Original Paper

The safety and tolerability of vortioxetine: Analysis of data from randomized placebo-controlled trials and open-label extension studies

Psychopharm

Journal of Psychopharmacology
2016, Vol. 30(3) 242–252

Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/0269881116628440
jop.sagepub.com

David S Baldwin[1,2], Lambros Chrones[3], Ioana Florea[4], Rebecca Nielsen[4], George G Nomikos[3], William Palo[3] and Elin Reines[4]

Abstract

The safety and tolerability of vortioxetine in adults with major depressive disorder was assessed. Tolerability was based on the nature, incidence and severity of treatment-emergent adverse events (TEAEs) during acute (6/8) week treatment in 11 randomized, double-blind placebo-controlled short-term studies in major depressive disorder: six with an active reference. Symptoms following discontinuation were assessed through the Discontinuation-Emergent Signs and Symptoms checklist in three studies. Long-term (⩽52 weeks) tolerability was evaluated in five open-label extension studies. Patients (*n* =5701) were acutely treated with either placebo (*n*=1817), vortioxetine (5–20mg/day; *n*=3018), venlafaxine XR (225mg/day; *n*=113) or duloxetine (60mg/day; *n*=753). The withdrawal rate due to TEAEs during treatment with vortioxetine (5–20mg/day) was 4.5–7.8%, compared with placebo (3.6%), venlafaxine XR (14.2%) or duloxetine (8.8%). Common TEAEs (incidence ⩾5% and >2 × placebo) with vortioxetine (5–20mg/day) were nausea (20.9–31.2%) and vomiting (2.9–6.5%). For vortioxetine (5–20mg/day), the incidence of TEAEs associated with insomnia was 2.0–5.1% versus 4.0% for placebo, and with sexual dysfunction 1.6–1.8% versus 1.0% for placebo. Discontinuation symptoms as assessed by the mean Discontinuation-Emergent Signs and Symptoms total score after abrupt discontinuation were comparable to placebo in the first and second week. Vortioxetine had no effect relative to placebo on clinical laboratory parameters, body weight, heart rate or blood pressure. Vortioxetine showed no clinically relevant effect on ECG parameters, including the QTcF interval. In long-term treatment, no new types of TEAEs were seen; the mean weight gain was 0.7–0.8kg. Thus, vortioxetine (5–20mg/day) appears safe and generally well tolerated in the treatment of major depressive disorder.

Keywords

Major depressive disorder, safety, tolerability, vortioxetine

Introduction

The tolerability of antidepressant treatment affects quality of life and adherence with medication (Cleare et al., 2015). There are differences between antidepressants in mode of action, efficacy and tolerability. Adverse effects often associated with antidepressant treatment include sexual dysfunction, discontinuation symptoms, weight gain, gastrointestinal effects, sleep disturbances and suicidal behaviour. For patients with major depressive disorder (MDD) long-term treatment (at least 6–12 months) is recommended for patients who have responded to acute treatment to prevent relapse and recurrence (Cleare et al., 2015; Lam et al., 2009). Long-term tolerability studies are therefore required during clinical development to determine whether safety concerns arise that were not identified in the acute treatment studies.

Vortioxetine is a novel antidepressant with multimodal activity: it is a $5HT_3$, $5HT_7$ and $5HT_{1D}$ receptor antagonist, a $5HT_{1B}$ partial agonist, a $5HT_{1A}$ agonist and an inhibitor of the serotonin (5-HT) transporter (Bang-Andersen et al., 2011). Vortioxetine was licensed in late 2013 in the USA and the EU and subsequently in other countries for the treatment of adults with MDD with approved dosages of 5 mg, 10 mg, 15 mg and 20 mg. The cytochrome P450 (CYP450) pathway is important for the oxidative metabolism of various drugs and is therefore implicated in drug–drug interactions (Chen et al., 2013). Vortioxetine is metabolized by multiple CYP450s and has little inhibition or induction effect on the CYP system. Vortioxetine has therefore a low potential for clinically relevant interactions with other drugs.

The present analysis was conducted to evaluate the safety and tolerability of vortioxetine using the vortioxetine clinical trial database. Patient-level data were pooled from 11 acute (6–8 weeks) randomized, placebo-controlled fixed-dose MDD, and pooled separately from five long-term (up to 52 weeks) open-label MDD studies. For completeness, safety and tolerability data pooled from four short-term (eight weeks) placebo-controlled studies in patients with generalized anxiety disorder (GAD) were

[1]Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK
[2]University Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa
[3]Takeda Development Center Americas, Deerfield, IL, USA
[4]H Lundbeck A/S, Copenhagen, Denmark

Corresponding author:
David S Baldwin, University Department of Psychiatry, Academic Centre, College Keep, 4-12 Terminus Terrace, Southampton SO14 3DT, UK.
Email: dsb1@soton.ac.uk

analysed. In addition, the results of clinical pharmacology studies involving potential safety issues are briefly discussed.

Methods

Data source

Safety and tolerability data were included from all published randomized, double-blind, placebo-controlled, studies and open-label studies with vortioxetine for the treatment of MDD, at the recommended therapeutic dosages of 5–20 mg/day. The analyses used patient-level data from clinical studies with vortioxetine sponsored by H Lundbeck A/S or the Takeda Pharmaceutical Company Ltd. The analyses are based on 11 placebo-controlled short-term studies and five long-term open-label studies in patients with MDD (Table 1). In 10 short-term MDD studies, eligible patients were aged ⩾18 and ⩽75 years and in one study (Katona et al., 2012) eligible patients were ⩾65 years of age. Six studies included an active reference (venlafaxine or duloxetine) to evaluate the internal validity (assay sensitivity) of the studies. Comparisons between vortioxetine and the active references were not made. Patients in the open-label MDD studies were completers of one of the acute studies and, in the clinical opinion of the investigator, were considered likely to benefit from 52-week treatment with vortioxetine.

Safety and tolerability was based on the nature, incidence and severity of treatment-emergent adverse events (TEAEs), electrocardiogram (ECG) parameters, vital signs and clinical safety laboratory values during acute treatment in placebo-controlled studies.

TEAEs were assessed during the studies by using open, non-leading questions to patients and observations by the study investigators or spontaneous reports by patients. Medically qualified personnel were responsible for ensuring that TEAEs were coded using the lowest level term according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 14.1. Investigators were asked to rate TEAEs as mild, moderate or severe, based on the patient's discomfort, health risk and interference with activities. For the short-term studies, TEAE incidence rates during the treatment period were presented for common TEAEs (incidence ⩾5%) and those with an incidence >2 × placebo were highlighted. Common TEAEs were also presented from the long-term (i.e. 52 weeks) MDD studies. Furthermore, to exclude TEAEs reported by patients switched from placebo or active reference treatment in the short-term lead-in studies, and for the two-week drug holiday due to the discontinuation period, analyses were made both with and without data from the first eight weeks of the open-label studies. This allowed the evaluation of long-term safety and tolerability in patients who received at least eight weeks of treatment with vortioxetine. When the data from the first eight weeks were excluded, TEAEs were defined as new adverse events that occurred after Week 8. Analyses of TEAEs were based on the core treatment period, which was from the first to the last dose of investigational medicine in the double-blind period for the short-term studies and the from first to the last dose of vortioxetine in the long-term open-label studies.

Suicidal ideation and behaviour were assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) in eight (NCT00672958, NCT00672620, NCT00735709, NCT01140906, NCT01153009, NCT01163266, NCT01422213, NCT01179516) of the eight-week placebo-controlled studies in MDD and in three of the open-label long-term studies (NCT00707980, NCT01323478, NCT01152996).

Discontinuation symptoms following the abrupt discontinuation of treatment with vortioxetine were assessed using the Discontinuation Emergent Signs and Symptoms (DESS) checklist (Rosenbaum et al., 1998) in three acute placebo-controlled studies in MDD in patients who completed the study (NCT01140906, NCT01153009 and NCT01163266). The DESS was assessed at Week 8 (baseline value), Week 9 (first week of discontinuation) and Week 10 (second week of discontinuation).

Clinical safety laboratory values included alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, albumin, calcium, creatinine, glucose, haemoglobin, haematocrit, potassium, sodium, bilirubin (total), platelets and leukocytes. Cardiovascular safety was assessed by examining changes in vital signs and ECG parameters from the clinical studies in patients and by a thorough QT study in healthy subjects (Wang et al., 2013). Vital signs including blood pressure and pulse rate were monitored as part of the safety assessments in each clinical study.

Statistical analyses

The analyses of safety and tolerability were based on the all-patients-treated set (APTS), which comprised all patients who took at least one dose of investigational medication. The number needed to harm (NNH) versus placebo was calculated for short-term treatment, stratifying by study, based on discontinuation rates due to TEAEs. The NNH is defined as the reciprocal of the risk difference and is given with the 95% confidence interval (CI). For modelling the vortioxetine dose effect of the TEAE incidence rates a logistic regression model was applied. A non-linear model was used to model the relationship between dose (0, 1, 2.5, 5, 10, 15, 20 mg) and the propensity to experience a TEAE, and included a random effect for study. The observed TEAE incidence rates at each dose level and a graph of the model fitted to these data are presented together. This was done for each of the TEAEs with an incidence ⩾5% in the short-term pool. Otherwise, statistical methods have been limited to summary tables, incidence rates and percentages.

The DESS data from the three studies were pooled and the mean DESS total scores at Weeks 8, 9 and 10 are presented using descriptive statistics. Duloxetine 60 mg/day was used as the active reference in all three studies.

Descriptive statistics are provided for the long-term open-label studies pooled according to the doses used in these studies (5 mg and 10 mg in NCT00761306, NCT00694304 and NCT00707980 and 15 mg and 20mg in NCT01323478 and NCT01152996). The open-label long-term studies were flexible-dose studies. Two of the studies (NCT00694304 and NCT00707980) included one dose (2.5 mg/day) that was lower than the recommended therapeutic dosage range and therefore patients on <5 mg/day for >50% of the treatment period were not included in the analyses.

In addition, safety and tolerability data from four published short-term placebo-controlled studies in GAD are also presented. In these studies, patients were treated with vortioxetine 2.5 mg, 5 mg and 10 mg/day, but only the 5 mg and 10 mg data are presented here, as these doses lie within the dosage range

Table 1. Summary data for studies included in the safety analyses (APTS).

NCT identifier	Treatment period	Dose, mg (*n*)	Inclusion criteria	Reference	Completion rate[a]
MDD Short-term studies					
NCT00839423 11492A	6 weeks	VOR 5 (108)	MADRS ⩾30	Alvarez et al., 2012	90.7%
		VOR 10 (100)	MDE ⩾3 months and <12		82.0%
		VLF 225 (113)	months		82.3%
		PBO (105)			82.9%
NCT00635219 11984A	8 weeks	VOR 2.5 (155)	MADRS ⩾26	Baldwin et al., 2012b	83.9%
		VOR 5 (157)	MDE ⩾3 months		77.7%
		VOR 10 (151)			77.5%
		DUL 60 (155)			72.9%
		PBO (148)			83.1%
NCT00735709 305	8 weeks	VOR 1 (140)	MADRS ⩾26	Henigsberg et al., 2012	90.7%
		VOR 5 (140)	MDE ⩾3 months		92.1%
		VOR 10 (139)			87.8%
		PBO (140)			90.7%
NCT01140906 13267A	8 weeks	VOR 15 (151)	MADRS ⩾26	Boulenger et al., 2014	77.5%
		VOR 20 (151)	CGI-S ⩾4		82.8%
		DUL 60 (147)	MDE ⩾3 months		89.1%
		PBO (158)	recurrent		84.2%
NCT01153009 315	8 weeks	VOR 15 (147)	MADRS ⩾26	Mahableshwarkar et al., 2015a	76.9%
		VOR 20 (154)	CGI-S ⩾4		73.4%
		DUL 60 (150)	MDE ⩾3 months		76.7%
		PBO (159)	recurrent		81.1%
NCT01163266 316	8 weeks	VOR 10 (155)	MADRS ⩾26	Jacobsen et al., 2015c	80.0%
		VOR 20 (150)	CGI-S ⩾4		81.3%
		PBO (157)	MDE ⩾3 months		88.5%
			recurrent		
NCT01422213 14122A	8 weeks	VOR 10 (195)	MADRS ⩾26	McIntyre et al., 2014	88.7%
		VOR 20 (207)	MDE ⩾3 months		86.0%
		PBO (196)	recurrent		83.2%
NCT00672958 303	6 weeks	VOR 5 (299)	MADRS ⩾30	Jain et al., 2013	81.6%
		PBO (298)	MDE ⩾3 months		79.2%
NCT00672620 304	8 weeks	VOR 2.5 (149)	MADRS ⩾22	Mahableshwarkar et al., 2013	66.4%
		VOR 5 (153)	MDE >3 months		79.7%
		DUL 60 (150)			73.3%
		PBO (151)			79.5%
NCT01179516 317	8 weeks	VOR 10 (154)	MADRS ⩾30	Mahableshwarkar et al., 2015b	85.1%
		VOR 15 (151)	CGI-S ⩾4		80.1%
		PBO (160)	MDE ⩾3 months		83.1%
NCT00811252 12541A	8 weeks	VOR 5 (156)	MADRS ⩾26	Katona et al., 2012	87.2%
		DUL 60 (151)	MDE >4 weeks		84.8%
		PBO (145)	⩾1 MDE before 60 years of age		88.3%
MDD Open-label long-term studies					
NCT00761306 11492C	52 weeks	VOR 5–10 (74)	Extension of NCT00839423	Florea et al., 2012	73.0%
NCT00694304 11984B	52 weeks	VOR 2.5–10 (535)	Extension of NCT00635219	Baldwin et al., 2012a	61.3%
NCT00707980 301	52 weeks	VOR 2.5–10 (834)	Extension of NCT00672620 and NCT00735709	Alam et al., 2014	63.1%
NCT01323478 13267B	52 weeks	VOR 15–20 (71)	Extension of NCT01140906	Filippov and Christens, 2013	66.2%
NCT01152996 314	52 weeks	VOR 15–20 (1073)	Extension of NCT0115300, NCT01163266 and NCT01179516	Jacobsen et al., 2015a	50.1%
GAD					
NCT00731120 308	8 weeks	VOR 2.5 (156)	HAM-A ⩾20	Mahableshwarkar et al., 2014b	76.9%
		VOR 5 (155)	MADRS ⩽16		75.5%
		VOR 10 (156)			71.2%

(Continued)

Table 1. (Continued)

NCT identifier	Treatment period	Dose, mg (*n*)	Inclusion criteria	Reference	Completion rate[a]
		DUL (154)			68.8%
		PBO (155)			78.1%
NCT00730691 309	8 weeks	VOR 2.5 (151)	HAM-A ⩾20	Mahableshwarkar et al., 2014a	72.2%
		VOR 10 (152)	MADRS ⩽16		76.3%
		PBO (153)			72.5%
NCT00734071 310	8 weeks	VOR 5 (148)	HAM-A ⩾20	Rothschild et al., 2012	84.5%
		PBO (151)	MADRS ⩽16		75.5%
NCT00744627 311	8 weeks	VOR 5 (150)	HAM-A ⩾20	Bidzan et al., 2012	85.3%
		PBO (150)	MADRS ⩽16		84.0%

[a]Based on the APTS.

APTS: all-patients treated set; CGI-S: Clinical Global Impression-Severity; DUL: duloxetine; GAD: generalized anxiety disorder; HAM-A: Hamilton Anxiety Rating Scale; MADRS: Montgomery Åsberg Depression Rating Scale; MDD: major depressive disorder; MDE: major depressive episode; NCT: National Clinical Trial registry number; PBO: placebo; VLF: venlafaxine XR; VOR: vortioxetine.

recommended for MDD. As for patients with MDD, the safety and tolerability of vortioxetine in patients with GAD are assessed based on the nature and incidence of adverse events, serious adverse events and adverse events leading to withdrawal.

Results

Short-term placebo-controlled MDD studies

In the short-term studies, 1817 patients were treated with placebo, 3018 with vortioxetine (5–20 mg/day), 113 with venlafaxine XR (225 mg/day) and 753 with duloxetine (60 mg/day). The majority of patients were women (approximately 66%) and Caucasian (approximately 83%), with a mean age of approximately 46 years (range 18–88 years); 692 patients (12.1%) were ⩾65 years of age, 96 of whom (1.7%) were ⩾75 years old.

TEAE withdrawal rates and NNH. The completion rates for each of the 11 short-term studies are shown in Table 1. The withdrawal rates due to TEAEs (stratified by study) in the short-term studies were vortioxetine 5 mg 4.5% versus placebo 3.7%, vortioxetine 10 mg 4.8% versus placebo 3.8%, vortioxetine 15 mg 7.8% versus placebo 3.8%, and vortioxetine 20 mg 7.1% versus placebo 3.3%. Based on these TEAE withdrawal rates, the NNHs (95% CI) for vortioxetine were 126 (non-significant) (5 mg), 94 (non-significant) (10 mg), 24 (14–99) (15 mg), and 26 (16–69) (20 mg). For the active references, the TEAE withdrawal rates were: venlafaxine XR 225 mg 14.2% versus placebo 3.8% and duloxetine 60 mg 8.8% versus placebo 4.6%, resulting in NNHs of 9 (5–33) (venlafaxine XR 225 mg) and 24 (14–60) (duloxetine 60 mg). For vortioxetine, the most common TEAE leading to withdrawal was nausea (Table 2).

Treatment-emergent adverse events. TEAEs with an incidence ⩾5% in any treatment arm are shown in Table 3. For vortioxetine, TEAEs with an incidence more than twice as high as with placebo were nausea and vomiting. There was a dose effect for vortioxetine for nausea and vomiting (Figure 1). In general, TEAEs with vortioxetine were rated as mild to moderate in intensity. The proportion of patients with TEAEs that were rated as severe was 4.6% (placebo), 5.8% (vortioxetine 5–20 mg), 8.2% (duloxetine) and 11.5% (venlafaxine XR). Of the patients who had nausea during treatment with vortioxetine, most reported nausea during the first two weeks of dosing. During the third week of treatment, the proportion of patients reporting nausea as a new TEAE was ~2% in all vortioxetine dose groups and 1% in the placebo group, and subsequently remained low. Nausea was transient with vortioxetine (5–20 mg/day), with a median duration of 9–16 days.

The overall incidence of TEAEs for the subgroup of patients aged ⩾65 years in the pooled analyses was 63.4% (185/292) for vortioxetine 5–20 mg and 59.8% (128/214) for placebo. The TEAEs reported by ⩾5% of patients were: nausea (22.3% and 7.0%), headache (8.9% and 15.4%), dizziness (7.5% and 6.5%), constipation (7.2% and 3.7%), diarrhoea (5.8% and 6.5%), dry mouth (5.8% and 4.7%) and fatigue (5.1% and 2.3%) for vortioxetine 5–20 mg and placebo, respectively. In a randomized placebo-controlled study in elderly patients with MDD treated with vortioxetine 5 mg (Katona et al., 2012) nausea was the only TEAE reported with an incidence ⩾5% that occurred > 2 x more frequently in the vortioxetine group than in the placebo group (21.8% *vs*. 8.3%).

Serious adverse events. The incidence of serious adverse events was 0.5% for placebo and 0.6% for vortioxetine (5–20 mg) with no dose relatedness or pattern in the nature of the events. Four deaths were reported in the MDD studies. A 74-year-old woman with a medical history of cholelithiasis and treated with vortioxetine 5 mg died from gall bladder cancer approximately one month after withdrawal from the study (NCT00635219). A 63-year-old man treated with vortioxetine 2.5 mg in the same study died after falling from a fourth-floor balcony (an event which was not judged by the investigator to represent a suicidal act). A 46-year-old man with a history of type 2 diabetes treated with open-label flexible dose of vortioxetine 5–10 mg died from pancreatic carcinoma eight months after withdrawal from the study (NCT00596817). A 56-year-old man treated with vortioxetine 5 mg died in a road traffic collision caused by another driver, in an open-label long-term extension study (NCT00694304).

Suicidal thoughts and behaviour. Suicide-related events (including the preferred terms *suicidal ideation*, *intentional overdose*, *intentional self-injury*, *self-injurious behaviour* and *suicide*

Table 2. TEAEs leading to withdrawal with an incidence ⩾0.5% in any vortioxetine group (APTS) in 11 short-term MDD studies.

Preferred term	Placebo (*n*=1817)	VOR 5 mg (*n*=1013)	VOR 10 mg (*n*=894)	VOR 15 mg (*n*=449)	VOR 20 mg (*n*=662)	VLF 225 mg (*n*=113)	DUL 60 mg (*n*=753)
Patients withdrawn	65 (3.6%)	46 (4.5%)	43 (4.8%)	35 (7.8%)	47 (7.1%)	16 (14.2%)	66 (8.8%)
Nausea	6 (0.3%)	12 (1.2%)	13 (1.5%)	17 (3.8%)	24 (3.6%)	4 (3.5%)	26 (3.5%)
Headache	4 (0.2%)	1 (<0.1%)	4 (0.4%)	4 (0.9%)	5 (0.8%)	3 (2.7%)	4 (0.5%)
Dizziness	6 (0.3%)	1 (<0.1%)	2 (0.2%)	2 (0.4%)	3 (0.5%)	2 (1.8%)	14 (1.9%)
Vomiting	2 (0.1%)	1 (<0.1%)	5 (0.6%)	2 (0.4%)	2 (0.3%)	1 (0.9%)	4 (0.5%)
Diarrhoea	2 (0.1%)	2 (0.2%)	3 (0.3%)	3 (0.7%)	1 (0.2%)	0	2 (0.3%)
Insomnia[a]	2 (0.1%)	5 (0.5%)	1 (0.1%)	1 (0.2%)	1 (0.2%)	4 (3.5%)	7 (0.9%)

[a]Includes the preferred terms: insomnia, initial insomnia, middle insomnia, hyposomnia, sleep disorder, dyssomnia, poor quality sleep, and terminal insomnia.
APTS: all patients treated set; DUL: duloxetine; MDD: major depressive disorder; TEAE: treatment-emergent adverse event; VLF: venlafaxine XR; VOR: vortioxetine.

Table 3. TEAEs with an incidence of ⩾5% in any group during the core treatment period (APTS) in 11 short-term MDD studies.

Preferred term	Placebo (*n*=1817)	VOR 5 mg (*n*=1013)	VOR 10 mg (*n*=894)	VOR 15 mg (*n*=449)	VOR 20 mg (*n*=662)	VLF 225 mg (*n*=113)	DUL 60 mg (*n*=753)
PYE	241.1	128.7	122.3	60.7	91.1	11.8	101.4
Patients with TEAEs	1052 (57.9%)	657 (64.9%)	546 (61.1%)	309 (68.8%)	433 (65.4%)	85 (75.2%)	571 (75.8%)
Nausea	148 (8.1%)	212 (**20.9**%)	208 (**23.3**%)	140 (**31.2**%)	184 (**27.8**%)	38 (**33.6**%)	257 (**34.1**%)
Headache	238 (13.1%)	144 (14.2%)	114 (12.8%)	66 (14.7%)	83 (12.5%)	32 (**28.3**%)	97 (12.9%)
Dry mouth	108 (5.9%)	71 (7.0%)	51 (5.7%)	27 (6.0%)	44 (6.6%)	19 (**16.8**%)	125 (**16.6**%)
Dizziness	101 (5.6%)	58 (5.7%)	48 (5.4%)	32 (7.1%)	42 (6.3%)	11 (9.7%)	92 (**12.2**%)
Diarrhoea	96 (5.3%)	71 (7.0%)	50 (5.6%)	42 (9.4%)	40 (6.0%)	5 (4.4%)	66 (8.8%)
Vomiting	20 (1.1%)	29 (2.9%)	37 (4.1%)	29 (**6.5**%)	30 (4.5%)	4 (3.5%)	31 (4.1%)
Constipation	54 (3.0%)	33 (3.3%)	34 (3.8%)	25 (5.6%)	28 (4.2%)	11 (**9.7**%)	73 (**9.7**%)
Insomnia[a]	73 (4.0%)	52 (5.1%)	33 (3.7%)	9 (2.0%)	22 (3.3%)	18 (**15.9%**)	61 (**8.1%**)
Somnolence	43 (2.4%)	31 (3.1%)	23 (2.6%)	12 (2.7%)	21 (3.2%)	1 (0.9%)	64 (**8.5**%)
Fatigue	51 (2.8%)	31 (3.1%)	25 (2.8%)	16 (3.6%)	16 (2.4%)	11 (**9.7**%)	60 (**8.0**%)
Decreased appetite	18 (1.0%)	20 (2.0%)	7 (0.8%)	3 (0.7%)	12 (1.8%)	1 (0.9%)	52 (**6.9**%)
Sexual dysfunction[b]	18 (1.0%)	16 (1.6%)	16 (1.8%)	7 (1.6%)	12 (1.8%)	14 (**12.4**%)	34 (4.5%)
Tremor	7 (0.4%)	12 (1.2%)	3 (0.3%)	6 (1.3%)	6 (0.9%)	6 (**5.3**%)	14 (1.9%)
Vision blurred	19 (1.0%)	7 (0.7%)	6 (0.7%)	9 (2.0%)	4 (0.6%)	6 (**5.3**%)	19 (2.5%)
Hyperhidrosis	32 (1.8%)	24 (2.4%)	21 (2.3%)	8 (1.8%)	3 (0.5%)	17 (**15.0**%)	55 (**7.3**%)

% values **in bold** are ⩾5% and >2 × placebo.
[a]Includes the preferred terms: insomnia, initial insomnia, middle insomnia, hyposomnia, sleep disorder, dyssomnia, poor quality sleep, and terminal insomnia.
[b]Includes the preferred terms: libido decreased, ejaculation delayed, ejaculation disorder, orgasm abnormal, anorgasmia, disturbance in sexual arousal, ejaculation failure, erectile dysfunction, loss of libido, orgasmic sensation decreased, sexual dysfunction, and vulvovaginal dryness.
APTS: all patients treated set; DUL: duloxetine; MDD: major depressive disorder; PYE: patient-years of exposure; TEAE: treatment-emergent adverse event; VLF: venlafaxine XR; VOR: vortioxetine.

attempt) were reported by 11 patients treated with vortioxetine (0.4%) and six patients treated with placebo (0.3%): there was no clinically relevant difference from placebo, and no indication of a dose effect with vortioxetine.

There were no clinically-relevant differences between the vortioxetine groups and placebo on newly-emergent suicidal ideation or behaviour. The proportion of patients with suicidal ideation (C-SSRS categories 1 to 5) was 16.1% (224/1393: placebo) compared with 14.6% (338/2322: vortioxetine 5–20 mg), with no indication of a dose effect or a clinically relevant difference from placebo. C-SSRS shift analysis compared all prior history and baseline (lifetime) events with any post-baseline event during the study using the most severe score for each patient over all visits in the time frame. Of the 836 patients in the placebo group who did not report suicidal ideation or behaviour during their lifetime, 34 patients (4.1%) reported treatment-emergent suicidal ideation during the study. Similarly, of 1464 patients in the vortioxetine 5–20 mg group who did not report suicidal ideation or behaviour during their lifetime, 39 patients (2.7%) reported treatment-emergent suicidal ideation and two patients (0.1%) reported treatment-emergent suicidal behaviour during the study. The proportion of patients aged 18–24 years with newly-emergent suicidal ideation (C-SSRS categories 1 to 5) was 13.2% (14/106: placebo) compared with 15.0% (25/167: vortioxetine 5–20 mg).

Akathisia, mania, hostility and aggression. In the short-term MDD studies, the incidence of *akathisia*, *restlessness* and *psychomotor hyperactivity* was 0.6% (placebo), 0.7% (vortioxetine 5–20 mg), 1.8% (venlafaxine XR) and 1.9% (duloxetine). The incidence of dyskinesia (including the preferred terms *muscle twitching* and *tic*) was 0.3% (placebo), 0.3% (vortioxetine 5–20 mg), 0% (venlafaxine XR) and 0.3% (duloxetine).The incidence

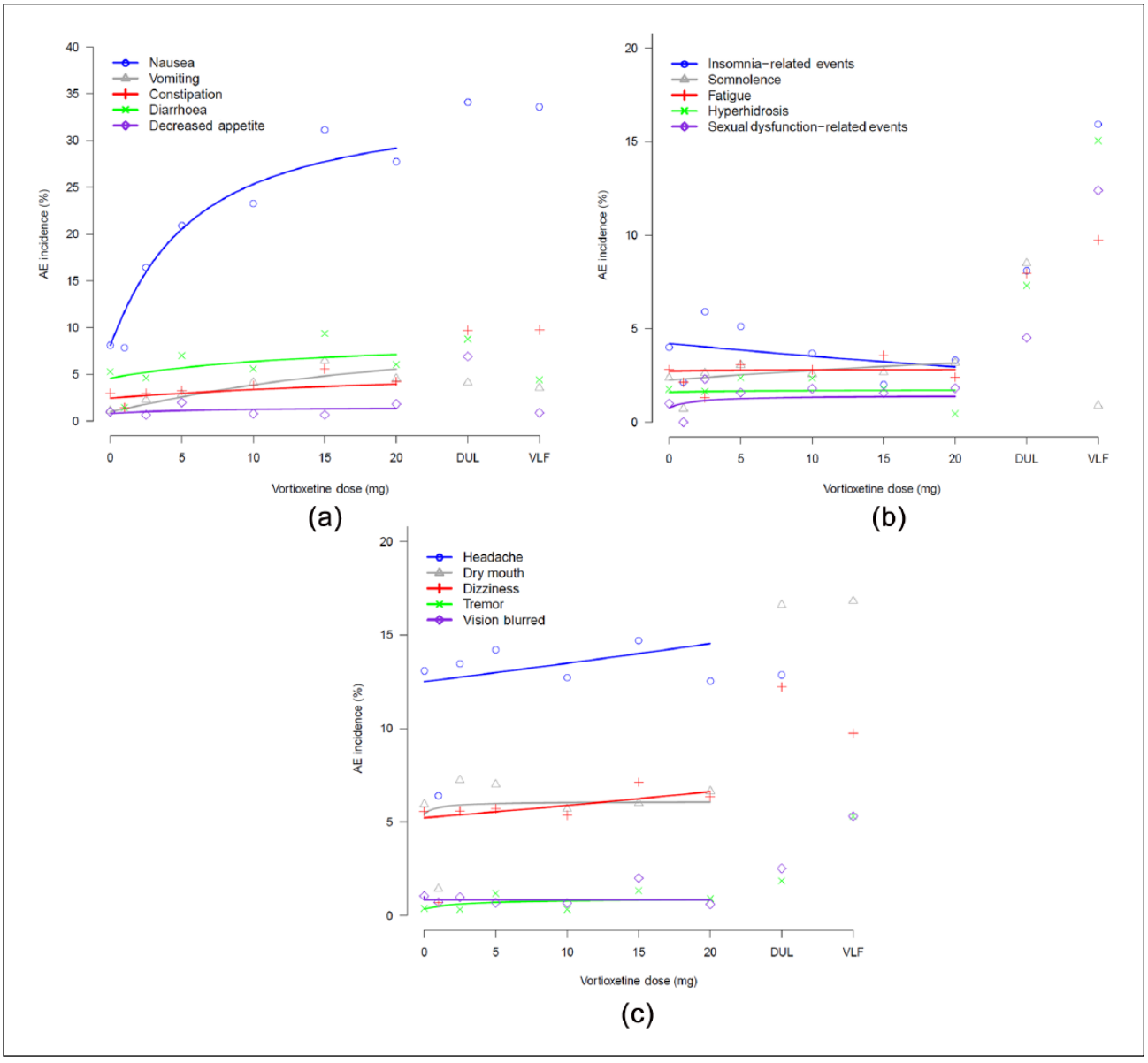

Figure 1. Treatment-emergent adverse event incidence from 11 placebo-controlled short-term major depressive disorder studies as a function of vortioxetine dose, with corresponding values for venlafaxine XR 225 mg and duloxetine 60 mg for comparison: (a) nausea, vomiting, constipation, diarrhoea and decreased appetite; (b) insomnia-related events, somnolence, fatigue, hyperhidrosis and sexual dysfunction-related events; (c) headache, dry mouth, dizziness, tremor and vision blurred.
AE: adverse event.

of events possibly associated with *hostility/aggression* (which includes the preferred terms *irritability*, *agitation*, *aggression*, *anger*, *psychomotor hyperactivity*, *affect lability*, *attention-seeking*, *behaviour*, *hypomania*, *impulsive behaviour*, *injury*, *laceration*, *mania*, *paranoia*) was 2.5% (placebo), 1.6% (vortioxetine 5–20 mg), 0% (venlafaxine XR) and 2.1% (duloxetine). For vortioxetine, none of these individual preferred terms had a higher incidence than for placebo. One vortioxetine-treated patient (out of 3018) had *hypomania* but none had *mania*.

Insomnia. The incidence of TEAEs associated with insomnia (*insomnia*, *initial insomnia*, *middle insomnia*, *hyposomnia*, *sleep disorder*, *dyssomnia*, *poor quality sleep* and *terminal insomnia*) was 4.0% for placebo, 2.0–5.1% for vortioxetine 5–20 mg, 15.9% for venlafaxine XR and 8.1% for duloxetine (Table 3).

Sexual dysfunction. The incidence of TEAEs associated with sexual dysfunction (*libido decreased*, *ejaculation delayed*, *ejaculation disorder*, *orgasm abnormal*, *anorgasmia*, *disturbance in sexual arousal*, *ejaculation failure*, *erectile dysfunction*, *loss of libido*, *orgasmic sensation decreased*, *sexual dysfunction* and *vulvovaginal dryness*) was 1.6–1.8% for vortioxetine and 1.0% for placebo (Table 3). For women, the incidence was 0.6–1.1% for vortioxetine versus 0.7% for placebo (compared with 4.8%

with venlafaxine XR and 1.2% with duloxetine) and for men, the incidence was 2.8–3.6% for vortioxetine versus 1.6% for placebo (compared with 21.6% with venlafaxine XR and 11.7% with duloxetine).

Discontinuation symptoms. Three studies (NCT01140906, NCT01153009 and NCT01163266) employed the DESS scale to assess for potential discontinuation symptoms in patients who completed short-term treatment with vortioxetine. Vortioxetine was abruptly discontinued at Week 8 (baseline value), whereas patients treated with duloxetine were down-tapered from 60 mg at Week 8 to 30 mg at Week 9 and to placebo at Week 10. Figure 2 presents a summary of the DESS total score at Weeks 8, 9 and 10 of the study. At Week 9, the DESS total scores for vortioxetine were 1.41 (10 mg), 1.58 (15 mg) and 1.58 (20 mg) compared with 0.96 (placebo) and 1.33 (duloxetine). At Week 10, the DESS total scores for vortioxetine were 1.60 (10mg), 1.60 (15 mg) and 1.56 (20 mg) compared with 1.19 (for placebo) and 2.85 (for duloxetine). These results are consistent with the incidence of TEAEs reported during the discontinuation period in these three studies.

Weight. During short-term treatment, the mean weight changes from baseline to Week 6/8 were similar for placebo (+0.1 kg change) and vortioxetine (–0.1 to 0.1 kg change). There was no trend for a dose effect for vortioxetine. The incidence of potentially clinically significant (PCS) weight increase (⩾7% increase from baseline) ranged from 0% (15 mg) to 1.2% (10 mg) for vortioxetine versus 0.6% for placebo. PCS weight decrease (⩾7% decrease from baseline) ranged from 0.2% (5 mg) to 1.3% (20 mg) for vortioxetine versus 0.6% for placebo.

Clinical safety laboratory values. The mean changes from baseline in haematology and clinical biochemical values were small, not judged clinically relevant, and similar in the placebo and vortioxetine groups; no trends over time or between the vortioxetine dose groups were seen. None of the clinical safety laboratory values demonstrated any clinically relevant differences between vortioxetine- and placebo-treated patients.

Cardiovascular parameters. There were no clinically relevant changes over time in blood pressure in patients treated with vortioxetine. In the short-term studies, the incidence of the TEAEs *hypertension* was 0.7% versus placebo (0.6%) and *blood pressure increased* was 0.4% versus placebo (0.6%) in the vortioxetine 5–20 mg group. All mean vital sign values were within the reference ranges. Overall, the mean changes from baseline in vital sign values were small, similar between the treatment groups and not clinically relevant. The incidences of PCS vital sign values were low (<2%) and similar between vortioxetine dose groups and placebo. The mean heart rate (in beats/min) was 68 (placebo) versus 67 (vortioxetine 5–20 mg).

In a thorough QT study (Wang et al., 2013) with 340 healthy men, the upper bound of the two-sided 90% CI around the least squares mean difference from placebo for baseline-adjusted QTcNi (linear) did not exceed 10 ms at any time point after multiple doses of vortioxetine 10 mg (therapeutic) or 40 mg (supratherapeutic). In the short-term studies, the mean QTcF interval at Week 8 was 408 ms (placebo) versus 408 ms (vortioxetine 5–20 mg), corresponding to a mean change from baseline to Week 6/8 of −0.65 ms (placebo) versus −0.1 ms (vortioxetine 5–20 mg). These results indicate that vortioxetine is unlikely to affect cardiac repolarization.

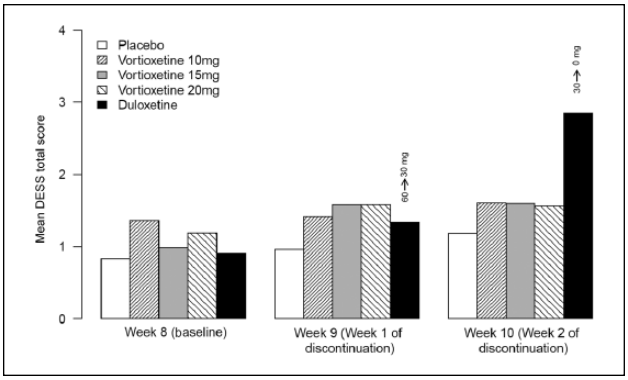

Figure 2. Discontinuation Emergent Signs and Symptoms (DESS) total score from three studies in patients treated with placebo (*n*=379), vortioxetine 10 mg (*n*=121), vortioxetine 15 mg (*n*=224), vortioxetine 20 mg (*n*=351) and duloxetine (*n*=241).

Long-term open-label studies

In the five extension studies (Table 1), 1313 patients were treated with 5–10 mg vortioxetine and 1144 patients with 15–20 mg vortioxetine, representing 1015 and 775 patient-years of exposure, respectively, with a median exposure of 52 weeks and 51 weeks, respectively. The completion rate for each of the five long-term studies is shown in Table 1. Patients had a mean age of approximately 45 years (5–10 mg studies) and approximately 44 years (15–20 mg studies) and the majority were women (approximately 65% for 5–10 mg studies and approximately 74% for the 15–20 mg studies). The most common TEAEs leading to withdrawal were nausea (0.8% and 2.7%), depression (0.7% and 0.4%), vomiting (0.2% and 1.0%), headache (0.2% and 0.7%), weight gain (0.2% and 0.5%) and insomnia related events (0.2% and 0.5%) for vortioxetine 5–10 mg and 15–20 mg, respectively.

Common TEAEs (reported by ⩾5 of patients in either dose group) in the long-term (52 weeks) open-label extension studies for vortioxetine 5–10 mg and 15–20 mg, respectively, were nausea (16.3% and 24.2%), headache (13.0% and 12.5%), diarrhoea (6.4% and 7.3%), nasopharyngitis (10.9% and 6.4%), weight gain (5.7% and 5.9%), dizziness (5.7% and 5.7%), insomnia-related events (5.0% and 7.1%), vomiting (3.5% and 6.3%), viral upper respiratory tract infection (1.8% and 6.2%), constipation (2.9% and 5.8%) and upper respiratory tract infection (4.6%, 5.1%). After omitting the first eight weeks of the open label study (see *Methods* and Figure 3), the incidences were: nausea (5.3% and 6.3%), headache (7.8% and 5.4%), diarrhoea (3.3% and 1.9%), nasopharyngitis (7.8% and 4.1%), weight gain (3.8% and 4.4%), dizziness (1.4% and 2.0%), insomnia related events (2.7% and 3.3%), vomiting (1.9% and 2.6%), viral upper respiratory tract infection (1.5% and 4.4%), constipation (1.1% and 2.2%) and upper respiratory tract infection (3.4% and

3.4%) for vortioxetine 5–10 mg and 15–20 mg, respectively. The proportion of patients with sexual dysfunction over 52 weeks was 1.7% (22/1313) (vortioxetine 5–10 mg) and 2.3% (26/1144) (vortioxetine 15–20 mg). No new types of TEAEs were seen in long-term treatment compared with acute vortioxetine treatment. The incidence of serious adverse events was 2.9% for vortioxetine 5–10 mg and 2.2% for vortioxetine 15–20 mg.

The mean weight change from the start of the lead-in studies to last assessment in the extension studies was +0.8 kg (n=1297) (5–10 mg) and +0.7 kg (n=1105) (15–20 mg). The mean weight change from the start of the extension studies was +0.8 (5–10 mg) and +0.5 kg (15–20 mg). The incidence of PCS weight increase (⩾7%) was similar in the 5–10 mg (13.3% (172/1297)) and 15–20 mg (11.0% (122/1105)) groups and the incidence of PCS weight decrease (⩾7%) was similar in the 5–10 mg (6.1% (79/1297)) and 15–20 mg (7.7% (85/1105)) groups.

The incidence of cardiovascular-related TEAEs was 1.8% for *hypertension* and 0.9% for *blood pressure increased*. All the mean vital sign values were within the reference ranges and changes from baseline to last assessment were small and not clinically relevant.

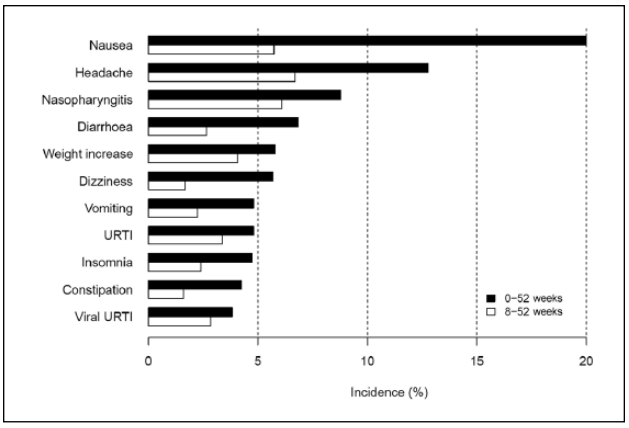

Figure 3. TEAE incidence (⩾5% for all patients during 52 weeks) with and without the first eight weeks (to exclude acute TEAEs from patients switched from other treatments and vortioxetine patients with a long drug holiday between the end of the lead-in study and start of the open-label extension study).
URTI: upper respiratory tract infection; TEAE: treatment-emergent adverse event.

Short-term placebo-controlled GAD studies

In the four short-term GAD studies, 609 patients were treated with placebo, 453 with vortioxetine 5 mg/day (62.5 patient-years of exposure), 308 with vortioxetine 10 mg/day (40.7 patient-years of exposure) and 154 with duloxetine 60 mg/day. The majority of patients were women (approximately 66%) and Caucasian (approximately 82%) with a mean age of approximately 41 years (range 18–89 years); 65 patients (4.3%) were ⩾65 years of age, 12 of whom (0.8%) were ⩾75 years old. The completion rates for each of the four short-term GAD studies are shown in Table 1.

The withdrawal rates due to TEAEs were vortioxetine 5.0% versus placebo 2.8%. TEAEs leading to withdrawal of >2 patients in the vortioxetine groups (5 mg and 10 mg, n=761) were nausea (10 patients), headache (four patients), irritability (four patients), dizziness (four patients), diarrhoea (three patients) and vomiting (three patients) versus none in the placebo group. TEAEs with an incidence ⩾5% in any treatment group in the eight-week core treatment period are shown in Table 4.

The incidence of serious adverse events was 0.5% for placebo and 0.1% for vortioxetine (5–10 mg) with no dose effect or pattern in the nature of the events. One death was reported in the GAD short-term studies. A 49-year-old woman randomized to vortioxetine 5mg/day in study NCT00734071 (Rothschild et al., 2012) died from morphine intoxication three days after the baseline visit. According to the autopsy and toxicology report, there was no vortioxetine in the stomach or body fluids.

During short-term treatment, the mean weight changes from baseline to Week 8 were similar for placebo (+0.40 kg change) and vortioxetine (+0.11 kg change). There was no trend for a dose effect for vortioxetine.

Pregnancies

During treatment, 39 women who received vortioxetine became pregnant during or shortly after stopping treatment in the clinical pharmacology and MDD studies. In the vortioxetine group, 13 women had an elective abortion, 10 women had a spontaneous abortion and 13 women gave birth to a healthy infant with no birth or developmental birth defects. For three women, the outcome was not known.

Discussion

This analysis of data compares the tolerability and safety profile of vortioxetine with placebo in acute randomized controlled clinical studies of 6/8 weeks' duration (3018 patients), and its tolerability and safety in long-term open-label treatment of up to 52 weeks (2457 patients).

The most common TEAEs (incidence ⩾5%) and occurring with at least twice the frequency that is seen with placebo during 6/8 weeks of treatment with vortioxetine are nausea and vomiting. Dose effects for vortioxetine were seen primarily for nausea and vomiting, the incidence of which plateaued at 15 mg/day vortioxetine. TEAEs commonly found with most antidepressants, such as headache, dry mouth, dizziness, constipation, insomnia, somnolence, fatigue, sexual dysfunction and hyperhidrosis, are seen at 'placebo levels' and show no dose effect. In addition, the proportion of patients with suicidal ideation is similar in placebo and vortioxetine groups, as measured by the C-SSRS and spontaneous patient reports. This was also found for the subgroup of patients aged 18–24 years.

The NNH for vortioxetine, based on the number of patients who discontinued treatment due to TEAEs during treatment, is markedly higher (i.e. better) for vortioxetine 5 mg and 10 mg than for the active references duloxetine and venlafaxine XR. An independent review of the published vortioxetine short-term studies concluded that vortioxetine 5–20 mg/day is 5.1 times more likely to result in a therapeutic response than a discontinuation due to a treatment-emergent adverse event (Citrome, 2014). Vortioxetine has a cardiovascular safety profile comparable to that of placebo, consistent with the results of a thorough QT

Table 4. TEAEs with an incidence of ⩾5% in any treatment group during the core treatment period (APTS) in four short-term GAD studies.

Preferred term	Placebo (*n*=609)	VOR 5 mg (*n*=453)	VOR 10 mg (*n*=308)	DUL 60 mg (*n*=154)
PYE	83.3	62.5	40.7	18.8
Patients with TEAEs	351 (57.6%)	294 (64.9%)	224 (72.7%)	124 (80.5%)
Nausea	52 (8.5%)	97 (**21.4**%)	89 (**28.9**%)	56 (**36.4**%)
Headache	57 (9.4%)	46 (10.2%)	42 (13.6%)	21 (13.6%)
Dry mouth	36 (5.9%)	32 (7.1%)	33 (10.7%)	25 (**16.2**%)
Dizziness	18 (3.0%)	28 (**6.2**%)	19 (**6.2**%)	14 (**9.1**%)
Diarrhoea	31 (5.1%)	19 (4.2%)	36 (**11.7**%)	6 (3.9%)
Vomiting	16 (2.6%)	10 (2.2%)	17 (**5.5**%)	9 (**5.8**%)
Constipation	14 (2.3%)	10 (2.2%)	18 (**5.8**%)	8 (**5.2**%)
Insomnia[a]	19 (3.1%)	16 (3.5%)	15 (4.9%)	8 (5.2%)
Somnolence	17 (2.8%)	27 (**6.0**%)	10 (3.2%)	19 (**12.3**%)
Fatigue	11 (1.8%)	11 (2.4%)	12 (3.9%)	13 (**8.4**%)
Decreased appetite	9 (1.5%)	12 (2.6%)	9 (2.9%)	12 (**7.8**%)
Sexual dysfunction[b]	4 (0.7%)	12 (2.6%)	10 (3.2%)	17 (**11.0**%)
Nasopharyngitis	20 (3.3%)	17 (3.8%)	16 (5.2%)	3 (1.9%)
URTI	16 (2.6%)	14 (3.1%)	17 (**5.5**%)	7 (4.5%)

% values **in bold** are ⩾5% and >2 × placebo.

[a]Includes the preferred terms: insomnia, initial insomnia, middle insomnia, hyposomnia, sleep disorder, dyssomnia, poor quality sleep, and terminal insomnia.

[b]Includes the preferred terms: libido decreased, ejaculation delayed, ejaculation disorder, orgasm abnormal, anorgasmia, disturbance in sexual arousal, ejaculation failure, erectile dysfunction, loss of libido, orgasmic sensation decreased, sexual dysfunction, and vulvovaginal dryness.

APTS: all patients treated set; DUL: duloxetine; GAD: generalized anxiety disorder; PYE: patient-years of exposure; TEAE: treatment-emergent adverse event; URTI: upper respiratory tract infection; VOR: vortioxetine.

study (Wang et al., 2013). The tolerability profiles of vortioxetine 5 mg and 10 mg are similar in GAD and MDD studies.

The present study uses a novel method for the analysis of TEAEs occurring during long-term treatment. Many patients in these studies had been switched from placebo or duloxetine (with or without a drug holiday) to vortioxetine. Analyses were made with and without data from the first eight weeks of the open-label studies; the latter reflecting the TEAE incidence for patients who had received at least eight weeks of treatment with vortioxetine. Both analyses show that long-term treatment with vortioxetine in MDD did not result in the emergence of TEAEs that had not been seen during acute treatment; that the incidence of TEAEs is <10% after omission of data from the first eight weeks; and that the majority of TEAEs are transient during acute treatment.

The low incidence of sleep disruption with vortioxetine may possibly be ascribed to modulatory effects at various receptors (Sanchez et al., 2015). Vortioxetine at a given serotonin transporter (SERT) occupancy seems to affect REM sleep to a lesser degree than paroxetine in healthy subjects, and suggests that 5-HT_3 receptor antagonism by vortioxetine contributes to its effect on sleep (Wilson et al., 2015). It is relevant to note that in a driving performance study, single and multiple doses of vortioxetine 10 mg/day did not impair driving performance compared with placebo during an on-the-road driving test (Theunissen et al., 2013).

The incidence of treatment-emergent sexual dysfunction (TESD) in patients treated with vortioxetine, as judged by the investigators, is not different from placebo, in contrast with the incidence with most selective serotonin reuptake inhibitor (SSRI) and serotonin noradrenaline reuptake inhibitor (SNRI) antidepressants. There was no dose effect for either men or women. There is evidence that antidepressants that are also 5-HT_{1A} receptor agonists (e.g. vortioxetine and vilazodone) may facilitate sexual performance in male rats in the presence of high levels of serotonin that usually inhibit sexual function (Sanchez et al., 2015). The effect of vortioxetine on sexual function has recently been explored in patients with significant SSRI-induced TESD, subsequently randomized to either vortioxetine 10–20 mg or escitalopram 10–20 mg. In this study (NCT01364649), vortioxetine was statistically significantly superior to escitalopram in improving TESD, as measured by the change from baseline in the Changes in Sexual Functioning Questionnaire Short-Form total score at Week 8, with a mean change difference of 2.2 points (95% CI: 0.48–4.02; p=0.013; mixed model for repeated measurement (MMRM)) in favour of vortioxetine (Jacobsen et al., 2015b).

The placebo level of discontinuation symptoms is possibly related to vortioxetine's relatively long elimination half-life of 66 h (Areberg et al., 2014). Comparisons across SSRIs suggest that a short elimination half-life increases the incidence of discontinuation symptoms (Rosenbaum et al., 1998).

The CYP450 pathway is important for the oxidative metabolism of various drugs and therefore implicated in drug–drug interactions. Biotransformation of vortioxetine is mainly through the liver by CYP2D6 but with some contribution from CYP2C9 (Hvenegaard et al., 2012). Co-administration of vortioxetine has no clinically relevant effect on the pharmacokinetics of fluconazole (CYP2C9, CYP2C19 and CYP3A inhibitor) or ketoconazole (CYP3A and P-glycoprotein inhibitor) (Chen et al., 2013). Multiple doses of vortioxetine 10 mg q.d. do not affect the steady-state pharmacokinetics of lithium 450 mg ER b.i.d. (Chen et al., 2012), diazepam (Chen et al., 2011), or aspirin or its metabolite salicylic acid, or (R)- and (S)-warfarin enantiomers, or the mean coagulation parameters of warfarin treatment alone (Chen et al., 2015). The same is true for co-administration of ethinyl estradiol/levonorgestrel (CYP3A substrates) or omeprazole /

5′-hydroxyomeprazole (CYP2C19 substrate and inhibitor), although dosage adjustment may be required when vortioxetine is co-administered with bupropion (a CYP2D6 inhibitor and CYP2B6 substrate) or rifampicin (a CYP inducer) (Chen et al., 2013). There is no clinically meaningful effect on the single dose pharmacokinetics of vortioxetine in patients with mild or moderate hepatic impairment (Wang et al., 2011) or renal impairment (mild, moderate, severe or end-stage renal disease) (Mayer et al, 2012).

Limitations of this analysis include the exclusion of patients with psychiatric or significant physical comorbidity, those at risk of suicidal behaviour, and a range of concomitant medications. This may reduce the generalizability of the findings to a wider patient population. TEAEs during double-blind treatment were reported spontaneously in response to non-leading questions and may underestimate the proportion of patients with adverse events. Long-term treatment was not placebo-controlled. In addition, foetal exposure to vortioxetine was limited, since women who became pregnant were withdrawn from the trials. These studies were carried out only in adults and therefore, vortioxetine is not recommended for the treatment of children or adolescents. Pharmacovigilance studies are needed to monitor safety and tolerability in patients seen in normal clinical practice and in much larger numbers than have been enrolled in randomized clinical studies.

Summary

This analysis of data pooled from randomized placebo-controlled acute treatment studies and open-label extension studies indicates that vortioxetine is safe and generally well tolerated in both short- and long-term treatment. Some of the tolerability issues seen with other antidepressants, including sexual dysfunction, insomnia-related events, weight gain and discontinuation symptoms occur with a low incidence, which may represent an advantage for vortioxetine during the long-term treatment which is recommended for patients with MDD.

Acknowledgements

The authors thank the investigators whose studies were involved in this analysis and DJ Simpson (H Lundbeck A/S) for providing support in the preparation, revision and editing of the manuscript. The authors are entirely responsible for the scientific content of this paper. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Some of this material was presented in a preliminary form at the 13th International Forum on Mood and Anxiety Disorders (IFMAD), Monaco, 2013.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: DSB has received honoraria for educational presentations from H Lundbeck A/S, and has acted as a paid consultant to Eli Lilly, Lundbeck, Pfizer and Servier, and currently holds research grants (on behalf of his employer) from Lundbeck and Pfizer. He has accepted paid speaking engagements in industry-supported satellite symposia or other meetings hosted by GlaxoSmithKline, Eli Lilly, Lundbeck, Pfizer and Servier. LC, GGN and WP are employed by the Takeda Pharmaceutical Company, Ltd. IF, RN and ER are employed by H Lundbeck A/S.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by H Lundbeck A/S and the Takeda Pharmaceutical Company, Ltd.

References

Alam M, Jacobsen PL, Chen Y, et al. (2014) Safety, tolerability and efficacy of vortioxetine (Lu AA21004) in subjects with major depressive disorder: Results of an open-label, flexible-dose, 52-week extension study. *Int Clin Psychopharmacol* 29: 36–44.

Alvarez E, Perez V, Dragheim M, et al. (2012) A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. *Int J Neuropsychopharmacol* 15: 589–600.

Areberg J, Petersen KB, Chen G, et al. (2014) Population pharmacokinetic meta-analysis of vortioxetine in healthy individuals. *Basic Clin Pharmacol Toxicol* 115: 552–559.

Baldwin DS, Hansen T and Florea I (2012a) Vortioxetine (Lu AA21004) in the long-term open-label treatment of major depressive disorder. *Curr Med Res Opin* 28: 1717–1724.

Baldwin DS, Loft H and Dragheim M (2012b) A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive disorder (MDD). *Eur Neuropsychopharmacol* 22: 482–491.

Bang-Andersen B, Ruhland T, Jørgensen M, et al. (2011) 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* 54: 3206–3221.

Bidzan L, Mahableshwarkar AR, Jacobsen P, et al. (2012) Vortioxetine (Lu AA21004) in generalized anxiety disorder: Results of an 8-week, multinational, randomized, double-blind, placebo-controlled clinical trial. *Eur Neuropsychopharmacol* 22: 847–857.

Boulenger JP, Loft H and Olsen CK (2014) Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: A randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder. *Int Clin Psychopharmacol* 29: 138–149.

Chen G, Lee R, Højer AM, et al. (2013) Pharmacokinetic drug interactions involving vortioxetine (Lu AA21004), a multimodal antidepressant. *Clin Drug Investig* 33: 727–736.

Chen G, Lee R, Zhao Z, et al. (2012) A phase 1 study to assess the effect of Lu AA21004 on the steady-state pharmacokinetics of lithium in healthy male subjects. *Clin Pharm Ther* 91(Suppl. 1): S39.

Chen G, Wang Y, Lee RD, et al. (2011) Effects of multiple doses of Lu AA21004 on the single-dose pharmacokinetics and pharmacodynamics of diazepam. *J Clin Pharmacol* 51: 1350.

Chen G, Zhang W and Serenko M (2015) Lack of effect of multiple doses of vortioxetine on the pharmacokinetics and pharmacodynamics of aspirin and warfarin. *J Clin Pharmacol* 55: 671–679.

Citrome L (2014) Vortioxetine for major depressive disorder: A systematic review of the efficacy and safety profile for this newly approved antidepressant – what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Pract* 68: 60–82.

Cleare A, Pariante CM, Young AH, et al. (2015) Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. *J Psychopharmacol* 29: 459–525.

Filippov G and Christens P (2013) Vortioxetine (Lu AA21004) 15 and 20 mg/day: Open-label long-term safety and tolerability in major depressive disorder. *Eur Neuropsychopharmacol* 23 (Suppl. 2): S325.

Florea I, Dragheim M and Loft H (2012) The multimodal antidepressant Lu AA21004: Open-label long-term safety and tolerability study in major depressive disorder. *Eur Neuropsychopharmacol* 22 (Suppl. 2): S255–S256.

Henigsberg N, Mahableshwarkar A, Jacobsen P, et al. (2012) A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. *J Clin Psychiatry* 73: 953–959.

Hvenegaard MG, Bang-Andersen B, Pedersen H, et al. (2012) Identification of the cytochrome P450 and other enzymes involved in the in vitro oxidative metabolism of a novel antidepressant, Lu AA21004. *Drug Metab Dispos* 40: 1357–1365.

Jacobsen PL, Harper L, Chrones L, et al. (2015a) Safety and tolerability of vortioxetine (15 and 20 mg) in patients with major depressive disorder: Results of an open-label, flexible-dose, 52-week extension study. *Int Clin Psychopharmacol* 30: 255–264.

Jacobsen PL, Mahableshwarkar AR, Chen Y, et al. (2015b) Effect of vortioxetine versus escitalopram on sexual functioning in adults with well-treated major depressive disorder experiencing SSRI-induced sexual dysfunction. *J Sex Med* 12: 2036–2048.

Jacobsen PL, Mahableshwarkar AR, Serenko M, et al. (2015c) A randomized, double-blind, placebo-controlled study of the efficacy and safety of vortioxetine 10 mg and 20 mg in adults with major depressive disorder. *J Clin Psychiatry* 76: 575–582.

Jain R, Mahableshwarkar AR, Jacobsen PL, et al. (2013) A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5 mg vortioxetine in adults with major depressive disorder. *Int J Neuropsychopharmacol* 16: 313–321.

Katona C, Hansen T and Olsen C (2012) A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *Int Clin Psychopharmacol* 27: 215–223.

Lam RW, Kennedy SH, Grigoriadis S, et al. (2009) Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. III. Pharmacotherapy. *J Affect Disord* 117 (Suppl. 1): S26–S43.

McIntyre RS, Lophaven S and Olsen CK (2014) A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol* 17: 1557–1567.

Mahableshwarkar AR, Jacobsen PL and Chen Y (2013) A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder. *Curr Med Res Opin* 29: 217–226.

Mahableshwarkar AR, Jacobsen PL, Chen Y, et al. (2014a) A randomised, double-blind, placebo-controlled, duloxetine-referenced study of the efficacy and tolerability of vortioxetine in the acute treatment of adults with generalised anxiety disorder. *Int J Clin Pract* 68: 49–59.

Mahableshwarkar AR, Jacobsen PL, Serenko M, et al. (2014b) A randomized, double-blind, fixed-dose study comparing the efficacy and tolerability of vortioxetine 2.5 and 10 mg in acute treatment of adults with generalized anxiety disorder. *Hum Psychopharmacol* 29: 64–72.

Mahableshwarkar AR, Jacobsen PL, Chen Y, et al. (2015a) A randomized, double-blind, duloxetine-referenced study comparing efficacy and tolerability of 2 fixed doses of vortioxetine in the acute treatment of adults with MDD. *Psychopharmacology (Berl)* 232: 2061–2070.

Mahableshwarkar AR, Jacobsen PL, Serenko M, et al. (2015b) A randomized, double-blind, placebo-controlled study of the efficacy and safety of 2 doses of vortioxetine in adults with major depressive disorder. *J Clin Psychiatry* 76: 583–591.

Mayer M, Wu R, Serenko M, et al. (2012) Effect of renal impairment on the pharmacokinetics of vortioxetine (Lu AA21004). *Clin Pharmacol Drug Dev* 1: 188–189.

Rosenbaum JF, Fava M, Hoog SL, et al. (1998) Selective serotonin reuptake inhibitor discontinuation syndrome: A randomized clinical trial. *Biol Psychiatry* 44: 77–87.

Rothschild AJ, Mahableshwarkar AR, Jacobsen P, et al. (2012) Vortioxetine (Lu AA21004) 5 mg in generalized anxiety disorder: Results of an 8-week randomized, double-blind, placebo-controlled clinical trial in the United States. *Eur Neuropsychopharmacol* 22: 858–866.

Sanchez C, Asin KE and Artigas F (2015) Vortioxetine, a novel antidepressant with multimodal activity: Review of preclinical and clinical data. *Pharmacol Ther* 145: 43–57.

Theunissen EL, Street D, Højer AM, et al. (2013) A randomized trial on the acute and steady-state effects of a new antidepressant, vortioxetine (Lu AA21004), on actual driving and cognition. *Clin Pharmacol Ther* 93: 493–501.

Wang Y, Munsaka M, Serenko M, et al. (2011) Evaluation of the single-dose pharmacokinetics of Lu AA21004 and its metabolites in subjects with and without hepatic impairment. *Clin Pharm Ther* 89 (Suppl. 1): S71.

Wang Y, Nomikos GG, Karim A, et al. (2013) Effect of vortioxetine on cardiac repolarization in healthy adult male subjects: Results of a thorough QT/QTc study. *Clin Pharmacol Drug Dev* 2: 298–309.

Wilson S, Højer AM, Buchberg J, et al. (2015) Differentiated effects of the multimodal antidepressant vortioxetine on sleep architecture: Part 1, a pharmacokinetic/pharmacodynamic comparison with paroxetine in healthy men. *J Psychopharmacol* 29: 1085–1091.