to dextrorphan is dominant in the majority of the population and is the principle behind using dextromethorphan as a probe to phenotype individuals as CYP2D6 extensive and poor metabolizers (Kupfer et al., Lancet. 1984;2:517-518; Guttendorf et al., Ther. Drug Monit. 1988;10:490-498). Approximately 7% of the Caucasian population shows the poor metabolizer phenotype, while the incidence of poor metabolizer phenotype in Chinese and Black African populations is even lower (Droll et al., Pharmacogenetics. 1998;8:325-333). A study examining the ability of dextromethorphan to increase pain threshold in extensive and poor metabolizers found antinociceptive effects of dextromethorphan were significant in poor metabolizers but not in extensive metabolizers (Desmeules et al., J. Pharmacol. Exp. Ther. 1999;288:607-612). The results are consistent with direct effects of parent dextromethorphan rather than the dextrorphan metabolite on neuromodulation.

SUMMARY

[011] As described above, there remains an urgent need for additional or improved forms of treatment for agitation, aggression and/or associated symptoms in subjects with Alzheimer's disease. This disclosure describes methods of treating agitation and/or aggression and/or associated symptoms in subjects with Alzheimer's disease without an increased risk of serious adverse effects.

[012] In one aspect, the present disclosure refers to the use of a combination of deuterated dextromethorphan and quinidine in the manufacture of a medicament for treating agitation and/or aggression in a subject with dementia. In another example, there is disclosed a method for treating agitation and/or aggression and/or associated symptoms in subjects with dementia by administering a dextromethorphan compound in combination with a CYP2D6 inhibitor, such as quinidine (Q). The disclosure also encompasses the use of pharmaceutically acceptable salts of either or both the dextromethorphan compound and quinidine in the

described methods. An analog or a derivative of quinidine may also be used in the methods described in the present disclosure. In one example, the dementia is Alzheimer's type dementia.

[013] In one example, there is disclosed a combination of the dextromethorphan compound and a CYP2D6 inhibitor, such as quinidine. The disclosure also encompasses the use of pharmaceutically acceptable salts of either or both the dextromethorphan compound and quinidine in the described combination. The combination can be used for treating agitation and/or aggression and/or associated symptoms in a subject with dementia. Analogs or derivatives of quinidine may also be used in the combination. In one example, the dementia is Alzheimer's type dementia.

[014] In some examples, the dextromethorphan compound is administered or used in an amount ranging from about 10 mg per day to about 200 mg per day, and quinidine is administered or used in an amount ranging from about 0.05 mg per day to less than about 50 mg per day.

[015] In some examples, quinidine is administered or used in an amount ranging from about 4.75 mg per day to about 20 mg per day. In some examples, the dextromethorphan compound is administered or used in an amount ranging from about 10 mg per day to about 90 mg per day.

[016] In some examples, either or both of quinidine and the dextromethorphan compound is in the form of a pharmaceutically acceptable salt. The pharmaceutically acceptable salts according to the present disclosure include alkali metals, salts of lithium, salts of sodium, salts of potassium, salts of alkaline earth metals, salts of calcium, salts of magnesium, salts of lysine, salts of N,N'dibenzylethylenediamine, salts of chloroprocaine, salts of choline, salts of diethanolamine, salts of ethylenediamine, salts of meglumine, salts of procaine, salts of tris, salts of free acids, salts of free bases, inorganic salts, salts of sulfate, salts of hydrochloride, and salts of hydrobromide. In some examples, the dextromethorphan compound is in the form of

dextromethorphan hydrobromide or deuterated dextromethorphan hydrobromide. In some examples, quinidine is in the form of quinidine sulfate.

[017] In some examples, the dextromethorphan compound and quinidine are administered or used in a unit dosage form. In some example, the unit dosage form includes about 4.75 mg, 4.9 mg, 9 mg, or 10 mg of quinidine (for example, quinidine sulfate) and about 45 mg, 34 mg, 30 mg, 28 mg, 24 mg, 23 mg, 20 mg, 18 mg, 15 mg, or 10 mg of dextromethorphan compound (for example, deuterated dextromethorphan hydrobromide or dextromethorphan hydrobromide). In one example, the unit dosage form comprises about 10 mg of quinidine (for example, quinidine sulfate) and about 20 mg or 30 mg of dextromethorphan compound (for example, dextromethorphan hydrobromide or deuterated dextromethorphan hydrobromide). In another example, the unit dosage form comprises about 9 mg of quinidine (for example, quinidine sulfate) and about 15 mg or 23 mg of dextromethorphan compound (for example, dextromethorphan hydrobromide or deuterated dextromethorphan hydrobromide). In another example, the unit dosage form comprises about 4.9 mg of quinidine (for example, quinidine sulfate) and about 18 mg, 24 mg, 28 mg, 30 mg, or 34 mg of dextromethorphan compound (for example, dextromethorphan hydrobromide or deuterated dextromethorphan hydrobromide). In yet another example, the unit dosage form comprises about 4.75 mg of quinidine (for example, quinidine sulfate) and about 18 mg, 24 mg, 28 mg, 30 mg, or 34mg of dextromethorphan compound (for example, dextromethorphan hydrobromide or deuterated dextromethorphan hydrobromide). In some examples, the unit dosage forms of the dextromethorphan compound and quinidine are in the form of a tablet or a capsule.

[018] In some examples, the dextromethorphan compound and quinidine are administered or used in a combined dose or a separate dose in a weight ratio of the dextromethorphan compound to quinidine of about 1:1 or less. In some examples, the weight ratio is about 1:1, 1:0.95, 1:0.9, 1:0.85, 1:0.8, 1:0.75, 1:0.7, 1:0.65, 1:0.6, 1:0.55 or 1:0.5 or less. Likewise, in certain examples, dosages have a weight ratio of the dextromethorphan compound to quinidine less than about 1:0.5, for example, about 1:0.45, 1:0.4, 1:0.35, 1:0.3, 1:0.25, 1:0.2, 1:0.15, or 1:0.1,

1:0.09, 1:0.08, 1:0.07, 1:0.06, 1:0.05, 1:0.04, 1:0.03, 1:0.02, or 1:0.01, or less. The weight ratios can be for example, about 1:0.75, about 1:0.68, about 1:0.6, about 1:0.56, about 1:0.5, about 1:0.44, about 1:0.39, about 1:0.38, about 1:0.31, about 1:0.30, about 1:0.29, about 1:0.28, about 1:0.27, about 1:0.26, about 1:0.25, about 1:0.24, about 1:0.23, about 1:0.22, about 1:0.21, about 1:0.20, about 1:0.19, about 1:0.18, about 1:0.17, 1:0.16, about 1:0.15, about 1:0.14, about 1:0.13, about 1:0.12, about 1:0.11 and about 1:0.10. In some examples, the weight ratios for free base of dextromethorphan to free base of quinidine is about 1:0.68, about 1:0.56, about 1: 0.44, about 1:0.38. In certain other examples, the weight ratios for free base of d6-deuterated dextromethorphan to free base of quinidine is about 1: 0.30, about 1:0.22, about 1: 0.19, about 1: 0.18, about 1:0.16, and about 1:0.15.

[019] The dextromethorphan compound and quinidine may be administered or used as one combined dose per day or as at least two combined doses per day. In one embodiment the dextromethorphan compound and quinidine are administered conjointly.

[020] In some examples, the improvement by treatment with a dextromethorphan compound in combination with quinidine in agitation and/or aggression and/or associated symptoms in subjects with Alzheimer's disease may be measured by improvements of one or more of the following scores:

- Neuropsychiatric Inventory (NPI) agitation/aggression domain;
- NPI total;
- Composite of NPI agitation/aggression; irritability/lability; aberrant motor behavior and anxiety domains (NPI4A);
- Composite of NPI agitation/aggression; irritability/lability; aberrant motor behavior and disinhibition domains (NPI4D)
- NPI caregiver distress – agitation/aggression domain;
- Modified Alzheimer Disease Cooperative Study – Clinical Global Impression of Change (ADCS – CGIC) score of agitation; and/or
- Patient Global Impression of Change (PGI-C) score of agitation.

[021] In one example, the subject's NPI score for agitation/aggression is reduced by at least 1.5 compared to untreated subjects or subjects administered a placebo.

[022] In one example, the subject's NP14A score is reduced by at least 2.4 compared to untreated subjects or subjects administered a placebo.

[023] In one example, the subject's NP14D score is reduced by at least 3.0 compared to untreated subjects or subjects administered a placebo.

[024] In one example, the subject's ADCS – CGIC score of agitation is improved by at least 0.5 compared to untreated subjects or subjects administered a placebo.

[025] In one example, the subject's PGI-C score of agitation is improved by at least 0.6 compared to untreated subjects or subjects administered a placebo.

[026] The pharmaceutical preparations disclosed herein may, optionally, include pharmaceutically acceptable carriers, adjuvants, fillers, or other pharmaceutical compositions, and may be administered in any of the numerous forms or routes known in the art.

[027] The methods disclosed herein may also, optionally, include administration of the dextromethorphan compound and a CYP2D6 inhibitor, such as quinidine, in conjunction with other therapeutic agents, such as, for example, one or more therapeutic agents known or identified for treatment of Alzheimer's disease.

[028] It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only, and are intended to provide further, non-limiting explanation of the disclosure.

WHAT IS CLAIMED:

1. Use of a combination of deuterated dextromethorphan and quinidine in the manufacture of a medicament for treating agitation and/or aggression in a subject with dementia.

2. The use according to claim 1, wherein the dementia is of the Alzheimer's type.

3. The use according to any preceding claim, wherein deuterated dextromethorphan is to be administered in an amount ranging from about 10 mg to about 200 mg per day.

4. The use according to any preceding claim, wherein quinidine is to be administered in an amount ranging from about 0.05 mg to less than about 50 mg per day.

5. The use according to any preceding claim, wherein the deuterated dextromethorphan is in a form of deuterated dextromethorphan hydrobromide.

6. The use according to any preceding claim, wherein the quinidine is in a form of quinidine sulfate.

7. The use of according to any preceding claim, wherein the deuterated dextromethorphan and the quinidine are to be administered in a unit dosage form comprising

(i) about 24 mg deuterated dextromethorphan hydrobromide and about 4.75 mg quinidine sulfate; or

(ii) about 34 mg deuterated dextromethorphan hydrobromide and about 4.75 mg quinidine sulfate; or

(iii) about 18 mg deuterated dextromethorphan hydrobromide and about 4.9 mg quinidine sulfate; or

(iv) about 28 mg deuterated dextromethorphan hydrobromide and about 4.9 mg quinidine sulfate; or

(v) about 30 mg deuterated dextromethorphan hydrobromide and about 4.9 mg quinidine sulfate; or

(vi) about 24 mg deuterated dextromethorphan hydrobromide and about 4.9 mg quinidine sulfate; or

(vii) about 34 mg deuterated dextromethorphan hydrobromide and about 4.9 mg quinidine sulfate.

8. The use according to any preceding claim, wherein the deuterated dextromethorphan and the quinidine are to be administered as one combined dose per day.

9. The use according to any preceding claim, wherein the deuterated dextromethorphan and the quinidine are to be administered as two or more combined doses per day.

10. The use according to any preceding claim, wherein the deuterated dextromethorphan and the quinidine are to be administered in a tablet unit dosage form or a capsule unit dosage form.