CLAIMS

1. A pharmaceutical composition for use in treating or ameliorating bradycardia or cardiovascular disease comprising (i) a phosphodiesterase inhibitor or an adenosine receptor antagonist, (ii) a calcium channel blocker, (iii) a histamine H_1-receptor agonist, a histamine H_2-receptor agonist, or a histamine H_3-receptor antagonist, and (iv) a β_2-adrenoreceptor agonist, and (v) a pharmaceutically acceptable excipient, wherein the pharmaceutical composition is formulated in a dosage form for injectable or oral administration,

wherein the phosphodiesterase inhibitor or adenosine receptor antagonist is theophylline or aminophylline,

wherein the calcium channel blocker is nifedipine,

wherein the histamine H_1-receptor agonist, histamine H_2-receptor agonist, or histamine H_3-receptor antagonist is betahistine, and

wherein the β_2-adrenergic receptor agonist is levalbuterol or albuterol.

2. A pharmaceutical composition for use in treating or ameliorating bradycardia or cardiovascular disease comprising three compounds selected from (i) a phosphodiesterase inhibitor or an adenosine receptor antagonist, (ii) a calcium channel blocker, (iii) a histamine H_1-receptor agonist, a histamine H_2-receptor agonist, or a histamine H_3-receptor antagonist, or (iv) a β_2- adrenoreceptor agonist; and a pharmaceutically acceptable excipient, wherein the pharmaceutical composition is formulated in a dosage form for injectable or oral administration.

wherein the phosphodiesterase inhibitor or adenosine receptor antagonist is theophylline or aminophylline,

wherein the calcium channel blocker is nifedipine,

wherein the histamine H_1-receptor agonist, histamine H_2-receptor agonist, or histamine H_3-receptor antagonist is betahistine, and

wherein the β_2-adrenergic receptor agonist is levalbuterol or albuterol.

3. The pharmaceutical composition of claim 1 or claim 2, wherein one or more active pharmaceutical composition is no less than 50% deuterium-enriched, provided in that the deuterated compounds increase pharmacokinetic half-life by increasing the duration of action and reduce side effects by allowing the reduction of the dose levels.

4. The pharmaceutical composition of any one of claims 1 to 3, comprising the phosphodiesterase inhibitor or adenosine receptor antagonist, selected from theophylline or aminophylline, is in an amount ranging from about 1 to about 900 mg, from about 1 to about 800 mg, from about 1 to about 600 mg, from about 2 to about 500 mg, from about 10 to about 300 mg, from about 10 to about 200 mg, from about 10 to about 100 mg, or from 10 to about 80 mg.

5. The pharmaceutical composition of any one of claims 1 to 4, comprising the calcium channel blocker, selected from nifedipine is in an amount ranging from about 0.1 to about 150 mg,from about 0.1 to about 100 mg, from about 0.2 to about 60 mg, from about 1 to about 30 mg, from about 1 to about 20 mg, or from about 1 to about 10 mg.

6. The pharmaceutical composition of any one of claims 1 to 4, comprising the histamine H_1-receptor agonist, histamine H_2-receptor agonist, or histamine H_3-receptor antagonist, selected from betahistine is in an amount ranging from about 0.1 to about 150 mg, from about 0.1 to about 100 mg, from about 0.2 to about 60 mg, from about 0.5 to about 30 mg, from about 1 to about 20 mg, or from about 1 to about 10 mg.

7. The pharmaceutical composition of any one of claims 1 to 4, comprising the β_2-adrenoreceptor agonist, selected from levalbuterol or albuterol, is in an amount ranging from about 0.01 to about 60 mg, from about 0.05 to about 40 mg, from about 0.05 to about 20 mg, from about 0.1 to about 10 mg, from about 0.1 to about 5 mg, or from about 0.1 to 2 mg.

8. The pharmaceutical composition of claim 1, comprising (i) theophylline, aminophylline, or no less than 50% an isotopic variant thereof in an amount ranging from about 5 to about 90% or from about 5 to about 35% by weight; (ii) nifedipine or no less than 50% an isotopic variant thereof in an amount ranging from about 1 to about 20% or from about 1 to about 5% by weight; (iii) betahistine dihydrochloride, or no less than 50% an isotopic variant thereof in an amount ranging from about 0.1 to about 20% or from about 1 to about 5% by weight; (iv) albuterol, or levalbuterol hydrochloride, or no less than 50% an isotopic variant thereof in an amount ranging from about 0.01 to about 5%, or from about 0.1 to about 0.5% by weight; and pharmaceutically acceptable excipients.

9. The pharmaceutical composition of any one of claims 1 to 8, wherein the pharmaceutical composition is formulated for administering simultaneous, separate, or sequential doses in single or multiple doses.

10. The pharmaceutical composition of any one of claims 1 to 9, wherein the pharmaceutical composition is formulated in a dosage form suitable for intravenous or intramuscular administration.

11. The pharmaceutical composition of any one of claims 1 to 10, wherein the pharmaceutical composition is formulated as a liquid dosage form, or semisolid dosage form, or a solid dosage form of tablet or capsules for oral administration.

12. The pharmaceutical composition of any one of claims 1 to 11, wherein the pharmaceutical composition is formulated for multiple-dose per day by an immediate release or two-dose per day by a controlled release or single dose per day by a modified or extended-release dosage form.

13. The pharmaceutical composition of any one of claims 1 to 12 is for use in treating or ameliorating bradycardia or cardiovascular disease.

14. Use of the pharmaceutical composition of any one of claims 1 to 12 in the manufacture of a medicament for treating or ameliorating abnormal heart rhythm with bradycardia in a subject.

15. Use of the pharmaceutical composition of any one of claims 1 to 12 in the manufacture of a medicament for increasing heart rate, cardiac output, or cerebral blood flow in a subject.

16. Use of the pharmaceutical composition of any one of claims 1 to 12 in the manufacture of a medicament for treating or ameliorating a cardiovascular disease in a subject, wherein the cardiovascular disease is selected from bradycardia, symptomatic sinus bradycardia, ventricular bradycardia, atrial bradycardia, junctional bradycardia, atrial block, junctional block, or atrioventricular block.