testosterone levels. Particularly, low testosterone levels can result in oligozoospermia (lower than normal sperm count in semen) or even azoospermia (no sperm in semen).

In recent years, testosterone replacement therapy (TRT), in which a pharmaceutical composition containing testosterone, or a salt, ester, or prodrug thereof, is administered by any of several known means, has become a standard treatment for low testosterone. Current delivery systems for TRT include transdermal gels and patches, injectable compositions, and long-acting subcutaneous pellets.

While TRT has been shown to increase serum testosterone levels to normal ranges and improve patients' bone mineral density, prostate volume, energy, and sexual function, the therapy can suppress pituitary gonadotropins, especially follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which can result in lower testicular volume and a corresponding impairment of spermatogenesis, semen quality (i.e. oligozoospermia or azoospermia), and therefore fertility. Various drugs, including clomiphene citrate, anastrozole, and human chorionic gonadotropin (HCG), have sometimes been administered to counteract these effects, but these drugs also have various undesirable side effects, including decreased libido and gynecomastia.

Moreover, the safety of TRT remains a primary concern. Most TRT delivery modes, especially injection of testosterone esters, can increase patients' hemoglobin and hematocrit concentrations, which can result in a condition known as secondary polycythemia. Unmanaged, polycythemia can lead to such complications as jaundice, pruritus, cerebrovascular accident, thrombosis, and bleeding. Additionally, elevated hematocrit levels are associated with an increased risk of death from cardiovascular disease.

Due to these and other drawbacks, treatment options for men suffering from low testosterone that are both safe and effective remain limited, especially for men already at risk for one or more of the negative side effects of TRT. There is thus a significant and long-felt need in the art for methods of treating low testosterone that increase serum testosterone levels and patients' sperm counts to normal levels, while mitigating or eliminating the unsafe and/or undesirable effects resulting from FSH and LH suppression and elevated hemoglobin and hematocrit levels.

SUMMARY

It is one example of the present disclosure to provide a method for administering testosterone to a patient at risk of, or in need of avoiding, at least one side effect associated with testosterone replacement therapy (TRT) or a pituitary gonadotropin deficiency, the method comprising pulsatile administration of testosterone to the patient, wherein the side

effect is selected from the group consisting of azoospermia, oligozoospermia, decreased libido, gynecomastia, cardiovascular disease, and cardiovascular accident.

In one aspect, the present disclosure refers to use of testosterone in the manufacture of a medicament for avoiding at least one side effect associated with testosterone replacement therapy (TRT) or a pituitary gonadotropin deficiency in a patient at risk of or in need of avoiding the side effect, wherein the mode of administration of the testosterone to the patient is pulsatile administration , wherein the side effect is selected from the group consisting of azoospermia, oligozoospermia, decreased libido, gynecomastia, cardiovascular disease, and cardiovascular accident.

In examples, each dose may be administered no less than three hours and no more than 24 hours after an immediately preceding dose.

In examples, a mode of administration may be selected from the group consisting of oral pulsatile administration, transdermal pulsatile administration, transmucosal pulsatile administration, and pulsatile injection. The mode of administration may, but need not, be transmucosal pulsatile administration. The testosterone may, but need not, be administered to the nasal mucosae of the patient in the form of a testosterone gel.

In examples, the testosterone may be administered to the patient in at least two doses per day. The testosterone may, but need not, be administered to the patient in at least three doses per day. The testosterone may, but need not, be administered to the patient in at least four doses per day

In examples, pulsatile administration may comprise administering multiple doses and each dose comprises between about 5 mg and about 15 mg testosterone. Each dose may, but need not, comprise about 11 mg testosterone.

In examples, a total amount of testosterone administered to the patient per day may be between about 10 mg and about 120 mg. The total amount of testosterone administered to the patient per day may, but need not, be between about 20 mg and about 40 mg.

In examples, the method may not comprise administration of any drug selected from the group consisting of clomiphene citrate, anastrozole, and human chorionic gonadotropin (HCG).

It is another example of the present disclosure to provide a method for treating a sexual disorder in a male human, the method comprising pulsatile administration of testosterone to the male human, wherein the sexual disorder is selected from the group consisting of azoospermia, oligozoospermia, decreased libido, and gynecomastia.

In another aspect, the present disclosure refers to use of testosterone in the manufacture of a medicament for treating a sexual disorder in a male human, wherein the mode of administration of the testosterone to the male human is pulsatile administration, wherein the sexual disorder is selected from the group consisting of azoospermia, oligozoospermia, decreased libido, and gynecomastia.

In examples, pulsatile administration may comprise administering multiple doses and each dose is administered no less than three hours and no more than 24 hours after an immediately preceding dose.

In examples, a mode of administration may be selected from the group consisting of oral pulsatile administration, transdermal pulsatile administration, transmucosal pulsatile administration, and pulsatile injection. The mode of administration may, but need not, be transmucosal pulsatile administration. The testosterone may, but need

not, be administered to the nasal mucosae of the patient in the form of a testosterone gel. The testosterone gel may, but need not, be administered to the patient in at least two doses per day. The testosterone gel may, but need not, be administered to the patient in at least three doses per day. The testosterone gel may, but need not, be administered to the patient in at least four doses per day.

In examples, pulsatile administration may comprise administering multiple doses and each dose comprises between about 5 mg and about 15 mg testosterone. Each dose may, but need not, comprise about 11 mg testosterone.

In examples, a total amount of testosterone administered to the patient per day may be between about 10 mg and about 120 mg. The total amount of testosterone administered to the patient per day may be between about 20 mg and about 40 mg.

In examples, the method may not comprise administration of any drug selected from the group consisting of clomiphene citrate, anastrozole, and human chorionic gonadotropin (HCG).

It is another example of the present disclosure to provide a method for preventing or mitigating a side effect associated with testosterone replacement therapy (TRT) or a pituitary gonadotropin deficiency in a patient, the method comprising pulsatile administration of testosterone to the patient, wherein the side effect is selected from the group consisting of azoospermia, oligozoospermia, decreased libido, gynecomastia, cardiovascular disease, and cardiovascular accident.

In another aspect, the present disclosure refers to use of testosterone in the manufacture of a medicament for preventing or mitigating a side effect associated with testosterone replacement therapy (TRT) or a pituitary gonadotropin deficiency in a patient, wherein the mode of administration of the testosterone to the patient is pulsatile administration, wherein the side effect is selected from the group consisting of azoospermia, oligozoospermia, decreased libido, gynecomastia, cardiovascular disease, and cardiovascular accident.

In examples, pulsatile administration may comprise administering multiple doses and each dose is administered no less than three hours and no more than 24 hours after an immediately preceding dose.

In examples, a mode of administration may be selected from the group consisting of oral pulsatile administration, transdermal pulsatile administration, transmucosal pulsatile administration, and pulsatile injection. The mode of administration may, but need not, be transmucosal pulsatile administration. The testosterone may, but need not, be administered to the nasal mucosae of the patient in the form of a testosterone gel. The testosterone gel may, but need not, be administered to the patient in at least two doses per day. The testosterone gel may, but need not, be administered to the patient in at least three doses per day. The testosterone gel may, but need not, be administered to the patient in at least four doses per day.

In examples, pulsatile administration may comprise administering multiple doses and each dose comprises between about 5 mg and about 15 mg testosterone. Each dose may, but need not, comprise about 11 mg testosterone.

In examples, a total amount of testosterone administered to the patient per day may be between about 10 mg and about 120 mg. The total amount of testosterone administered to the patient per day may, but need not, be between about 20 mg and about 40 mg.

In examples, the method may further comprise, before the administering step, ceasing a TRT regimen.

In examples, the method may not comprise administration of any drug selected from the group consisting of clomiphene citrate, anastrozole, and human chorionic gonadotropin (HCG).

It is another example of the present disclosure to provide a method for increasing at least one of a level of follicle stimulating hormone (FSH), a level of luteinizing hormone (LH), and a total motile sperm count (TMSC) in a patient, comprising pulsatile administration of testosterone to the patient.

In another aspect, the present disclosure refers to use of testosterone in the manufacture of a medicament for increasing at least one of a level of follicle stimulating hormone (FSH), a level of luteinizing hormone (LH), and a total motile sperm count (TMSC) in a patient, wherein the mode of administration of the testosterone to the patient is pulsatile administration.

In examples, pulsatile administration may comprise administering multiple doses and each dose is administered no less than three hours and no more than 24 hours after an immediately preceding dose.

In examples, a mode of administration may be selected from the group consisting of oral pulsatile administration, transdermal pulsatile administration, transmucosal pulsatile administration, and pulsatile injection. The mode of administration may, but need not, be transmucosal pulsatile administration. The testosterone may, but need not, be administered to the nasal mucosae of the patient in the form of a testosterone gel. The testosterone gel may, but need not, be administered to the patient in at least two doses per day. The testosterone gel may, but need not, be administered to the patient in at least three doses per day. The testosterone gel may, but need not, be administered to the patient in at least four doses per day.

In examples, pulsatile administration may comprise administering multiple doses and each dose comprises between about 5 mg and about 15 mg testosterone. Each dose may, but need not, comprise about 11 mg testosterone.

In examples, a total amount of testosterone administered to the patient per day may be between about 10 mg and about 120 mg. The total amount of testosterone

administered to the patient per day may, but need not, be between about 20 mg and about 40 mg.

In examples, the method may not comprise administration of any drug selected from the group consisting of clomiphene citrate, anastrozole, and human chorionic gonadotropin (HCG).

It is another example of the present disclosure to provide a method for treating a patient in need of testosterone replacement therapy (TRT), comprising pulsatile administration of testosterone to the patient in at least N doses per day, wherein N is an integer equal to or greater than four.

In another aspect, the present disclosure refers to use of testosterone in the manufacture of a medicament for treating a patient in need of testosterone replacement therapy (TRT), wherein the mode of administration of the testosterone to the patient is pulsatile administration, wherein the testosterone is to be administered to the patient in at least N doses per day, wherein N is an integer equal to or greater than four.

In examples, N may be an integer equal to or greater than five. N may, but need not, be an integer equal to or greater than six. N may, but need not, be an integer equal to or greater than seven. N may, but need not, be an integer equal to or greater than eight.

In examples, each dose may comprise between about 5 mg and about 15 mg testosterone. Each dose may, but need not, comprise about 11 mg testosterone.

In examples, a total amount of testosterone administered to the patient per day may be between about 10 mg and about 120 mg. The total amount of testosterone administered to the patient per day may, but need not, be between about 20 mg and about 40 mg.

In examples, a mode of administration may be transmucosal pulsatile administration. The testosterone may, but need not, be administered to the nasal mucosae. At least one dose may, but need not, comprise at least two sub-doses, wherein at least one sub-dose is administered in each of two nostrils of a patient. Each sub-dose may, but need not, comprise an approximately equal quantity of testosterone. At least one sub-dose may, but need not, comprise a quantity of testosterone different from a quantity of testosterone in a different sub-dose.

In examples of any of the above methods, after at least about two weeks of treatment, at least one of the following may be true: (i) a level of follicle-stimulating hormone (FSH) in the patient is between about 1.5 IU/L and about 12.4 IU/L; (ii) a level of luteinizing hormone (LH) in the patient is at least about 1.80 IU/L; (iii) a hematocrit of the patient is less than about 60%; and (iv) a level of hemoglobin in the patient is less than about 20.0 g/dL.

The advantages of the present disclosure will be apparent from the disclosure contained herein. The examples and configurations described herein are neither complete nor exhaustive. As will be appreciated, other examples of the disclosure are possible utilizing, alone or in combination, one or more of the features set forth above or described in detail below.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an illustration of a study design used to obtain the experimental results of Example 1.

Figure 2 is a graph of the mean follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations of the subjects of the study of Example 1 who received an intranasal testosterone formulation twice daily (BID), at the start of the study and at 90 days.

Figure 3 is a graph of the mean serum testosterone levels of the subjects of the study of Example 1 who received an intranasal testosterone formulation BID on day 90.

Figure 4 is a graph of the mean follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations of the subjects of the study of Example 1 who received an intranasal testosterone formulation three times daily (TID), at the start of the study and at 90 days.

Figure 5 is a graph of the mean serum testosterone levels of the subjects of the study of Example 1 who received an intranasal testosterone formulation TID on day 90.

Figures 6A, 6B, and 6C are graphs of the mean serum testosterone levels of the subjects of the study of Example 1, relative to a pre-study baseline, at 90, 180, and 360 days, respectively.

Figures 7A, 7B, and 7C are graphs of the mean serum testosterone levels, FSH and LH concentrations, and semen parameters, respectively, of the subjects of the study of Example 2.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the phrases “at least one,” “one or more,” “or,” and “and/or” are open-ended expressions that are both conjunctive and disjunctive in operation. For example, each of the expressions “at least one of A, B and C,” “at least one of A, B, or C,” “one or more of A, B, and C,” “one or more of A, B, or C,” “A, B, and/or C,” and “A, B, or C” means A alone, B alone, C alone, A and B together, A and C together, B and C together, or A, B, and C together.

As used herein, the term “pulsatile administration” and related terms refer to methods of administration of a drug to a patient that result in a pulsatile dosing profile.

CLAIMS

1. Use of testosterone in the manufacture of a medicament for avoiding at least one side effect associated with testosterone replacement therapy (TRT) or a pituitary gonadotropin deficiency in a patient at risk of or in need of avoiding the side effect, wherein the mode of administration of the testosterone to the patient is pulsatile administration , wherein the side effect is selected from the group consisting of azoospermia, oligozoospermia, decreased libido, gynecomastia, cardiovascular disease, and cardiovascular accident.

2. The use of claim 1, wherein each dose is to be administered no less than three hours and no more than 24 hours after an immediately preceding dose.

3. The use of claim 1, wherein the mode of administration is selected from the group consisting of oral pulsatile administration, transdermal pulsatile administration, transmucosal pulsatile administration, and pulsatile injection.

4. The use of claim 3, wherein the mode of administration is transmucosal pulsatile administration.

5. The use of claim 4, wherein the testosterone is to be administered to the nasal mucosae of the patient in the form of a testosterone gel.

6. The use of claim 1, wherein the testosterone is to be administered to the patient in at least two doses per day.

7. The use of claim 6, wherein the testosterone is to be administered to the patient in at least three doses per day.

8. The use of claim 7, wherein the testosterone is to be administered to the patient in at least four doses per day.

9. The use of claim 1, wherein multiple doses are to be administered in the pulsatile administration, and each dose comprises between about 5 mg and about 15 mg testosterone.

10. The use of claim 9, wherein each dose comprises about 11 mg testosterone.

11. The use of claim 1, wherein a total amount of testosterone to be administered to the patient per day is between about 10 mg and about 120 mg.

12. The use of claim 11, wherein the total amount of testosterone to be administered to the patient per day is between about 20 mg and about 40 mg.

13. The use of claim 1, wherein any drug selected from the group consisting of clomiphene citrate, anastrozole, and human chorionic gonadotropin (HCG) is not to be administered.

14. Use of testosterone in the manufacture of a medicament for treating a sexual disorder in a male human, wherein the mode of administration of the testosterone to the male human is pulsatile administration, wherein the sexual disorder is selected from the group consisting of azoospermia, oligozoospermia, decreased libido, and gynecomastia.

15. The use of claim 14, wherein multiple doses are to be administered in the pulsatile administration, and each dose is to be administered no less than three hours and no more than 24 hours after an immediately preceding dose.

16. The use of claim 14, wherein the mode of administration is selected from the group consisting of oral pulsatile administration, transdermal pulsatile administration, transmucosal pulsatile administration, and pulsatile injection.

17. The use of claim 16, wherein the mode of administration is transmucosal pulsatile administration.

18. The use of claim 17, wherein the testosterone is to be administered to the nasal mucosae of the patient in the form of a testosterone gel.

19. The use of claim 18, wherein the testosterone gel is to be administered to the patient in at least two doses per day.

20. The use of claim 19, wherein the testosterone gel is to be administered to the patient in at least three doses per day.

21. The use of claim 20, wherein the testosterone gel is to be administered to the patient in at least four doses per day.

22. The use of claim 14, wherein multiple doses are to be administered in the pulsatile administration, and each dose comprises between about 5 mg and about 15 mg testosterone.

23. The use of claim 22, wherein each dose comprises about 11 mg testosterone.

24. The use of claim 14, wherein a total amount of testosterone to be administered to the patient per day is between about 10 mg and about 120 mg.

25. The use of claim 24, wherein the total amount of testosterone to be administered to the patient per day is between about 20 mg and about 40 mg.

26. The use of claim 14, wherein any drug selected from the group consisting of clomiphene citrate, anastrozole, and human chorionic gonadotropin (HCG) is not to be administered.

27. Use of testosterone in the manufacture of a medicament for preventing or mitigating a side effect associated with testosterone replacement therapy (TRT) or a pituitary gonadotropin deficiency in a patient, wherein the mode of administration of the testosterone to the patient is pulsatile administration, wherein the side effect is selected from the group consisting of azoospermia, oligozoospermia, decreased libido, gynecomastia, cardiovascular disease, and cardiovascular accident.

28. The use of claim 27, wherein multiple doses are to be administered in the pulsatile administration and each dose is to be administered no less than three hours and no more than 24 hours after an immediately preceding dose.

29. The use of claim 27, wherein the mode of administration is selected from the group consisting of oral pulsatile administration, transdermal pulsatile administration, transmucosal pulsatile administration, and pulsatile injection.

30. The use of claim 29, wherein the mode of administration is transmucosal pulsatile administration.

31. The use of claim 30, wherein the testosterone is to be administered to the nasal mucosae of the patient in the form of a testosterone gel.

32. The use of claim 31, wherein the testosterone gel is to be administered to the patient in at least two doses per day.

33. The use of claim 32, wherein the testosterone gel is to be administered to the patient in at least three doses per day.

34. The use of claim 33, wherein the testosterone gel is to be administered to the patient in at least four doses per day.

35. The use of claim 27, wherein multiple doses are to be administered in the pulsatile administration and each dose comprises between about 5 mg and about 15 mg testosterone.

36. The use of claim 35, wherein each dose comprises about 11 mg testosterone.

37. The use of claim 27, wherein a total amount of testosterone to be administered to the patient per day is between about 10 mg and about 120 mg.

38. The use of claim 37, wherein the total amount of testosterone to be administered to the patient per day is between about 20 mg and about 40 mg.

39. The use of claim 27, wherein a TRT regimen is ceased before the administration step.

40. The use of claim 27, wherein any drug selected from the group consisting of clomiphene citrate, anastrozole, and human chorionic gonadotropin (HCG) is not to be administered.

41. Use of testosterone in the manufacture of a medicament for increasing at least one of a level of follicle stimulating hormone (FSH), a level of luteinizing hormone (LH), and a total motile sperm count (TMSC) in a patient, wherein the mode of administration of the testosterone to the patient is pulsatile administration.

42. The use of claim 41, wherein multiple doses are to be administered in the pulsatile administration and each dose is to be administered no less than three hours and no more than 24 hours after an immediately preceding dose.

43. The use of claim 41, wherein the mode of administration is selected from the group consisting of oral pulsatile administration, transdermal pulsatile administration, transmucosal pulsatile administration, and pulsatile injection.

44. The use of claim 43, wherein the mode of administration is transmucosal pulsatile administration.

45. The use of claim 44, wherein the testosterone is to be administered to the nasal mucosae of the patient in the form of a testosterone gel.

46. The use of claim 45, wherein the testosterone gel is to be administered to the patient in at least two doses per day.

47. The use of claim 46, wherein the testosterone gel is to be administered to the patient in at least three doses per day.

48. The use of claim 47, wherein the testosterone gel is to be administered to the patient in at least four doses per day.

49. The use of claim 41, wherein multiple doses are to be administered in the pulsatile administration and each dose comprises between about 5 mg and about 15 mg testosterone.

50. The use of claim 49, wherein each dose comprises about 11 mg testosterone.

51. The use of claim 41, wherein a total amount of testosterone to be administered to the patient per day is between about 10 mg and about 120 mg.

52. The use of claim 51, wherein the total amount of testosterone to be administered to the patient per day is between about 20 mg and about 40 mg.

53. The use of claim 41, wherein any drug selected from the group consisting of clomiphene citrate, anastrozole, and human chorionic gonadotropin (HCG) is not to be administered.

54. Use of testosterone in the manufacture of a medicament for treating a patient in need of testosterone replacement therapy (TRT), wherein the mode of administration of the testosterone to the patient is pulsatile administration, wherein the testosterone is to be administered to the patient in at least N doses per day, wherein N is an integer equal to or greater than four.

55. The use of claim 54, wherein N is an integer equal to or greater than five.

56. The use of claim 55, wherein N is an integer equal to or greater than six.

57. The use of claim 56, wherein N is an integer equal to or greater than seven.

58. The use of claim 57, wherein N is an integer equal to or greater than eight.

59. The use of claim 54, wherein each dose comprises between about 5 mg and about 15 mg testosterone.

60. The use of claim 59, wherein each dose comprises about 11 mg testosterone.

61. The use of claim 54, wherein a total amount of testosterone to be administered to the patient per day is between about 10 mg and about 120 mg.

62. The use of claim 61, wherein the total amount of testosterone to be administered to the patient per day is between about 20 mg and about 40 mg.

63. The use of claim 54, wherein the mode of administration is transmucosal pulsatile administration.

64. The use of claim 63, wherein the testosterone is to be administered to the nasal mucosae.

65. The use of claim 64, wherein at least one dose comprises at least two sub-doses, wherein at least one sub-dose is to be administered in each of two nostrils of a patient.

66. The use of claim 65, wherein each sub-dose comprises an approximately equal quantity of testosterone.

67. The use of claim 65, wherein at least one sub-dose comprises a quantity of testosterone different from a quantity of testosterone in a different sub-dose.

68. The use of any one of claims 1, 14, 27, 41, and 54, wherein, after at least about two weeks of treatment, at least one of the following is true:

(i) a level of follicle-stimulating hormone (FSH) in the patient is between about 1.5 IU/L and about 12.4 IU/L; and

(ii) a level of luteinizing hormone (LH) in the patient is at least about 1.80 IU/L.

69. The use of any one of claims 1, 14, 27, 41, and 54, wherein, after at least about two weeks of treatment, at least one of the following is true:

(i) a hematocrit of the patient is less than about 60%; and

(ii) a level of hemoglobin in the patient is less than about 20.0 g/dL.