, can be usefully used to improve cognitive function in patients with schizophrenia for similar reasons.

These, and other advantages of the invention, will be discussed in further detail below.

Summary of the Invention

According to a first aspect, this invention relates to a norepinephrine reuptake inhibitor, or a pharmaceutically acceptable salt thereof, to improve cognitive function in patients with fibromyalgia.

According to a further aspect, this invention relates to a method of improving cognitive function in patients with fibromyalgia comprising administering to the patient in need of such improvement a norepinephrine reuptake inhibitor, or a pharmaceutically acceptable salt thereof.

According to another aspect, this invention relates to the use of a norepinephrine reuptake inhibitor, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament to improve cognitive function in patients with fibromyalgia.

According to yet another aspect, this invention relates to a norepinephrine reuptake inhibitor, or a pharmaceutically acceptable salt thereof, to improve cognitive function in patients with chronic fatigue syndrome.

According to a still further aspect, this invention relates to a method of improving cognitive function in patients with chronic fatigue syndrome comprising administering to the patient in need of such improvement a norepinephrine reuptake inhibitor, or a pharmaceutically acceptable salt thereof.

According to a yet still further aspect, this invention relates to the use of a norepinephrine reuptake inhibitor, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament to improve cognitive function in patients with chronic fatigue syndrome.

According to yet another aspect, this invention relates to a norepinephrine reuptake inhibitor, or a pharmaceutically acceptable salt thereof, to improve cognitive function in patients with schizophrenia.

According to a still further aspect, this invention relates to a method of improving cognitive function in patients with schizophrenia comprising administering to the patient in need of such improvement a norepinephrine reuptake inhibitor, or a pharmaceutically acceptable salt thereof.

According to a yet still further aspect, this invention relates to the use of a norepinephrine reuptake inhibitor, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament to improve cognitive function in patients with schizophrenia.

These, and other aspects of the invention, will be discussed in more detail below.

Detailed Description

The present invention relates to methods to improve cognitive function using a norepinephrine reuptake inhibitor, preferably esreboxetine or racemic reboxetine, more preferably esreboxetine.

Within the scope of this invention “to improve” includes for example demonstrating a clinically determined improvement from baseline using established methodology compared to placebo, in at least one objective cognitive test. Within the scope of this invention “to improve” also includes for example demonstrating a clinically determined improvement from baseline using established methodology compared to placebo, in at least one subjective cognitive test. “To improve” should also be taken to include demonstrating a clinically determined improvement from baseline using established methodology compared to placebo, in at least one cognitive domain as assessed using one or more objective or subjective cognitive tests either alone or in combination. Clinically suitable objective and subjective tests for measuring cognitive function are well known in the art. The exact test, or combination of tests, most suitable to demonstrate any particular improvement will depend upon the specific objective(s) of a given study and can be readily determined by one skilled in the art on a case by case basis.

As used herein the term “cognitive function” shall be taken to mean a person’s ability to concentrate, remember things, make decisions / solve problems and think. Cognitive function is well known to be divided into several different cognitive domains. Such domains include, but are not limited to, attention,

memory, working memory, executive function, impaired information processing speed and efficiency, verbal fluency, impairments in memory, learning, memory capacity, long term memory, mental alertness, free recall, generalised dysregulation of the attention system, vocabulary deficits including verbal knowledge and verbal fluency and the like.

As used herein the term “norepinephrine reuptake inhibitor” (NRI) shall be taken to mean those compounds that selectively inhibit the reuptake of norepinephrine, in particular those compounds that inhibit the reuptake of norepinephrine to a greater extent than they inhibit the reuptake of serotonin. In a preferred embodiment the norepinephrine reuptake inhibitor has a pharmacological selectivity of serotonin (K_i) / norepinephrine (K_i) of at least about 5, more preferably of at least about 25, even more preferably of at least about 100 and still more preferably of at least about 1000. Methods for measuring selectivity ratios are well known in the art and include, for example, those described in International Patent Application WO 00/01973. Examples of norepinephrine reuptake inhibitors include, but are not limited to, atomoxetine, racemic reboxetine and esreboxetine. Preferred examples of norepinephrine reuptake inhibitors include racemic reboxetine and esreboxetine. The most preferred norepinephrine reuptake inhibitor is esreboxetine.

As used herein the term “esreboxetine”, sometimes known as (S, S)-reboxetine, shall be taken to mean the single enantiomer (2S,3S)-2-[α -(2-ethoxyphenoxy)benzyl]morpholine and which is substantially free of its (R, R) enantiomer. In a preferred embodiment this shall mean that the (S, S)-reboxetine comprises at least 90 wt% of (S, S)-reboxetine and less than 10 wt% of (R, R)-reboxetine. In a more preferred embodiment the (S, S)-reboxetine comprises at least 95 wt% of (S, S)-reboxetine and less than 5 wt% of (R, R)-reboxetine. In an even more preferred embodiment (S, S)-reboxetine comprises at least 97 wt% of (S, S)-reboxetine and less than 3 wt% of (R, R)-reboxetine. In a yet further preferred embodiment (S, S)-reboxetine comprises at least 99 wt% of (S, S)-reboxetine and less than 1 wt% of (R, R)-reboxetine.

As used herein the term “racemic reboxetine” shall be taken to mean a mixture of the two enantiomers of (2RS,3RS)-2-[α -(2-ethoxyphenoxy)benzyl]morpholine. Usually such a mixture will comprise equal amounts of each of the two enantiomers but mixtures which are enriched in one enantiomer or another will still be considered to fall into the scope of the present invention.

As used herein the term “dual serotonin and norepinephrine reuptake inhibitor” (SNRI) shall be taken to mean those compounds that inhibit the reuptake of both norepinephrine and serotonin, in particular those compounds that inhibit the reuptake of both norepinephrine and serotonin to the same extent or those that inhibit the reuptake of serotonin to a greater extent than they inhibit the reuptake of norepinephrine. In a preferred embodiment the dual serotonin and norepinephrine reuptake inhibitor has a pharmacological selectivity of serotonin (K_i) / norepinephrine (K_i) of about 1, more preferably of less than about 1. Methods for measuring selectivity ratios are well known in the art and include, for example, those described in International Patent Application WO 00/01973. Examples of dual serotonin and norepinephrine reuptake inhibitor include, but are not limited to, venlafaxine, milnacipram, desipramine and duloxetine.

In a preferred embodiment, the present invention relates to methods to improve cognitive function in patients with fibromyalgia using a norepinephrine reuptake inhibitor, preferably esreboxetine or racemic reboxetine, more preferably esreboxetine. To improve cognitive function in patients with fibromyalgia includes, but is not limited to, demonstrating an improvement in at least one of the cognitive domains of attention, memory, working memory, executive function, impairments in memory, learning, memory capacity, long term memory, mental alertness, free recall, generalised dysregulation of the attention system, and vocabulary deficits including verbal knowledge and verbal fluency.

As used herein the term “patients with fibromyalgia” shall be taken to mean patients who have been diagnosed to be suffering from fibromyalgia according to the American College of Rheumatology criteria (Wolfe et al, 1990). This includes in particular those patients who experience comorbid or concomitant cognitive dysfunction or impairment which is associated with their fibromyalgia and are therefore in need of an improvement in their cognitive functioning. In particular this invention is particularly useful for those fibromyalgia patient sub-populations which may be identified for whom cognitive impairment or cognitive dysfunction is of greater concern.

In one embodiment, the present invention relates to methods to improve cognitive function in patients with fibromyalgia using a norepinephrine reuptake inhibitor, preferably esreboxetine or racemic reboxetine, more preferably esreboxetine, where the improved cognitive domain is “attention”.

As used herein the term “attention” shall be taken to mean the ability of a patient to selectively concentrate on one aspect of the environment while ignoring other things.

In one embodiment the present invention relates to methods to improve cognitive function in patients with fibromyalgia using a norepinephrine reuptake inhibitor, preferably esreboxetine or racemic reboxetine, more preferably esreboxetine, where the improved cognitive domain is “memory”.

As used herein the term “memory” shall be taken to mean the ability of the patient to remember specific events or episodes.

In a yet further embodiment the present invention relates to methods to improve cognitive function in patients with fibromyalgia using a norepinephrine reuptake inhibitor, preferably esreboxetine or racemic reboxetine, more preferably esreboxetine, where the improved cognitive domain is “working memory”.

As used herein the term “working memory” shall be taken to mean the amount of mental power or online cognitive resource a person has available in any given situation.

In a still further embodiment the present invention relates to methods to improve cognitive function in patients with fibromyalgia using a norepinephrine reuptake inhibitor, preferably esreboxetine or racemic reboxetine, more preferably esreboxetine, where the improved cognitive is “executive function”.

As used herein the term “executive function” shall be taken to mean the ability of the patient to plan, demonstrate cognitive flexibility and to select relevant sensory information.

The present invention also relates to methods to improve cognitive function in patients with chronic fatigue syndrome using a norepinephrine reuptake inhibitor, preferably esreboxetine or racemic reboxetine, more preferably esreboxetine. Improvements of cognitive function in patients with chronic fatigue syndrome include, but are not limited to, improvements in at least one of the cognitive domains of attention, memory, working memory and executive function, impairment in memory, learning, memory capacity, impaired information processing speed and efficiency.

As used here in the term “patients with chronic fatigue syndrome” shall be taken to mean patients who have been diagnosed to be suffering from chronic fatigue syndrome according to one or both of the two widely used criteria for diagnosing chronic fatigue syndrome, namely that established by the “US Centers for Disease and Prevention” and that established in the “Oxford criteria” and both as set out in Reid et al (British Medical journal, 200, 320, pp292-296). This includes those patients who experience comorbid or concomitant cognitive dysfunction or impairment which is associated with their chronic fatigue syndrome and are therefore in need of an improvement in their cognitive functioning.

The present invention also relates to methods to improve cognitive function in patients with schizophrenia using a norepinephrine reuptake inhibitor, preferably esreboxetine or racemic reboxetine, more preferably esreboxetine. Improvements of cognitive function in patients with schizophrenia include, but are not limited to, improvements in at least one of the cognitive domains of attention, memory, working memory and executive function.

As used here in the term "patients with schizophrenia" shall be taken to mean patients who have been diagnosed to be suffering from schizophrenia according to one or both of the two widely used criteria for diagnosing schizophrenia, namely that set out by the American Psychiatric Association's diagnostic and statistical manual of mental disorders version DSM-IV-TR as set out in American Psychiatric Association (2000). "Schizophrenia", *Diagnostic and statistical manual of mental disorders: DSM-IV*. Washington, DC: American Psychiatric Publishing, Inc; and the World Health Organisation's international statistical classification of diseases and related health problems, the ICD-10 Jakobsen KD; Frederiksen JN, Hansen T, Jansson LB, Parnas J, Werge T (2005). "Reliability of clinical ICD-10 schizophrenia diagnoses". *Nordic Journal of Psychiatry* 59 (3): 209–12. This includes those patients who experience comorbid or concomitant cognitive dysfunction or impairment which is associated with their schizophrenia and are therefore in need of an improvement in their cognitive functioning.

Esreboxetine and racemic reboxetine contain a basic group, and may therefore be converted to a pharmaceutically acceptable salt by reaction with an acid. Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate,

tosylate and trifluoroacetate salts. Preferred examples of salts include the mesylate, fumarate and succinate salts, and the succinate is especially preferred. Specifically esreboxetine succinate is preferred. Similarly racemic reboxetine mesylate is preferred.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

A pharmaceutically acceptable salt of esreboxetine or racemic reboxetine may be readily prepared in a conventional manner by mixing together solutions of esreboxetine or racemic reboxetine and the desired acid, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the salt may vary from completely ionised to almost non-ionised.

Esreboxetine or racemic reboxetine, or pharmaceutically acceptable salts thereof, may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

Pharmaceutical compositions suitable for the delivery of esreboxetine or racemic reboxetine, or pharmaceutically acceptable salts thereof, and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995).

According to the invention, esreboxetine or racemic reboxetine, or pharmaceutically acceptable salts thereof, may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled lozenges), chews, multi- and nano-particulates, gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays. Formulations suitable for oral administration also include liquid formulations such as suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet. esreboxetine or racemic reboxetine, or pharmaceutically acceptable salts thereof, may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and

dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 wt% to 5 wt% of the tablet, and glidants may comprise from 0.2 wt% to 1 wt% of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X).

Solid formulations for oral administration may be formulated to have immediate and / or modified release. Modified release formulations include

delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma *et al*, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

Esreboxetine or racemic reboxetine, or pharmaceutically acceptable salts thereof, may also be administered parenterally, that is directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water. The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art. The solubility of esreboxetine or racemic reboxetine, or pharmaceutically acceptable salts thereof, used in the preparation of parenteral solutions may be increased by techniques which are commonly used in the art such as by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to have immediate and / or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

Esreboxetine or racemic reboxetine, or pharmaceutically acceptable salts thereof, may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and microemulsions. Liposomes may also be used. Typical carriers for such formulations include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999). Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject™, Bioject™, etc.) injection.

Formulations for topical administration may be formulated to have immediate and / or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Esreboxetine or racemic reboxetine, or pharmaceutically acceptable salts thereof, can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin. The pressurised container, pump, spray, atomizer, or nebuliser

typically contains a solution or suspension of esreboxetine or racemic reboxetine, or pharmaceutically acceptable salts thereof, comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid. In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff".

Capsules (made, for example, from gelatin or HPMC), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of esreboxetine or racemic reboxetine, or pharmaceutically acceptable salts thereof, a suitable powder base such as lactose or starch and a performance modifier such as *L*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 20mg of esreboxetine or racemic reboxetine, or pharmaceutically acceptable salts thereof, per actuation and the actuation volume may vary from 1µl to 100µl. A typical formulation may comprise esreboxetine or racemic reboxetine, or pharmaceutically acceptable salts thereof, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to have immediate and / or modified release using, for example, poly(DL-lactic-

coglycolic acid) (PGLA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Esreboxetine or racemic reboxetine, or pharmaceutically acceptable salts thereof, may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (e.g. absorbable gel sponges, collagen) and non-biodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/aural administration may be formulated to have immediate and / or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

Desirably, daily dose of the composition (e.g., tablet, sachet, or capsule) contains from about 0.1 to about 10 mg of esreboxetine or racemic reboxetine. Preferably, each dose of the composite contains about 0.5 to about 10 mg of the active ingredient, esreboxetine or racemic reboxetine. This dosage form permits the full daily dosage of about 0.5 to about 10 mg to be administered in one or two doses. More preferably the dosage form permits the full daily dose to be administered in one dose. Specific embodiments include oral doses which comprise 2mg, 4mg, 6mg, 8mg or 10mg of esreboxetine. Alternative embodiments include oral doses which comprise 2mg, 4mg, 6mg, 8mg or 10mg of racemic reboxetine.

According to the present invention the norepinephrine reuptake inhibitor, including esreboxetine or racemic reboxetine can be administered alone or in combination with one or more other drugs (or as any combination thereof). In

particular, other active compounds which can be usefully administered with esreboxetine or racemic reboxetine include, for example, anti-depressants, analgesics, muscle relaxants, anoretics, stimulants, anti-epileptic drugs, beta blockers, and sedative or hypnotics. Specific examples of such compounds include, but are not limited to, gabapentin, pregabalin, duloxetine, milnacipram, pramipexole, and combinations thereof.

As used herein administration in combination with another drug includes simultaneous administration in the same dosage forms, simultaneous administration in separate dosage forms and separate administration of the compounds.

The following examples are merely illustrative of the present invention and should not be construed as limiting the scope of the invention in any way as many variations and equivalents that are encompassed by the present invention will become apparent to those skilled in the art upon reading the present disclosure.

Example

A randomised double blind placebo controlled crossover study assessing the ability of esreboxetine to improve cognitive function in fibromyalgia patients.

The primary objective of this study is to evaluate if esreboxetine improves specific cognitive domains, namely attention, memory, working memory and executive function, in fibromyalgia patients using objective testing. Another objective of this study is to evaluate if esreboxetine improves cognitive functioning in general in patients with fibromyalgia as assessed using certain subjective questionnaires.

Methodology

This is a randomised, double blind placebo controlled two way cross over study in which there are two sequences and two treatment periods, separated by a washout period which will enrol 40 patients who meet the 1990 ACR criteria for fibromyalgia as well as more detailed admission criteria outlined in

the protocol. After 1 week screening period patients will be randomised in a 1:1 ratio and receive either esreboxetine (4 mg once daily for 2 weeks followed by 8mg once daily for 2 weeks) or matched placebo tablets for a 4 week double blind treatment period. This will be followed by two weeks washout. After the washout there will be a 4 weeks double blind treatment during which patients who were on placebo will be allocated to esreboxetine and patients who were on active treatment will be allocated to placebo. Finally there will be a 1 week follow up period. During the screening and washout periods patients will receive single blind placebo.

The primary objective of the study will be tested using objective computer based testing – CogState cognitive function testing (Cogstate Ltd, Melbourne, Australia). This consists of two specific tests related to each of the four different cognitive domains, namely:

Attention domain – the detection test and the identification test

Memory domain – one card learning and the continuous paired associate learning

Working memory domain – one back test and the two back test

Executive function – Groton maze learning test and the monitoring task

These tests will be completed on visits 1-7 as detailed in the schedule of study assessments.

Other well known subjective questionnaires and global questions will be used to assess other objectives of this test. Such test methods include:

Multiple ability self-report questionnaire (MASQ) (Seidenberg et al, Journal of Clinical and Experimental Neuropsychology, 1994, 16(1), pp93-104);

Multifactorial memory questionnaire (MMQ) (Troyer and Rich, Journal of Gerontology, 2002, 57B(1), pp19-27);

Daily pain diary and pain visual analogue scales; and

Hospital anxiety and depression scale.

Again these tests will be completed in accordance with the details set out in the schedule of study assessments.

Statistical Analysis

The eight primary end points used to determine cognitive function will be analysed separately and no formal adjustment will be made for multiplicity. To determine the effect of esreboxetine compared to placebo on cognitive function the change from baseline for each primary endpoint will be analysed using a mixed effect analysis of covariance including fixed terms for treatment, period and sequence and a random effect term for subject. The baseline visit will be defined as the pre-dose assessment in each treatment period. The treatment difference and corresponding 80% confidence interval will be presented. Descriptive statistics will also be used to summarise both the absolute and change from baseline for each endpoint by treatment group, timepoint and period. All analysis will be carried out on the full analysis set. Furthermore each sub-scale of the MASQ, the daily pain diary and the pain visual analogue scale will be analysed and summarised as for the primary endpoints. Each dimension of the MMQ will be summarised only at randomisation. Each patient rating of cognition question will be summarised descriptively by frequency of each response to each question split by treatment group, timepoint and period.

Adverse events, laboratory, vital signs and ECG results will be collected and analysed as detailed in the schedule of study assessments.

Claims

1. A norepinephrine reuptake inhibitor, or a pharmaceutically acceptable salt thereof, to improve cognitive function in patients with fibromyalgia.
2. Use according to Claim 1, where cognitive function is improved as a result of an improvement in the cognitive domain of attention.
3. Use according to Claim 1, where cognitive function is improved as a result of an improvement in the cognitive domain of memory.
4. Use according to Claim 1, where cognitive function is improved as a result of an improvement in the cognitive domain of working memory.
5. Use according to Claim 1, where cognitive function is improved as a result of an improvement in the cognitive domain of executive function.
6. Use according to any of Claims 1 to 5, wherein the norepinephrine reuptake inhibitor is esreboxetine, or a pharmaceutically acceptable salt thereof.
7. Use according to Claim 6, wherein esreboxetine is administered in an amount of from 4 to 10 mg/day.
8. Use according to Claim 6, wherein the pharmaceutically acceptable salt is the succinate salt.
9. Use according to any of Claims 1 to 5 wherein the norepinephrine reuptake inhibitor is racemic reboxetine, or a pharmaceutically acceptable salt thereof.
10. Use according to Claim 9, wherein the pharmaceutically acceptable salt is the methanesulphonate salt.

11. A method of improving cognitive function in patients with fibromyalgia comprising administering to the patient in need of such improvement a norepinephrine reuptake inhibitor, or a pharmaceutically acceptable salt thereof.
12. A norepinephrine reuptake inhibitor, or a pharmaceutically acceptable salt thereof, to improve cognitive function in patients with chronic fatigue syndrome.
13. A norepinephrine reuptake inhibitor, or a pharmaceutically acceptable salt thereof, to improve cognitive function in patients with schizophrenia.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2009/054396

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/5375 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/128705 A1 (WONG ERIK H [US] ET AL WONG ERIK H F [US] ET AL) 15 June 2006 (2006-06-15) abstract paragraphs [0026], [0028], [0029], [0031], [0047] claim 1	1-13
X	US 2005/096349 A1 (SHAPIRA NATHAN A [US] ET AL) 5 May 2005 (2005-05-05) claims 1,2 paragraphs [0002], [0006] abstract	1-13
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

International application No

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