1-[2-(2,4-DIMETHYLPHENYLSULFANYL)-PHENYL]PIPERAZINE FOR PREVENTION OR TREATMENT OF EMOTIONAL BLUNTING

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to European Application No. 20167895.0, filed on April 3, 2020, and European Application No. 20185247.2, filed on July 10, 2020, the contents of each of which are hereby incorporated by reference in their entireties.

INCORPORATION BY REFERENCE

All patents, patent applications, and publications cited herein are hereby incorporated by reference in their entirety in order to more fully describe the state of the art as known to those skilled therein as of the date of the invention described herein.

FIELD OF THE INVENTION

The present invention relates to the therapeutic use of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine.

BACKGROUND OF THE INVENTION

CNS disorders and conditions, such as major depressive disorder ("MDD"), major depressive episodes ("MDE"), schizophrenia, or post-traumatic stress disorder ("PTSD") are disabling and recurrent illnesses, that are highly prevalent worldwide. Some of these patients experience a restriction in emotions that are a normal part of everyday life, such as the ability to feel happy or concerned.

MDD is a severe, recurrent, and disabling illness that can be treated with selective serotonin reuptake inhibitors ("SSRIs") and serotonin-noradrenalin reuptake inhibitors ("SNRIs"). However, approximately 50% of all patients only have a partial response to these therapies in terms of depressive symptoms resolution (Rush et al., Am. J. Psychiatry (2006), 163, 1905-1917 (incorporated herein by reference in its entirety)).

In addition, about 50% of all patients with MDD treated with SSRI or SNRIs report some degree of emotional blunting, which may be related to the medication (Goodwin et al., Journal of Affective Discorders, (2017), 221, 31-35; Bolling and Kohlenberg, (2004), 73, 380-

385 (each incorporated herein by reference in their entireties)). Emotional blunting is a condition characterized by a restriction in emotions that clinically presents as emotional indifference and detachment, reduced responsiveness, low motivation, and apathy (Price J, Cole V, Goodwin GM., Br. J. Psychiatry, (2009), 195(3), 211-217 (incorporated herein by reference in its entirety)). People with emotional blunting report feeling numb, less able to laugh or cry, unable to enjoy what they used to enjoy, feeling less empathy, and feeling indifference towards others. Also, they often complain about having lost inspiration or passion for creative activities and feeling reduced social responsibility or concern for other people.

MDD, with a prevalence of 15% worldwide, is treated with commonly used antidepressants, such as SSRIs or SNRIs as first- and second-line treatments. SSRIs have for years been favored by physicians for the treatment of many central nervous system ("CNS") diseases, such as depression and anxiety, because they are effective and have favorable safety profiles compared to the previous generation of CNS drugs, *i.e.*, the so-called tri-cyclic anti-depressants. Known adverse events from the treatment of MDD with antidepressants, such as SSRIs and SNRIs, are changes in sleep pattern, changes in sexual functioning, headache, and weight gain. A side-effect less commonly investigated in clinical trials is the blunting of emotions experienced by patients taking these medications, which also include anti-psychotic medications used in the treatment of schizophrenia.

Currently, most available antipsychotics improve positive symptoms of schizophrenia while failing to manage the negative symptoms and cognitive dysfunctions adequately. This leaves a significant unmet need for satisfying treatment options for the subpopulation of up to 35-40% of schizophrenic patients, who suffer from persistent negative symptoms (Mucci A. et al., Schizophr. Res., (2017), 186, 19-28; Rabinowitz J. et al., Schizophr. Res., (2013), 150(2-3), 339-342 (each incorporated herein by reference in their entireties)). Poorly managed negative symptoms are also present in 50-60% of schizophrenic patients, who are considered clinically stable with regard to their positive symptoms, and this constitutes a major source of impaired functioning in this patient group (Bobes J. et al., J. Clin. Psychiatry, (2010),71(3), 280-286 (incorporated herein by reference in its entirety)).

Moreover, most available antipsychotics are known to cause severe side-effects, such as extrapyramidal symptoms ("EPS"). Therefore, the search for CNS active drugs with

improved efficacy on negative and cognitive symptoms, as well as better side effect profiles, is important to the development of better treatment options for patients suffering from persistent negative symptoms, persistent prominent negative symptoms, and/or cognitive dysfunctions, particularly in schizophrenia. Such new treatments may also prove beneficial for non-schizophrenic patients suffering from negative symptoms and cognitive impairments.

Emotional blunting is clinically important as it affects patient functioning in work life, social life, and family life and thus prevents full functional recovery. For instance, patients experiencing emotional blunting may evade or ignore responsibilities, which may result in financial problems or problems at work/school, and experience a reduction in the quality of family life or parenting. Hence, emotional blunting is burdensome for the patient and negatively affects health-related quality of life and daily functioning (Price et al., 2009 (*supra*)). Functional impairment and residual symptoms, like emotional blunting, are important as research has shown that patients with remitted MDD or stable schizophrenia with functional impairment are at higher risk of relapse (Bobes J. et al., 2010 (*supra*)).

Emotional blunting and anhedonia have been implicated in disturbances of central dopaminergic, mesolimbic, and mesocortical reward circuit pathways (Pan et al., Curr. Pharm. Des. (2017), 23, 2065-2072; Sternat and Katzman, Neuropsychiatr. Dis. Treat. (2016), 12, 2149-2164 (each of which is incorporated herein by reference in their entireties)). Anhedonia is a state of reduced ability to experience feelings of pleasure and is a common symptom of MDD—reported in about 75% of patients (Franken et al., J. Affect. Disord. (2007), 99, 83-89 (incorporated herein by reference in its entirety); Sternat and Katzman, 2016 (*supra*)) and is part of the negative symptoms of schizophrenic patients (Mucci A. et al., Schizophrenia Research, (2017), 186, 19-28; Rabinowitz J. et al., Schizophr Res., (2013) 150(2-3), 339-342 (each of which is incorporated herein by reference in their entireties)). It depends on the hedonic tone, where a low hedonic tone represents a reduced capacity to experience pleasure, increasing the likelihood of anhedonia (Franken et al., 2007 (*supra*)). Anhedonia and impaired reward circuit pathways are associated with a poorer prognosis and suboptimal treatment response (Buckner et al., Psychiatry Res., (2008), 159, 25-30; Uher et al., Psychol Med (2012), 42, 967-980 (each of which is incorporated herein by reference in their entireties)).

Emotional blunting phenotypically overlaps with anhedonia but the two conditions are not identical (Cao et al., Prog. Neuropsyhopharmacol. Biol. Psychiatry, (2019), 92, 109-117; Esperidião-Antonio et al., Int Rev Psychiatry (2017), 29, 293-307; Loas et al., Compr. Psychiatry (1994), 35, 366-372 (each of which is incorporated herein by reference in their entireties)). Cao et. al. (Cao et al., Frontiers in Psychiatry, (2019), 10, 17 (incorporated herein by reference in its entirety)) describe anhedonia as a common, persistent, and disabling phenomenon in treated adults with MDD. Hitherto, relatively few antidepressant agents have been evaluated with respect to their effect on anhedonia in MDD. Cao et al. (*supra*) also review results that vortioxetine significantly improved anhedonia as evidenced by significant baseline to endpoint improvements in Snaith-Hamilton Pleasure Scale ("SHAPS") and Montgomery Åsberg Depression Rating Scale ("MADRS") anhedonia factor scores. Improvements in the SHAPS and the MADRS anhedonia factor correlated with improvements in general function (*i.e.*, Sheehan Disability Scale ("SDS")) and quality of life (*i.e.*, World Health Organization Well-Being Index ("WHO-5")), and emotional blunting and anhedonia have phenotypical overlap in some patients.

Anhedonia concerns a state with lack of positive emotions, whereas emotional blunting is a state where **all** emotions are lacking or blunted, both positive and negative. It cannot be foreseen whether a drug, which relieves anhedonia, also relieves emotional blunting. The term 'anhedonia' is primarily referred to the inability to experience pleasure (Rizvi SJ, Pizzagalli DA, Sproule BA, Kennedy SH, Neuroscience and Biobehavioral Reviews, (2016), 65, 21–35 (incorporated herein by reference in its entirety)). Anhedonia is a core diagnostic feature of a major depressive episode and patients with anhedonia may endorse a diagnosis of MDD even if the 'depressed mood' criterion is not endorsed (American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders: DSM-5. Washington, D.C.: American Psychiatric Association (incorporated herein by reference in its entirety).

Patients with emotional blunting very frequently experience anhedonia but the emotions that are blunted **are not limited to pleasure** and **include several other emotions**, including negative emotions. On the contrary, patients with anhedonia are very well able to experience negative emotions, whose perception is rather heightened than blunted. This may explain the reason why several antidepressants, including the SSRIs, have shown efficacy

on anhedonia during a major depressive episode but, at the same time, have also shown the ability to cause emotional blunting. Indeed, many antidepressants can improve the inability to experience pleasure and to reduce the intensity of negative emotions. However, the same antidepressants may cause emotional blunting, in that they reduce the ability to experience physiological negative emotions (*e.g.*, going to a funeral and crying; feeling sad when something bad happens) and, at the same time, they 'stabilize' positive emotions, flattening them in a range that is better than the intensity experienced during depression but is not normal. Hence, patients may be improved in their **anhedonia**, *i.e.*, they are no longer tormented by excessive negative emotions or unable to experience pleasure, but they are **emotionally blunted**, for instance in their creativity, in their ability to enjoy and engage in things, and in their reactivity to life events.

As mentioned above, emotional blunting may be related to antidepressant treatment with a SSRI or SNRI. Usually, emotional blunting is related to SSRI dosing, with higher doses being more likely to precipitate the syndrome (Sansone and Sansone, Psychiatry (Edgmont) (2010), 7, 14-18 (incorporated herein by reference in its entirety)), which, in some cases, may resolve with lowering the dose. In other cases, the condition does not resolve until the SSRI is discontinued. Emotional blunting has been proposed to relate to serotonergic effects in the frontal lobes and/or serotonergic modulation of midbrain dopaminergic systems, which project to the prefrontal cortex. By broadly enhancing serotoninergic transmission, SSRI drugs activate gamma-aminobutyric acid ("GABA") interneurons, thereby dampening the noradrenergic as well as the dopaminergic input (Blier, Int. J. Neuropsychopharmacol., (2014), 17, 997-1008 (incorporated herein by reference in its entirety)).

This phenomenon of emotional blunting has been variously described as emotional indifference, a diminution of emotional responsiveness or sensitivity, or a sense of numbing of emotion. In a study by Price et al., patients commonly described this phenomenon as feelings of emotions being "dulled," "numbed," "flattened," or completely "blocked," as well as feeling "blank" or "flat." Generally, emotional blunting often co-occurs with other symptoms, such as slowed thinking, loss of concentration, and decreased libido.

Emotional blunting is burdensome, and negatively affects quality of life and daily functioning (Price J, Cole V, Goodwin GM., Br. J. Psychiatry, (2009), 195(3), 211-217 (incorporated herein by reference in its entirety)). The blunting of emotions has real

functional consequences for patients´ social, family, and work life. Some patients describe how they experience reduced love, affection, and pride towards their partner and family, reduced sympathy and empathy during social interactions, and reduced concern and interest about their responsibilities at work. A feeling of "just not caring" about things that used to matter to them was expressed by a significant proportion of the patients, and the effect was attributed to their antidepressant treatment. A recent study by Goodwin et al. found that emotional blunting may be experienced by nearly half of patients (46%) on SSRIs or SNRIs. (Goodwin GM, Price J, Bodinat CD, J. Affect. Disord. (2017), 221, 31-35 (incorporated herein by reference in its entirety)), *i.e.*, restrictions in the full range of emotions that they would normally experience, even during remission. Emotional blunting has also been identified as a common reason for patients with MDD to stop treatment (Rosenblat et al., J Affect. Disord. (2019), 243, 116-120 (incorporated herein by reference in its entirety)).

An alternative explanation for the phenomenon of emotional blunting is that it is a symptom of depressed mood and that its association with SSRIs and related drugs reflects their failure to produce full remission of symptoms, rather than it being solely a side effect of therapy *per se* (Goodwin et al., 2017 (*supra*)). This appears to be a possibility because of the neurobiologic and phenotypic overlap between emotional blunting and other characteristics of MDD, particularly anhedonia (Cao et al., Prog Neuropsyhopharmacol Biol. Psychiatry, 2019; Esperidião-Antonio et al., 2017; Loas et al., 1994; Pan et al., 2017; Sternat and Katzman, 2016 (each of which is incorporated herein by reference in their entireties)). However, emotional blunting represents a clinical state of absence of both positive and negative emotions, while anhedonia is characterized by the absence of positive emotions alone (Sternat and Katzman, 2016 (*supra*)).

This may explain why SSRIs may show efficacy against symptoms of anhedonia during a major depressive episode (*i.e.*, patients no longer experience excessive negative emotions or are unable to experience pleasure), but symptoms of emotional blunting may persist (*e.g.*, patients still experience inability to enjoy and engage in usually pleasurable activities and show impaired reactivity to life events). Emotional blunting and anhedonia have been implicated in disturbances of central dopaminergic, mesolimbic, and mesocortical reward circuit pathways (Pan et al., 2017 (*supra*); Sternat and Katzman, 2016 (*supra*)).

Patients suffering with emotional blunting may also demonstrate a persistent inability to experience positive emotions (*e.g.*, happiness, satisfaction, or loving feelings), a markedly diminished interest or participation in significant activities, and, possibly, with feelings of detachment or estrangement from others. Other related subjective experiences that may be reported by patients who feel emotionally numb can include feeling emotionally dead, shutdown, hollow and/or empty, and without any feelings. These subjective experiences are associated with degrees of lack of care and concern for the welfare of self and others.

A high degree of emotional dysfunction is likely to be associated with poor overall life functioning, a poorer quality of remission from depressive symptoms, and a more negative perception of the condition and could be a reason for treatment cessation (Goodwin GM, Price J, Bodinat CD, Laredo J., J. Affect. Disord. (2017), 221, 31-35 (incorporated herein by reference in its entirety)).

Emotional numbness is not only a reaction seen as an adverse event in medical treatment with, *e.g.*, SSRIs or SNRIs as described above, but may also be conceptualized as part of the symptomatology of certain CNS diseases or disorders as such, *e.g.*, as part of the development of depression or even as a biopsychological response to extreme emotional or physical trauma. Emotional numbness or blunting can thus be observed in patients who have experienced extreme emotional or physical trauma, *e.g.*, patients diagnosed with PTSD. Patients with PTSD usually present in primary care with unexplained somatic and/or psychological symptoms, including sleep disturbances, night sweats, fatigue, and difficulty with memory or concentration (Walter A., Pharmacotherapy for Post-traumatic Stress Disorder In Combat Veterans P T. (2012); 37(1): 32–38 (incorporated herein by reference in its entirety)). The U.S. Food and Drug Administration ("FDA") has approved paroxetine and sertraline for the treatment of PTSD. Some treatment guidelines recommend these or other antidepressants, including fluoxetine and venlafaxine, as equivalently first choice together with focused cognitive behavioral therapy ("CBT") (Toll WA, Barbui C, Ommeren, JAMA, (2013); 310:477-478 (incorporated herein by reference in its entirety)). Others regard focused CBT as having better evidence and suggest antidepressants only when therapy has failed or is not available, or in cases of severe depression (Bajor LA, Ticlea AN, Osser DN, Harv. Rev. Psychiatry (2011), 19:240-258; (incorporated herein by reference in its entirety); Toll WA, Barbui C, Ommeren, JAMA (2013), 310:477-478 (*supra*)). This reflects a number of

negative randomized clinical trials ("RCTs") with SSRIs, and small-to-moderate effect sizes relative to trauma-focused ("TF")-CBT. It is known that nalmefene, an opiod receptor antagonist, which is used to treat, *e.g.*, alcohol dependency, has been studied for establishing its effect om emotional blunting. Between the years 1988-1990, in an open-label pilot study, nalmefene was administered to combat veterans diagnosed with PTSD. The published pilot study reported the administration of low doses of the drug, incrementing doses gradually from one milligram twice a day up to a maximum of 200 milligrams twice a day. Based on the study results, nalmefene was observed to significantly reduce, and in some cases remit, the symptom of emotional blunting, and to facilitate the veterans' abilities to experience a range of normal human responses, including feelings of empathy, love, care, and concern for others. The drug was also found to significantly improve all core symptoms of PTSD, including nightmares, intrusive thoughts, flashbacks; the inability to engage in topics dealing with combat experiences without the onset of symptoms of emotional distress or behavioral avoidance; dissociative amnesia; mistrust of others; and states of hyper arousal and reactivity associated with the traumatic events (Diagnostic Statistical Manual- 5. American Psychiatric Association, pub, 2013 (incorporated herein by reference in its entirety)).

A Study from Oxford University has shown that 46-71% of antidepressant users have experienced emotional blunting during treatment. According to the research, the antidepressants most commonly associated with emotional blunting fall into one of three classes:

1. SSRIs, like Lexapro (escitalopram), Prozac (fluoxetine), Zoloft (sertraline), and Paxil (paroxetine) (Goodwin GM, Price J, Bodinat CD, Laredo J. Emotional blunting with antidepressant treatments: A survey among depressed patients. J. Affect. Disord. 2017; 221: 31-35 (incorporated herein by reference in its entirety));
2. SNRIs, such as Cymbalta (duloxetine), Pristiq (desvenlafaxine), and Effexor XR (venlafaxine); and
3. tricyclic and tetracyclic antidepressants, like Elavil (amitriptyline) and Remeron.

Though the percentage of people who experienced emotional blunting was similar between the three drug classes, there were variations. About 33% experienced emotional blunting while on Wellbutrin (bupropion) (Goodwin GM, Price J, Bodinat CD, Laredo J., J Affect Disord. (2017), 221: 31-35 (*supra*)) while 75% experienced the same effect on Cymbalta.

Another study concluded that emotional blunting was less frequent on agomelatine than on escitalopram. Indeed, about 28% of patients on agomelatine versus about 60% on escitalopram felt that their emotions lacked intensity, and about 16% of patients on agomelatine versus about 53% on escitalopram felt that things that they cared about before illness did not seem important any more ($p = 0.024$) (Christian de Bodinatet al., Journal of Neuropsychopharmacology, (2013), 16 (10), 2219–2234 (incorporated herein by reference in its entirety)).

Wellbutrin (bupropion) differentiates itself from the other antidepressant drugs in being a dopamine and norepinephrine reuptake inhibitor. Unlike the others, Wellbutrin (bupropion) does not target serotonin transporter ("SERT") (Patel K, Allen S, Haque MN, Angelescu I, Baumeister D, Tracy DK., Ther. Adv. Psychopharmacol. (2016), 6(2), 99-144 (incorporated herein by reference in its entirety)). This may thus suggest that inhibition of serotonin may be one of the prime causes of emotional blunting for antidepressants, such as SSRIs or SNRIs.

Nonetheless, it has been difficult to determine the precise reason for the emotional blunting, since emotional blunting is not reported in all patients receiving antidepressants. It has even been questioned whether blunting is a side effect of antidepressant treatment or perhaps a partial failure of the drug itself, *i.e.*, leading to residual depressive symptoms.

Given the lower incidence of emotional blunting in patients treated with Wellbutrin (bupropion), research suggests that the effect of antidepressants in SERT plays a major role in emotional blunting, however it is also viewed as unlikely that a single hormone is solely responsible for this phenomenon. Further, it has been suggested that emotional blunting is better understood as a symptom revealed (Jones JD, Butterfield LC, Song W, et al., J Neuropsychiatry Clin. Neurosci. (2015), 27(3), 213-8 (incorporated herein by reference in its entirety)), rather than a side-effect of medication; meaning that once the antidepressants alleviate depression, the underlying symptoms of emotional blunting are revealed rather than caused.

The data presented herein shows that vortioxetine is able to provide relief in about half of the patients experiencing emotional blunting and significantly reduce symptoms of emotional blunting in all patients participating in the study, an effect observed already after 1 week of treatment and increasing in size over the next 7 weeks of treatment. This effect

should be expected regardless of whether the emotional blunting is a direct result of the medical treatment with antidepressant or whether the medical treatment with antidepressants revealed an underlying symptom to be treated. Similar effects can be expected for the treatment of emotional blunting as part of the negative symptoms in, *e.g.*, schizophrenia or psychosis or in patients who experience a worsening of negative symptoms due to treatment with medicaments for the treatment of schizophrenia or psychosis, such as antipsychotics.

Excessive neurotransmission of dopamine is associated with schizophrenia. Antipsychotics, also called neuroleptics, are a class of compounds with a high affinity for several subtypes of dopamine receptors. The chemical structure of the various antipsychotics allows them to bind to dopamine receptors without triggering the postsynaptic response that the binding of dopamine normally would. Because of their ability to block dopamine receptors without causing the opening of ion channels and setting off an action potential, neuroleptics can be administered to schizophrenic patients to help reduce excess levels of dopamine, and to thus help alleviate the positive symptoms of the disorder. The traditional typical and atypical antipsychotics demonstrate clinical efficacy in treating positive symptoms, such as hallucinations and delusions, while are largely ineffective and may even worsen negative symptoms, such as emotional blunted affect and social withdrawal, as well as cognitive function. The inability to treat these latter symptoms may contribute to social function impairment associated with schizophrenia. The dysfunction of multiple neurotransmitter systems in schizophrenia suggests that drugs selectively targeting one neurotransmission pathway are unlikely to meet all the therapeutic needs of this heterogeneous disorder (Peng Li et al. Current Topics in Medicinal Chemistry, (2016), 16, 3385-3403 (incorporated herein by reference in its entirety).

WO 2003/029232 (incorporated herein by reference in its entirety) and WO 2007/144005 (incorporated herein by reference in its entirety) disclose the compound 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine and pharmaceutically acceptable salts thereof. Vortioxetine (which is 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine) is a multimodal antidepressant that works through modulation of receptor activity and serotonin transporter inhibition. As of July 1, 2020, vortioxetine has been approved for the treatment of major depression globally in more than 80 countries, including by the FDA in September

2013 and European Commission on December 18, 2013. In the clinical development program, vortioxetine was efficacious, safe, and well tolerated in adults and the elderly with MDD, in short-term treatment and long-term maintenance treatment. The approved therapeutic dose range for vortioxetine in adults is 5-20 mg/day.

Vortioxetine is a multi-modal antidepressant sharing some common features with SSRIs and SNRIs. However, since vortioxetine is a multi-modal antidepressant which has also shown a different pattern of effects and side effects than SSRI and SNRIs, a clinical trial under the name study name COMPLETE, study number 17797A (EudraCT No. 2017-004829-33 (incorporated herein by reference in its entirety)), sponsored by H. Lundbeck A/S, was set up to assess the effect of vortioxetine on emotional blunting. In clinicaltrial.gov study No. NCT 03835715 (incorporated herein by reference in its entirety), the Brief Summary summarizes the study's aim as: "The study will evaluate effectiveness of flexible dose vortioxetine on Emotional Functioning in patients with Major Depressive Disorder with an inadequate response to SSRI/SNRI". The EudraCT trial register cites the same purpose in the Full Title of the Trial.

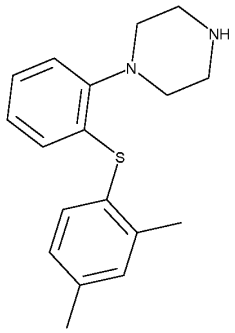
Goodwin et al. (Goodwin et al., Journal of Affective Discorders, (2017), 211, 31-35) and Jonathan Price et al. (Jonathan Price et al., Journal of Affective Discorders, (2012), 140, 66-74) (each of which is incorporated herein by reference in their entireties) report the use of the Oxford Questionaire on emotional side effects.

Emmanuelle Corruble et al. (International Journal of Neuropsychopharmacology, (2013), 16 (10), 2219-2234 (incorporated herein by reference in its entirety)) discloses the the Oxford Questionaire to establish emotional side-effects in patients after treatment with escitalopram, and agomelatine in the treatment of emotional blunting. The article states that emotional blunting was less frequent on agomelatine than on escitalopram. Indeed, 28% of patients on agomelatine versus 60% on escitalopram felt that their emotions lacked intensity, and 16% of patients on agomelatine versus 53% on escitalopram felt that things that they cared about before illness did not seem important any more (p=0.024). The mechanism by which vortioxetine is efficacious in adults with MDD who experience emotional blunting is not fully understood. However, it is expected that the effect of vortioxetine on emotional blunting in other patients suffering from CNS disease or conditions is likewise positively affected; such CNS disease or condition could, for example, be psychotic

disorders or mood disorders. Theoretical reasons for why compounds that are 5-HT1A agonists and/or 5-HT3 antagonists are expected to be useful in the treatment of cognitive deficits have been reported and clinical evidence proven by, *e.g.*, WO 2009/062517 (incorporated herein by reference in its entirety). T. Sumiyoshi in Am.J.Psych., 158, 1722-1725, 2001 (incorporated herein by reference in its entirety) reports a study wherein patients received typical anti-psychotics, such as haloperidol, sulpride, and pimozide, which all lack 5-HT1A activity in combination with placebo or tandospirone, which is a 5-HT1A agonist. Patients receiving tandospirone on top of the anti-psychotic showed an improvement in their cognitive performance, whereas patients receiving placebo did not. Similarly, atypical anti-psychotics, such as clozapine, which are also 5-HT1A agonists, enhance cognition in schizophrenic patients, whereas typical anti-psychotics, such as haloperidol, which have no 5-HT1A activity, do not (Y. Chung, Brain Res., (2004),1023, 54-63 (incorporated herein by reference in its entirety)). In a randomised double-blind crossover study in healthy male subjects, assessments of verbal and spatial memory and sustained attention demonstrated that the 5-HT3 antagonist alosetron attenuated scopolamine induced deficits in verbal and spatial memory (Preston, Recent Advances in the Treatment of Neurodegenerative Disorders and Cognitive Function, 1994, (eds.) Racagni and Langer, Basel Karger, p. 89-93 (incorporated herein by reference in its entirety). WO 2009/062517 (*supra*) at example 5 demonstrates that 1-[2-(2,4-dimethylphenyl¬sulfanyl)-phenyl]piperazine compounds give rise to an increase in extra-cellular levels of acetylcholine in the prefrontal cortex and the ventral hippocampus in rats, and example 6 demonstrates that they improved contextual memory in rats. However, no data has been reported on the effects of vortioxetine on emotional blunting.

SUMMARY OF THE INVENTION

The invention relates to 1-[2-(2,4-dimethylphenyl-sulfanyl)-phenyl]piperazine, the structure of which is



and pharmaceutically acceptable salts thereof, for use in the treatment, prevention, or reduction of emotional blunting.

Oral dosage forms, and in particular tablets, are often preferred by the patients and the medical practitioner due to the ease of administration and the consequent better compliance. For tablets, it is preferable that the active ingredients are crystalline. In some aspect, the invention relates to compounds that are crystalline.

WO 2007/144005 (incorporated herein by reference in its entirety) discloses several pharmaceutically acceptable salts and solvates of 1-[2-(2,4-dimethylphenyl-sulfanyl)-phenyl]piperazine. A preferred salt of 1-[2-(2,4-dimethylphenyl-sulfanyl)-phenyl]piperazine is the hydrobromide salt; 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine HBr. WO 2007/144005 (*supra*) further discloses X-ray powder diffraction ("XRPD") reflections of further salts used in the present invention. The table below summarizes the major XRPD reflections of some compounds used in the present invention.

Selected X-ray peak positions (Θ2°); all values ± 0.2°, preferably ± 0.1°.

Polymorph form of 1-[2-(2,4-dimethylphenyl¬sulfanyl) -phenyl]piperazine	**Peak**	**Peak**	**Peak**	**Peak**
Crystalline base	11.10	16.88	17.42	22.23
hydrobromide (α)	5.85	9.30	17.49	18.58
hydrobromide (β)	6.89	9.73	13.78	14.62
hydrobromide (γ)	11.82	16.01	17.22	18.84
hydrobromide (hydrate)	10.69	11.66	15.40	17.86

The crystalline compounds used herein may exist in more than one form, *i.e.*, they may exist in polymorphic forms. Polymorphic forms exist if a compound can crystallize in more than one form. The present invention is intended to encompass all such polymorphic forms, either as pure compounds or as mixtures thereof.

In some aspect, the present invention uses compounds in a purified form. The term "purified form" is intended to indicate that the compound is essentially free of other compounds or other forms of the same compound.

The mechanism of action of vortioxetine is thought to be related to its direct modulation of serotonergic receptor activity and inhibition of the serotonin (5-HT) transporter (SERT). Nonclinical data indicate that vortioxetine is a 5-HT3, 5-HT7, and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, and 5-HT1A receptor agonist and inhibitor of the SERT, leading to modulation of neurotransmission in several systems. This multimodal activity is considered to be responsible for the antidepressant and anxiolytic-like effects and the improvement of cognitive function, learning, and memory observed with vortioxetine in animal studies.

The present invention relates to prevention, treatment or reduction of signs and symptoms of emotional blunting in patients. Such patients may or may not be diagnosed with one or more CNS diseases or conditions and such patients may or may not have a history of signs and symptoms of emotional blunting resulting from an administration of a medicament. In some aspects of this invention, a CNS disease or disorder is selected from the group of psychiatric disorders, such as psychosis, schizophrenia, schizoaffective disorder, schizophreniform disorder, catatonia, delusional disorder; mood disorders, such as bipolar disorder, cyclothymic disorder, major depression disorder, dysthymia, premenstrual dysphoric disorder, and substance use disorders.

In some aspects of this invention, said one or more CNS diseases or conditions is selected from the group consisting of PTSD, depression, including MDD and major depressive episodes ("MDE"), cognitive impairment, schizophrenia, psychosis, Parkinson's disease, autism, vascular dementia, and multiple system atrophy and wherein said patients experience an inadequate response to said treatment, resulting in reporting or diagnosis or diagnosis of adverse events, symptoms or signs of emotional blunting as a result of such treatment.

The invention also relates to prevention or treatment of emotional blunting in patients receiving treatment for one or more CNS diseases or conditions, wherein said emotional blunting is a result of inadequate response to said treatment for one or more CNS diseases or conditions.

The invention also relates to prevention or treatment of emotional blunting in patients receiving medical treatment for one or more CNS diseases or conditions, wherein said emotional blunting is a result of said medical treatment for one or more CNS diseases or conditions.

The invention further relates to prevention, treatment, or reduction of signs and symptoms of emotional blunting in patients receiving treatment for one or more CNS diseases or conditions; PTSD, depression, including MDD and MDE, cognitive impairment, schizophrenia, psychosis, Parkinson's disease, autism, vascular dementia, and multiple system atrophy and wherein said patients experience an inadequate response to said treatment, resulting in reporting or diagnosis of adverse events, symptoms or signs of emotional blunting as a result of such treatment.

The invention further relates to prevention or treatment or reduction of signs and symptoms of emotional blunting in patients who were treated for one or more diseases or conditions; PTSD, depression, cognitive impairment, schizophrenia, psychosis,Parkinson's disease, autism, vascular dementia, and multiple system atrophy and wherein said patients experienced an inadequate response associated with said treatment for one or more diseases or conditions, resulting in reporting or diagnosis of adverse events, symptoms or signs of emotional blunting as a result of such treatment.

The invention further relates to prevention or treatment or reduction of signs and symptoms of emotional blunting in patients who were diagnosed and/or treated for one or more diseases or conditions; PTSD, depression, cognitive impairment, schizophrenia, psychosis, Parkinson's disease, autism, vascular dementia, and multiple system atrophy and wherein said patients experienced an inadequate response associated with said treatment for one or more diseases or conditions, resulting in reporting or diagnosis of adverse events, symptoms or signs of emotional blunting as a result of such treatment.

The invention further relates to prevention of signs and symptoms of emotional blunting in patients who were diagnosed and/or treated for one or more diseases or conditions; PTSD, depression, cognitive impairment, schizophrenia, psychosis, Parkinson's disease, autism, vascular dementia, and multiple system atrophy and wherein said patients experienced an inadequate response associated with said treatment for one or more diseases or conditions, resulting in reporting or diagnosis of adverse events, symptoms or signs of emotional blunting as a result of such treatment.

The invention further relates to treatment or reduction of signs and symptoms of emotional blunting in patients who were diagnosed and/or treated for one or more diseases or conditions; PTSD, depression, cognitive impairment, schizophrenia, psychosis, Parkinson's disease, autism, vascular dementia, and multiple system atrophy and wherein said patients experienced an inadequate response associated with said treatment for one or more diseases or conditions, resulting in reporting or diagnosis of adverse events, symptoms or signs of emotional blunting as a result of such treatment.

The invention further relates to prevention or treatment or reduction of signs and symptoms of emotional blunting in patients who were diagnosed but not treated for one or more diseases or conditions; PTSD, depression, cognitive impairment, schizophrenia, psychosis, Parkinson's disease, autism, vascular dementia, and multiple system atrophy and wherein said patients experienced an inadequate response associated with said treatment for one or more diseases or conditions, resulting in reporting or diagnosis of adverse events, symptoms or signs of emotional blunting as a result of such treatment.

The invention further relates to prevention of signs and symptoms of emotional blunting in patients who were diagnosed but not treated for one or more diseases or conditions; PTSD, depression, cognitive impairment, schizophrenia, psychosis, Parkinson's disease, autism, vascular dementia, and multiple system atrophy and wherein said patients experienced an inadequate response associated with said treatment for one or more diseases or conditions, resulting in reporting or diagnosis of adverse events, symptoms or signs of emotional blunting as a result of such treatment.

The invention further relates to treatment or reduction of signs and symptoms of emotional blunting in patients who were diagnosed but not treated for one or more diseases or conditions; PTSD, depression, cognitive impairment, schizophrenia, psychosis, Parkinson's

disease, autism, vascular dementia, and multiple system atrophy and wherein said patients experienced an inadequate response associated with said treatment for one or more diseases or conditions, resulting in reporting or diagnosis of adverse events, symptoms or signs of emotional blunting as a result of such treatment.

The invention further relates to prevention or treatment or reduction of signs and symptoms of emotional blunting in patients who are treated for a CNS disease selected from the group of psychiatric disorders, such as schizophrenia, psychosis, schizoaffective disorder, schizophreniform disorder, catatonia, delusional disorder; mood disorders, such as bipolar disorder, cyclothymic disorder, major depression, dysthymia, premenstrual dysphoric disorder, and substance use disorders.

The invention further relates to prevention or treatment or reduction of signs and symptoms of emotional blunting in patients who are treated for a CNS disease that is a psychiatric disorder, such as psychosis, schizophrenia, schizoaffective disorder, schizophreniform disorder, catatonia, and delusional disorder.

The invention further relates to prevention or treatment or reduction of signs and symptoms of emotional blunting in patients who are treated for a CNS disease that is a mood disorder, such as bipolar disorder, cyclothymic disorder, major depression, dysthymia, and premenstrual dysphoric disorder.

The invention further relates to prevention or treatment or reduction of signs and symptoms of emotional blunting in patients who are treated for a CNS disease which is a substance use disorder or associated with a substance use disorder.

BRIEF DESCRIPTION OF DRAWINGS

The application is described with reference to the following figures, which are presented for the purpose of illustration only and are not intended to be limiting. In the Drawings:

Figure 1 provides a schematic overview of the study described in Assay I-XI; results are disclosed in Examples 1-12.

Figure 2 shows an overview of the Oxford Depression Questionnaire ("ODQ") (© Oxford University Innovation Limited, 2011) total score (FAS, MMRM) from baseline, over week 1, 4, and the end of the study at week 8, and reflects the numbers as described in Table 3.

Figure 3 shows the base line scores of ODQ (© Oxford University Innovation Limited, 2011) total scores, showing that the scores are normally distributed.

Figure 4 is a graph visualizing the base line scores of MEI total scores, showing that the scores are normally distributed.

Figure 5 summarizes the clinical assessment of emotional blunting and partial correlation and mediation analyses; *** means $p < 0.0001$.

Figure 6 shows that improvements in motivation and energy assessed using the MEI were substantial and significant already from week 4 and across all subdomains: cognitive and mental energy, social motivation, and physical energy; *** means $p < 0.0001$.

Figure 7 depicts that the mediation analysis further shows that 63.4% of the change in SDS total score explained by change in ODQ (© Oxford University Innovation Limited, 2011) total score was a *direct effect* of improvement in ODQ (© Oxford University Innovation Limited, 2011) after switching to vortioxetine that could not be explained by improved depressive symptoms (MADRS), which accounted for 36.6% of the effect on SDS total score.

DETAILED DESCRIPTION OF THE INVENTION

The present inventors have found that 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine, exerting a combination of SERT inhibition, 5-HT3 antagonism, and 5-HT1A agonism, is useful in the prevention of treatment of emotional blunting in patients with CNS disorders and/or in patients receiving medicament for the treatment of one or more CNS disorders.

Accordingly, the invention provides a method for the prevention or treatment of or reducing emotional blunting related to one or more CNS diseases or conditions, the method comprising the administration of a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]-piperazine or a pharmaceutically acceptable salt thereof to a patient in need thereof.

In some aspects, the invention provides a method for the prevention or treatment of or reducing emotional blunting related to one or more CNS diseases or conditions, the method comprising the administration of a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]-piperazine or a pharmaceutically acceptable salt thereof to a patient in need thereof, wherein said administration of a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]-piperazine or a pharmaceutically acceptable salt thereof is either provided as a monotherapy or concomitant with other medicaments for the prevention or treatment of one or more CNS diseases or disorders.

The present invention further relates to a method of preventing or treating emotional blunting or signs and symptoms thereof in a patient, the method comprising administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

The present invention further relates to a method of preventing or treating emotional blunting in a patient wherein said patient experiences emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting resulting from an inadequate response to a medicament, the method comprising administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

The present invention also relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in preventing or treating emotional blunting in a patient. It further relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in preventing or treating emotional blunting in a patient wherein said patient experiences emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting resulting from an administration of a medicament, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

The emotional blunting as seen in patients, which are proposed to receive 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof,

administered either as monotherapy or concomitant with other medicaments for the treatment of one or more CNS diseases or disorders, may be seen in connection with administration of an adequate dose of a medicament for the treatment of one or more CNS diseases or disorders, wherein said adequate dose of said medicament is a dose as described in said medicament's label. In some situations, said medicament for treatment of one or more CNS disease or disorders is an antidepressant, anti-psychotic, or a medicament for the treatment of psychosis or schizophrenia. In some aspects of this invention, monotherapy of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof necessitates that a previously administered antidepressant, such as SSRIs or SNRIs, are discontinued before said monotherapy is begun.

Thus, in some aspects of this invention, monotherapy of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine is a replacement of a previous monotherapy of an antidepressant enhancing the serotonergic transmission. In some aspects of this invention, monotherapy of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine is the first therapeutic measure for the treatment of a CNS disease or disorder.

In some aspects of this invention, concomitant administration of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine is with another medicament for the treatment of one or more CNS disease or disorder is an administration of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine at the same time (or alongside) the administration of another medicament. Such an "another medicament" can be a medicament reducing the dopaminergic transmission or any other medicament used in the treatment of CNS disease or disorder. In some aspects, such an "another medicament" can be an antipsychotic.

SSRIs have been associated with 5-HT-mediated cognitive and emotional blunting and weaker effects on anhedonia than drugs that also enhance NE and DA release (Dale E, Bang-Andersen B, Sánchez C. Emerging mechanisms and treatments for depression beyond SSRIs and SNRIs. Biochem Pharmacol. 2015; 95(2): 81-97; Gardier AM, Lepoul E, Trouvin JH, Chanut E, Dessalles MC, Jacquot C. Changes in dopamine metabolism in rat forebrain regions after cessation of long-term fluoxetine treatment: relationship with brain concentrations of fluoxetine and norfluoxetine. Life Sci. 1994; 54: l51-l56; Lane RM. Restoration of positive mood states in major depression as a potential drug development target. J.

Psychopharmacol. 2014; 28(6): 527-535 (each of which is incorporated herein by reference in their entireties)). It is known that long-term use of SSRIs decreases NE transmission (Szabo ST, de Montigny C, Blier P. Progressive attenuation of the firing activity of locus coeruleus noradrenergic neurons by sustained administration of selective serotonin reuptake inhibitors. Int J Neuropsychopharmacol. 2000; 3(1): 1-11; Kawahara Y, Kawahara H, Kaneko F, Tanaka M. Long-term administration of citalopram reduces basal and stress-induced extracellular noradrenaline levels in rat brain. Psychopharmacology (Berl). 2007; 194: 73-81 ((each of which is incorporated herein by reference in their entireties)).

In animal studies, vortioxetine increased extracellular levels of 5-HT, DA, and NE in both the medial prefrontal cortex and the ventral hippocampus (Mørk A, Pehrson A, Brennum LT, Nielsen SM, Zhong H, Lassen AB, et al. Pharmacological effects of Lu AA21004: a novel multimodal compound for the treatment of Major Depressive Disorder. J Pharmacol Exp Ther. 2012; 340(3): 666-675; Bang-Andersen B, Ruhland T, Jørgensen M, Smith G, Frederiksen K, Jensen KG, et al. Discovery of 1-[2-(2,4-dimethylphenylsulfanyl) phenyl] - piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. J. Med. Chem. 2011; 54: 3206-3221 (each of which is incorporated herein by reference in their entireties)). Vortioxetine shows low potency in functional assays of NE and DA transporter inhibition. However, the effect on the NE and DA levels is probably exerted indirectly through receptor modulation. For instance, many interneurons in the brain are regulated by 5-HT3 receptors and when blocked can lead to increases in 5-HT, DA, NE, acetylcholine, and histamine (D'Agostino A, English CD, Rey JA. Vortioxetine (Brintellix): a new serotonergic antidepressant. P T. 2015; 40(1): 36–40 (incorporated herein by reference in its entirety)).

Vortioxetine is a multi-modal antidepressant sharing some common features with SSRIs and SNRIs. However, since vortioxetine is a multi-modal antidepressant which has also shown a different pattern of effects and side effects than SSRI and SNRIs, a clinical trial under the name study name COMPLETE, study number 17797A (EudraCT No. 2017-004829-33 (*supra*)) sponsored by H. Lundbeck A/S was set up to assess the effect of vortioxetine on emotional blunting. In clinicaltrial.gov study No. NCT 03835715 (*supra*), the Brief Summary summarizes the study's aim as: "The study will evaluate effectiveness of flexible dose vortioxetine on Emotional Functioning in patients with Major Depressive Disorder with an

inadequate response to SSRI/SNRI". The EudraCT trial register cites the same purpose in the Full Title of the Trial.

The results of this study were used to evaluate the effectiveness of vortioxetine 10-20 mg/day for preventing and/or treating emotional blunting in patients with MDD who are known to experience inadequate response to an SSRI/SNRI for a current depressive episode, and who have a desire to switch to an alternative antidepressant, wherein such inadequate response is determined in the form of reporting or diagnosis, and may include all symptoms of depression, including symptoms or signs of emotional blunting.

It has surprisingly been found that the emotional blunting can be significantly improved, *i.e.*, reduced or removed completely, in patients who previously reported such effects as evaluated, for example, by replying to investigator's questions in line with the ODQ (© Oxford University Innovation Limited, 2011).

A fast onset of this reduction or removal of emotional blunting was seen within the 1st week of treatment with vortioxetine (10 mg) and was more pronounced after 8 weeks of treatment. About 50% of patients were relieved of their perception of emotional blunting. A significant effect (nominal $p < 0.05$) was seen across all efficacy measures and study endpoints (primary and secondary) at all assessed time points on emotional blunting assessed by ODQ (© Oxford University Innovation Limited, 2011), functioning assessed by SDS, cognitive performance assessed by Digit Symbol Substitution test ("DSST"), motivation and energy assessed by Motivation and Energy Inventory ("MEI") test, and depressive symptoms assessed by MADRS. A correlation between relief of emotional blunting and improvement of overall functioning (work, family, social) and motivation and energy (mental, social, and physical) was seen. Further, the depressive symptom resolution was seen in about 47%. Safety and tolerability were reported in line with the established profile of vortioxetine.

In broad assessments of schizophrenic symptomatology, negative symptoms have repeatedly emerged as a separate factor, independent of positive symptoms, disorganization, and affective symptoms, including depression and anxiety. Additional research focusing on the latent structure of negative symptoms themselves suggests that this symptom domain is not unidimensional. The most reliable factors to emerge within negative symptoms include diminished expression (typically involving symptoms of reduced facial and vocal expressivity

and reduced verbal output) and a factor tapping anhedonia and asociality (composed of symptoms of anhedonia, diminished interest, and decreased social engagement) (Blanchard JJ, Cohen AS. The structure of negative symptoms within schizophrenia: implications for assessment. Schizophr Bull. 2006;32: 238–245 (incorporated herein by reference in its entirety)). All the widely used negative symptom rating and categorization instruments include blunted or restricted affect, *e.g.*, the Scale for the Assessment of Negative Symptoms ("SANS"), the Clinical Assessment Interview for Negative Symptoms ("CAINS"), and the Brief Negative Symptom Scale ("BNSS"). Blunted affect can be considered to have 3 components: (1) decrease in facial expression; (2) decrease in expressive gestures and other body language; and (3) decrease in modulation of the volume, pitch, and speed of speaking. Blunted affect should be distinguished from flat affect, which refers to the extreme end of the spectrum of blunting.

Blunted affect can be found in several disorders other than schizophrenia, including, *e.g.*, Parkinson's disease, depression, autism, vascular dementia, and multiple system atrophy. In the context of schizophrenia, antipsychotic medications complicate the assessment of blunted affect, as they can induce this symptom (Constantino JN, Gruber CP, Davis S, Hayes S, Passanante N, Przybeck T. The factor structure of autistic traits. J. Child Psychol. Psychiatry. 2004; 45:719–726; Fetoni V, Soliveri P, Monza D, Testa D, Girotti F. Affective symptoms in multiple system atrophy and Parkinson's disease: response to levodopa therapy. J. Neurol. Neurosurg. Psychiatry. 1999; 66:541–544; Tremeau F, Malaspina D, Duval F, et al. Facial expressiveness in patients with schizophrenia compared to depressed patients and nonpatient comparison subjects. Am. J. Psychiatry. 2005; 162:92–101; Jouvent R, Le Houezec J, Payan C, et al. Dimensional assessment of onset of action of antidepressants: a comparative study of moclobemide vs. clomipramine in depressed patients with blunted affect and psychomotor retardation. Psychiatry Res. 1998;79(3):267–275; Robertson JM, Tanguay PE, L'ecuyer S, Sims A, Waltrip C. Domains of social communication handicap in autism spectrum disorder. J. Am. Acad. Child Adolesc. Psychiatry. 1999; 38:738–745; Sultzer DL, Levin HS, Mahler ME, High WM, Cummings JL. A comparison of psychiatric symptoms in vascular dementia and Alzheimer's disease. Am. J. Psychiatry. 1993; 150:1806–1812 (each of which are incorporated herein by reference in their entireties)).

The prevention, treatment or reduction of signs and symptoms of emotional blunting according to the present invention may involve daily administration of the compounds of the present invention. This may involve once daily administration, administration twice a day, or even more frequently.

In some aspects, a 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine compound as used in this invention is the hydrobromic acid salt.

In some aspects, a 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine compound as used in this invention is the hydrobromic acid salt, *e.g.*, in the beta form.

In some aspects, a 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine compound as used in this invention is the hydrobromic acid salt, and suitable tablets may be composed of the following ingredients:

Ingredient	**Amount (w/w-%)**
HBr salt of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine	About 3-8%
Anhydrous calcium hydrogen phosphate	About 35-45%
Corn starch	About 15-25%
Copovidone	About 2-6%
Microcrystalline cellulose	About 20-30%
Sodium starch glycolate	About 1-3%
Talc	About 2-6%
Magnesium stearate	About 0.5-2%

In particular, the tablets may be composed of the following ingredients:

Ingredient	**Amount (w/w-%)**
HBr salt of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine	About 5%
Anhydrous calcium hydrogen phosphate	About 39%
Corn starch	About 20%
Copovidone	About 3%
Microcrystalline cellulose	About 25%
Sodium starch glycolate	About 3%
Talc	About 4%
Magnesium stearate	About 1%

Tablets with different amounts of active compound, such as corresponding to, *e.g.*, 2.5, 5, 10, 20, 25, 30, 40, 50, 60, or 80 mg of the free base, may be obtained by choosing the

right amount of the 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine compound in combination with a tablet of an appropriate size. Preferred concentrations of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine HBr salt are about 5 mg, about 10 mg, or about 20 mg per tablet. Preferred concentrations of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine HBr salt are about 5 mg per tablet. Preferred concentrations of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine HBr salt are about 10 mg per tablet. Preferred concentrations of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine HBr salt are about 20 mg per tablet. Preferred administration frequency for tablets ether comprising about 5 mg, about 10 mg, or about 20 mg 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or any pharmaceutically acceptable salt thereof is once daily. Patients starting in about 5 mg daily may increase the concentration to about 10 mg per day or about 20 mg per day. Patients starting in about 10 mg daily may increase the concentration to about 20 mg per day or reduce the concentration to about 10 mg per day. Therapeutically effective amounts of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof may for example be about 5 mg, about 10mg, or about 20mg 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine per day.

In some aspects, the invention relates to a method of preventing or treating emotional blunting or signs and symptoms thereof in a patient, the method comprising administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some aspects, the invention relates to a method of preventing or treating emotional blunting or signs and symptoms thereof in a patient, wherein said patient experiences signs and symptoms of emotional blunting, the method comprising administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some aspects said method of preventing or treating emotional blunting or signs and symptoms thereof in a patient, is a method wherein said patient experiences signs and symptoms of emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some aspects, said method of preventing or treating emotional blunting or signs and symptoms thereof in a patient, is a method wherein said patient experiences emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting in connection with the administration of a medicament, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some aspects, said method of preventing or treating emotional blunting or signs and symptoms thereof in a patient, is a method wherein said patient experiences emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting resulting from an administration of a medicament, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some aspects, said method of preventing or treating emotional blunting or signs and symptoms thereof in a patient, is a method wherein said patient experiences emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting resulting from an administration of a medicament at an adequate dose, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some aspects, said method of preventing or treating emotional blunting or signs and symptoms thereof in a patient, is a method wherein said patient experiences emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting resulting from an inadequate response to a medical treatment, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some aspects, said method of preventing or treating emotional blunting or signs and symptoms thereof in a patient, is a method wherein said patient experiences emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting resulting from an inadequate response to a medical treatment of a CNS disease or disorder, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some aspects said method of preventing or treating emotional blunting or signs and symptoms thereof in a patient, wherein said patient has a history of showing signs and symptoms of emotional blunting in connection with a CNS disease or disorder or a medical treatment of one or more CNS disease or disorder, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof the method comprising the steps of:

i) evaluation of said patient by a practicing clinician or physician, wherein said evaluation includes

1) an evaluation of said patient's history of signs and symptoms of emotional blunting;
2) an evaluation of current signs or symptoms of emotional blunting; and/or
3) an evaluation of the risk of said patient developing or worsening of signs and/or symptoms of emotional blunting.

In some aspects, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in preventing or treating emotional blunting or signs and symptoms thereof in a patient.

In some aspects, the invention relates to said use for preventing or treating emotional blunting or signs and symptoms thereof in a patient, wherein said patient experiences signs and symptoms of emotional blunting.

In some aspects, the invention relates to said use for preventing or treating emotional blunting or signs and symptoms thereof in a patient, wherein said patient experiences signs and symptoms of emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some aspects, the invention relates to said use for preventing or treating emotional blunting or signs and symptoms thereof in a patient, wherein said patient experiences emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting in connection with the administration of a medicament, wherein said medicament

resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some aspects, the invention relates to said use for preventing or treating emotional blunting in a patient wherein said patient experiences emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting resulting from an administration of a medicament, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some aspects, the invention relates to said use for preventing or treating emotional blunting in a patient wherein said patient experiences emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting resulting from an administration of a medicament or treating one or more CNS disease or disorder, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some aspects, the invention relates to said use for preventing or treating emotional blunting in a patient wherein said patient has experienced emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting resulting from an administration of a medicament at an adequate dose, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some aspects, the invention relates to said use for preventing or treating emotional blunting in a patient wherein said patient has a history of showing signs and symptoms of emotional blunting in connection with a CNS disease or disorder or a medical treatment of one or more CNS disease or disorder, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof, the method comprising the steps of:

i) evaluation of said patient by a practicing clinician or of physician, wherein said evaluation includes

1) an evaluation of said patient's history of signs and symptoms of emotional blunting;
2) an evaluation of current signs or symptoms of emotional blunting; and
3) an evaluation of the risk of said patient developing or worsening of signs and/or symptoms of emotional blunting.

In some aspects, an adequate dose of said medicament is a dose as described in said medicament's label. In some aspects, a method or 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in preventing or treating emotional blunting according to this invention refers to a medicament for the treatment of one or more CNS disease or disorder an adequate dose thereof, wherein adequate dose of said medicament, which is not-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof, is a dose described in said medicament's label and selected from any one of doses described for efficient treatment in the label of said medicament.

In some aspects, wherein said emotional blunting is seen in connection with or as a result of an administration of a medicament, a method or for preventing or treating emotional blunting or signs and symptoms thereof as described herein comprises the steps of:

1) discontinuation of said medicament; and
2) administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some aspects, wherein said emotional blunting is seen in connection with or as a result of an administration of a medicament, a method or for preventing or treating emotional blunting or signs and symptoms thereof as described herein comprises the steps of:

1) maintaining the administration of said medicament; and
2) administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some aspects, wherein said emotional blunting is seen in connection with or as a result of an administration of a medicament a method or for preventing or treating emotional blunting or signs and symptoms thereof as described herein comprises the steps of:

a. discontinuation of said medicament for the treatment of a CNS disease or disorder; and
b. administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some aspects, wherein said emotional blunting is seen in connection with or as a result of an administration of a medicament a method or for preventing or treating emotional blunting or signs and symptoms thereof as described herein comprises the steps of:

a. maintaining administration of said medicament for the treatment of a CNS disease or disorder; and
b. administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some aspects, the method or 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in prevention or treatment of emotional blunting, is for preventing emotional blunting in a patient.

In some aspects, the method or 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in prevention or treatment of emotional blunting, is for treating emotional blunting in a patient. In some aspects, said emotional blunting is associated with a CNS disease or disorder. In some aspects, said emotional blunting is associated with an underlying CNS disease or disorder.

In some aspects, wherein said emotional blunting is seen in connection with or as a result of an administration of a medicament, said medicament is for treatment of one or more CNS diseases or disorder, or signs and symptoms thereof. In some aspects, said emotional blunting is reported by said patient. In some aspects, said emotional blunting is diagnosed by a practicing clinician or physician. In some aspects, said emotional blunting is reported by said patient, as being caused by of an inadequate response of a medical treatment of a CNS disease or disorder.

In some aspects, said emotional blunting is diagnosed by a practicing clinician or physician by evaluating the patient, wherein said evaluation comprises the steps of:

a) explaining to said patient that: "*Emotional effects vary, but may include, for example, feeling emotionally "numbed" or "blunted" in some way; lacking positive emotions or negative emotions; feeling detached from the world around you; or "just not caring" about things that you used to care about*";

b) asking the question: *"Have you experienced such emotional effects during the last 6 weeks?"*;

c) evaluating the response to question b) and concluding if symptoms or signs of emotional blunting is present in said patient; and, optionally,

d) if the evaluation of step c) is that said patient experiences emotional blunting, said practicing clinician or physician decides to apply the method or use for treating emotional blunting as described in aspects and embodiments herein.

In some aspects, step c) of said practicing clinician or physician's evaluation leads to the conclusion of the presence of emotional blunting, if said patient's answer to the question asked in step b) is "yes."

In some aspects, said emotional blunting is diagnosed by a practicing clinician or physician by evaluating the patient, wherein said evaluation comprises the steps of:

a) explaining to said patient that: "*Emotional effects vary, but may include, for example, feeling emotionally "numbed" or "blunted" in some way; lacking positive emotions or negative emotions; feeling detached from the world around you; or "just not caring" about things that you used to care about*";

b) asking the question: *"Have you experienced such emotional effects during the last 6 weeks?"*;

c) evaluating the response to question b) and, if question b) was answered with a "yes," concluding that symptoms or signs of emotional blunting is present in said patient. In some aspects, said step a)-c) of said practicing clinician or physician's evaluation may be supplemented or replaced by an evaluation according to or equivalent to the ODQ total score, wherein said ODQ total score is calculated based on the ODQ guidelines; and, optionally,

d) if the evaluation of step c) is that said patient experiences emotional blunting, said practicing clinician or physician decides to apply the method or use for treating emotional blunting as described in aspects and embodiments herein.

The ODQ was developed to specifically evaluate symptoms of emotional blunting in patients with MDD (Price et al., 2012 (*supra*)). Results of this analysis of data from the COMPLETE study demonstrate that the ODQ (© Oxford University Innovation Limited, 2011), both the part of the questionnaire that covers the two first sections and the full questionnaire with all 3 sections, captures aspects and symptoms of MDD that are not adequately covered by other scales commonly used to assess depression severity.

Low correlation was observed between ODQ scores (© Oxford University Innovation Limited, 2011) and MADRS total score at baseline, with low correlations also observed between ODQ scores and the MADRS items that specifically assess symptoms of anhedonia, namely, "inability to feel" and "lassitude."

Highest correlation was seen between ODQ scores (© Oxford University Innovation Limited, 2011) and MEI total score at baseline, showing some overlap with this motivational measure. Without being bound by this theory, this may be due to the fact that patients with emotional blunting likely under-report symptoms of depression and disability, given that they are detached from, and numbed to, most emotions and feelings (including emotional blunting itself). Improvement was seen across all the different scales in response to therapy. Significant correlation was seen between mean changes in ODQ scores (© Oxford University Innovation Limited, 2011) and other assessment scores after 8 weeks of vortioxetine treatment, suggesting that the ODQ is sensitive to changes in the clinical state.

It has the advantage of being able to assess the full spectrum of symptoms of emotional blunting from the patient's perspective, *i.e.*, absence of both positive and negative emotions. For example, patients may report: "All my emotions, both 'pleasant' and 'unpleasant', are toned down," or "I don't fully enjoy things that should give me pleasure, such as beautiful places or things or music," or "Unpleasant emotions, such as sadness, disappointment, and upset, feel toned down or different in some way." With regard to the impact of emotional blunting, patients may report that "Day to day life just doesn't have the same emotional impact on me that it did before my illness/problem."

Definitions

The term "vortioxetine" as used herein can be used interchangeably with the term "1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine" or "Lu AA21004," it is known as the active ingredient in Brintellix® or Trintellix®. Thus, the phrase "1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof" as used herein discloses all pharmaceutically acceptable salts of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine and the phrase "1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof" specifically includes "vortioxetine," "1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine HBr," or "Lu AA21004".

The term "emotional blunting" as used herein can be used interchangeably with the term "emotional numbness" and refers to a person's subjective experience of the inability to feel emotions, and is accompanied by a lack of care and concern for self and others. In a similar fashion, the terms "numbness" or "numbing" or other versions of the word and "blunting" or "blunted" and other versions of the word can be used interchangeably. "Emotional numbness" or "emotional blunting" as used herein is distinguished from depression. In some aspects, the emotional blunting is a direct result of the medical treatment of CNS diseases or conditions, such as, *e.g.*, antidepressants or anti-psychotics. In some aspects, the emotional blunting is a direct result of the medical treatment of CNS diseases or conditions, such as, *e.g.*, antidepressants. In some aspects, the emotional blunting is a direct result of the medical treatment of CNS diseases or conditions, such as SSRI or SNRIs. In some aspects, the emotional blunting described herein may be an underlying symptom of a CNS disease or condition. In some aspects, the emotional blunting described herein may be an underlying symptom of a CNS disease or condition revealed by the treatment with medicaments for related or unrelated CNS diseases or conditions, such as, *e.g.*, antidepressant or anti-psychotics. The term "underlying" in this context means that once the antidepressants alleviate depression, the underlying symptoms of emotional blunting may be revealed rather than caused.

Emotional blunting thus denotes herein an absence of feelings (including those of depression and sadness). In contrast to a depressed person, a numbed or blunted individual lacks feeling of regard, concern, caring or empathy for himself/herself and others. Common

terms which traumatized persons use to describe this numb state of mind include shutdown, numb, ice cold, hollow, dead, and empty and no feelings, care, or concern for anyone or anything. Family members commonly regard relations who are numb as being cold, heartless, and emotionally unresponsive. A profoundly numb individual may have a wooden facial expression rather than one that is depressed. Very occasionally, the emotionally numbed individual may appear to be angry or sad to others yet respond with bewilderment or denial when questioned about his/her look of anger or sadness.

The term "CNS disease or condition" can be used interchangeably with the term "CNS disease or disorder" and is meant to describe CNS disease, which is a broad category of conditions in which the brain does not function as it should, limiting health and the ability to function. The condition may be an inherited metabolic disorder; the result of damage from an infection, a degenerative condition, stroke, a brain tumor, or other problem; or arise from unknown or multiple factors. Movement disorders such as Parkinson's disease, dystonia, and essential tremor are CNS conditions. What they have in common is the loss of sufficient, intact nervous system circuits that orchestrate functions as varied as memory formation (in Alzheimer's disease) or voluntary motion (in movement disorders). While most conditions in this group cannot be completely cured, symptoms of central nervous system diseases can often be managed through a range of therapies, from medical to surgical treatment. Emerging therapies are also being explored. For instance, physicians studying chemotherapy for brain tumors, or the potential of gene therapy for Parkinson's disease, are interested in brain and cerebrospinal infusion therapies to deliver anti-cancer agents or supplemental genes to brain areas where their activity might help to control or limit impact of the disease. The term "CNS disease or condition" or "CNS disease or disorder" is meant to include disorders or conditions such as psychiatric disorders, such as schizophrenia, schizoaffective disorder, schizophreniform disorder, catatonia, delusional disorder; mood disorders, such as bipolar disorder, cyclothymic disorder, major depression, dysthymia, premenstrual dysphoric disorder; and substance use disorders.

The term "CNS diseases or conditions" as used herein may be used interchangeably with the term "CNS diseases or disorders" and include psychiatric and neurological disorders. In some aspects, "CNS diseases or conditions" include psychiatric and neurological disorders, such as depression, *e.g.*, MDD or MDE, PTSD, schizophrenia, Parkinson's disease, autism,

vascular dementia, and multiple system atrophy. In some embodiments, CNS diseases or conditions comprise any one or more of the following: MDD or MDE, PTSD, schizophrenia, Parkinson's disease, autism, vascular dementia, and multiple system atrophy.

Psychosis is part of schizophrenia, and it can be part of other disorders as well. Psychosis is a concept that describes specific symptoms. Schizophrenia is a mental illness that has psychotic features. Psychotic symptoms include hallucination, delusion, confusion, inability to think clearly, rapid and/or racing thoughts, confused speech, disorganized behavior, and catatonic behavior, however not all of these symptoms need be present. In schizophrenia, psychosis is the first criteria that must be met for a diagnosis of schizophrenia. Without psychosis, there is no schizophrenia, however psychosis can present alone, without schizophrenia. Other disorders which may involve "psychosis" can be other psychotic disorders (schizophrenia, schizoaffective disorder, schizophreniform disorder, catatonia, delusional disorder), mood disorders (bipolar disorder, cyclothymic disorder, major depression, dysthymia, premenstrual dysphoric disorder), and substance use disorders.

Patients suffering from schizophrenia experience, *e.g.*, psychosis, negative symptoms, and have a reduced level of functioning in everyday life. "Emotional blunting" may also include, co-exist, or be part of negative symptoms associated with schizophrenia (also known as schizoaffective disorder) or symptoms found in non-schizophrenic patients suffering from other CNS diseases or disorders and may be closely associated with "negative symptoms". "Negative symptoms" may include apathy, alogia, amotivation, anhedonia, asociality, emotional withdrawal, and social withdrawal. Patients with schizophrenia are sometimes prescribed antidepressants or mood stabilizers to manage mood symptoms.

Thus, the term "antipsychotics" or "antipsychotic drugs" or "neuroleptics" as used herein may be used interchangeably and may be included in the term "medicament for the treatment of schizophrenia" or "medical treatment of schizophrenia" or similar phrases used herein, because schizophrenic patients often are treated for the psychosis with such drugs.

The term "medicament for the treatment of schizophrenia" or "medical treatment of schizophrenia" or similar phrases used herein may thus include "atypical antipsychotics" and/or "typical antipsychotics."

In the present invention, "atypical antipsychotics" may, for example, be selected from the group comprising aripiprazole, iloperidone, ziprasidone, lurasidone, risperidone, brexpriprazole, asenapine, quetiapine, cariprazine, and olanzapine. Clozapine is a special atypical antipsychotic, which is usually only prescribed when other antiphycotics fail to relief symptoms, or when the schizophrenic patient suffers from suicidal thoughts.

In the present invention, "typical antipsychotics" may for example be selected from the group comprising haloperidol, loxapine, thiothixene, fluphenazine, chlorpromazine, perphenazine, and trifluoperazine.

Other ways of classifying based on the chemical structure of antipsychotics exist. According to the ATC/DDD index of the World Health Organization ("WHO"), antipsychotics are grouped in the class N05A, wherein the subdivision is performed mainly based on chemical structure; sub class A is phenothiazines with aliphatic side-chain, including N05AA01 chlorpromazine, N05AA02 levomepromazine, N05AA03 promazine, N05AA04 acepromazine, N05AA05 triflupromazine, N05AA06 cyamemazine, and N05AA07 chlorproethazine; sub class B is phenothiazines with piperazine structure, including N05AB01 dixyrazine, N05AB02 fluphenazine, N05AB03 perphenazine, N05AB04 prochlorperazine, N05AB05 thiopropazate, N05AB06 trifluoperazine, N05AB07 acetophenazine, N05AB08 thioproperazine, N05AB09 butaperazine, and N05AB10 perazine; sub class C is phenothiazines with piperidine structure, including N05AC01 periciazine, N05AC02 thioridazine, N05AC03 mesoridazine, and N05AC04 pipotiazine; sub class D is butyrophenone derivatives, including N05AD01 haloperidol N05AD02 trifluperidol, N05AD03 melperone, N05AD04 moperone, N05AD0 pipamperone, N05AD06 bromperidol, N05AD07 benperidol, N05AD08 droperidol, and N05AD09 fluanisone; sub class E is indole derivatives, including N05AE01 oxypertine, N05AE02 molindone, N05AE03 sertindole, N05AE04 ziprasidone, and N05AE05 lurasidone; sub class F is thioxanthene derivatives, including N05AF01 flupentixol, N05AF02 clopenthixol, N05AF03 chlorprothixene, N05AF04 tiotixene, and N05AF05

zuclopenthixol; sub class G is diphenylbutylpiperidine derivatives, including N05AG01 fluspirilene, N05AG02 pimozide, and N05AG03 penfluridol; sub class H is diazepines, oxazepines, thiazepines and oxepines, including N05AH01 loxapine, N05AH02 clozapine, N05AH03 olanzapine, N05AH04 quetiapine, N05AH05 asenapine, and N05AH06 clotiapine; sub class L is benzamides, including N05AL01 sulpiride, N05AL02 sultopride, N05AL03 tiapride, N05AL04 remoxipride, N05AL05amisulpride, N05AL06 veralipride, and N05AL07 levosulpiride; and sub class N is lithium, including N05AN01 lithium.

According to the ATC/DDD index of the WHO other antiphycotics are grouped in the class N05AX, which included the code N05AX07 for prothipendyl, N05AX08 for risperidone, N05AX10, mosapramine, N05AX11 zotepine, N05AX12 aripripazole, N05AX13 paliperidone, N05AX14 iloperioden, N05AX15 ccariprazine, N05AX16 brexpriprazole, and N05AX17 pimavanserin.

In some embodiments, “emotional blunting” is seen in patients with signs and/or symptoms of one or more CNS diseases or conditions, in patients diagnosed with one or more CNS diseases and/or in patients who receive medical treatment for one or more CNS diseases or condition.

In some aspects, when blunting is profound, the patient may experience no feeling and the person may take on an expressionless and lifeless appearance. In some aspects, individuals with numbed emotions are generally unresponsive to the environment and they are socially withdrawn. Unresponsiveness to the environment may be a composite disturbance representing a diminished level of mental alertness and awareness and a loss of interest in the outside world. Individuals with blunted emotions may not experience an empathic bond or a sense of relatedness to others. In social situations they tend to feel alienated and apart. In some aspects, emotional blunting is associated with numbness and/or paresthesia of the body and feelings of heaviness or paralysis. In some aspects, severe emotional blunting may be accompanied by a profound impairment of concentration and memory with an amnesia for events occurring during the numb state. In some aspects, information processing of any kind may be severely impaired. When emotional blunting is severe and prolonged, it is usually accompanied by a lack of motivation, interest, or pleasure in life activities. In some aspects, blunted individuals may thus be emotionally, mentally, psychologically, and socially impaired.

Emotional numbing is generally appreciated as a subjective complaint. In some aspects, emotional numbness or blunting can vary along three parameters: duration, severity, and social context. In some aspects, such numbness or blunting can be experienced for minutes, hours, days, months, or years on a continuous or intermittent basis. In some aspects, a person who has severe or profound emotional numbing or blunting does not have any feelings at all. In some aspects, with less severe numbing or blunting, emotions associated with high levels of physiological arousal may be experienced, *e.g.*, rage, fear, and vulnerability. In some aspects, tender affectionate feelings are not felt. For periods of time, some individuals with severely blunted emotions, may be able to experience love and concern towards a specific individual(s). This may be a child, trusted spouse, or fellow survivor of a traumatic episode.

In some aspects, emotional numbing may be accompanied by a physical experience of heaviness or paralysis of the body, pins and needles, tingling or numbness of parts of the body, feelings of unreality, alienation, and detachment from others. In some aspects, cognitive disturbances can include mental confusion, amnesia, impaired concentration, indecisiveness, inability to plan future actions, and a paralysis of will. In some aspects cognitive disturbances may occur independent of the level of physiological arousal or distress; forgetfulness, disorientation, or confusion can occur without any apparent preceding increase in stress or anxiety.

In some aspects, patients are not able to make the distinction between the mental states of numbness and depression. In some aspects, impaired cognitions, including an absence of self-awareness, may interfere with an individual's ability to distinguish between numbness and depression. In some aspects, individuals may frequently shift between states of depression and numbness or blunting, which makes it difficult for them to distinguish their subjective experiences. In some aspects, numbness and depression also share certain symptoms, including impaired concentration and memory and lack of interest and pleasure in life activities.

In some aspects, the mental state of emotional numbness or blunting is a disabling condition for the patient and his or her family members. In some aspects, numbness or blunting interferes with a person's ability to enjoy and participate in life activities (work, intimacy, sex, etc.) and with the individual's ability to respond with genuine affection,

interest or concern about anybody or anything, which can oftentimes lead to marital and family discord.

In some aspects, individuals with emotional numbing may seek out sensation and risk-taking activities, such as skydiving, racing cars, gambling, drug abuse, self-inflicted pain, etc., in an effort to escape the deadening effect of numbness. In some aspects, these activities can assume a compelling addictive drive accompanied by intense feelings of craving.

In some aspects, the presence of emotional numbing or blunting can be evaluated clinically with, *e.g.*, the tests and assessment methods described herein.

In one aspect, a neuropsychological test for evaluating cognitive functioning may be the Digit-Symbol Substitution Test ("DSST").

In some aspects, the presence of emotional blunting can be evaluated clinically as part of the psychiatric diagnosis of PTSD.

In some aspects patient-reported signs and/or symptoms of emotional blunting may be collected at least an answer from said patient to the question: *Have you experienced such emotional effects during the last 6 weeks?".*

In some aspects, patient-reported signs and/or symptoms of emotional blunting may be collected at least an answer from said patient to the question: *"Have you experienced such emotional effects during the last 6 weeks?",* wherein said patient has been informed about the general emotional effects of emotional blunting.

In some aspects, patient-reported signs and/or symptoms of emotional blunting may be collected at least an answer from said patient to the question: *"Have you experienced such emotional effects during the last 6 weeks?",* wherein said patient has been informed about the general emotional effects of emotional blunting, wherein said general emotional effects may be described as: *"Emotional effects vary, but may include, for example, feeling emotionally "numbed" or "blunted" in some way; lacking positive emotions or negative emotions; feeling detached from the world around you; or "just not caring" about things that you used to care about.*

The term "Oxford Depression Questionnaire (ODQ)" or "ODQ" as used herein refers to the Oxford Depression Questionnaire ("ODQ"). ODQ is a patient-centred, self-report

measure of emotional symptoms present in patients treated with antidepressants, which was formerly called the Oxford Questionnaire on the Emotional Side-Effects of Antidepressants ("OQuESA" or "OQESA"). (Jonathan Price et al. "The Oxford Quastionaire on Emotional Side-Effects on Atidepressants (OQuESA): Development, validity, reliability and sensetivity change" Journal of Affective Discorders, 140 (2012), 66-74; Goodwin GM, Price J, Bodinat CD, Laredo J. Emotional blunting with antidepressant treatments: A survey among depressed patients. J Affect Disord. 2017; 221: 31-35 (each of which is incorporated herein by reference in its entirety)).

The ODQ, which is used and referred to in the present invention, is the Oxford Depression Questionnaire (ODQ) (© Oxford University Innovation Limited, 2011), and is subject to a license to Oxford University Innovation Limited. The ODQ is a 26-item patient self-complete measure, spread over 3 sections and covering 4 dimensions (derived from qualitative research) of not caring ("NC"), emotional detachment ("ED"), positive reduction ("PR"), and general reduction ("GR"). If required, an additional dimension, Antidepressant as cause ("AC"), can also be scored. The ODQ as referred to herein comprises 3 sections. Section 1 evaluates the experience of emotional blunting during the past week: 12 items, three items from each of the 4 dimensions (NC, ED, PR and GR). Recall period is the last week. Section 2 compares the experience of emotional blunting during the past week to the experience of emotional blunting before their depression: 8 items, 2 from each of the four dimensions, comparing respondents' experiences during the previous week in comparison to their experiences before they developed their illness/problem. Section 3 (6 items) assesses the patient's perception of a relationship between the current antidepressant medication and emotional blunting, as well as whether this effect had affected adherence to treatment. Section 3 describes the dimension AC. Section 3 is only for completion by those respondents currently prescribed antidepressants. This section addresses the extent to which participants attribute their emotional difficulties to their antidepressant, and the extent to which they would therefore be considered by participants to be "emotional side-effects." It also addresses the possible impact of emotional side-effects on antidepressant adherence. Response options are based on 5-point Likert scale. Thus, each item is rated on the 5-point Likert scale ranging from 1 (disagree) to 5 (agree); *higher scores (4 or 5 on each item) indicate greater emotional blunting, i.e., higher values on the ODQ reflect higher levels of emotional*

blunting. Results can be presented on a dimension basis or summed to give an overall ODQ score. The ODQ score *excluding* the AC domain dimension (ODQ-20) ranges from 20 to 100, while that *including* the AC domain dimension (ODQ-26) ranges from 26 to 130. In the COMPLETE study, patients completed the ODQ-26.

Thus, the ODQ scores as referred to throughout the present application are according to Oxford Depression Questionnaire (ODQ) (© Oxford University Innovation Limited, 2011).

The ODQ comprises the following questions.

Section 1: All my emotions, both 'pleasant' and 'unpleasant', are 'toned down'; I don't fully enjoy things that should give me pleasure, such as beautiful places or things or music; I care less about other people's feelings than I think I should; Because I don't care so much about things, I'm having problems at home; Unpleasant emotions, such as sadness, disappointment, and upset, feel toned down or different in some way; I don't look forward to things with eager anticipation; I don't have much sympathy for people; I feel 'spaced out' and distant from the world around me; My emotions lack intensity; I don't have the passion and enthusiasm for life that I should; Other people being upset doesn't affect me; Because I don't care so much about things, I'm having problems at work or college.

Section 2: Day to day life just doesn't have the same emotional impact on me that it did before my illness/problem; I don't experience pleasant emotions as much as I did before I developed my illness/problem; I don't react to other people's emotions (such as their sadness, anger or upset) as much as I did before my illness/problem; I don't care as much about my day to day responsibilities as I did before I developed my illness/problem; My emotions are numbed/dulled/flattened compared to before I developed my illness/problem; I don't get as much of a 'high' from good things in my life as I did before my illness/problem; I don't have as much sympathy for other people as I did before my illness/problem; I just don't care about things as much as I did before my illness/problem.

Section 3: The antidepressant is preventing me from feeling my emotions in some way; The antidepressant seems to make me just not care about things that should matter to me; The antidepressant seems to make me feel emotionally disconnected from people around me; The antidepressant is preventing me from feeling pleasant emotions; The antidepressant changes the way that I experience my emotions in a way that is unhelpful/not helpful to me

at the moment; I have considered stopping (or have already stopped) my antidepressant because of its emotional side-effects.

It could be that the ODQ in the future were replaced by a later version of the ODQ to establish whether a patient is experiencing emotional blunting. Thus, the term "or equivalent" as used herein in connection with the ODQ scale, means that the ODQ may be replaced by a later version of the questionnaire. The scale and score system should thus be adapted to the updated scale, and the guidelines of the ODQ scale as provided with the new version. Thus the term "ODQ guideline" or similar phrases as used herein means the guidance provided with the licence for the ODQ, which guide the user of the ODQ regarding which questions to ask and how to score them, including the cut off values for when emotional blunting is present and when not.

In one aspect, patient-reported signs and/or symptoms of emotional blunting may be collected by the one or more of the following standardized questionnaires ODQ, MEI, or SDS.

In one aspect, patient-reported signs and/or symptoms of emotional blunting may be collected by at least the ODQ.

In some embodiments, emotional blunting is evaluated by using the guidelines as set forth in The American Psychiatric Association's Diagnostic Statistical Manual's definition of numbing and avoidance.

In one aspect, patient-reported signs and/or symptoms of emotional blunting may be collected by one or more of the following scales can be used to evaluate the signs and/or symptoms of emotional blunting of a patient; Assessment of Negative Symptoms ("SANS"), the Clinical Assessment Interview for Negative Symptoms ("CAINS"), and the Brief Negative Symptom Scale ("BNSS").

In one aspect, patient-reported signs and/or symptoms of emotional blunting may be collected by the one or more of the following standardized questionnaires: ODQ, Positive and Negative Schizophrenia Symptoms Scale ("PANSS") (Peralta V, & Cuesta MJ. Psychometric properties of the positive and negative syndrome scale (PANSS) in schizophrenia. Psychiatry Research. 1994; 53: 31–40; Iancu I, Poreh A, Lehman B, Shamir E, & Kotler M. The positive and negative symptom questionnaire: a self-report scale in schizophrenia. Comprehensive Psychiatry. 2005;46:61–66 (each of which is incorporated herein by reference in its entirety)),

including "blunted effect" and "emotional withdrawal" and rating scale for emotional blunting ("RSEB") (Kilian, S. , Asmal, L. , Goosen, A. , Chiliza, B. , Phahladira, L. , & Emsley, R. (2015). Instruments measuring blunted affect in schizophrenia: A systematic review. PLoS One, 10(6) (incorporated herein by reference in its entirety)).

In some aspects, the presence of emotional blunting can be evaluated clinically with, *e.g.*, tests and assessment methods described herein. In one aspect, patient-reported signs, symptoms, and/or functional consequences of emotional blunting may be collected by one or more of the following standardized questionnaires: ODQ, MEI, and SDS. In one aspect, patient-reported signs and/or symptoms of emotional blunting may be collected by the ODQ.

In some aspects, the presence of emotional blunting can be evaluated clinically with, *e.g.*, tests and assessment methods described herein. In one aspect patient-reported signs, symptoms and/or functional consequences of emotional blunting may include collection of information by the one or more of the following standardized questionnaires: ODQ, MEI, and SDS. In one aspect, patient-reported signs and/or symptoms of emotional blunting may be collected by the ODQ.

In some aspects, the presence of emotional blunting can be evaluated clinically with, *e.g.*, tests and assessment methods described herein. In one aspect, patient-reported signs, and/or symptoms of emotional blunting may include collection of information by the one or more of the following standardized questionnaires: ODQ or MEI. In one aspect, patient-reported signs and/or symptoms of emotional blunting may be collected by the ODQ.

In one aspect, the clinician-rated assessment of signs and symptoms of emotional blunting may include collection of information by one or more of the following standardized methods: Montgomery and Åsberg Depression Rating Scale ("MADRS"), Clinical Global Impression-Severity of Illness ("CGI-S"), and Clinical Global Impression-Global Improvement ("CGI-I").

In one aspect, the clinician-rated assessment of signs and symptoms of emotional blunting may include collection of information by one or more of the following standardized methods: CGI-S and CGI-I.

In some aspects, the presence of emotional blunting can be evaluated clinically with, *e.g.*, tests and assessment methods described herein. In one aspect, patient-reported signs,

and/or symptoms of emotional blunting may be collected by the one or more of the following standardized questionnaires: ODQ and MEI. In one aspect, patient-reported signs and/or symptoms of emotional blunting may be collected by the ODQ.

In one aspect, the clinician-rated assessment of signs and symptoms of emotional blunting may be collected by one or more of the following standardized methods: MADRS, CGI-S, and CGI-I.

In one aspect, the clinician-rated assessment of signs and symptoms of emotional blunting may be collected by one or more of the following standardized methods: CGI-S and CGI-I.

Numbing (and avoidance) is one of four categories of psychiatric disturbance that must be fulfilled for an individual to receive the diagnosis of PTSD. The American Psychiatric Association's Diagnostic Statistical Manual's definition of numbing (and avoidance) includes seven items, any three of which must be present for that category (numbing and avoidance) to be fulfilled. Emotional numbness is specifically represented by two of seven items. One item describes the presence of a restricted range of affect, *e.g.*, the inability to have loving feelings. A second item describes a markedly diminished interest in significant activities. Numbing is defined by this Manual as "persistent avoidance of stimuli associated with the trauma or numbing of general responsiveness (not present before the trauma), as indicated by at least three of the following: (1) efforts to avoid thoughts or feeling associated with the trauma, (2) efforts to avoid activities or situations that arouse recollections of the trauma, (3) inability to recall an important aspect of the trauma (psychogenic amnesia), (4) markedly diminished interest in significant activities (in young children, loss of recently acquired developmental skills such as toilet training or language skills), (5) feeling of detachment or estrangement from others, (6) restricted range of affect, *e.g.*, unable to have loving feelings, and (7) sense of foreshortened future, *e.g.*, does not expect to have a career, marriage, children, or a long life.

In one aspect, adverse events, including signs and symptoms of emotional blunting may recorded or reported using safety assessments, such as generally used for recording of a reporting or diagnosis of adverse events (“AEs”).

In one aspect, discontinuation of patients from a treatment due to adverse events associated with emotional blunting may be recorded or reported according to the general methods of the Discontinuation-Emergent Signs and Symptoms Scale ("DESS").

In one aspect, symptoms and signs of emotional blunting may be recorded by voice recording and passively collected data from the patient obtained with a cell phone application, such as, *e.g.*, Discovery by Mindstrong.

The term "treatment" and "treating" as used herein means the management and care of a patient for the purpose of combating a condition, such as a disease or a disorder. The term is intended to include the full spectrum of treatments for a given condition from which the patient is suffering, such as administration of the active compound to alleviate the symptoms or complications, to delay the progression of the disease, disorder or condition, to alleviate or relief the symptoms and complications, and/or to cure or eliminate the disease, disorder or condition as well as to prevent the condition, wherein prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of the active compounds to prevent the onset of the symptoms or complications. In addition, "treating" or "treatment" may lead to, but does not require, complete alleviation of signs and/or symptoms, does not require a cure, and include protocols that may only have a marginal effect on the patient.

The term "reduction" or "reducing" as used herein includes a decrease, alleviation, or relief in or of symptoms or signs of, *e.g.*, emotional blunting and does not require complete removal of emotional blunting signs and/or symptoms and does not require a cure.

The term "prevents " or "preventing" as used herein may be interchangeably be used with the term "prophylactic" and means that signs and/or symptoms of a disease or condition can be partly or completely avoided, following specific instructions, treatment regimen or administration of a medicament. Thus, a method as described in the aspects and embodiments of this invention may prevent development of signs and symptoms of emotional blunting as a result of treatment of a patient with an antidepressant or may prevent development of signs and symptoms of emotional blunting as a result of the underlying CNS disease or disorder as such, *e.g.*, depression or PTSD.

Nonetheless, in some embodiments prophylactic (preventive) and therapeutic (curative) treatment are two separate aspects of the invention. The patient to be treated is preferably a mammal, in particular a human.

The term "signs" as used herein, when referring to a disease, disorder, or condition means the signs that a health practitioner, *e.g.*, a physician/doctor, observes. "Signs" thus include physical manifestations and other objective measures. The term "symptoms" as used herein referring to a disease, disorder, or condition refers to what a patient experiences or reports and are often subjective. Thus, the ODQ is a patient-centered, self-report measure of emotional symptoms present in patients treated with antidepressants. The ODQ can be used as a clinical tool, to facilitate the identification of patients with the syndrome of emotional blunting. The ODQ can be also used in research studies, to advance understanding of the nature, causes, and, particularly, the treatment of this phenomenon. The Digit Symbol Substitution Test ("DSST") was initiated over a century ago as an experimental tool to understand human associative learning. Its clinical utility, owing to its brevity and high discriminant validity, was first recognized in the 1940s, and now the DSST is among the most commonly used tests in clinical neuropsychology. The DSST is a paper-and-pencil cognitive test presented on a single sheet of paper that requires a subject to match symbols to numbers according to a key located on the top of the page. The subject copies the symbol into spaces below a row of numbers. The DSST is perhaps the most commonly used test in all of neuropsychology, owing to several inherent properties: brevity, reliability, and the minimal impact of language, culture, and education on test performance. DSST offers a practical and effective method to monitor cognitive functions over time in clinical practice. The MEI is a 27-item scale created to assess fatigue and lassitude. The scale was initially developed for the purpose of evaluating interventions to improve motivation and energy in patients with depression, though with further evaluation, its clinical applications could be extended to other patient groups (Fehnel, S. E., Bann, C. M., Hogue, S. L., Kwong, W. J., Mahajan, S. S. (2004) The development and psychometric evaluation of the motivation and energy inventory. Qual. Life. Res. 13, 1321–1336 (incorporated herein by reference in its entirety)). The MEI assesses three factors: mental or cognitive energy, social motivation, and physical energy. The SDS was developed to assess functional impairment in three inter-related domains: work/school, social life, and family life. It is well known and used by researchers

and practicing clinicians. The SDS is a patent self-report tool, in which the patient rates the extent to which said domain-responsibilities are impaired by his or her symptoms on a 10 point visual analogue scale, which uses spatio-visual, numeric, and verbal descriptive anchors simultaneously to assess the level of disability.

The use of the terms “a” and “an” and “the” and similar referents in the context of describing the invention are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. For example, the phrase "the compound" is to be understood as referring to various compounds of the invention or particular described aspect, unless otherwise indicated.

Unless otherwise indicated, all exact values provided herein are representative of corresponding approximate values. In some aspects, all exact exemplary values provided with respect to a particular factor or measurement can be considered to also provide a corresponding approximate measurement, modified by "about," where appropriate.

The description herein of any aspect or aspect of the invention using terms such as “comprising”, “having,” “including,” or “containing” with reference to an element or elements is intended to provide support for a similar aspect or aspect of the invention that “consists of,” “consists essentially of,” or “substantially comprises” that particular element or elements, unless otherwise stated or clearly contradicted by context (*e.g.*, a composition described herein as comprising a particular element should be understood as also describing a composition consisting of that element, unless otherwise stated or clearly contradicted by context).

The term “adequate dose” as used herein means that a dose has been reached from which treatment efficacy can be expected and the attempted treatment can be discontinued and/or replaced with another medicament, due to non-response, partial response or inadequate response.

An “adequate dose” for a medicament for treating one or more CNS disease or disorder is selected based on an evidence-based doses disclosed in said medicament’s label.

The term “inadequate response” as used herein means no response to a treatment with a medicament, partial response to a treatment with a medicament or a response to a medicament revealing signs and symptoms of emotional blunting.

The term "developing" as used herein and referring to signs and/or symptoms of emotional blunting is meant to describe a change from no signs and/or symptoms of emotional blunting to one or more signs and/or symptoms of emotional blunting. Such one or more signs and/or symptoms of may be evaluated as described herein. Non-limiting examples of one or more signs and/or symptoms of emotional blunting may be an answer "yes" to screening question b) as described herein in the context of an evaluation performed by a practicing clinician or physician evaluation or a rating score equivalent to an ODQ total score of above 30 or more. Such no signs and/or symptoms of may be evaluated as described herein. Non-limiting examples of no signs and/or symptoms of emotional blunting may be an answer "no" to screening question b) as described herein in the context of an evaluation performed by a practicing clinician or physician evaluation or a rating score equivalent to an ODQ total score of 26 or less.

The term "worsening of" as used herein and referring to signs and/or symptoms of emotional blunting is meant to describe a change from one or more signs and/or symptoms of emotional blunting to a more sever stage of signs and/or symptoms of emotional blunting, such as ratings in the ODQ total score of above about 30 to about 60, about 40 to about 55, or about 50.

The term "said medicament has enhancing effects on serotonin transmission" or similar phrases referring to one or more medicaments, is used to describe medicaments such as antidepressants. Such medicaments can affect the serotonin transmission by, *e.g.*, increasing the level of serotonin on several levels. That is, some will affect the reuptake of serotonin, whereas others may inhibit release of serotonin.

The term "said medicament has reducing effects on dopaminergic transmission" or similar phrases referring to one or more medicaments, is used to describe medicaments such as antipsychotics and medicaments used in the treatment of schizophrenia. Such medicaments can affect the dopaminergic transmission by, *e.g.*, lowering the level of dopamine on several levels.

The term "fast onset" as used herein, when referring to the treatment described herein includes a reduction of signs and symptoms, such as ODQ or MEI score, or an answer "yes" is switched to "no" to screening question b) as described herein in the context of an evaluation performed, within the first 4 weeks of treatment, preferably within 2 or 1 week of

treatment. About 50% of patients may experience an effect of the treatment described herein within 1 week of receiving 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof in a dose of about 5 mg per day, about 10 mg per day, or about 20 mg per day, preferably about 10 mg per day or 20 mg per day.

Embodiments

The following embodiments describe the invention as outlined by the aspects above in further detail. It will be recognized that one or more features of any embodiments disclosed herein may be combined and/or rearranged within the scope of the invention to provide further embodiments that are also within the scope of the invention.

In some embodiments the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salts thereof for use in prevention or treatment of emotional blunting in a patient, such as a patient suffering from a CNS disease or disorder.

In some embodiments the invention said CNS disease or disorder is selected from the group of psychotic disorders, such as, psychosis, schizophrenia, schizoaffective disorder, schizophreniform disorder, catatonia, delusional disorder; mood disorders, such as bipolar disorder, cyclothymic disorder, major depression, dysthymia, premenstrual dysphoric disorder; and substance use disorders

In some embodiments, the invention relates to a method of preventing or treating emotional blunting or signs and symptoms thereof in a patient, the method comprising administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof, preferably the administration of vortioxetine.

In some embodiments, the invention relates to a method of preventing or treating emotional blunting or signs and symptoms thereof in a patient, wherein said patient experiences signs and symptoms of emotional blunting, the method comprising administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments the invention relates to a method of preventing or treating emotional blunting or signs and symptoms thereof in a patient, wherein said patient

experiences signs and symptoms of emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting resulting from an administration of a medicament, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salts thereof for use in prevention or treatment of emotional blunting in a patient, wherein said patient experiences emotional blunting as part of a CNS disease or disorder or wherein said patient has a history of signs and symptoms of emotional blunting resulting from an administration of a medicament, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salts thereof.

In some embodiments, the invention relates to a method of preventing or treating emotional blunting or signs and symptoms thereof in a patient who experiences emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting in connection with the administration of a medicament, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, the invention relates to a method of preventing or treating emotional blunting in a patient wherein said patient experiences emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting resulting from an administration of a medicament, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof, the method comprising

administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, the invention relates to a method of preventing or treating emotional blunting in a patient wherein said patient has experienced emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting resulting from an administration of a medicament at an adequate dose, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, the invention relates to a method of preventing or treating emotional blunting in a patient wherein said patient experiences emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting resulting from an inadequate response to a medical treatment, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, the invention relates to a method of preventing or treating emotional blunting in a patient wherein said patient experiences emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting resulting from an inadequate response to a medical treatment of a CNS disease or disorder, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salts thereof for use in prevention or

treatment of emotional blunting according to any one of the preceding embodiments wherein said emotional blunting is seen in connection with administration of an adequate dose of a medicament for the treatment of one or more CNS diseases or disorders, wherein said one or more CNS diseases or disorders optionally selected from the group of psychotic disorders, such as schizophrenia, schizoaffective disorder, schizophreniform disorder, catatonia, delusional disorder; mood disorders, such as bipolar disorder, cyclothymic disorder, major depression, dysthymia, premenstrual dysphoric disorder; and substance use disorders, wherein said medicament is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salts thereof and wherein said adequate dose of said medicament is a dose as described in said medicaments label.

In some embodiments, said medicament or medical treatment of a CNS disease or disorder which may result in emotional blunting due to an inadequate response to said medicament or medical treatment, said medicament or medical treatment has an enhancing effect on serotonergic transmission.

In some embodiments, said medicament or medical treatment of a CNS disease or disorder which may result in emotional blunting due to an inadequate response to said medicament or medical treatment, said medicament or medical treatment has an enhancing effect on serotonergic transmission, without affecting other neurotransmitters.

In some embodiments, said medicament or medical treatment of a CNS disease or disorder, which may result in emotional blunting due to an inadequate response to said medicament or medical treatment, said medicament or medical treatment is selected from the classes of SSRIs or SNRIs.

In some embodiments, said medicament or medical treatment of a CNS disease or disorder, which may result in emotional blunting due to an inadequate response to said medicament or medical treatment, said medicament or medical treatment is a SSRI.

In some embodiments, said medicament or medical treatment of a CNS disease or disorder, which may result in emotional blunting due to an inadequate response to said medicament or medical treatment, said medicament or medical treatment is a SSRI and is selected from the group consisting of Escitalopram, Paroxetine, Sertraline, and Citalopram.

In some embodiments, said medicament or medical treatment of a CNS disease or disorder, which may result in emotional blunting due to an inadequate response to said medicament or medical treatment, said medicament or medical treatment is a SNRI and is selected from the group consisting of Venlafaxine and Duloxetine.

In some embodiments, said medicament or medical treatment of a CNS disease or disorder, which may result in emotional blunting due to an inadequate response to said medicament or medical treatment, said medicament or medical treatment is selected from medicaments reducing dopaminergic transmission.

In some embodiments, said medicament or medical treatment of a CNS disease or disorder, which may result in emotional blunting due to an inadequate response to said medicament or medical treatment, said medicament or medical treatment is selected from medicaments used in the treatment of schizophrenia.

In some embodiments, said medicament or medical treatment of a CNS disease or disorder, which may result in emotional blunting due to an inadequate response to said medicament or medical treatment, said medicament or medical treatment is selected from medicaments used in the treatment of schizophrenia, wherein such medicaments can be selected from the group of psychiatric disorders, such as psychosis, schizophrenia, schizoaffective disorder, schizophreniform disorder, catatonia, delusional disorder; mood disorders, such as bipolar disorder, cyclothymic disorder, major depression, dysthymia, premenstrual dysphoric disorder; and substance use disorders.

In some embodiments, said medicament or medical treatment of a CNS disease or disorder, which may result in emotional blunting due to an inadequate response to said medicament or medical treatment, said medicament or medical treatment is selected from the ATC/DDD WHO class N05A.

In some embodiments, said medicament or medical treatment of a CNS disease or disorder, which may result in emotional blunting due to an inadequate response to said medicament or medical treatment, said medicament or medical treatment is selected from the classes of typical or atypical antipsychotic.

In some embodiments, a patient is treated, including preventive treatment, according to the present invention, by administration of 1-[2-(2,4-dimethylphenylsulfanyl)-

phenyl]piperazine or pharmaceutically acceptable salts thereof if said patient experiences signs and symptoms of emotional blunting. The below table indicates patient type in the middle column, which may experience emotional blunting and for which a treatment according to this invention may be beneficial. The right column indicates a recommended treatment scheme:

Example #	If a patient experiences (signs and symptoms) …	Then (recommended treatment) …
A	Signs and symptoms of emotional blunting, without diagnosis of CNS disease or disorder.	Initiate treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.
A1	History of and symptoms of emotional blunting, without diagnosis of CNS disease or disorder, current signs and symptoms of emotional blunting.	Initiate treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.
A2	History of and symptoms of emotional blunting, without diagnosis of CNS disease or disorder, current signs and symptoms of emotional blunting in response to a medicament for the treatment of one or more CNS disease or disorder.	Initiate treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.
A3	History of and symptoms of emotional blunting, without diagnosis of CNS disease or disorder, current signs and symptoms of emotional blunting in response to a medicament for the treatment of a mood disorder.	Initiate treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.
A4	History of and symptoms of emotional blunting, without diagnosis of CNS disease or disorder, current signs and symptoms of emotional blunting in response to a medicament for the treatment of a psychiatric disorder.	Initiate treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof, optionally in addition and concomitantly provide treatment for psychiatric disorder.
B	Signs and symptoms of emotional blunting, with diagnosis of CNS disease or disorder, wherein said CNS disease or disorder is a mood disorder.	Initiate treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.
C	Signs and symptoms of emotional blunting, with diagnosis of CNS disease or disorder, wherein said CNS disease or disorder is a mood disorder, such as MDD .	Initiate treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

D	Signs and symptoms of emotional blunting, with diagnosis of CNS disease or disorder, wherein said CNS disease or disorder is a mood disorder, such as PTSD.	Initiate treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.
E	Signs and symptoms of emotional blunting, with diagnosis of CNS disease or disorder, wherein said CNS disease or disorder is a psychiatric disorder.	Initiate treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.
F	Signs and symptoms of emotional blunting, with diagnosis of CNS disease or disorder, wherein said CNS disease or disorder is psychosis.	Initiate treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.
G	Signs and symptoms of emotional blunting, with diagnosis of CNS disease or disorder, wherein said CNS disease or disorder is a psychiatric disorder, such as schizophrenia.	Initiate treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.
H	Signs and symptoms of emotional blunting, currently treated with an antidepressant affecting serotonin transmission, wherein said antidepressant is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.	Terminate current antidepressant and initiate treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.
I	Signs and symptoms of emotional blunting, currently treated with an antidepressant affecting serotonin transmission, without affecting other neurotransmitters directly.	Terminate current antidepressant and initiate treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.
J	Signs and symptoms of emotional blunting, currently treated with an antidepressant affecting serotonin transmission, such as SSRI or SNRI.	Terminate current antidepressant and initiate treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.
K	Signs and symptoms of emotional blunting, currently treated with a medicament reducing dopaminergic transmission.	Initiate treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof, concomitant with medicaments reducing dopaminergic transmission.
L	Signs and symptoms of emotional blunting, currently treated with an antidepressant reducing dopaminergic transmission, such as antipsychotics.	Initiate treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof, concomitant with medicaments reducing

		dopaminergic transmission, such as antipsychotics.
M	Any one of B, C or D in combination with I or J; B in combination with I; B in combination with J; C in combination with I; C in combination with J; D in combination with I; or D in combination with J	Switch from the treatment of I and J to the treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.
N	Any one of E, F or G in combination with K or L; E in combination with K; E in combination with L; F in combination with K; F in combination with L; G in combination with K; or G in combination with L.	Initiate treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof concomitant with the administration of a medicament for the treatment of a CNS disorder indicated in E, F, or G or the suggested medicaments of K or L.
O	Any one of E, F or G in combination with K or L and I or J; E in combination with K and I; E in combination with L and I; F in combination with K and I; F in combination with L and I; G in combination with K and I; G in combination with L and I; E in combination with K and J; E in combination with L and J; F in combination with K and J; F in combination with L and J; G in combination with K and J; or G in combination with L and J.	Switch from the treatment of I and J to the treatment with of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof, maintain concomitant administration of a medicament for the treatment of a CNS disorder indicated in E, F, or G or the suggested medicaments of K or L.

In some aspects, a patient is treated according to this invention, wherein a patient and treatment is selected according to the Table directly above to any one of the indicated examples A, A1-A4, and B-O.

In some aspects the patient is selected and treated according to any one of the criteria of the Table directly above.

In some aspects, the patient is selected and treated according to scenario A of the above table. In some aspects, the patient is selected and treated according to scenario A1 of the above table. In some aspects, the patient is selected and treated according to scenario A2 of the above table. In some aspects, the patient is selected and treated according to

scenario A3 of the above table. In some aspects, the patient is selected and treated according to scenario A4 of the above table. In some aspects, the patient is selected and treated according to scenario B of the above table. In some aspects, the patient is selected and treated according to scenario C of the above table. In some aspects, the patient is selected and treated according to scenario D of the above table. In some aspects, the patient is selected and treated according to scenario E of the above table. In some aspects, the patient is selected and treated according to scenario F of the above table. In some aspects, the patient is selected and treated according to scenario G of the above table. In some aspects, the patient is selected and treated according to scenario H of the above table. In some aspects, the patient is selected and treated according to scenario I of the above table. In some aspects, the patient is selected and treated according to scenario J of the above table. In some aspects, the patient is selected and treated according to scenario K of the above table. In some aspects, the patient is selected and treated according to scenario L of the above table. In some aspects, the patient is selected and treated according to scenario M of the above table. In some aspects, the patient is selected and treated according to scenario N of the above table. In some aspects, the patient is selected and treated according to scenario O of the above table.

In some aspects of this invention, a practicing clinician or physician may decide to apply the method or use for treating emotional blunting as described in aspects and embodiments herein, if an evaluation of the patient confirms that signs and symptoms of emotional blunting are present in said patient.

In some aspects of this invention, a practicing clinician or physician may decide to apply the method or use for treating emotional blunting as described in aspects and embodiments herein, if an evaluation of the patient confirms that said patient experienced emotional blunting.

In some aspects of this invention, a practicing clinician or physician may decide to apply the method or use for treating emotional blunting as described in aspects and embodiments herein, if an evaluation of the patient confirms that signs and symptoms of emotional blunting are present in said patient as a result of a treatment with a medicament, wherein said medicament is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some aspects of this invention, a practicing clinician or physician may decide to apply the method or use for treating emotional blunting as described in aspects and embodiments herein, if an evaluation of the patient confirms that signs and symptoms of emotional blunting are present in said patient as a result of a treatment with a medicament, wherein said medicament is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof, wherein said method or use for treating emotional blunting as described in aspects and embodiments herein, comprise the steps of:

1) discontinuing said medicament resulting in signs and symptoms of emotional blunting in said patient; and

2) administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, the invention relates to a method of preventing or treating emotional blunting in a patient wherein said patient has a history of showing signs and symptoms of emotional blunting in connection with a CNS disease or disorder or a medical treatment of one or more CNS disease or disorder, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof, the method comprising the steps of:

i) evaluation of said patient by a practicing clinician or physician, wherein said evaluation includes

1) an evaluation of said patient's history of signs and symptoms of emotional blunting;
2) an evaluation of current signs or symptoms of emotional blunting; and/or
3) an evaluation of the risk of said patient developing or worsening signs and/or symptoms of emotional blunting;

ii) if said practicing physician in step 1) evaluates that signs and symptoms of emotional blunting are present or a risk of developing such signs and symptoms of emotional blunting is present, administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof; and

iii) depending on the underlying CNS disease, said practicing clinician or physician evaluates if one or more additional medicaments are administered for the treatment of said one or more CNS disease or disorder or if one or more medicament for the treatment of said one or more CNS disease is discontinued and replaced with administration of a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof in step 2).

In some embodiments the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salts thereof for use in prevention or treatment of emotional blunting according to any one of the embodiments, wherein a practicing clinician or physician decides to apply the use for treating emotional blunting according to said preceding embodiments, if an evaluation of the patient confirms that signs and symptoms of emotional blunting are present in said patient or a risk of emotional blunting is based on the use of medicaments for treating the CNS disease or disorder is established, optionally such treatment comprises the steps of:

1) in cases where said CNS disease or disorder is a mood disorder and said medicament is an antidepressant, the first step is continuation of said medicament, wherein said medicament is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salts thereof; or

2) in cases where said CNS disease or disorder is selected from the group of psychiatric disorders, such as schizophrenia, schizoaffective disorder, schizophreniform disorder, catatonia, delusional disorder and substance use disorders, the first step is to continuate any antidepressant or mood stabilizer, if such medicaments have been used in the treatment of said CNS disease or disorder or to maintain the administration of medicaments for the treatment of Schizophrenia or psychosis which are not antidepressants or mood stabilizers.

The second step is administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salt thereof.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salts thereof for use in prevention or treatment of emotional blunting according to any one of the preceding embodiments,

wherein a practicing clinician or physician decides to apply the use for treating emotional blunting according to said preceding embodiments, if an evaluation of the patient confirms that signs and symptoms of emotional blunting are present in said patient, optionally such treatment comprises the steps of:

a) discontinuation of said medicament, wherein said medicament is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salt thereof; and

b) administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salt thereof.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salts thereof for use in prevention or treatment of emotional blunting according to any one of the preceding embodiments, wherein said medicament is administered for the prevention or treatment of one or more CNS diseases or disorder, or signs and symptoms thereof and wherein said medicament is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salts thereof, wherein said emotional blunting is (1) a result of said CNS disease or disorder, (2) a result if inadequate response to said medical treatment, or (3) reported as being caused by an inadequate response of a medical treatment of a CNS disease or disorder.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in preventing or treating emotional blunting or signs and symptoms thereof in a patient.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in preventing or treating emotional blunting or signs and symptoms thereof in a patient, wherein said patient experiences signs and symptoms of emotional blunting.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in preventing or treating emotional blunting or signs and symptoms thereof in a patient, wherein said patient experiences signs and symptoms of emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting, wherein said medicament resulting in signs

and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in preventing or treating emotional blunting or signs and symptoms thereof in a patient, wherein said patient experiences emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting in connection with the administration of a medicament, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in preventing or treating emotional blunting in a patient wherein said patient experiences emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting resulting from an administration of a medicament, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in preventing or treating emotional blunting in a patient wherein said patient experiences emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting resulting from an administration of a medicament or treating one or more CNS disease or disorder, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in preventing or treating emotional blunting in a patient wherein said patient has experienced emotional blunting or wherein said patient has a history of signs and symptoms of emotional blunting resulting from an administration of a medicament at an adequate dose, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in preventing or treating emotional blunting in a patient wherein said patient has not received any treatment for CNS diseases or disorders before experiencing signs and/or symptoms of emotional blunting.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in preventing or treating emotional blunting in a patient, wherein said patient has a history of signs and symptoms of emotional blunting resulting from an administration of a medicament, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in preventing or treating emotional blunting in a patient wherein said patient has a history of showing signs and symptoms of emotional blunting in connection with a CNS disease or disorder or a medical treatment of one or more CNS disease or disorder, wherein said medicament resulting in signs and symptoms of emotional blunting in said patient is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof, the use comprising the steps of:

i) evaluation of said patient by a practicing clinician or physician, wherein said evaluation includes:

1) an evaluation of said patient's history of signs and symptoms of emotional blunting;
2) an evaluation of current signs or symptoms of emotional blunting; and
3) an evaluation of the risk of said patient developing or worsening of signs and/or symptoms of emotional blunting;

ii) if said practicing physician in step 1) evaluates that signs and symptoms of emotional blunting are present or a risk of developing such signs and symptoms of emotional

blunting is present, administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof; and

iii) depending on the underlying CNS disease, said practicing clinician or physician evaluates if one or more additional medicaments are administered for the treatment of said one or more CNS disease or disorder or if one or more medicament for the treatment of said one or more CNS disease is discontinued and replaced with administration of a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof in step 2).

In some embodiments, an adequate dose of said medicament is a dose as described in said medicament's label. In some embodiments, a method or the use of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof this invention refer to an adequate dose of a medicament, wherein said medicament is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof and wherein adequate dose of said medicament is a dose described in said medicament's label and selected from any one of doses described for efficient treatment in the label of said medicament.

In some embodiments, wherein said emotional blunting is seen in connection with or as a result of an administration of a medicament, comprises the steps of:

1) discontinuation of said medicament; and
2) administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, wherein said emotional blunting is seen in connection with or as a result of an administration of a medicament, comprises the steps of:

1) discontinuation of said medicament for the treatment of a CNS disease or disorder; and
2) administering to a patient in need thereof a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, the invention relates to 1 -[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in the treatment of a CNS disease or disorder, wherein said medicament is for use in a patient who has previously received another medication for the treatment of said disease or disorder which medication was ceased, reduced or has to be ceased, due to emotional blunting.

In some embodiments, the invention relates to 1 -[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use according to the embodiment above, wherein said CNS disease or disorder is depression, such as MDD.

In some embodiments, the method or 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in prevention or treatment of emotional blunting, is for preventing emotional blunting in a patient.

In some embodiments, the method or 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in prevention or treatment of emotional blunting, is for treating emotional blunting in a patient. In some embodiments, said emotional blunting is associated with a CNS disease or disorder. In some embodiments, said emotional blunting is associated with an underlying CNS disease or disorder.

In some embodiments, wherein said emotional blunting is seen in connection with or as a result of an administration of a medicament, said medicament is for treatment of one or more CNS diseases or disorder or signs and symptoms hereof and is not 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof. In some embodiments, said emotional blunting is reported by said patient. In some embodiments, said emotional blunting is diagnosed by a practicing clinician or physician. In some embodiments, said emotional blunting is reported by said patient, as being caused by of an inadequate response of a medical treatment of a CNS disease or disorder.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salts thereof for use in prevention or treatment of emotional blunting according to any one of the preceding embodiments, wherein said medicament is provided for the treatment of one or more CNS disease or disorder and wherein said CNS disease or disorder is selected from the group consisting of:

MDD, MDE, PTSD, schizophrenia, cognitive impairment, Parkinson's disease, autism, vascular dementia, and multiple system atrophy.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salts thereof for use in prevention or treatment of emotional blunting according to any one of the preceding embodiments, wherein said medicament is has enhancing effects on serotonergic transmission, optionally selected from the classes of SSRIs or SNRIs.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salt thereof for use in prevention or treatment of emotional blunting according to any one of the preceding embodiments, wherein said medicament is reducing the dopaminergic transmission, optionally selected from typical or atypical antipsychotics.

In some embodiments, said emotional blunting is diagnosed by a practicing clinician or physician by evaluating the patient, wherein said evaluation comprises the steps of:

a) starting a conversation with said patient;

b) asking the question: *"Have you experienced such emotional effects during the last 6 weeks?"*; and

c) evaluating the response to question b) and concluding if symptoms or signs of emotional blunting is present in said patient.

In some embodiments, said emotional blunting is diagnosed by a practicing clinician or physician by evaluating the patient, wherein said evaluation comprises the steps of:

a) starting a conversation with said patient, explaining the general emotional effects of emotional blunting;

b) asking the question: *"Have you experienced such emotional effects during the last 6 weeks?"*; and

c) evaluating the response to question b) and concluding if symptoms or signs of emotional blunting is present in said patient.

In some embodiments, said emotional blunting is diagnosed by a practicing clinician or physician by evaluating the patient, wherein said evaluation comprises the steps of:

a) starting a conversation with said patient, explaining the general emotional effects of emotional blunting, wherein said explaining can comprise information to the patient that: *Emotional effects vary, but may include, for example, feeling emotionally "numbed" or "blunted" in some way; lacking positive emotions or negative emotions; feeling detached from the world around you; or "just not caring" about things that you used to care about*;

b) asking the question: *"Have you experienced such emotional effects during the last 6 weeks?"*; and

c) evaluating the response to question b) and concluding if symptoms or signs of emotional blunting is present in said patient.

In some embodiments, step c) of said practicing clinician or physician's evaluation leads to the conclusion of the presence of emotional blunting, if said patient's answer to the question asked in step b) is "yes."

In some embodiments, said emotional blunting is diagnosed by a practicing clinician or physician by evaluating the patient, wherein said evaluation comprises the steps of:

a) explaining to said patient that: *Emotional effects vary, but may include, for example, feeling emotionally "numbed" or "blunted" in some way; lacking positive emotions or negative emotions; feeling detached from the world around you; or "just not caring" about things that you used to care about*;

b) asking the question: *"Have you experienced such emotional effects during the last 6 weeks?"*; and

c) evaluating the response to question b), where if question b) was answered with a "yes," concluding that symptoms or signs of emotional blunting is present in said patient.

In some embodiments, said steps a)-c) of said practicing clinician or physician's evaluation may be supplemented or replaced by an evaluated according to or equivalent to the ODQ scale and ODQ total score, wherein said ODQ total score is calculated based on the ODQ guidelines.

In some embodiment, said steps a)-c) of said practicing clinician or physician's evaluation may be supplemented or replaced by an evaluation according to or equivalent to the ODQ scale and wherein the ODQ total score is 30 points or more, wherein said ODQ total score is calculated based on the ODQ guidelines.

In some embodiments, said steps a)-c) of said practicing clinician or physician's evaluation may be supplemented or replaced by an evaluation according to or equivalent to the ODQ scale and wherein the ODQ total score is 40 points or more, wherein said ODQ total score is calculated based on the ODQ guidelines.

In some embodiments, said steps a)-c) of said practicing clinician or physician's evaluation may be supplemented or replaced by an evaluation according to or equivalent to the ODQ scale and wherein the ODQ total score is 50 points or more, wherein said ODQ total score is calculated based on the ODQ guidelines.

In some embodiments, said steps a)-c) of said practicing clinician or physician's evaluation may be supplemented or replaced by an evaluation according to or equivalent to the ODQ scale and wherein the ODQ total score is 70 points or more, wherein said ODQ total score is calculated based on the ODQ guidelines.

In some embodiments, said steps a)-c) of said practicing clinician or physician's evaluation may be supplemented or replaced by an evaluation according to or equivalent to the ODQ scale and wherein the ODQ total score is 90 points or more, wherein said ODQ total score is calculated based on the ODQ guidelines.

In some embodiments, said emotional blunting in seen in combination with a total MEI total score of about 45 or less, wherein said MEI total score is evaluated according to the guideline of said MEI.

In some embodiments, emotional blunting is seen in combination with a MEI total score of about 40 or less, wherein said MEI total score is calculated according to the guideline of said MEI.

In some embodiments, said emotional blunting is seen in combination with a MEI total score of about 30 or less, wherein said MEI total score is calculated according to the guideline of said MEI.

In some embodiments, said emotional blunting is seen in combination with a total SDS total score of about 15 or more, wherein said SDS total score is calculated according to the guideline of said SDS.

In some embodiments, said emotional blunting is seen in combination with a total SDS total score of about 20 or more, wherein said SDS total score is calculated according to the guideline of said SDS.

In some embodiments, said emotional blunting is seen in combination with a total SDS total score of about 25 or more, wherein said SDS total score is calculated according to the guideline of said SDS.

In some embodiments, said steps a)-c) of said practicing clinician or physician's evaluation may be supplemented or replaced by an evaluated according to or equivalent to the SANS scale and relevant scores are calculated based on the guidelines of said SANS.

In some embodiments, said steps a)-c) of said practicing clinician or physician's evaluation may be supplemented or replaced by an evaluated according to or equivalent to the CAINS scale and relevant scores are calculated based on the guidelines of said CAINS.

In some embodiments, said steps a)-c) of said practicing clinician or physician's evaluation may be supplemented or replaced by an evaluated according to or equivalent to the BNSS scale and relevant scores are calculated based on the guidelines of said BNSS.

In some embodiments, said steps a)-c) of said practicing clinician or physician's evaluation may be supplemented or replaced by an evaluated according to or equivalent to the PANSS scale and relevant scores are calculated based on the guidelines of said PANSS.

In some embodiments, said steps a)-c) of said practicing clinician or physician's evaluation may be supplemented or replaced by an evaluated according to or equivalent to the RSEB scale and relevant scores are calculated based on the guidelines

In some embodiments, said steps a)-c) of said practicing clinician or physician's evaluation may be supplemented or replaced by an evaluated according to or equivalent to The American Psychiatric Association's Diagnostic Statistical Manual's definition of numbing and avoidance.

In some embodiments, said steps a)-c) of said practicing clinician or physician's evaluation may be supplemented or replaced by an evaluated according to or equivalent to The American Psychiatric Association's Diagnostic Statistical Manual's definition of numbing and avoidance comprising the steps of the steps of:

i) Providing to said patient a questionnaire regarding the experience of one or more of:

1) presence of a restricted range of affect, *e.g.*, the inability to have loving feelings; and

2) markedly diminished interest in significant activities, wherein significant activities can be defined as activities, which previously were of interest and importance to said patient; and

ii) evaluating the questionnaire and concluding if symptoms or signs of emotional blunting is present in said patient.

In some embodiments, said steps a)-c) of said practicing clinician or physician's evaluation may be supplemented or replaced by an evaluated according to or equivalent to The American Psychiatric Association's Diagnostic Statistical Manual's definition of numbing and avoidance comprising the steps of:

i) providing to the patient a questionnaire comprising one or more of the questions according to The American Psychiatric Association's Diagnostic Statistical Manual's definition of numbing and avoidance, including one of more of the following items:

1) efforts to avoid thoughts or feeling associated with the trauma;

2) efforts to avoid activities or situations that arouse recollections of the trauma;

3) inability to recall an important embodiment of the trauma (psychogenic amnesia);

4) markedly diminished interest in significant activities (in young children, loss of recently acquired developmental skills such as toilet training or language skills);

5) feeling of detachment or estrangement from others;

6) restricted range of affect, *e.g.*, unable to have loving feelings;

7) sense of foreshortened future, *e.g.*, does not expect to have a career, marriage, children, or a long life; and

ii) evaluating the questionnaire and concluding if symptoms or signs of emotional blunting is present in said patient.

In some embodiments, wherein said method or use described herein said method or treatment is a fast-onset method or use for the treatment of emotional blunting. In some embodiments, wherein said method or use described herein is a fast-onset method or use for the treatment of emotional blunting, wherein a reduction of signs or symptoms is detectable

within one week by either the patient or evaluated by the doctor of, *e.g.*, questionnaires answered by the patient. In some embodiments, wherein said method or use described herein is a fast-onset method or use for the treatment of emotional blunting, wherein a reduction of signs or symptoms is detectable within two weeks by either the patient or evaluated by the doctor of, *e.g.*, questionnaires answered by the patient. In some embodiments, wherein said method or use described herein is a fast-onset method or use for the treatment of emotional blunting, wherein a reduction of signs or symptoms is detectable within four weeks by either the patient or evaluated by the doctor of, *e.g.*, questionnaires answered by the patient.

In some embodiments, wherein said method or use as described herein is applied, said ODQ total score is reduced by about 6 to about 10 points within about one week of administration of said therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, wherein said method or use as described herein is applied, said ODQ total score is reduced by about 6.5 to about 13 points within about one week of administration of said therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, wherein said method or use as described herein is applied, said ODQ total score is reduced by about 15 to about 25 points within about four weeks of administration of said therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, wherein said method or use as described herein is applied, said ODQ total score is reduced by about 17.6 to about 24.8 points within about four weeks of administration of said therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, wherein said method or use as described herein is applied, said ODQ total score is reduced by about 25 to about 30 points within about eight weeks of administration of said therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, wherein said method or use as described herein is applied, said ODQ total score is reduced by about 26 to about 29.8 points within about eight weeks of administration of said therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, wherein said method or use as described herein is applied, said ODQ total score is reduced by about 30 points or more after about eight weeks of administration of said therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, wherein said method or use as described herein is applied, said MEI total score is increased by about 18 to about 30 points within about four weeks of administration of said therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, wherein said method or use as described herein is applied, said MEI total score is increased by about 18.8 to about 28.3 points within about four weeks of administration of said therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, wherein said method or use as described herein is applied, said MEI total score is increased by about 28 to about 40 points within about eight weeks of administration of said therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, wherein said method or use as described herein is applied, said MEI total score is increased by about 28.9 to about 39.7 points within about eight weeks of administration of said therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, wherein said method or use as described herein is applied, said MEI total score is increased by about 40 points or more after about eight weeks of administration of said therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, wherein said method or use as described herein is applied, said SDS total score is reduced by about 5 to about 10 points within about eight weeks of

administration of said therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, wherein said method or use as described herein is applied, said SDS total score is reduced by about 5.9 to about 9.5 points within about eight weeks of administration of said therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, wherein said method or use as described herein is applied, said SDS total score is reduced by about 10 points or more after about eight weeks of administration of said therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof.

In some embodiments, wherein said method or use as described herein is applied, about 50% of said patients answer “no” to the screening question describes as item b) in aspects and embodiments herein and reads as follows: “*Have you experienced such emotional effects during the last 6 weeks?*”, wherein said answer from said patient is “no” after about 8 weeks or more of administration of a therapeutically effective amount of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl] piperazine or pharmaceutically acceptable salts daily at a dose of at least 10 mg/day.

In some embodiments, said emotional blunting has been reported or diagnosed at least once before onset of any medical treatment.

In some embodiments, said emotional blunting has been reported or diagnosed at least once before or after onset of any medical treatment.

In some embodiments, said emotional blunting has been reported or diagnosed once after onset of any medical treatment.

In some embodiments, said emotional blunting has been reported or diagnosed at least once before onset of any medicament.

In some embodiments, said emotional blunting has been reported or diagnosed at least once before or after onset of any medicament.

In some embodiments, said emotional blunting has been reported or diagnosed once after onset of any medicament.

In some embodiments, said method or use or method as described herein, said CNS disease or disorder is selected from the group consisting of MDD, MDE, PTSD, schizophrenia, cognitive impairment, Parkinson's disease, autism, vascular dementia, and multiple system atrophy.

In some embodiments, said CNS disease or disorder is MDD. In some embodiments, said CNS disease or disorder is MDE. In some embodiments, said CNS disease or disorder is PTSD. In some embodiments, said CNS disease or disorder is schizophrenia. In some embodiments, said CNS disease or disorder is Parkinson's disease. In some embodiments, CNS disease or disorder is autism. In some embodiments, said CNS disease or disorder is vascular autism. In some embodiments, said CNS disease or disorder is vascular dementia. In some embodiments, said CNS disease or disorder is Multiple System Atrophy ("MSA"). In some embodiments, said CNS disease or disorder is cognitive impairment. In some embodiments, said cognitive impairment, is associated with Alzheimer's disease or schizophrenia.

In some embodiments, said cognitive impairment, is diagnosed by a practicing clinician or physician.

In some embodiments, said cognitive impairment, is diagnosed by a physician, therapist, or physiatrist by the use of a scale similar to DSST. In some embodiments, said Cognitive impairment is reported by a patient.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salts thereof according to any one of the preceding embodiments, for use in prevention or treatment of emotional blunting or a use according to any one of the preceding embodiments, wherein said patient has not received any treatment for CNS diseases or disorders before experiencing signs and/or symptoms of emotional blunting.

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered in any of the uses or methods disclosed herein, is a crystalline salt.

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered in any of the uses or methods

disclosed herein, is a crystalline salt, wherein said crystalline salt is selected from the group consisting of the hydrobromide (α), hydrobromide (β), and hydrobromide (γ).

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered in any of the uses or methods disclosed herein, is a crystalline salt, wherein said crystalline salt is selected from the group consisting of the DL, D- and L-lactic acid addition salt.

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered in any of the uses or methods disclosed herein, is a crystalline salt, wherein said crystalline salt is selected from the group consisting of the DL, D- and L-pyropyroglutamate.

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered in any of the uses or methods disclosed herein, is a crystalline salt, wherein said crystalline salt is selected from the group consisting of the hydrobromide (α), having major XRPD peaks at 5.85 ± 0.2, optionally ± 0.1 (˚2Θ), 9.30 ± 0.2, optionally ± 0.1 (˚2Θ), 17.49 ± 0.2, optionally ± 0.1 (˚2Θ), and 18.58 ± 0.2, optionally ± 0.1 (˚2Θ); hydrobromide (β), having major XRPD peaks at 6.89 ± 0.2, optionally ± 0.1 (˚2Θ), 9.73 ± 0.2, optionally ± 0.1 (˚2Θ), 13.78 ± 0.2, optionally ± 0.1 (˚2Θ), and 14.62 ± 0.2, optionally ± 0.1 (˚2Θ); and hydrobromide (γ), having major XRPD peaks at 11.82 ± 0.2, optionally ± 0.1 (˚2Θ), 16.01 ± 0.2, optionally ± 0.1 (˚2Θ), 17.22 ± 0.2, optionally ± 0.1 (˚2Θ), and 18.84 ± 0.2, optionally ± 0.1 (˚2Θ).

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered in any of the uses or methods disclosed herein, is a crystalline salt, wherein said crystalline salt is hydrobromide (β), having major XRPD peaks at 6.89 ± 0.2, optionally ± 0.1 (˚2Θ), 9.73 ± 0.2, optionally ± 0.1 (˚2Θ), 13.78 ± 0.2, optionally ± 0.1 (˚2Θ), and 14.62 ± 0.2, optionally ± 0.1 (˚2Θ). In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered in any of the uses or methods disclosed herein, is a crystalline salt, wherein said crystalline salt is selected from the group consisting of the DL-lactic acid addition salt, having major XRPD peaks at 6.01 ± 0.2, optionally ± 0.1 (˚2Θ), 10.10 ± 0.2, optionally ± 0.1 (˚2Θ), 10.32 ± 0.2, optionally ± 0.1 (˚2Θ), 12.06 ± 0.2, optionally ± 0.1 (˚2Θ), 12.84 ± 0.2, optionally ± 0.1 (˚2Θ), 13.08 ± 0.2, optionally ± 0.1 (˚2Θ), and 13.58 ± 0.2,

optionally ± 0.1 (˚2Θ); L-lactic acid addition salt having major XRPD peaks at 5.33 ± 0.2, optionally ± 0.1 (˚2Θ), 9.75 ± 0.2, optionally ± 0.1 (˚2Θ), 10.10 ± 0.2, optionally ± 0.1 (˚2Θ), and 14.63 ± 0.2, optionally ± 0.1 (˚2Θ); or D-lactic acid addition salt having major XRPD peaks at 5.33 ± 0.2, optionally ± 0.1 (˚2Θ), 9.75 ± 0.2, optionally ± 0.1 (˚2Θ), 10.10 ± 0.2, optionally ± 0.1 (˚2Θ), and 14.63 ±0.2, optionally ± 0.1 (˚2Θ).

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered in any of the uses or methods disclosed herein, is a crystalline salt, wherein said crystalline salt is selected from the group consisting of the L-pyroglutamate, having major XRPD peaks at 10.72 ± 0.2, optionally ± 0.1 (˚2Θ), 12.14 (˚2Θ) ± 0.2, optionally ± 0.1, 16.22 ± 0.2, optionally ± 0.1 (˚2Θ), and 18.59 ± 0.2, optionally ± 0.1 (˚2Θ); D-pyroglutamate, having major XRPD peaks at 10.72 ± 0.2, optionally ± 0.1 (˚2Θ), 12.14 (˚2Θ), 16.22 ± 0.2, optionally ± 0.1 (˚2Θ), and 18.59 ± 0.2, optionally ± 0.1 (˚2Θ); and DL-pyroglutamate, having major XRPD peaks at 6.16 ± 0.2, optionally ± 0.1 (˚2Θ), 9.25± 0.2, optionally ± 0.1 (˚2Θ), 17.68 ± 0.2, optionally ± 0.1 (˚2Θ), and 18.59 ±0.2, optionally ± 0.1 (˚2Θ).

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered in any of the uses or methods disclosed herein, is administered to said patient in a dose between about 1 mg to about 50 mg, preferably about 5 mg, about 10 mg, or about 20 mg per day.

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered in any of the uses or methods disclosed herein, is administered to said patient in a dose of about 10 mg or about 20 mg per day.

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered in any of the uses or methods disclosed herein, is administered to said patient in a dose of about 10 mg per day in the first week, *i.e.*, day 1 to about day 6 or about day 7, and about 10 mg or about 20mg per day after the first week, *i.e.*, about day 7 or about day 8 for as long as a treatment for which said administration of said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof is needed by said patient.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salts thereof according to any one of the preceding embodiments, for use in prevention or treatment of emotional blunting, wherein said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salts thereof is a crystalline salt, wherein said crystalline salt is selected from the group consisting of the hydrobromide (α), hydrobromide (β), and hydrobromide (y), DL-, D- or L-lactic acid addition salt, or DL-, D-, or L-pyroglutamate salt in a daily dose of about 10 mg or about 20 mg, wherein said patient is administered about 1 0mg per day for about 1 week and either remains on the dose of about 10 mg per day after the first week or increases the dose in agreement with their practicing clinician or physician.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salts thereof according to any one of the preceding embodiments for use in prevention or treatment of emotional blunting wherein said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salts thereof is vortioxetine in a daily dose of about 10 mg or about 20 mg, wherein said patient is administered about 10 mg per day for about 1 week and either remains on the dose of about 10 mg per day after the first week or increases the dose, preferably to about 20 mg per day, in agreement with their practicing clinician or physician.

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered to said patient in any of the uses or methods disclosed herein, an administration of said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof is performed by any suitable route of administration.

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered to said patient in any of the uses or methods disclosed herein, an administration of said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof is performed by any suitable route of administration, wherein said route of administration may be subcutaneous, intravenous, sub lingual, or oral.

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered to said patient in any of the uses

or methods disclosed herein, an administration of said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof is performed by any suitable route of administration, wherein said route of administration is oral.

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered to said patient in any of the uses or methods disclosed herein, an administration of said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof is performed by any suitable route of administration, wherein said route of administration is oral in the form of a tablet.

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered to said patient in any of the uses or methods disclosed herein, an administration of said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof is performed by any suitable route of administration, wherein said route of administration is oral in the form of a tablet comprising the following ingredients:

Ingredient	**Amount (w/w-%)**
HBr salt of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine	About 3-8%
Anhydrous calcium hydrogen phosphate	About 35-45%
Corn starch	About 15-25%
Copovidone	About 2-6%
Microcrystalline cellulose	About 20-30%
Sodium starch glycolate	About 1-3%
Talc	About 2-6%
Magnesium stearate	About 0.5-2%

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered to said patient in any of the uses or methods disclosed herein, an administration of said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof is performed by any suitable route of administration, wherein said route of administration is oral in the form of a tablet comprising one, one or more, or all of the following ingredients:

Ingredient	**Amount (w/w-%)**
HBr salt of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine	About 5%
Anhydrous calcium hydrogen phosphate	About 39%

Corn starch	About 20%
Copovidone	About 3%
Microcrystalline cellulose	About 25%
Sodium starch glycolate	About 3%
Talc	About 4%
Magnesium stearate	About 1%

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered to said patient in any of the uses or methods disclosed herein, an administration of said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof is performed by any suitable route of administration, wherein said route of administration is oral in the form of oral drops as described in WO 2010/121621 (incorporated herein by reference in its entirety) comprising the DL-, D-, or L-lactic acid salt of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine.

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered to said patient in any of the uses or methods disclosed herein, an administration of said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof is performed by any suitable route of administration, wherein said route of administration is oral in the form of oral drops which are a liquid pharmaceutical formulation comprising a salt of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine selected from the 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine DL-lactic acid addition salt, 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine L- lactic acid addition salt, and the 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine D-lactic acid addition salt.

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered to said patient in any of the uses or methods disclosed herein, an administration of said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof is performed by any suitable route of administration, wherein said route of administration is oral in the form of a sublingual composition.

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered to said patient in any of the uses

or methods disclosed herein, an administration of said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof is performed by any suitable route of administration, wherein said route of administration is oral in the form of a sublingual gel composition as described in WO 2016/180870 (incorporated herein by reference in its entirety) comprising 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine DL-, D-, or L-pyroglutamate salt.

In some embodiments, said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof as administered to said patient in any of the uses or methods disclosed herein, an administration of said 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof is performed by any suitable route of administration, wherein said route of administration is oral in the form of a sublingual gel composition as described in WO2016/180870 (*supra*) comprising 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine DL-, D-, or L-pyroglutamate salt and least one pharmaceutically acceptable carrier or diluent.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use in prevention, reduction, or treatment of emotional blunting in a patient.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use according to the embodiment above, wherein said patient is suffering from a CNS disease or disorder.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use according to anyone of the embodiments above, wherein said patient experiences emotional blunting as part of a CNS disease or disorder.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use according to any one of the embodiments above, wherein said patient has previously received, or is still receiving, medication for the treatment of said CNS disease.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use according to any one

of the embodiments above, said medication resulting in symptom and signs of emotional blunting, wherein said medication was ceased, or has to be ceased, due to emotional blunting.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use according to any one of the embodiments above, wherein said CNS disease or disorder is selected from psychiatric disorders, such as, psychosis, schizophrenia, schizoaffective disorder, schizophreniform disorder, catatonia, delusional disorder; mood disorders, such as bipolar disorder, cyclothymic disorder, major depression, dysthymia, premenstrual dysphoric disorder; and substance use disorders.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use according to any one of the embodiments above wherein said CNS disease or disorder is selected from PTSD, depression including MDD and MDE, cognitive impairment, schizophrenia, psychosis, Parkinson's disease, autism, vascular dementia, and multiple system atrophy.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use according to any one of the embodiments above, wherein said CNS disease or disorder is selected from MDD and schizophrenia.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use according to any one of the embodiments above, wherein said medication is a SSRI or a SNRI.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use according to any one of the embodiments above, wherein said CNS disease or disorder is selected from MDD and schizophrenia, and wherein said medication is a SSRI or a SNRI.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use according to any one of the embodiments above, wherein said medication is selected from Escitalopram, Fluoxetine, Paroxetine, Sertraline, Venlafaxine, Desvenlafaxine, and Duloxetine.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use according to any one of the embodiments above, wherein said patient has a total score of above 30, such as above 40, such as above 50 in an ODQ.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use according to according to any one of the embodiments above, wherein said pharmaceutically acceptable salt is selected from the group consisting of hydrobromide salt, lactic acid salt, and pyroglutamate salt.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use according to embodiments, wherein said pharmaceutically acceptable salt is selected from the hydrobromide (α) salt, hydrobromide (β) salt, and hydrobromide (γ) salt.

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use according to any one of the preceding embodiments, wherein 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof is administered in a unit dose of about 5 mg, about 10 mg, or about 20 mg of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine (calculated as free base).

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use according to any one of the embodiments above, wherein 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof is administered in a dose of about 5 mg/day, about 10 mg/day, or about 20 mg/day of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine (calculated as free base).

In some embodiments, the invention relates to 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof for use according to any one of the embodiments above, wherein 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or pharmaceutically acceptable salts thereof is administered as oral tablets or oral drops.

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, equivalents to the specific aspects of the invention described herein. Such equivalents are considered to be within the scope of the present invention.

EXAMPLES

General Methods

WO 03/029232, WO 2007/144005, WO 2010/121621, and WO 2016/180870 (each of which is incorporated herein by reference in their entireties) disclose the compound 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine and pharmaceutically acceptable salts thereof, and methods of making them.

General Clinical Trial Methods

In this 8-week, open-label, single-arm study, patients were switched directly from the SSRI/SNRI to 8 weeks of treatment with vortioxetine (1 week of 10 mg/day followed by 7 weeks of 10-20 mg/day, flexible-dose).

The study included outpatients ages 18-65 years with a primary diagnosis of MDD (per DSM-5) and a current depressive episode of less than 12 months duration. Patients with an inadequate (*i.e.*, partial) response to a SSRI or SNRI monotherapy at approved doses for at least 6 weeks prior to the screening visit (SSRIs: escitalopram, paroxetine, sertraline; SNRIs: duloxetine and venlafaxine) were eligible. A MADRS total score >21 and <29 (depression severity), and ODQ total score ≥50 (emotional blunting severity) at baseline were required for inclusion. In addition, all patients had to respond yes to the “gold standard” standardized screening question on emotional blunting as developed by Price et al (2012) (*supra*): "*Emotional effects vary, but may include, for example, feeling emotionally "numbed" or "blunted" in some way; lacking positive emotions or negative emotions; feeling detached from the world around you; or "just not caring" about things that you used to care about. Have you experienced such emotional effects during the last 6 weeks?*". All patients had to be candidates for a change of medication by their own and the investigator’s opinions.

Patients with other current primary psychiatric diagnoses than MDD or abuse of any substance within 6 months before the beginning of the study were excluded, as were patients with inadequate response to two previous antidepressant treatment courses of

adequate dosage and duration. Other key exclusion criteria included mental retardation, pregnancy, and risk of suicide.

The study was conducted between February 2019 and February 2020 at a total of 23 sites in France, Spain, Italy, and Lithuania in accordance with the principles of Good Clinical Practice (ICH, 2016) and the Declaration of Helsinki (World Medical Association, 2002), and approved by the local ethics committees of each study site. Eligible patients provided written informed consent before participating any study procedure. The study is registered at ClinicalTrials.gov (NCT03835715) and in EU Clinical Trials Register (EudraCT No. 2017-004829-33).

The following "ASSAYS" describe, in general terms, the study conducted for evaluating the effectiveness of 10 or 20 mg vortioxetine treatment on emotional functioning, *i.e.*, the effect of vortioxetine on emotional blunting. One aspect of the study concerned evaluating the effectiveness of 10 or 20 mg vortioxetine treatment on emotional functioning with MDD with inadequate response to SSRI or SNRI treatment, which are known to induce some degree of emotional numbness or blunting in about 50% of patients. Some aspects of this objective were to evaluate the effectiveness of 10-20 mg flexible-dose vortioxetine after 8 weeks of treatment on motivation and energy, family, social, and work functioning, cognitive functioning, and depressive symptoms, and to evaluate safety of said vortioxetine doses and assess potential discontinuation symptoms following abrupt discontinuation of the previous treatment with SSRI or SNRI and initiation of treatment with vortioxetine. An additional objective was to explore association between digital biomarkers or digital phenotypes and clinical features, which included disease symptoms, functioning, and cognitive performance, however this objective was not explored due to time constraints.

ASSAY I – Study Methodology

The study with the above objective was designed as an interventional, multi-national, multi-site and open label, and flexible dose study.

The study comprised an 8-week treatment period with vortioxetine and was followed by a follow up period of 4 weeks for safety assessments. Effectiveness and safety assessments were done at weeks 0, 1, 4, and 8, and unscheduled visits for dose adjustments are allowed any time during the treatment period.

An overview of the study design is shown in Figure 1.

All assessments and evaluations of the different scales described in the following ASSAYs were performed by the investigator, *i.e.*, clinicians.

ASSAY II – Enrollment Criteria

The patient was a man or woman, aged ≥18 and ≤65 years with a primary diagnosis of single or recurrent MDD and fulfilling criteria for MDE according to DSM-5®. Further, the patient had a primary diagnosis of MDD and a current depressive episode lasting for ≥12 months and depressive symptoms corresponding to a MADRS total score >21 and <29 after ≥6 weeks of monotherapy with an SSRI or an SNRI at an adequate dose, wherein said patient experienced emotional blunting as indicated by ODQ total score >50 and the answer "yes" on a screening question on emotional blunting (*"Emotional effects vary, but may include, for example, feeling emotionally "numbed" or "blunted" in some way; lacking positive emotions or negative emotions; feeling detached from the world around you; or "just not caring" about things that you used to care about. Have you experienced such emotional effects during the last 6 weeks?"*). If the patients were considered themselves suitable and/or if the investigator's considered the patient as suitable for a change of antidepressant medication, they were enrolled.

The patient was treated with SSRI/SNRI monotherapy (citalopram, escitalopram, paroxetine, duloxetine, or venlafaxine) for at least 6 weeks at an adequate dose for the current MDE and with an inadequate response and is a candidate for a switch in the investigator's opinion. Furthermore, the patient had a desire to switch treatment due to this inadequate response and complain about emotional blunting as assessed by the screening question on emotional effects (inclusion criterion 8) and a total score on the ODQ ≥50. The severity of depressive symptoms as assessed by MADRS total score must have been of ≥22 and ≤28, corresponding to moderate to severe level of depression.

Approximately 150 patients were planned to be enrolled. The study consisted of an 8-week open-label, flexible-dose treatment period. A safety follow-up assessment was planned to be performed 30 days after the Primary Outcome Visit or Withdrawal Visit.

Patient Flow and Baseline Characteristics

Of 151 patients enrolled, 150 were treated; of those, 131 (87.3%) completed treatment and 143 (95.3%) were included the analyses. A total of 19 patients discontinued the study; the primary reasons were adverse event (6 patients [4%]), loss to follow-up (6 patients [4%]), lack of efficacy (2 patients [1.3%]), protocol violation (3 patients [2%]), withdrawal of consent (1 patient [0.7%]), and "Other reason" (1 patient [0.7%]). Patients' mean age was 47 years (SD = 12), and 105 (70.0%) were women (Table 0). The mean MADRS total score at baseline was 25.5 (SD = 1.7) and the mean ODQ total score was 89.4 (SD = 15.1). Most patients (82%) were switched from an SSRI at the beginning of the study, most commonly escitalopram, while 18% were switched from an SNRI, mostly venlafaxine (Table 0). Approximately half of patients (51.4%) had an end dose at week 8 of 20 mg vortioxetine.

Table 0. Demographic and clinical characteristics.

	N (%)
Demographic and clinical characteristics	
N treated	150
Women	105 (70%)
Mean age (SD), years	47.1 (12.0)
Country	
Spain	67 (44.7)
France	49 (32.7)
Lithuania	20 (13.3)
Italy	14 (9.3)
Previous treatment	
SSRI	123 (82.0)
Escitalopram	63 (42.0)
Paroxetine	26 (17.3)
Sertraline	21 (14.0)
Citalopram	13 (8.7)
SNRI	27 (18.0)
Venlafaxine	17 (11.3)
Duloxetine	10 (6.7)
Mean duration of current episode (SD), weeks	22.3 (12.3)
Range	3 – 56
Number of previous episodes	
0	57 (38.0)
1	34 (22.7)
2	28 (18.7)
3+	31 (20.6)
Clinical assessments at baseline, mean (SD)	

	N (%)
N (FAS)	143
ODQ total score	89.4 (15.1)
MADRS total score	25.5 (1.7)
CGI-S score	4.5 (0.6)
MEI	44.1 (19.4)
SDS	20.8 (4.9)
DSST	45.4 (13.8)

ASSAY III – Switching of Patients from SSRI or SNRI to Vortioxetine

Patients complying with the enrollment criteria were switched directly from the SSRI/SNRI to 8 weeks of open-label vortioxetine. Vortioxetine (Lu AA21004) – 10 or 20 mg/day are oral tablets.

At the Baseline Visit, all patients were switched from the previous treatment with an SSRI or SNRI to open-label treatment with vortioxetine. The starting dose was 10 mg/day vortioxetine during the first week. Hereafter, the dose may have been increased to 20 mg/day at Visit 2 (Week 1) or remain at 10 mg/day. The dose may have been adjusted (10 or 20 mg/day) at scheduled and unscheduled visits according to the patient's response and the investigator's judgement.

Patients were dispensed vortioxetine 10 or 20 mg at each visit and were instructed to take a daily dose, orally, preferably at the same time of the day. The first dose of vortioxetine was instructed to be taken the day after the vortioxetine had been dispensed to the patient (Day 1).

All patients received 10 mg/day in the first week, starting from the day after Visit 1 (Week 1). The study was designed as a flexible dose study, which means that after the first week a visit at the investigator's clinic was mandatory (Visit 2) and the patient could decide, in collaboration with the investigator, if s/he continued with the 10 mg/day vortioxetine dose or increased the dose to 20mg/day from the day after Visit 2. Patients were furthermore allowed to adjust the dose of vortioxetine following scheduled or unscheduled Visits at the investigator's clinic, said unscheduled Visits could be allowed at any time during the 7 weeks of treatment. Thus, the following 7 weeks, patients received 10-20 mg/day depending on their choice after week 1, Table 1 indicated how many patients increased the dose after week

1 and/or reduced or increased the dose at some point after week 2, *e.g.*, at weeks 2.5, 3, or 4 or any other time before the end of week 8.

Table 1. Patients grouped according to the sequence of vortioxetine doses taken during 8 weeks of the study (APTS). About 50% of patients increased the dose to 20 mg/day, about 4 % discontinued the treatment, and about 46% stayed on 10 mg/day of vortioxetine.

Dose week 1 (mg/day)	Dose week 2 (mg/day)	Dose after week 2 (mg/day)	Number of patients	Percentage (%) of patients
10	10	10	62	43.7
10	10	20	38	26.8
10	20	10	3	2.1
10	20	20	33	23.2
10	10	discontinued	4	4
10	20	discontinued	2	2

Most patients where switched from the prior treatment with SSRI or SNRI to vortioxetine from one day to the other, however in some cases the doses of SSRI and SNRI may have been reduced prior to the first dose of vortioxetine.

ASSAY IV – Efficacy Assessment

Patient-reported signs and/or symptoms of emotional blunting were collected by one or more of the following standardized questionnaires: ODQ, MEI, or SDS.

Clinician-rated assessment of signs and symptoms of emotional blunting were collected by one or more of the following standardized methods: MADRS, CGI-S, or CGI-I.

The efficacy of vortioxetine in the treatment of MDD was evaluated in a total of 14 short-term, placebo-controlled studies (including a dedicated study in the elderly); 3 short-term, active-comparator studies; 1 long-term, relapse-prevention study; and six long-term, open-label extension studies. The clinical value of vortioxetine in the dose range of 5-20 mg/day was demonstrated versus placebo on well-established efficacy measures with clinically relevant effect sizes and by the clinically relevant results in the analyses of the proportions of responders and remitters, the CGI-I score, and improvement in health-related quality of life and overall functioning. The favorable effects of vortioxetine were seen both in short- and in long-term treatment and were independent of age, sex, race, body mass index, and baseline disease characteristics. Additionally, results from 3 large, randomized, placebo-controlled trials in adult patients with MDD showed a consistent and clinically meaningful

improvement in patients´ cognitive performance as assessed by the DSST as well as other objective and subjective measures of cognitive functioning. A significant and clinically meaningful improvement was also observed in ability to perform activities of daily living as measured by the UCSD Performance-based Skills Assessment ("UPSA"), an objective test of functional capacity.

ASSAY V – Neuropsychological Tests

Neuropsychological test for evaluating signs and symptoms of emotional blunting were, *e.g.*, DSST.

ASSAY VI - Safety Assessments

Adverse events, including signs and symptoms of emotional blunting may recorded or reported using safety assessments, such as generally used for recording of a reporting or diagnosis of adverse events.

Discontinuation of patients from a treatment due to adverse events associated with emotional blunting may be recorded or reported according to the general methods of the Discontinuation-Emergent Signs and Symptoms Scale ("DESS").

The safety of vortioxetine has been investigated in an extensive clinical trial program, including approximately 12,500 patients (including healthy volunteers) exposed to vortioxetine treatment. Based upon adverse events reporting or diagnosis, evaluation of laboratory safety test values, ECG parameters (including QTc), vital signs, and weight over time relative to placebo, vortioxetine was found to be safe and well-tolerated. The safety profile of vortioxetine in adults and the elderly was found to be similar. Experience from post-marketing use, including an exposure of approximately 2.7 million patient years, confirm the safety profile as found in the clinical trials.

A total of 71 patients (47.3%) reported a TEAEs (Table 1A). The most common TEAEs (reported by >2%) were nausea, headache, dizziness, vomiting, and diarrhea; one patient reported a serious adverse event ('abortion missed'). No patients died during the study. Six patients discontinued the study due to TEAEs; TEAEs leading to withdrawal in two patients or more comprised vomiting, nausea, and diarrhea. The mean DESS total score was 1.9 (SD = 3.8) and 2.2 (SD = 4.2) at baseline and week 1, respectively.

Table 1A. Summary of TEAEs. TEAEs with an incidence of >2%, and TEAEs leading to discontinuation in the 8-week treatment period.

		N (%)
Patients treated		150
Patients with TEAEs		71 (47.3)
Patients with serious adverse events		1 (0.7)
Patients with TEAEs leading to discontinuation		6 (4.0)
TEAEs with an incidence ≥5%		
Nausea		31 (20.7)
Headache		12 (8.0)
Dizziness		10 (6.7)
Vomiting		10 (6.7)
Diarrhea		9 (6.0)
Nightmare		6 (4.0)
Abdominal distension		5 (3.3)
Pruritus		5 (3.3)
Abnormal dreams		4 (2.7)
Pruritus generalized		4 (2.7)
TEAEs leading to discontinuation		
Vomiting		4 (2.7)
Nausea		3 (2.0)
Diarrhea		2 (1.3)
Abdominal pain upper		1 (0.7)
Chromaturia		1 (0.7)
Dizziness		1 (0.7)
Feeling abnormal		1 (0.7)
Nightmare		1 (0.7)

ASSAY VII – Other Assessments

Aspect symptoms and signs of emotional blunting may be recorded by voice recording and passively collected data from the patient obtained with a cell phone application, such as, *e.g.*, Discovery by Mindstrong Version 2.2.

ASSAY VIII – Endpoints of the Study

One endpoint of particular interest of this study was basement of emotional blunting relative to baseline, using the QDQ, a 26-item rating scale assessing four dimensions of emotional blunting, as well as possible attribution to antidepressant treatment.

Depressive symptoms were assessed by clinicians using the MADRS:

Method/Evaluation tool	Endpoints: Primary (1) / Secondary (2) / Safety (S) / Exploratory (E)	Comment
Change from baseline ODQ to week 8	1	**Emotional Blunting** Total scores
Change from baseline MEI to week 8	2	**Motivation and Energy** Total scores and subscale scored (mental or cognitive energy, social motivation and physical energy)
Change from baseline DSST to week 8	2	**Cognitive functioning** Total scores
Change from baseline ODQ to week 8	2	**Emotional Functioning** Domain scores: Not caring (NC), Emotional detachment (ED), Positive Reduction (RD), General Reduction (RD), Antidepressant as Cause (AC)
Change from baseline MADRS to week 8	2	**Depressive symptoms**
Change from baseline SDS, CGI-S and CGI-I to week 8	2	**Overall functioning** SDS total and individual item scores (family, work, and social life) CGI-S score CGI-I score
Adverse events and potential discontinuations	S	**Safety** Potential discontinuation symptoms assessed at Week 1 after abrupt discontinuation of the current SSRI/SNRI by DESS total score
Digital biomarkers and digital phenotypes	E	Obtained with the phone application Discovery by Mindstrong.

ASSAY IX – Statistical Methodology

The change from baseline in ODQ total score was analyzed using a mixed model for repeated measurements ("MMRM") approach including site and week as fixed effects, baseline score as a continuous covariate and the baseline score-by-week interaction, based

on all available observations. Adjusted means with standard errors ("SEs") and p-values were reported. Safety and tolerability were assessed using descriptive statistics.

The following analysis sets were used for the analyses:

- All-patients-enrolled set ("APES") – all enrolled patients.
- All-patients-treated set ("APTS") – all patients in the APES wherein said patient took at least one dose of vortioxetine.
- Full-analysis set ("FAS") – all patients in the APTS wherein said patient had a valid baseline assessment and at least one valid post-baseline assessment of the ODQ total score.
- The effectiveness analyses were based on the FAS and the safety analyses were based on the APTS.

ASSAY X – Analysis of the Primary Endpoint:

Method	**Endpoints: Primary (1) / Secondary (2) / Safety (S) / Exploratory (E)**	**Comment**
Change from baseline ODQ to week 8	1	**Emotional Blunting** Total scores

The change from baseline in ODQ total score were analyzed using a MMRM approach. The model includes site and week as fixed effects, the baseline score as a continuous covariate and the baseline score-by-week interaction. The analysis was based on all available observations. The adjusted means of the model will be presented with two-sided 95% confidence intervals ("CIs").

ASSAY XI – Analysis of the Secondary Endpoints

Method	**Endpoints: Primary (1) / Secondary (2) / Safety (S) / Exploratory (E)**	**Comment**
Change from baseline MEI to week 8	2	**Motivation and Energy** Total scores and subscale scored (mental or cognitive energy, social motivation and physical energy)
Change from baseline DSST to week 8	2	**Cognitive functioning** Total scores

Change from baseline ODQ to week 8	2	**Emotional Functioning** Domain scores: Not caring (NC), Emotional detachment (ED), Positive Reduction (RD), General Reduction (RD), Antidepressant as Cause (AC)
Change from baseline MADRS to week 8	2	**Depressive symptoms**
Change from baseline SDS, CGI-S and CGI-I to week 8	2	**Overall functioning** SDS total and individual item scores (family, work, and social life) CGI-S score CGI-I score

For the secondary endpoints, the same methodology as that described for the primary analysis were used. All analyses include the baseline score for the specific endpoint as the baseline covariate, except for CGI-I, where the baseline score for the CGI-S were used. The SDS total score is defined as the sum of the 3 single items (work, social, family).

Descriptive Statistics

For the primary and secondary endpoints, descriptive statistics were presented by week for absolute values and, where relevant, changes from baseline. The distribution for the screening question on emotional effects were presented at week 8 with two-sided 95% confidence intervals.

Analyses of safety endpoints

Adverse events will be summarized using descriptive statistics.
Descriptive statistics will be presented for the DESS total score at Baseline and Week 1 with frequency tables for discontinuation emergent symptoms per DESS item.

The following examples show the results of the clinical trial methods described above.

Example 1 – Evaluation on emotional blunting by ODQ Total Score in patients with MDD wherein said patient experienced an inadequate response to SSRI or SNRI treatment and wherein said patient was switched to a treatment with 10-20 mg vortioxetine.

Patients were enrolled and treated as described in ASSAY I-III.

Data was collected according to ASSAY IV-VIII and analyzed according to ASSAY IX-XI. The below Table 2 and Figure 2 provides an overview of the ODQ total score (FAS, MMRM) from baseline, over week 1, 4 and the end of the study at week 8.

Table 2. Change from Baseline in ODQ Total Score (FAS, MMRM). The ODQ total score starting at about 90 was reduced by about 30 points at week 8.

Baseline			Treatment			95% CI		
N	Mean	Week	N	Mean	SE	lower	Upper	p-value
143	89.37	1	143	-9.62	1.59	-12.77	-6.48	<0.0001
-	-	4	141	-21.19	1.83	-24.80	-17.58	<0.0001
-	-	8	131	-29.84	1.91	-26.05	-26.05	<0.0001

The ODQ total score starting at about 90 was reduced by about 30 points at week 8, thus a relative reduction of the ODQ Score by a third. Patients switched from SSRI or SNRI to vortioxetine felt relief of the emotional blunting within the first week of switching to vortioxetine 10 mg treatment.

These data demonstrate that in this sub-group of patients experiencing emotional blunting resulting from an inadequate response to SSRI or SNRI treatment, vortioxetine provides a surprisingly fast and efficient relief of these unwanted effects. It is noteworthy that the effect of vortioxetine on emotional blunting as measured by the ODQ was significant already after 1 week of treatment and continued to increase in size over the next 7 weeks of treatment. To the extent that the emotional blunting the patients experienced prior to entering the study was a cause and side effect of their prescribed antidepressant (either SSRI or SNRI), it is clear that side-effect was resolved within 1-2 weeks after stopping treatment given the half-life of these medications. Vortioxetine thereby continued to improve symptoms of emotional blunting irrespective of prior medication.

The distribution of the ODQ at baseline was checked and can be reported as histograms in normally distributed patterns, see Figure 3.

Example 2 – Evaluation of ODQ domain score domains in patients with MDD wherein said patient experienced an inadequate response to SSRI or SNRI treatment and wherein said patient was switched to a treatment with 10-20 mg vortioxetine.

Patients were enrolled and treated as describe in ASSAY I-III. Data was collected according to ASSAY IV-VIII and analyzed according to ASSAY IX-XI.

The below Tables 3-8 provide an overview of the ODQ domain scores Not Caring (NC), Emotional Detachment (ED), Positive Reduction (RD), General Reduction (RD), Antidepressant as Cause (AC) and ODQ total score without AC (FAS, MMRM) from baseline, over weeks 1, 4 and the end of the study at week 8.

Table 3. Change from Baseline in ODQ Not Caring (NC) Score (FAS, MMRM). The ODQ NC score starting at about 18 was reduced by about 6 points at week 8.

Baseline			Treatment			95% CI		
N	Mean	Week	N	Mean	SE	lower	Upper	p-value
143	18.15	1	143	-1.40	0.42	-2.22	-0.57	0.0010
-	-	4	141	-3.94	0.46	-4.84	-3.04	<0.0001
-	-	8	131	-5.98	0.52	-7.02	-4.95	<0.0001

Table 4. Change from Baseline in ODQ Emotional Detachment (ED) Score (FAS, MMRM). The ODQ ED score starting at about 15 was reduced by about 5 points at week 8.

Baseline			Treatment			95% CI		
N	Mean	Week	N	Mean	SE	lower	Upper	p-value
143	14.69	1	143	-1.04	0.45	-1.92	-0.16	0.0212
-	-	4	141	-3.10	0.46	-4.00	-2.20	<0.0001
-	-	8	131	-4.72	0.46	-5.63	-3.81	<0.0001

Table 5. Change from Baseline in ODQ Positive Reduction (PR) Score (FAS, MMRM). The ODQ PR score starting at about 22 was reduced by about 8 points at week 8.

Baseline			Treatment			95% CI		
N	Mean	Week	N	Mean	SE	lower	Upper	p-value
143	21.97	1	143	-2.60	0.40	-3.39	-1.81	<0.0001
-	-	4	141	-5.61	0.50	-6.59	-4.62	<0.0001
-	-	8	131	-7.81	0.55	-8.89	-6.73	<0.0001

Table 6. Change from Baseline in ODQ General Reduction (GR) Score (FAS, MMRM). The ODQ GR score starting at about 19 was reduced by about 7 points at week 8.

Baseline			Treatment			95% CI		
N	Mean	Week	N	Mean	SE	lower	Upper	p-value
143	18.85	1	143	-2.29	0.43	-3.14	-3.14	<0.0001
-	-	4	141	-4.49	0.44	-5.35	-5.35	<0.0001
-	-	8	131	-6.56	0.44	-7.44	-5.68	<0.0001

Table 7. Change from Baseline in ODQ General Reduction (GR) Score (FAS, MMRM). The ODQ GR score starting at about 16 was reduced by about 5 points at week 8.

Baseline			Treatment			95% CI		
N	Mean	Week	N	Mean	SE	lower	Upper	p-value
143	15.72	1	143	-2.49	0.53	-3.53	-1.44	<0.0001
-	-	4	141	-4.28	0.52	-5.31	-3.25	<0.0001
-	-	8	131	-5.08	0.50	-6.07	-4.09	<0.0001

Table 8. Change from Baseline in ODQ total score without AC (FAS, MMRM). The ODQ Section 1+2 score starting at about 74 was reduced by about 25 points at week 8.

Baseline			Treatment			95% CI		
N	Mean	Week	N	Mean	SE	lower	Upper	p-value
143	73.64	1	143	-7.07	1.29	-9.62	-4.53	<0.0001
-	-	4	141	-16.83	1.52	-19.83	-13.83	<0.0001
-	-	8	131	-24.73	1.62	-27.92	-21.54	<0.0001

From the above presented data, it is evident that a reduction in ODQ total score was not driven by one or a few domains. The decrease in ODQ total scores were seen across all domains of the emotional blunting, NC, PR, ED, GR, and AC. AC indicated to which degree patients considered their symptoms related to the antidepressant they were taking.

Evaluating the ODQ total score without AC, the change from baseline of about 74 by about 25 points at week 8 was the same relative change of about a third, as reported in Example 1.

Example 3 – Evaluation of Screening Question on emotional effects in patients with MDD wherein said patient experienced an inadequate response to SSRI or SNRI treatment and wherein said patient was switched to a treatment with 10-20 mg vortioxetine.

Patients were enrolled and treated as described in ASSAY I-III. Data was collected according to ASSAY IV-VIII and analyzed according to ASSAY IX-XI.

As part of the patient enrollment as described in ASSAY II, the question *"Emotional effects vary, but may include, for example, feeling emotionally "numbed" or "blunted" in some way; lacking positive emotions or negative emotions; feeling detached from the world around you; or "just not caring" about things that you used to care about. Have you experienced such emotional effects during the last 6 weeks?"* was answered with "yes" by all patients enrolled in the study.

The below Table 9 reviews how many of the patients after treatment with vortioxetine answered "No" to the same question.

Table 8. Response to Screening Question on Emotional Effects at week 8.

Week 8			95% CI	
N	n (answered "NO")	%	lower	Upper
138	68	49.3	40.9	57.6

From the above presented data, it is evident that about 50% of the patients, wherein said patient replied that they had indeed experienced emotional effects of numbing or blunting within the last 6 weeks during a treatment with SSRI or SNRI, now answered that these effects are not present anymore after 8 weeks of treatment with vortioxetine.

Example 4 – Evaluation of MADRS in patients with MDD wherein said patient experienced an inadequate response to SSRI or SNRI treatment and wherein said patient was switched to a treatment with 10-20 mg vortioxetine.

Patients were enrolled and treated as describe in ASSAY I-III. Data was collected according to ASSAY IV-VIII and analyzed according to ASSAY IX-XI. For the MADRS scale, lower scores indicated less severe depression.

The total MADRS Score baseline (FAS, MMRM) from about 25 was reduced by about 14 points over the course of 8 weeks after switching the patients to vortioxetine treatment. Response defined as at least 50% reduction in total MADRS score from baseline (FAS, observed cases (OC)) was registered in about 62% of patients at week 8. Remission defined as a MADRS total score (FAS, OC) of 10 or less at week 8 was registered to about 47%.

Example 5 – Evaluation of CGI-S of patients with MDD wherein said patient experienced an inadequate response to SSRI or SNRI treatment and wherein said patient was switched to a treatment with 10-20 mg vortioxetine.

Patients were enrolled and treated as describe in ASSAY I-III. Data was collected according to ASSAY IV-VIII and analyzed according to ASSAY IX-XI. For the CGI-S scale, lower scores indicated less severity of disease.

CGI baseline scores (FAS, MMRM) of about 4.5 were reduced by about 2 points and the remission expressed by CGI-S Score (FAS, OC) was found to be about 48%, which is similar to the findings of the level of remission reported in Example 4.

Example 6 – Evaluation of MEI in patients with MDD wherein said patient experienced an inadequate response to SSRI or SNRI treatment and wherein said patient was switched to a treatment with 10-20 mg vortioxetine.

Patients were enrolled and treated as describe in ASSAY I-III. Data was collected according to ASSAY IV-VIII and analyzed according to ASSAY IX-XI. In the MEI scores, higher scores equal higher motivation and energy.

The below Table 10 provides insight into the MEI total Score.

Table 10. Change from Baseline in MEI (FAS, MMRM). The MEI score starting at about 44 was increased by about 34 points at week 8.

Baseline			Treatment			95% CI		
N	Mean	Week	N	Mean	SE	lower	Upper	p-value
141	44.45	4	141	23.54	2.40	18.78	28.29	<0.0001
-	-	8	130	34.28	2.75	28.85	39.72	<0.0001

The MEI total score starting at about 44 was increased by about 34 points at week 8, thus a relative increase of the MEI Score by more than 85%. Patients switched from SSRI to SNRI to vortioxetine felt an increase in levels of motivation and energy.

The distribution of the MEI at baseline was checked and can be reported as histograms in normally distributed patterns, see Figure 4.

Example 7 – Evaluation of MEI sub scores in patients with MDD wherein said patient experienced an inadequate response to SSRI or SNRI treatment and wherein said patient was switched to a treatment with 10-20 mg vortioxetine.

Patients were enrolled and treated as describe in ASSAY I-III. Data was collected according to ASSAY IV-VIII and analyzed according to ASSAY IX-XI. In the MEI scores, higher scores equaled higher motivation and energy.

The below Tables 11-13 provide insight into the MEI total sub scores; mental and cognitive energy score, Social Motivation score, and physical energy score (FAS, MMRM).

Table 11. Change from Baseline in MEI sub score Mental and cognitive energy score (FAS, MMRM). The Mental and cognitive energy score starting at about 21 was increased by about 15 points at week 8.

Baseline			Treatment			95% CI		
N	Mean	Week	N	Mean	SE	lower	Upper	p-value
141	21.61	4	141	10.99	1.12	8.78	13.20	<0.0001
-	-	8	130	14.98	1.23	12.55	17.40	<0.0001

Table 12. Change from Baseline in MEI sub score Social Motivation score (FAS, MMRM). The Social Motivation score starting at about 14 was increased by about 10 points at week 8.

Baseline			Treatment			95% CI		
N	Mean	Week	N	Mean	SE	lower	Upper	p-value
141	13.51	4	141	5.79	0.81	4.16	7.37	<0.0001
-	-	8	130	9.55	0.92	7.73	11.37	<0.0001

Table 13. Change from Baseline in MEI sub score physical energy (FAS, MMRM). The physical energy score starting at about 9 was increased by about 10 points at week 8.

Baseline			Treatment			95% CI		
N	Mean	Week	N	Mean	SE	lower	Upper	p-value
141	9.33	4	141	7.16	0.78	5.61	8.70	<0.0001
-	-	8	130	10.30	0.88	8.57	12.03	<0.0001

From the above presented data, it is evident that an increase in MEI total score reported in Example 6 was not driven by one MEI sub score alone. The increase in MEI total scores was seen across all three sub scores—cognitive energy, social motivation, and physical energy.

Example 8 – Evaluation of SDS in patients with MDD wherein said patient experienced an inadequate response to SSRI or SNRI treatment and wherein said patient was switched to a treatment with 10-20 mg vortioxetine.

Patients were enrolled and treated as describe in ASSAY I-III. Data was collected according to ASSAY IV-VIII and analyzed according to ASSAY IX-XI. For the SDS scale, the lower the score the greater the overall functioning, and the less functional impairment.

The below Table 14 provides insight into the SDS total Score.

Table 14. Change from Baseline in SDS (FAS, MMRM). The SDS total score starting at about 21 was decreased by about 8 points at week 8.

Baseline			Treatment			95% CI		
N	Mean	Week	N	Mean	SE	lower	Upper	p-value
141	20.61	8	131	-7.73	0.91	-9.53	-5.94	<0.0001

The above data supports that the total disability score covering activities at work, at home, and social life is improved after 8 weeks of treatment with vortioxetine.

Example 9 – Evaluation of SDS sub scores in patients with MDD wherein said patient experienced an inadequate response to SSRI or SNRI treatment and wherein said patient was switched to a treatment with 10-20 mg vortioxetine

Patients were enrolled and treated as describe in ASSAY I-III. Data was collected according to ASSAY IV-VIII and analyzed according to ASSAY IX-XI.

The below Tables 15-17 provide insight into the SDS sub scores; Work/school score, Social life score, Life/Home Responsibility Score (FAS, MMRM).

Table 15. Change from Baseline in SDS sub score Work/school score (FAS, MMRM). The Work/school score starting at about 7 was decreases by about 3 points at week 8.

Baseline			Treatment			95% CI		
N	Mean	Week	N	Mean	SE	lower	Upper	p-value
90	7.48	8	90	-3.19	0.40	-9.98	-2.40	<0.0001

Table 16. Change from Baseline in SDS sub score Social life score (FAS, MMRM). The Social life score starting at about 7 was decreased by about 2 points at week 8.

Baseline			Treatment			95% CI		
N	Mean	Week	N	Mean	SE	lower	Upper	p-value
131	6.74	8	131	-2.42	0.30	-3.02	-1.82	<0.0001

Table 17. Change from Baseline in SDS sub score Life/Home Responsibility (FAS, MMRM). The Life/Home Responsibility score starting at about 7 was decreased by about 2.5 points at week 8.

Baseline			Treatment			95% CI		
N	Mean	Week	N	Mean	SE	lower	Upper	p-value
131	6.66	8	131	-2.54	0.32	-3.18	-1.89	<0.0001

The above data supports that the total disability across at work at home and in social contexts is improved after 8 weeks of treatment with vortioxetine.

Example 10 – Evaluation of cognition by DSST scores in patients with MDD wherein said patient experienced an inadequate response to SSRI or SNRI treatment and wherein said patient was switched to a treatment with 10-20 mg vortioxetine.

Patients were enrolled and treated as describe in ASSAY I-III. Data was collected according to ASSAY IV-VIII and analyzed according to ASSAY IX-XI. For the DSST, a higher score indicated greater cognitive performance.

The below Table 18 provides an overview of the effect of vortioxetine on cognitive performance as measured by the DSST (FAS, MMRM).

Table 18. Change from Baseline in DSST score (FAS, MMRM). The DSST score starting at about 46 was increased by about 8 points at week 8.

Baseline			Treatment			95% CI		
N	Mean	Week	N	Mean	SE	lower	Upper	p-value
142	45.93	1	142	4.31	0.88	2.56	6.05	<0.0001
-	-	8	130	7.83	0.92	6.01	9.65	<0.0001

The above data shows that vortioxetine has pro-cognitive effects, increasing the baseline score of the DSST of 46 by 8 points.

Example 11 – Evaluation of correlation between MEI total Score and ODQ total score in patients with MDD wherein said patient experienced an inadequate response to SSRI or SNRI treatment and wherein said patient was switched to a treatment with 10-20 mg vortioxetine.

Patients were enrolled and treated as describe in ASSAY I-III. Data was collected according to ASSAY IV-VIII and analyzed according to ASSAY IX-XI.

The correlation analysis showed that, for vortioxetine, there is a correlation between the total scores of MEI and ODQ ($r = -0,778$; $p<0,001$), namely the less emotional blunted, the more energy and motivation was reported by the patient. Even after adjustment for improvements of MADR total score, the associations were still of moderate strength having high significance ($r = -0,532$; $p<0,001$). See Table 20 and Example 13.

Example 12 – Evaluation of correlation between ODQ total Score and SDS total score in patients with MDD wherein said patient experienced an inadequate response to SSRI or SNRI treatment and wherein said patient was switched to a treatment with 10-20 mg vortioxetine.

Patients were enrolled and treated as describe in ASSAY I-III. Data was collected according to ASSAY IV-VIII and analyzed according to ASSAY IX-XI.

The correlation analysis showed that, for vortioxetine, there is a correlation between the total scores of the SDS and ODQ (r = 0,699, p<0,001), namely the less emotional blunted, the greater the overall functioning. Even after adjustment for improvements of MADR total score, the associations were still of moderate strength having high significance (r = -0,5438; p<0,001). See Table 20 and Example 13.

Example 13 – Summary of clinical assessment of emotional blunting and partial correlation and mediation analyses.

At week 8, the mean change from baseline in ODQ total score was -29.8 (SE = 1.9; p <0.0001), and with significant changes seen already from week 1 (Table 19; Figure 5). Significant changes were seen across all ODQ subdomains, ranging from -7.8 (SE = 0.6; p<0.0001) (Positive Reduction) to -4.7 (SE = 0.5; p<0.0001) (Emotional Detachment) at week 8. The change from baseline in the 'Antidepressant as Cause' domain was -5.1 (SE = 0.5); omitting the subscale score for this domain from the total score in the primary analysis resulted in a change from baseline to week 8 of -24.7 (SE = 1.6) points. At week 8, 50% of all patients reported no emotional blunting on the standardized screening question. On the MADRS anhedonia factor score, a significant effect was observed from week 1 (-2.2; p<0.0001), increasing to week 4 (-5.9; p<0.0001) and week 8 (-8.9; p<0.0001).

Table 19. Effect on Emotional Blunting, Motivation/Energy, Cognitive Performance, Depressive Symptoms and Overall Functioning (FAS, MMRM).

	Mean change from baseline (SE)		
	Week 1	**Week 4**	**Week 8**
ODQ total score	-9.6 (1.6)	-21.2 (1.8)	-29.8 (1.9)
MADRS total score	-3.3 (0.5)	-9.2 (0.6)	-13.8 (0.7)
MADRS anhedonia factor score	-2.2 (0.3)	-5.9 (0.4)	-8.9 (0.4)
CGI-S	-0.3 (0.1)	-1.1 (0.1)	-1.8 (0.1)
CGI-I1	2.6 (0.1)	2.0 (0.1)	2.0 (0.1)
MEI total score	-	23.5 (2.4)	34.3 (2.8)
Mental or Cognitive Energy	-	11.0 (1.1)	15.0 (1.2)

Social Motivation	-	5.7 (0.8)	9.6 (0.9)
Physical Energy	-	7.1 (0.8)	10.3 (0.9)
SDS total score	-	-	-7.7 (0.9)
Work/School	-	-	-3.2 (0.4)
Social Life	-	-	-2.4 (0.3)
Family/Home	-	-	-2.5 (0.3)
DSST	4.3 (0.9)	-	7.8 (0.9)

$p<0.0001$ for all changes vs baseline. *Absolute scores.

Other Clinical Assessments

Improvements in motivation and energy assessed using the MEI were substantial and significant already from week 4 and across all subdomains; cognitive and mental energy, social motivation, and physical energy (Table 18; Figure 6). Significant improvement in cognitive performance (DSST) was observed already at week 1 (4.3; $p<0.0001$) and increasing to week 8 (7.8; $p<0.0001$) (Table 18). Significant improvements from baseline to week 8 in overall functioning as measured by the SDS were observed for the total score as well as the single items, most pronouncedly in the Work/School domain (Table 19). Overall depressive symptom resolution as measured by the MADRS total score improved significantly from week 1 (-3.3; $p<0.0001$) and continuously increasing to week 8 (13.8; $p<0.0001$). The rates of response and remission at week 8 as measured by the MADRS were 61.8% and 46.6%, respectively.

Repeating the primary analysis with additional correction for baseline and change from baseline in MADRS total score resulted in a change from baseline to week 8 in ODQ total score of -30.2 (SE = 1.9), which was reduced to -10.8 (SE = 2.4) when adjusting for the change from baseline in MADRS total score, corresponding to 36% of the improvement in ODQ being independent of the observed MADRS improvement.

The partial correlation analyses showed that the changes from baseline to week 8 in QDQ total score and SDS total score were strongly and positively correlated ($r = 0.699$; $p<0.0001$; Table 19). Further, change in ODQ was negatively correlated with change in MEI total score ($r = -0.778$; $p <0.0001$); *i.e.*, improved emotional blunting was associated with better outcomes in functioning outcome as well as energy and motivation. After adjustment for improvement in MADRS total score, these associations were still of moderate strength and highly significant, with partial *r*'s between changes in ODQ and SDS of 0.438 ($p<0.0001$) and ODQ and MEI of -0.532 ($p<0.0001$) (Table 20).

The mediation analysis further showed that 63.4% of the change in SDS total score explained by change in ODQ total score was a *direct effect* of improvement in ODQ after switching to vortioxetine that could not be explained by improved depressive symptoms (MADRS), which accounted for 36.6% of the effect on SDS total score (Figure 7).

Table 19. Partial correlations among improvements in emotional blunting, motivation and energy, functional outcomes at week 8.

	ODQ total score			
	N	MADRS unadjusted[a]	N	MADRS adjusted[b]
MEI total score	130	-0.778	130	-0.532
SDS total score	131	0.699	131	0.438
SDS Work/School	90	0.700	90	0.514
SDS Social Life	131	0.674	131	0.434
SDS Family Life/Home Responsibilities	131	0.662	131	0.383

$p<0.0001$ for all coefficients. a. Adjusted for site and baseline scores. b. Adjusted for site, baseline scores, and MADRS total score at baseline and change from baseline.