[08] Thus, there remains an unmet need for a safe and effective pharmacologic intervention for treating negative symptoms of schizophrenia. “This is undoubtedly driven, at least in part, by evidence that negative symptoms play a critical role in functional decline that is not necessarily addressed with adequate control of positive symptoms” (Remington et al. Curr Treat Options Psychiatry. 2016;3:133-150 at 145). An effective treatment for patients with negative symptoms of schizophrenia could profoundly improve patients’ mental health, quality of life, caregiver burden, and reduce healthcare costs.

Summary

[08a] In one aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for treating negative symptoms of schizophrenia in a patient having schizophrenia and as having clinically stable positive symptoms.

[08b] In another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is to be administered d6-DM in a 27 mg to 54 mg dose twice daily and Q in a 4 mg to 7.5 mg dose twice daily.

[08c] In yet another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is to be

administered d6-DM in a 30 mg to 45 mg dose twice daily and Q in a 4 mg to 6 mg dose twice daily.

[08d] In one aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is to be administered d6-DM in a 34 mg to 42.63 mg dose twice daily and Q in a 4.9 mg dose twice daily.

[08e] In another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient has not had an inpatient psychiatric hospitalization within 4 months prior to treatment.

[08f] In yet another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient has not had a psychiatric hospital admission or acute exacerbation within 6 months prior to treatment.

[08g] In one aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient has been assessed

as having a score of less than or equal to 4 on the Positive and Negative Syndrome Scale (PANSS) items of delusions, hallucinations, and hostility.

[08h] In another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient has been assessed as having a score of less than or equal to 4 on the Positive and Negative Syndrome Scale (PANSS) items of delusions, hallucinations, suspiciousness/persecution, and hostility.

[08i] In yet another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is being treated with an atypical antipsychotic, wherein the patient has been treated with the atypical antipsychotic for at least 3 months prior to the medicament to be administered and the dose of the atypical antipsychotic has been stable for at least 1 month prior to the medicament to be administered.

[08j] In one aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is being treated with an antidepressant, wherein the patient has been treated with the antidepressant for at least 3 months, and the dose of the antidepressant has been stable for at least 1 month, prior to the medicament to be administered.

[08k] In another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is being treated with a hypnotic, wherein the dose of the hypnotic has been stable for at least 1 month prior to the medicament to be administered.

[08l] In yet another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is being treated with lorazepam up to a total dose of 2 mg per day for insomnia, anxiety, restlessness, or agitation, wherein the dose of the lorazepam has been stable for at least 1 month prior to the medicament to be administered.

[08m] In one aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is not being treated with one or more monoamine oxidase inhibitors (MAOIs).

[08n] In another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is not being treated with clozapine.

[08o] In yet another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is not being treated with a benzodiazepine other than lorazepam.

[08p] In one aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is not being treated with levodopa.

[08q] In another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is not being treated with a typical antipsychotic.

[08r] In yet another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6 DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is not being treated with an agent that: (a) increases plasma levels of quinidine; (b) is metabolized by CYP2D6; (c) is related to quinidine; (d) produces serotonin syndrome when co-administered with dextromethorphan; (e) decreases plasma levels of dextromethorphan and quinidine; (f) is clozapine; or (g) is a typical antipsychotic.

[08s] In one aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6 DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is not being treated with an anticholinergic medication.

[08t] In another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient has not received electroconvulsive treatment, repetitive transcranial magnetic stimulation, or deep brain stimulation within one year prior to treatment.

[08u] In yet another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not have myasthenia gravis.

[08v] In one aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not have schizoaffective disorder.

[08w] In another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and

use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not have bipolar disorder.

[08x] In yet another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia wherein the patient does not have a depressive disorder and/or a Calgary Depression Scale for Schizophrenia (CDSS) score of greater than or equal to 6.

[08y] In one aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not have a score of greater than 3 on the sum of eight items of the Simpson-Angus Scale (SAS): gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head rotation, and glabella tap.

[08z] In another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not have a concurrent clinically significant or unstable systemic disease, neurological disorder, cognitive disorder, neurodegenerative disorder, hepatic disorder, renal disorder, metabolic

disorder, hematological disorder, immunological disorder, cardiovascular disorder, pulmonary disorder, or gastrointestinal disorder, as determined by the prescribing doctor.

[08aa] In yet another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not have a suicide risk.

[08bb] In one aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidi ne sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not have a cardiovascular history of any one or more of: (a) history or evidence of complete heart block, ventricular tachycardia, presence of clinically significant premature ventricular contractions (PVCs) as evaluated by a central reader, QTc prolongation, or torsades de pointes; (b) QTc using the Fridericia's formula (QTcF) greater than 450 msec for males and greater than 470 msec for females based on central review, unless due to ventricular pacing; (c) family history of congenital QT interval prolongation syndrome; and (d) history or presence of clinically significant syncope, orthostatic hypotension, or postural tachycardia.

[08cc] In another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not have pseudoparkinsonism secondary to treatment with an antipsychotic.

[08dd] In yet another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not have a history of substance and/or alcohol abuse, but may use tobacco and/or nicotine products.

[08ee] In one aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not use recreational or medicinal marijuana, as evidenced by a negative urine drug screen for cannabis.

[08ff] In another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not test positive for hepatitis B surface antigen, hepatitis C antibody, or HIV antibody.

[08gg] In yet another aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein during the first week of treatment, the d6-DM is to be administered in a 24 mg dose once daily and the Q is to be administered in a 4.9 mg dose once daily; during the second week of treatment, the d6-

DM is to be administered in a 24 mg dose twice daily and the Q is to be administered in a 4.9 mg dose twice daily; and during the remainder of the treatment, the d6-DM is to be administered in a 34 mg dose twice daily and the Q is to be administered in a 4.9 mg dose twice daily.

[08hh] In one aspect, the present disclosure provides a use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein during the first three days of treatment, the d6-DM is to be administered in a 28 mg dose once daily and the Q is to be administered in a 4.9 mg dose once daily; during the next four days of treatment, the d6-DM is to be administered in a 28 mg dose twice daily and the Q is to be administered in a 4.9 mg dose twice daily; and during the remainder of the treatment, the d6-DM is to be administered in a 42.63 mg dose twice daily and the Q is to be administered in a 4.9 mg dose twice daily.

[09] This disclosure provides, in some ~~embodiments~~examples, methods of treating negative symptoms in patients with schizophrenia using deuterated [d6]-dextromethorphan, or a salt thereof, in combination with quinidine, or a salt thereof. In some ~~embodiments~~examples, this disclosure provides methods of treating negative symptoms in patients with schizophrenia using deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in combination with quinidine sulfate (Q). As used herein, the term “d6-DM” means deuterated [d6]-dextromethorphan hydrobromide. As used herein, the term “Q” means quinidine sulfate.

[10] More specifically, in some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q. In some ~~embodiments~~examples, the d6-DM is administered in a 27 mg to 54 mg dose

twice daily and the Q is administered in a 4 mg to 7.5 mg dose twice daily. In some ~~embodiments~~examples, the d6-DM is administered in a 30 mg to 45 mg dose twice daily and the Q is administered in a 4 mg to 6 mg dose twice daily. In some ~~embodiments~~examples, the d6-DM is administered in a 34 mg to 42.63 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily. In some ~~embodiments~~examples, the d6-DM is administered in a 34 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily. In some ~~embodiments~~examples, the d6-DM is administered in a 42.63 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily.

[11] In some ~~embodiments~~examples, the present disclosure provides a method of treating negative symptoms of schizophrenia in a patient having schizophrenia and having clinically stable positive symptoms, comprising administering to the patient therapeutically effective amounts of d6-DM and Q.

[12] In some ~~embodiments~~examples, the present disclosure provides a method of treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has not had an inpatient psychiatric hospitalization within 4 months prior to treatment.

[13] In some ~~embodiments~~examples, the present disclosure provides a method of treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has not had a psychiatric hospital admission or acute exacerbation within 6 months prior to treatment.

[14] In some ~~embodiments~~examples, the present disclosure provides a method of treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has been assessed as having a score of less than or equal to 4 on the Positive and Negative Syndrome Scale (PANSS) items of delusions, hallucinations, and hostility. In some ~~embodiments~~examples, the patient has been assessed as having a score of greater than or equal to 4 on any two, or greater than or equal to 5 on any one, of the PANSS items of blunted affect (N1), emotional withdrawal (N2), passive/apathetic social withdrawal (N4), and lack of spontaneity/flow of conversation (N6). In some ~~embodiments~~examples, that patient has been assessed as having a total PANSS negative subscale score (N1 to N7) of greater than or equal to 18.

[15] In some ~~embodiments~~examples, the present disclosure provides a method of treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising

administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has been assessed as having a score of less than or equal to 4 on the Positive and Negative Syndrome Scale (PANSS) items of delusions, hallucinations, suspiciousness/persecution, and hostility. In some ~~embodiments~~examples, the patient has been assessed as having a score of greater than or equal to 4 on any two, or greater than or equal to 5 on any one, of the PANSS items of blunted affect (N1), emotional withdrawal (N2), passive/apathetic social withdrawal (N4), and lack of spontaneity/flow of conversation (N6). In some ~~embodiments~~examples, the patient has been assessed as having a total PANSS Marder negative factors score (N1:blunted effect; N2: emotional withdrawal; N3: poor rapport; N4: passive/apathetic social withdrawal; N6: lack of spontaneity/flow of conversation; G7: motor retardation; and G16: active social avoidance) of greater than or equal to 20.

[16] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is being treated with an atypical antipsychotic. In some ~~embodiments~~examples, the patient has been treated with the atypical antipsychotic for at least 3 months, the dose of the atypical antipsychotic has been stable for at least 1 month. In some ~~embodiments~~examples, the patient has not had an inpatient psychiatric hospitalization within 4 months, prior to treatment with d6-DM and Q.

[17] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is being treated with an antidepressant. In some ~~embodiments~~examples, the patient has been treated with the antidepressant for at least 3 months, and the dose of the antidepressant has been stable for at least 1 month, prior to treatment with d6-DM and Q.

[18] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is being treated with a hypnotic. In some ~~embodiments~~examples, the dose of the hypnotic has been stable for at least 1 month prior to treatment with d6-DM and Q.

[19] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is being treated with lorazepam up to a total dose of 2 mg per day for insomnia, anxiety, restlessness, or agitation. In some ~~embodiments~~examples, the dose of the lorazepam has been stable for at least 1 month prior to treatment with d6-DM and Q.

[20] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with one or more monoamine oxidase inhibitors (MAOIs).

[21] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with clozapine.

[22] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with a benzodiazepine other than lorazepam.

[23] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia,

comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with levodopa.

[24] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with a typical antipsychotic.

[25] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with an agent that:

(a) increases plasma levels of quinidine;

(b) is metabolized by CYP2D6;

(c) is related to quinidine;

(d) produces serotonin syndrome when co-administered with dextromethorphan;

(e) decreases plasma levels of dextromethorphan and quinidine;

(f) is clozapine; or

(g) is a typical antipsychotic.

[26] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient is not being treated with an anticholinergic medication.

[27] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient has not received electroconvulsive treatment, repetitive transcranial magnetic stimulation, or deep brain stimulation within one year prior to treatment.

[28] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have myasthenia gravis.

[29] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have schizoaffective disorder.

[30] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have bipolar disorder.

[31] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a depressive disorder and/or a Calgary Depression Scale for Schizophrenia (CDSS) score of greater than or equal to 6.

[32] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a score of greater than 3 on the sum of eight items of the Simpson-Angus Scale (SAS): gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head rotation, and glabella tap.

[33] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a concurrent clinically significant or unstable systemic

disease, neurological disorder, cognitive disorder, neurodegenerative disorder, hepatic disorder, renal disorder, metabolic disorder, hematological disorder, immunological disorder, cardiovascular disorder, pulmonary disorder, or gastrointestinal disorder, as determined by the prescribing doctor.

[34] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a suicide risk. In some ~~embodiments~~examples, suicide risk is determined by one or more of the following:

(a) judgment of the prescribing doctor;

(b) the patient answers yes on the Columbia Suicide Severity Rating Scale (C-SSRS Suicidal Ideation Item 4 (active suicidal ideation with some intent to act, without a specific plan) and the patient's most recent episode meeting this C-SSRS Item 4 occurred within six months;

(c) the patient answers yes on the C-SSRS Suicidal Behavior Item 5 (active suicidal ideation with specific plan and intent) and the patient's most recent episode meeting this C-SSRS Item 5 occurred within six months; and

(d) the patient answers yes on any of the 5 on the C-SSRS Suicidal Behavior Items (active attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) and the patient's most recent episode meeting any of these C-SSRS Items occurred within two years prior to treatment. For example, in some such ~~embodiments~~examples, suicide risk is determined by all of (a), (b), (c), and (d). For example, in some such ~~embodiments~~examples, suicide risk is determined by (a), (b), and (c). For example, in some such ~~embodiments~~examples, suicide risk is determined by (a) and (b). For example, in some such ~~embodiments~~examples, suicide risk is determined by any one of (a), (b), (c), or (d).

[35] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia,

comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a cardiovascular history of any one or more of:

(a) history or evidence of complete heart block, ventricular tachycardia, presence of clinically significant premature ventricular contractions (PVCs) as evaluated by a central reader, QTc prolongation, or torsades de pointes;

(b) QTc using the Fridericia's formula (QTcF) greater than 450 msec for males and greater than 470 msec for females based on central review, unless due to ventricular pacing;

(c) family history of congenital QT interval prolongation syndrome; and

(d) history or presence of clinically significant syncope, orthostatic hypotension, or postural tachycardia. For example, in some such ~~embodiments~~examples, the patient does not have a history of all of (a), (b), (c), and (d). For example, in some such ~~embodiments~~examples, the patient does not have a history of (a), (b), and (c). For example, in some such ~~embodiments~~examples, the patient does not have a history of (a) and (b). For example, in some such ~~embodiments~~examples, does not have a history of any one of (a), (b), (c), or (d).

[36] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have pseudoparkinsonism secondary to treatment with an antipsychotic.

[37] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not have a history of substance and/or alcohol abuse, but may use tobacco and/or nicotine products.

[38] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia,

comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not use recreational or medicinal marijuana, as evidenced by a negative urine drug screen for cannabis.

[39] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein the patient does not test positive for hepatitis B surface antigen, hepatitis C antibody, or HIV antibody.

[40] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein during the first week of treatment, the d6-DM is administered in a 24 mg dose once daily and the Q is administered in a 4.9 mg dose once daily; during the second week of treatment, the d6-DM is administered in a 24 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily; and during the remainder of the treatment, the d6-DM is administered in a 34 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily.

[41] In some ~~embodiments~~examples, the present disclosure provides a method of specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, comprising administering to the patient therapeutically effective amounts of d6-DM and Q, wherein during the first three days of treatment, the d6-DM is administered in a 28 mg dose once daily and the Q is administered in a 4.9 mg dose once daily; during the next four days of treatment, the d6-DM is administered in a 28 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily; and during the remainder of the treatment, the d6-DM is administered in a 42.63 mg dose twice daily and the Q is administered in a 4.9 mg dose twice daily.

[42] In some ~~embodiments~~examples of the methods disclosed herein, the patient is further administered an atypical antipsychotic other than clozapine.

[43] In some ~~embodiments~~examples of the methods disclosed herein, the patient is a male or female patient from 18 to 60 years of age.

[44] In some ~~embodiments~~examples of the methods disclosed herein, the patient is a female of childbearing potential. In some ~~embodiments~~examples, the patient: (a) has a negative urine pregnancy test; (b) is not nursing or planning a pregnancy for the duration of treatment through 30 days after the last dose; and (c) is abstinent or willing to use a method of birth control prior to treatment, and to continue with the same method until 28 days after the last dose.

[45] In some ~~embodiments~~examples of the methods disclosed herein, the patient does not have hypersensitivity to dextromethorphan, quinidine, an opiate drug, d6-DM, Q, or any ingredient thereof.

[46] In some ~~embodiments~~examples of the methods disclosed herein, the patient does not have allergy or hypersensitivity to one or more medications.

[47] In some ~~embodiments~~examples of the methods disclosed herein, the patient does not have one or more clinically significant laboratory abnormalities, one or more safety values of clinical concern, or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels greater than two times the upper limit of normal, as determined by the prescribing doctor.

[48] In some ~~embodiments~~examples of the methods disclosed herein, the patient has been diagnosed as having schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for schizophrenia. In some ~~embodiments~~examples, the diagnosis based on the DSM criteria has been confirmed by the Mini International Neuropsychiatric Interview (M.I.N.I.).

[49] In some ~~embodiments~~examples of the methods disclosed herein, the patient does not have schizoaffective disorder. In some ~~embodiments~~examples, the patient does not have bipolar disorder.

[50] In some ~~embodiments~~examples of the methods disclosed herein, the treatment results in an at least 20% decrease in the PANSS Marder Negative Factor Score from baseline prior to treatment. In some ~~embodiments~~examples, the treatment results in an at least 2 point decrease in the PANSS Marder Negative Factor Score from baseline prior to treatment.

[51] The methods disclosed herein may also, optionally, include administration of the d6-DM and the Q in conjunction with other therapeutic agents, such as, for example, one or more therapeutic agents useful for the treatment of schizophrenia. In some ~~embodiments~~examples, the d6-DM and the Q may be administered in combination with an atypical antipsychotic other than clozapine (e.g., a second-generation atypical antipsychotic drug (SGA)).

[52] Also provided herein are therapeutic uses of d6-DM and Q. In some ~~embodiments~~examples, the present disclosure provides d6-DM and Q for use in specifically treating negative symptoms of schizophrenia in a patient having schizophrenia. In some ~~embodiments~~examples, the present disclosure provides the use of d6-DM and Q in specifically treating negative symptoms of schizophrenia in a patient having schizophrenia. In some ~~embodiments~~examples, the present disclosure provides the use of d6-DM and Q in a method of manufacturing a medicament for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia. Compositions useful for treating negative symptoms of schizophrenia are also provided.

[53] In some ~~embodiments~~examples, the present disclosure provides a medicament comprising a therapeutically effective amount of d6-DM for use in the treatment of negative symptoms of schizophrenia in a patient having schizophrenia, which is used in combination with a therapeutically effective amount of Q simultaneously, separately, or sequentially.

[54] In some ~~embodiments~~examples, the present disclosure provides a therapeutically effective amount of d6-DM for use in treating negative symptoms of schizophrenia in a patient having schizophrenia, characterized in that the d6-DM is administered in combination with a therapeutically effective amount of Q, wherein both medicaments are administered simultaneously, separately, or sequentially.

[55] In some ~~embodiments~~examples, the present disclosure provides a combination of a therapeutically effective amount of d6-DM and a therapeutically effective amount of Q for use in treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein both medicaments are administered simultaneously, separately, or sequentially.

[56] In some ~~embodiments~~examples, the present disclosure provides a pharmaceutical composition comprising a therapeutically effective amount of d6-DM, which is used in combination with a therapeutically effective amount of Q simultaneously, separately, or sequentially, for treating negative symptoms of schizophrenia in a patient having schizophrenia.

BRIEF DESCRIPTION OF THE DRAWINGS

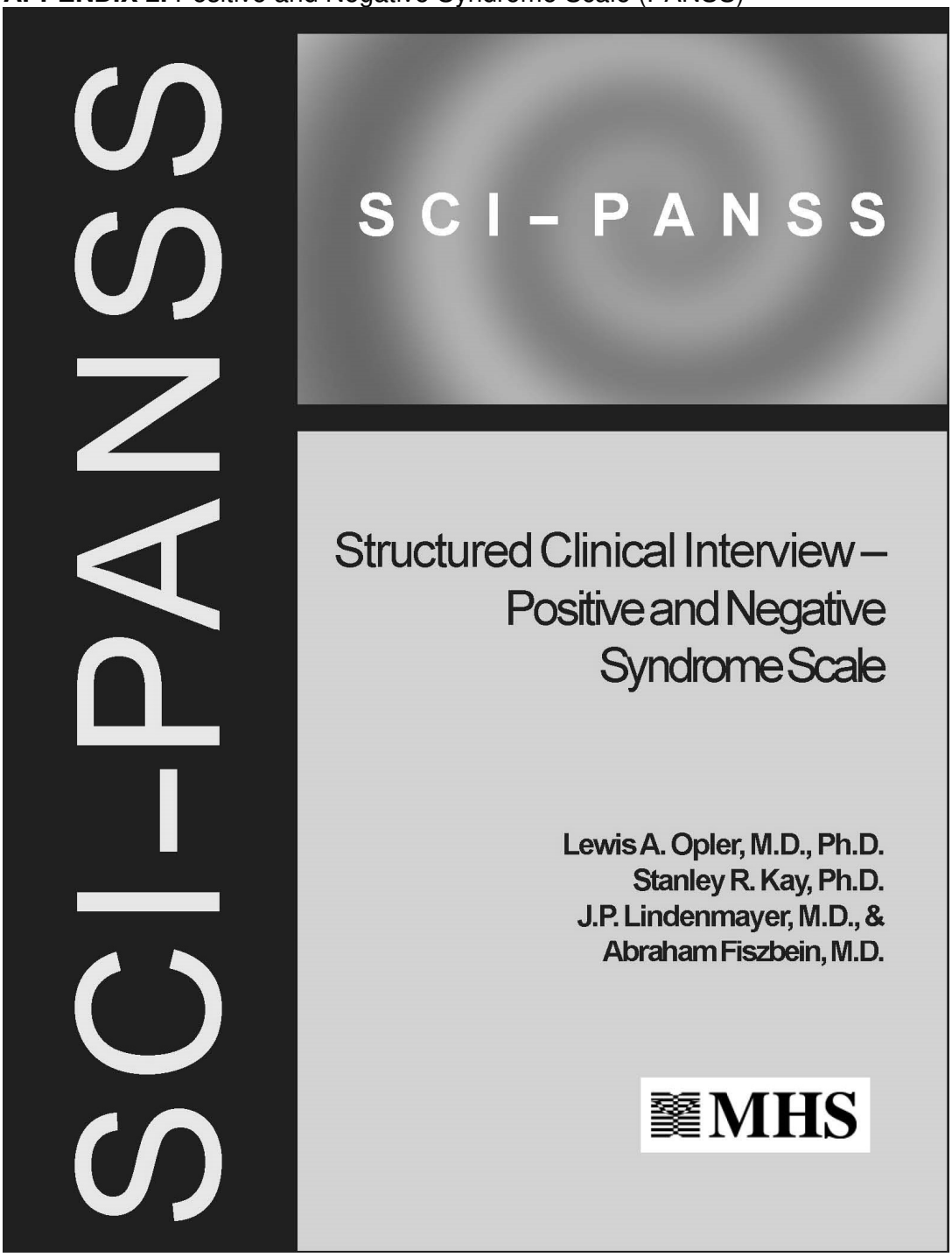
[57] **FIG. 1** shows the chemical structure of deuterated [d6]-dextromethorphan hydrobromide (d6-DM).

[58] **FIG. 2** shows the study design and schedule of assessments in the study from Example 1. Study medication (active or placebo) was administered as 1 capsule in the morning and 1 capsule in the evening approximately 12 hours apart. M: Morning Dose (in mg d6-DM/mg Q); E: Evening Dose (in mg d6-DM/mg Q); *: Visit 4 (Day 43) stratification was based on treatment response criteria followed by Re-Randomization (1:1).

[59] **FIG. 3** shows disposition of patients in the modified intent-to-treat (mITT) population in the study from Example 1.

[60] **FIG. 4** shows NSA-16 Total Mean Scores by visit (sequential parallel comparison design (SPCD), mITT population) in the study from Example 1.

APPENDIX 2. Positive and Negative Syndrome Scale (PANSS)



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Structured Clinical Interview for the Positive and Negative Syndrome Scale

SCI-PANSS

L. A. Opler, M.D., Ph.D. S. R. Kay, Ph.D. J. P. Lindenmayer, M.D. A. Fiszbein, M.D.

Data on "Lack of Spontaneity and Flow of Conversation" (N6), "Poor Rapport" (N3), and "Conceptual Disorganization" (P2)

Hi, I'm ... We're going to be spending the next 30 to 40 minutes talking about you and your reasons for being here. Maybe you can start out by telling me something about yourself and your background?

(Instruction to interviewer: Allow at least 5 minutes for a non-directive phase serving to establish rapport in the context of an overview before proceeding to the specific questions listed below.)

Data on "Anxiety" (G2)

1. Have you been feeling worried or nervous in the past week?
   _____

   IF YES, skip to question 3. IF NO, continue.

2. Would you say that you're usually calm and relaxed?
   _____

   IF YES, skip to question 8. IF NO, continue.

3. What's been making you feel nervous (worried, not calm, not relaxed)?
   _____

4. Just how nervous (worried, etc.) have you been feeling?
   _____

5. Have you been shaking at times, or has your heart been racing?
   _____

6. Do you get into a state of panic?
   _____

7. Has your sleep, eating, or participation in activities been affected?

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_____

Data on "Delusions (General)" (P1) and "Unusual Thought Content" (G9)

8. Have things been going well for you?
_____

9. Has anything been bothering you lately?
_____

10. Can you tell me something about your thoughts on life and its purpose?
_____

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11. Do you follow a particular philosophy (any special rules, teachings, or religious doctrine)? _____

12. Some people tell me they believe in the Devil; what do you think?
_____

IF NO (i.e., he/she doesn't believe in the Devil), skip to question 14.

IF YES (i.e., he/she does believe), continue.

13. Can you tell me more about this?
_____

14. Can you read other people's minds?
_____

IF NO, skip to question 16. IF YES, continue.

15. How does that work?
_____

16. Can others read your mind?
_____

IF NO, skip to question 19. IF YES, continue.

17. How can they do that?
_____

18. Is there any reason that someone would want to read your mind?
_____

19. Who controls your thoughts?
_____

Data on "Suspiciousness/Persecution" (P6) and "Poor Impulse Control" (G14)

20. How do you spend your time these days?
_____

21. Do you prefer to be alone?
_____

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22. Do you join in activities with others?

_____

IF YES, skip to question 25. IF NO, continue.

23. Why not? ... Are you afraid of people, or do you dislike them?

_____

IF NO, skip to question 26. IF YES, continue.

24. Can you explain?

_____

Skip to question 26.

25. Tell me about it.

_____

26. Do you have many friends?

_____

IF YES, skip to question 30. IF NO, continue.

27. Just a few?

_____

IF YES, skip to question 29. IF NO, continue

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28. Any? …
Why?_____

Skip to question 32.

29. Why just a few friends?
_____

30. Close friends?
_____

IF YES, skip to question 32. IF NO, continue.

31. Why not?

_____

32. Do you feel that you can trust most people?
_____

IF YES, skip to question 34. IF NO, continue.

33. Why not?
_____

34. Are there some people in particular who you don't trust?
_____

IF NO to question 34 and YES to question 32, skip to question 41.

IF NO to question 34 and NO to question 32, skip to question 36.

IF YES to question 34, continue.

35. Can you tell me who they are?
_____

36. Why don't you trust people (or name specific person)?
_____

IF "DON'T KNOW" OR "DON'T WANT TO SAY," continue. Otherwise, skip to question 41.

37. Do you have a good reason not to trust ...?

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_____
___

38. Is there something that .... did to you?
_____

39. Perhaps something that ... might do to you now?
_____

IF NO, skip to question 41. IF YES, continue.

40. Can you explain to me?
_____

41. Do you get along well with others?
_____

IF YES, skip to question 43. IF NO, continue.

42. What's the problem?
_____

43. Do you have a quick temper?
_____

44. Do you get into fights?
_____

IF NO, skip to question 48. IF YES, continue.

45. How do these fights start?
_____

46. Tell me about these fights.
_____

47. How often does this happen?
_____

48. Do you sometimes lose control of yourself?
_____

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IF NO, skip to question 50. IF YES, continue.

49. What happens when you lose control of yourself?
_____

50. Do you like most people?
_____

IF YES, skip to question 52. IF NO, continue.

51. Why not?
_____

52. Are there perhaps some people who don't like you?
_____

IF NO, skip to question 54. IF YES, continue.

53. For what reason?
_____

54. Do others talk about you behind your back?
_____

IF NO, skip to question 57. IF YES, continue.

55. What do they say about you?
_____

56. Why?_____
_____

57. Does anyone ever spy on you or plot against you?
_____

58. Do you sometimes feel in danger?
_____

IF NO, skip to question 64. IF YES, continue.

59. Would you say that your life is in danger?
_____

60. Is someone thinking of harming you or even perhaps thinking of killing you?

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_____

61. Have you gone to the police for help?
_____

62. Do you sometimes take matters into your own hands or take action against those who might harm you?
_____
_____

IF NO, skip to question 64. IF YES, continue.

63. What have you done?
_____

Data on "Hallucinatory Behavior" (P3) and associated delusions

64. Do you once in a while have strange or unusual experiences?
_____

65. Sometimes people tell me that they can hear noises or voices inside their head that others can't hear. What about you?
_____

IF YES, skip to question 68. IF NO, continue.

66. Do you sometimes receive personal communications from the radio or TV?
_____

IF YES, skip to question 68. IF NO, continue.

67. From God or the Devil?:
_____

IF NO, skip to question 83. IF YES, continue.

68. What do you hear?
_____

69. Are these as clear and loud as my voice?
_____

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70. How often do you hear these voices, noises, messages, etc.?
_____

71. Does this happen at a particular time of day or all the time?
_____

IF HEARING NOISES ONLY, skip to question 80. IF HEARING VOICES, continue.

72. Can you recognize whose voices these are?
_____

73. What do the voices say?
_____

74. Are the voices good or bad?
_____

75. Pleasant or unpleasant?
_____

76. Do the voices interrupt your thinking or your activities?
_____

77. Do they sometimes give you orders or instructions?
_____

IF NO, skip to question 80. IF YES, continue.

78. For example?
_____

79. Do you usually obey these orders (instructions)?
_____

80. What do you make of these voices (or noises); where do they really come from?
_____

81. Why do you have these experiences?_____

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82. Are these normal experiences?_____

83. Do ordinary things sometimes look strange or distorted to you?_____

84. Do you sometimes have "visions" or see things that others can't see?
_____

IF NO, skip to question 88. IF YES, continue.

85. For example?
_____

86. Do these visions seem very real or life-like?
_____

87. How often do you have these experiences?
_____

88. Do you sometimes smell things that are unusual or that others don't smell?
_____

IF NO, skip to question 90. IF YES, continue.

89. Please explain.
_____

90. Do you get any strange or unusual sensations from your body?
_____

IF NO, skip to question 92. IF YES, continue.

91. Tell me about this.
_____

Data on "Somatic Concern" (G1)

92. How have you been feeling in terms of your health?_____

IF OTHER THAN "GOOD," skip to question 94. IF "GOOD," continue.

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93. Do you consider yourself to be in top health?
_____

IF YES, skip to question 95. IF NO, continue.

94. What has been troubling you?
_____

95. Do you have any medical illness or disease?
_____

96. Has any part of your body been troubling you?
_____

IF YES, skip to question 98. IF NO, continue.

97. How is your head? Your heart? Stomach? The rest of your body?
_____

98. Could you explain?_____
_

99. Has your head or body changed in shape or size?
_____

IF NO, skip to question 102. IF YES, continue.

100. Please explain.
_____

101. What is causing these changes?
_____

Data on "Depression" (G6)

102. How has your mood been in the past week: mostly good, mostly bad?
_____

IF "MOSTLY BAD," skip to question 104. IF "MOSTLY GOOD," continue.

103. Have there been times in the past week when you were feeling sad or unhappy?

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_____

IF NO, skip to question 114. IF YES, continue.

104. Is there something in particular that is making you sad?
_____

105. How often do you feel sad?
_____

106. Just how sad have you been feeling?
_____

107. Have you been crying lately?
_____

108. Has your mood in any way affected your sleep?
_____

109. Has it affected your appetite?
_____

110. Do you participate less in activities on account of your mood?
_____

111. Have you had any thoughts of harming yourself?
_____

IF NO, skip to question 114. IF YES, continue.

112. Any thoughts about ending your life?_____

IF NO, skip to question 114. IF YES, continue.

113. Have you attempted suicide?
_____

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Data on "Guilt Feelings" (G3) and "Grandiosity" (P5)

114. If you were to compare yourself to the average person, how would you come out: a little better, maybe a little worse, or about the same?

_____

IF "BETTER," skip to question 117.

IF "ABOUT THE SAME," skip to question 118.

IF "WORSE," continue.

115. Worse in what ways?

_____

116. Just how do you feel about yourself?

_____

Skip to question 120.

117. Better in what ways?

_____

Skip to question 120.

118. Are you special in some ways?

_____

IF NO, skip to question 120. IF YES, continue.

119. In what ways?

_____

120. Would you consider yourself gifted?

_____

121. Do you have talents or abilities that most people don't have?

_____

IF NO, skip to question 123. IF YES, continue.

122. Please explain.

_____

123. Do you have any special powers?

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_____

IF NO, skip to question 126. IF YES, continue.

124. What are these?
_____

125. Where do these powers come from?
_____

126. Do you have extrasensory perception (ESP), or can you read other people's minds?_____

127. Are you very wealthy?
_____

IF NO, skip to question 129. IF YES, continue.

128. Explain please.
_____

129. Can you be considered to be very bright?
_____

IF NO, skip to question 131. IF YES, continue.

130. Why would you say so?
_____

131. Would you describe yourself as famous?_____

132. Would some people recognize you from TV, radio, or the newspaper?
_____

IF NO, skip to question 134. IF YES, continue.

133. Can you tell me about it?
_____

134. Are you a religious person?
_____

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IF NO, skip to question 140. IF YES, continue.

135. Are you close to God?
_____

IF NO, skip to question 140. IF YES, continue.

136. Did God assign you some special role or purpose?
_____

137. Can you be one of God's messengers or angels?
_____

IF NO, skip to question 139. IF YES, continue.

138. What special powers do you have as God's messenger (angel)?
_____

139. Do you perhaps consider yourself to be God?
_____

140. Do you have some special mission in life?
_____

IF NO, skip to question 143. IF YES, continue.

141. What is your mission?
_____

142. Who assigned you to that mission?
_____

143. Did you ever do something wrong — something you feel bad or guilty about?
_____

IF NO, skip to question 149. IF YES, continue.

144. Just how much does that bother you now?
_____

145. Do you feel that you deserve punishment for that?
_____

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IF NO, skip to question 149. IF YES, continue.

146. What kind of punishment would you deserve?
_____

147. Have you at times thought of punishing yourself?_____

IF NO, skip to question 149. IF YES, continue.

148. Have you ever acted on those thoughts of punishing yourself?
_____

Data on "Disorientation" (G10)

149. Can you tell me today's date (i.e., the day, month, and year)?
_____

IF YES, skip to question 151. IF NO, continue.

150. Can you tell me what day of the week it is?
_____

151. What is the name of the place that you are in now?_____

IF NOT HOSPITALIZED, skip to question 154. IF HOSPITALIZED, continue.

152. What ward are you on?_____

153. What is the address of where you're now staying?
_____

IF ABLE TO TELL, skip to question 155. IF NOT ABLE TO TELL, continue.

154. Can you tell me your home address?
_____

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IF NOT HOSPITALIZED, skip to question 156. IF HOSPITALIZED, continue.

155. If someone had to reach you by phone, what number would that person call?
_____

156. If someone had to reach you at home, what number would that person call?
_____

157. What is the name of the doctor who is treating you?
_____

IF NOT HOSPITALIZED, skip to question 159. IF HOSPITALIZED, continue.

158. Can you tell me who else is on the staff and what they do?
_____

159. Do you know who is currently the president (prime minister, etc.)?
_____

160. Who is our governor (premier, etc.)?
_____

161. Who is the mayor (town supervisor, etc.) of this city (town, etc.)?
_____

Data on "Difficulty in Abstract Thinking" (N5)

I'm going to now say a pair of words, and I'd like you to tell me in what important way they're alike. Let's start, for example, with the words "apple" and "banana." How are they alike — what do they have in common? **IF THE RESPONSE IS THAT "THEY'RE BOTH FRUIT", THEN SAY:** Good. Now what about ...? *(Select three other items from the Similarities list at varying levels of difficulty from Appendix A.)*

IF AN ANSWER IS GIVEN THAT IS CONCRETE, TANGENTIAL, OR IDIOSYNCRATIC (E.G., "THEY BOTH HAVE SKINS," "YOU CAN EAT THEM," "THEY'RE SMALL," OR "MONKEYS LIKE THEM"), THEN SAY: OK, but they're both fruit. Now how about ... and ... : how are these alike? *(Select three other items from the Similarities list at varying levels of difficulty from Appendix A.)*

APPENDIX A

Items for Similarities in the evaluation of "Difficulty in Abstract Thinking"

1. How are a ball and an orange alike?
2. Apple and banana ?
3. Pencil and pen?
4. Nickel and dime?

Note on Appendix A: Similarities are generally assessed by sampling four items at different levels of difficulty (i.e., one item selected from each quarter of the full set). When using the PANSS longitudinally, items should be systematically altered with

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5. Table and chair?
6. Tiger and elephant?
7. Hat and shirt?
8. Bus and train?

_____

9. Arm and leg?
10. Rose and tulip?
11. Uncle and cousin?
12. The sun and the moon?

_____

13. Painting and poem?
14. Hilltop and valley?
15. Air and water?
16. Peace and prosperity?

successive interviews so as to provide different selections from the various levels of difficulty and thus minimize repetition.

Notes on Similarities responses:

_____

_____

_____

_____

_____

You've probably heard the expression, "Carrying a chip on the shoulder." What does that really mean? There's a very old saying, "Don't judge a book by its cover." What is the deeper meaning of this proverb? *(Select two other proverbs from the list in Appendix B at varying levels of difficulty.)*

APPENDIX B

Items for assessing PROVERB INTERPRETATION in the evaluation of "Difficulty in Abstract Thinking"

Circle the Similarities Used

What does the saying mean:

1. "Plain as the nose on your face"
2. "Carrying a chip on your shoulder"
3. "Two heads are better than one"
4. "Too many cooks spoil the broth"

_____

5. "Don't judge a book by its cover"
6. "One man's food is another man's poison"
7. "All that glitters is not gold"
8. "Don't cross the bridge until you come to it"

_____

9. "What's good for the goose is good for the gander"
10. "The grass always looks greener on the other side"
11. "Don't keep all your eggs in one basket"
12. "One swallow does not make a summer"

_____

13. "A stitch in time saves nine"
14. "A rolling stone gathers no moss"
15. "The acorn never falls far from the tree"
16. "People who live in glass houses should not throw stones at others"

Note on Appendix B: Proverb interpretation is generally assessed by sampling four items at different levels of difficulty (i.e., one item selected from each quarter of the full set). When using the PANSS longitudinally, items should be systematically altered with successive interviews so as to provide different selections from the various levels of difficulty and thus minimize repetition.

Notes on Proverb responses:

_____

_____

_____

_____

Data on "Lack of Judgment and Insight" (G12)

162. How long have you been in the hospital (clinic, etc.)?

_____

163. Why did you come to the hospital (clinic, etc.)?

_____

164. Did you need to be in a hospital (clinic, etc.)?

_____

IF YES, skip to question 167. IF NO, continue.

165. Did you have a problem that needed treatment?

_____

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IF NO, skip to question 169. IF YES, continue.

166. Would you say that you had a psychiatric or mental problem?
_____

IF NO, skip to question 169. IFYES, continue.

167. Why?....would you say that you had a psychiatric or mental problem?
_____

IF NO, skip to question 169. IF YES, continue.

168. Can you tell me about it and what it consisted of?
_____

169. In your own opinion, do you need to be taking medicine?
_____

IF YES, skip to question 171.

IF NO and <u>unmedicated</u>, skip to question 172.

IF NO and <u>medicated</u>, continue.

170. Why then are you taking medicines?
_____

Skip to question 172.

171. Why?... Does the medicine help you in any way?
_____

172. Do you at this time have any psychiatric or mental problems?
_____

IF YES, skip to question 174. IF NO, continue.

173. For what reason are you at the hospital (clinic, etc.)?
_____

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Skip to question 175.

174. Please explain
_____

175. Just how serious are these problems?
_____

IF UNHOSPITALIZED, skip to question 178.

IF HOSPITALIZED, continue.

176. Are you ready yet for discharge from the hospital?
_____

177. Do you think you'll be taking medicine for your problems after discharge?
_____

178. What are your future plans?
_____

179. What about your longer-range goals?
_____

Well, that's about all I have to ask of you now. Are there any questions that you might like to ask of me? Thank you for your cooperation.

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APPENDIX 6. Calgary Depression Scale for Schizophrenia (COSS)

The Calgary Depression Scale for Schizophrenia

Interviewer: Ask the first question as written. Use follow up probes or qualifiers at your discretion. Time frame
refers to last one week unless stipulated. **N.B.** The last item, #9, is based on observations of the entire interview.

1. DEPRESSION: How would you describe your mood over the last one week? Do you keep reasonably cheerful or have you been very depressed or low spirited recently? In the last one week how often have you (own words) every day? All day?

0. Absent	
1. Mild	Expresses some sadness or discouragement on questioning.
2. Moderate	Distinct depressed mood persisting up to half the time over last 1 week: present daily.
3. Severe	Markedly depressed mood persisting daily over half the time interfering with normal motor and social functioning.

2. HOPELESSNESS: How do you see the future for yourself? Can you see any future? - or has life seemed quite hopeless? Have you given up or does there still seem some reason for trying?

0. Absent	
1. Mild	Has at times felt hopeless over the last one week but still has some degree of hope for the future.
2. Moderate	Persistent, moderate sense of hopelessness over last week. Can be persuaded to acknowledge possibility of things being better.
3. Severe	Persisting and distressing sense of hopelessness.

3. SELF DEPRECIATION: What is your opinion of your self compared to other people? Do you feel better, not as good, or about the same as others? Do you feel inferior or even worthless?

0. Absent	
1. Mild	Some inferiority; not amounting to feeling of worthlessness.
2. Moderate	Subject feels worthless, but less than 50% of the time.
3. Severe	Subject feels worthless more than 50% of the time. May be challenged to acknowledge otherwise.

4. GUILTY IDEAS OF REFERENCE: Do you have the feeling that you are being blamed for something or even wrongly accused? What about? (Do not include justifiable blame or accusation. Exclude delusions of guilt.)

0. Absent	
1. Mild	Subject feels blamed but not accused less than 50% of the time.
2. Moderate	Persisting sense of being blamed, and/or occasional sense of being accused.
3. Severe	Persistent sense of being accused. When challenged, acknowledges that it is not so.

5. PATHOLOGICAL GUILT: Do you tend to blame yourself for little things you may have done in the past? Do you think that you deserve to be so concerned about this?

0. Absent	
1. Mild	Subject sometimes feels over guilty about some minor peccadillo, but less than 50% of time.
2. Moderate	Subject usually (over 50% of time) feels guilty about past actions the significance of which he exaggerates.
3. Severe	Subject usually feels s/he is to blame for everything that has gone wrong, even when not his/her fault.

6. MORNING DEPRESSION: When you have felt depressed over the last one week have you noticed the depression being worse at any particular time of day?

0. Absent	No depression
1. Mild	Depression present but no diurnal variation.
2. Moderate	Depression spontaneously mentioned to be worse in a.m.
3. Severe	Depression markedly worse in a.m., with impaired functioning which improves in p.m.

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7. EARLY WAKENING: Do you wake earlier in the morning than is normal for you? How many times a week does this happen?

0. Absent	No early wakening.
1. Mild	Occasionally wakes (up to twice weekly) 1 hour or more before normal time to wake or alarm time.
2. Moderate	Often wakes early (up to 5 times weekly) 1 hour or more before normal time to wake or alarm.
3. Severe	Daily wakes 1 hour or more before normal time

8. SUICIDE: Have you felt that life wasn't worth living? Did you ever feel like ending it all? What did you think you might do? Did you actually try?

0. Absent	
1. Mild	Frequent thoughts of being better off dead, or occasional thoughts of suicide.
2. Moderate	Deliberately considered suicide with a plan, but made no attempt.
3. Severe	Suicidal attempt apparently designed to end in death (i.e.: accidental discovery or inefficient means).

9. OBSERVED DEPRESSION: Based on interviewer's observations during the entire interview. The question "Do you feel like crying?" used at appropriate points in the interview, may elicit information useful to this observation.

0. Absent	
1. Mild	Subject appears sad and mournful even during parts of the interview, involving affectively neutral discussion.
2. Moderate	Subject appears sad and mournful throughout the interview, with gloomy monotonous voice and is tearful or close to tears at times.
3. Severe	Subject chokes on distressing topics, frequently sighs deeply and cries openly, or is persistently in a state of frozen misery if examiner is sure that this is present.

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CLAIMS

1. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for treating negative symptoms of schizophrenia in a patient having schizophrenia and as having clinically stable positive symptoms.

2. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is to be administered d6-DM in a 27 mg to 54 mg dose twice daily and Q in a 4 mg to 7.5 mg dose twice daily.

3. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is to be administered d6-DM in a 30 mg to 45 mg dose twice daily and Q in a 4 mg to 6 mg dose twice daily.

4. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is to be administered d6-DM in a 34 mg to 42.63 mg dose twice daily and Q in a 4.9 mg dose twice daily.

5. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient has not had an inpatient psychiatric hospitalization within 4 months prior to treatment.

6. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient has not had a psychiatric hospital admission or acute exacerbation within 6 months prior to treatment.

7. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient has been assessed as having a score of less than or equal to 4 on the Positive and Negative Syndrome Scale (PANSS) items of delusions, hallucinations, and hostility.

8. The use of claim 7, wherein the patient has been assessed as having a score of greater than or equal to 4 on any two, or greater than or equal to 5 on any one, of the PANSS items of blunted affect (N1), emotional withdrawal (N2), passive/apathetic social withdrawal (N4), and lack of spontaneity/flow of conversation (N6).

9. The use of claim 7 or 8, wherein the patient has been assessed as having a total PANSS negative subscale score (N1 to N7) of greater than or equal to 18.

10. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient has been assessed as having a score of less than or equal to 4 on the Positive and Negative Syndrome Scale (PANSS) items of delusions, hallucinations, suspiciousness/persecution, and hostility.

11. The use of claim 10, wherein the patient has been assessed as having a score of greater than or equal to 4 on any two, or greater than or equal to 5 on any one, of the PANSS items of blunted affect (N1), emotional withdrawal (N2), passive/apathetic social withdrawal (N4), and lack of spontaneity/flow of conversation (N6).

12. The use of claim 10 or 11, wherein the patient has been assessed as having a total PANSS Marder negative factors score of greater than or equal to 20.

13. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is being treated with an atypical antipsychotic, wherein the patient has been treated with the atypical antipsychotic for at least 3 months prior to

the medicament to be administered and the dose of the atypical antipsychotic has been stable for at least 1 month prior to the medicament to be administered.

14. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is being treated with an antidepressant, wherein the patient has been treated with the antidepressant for at least 3 months, and the dose of the antidepressant has been stable for at least 1 month, prior to the medicament to be administered.

15. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is being treated with a hypnotic, wherein the dose of the hypnotic has been stable for at least 1 month prior to the medicament to be administered.

16. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is being treated with lorazepam up to a total dose of 2 mg per day for insomnia, anxiety, restlessness, or agitation, wherein the dose of the lorazepam has been stable for at least 1 month prior to the medicament to be administered.

17. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is not being treated with one or more monoamine oxidase inhibitors (MAOIs).

18. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is not being treated with clozapine.

19. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is not being treated with a benzodiazepine other than lorazepam.

20. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is not being treated with levodopa.

21. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is not being treated with a typical antipsychotic.

22. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is not being treated with an agent that:

(a) increases plasma levels of quinidine;

(b) is metabolized by CYP2D6;

(c) is related to quinidine;

(d) produces serotonin syndrome when co-administered with dextromethorphan;

(e) decreases plasma levels of dextromethorphan and quinidine;

(f) is clozapine; or

(g) is a typical antipsychotic.

23. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient is not being treated with an anticholinergic medication.

24. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a

second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient has not received electroconvulsive treatment, repetitive transcranial magnetic stimulation, or deep brain stimulation within one year prior to treatment.

25. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not have myasthenia gravis.

26. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not have schizoaffective disorder.

27. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not have bipolar disorder.

28. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in

combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia wherein the patient does not have a depressive disorder and/or a Calgary Depression Scale for Schizophrenia (CDSS) score of greater than or equal to 6.

29. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not have a score of greater than 3 on the sum of eight items of the Simpson-Angus Scale (SAS): gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head rotation, and glabella tap.

30. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not have a concurrent clinically significant or unstable systemic disease, neurological disorder, cognitive disorder, neurodegenerative disorder, hepatic disorder, renal disorder, metabolic disorder, hematological disorder, immunological disorder, cardiovascular disorder, pulmonary disorder, or gastrointestinal disorder, as determined by the prescribing doctor.

31. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not have a suicide risk.

32. The use of claim 31, wherein suicide risk is determined by one or more of the following:

(a) judgment of the prescribing doctor;

(b) the patient answers yes on the Columbia Suicide Severity Rating Scale (C-SSRS Suicidal Ideation Item 4 (active suicidal ideation with some intent to act, without a specific plan) and the patient's most recent episode meeting this C-SSRS Item 4 occurred within six months;

(c) the patient answers yes on the C-SSRS Suicidal Behavior Item 5 (active suicidal ideation with specific plan and intent) and the patient's most recent episode meeting this C-SSRS Item 5 occurred within six months; and

(d) the patient answers yes on any of the 5 on the C-SSRS Suicidal Behavior Items (active attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) and the patient's most recent episode meeting any of these C-SSRS Items occurred within two years prior to treatment.

33. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not have a cardiovascular history of any one or more of:

(a) history or evidence of complete heart block, ventricular tachycardia, presence of clinically significant premature ventricular contractions (PVCs) as evaluated by a central reader, QTc prolongation, or torsades de pointes;

(b) QTc using the Fridericia's formula (QTcF) greater than 450 msec for males and greater than 470 msec for females based on central review, unless due to ventricular pacing;

(c) family history of congenital QT interval prolongation syndrome; and

(d) history or presence of clinically significant syncope, orthostatic hypotension, or postural tachycardia.

34. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not have pseudoparkinsonism secondary to treatment with an antipsychotic.

35. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not have a history of substance and/or alcohol abuse, but may use tobacco and/or nicotine products.

36. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not use recreational or medicinal marijuana, as evidenced by a negative urine drug screen for cannabis.

37. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein the patient does not test positive for hepatitis B surface antigen, hepatitis C antibody, or HIV antibody.

38. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia, wherein

during the first week of treatment, the d6-DM is to be administered in a 24 mg dose once daily and the Q is to be administered in a 4.9 mg dose once daily;

during the second week of treatment, the d6-DM is to be administered in a 24 mg dose twice daily and the Q is to be administered in a 4.9 mg dose twice daily; and

during the remainder of the treatment, the d6-DM is to be administered in a 34 mg dose twice daily and the Q is to be administered in a 4.9 mg dose twice daily.

39. Use of deuterated [d6]-dextromethorphan hydrobromide (d6-DM) in the manufacture of a first medicament and use of quinidine sulfate (Q) in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination for specifically treating negative symptoms of schizophrenia in a patient having schizophrenia,~~,~~ wherein

during the first three days of treatment, the d6-DM is to be administered in a 28 mg dose once daily and the Q is to be administered in a 4.9 mg dose once daily;

during the next four days of treatment, the d6-DM is to be administered in a 28 mg dose twice daily and the Q is to be administered in a 4.9 mg dose twice daily; and

during the remainder of the treatment, the d6-DM is to be administered in a 42.63 mg dose twice daily and the Q is to be administered in a 4.9 mg dose twice daily.

40. The use of any one of claims 1 to 39, wherein the patient is to be further administered an atypical antipsychotic other than clozapine.

41. The use of any one of claims 1 to 40, wherein the patient is a male or female patient from 18 to 60 years of age.

42. The use of any one of claims 1 to 41, wherein the patient is a female of childbearing potential.

43. The use of claim 42, wherein the patient:

(a) has a negative urine pregnancy test;

(b) is not nursing or planning a pregnancy for the duration of treatment through 30 days after the last dose; and

(c) is abstinent or willing to use a method of birth control prior to treatment, and to continue with the same method until 28 days after the last dose.

44. The use of any one of claims 1 to 43, wherein the patient does not have hypersensitivity to dextromethorphan, quinidine, an opiate drug, d6-DM, Q, or any ingredient thereof.

45. The use of any one of claims 1 to 44, wherein the patient does not have allergy or hypersensitivity to one or more medications.

46. The use of any one of claims 1 to 45, wherein the patient does not have one or more clinically significant laboratory abnormalities, one or more safety values of clinical concern, or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels greater than two times the upper limit of normal, as determined by the prescribing doctor.

47. The use of any one of claims 1 to 46, wherein the patient has been diagnosed as having schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for schizophrenia.

48. The use of claim 47, wherein the diagnosis based on the DSM criteria has been confirmed by the Mini International Neuropsychiatric Interview (M.I.N.I.).

49. The use of any one of claims 1 to 48, wherein the treatment results in an at least 20% decrease in the PANSS Marder Negative Factor Score from baseline prior to treatment.

50. The use of any one of claims 1 to 49, wherein the treatment results in an at least 2 point decrease in the PANSS Marder Negative Factor Score from baseline prior to treatment.

51. The use of any one of claims 1 to 3 or 5 to 50, wherein the d6-DM is to be administered in a dose of 34 mg to 42.63 mg twice daily and the Q is to be administered in a dose of 4.9 mg twice daily.

52. The use of claim 4 or 51, wherein the d6-DM is to be administered in a 34 mg dose twice daily.

53. The use of claim 4 or 51, wherein the d6-DM is to be administered in a 42.63 mg dose twice daily.

54. The use of any one of claims 1 to 53, wherein ~~further comprising treating~~ prosocial factors are to be treated by the administration of the d6-DM and the Q.