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NALTREXONE LONG ACTING FORMULATIONS AND METHODS OF USE

BACKGROUND OF THE INVENTION

Alcohol dependence is a chronic disorder that results from a variety of genetic, psychological and environmental factors. Traditional treatment has consisted of two phases: detoxification and rehabilitation. Detoxification ameliorates the symptoms and signs of withdrawal; rehabilitation helps the patient avoid future problems with alcohol. In the past, most rehabilitative treatments have been psychosocial. With advances in neurobiology, there is increasing interest in drug therapy for alcohol dependence. For a discussion of the development of this field, see Swift, R., Drug Therapy for Alcohol Dependence, NEJM, May 13, 1999, 1482-1490. Yet, the successful treatment of alcoholism has many serious challenges and complications. Patient compliance is a serious problem.

Accordingly, there is a need for improving naltrexone therapies.

SUMMARY OF THE INVENTION

The inventions described herein arose from unexpected discoveries made during clinical trials with a long acting formulation of naltrexone. As such, the invention includes a method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation comprising naltrexone to the individual wherein the serum AUC of naltrexone is at least about two times, preferably at least about three times, more preferably about 3.3 times greater than that achieved by 50 mg/day oral administration.

The inventions also include a method of treating an individual in need of naltrexone comprising administering a long acting formulation in a dose comprising at least about 160 mg of naltrexone, preferably between about 160 mg and about 480 mg naltrexone, more preferably between about 160 and 240 mg of naltrexone or about 310 to about 480 mg of naltrexone.

The inventions also include a method of treating an individual in need of naltrexone comprising administering naltrexone, such as in a long acting formulation, in the absence of co-administering alcohol, to an individual who has not abstained from alcohol within three days, such as five days, prior to the naltrexone administration.

The inventions include a method of increasing the days prior to occurrence of alcohol consumption in an individual in need of naltrexone comprising administering a long acting formulation comprising naltrexone, in the absence of co-administering alcohol, to an individual who has not abstained from alcohol within three days, such as five days, prior to the naltrexone administration.

The inventions include a method of treating an individual in need of naltrexone comprising administering a long acting formulation comprising naltrexone in a dosage between about 160 mg to about 480 mg naltrexone every four weeks for a period of about 24 weeks or more wherein the individual has not used oral naltrexone within five days, such as within ten days, before said administration.

BRIEF SUMMARY OF THE DRAWINGS

Figure 1A-1C shows the cumulative mean event rate of heavy drinking during the study by treatment group and gender. As an example, at day 100, the mean number of cumulative heavy drinking days for the overall study population was 22.3 for the long-acting naltrexone 380 mg patients, 27.3 for long-acting naltrexone 190 mg patients, and 30.0 for placebo patients.

Figure 2 shows median heavy drinking days per month for each treatment group, overall and by gender.

DETAILED DESCRIPTION OF THE INVENTION

The inventions relate to the administration of a naltrexone containing formulation, preferably a long acting naltrexone formulation, to patients in need thereof and to the use of naltrexone in the manufacture of medicaments for use in such methods.

In one embodiment, the invention includes a method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation comprising naltrexone to the individual wherein the serum AUC of naltrexone is at least about two times, preferably at least about three times, more preferably about 3.3 times greater than that achieved by 50 mg/day oral administration. This invention arose from the unexpected discovery that substantially improved serum levels of naltrexone can be achieved by administering long acting formulations of naltrexone, such as the Alkermes, Inc. formulation, Vivitrex® injectable suspension, made employing its Medisorb® delivery system. Indeed, it was not expected that serum levels of about 3.3 times that achieved by a 50 mg/day oral dose could be achieved by a single IM administration of Vivitrex®.

The inventions also include a method of treating an individual in need of naltrexone comprising administering naltrexone, such as in a long acting formulation, in the absence of co-administering alcohol, to an individual who has not abstained from alcohol within three days, such as five days, prior to the naltrexone administration. In this embodiment, it was unexpectedly discovered that good to excellent results could be achieved without either requiring alcohol abstinence or requiring alcohol consumption during therapy, as taught by Sinclair, United States Patent No. 4,882,335. Further, good to excellent results were achieved in patients that did not receive oral naltrexone in advance of the long acting formulation administration, contrary to the clinical protocols as taught by Drug Abuse Sciences. Thus, the inventions also include administering a long acting formulation to individuals who did not receive a prior oral dose of naltrexone, for example, within 3, such as within about 5 days or about 10 days of commencing therapy.

As such, the inventions also include a method of treating an individual in need of naltrexone comprising administering a long acting formulation in a dose comprising between about 160 mg and 240 mg of naltrexone or about 310 mg to about 480 mg of naltrexone and formulations for use in the methods described herein. Preferred formulations are administered in a dose comprising about 190 mg or about 380 mg naltrexone.

The naltrexone can be in any form, including anhydrous, hydrate, solvate or salt forms or combinations thereof. It can be crystalline or non-crystalline or combinations thereof. A preferred naltrexone form comprises a naltrexone ethanolate, such as that described in United States Patent Application No. 60/475,863, filed on June 4, 2003, which is incorporated herein by reference and/or anhydrous naltrexone. A particularly preferred naltrexone form is that produced by the encapsulation process described in United States Patent No. 6,264,987, by Wright et al., which is incorporated herein by reference.

The naltrexone can be combined with any of the well-known biodegradable and bioerodible carriers, such as polylactides, poly(lactic acids) and poly-lactide-co-glycolides and collagen formulations. A particularly preferred polymer is a polylactide-co-glycolide polymer which possesses a molecular weight of at least 100,000 daltons, such as those described below in the exemplification. Such materials may be in the form of solid implants, sponges, and the like.

As stated above, the naltrexone is preferably in a long acting formulation. Long acting (also referred to as extended, sustained, or controlled release) preparations may be achieved through the use of polymers (preferably poly-lactide or poly-lactide-co-glycolide polymers) to entrap or encapsulate the naltrexone described herein. Extended release formulations can be made by spray drying polymer-drug mixtures, emulsion-based technologies, coacervation based technologies, film casting, extrusion based technologies and other processes to manufacture polymer-drug microparticles possessing an extended release profile. Examples of suitable extended release technologies that can be used to incorporate the novel naltrexone forms described herein include, without limitation, the MEDISORB® technology, as described in, for example,

US Patent Nos. 6,264,987 to Wright, 5,654,008 and/or 5,792,477, for example; the PROLEASE® technology, as described, for example in US Patent 6,358,443 to Herbert; the technologies described by Southern Research Institute, as described for example in US Patents 6,306,425 and 5,407,609; and "Method of Preparing Sustained Release Microparticles," U.S. Application No. 60/441,946, filed January 23, 2003, and the technologies described by Alza Corp., including the ALZAMER® Depot injection technology. The contents of these patents are incorporated herein by reference in their entirety.

In a preferred embodiment, the long acting formulation delivers therapeutically beneficial amounts of naltrexone to the patient for a period of at least one week, preferably at least about two weeks, more preferably at least about 3 or about 4 or more weeks. A four week delivery is often referred to as a monthly delivery.

In one preferred embodiment, the naltrexone is present in the extended release device or formulation in an amount of at least about 5% by weight, preferably at least about 10% by weight, more preferably at least about 30% by weight, such as about 35% by weight naltrexone of the total weight of the device, or formulation.

Alternatively, instead of incorporating naltrexone into polymeric particles, it is possible to entrap these materials in microparticles prepared, for example, by coacervation techniques or by interfacial polymerization (for example, hydroxymethylcellulose or gelatine-microcapsules and poly-(methylmethacrylate) microcapsules, respectively), in colloidal drug delivery systems (for example, liposomes, albumin, microparticles, microemulsions, nanoparticles, and nanocapsules), or in macroemulsions.

When the composition is to be used as an injectable material, including but not limited to needle-less injection, it can be formulated into a conventional injectable carrier. Suitable carriers include biocompatible and pharmaceutically acceptable solutions. The injection can be intramuscular or subcutaneous.

While the formulation may contain additional excipients, as is well known in the art, the present invention can achieve an excellent release profile with the simple formulation described herein. Such additional excipients can increase or decrease the

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