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ORIGINAL RESEARCH ARTICLE

Effectiveness and Tolerability of Vortioxetine in Major Depressive Disorder: A Real-World Study in Switzerland

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Abstract

Background and Objectives Vortioxetine is widely used in Switzerland for treating major depressive episodes, but systematically collected data from routine clinical practice are not available. We evaluated real-world effectiveness and tolerability of vortioxetine for treating major depressive episodes in Swiss clinical practice.

Methods A prospective non-interventional observational study was conducted with an observation period of approximately 8 weeks from vortioxetine initiation. Adults with a current major depressive episode for whom a decision to initiate vortioxetine had been made independent of the study were eligible for inclusion. Assessment of depressive symptoms, functioning, safety and tolerability were performed at four study visits. Pre-planned explorative descriptive statistics were applied.

Results Of 226 patients enrolled, 208 (92.0%) completed the study. At baseline, the mean (standard deviation) sum of the unanchored Montgomery–Åsberg Depression Rating Scale items was 34.3 (8.89), indicating severe depression. Depression severity tended to be underestimated when relying on clinical estimation without any scale alone. Significant reductions were observed from baseline to visit 4 in the sum of the unanchored Montgomery–Åsberg Depression Rating Scale items, in all individual items, and in the Clinical Global Impression-Severity scale (all $p < 0.001$). The severity of impairment of all assessed functioning domains also decreased. Adverse drug reactions were reported in 7.5% of patients. Effectiveness and tolerability of vortioxetine was rated good or very good by >88% of clinicians and patients.

Conclusions Patients who initiated vortioxetine for treating a major depressive episode experienced improvements in depressive symptoms and functioning. Vortioxetine was well tolerated. Underestimation of depressive episode severity by clinicians reinforces the importance of using rating scales in clinical practice.

Key Points

Improvements in depressive symptoms and everyday functioning were observed over approximately 8 weeks in patients who initiated vortioxetine for the treatment of a major depressive episode in routine Swiss clinical practice.

Vortioxetine was well tolerated, with a low incidence of adverse drug reactions, of which most were not serious.

Clinicians tended to underestimate the severity of depressive episodes at baseline when relying on clinical estimation without any scale alone, which highlights the importance of using rating scales in clinical practice, even if simplified, such as the unanchored Montgomery–Åsberg Depression Rating Scale items or the Clinical Global Impression-Severity scale.

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1 Introduction

Major depressive disorder (MDD) is a major public health issue. In 2019, depressive disorders were estimated to affect approximately 280 million people worldwide and were the highest contributor to the burden of mental disorders [1]. Major depressive disorder is not only economically burdensome [2], but has substantial negative effects on cognitive and social functioning, quality of life and productivity [3–5]. Consequently, effective management of major depressive episodes is essential to restore long-term functioning and improve quality of life [5].

Antidepressants are an important tool in the management of MDD. Vortioxetine is an antidepressant that is approved for the treatment of major depressive episodes in adults [6], and has been available in Switzerland since 2016 [7]. Two bioequivalent oral formulations of vortioxetine are available in Switzerland — tablets and drops [8, 9]. Vortioxetine has multimodal activity in the central nervous system [10, 11]. Indeed, pre-clinical data indicate that, in addition to inhibiting the serotonin (5-HT) reuptake transporter, vortioxetine is a 5-HT_3, 5-HT_7 and 5-HT_{1D} receptor antagonist, a 5-HT_{1B} receptor partial agonist and a 5-HT_{1A} agonist [10, 12, 13]. This multimodal activity is thought to account for the improvements in cognitive and global functioning that have been associated with vortioxetine, together with its antidepressive properties [9, 14–17].

The efficacy, safety and tolerability of vortioxetine for the treatment of MDD has been demonstrated in numerous short-term placebo- and active-controlled clinical trials [18–24], and in open-label extension studies for long-term maintenance treatment up to 52 weeks [25, 26]. Efficacy for relapse prevention has been demonstrated in placebo-controlled withdrawal studies [27, 28]. Randomised controlled trials (RCTs) are regarded as the 'gold standard' of clinical research and are essential for establishing the efficacy and tolerability of interventions and, therefore, supporting applications for regulatory approval [29, 30]. The importance of real-world data is also widely recognised. Real-world studies complement the findings from RCTs by providing insight into the effectiveness of a treatment under everyday conditions and in a broader, more representative patient population [29].

Since receiving approval in Switzerland in 2016 [7], vortioxetine has been widely used in Swiss clinical practice for the treatment of major depressive episodes in adults. However, systematically collected data documenting the use of vortioxetine in routine clinical practice are not available for Switzerland. To our knowledge, this is the first real-world study of vortioxetine conducted in Switzerland. The study aimed to provide real-world evidence for vortioxetine and to evaluate its effectiveness and tolerability for the treatment of major depressive episodes in Swiss clinical practice.

2 Methods

2.1 Study Design and Patient Population

This was a prospective, non-interventional, uncontrolled, multicentre, real-world study that evaluated the effectiveness and tolerability of vortioxetine (Brintellix®; manufactured by H. Lundbeck A/S) when initiated for the treatment of major depressive episodes in Swiss clinical practice. Practicing psychiatrists across Switzerland, who routinely prescribed vortioxetine in clinical practice, selected patients eligible for inclusion in the study only once the decision to initiate vortioxetine had been made.

The study consisted of an observation period of approximately 8 weeks for each patient beginning from the initiation of vortioxetine. Four study visits were scheduled during the observation period: visit 1 (baseline and treatment initiation), visit 2 (approximately 2–3 weeks post-baseline), visit 3 (approximately 4–6 weeks post-baseline) and visit 4 (approximately 8 weeks post-baseline) according to usual clinical practice. At each visit, the patient was reviewed by their clinician who recorded assessment data on case report forms and adverse drug reaction (ADR) report forms.

Eligible patients were recruited for, and participated in, the study between 16 September 2019 and 30 September 2021. Adults aged ≥18 years who were receiving treatment as an outpatient in accordance with the summary of product characteristics for vortioxetine and were, currently, experiencing a major depressive episode were eligible for inclusion. Moreover, the decision to initiate treatment with vortioxetine must have been made at the discretion of the treating clinician, independent of inclusion in the study. Patients who were already receiving treatment with vortioxetine for the current depressive episode; had any contraindication to treatment with vortioxetine according to the summary of product characteristics; were a study staff member, or were related to, or dependent on, the study staff; had previously been included in the study or were, currently, participating in an interventional study were excluded.

On the 2 April 2017, the Ethics Committee of the Canton of Zurich confirmed that the study protocol did not require specific ethics approval because of its purely observational nature. The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to participation in the study.

2.2 Endpoints

Demographics and clinical characteristics were recorded at baseline (visit 1). Endpoints included the sum of the unanchored Montgomery–Åsberg Depression Rating Scale

(MADRS) item scores at baseline and at each study visit and the change in the sum of the MADRS from baseline to each study visit. The MADRS is a clinician-rated scale used to assess the severity of ten depressive symptoms [31]. However, in Switzerland, for non-interventional/observational studies, no additional diagnostic tools are permitted in addition to those used in routine clinical practice [32]. The unanchored MADRS was therefore used, where categories remained the same as in the conventional MADRS but there was not a structured interview, and items were unanchored to ensure that the assessment was not considered an intervention. This meant that items were scored on a simplified 7-point scale reflecting the severity of each symptom (0, none; 1, almost none; 2, mild; 3, moderate; 4, marked; 5, intense; 6, extreme) and did not use the anchors associated with the original MADRS (i.e. descriptions of patient characteristics at each level as defined in the accompanying manual). Scores were analogous to the conventional MADRS and were assessed by a clinician at each study visit and recorded in the case report form. Analogous to the conventional MADRS mild depression was defined as a sum of item scores of <20, moderate as ≥20–29 and severe as ≥30; the maximum possible score was 60. The change in individual unanchored MADRS item scores from baseline to visit 4 (approximately 8 weeks) and the MADRS response rate (proportion of patients with a ≥50% reduction in the sum of the unanchored MADRS items) and remission rate (proportion of patients with a sum of the unanchored MADRS items ≤10) at visit 4 (approximately 8 weeks) were also assessed.

Severity of illness at baseline, at each study visit, and the change from baseline to each study visit was assessed using the Clinical Global Impression-Severity (CGI-S) scale. The CGI-S is a 7-point clinician-rated scale used to assess the severity of a patient's illness at the time of assessment relative to the clinician's past experience of patients with identical diagnosis, ranging from 1 (not at all ill) to 7 (extremely ill) [33]. Improvement in the state of illness at visit 4 (approximately 8 weeks) was assessed using the Clinical Global Impression-Improvement (CGI-I) scale. The CGI-I is a 7-point clinician-rated scale used to assess overall improvement in a patient's illness at the time of assessment compared to their condition at first presentation, with a range from very much improved to very much worse [33]. As depression severity is closely associated with impairment of everyday functionality, the CGI scale can provide an estimation of a patient's psychosocial functional level. However, to assess the change in functioning more specifically in relevant domains, clinician-rated impairment of everyday functioning was assessed at baseline and visit 4 (approximately 8 weeks) across six domains: cognition, professional activities, family life, social and leisure activities, physical well-being and quality of life. Level of impairment was rated on a 4-point scale (none, mild, moderate or severe). Clinician- and patient-rated assessment of overall efficacy at the end of observation was also assessed and was reported using a 4-point scale (very good, good, moderate or sufficient, or inadequate or insufficient).

The tolerability of vortioxetine was assessed by the incidence of ADRs and all adverse events for which a causal connection with the study drug could not be ruled out (hereinafter termed ADRs), as well as pre-defined special notifiable cases, which required reporting in line with the pharmacovigilance obligations of the marketing authorisation holder of the drug and study sponsor. These obligations apply for all marketed medications regardless of the probability that these listed events could occur with a particular drug (no or little effect; use in an unapproved indication [off-label use]; overdose, misuse or abuse; drug interactions; use in paediatric patients; use during pregnancy/breastfeeding; incorrect use; occupational or accidental exposure; withdrawal symptoms; transmission of infectious diseases; unexpected positive effect; and transfer of the medicinal product via semen). Subjective clinician- and patient-rated assessment of overall tolerability was also reported at the end of observation and was recorded using a 4-point scale (very good, good, moderate or sufficient, or inadequate or insufficient).

2.3 Statistical Analysis

Baseline demographics, clinical characteristics and study outcomes were reported using descriptive statistics, consisting of mean (standard deviation [SD]) for continuous variables, and numbers and percentages for categorical and binary variables. Changes from baseline to each study visit in the sum of the unanchored MADRS items, the individual unanchored MADRS items and in the CGI-S score were analysed using signed rank tests. Comparison of depression severity at baseline between patients receiving monotherapy or combination treatment were analysed using Fisher's exact test for CGI-S scores and using a two-sample t test for MADRS total scores and average starting dose of vortioxetine. Comparison of response and remission rates until the final visit were made between patients receiving monotherapy or combination treatment using Fisher's exact test. A p-value of <0.05 was considered nominally statistically significant for comparisons without adjustment for multiple testing, in line with the exploratory nature of the analyses. Missing data were imputed using the last observation carried forward (LOCF) method for the change of depression severity and symptoms during treatment including response and remission, as well as for the CGI-S score and impairment of functioning. To assess the robustness of the results and to explore the potential impact of missing data and model assumptions, a sensitivity analysis was conducted

using a mixed model for repeated measures. This model included fixed effects for starting dose and visit number, as well as the baseline depression severity sum score as a covariate (data not shown). Data processing and statistical analysis were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA), independently by ANFOMED (Möhrendorf, Germany).

3 Results

3.1 Patients and Treatment

A total of 226 patients were enrolled across 40 centres in Switzerland, of which 208 (92.0%) completed the observation period of approximately 8 weeks. Reasons for not completing the observation period comprised ADRs ($n = 6$); patient decision ($n = 4$); non-compliance/lost to follow-up ($n = 3$); hospitalisation ($n = 2$); inadequate efficacy ($n = 2$); and new workplace, therapy objectives achieved and relocation (each $n = 1$). The mean (SD) duration of observation was 10.1 (5.5) weeks (median 9 weeks) (Fig. 1).

Of the 225 patients for whom vortioxetine dosage form was known, 165 (73.3%) initiated treatment with oral tablets and 60 (26.7%) initiated treatment with oral drops. The mean (SD) dose of vortioxetine at initiation was 6.8 (3.3) mg and the most common initiation dose was 5 mg, which was administered to 49.6% ($n = 112$) of patients. Some patients ($n = 26$, 11.5%) initiated treatment with a dose ≤5 mg, whereas 37.2% ($n = 84$) and 1.8% ($n = 4$) started with 10 mg and 20 mg, respectively.

At day 56 (end of week 8), the mean (SD) dose of vortioxetine was 12.9 (4.7) mg. At this timepoint 4.9% of patients were taking 4–5 mg, 1.6% of patients were taking 6–8 mg, 54.6% of patients were taking 10 mg, 13.7% of patients were taking 15 mg and 25.1% of patients were taking 20 mg of vortioxetine. Baseline demographics and clinical characteristics for the study population are summarised in Table 1.

Of the patients initiating vortioxetine, 51.3% ($n = 116$) were experiencing their first depressive episode. Previous depressive episodes were mainly considered moderate (75.2%) or severe (20.2%). For the current depressive episode, the mean (SD) sum of the unanchored MADRS items was 34.3 (8.89), indicating severe depression and the mean (SD) CGI-S score of 4.9 (0.84) indicated marked illness. Clinicians tended to underestimate the severity of the depressive episode at baseline when relying on clinical estimation without any scale alone (Fig. 2). Severity was, generally, higher when assessed using the unanchored MADRS items than by clinical estimation without any scale. The distribution of severity levels by unanchored MADRS corresponded to that determined by the CGI-S with 3.5% of patients rated not more than slightly ill, 28.8% moderately ill and 67.7% being clearly to extremely ill.

At baseline, the majority of patients experienced moderate (34.5–59.6%) or severe (22.9–38.1%) impairment of everyday functioning in the six domains assessed. Vortioxetine was first-line treatment for the current depressive episode in 43.8% ($n = 99$) of all patients, while 56.2% ($n = 127$) of patients had received prior pharmacological treatment

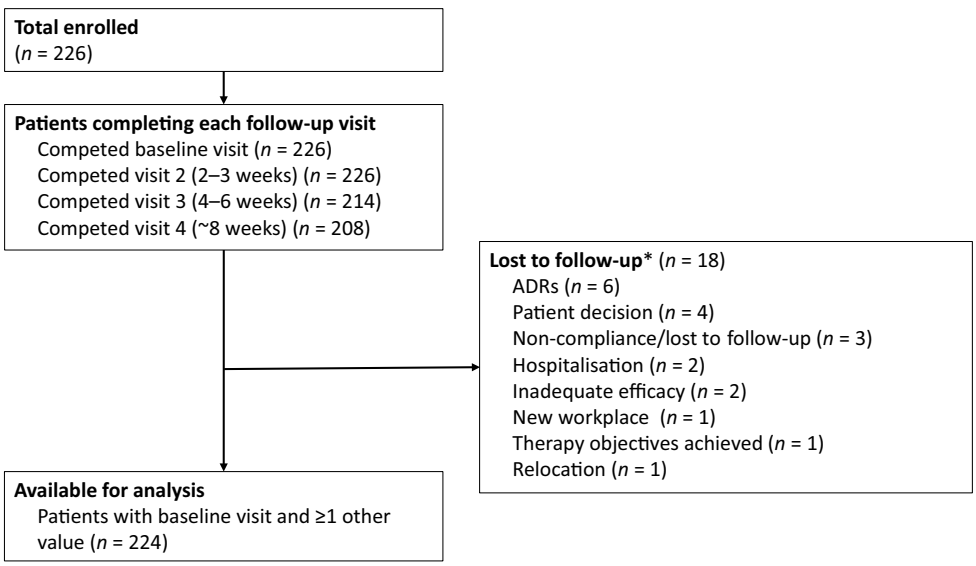


Fig. 1 Patient flow diagram of patients with a current major depressive episode receiving vortioxetine in Swiss clinical practice enrolled and analysed in this Swiss real-world prospective study. *≥1 reason for not completing the observation period may be provided per patient. Note: Denominators vary depending on data availability (e.g. $n = 224$ for effectiveness analyses requiring baseline plus ≥1 post-baseline assessment; $n = 225$ for variables where formulation was reported). *ADR* adverse drug reaction

Table 1 Baseline demographics and clinical characteristics of patients with a current major depressive episode receiving vortioxetine in Swiss clinical practice

	Patients ($N = 226$)
Demographics	
Mean (SD) age at treatment initiation, years	43.3 (13.5)
Female, *n* (%)	125 (55.3)
Mean (SD) BMI, kg/m^2	24.7 (4.0) [$n = 219$]
Clinical characteristics	
Previous depressive episodes	
At least one previous depressive episode, *n* (%)	110 (48.7)
Mean (SD) number of previous depressive episodes	3.5 (4.1)
Mean (SD) age at first depressive episode, years	28.4 (12.4)
Mean (SD) duration of previous depressive episodes, weeks	21.4 (18.8)
Mean severity of previous depressive episodes, *n* (%)	[$n = 109$]
Mild	5 (4.6)
Moderate	82 (75.2)
Severe	22 (20.2)
Current depressive episode	
Mean (SD) duration of current depressive episode, weeks	18.8 (30.1) [$n = 225$]
Mean (SD) sum of the unanchored MADRS items	34.3 (8.89) [$n = 224$]
Mean (SD) CGI-S score	4.9 (0.84) [$n = 224$]
Received prior pharmacological treatment for the current depressive episode and/or its accompanying symptoms,[a] *n* (%)	127 (56.2)
Receiving psychotherapy for the current depressive episode, *n* (%)	140 (62.2) [$n = 225$]
Comorbid conditions and treatment for comorbid conditions	
At least one comorbid condition, *n* (%)	72 (31.9)
Comorbid conditions present in ≥1% of patients, *n* (%)	
Overweight	14 (6.2)
Hypertension	13 (5.8)
Diabetes mellitus	7 (3.1)
ADHD	5 (2.2)
Hypothyroidism	3 (1.3)
Migraine	3 (1.3)
Receiving treatment for a comorbid condition, *n* (%)	51 (22.6)
Number of treatments for a comorbid condition, *n* (%)	
1	40 (17.7)
2	8 (3.5)
≥3	3 (1.3)
Treatment of comorbid conditions by anatomical main group (≥1% of patients), *n* (%)	
Cardiovascular system	17 (7.5)
Nervous system	16 (7.1)
Alimentary tract and metabolism	14 (6.2)
Musculoskeletal system	9 (4.0)
Blood and blood forming organs	4 (1.8)
Systemic hormonal preparations, excluding sex hormones	3 (1.3)

ADHD attention-deficit hyperactivity disorder, *BMI* body mass index, *CGI-S* Clinical Global Impression-Severity, *MADRS* Montgomery–Åsberg Depression Rating Scale, *SD* standard deviation

[a]Initiated prior to the start of vortioxetine treatment

for the current depressive episode and/or for accompanying symptoms, such as insomnia. The most common prior treatments were escitalopram (9.7% of all patients, $n = 22$; mean dose 14 mg), quetiapine (8.9% of all patients, $n = 20$; mean dose 48 mg), and trazodone (8.9% of all patients, $n = 20$; mean dose 84 mg). Prior treatment with escitalopram

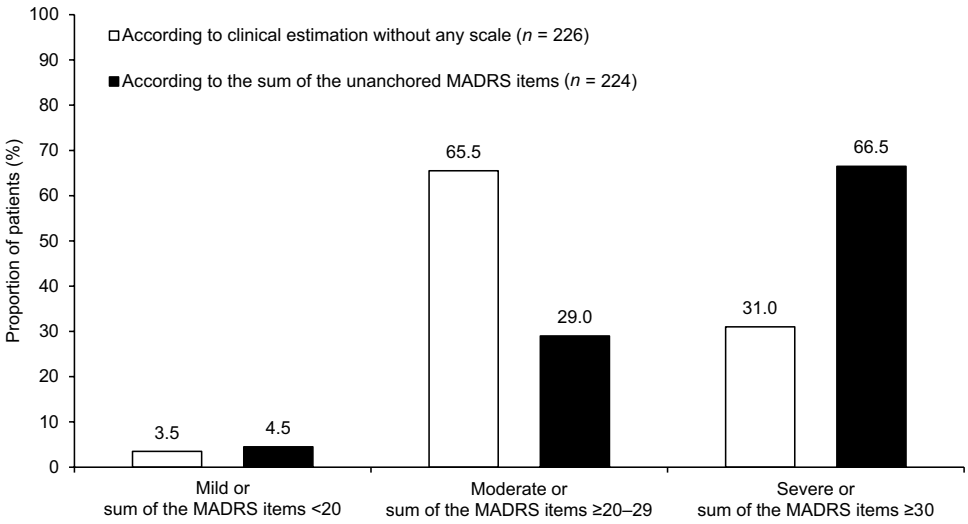


Fig. 2 Concordance between assessment of the severity of the current depressive episode at baseline as evaluated by clinical estimation without any scale, or the sum of the unanchored MADRS items. *MADRS* Montgomery–Åsberg Depression Rating Scale

was considered ineffective in 72.7% ($n = 16/22$) of patients, and in 5.0% ($n = 1/20$) for quetiapine and 20.0% ($n = 4/20$) for trazodone.

Concomitant pharmacological treatment for the current depressive episode and/or accompanying symptoms was reported in 50.9% ($n = 115$) of patients at any time during the study period, including during a possible cross-titration period. Quetiapine and trazodone were the most common concomitant treatments, reported in 9.7% of all patients ($n = 22$; mean dose 45 mg) and 8.9% ($n = 20$; mean dose 74 mg) of all patients, respectively, followed by escitalopram in 5.8% of all patients ($n = 13$; mean dose 15 mg).

A detailed analysis of concomitant medication revealed that the following substances were discontinued in ≥2% of patients at any time during observation: escitalopram ($n = 22$, 9.7%), clomethiazole ($n = 13$, 5.8%), sertraline ($n = 9$, 4.0%), duloxetine ($n = 9$, 4.0%), mirtazapine ($n = 8$, 3.5%), lorazepam ($n = 7$, 3.1%), venlafaxine ($n = 7$, 3.1%), quetiapine ($n = 6$, 2.7%), trazodone ($n = 6$, 2.7%), combinations of plant-based hypnotics and sedatives ($n = 5$, 2.2%). Medications that were not discontinued in ≥2% of patients during the observation period were quetiapine ($n = 17$, 7.5%), trazodone ($n = 16$, 7.1%), valerian combinations ($n = 9$, 4.0%), lorazepam ($n = 7$, 3.1%) and mirtazapine ($n = 5$, 2.2%). To account for a comedication during a possible cross-titration to vortioxetine, a sub-analysis of patients with versus without comedication at visit 2 (2–3 weeks after baseline) was performed. More patients ($n = 128$, 56.6%) received monotherapy at visit 2 than combination treatment ($n = 98$, 43.4%). Patients who received combination therapy were more severely depressed at baseline than patients with monotherapy, according to the mean sum of unanchored MADRS items 35.7 versus 33.1 ($p < 0.05$), and distribution of CGI-S ($p < 0.001$), mean CGI-S 5.0 versus 4.7. Patients with a comedication received a lower mean starting dose of vortioxetine (6.3 mg) than patients with monotherapy (7.2 mg; $p < 0.05$). All other baseline characteristics were comparable.

A high proportion of patients (85.4%; $n = 193$) received maintenance treatment with vortioxetine following the observation period and most (74.8% of all patients; $n = 169/226$) received vortioxetine as monotherapy. Of the 26 patients who received medication other than vortioxetine for maintenance treatment, most ($n = 24$) received the medication adjunctive to vortioxetine, and the most common medicines (used by ≥1% of patients) were trazodone (4.0%; $n = 9$) and quetiapine (3.5%; $n = 8$). No patients received escitalopram as concomitant or monotherapy during the maintenance phase. Overall, 31.9% ($n = 72$) of patients had at least one comorbid condition, and a total of 74 different comorbid conditions were reported.

3.2 Effectiveness

The severity of depression, as indicated by the sum of the unanchored MADRS item scores, decreased significantly from a mean (SD) value of 34.3 (8.9) at baseline to each study visit (all $p < 0.001$, LOCF, $n = 224$) (Fig. 3a). There was a mean (SD) decrease of 21.3 (10.1) points from baseline (95% CI −22.6, −19.9; $p < 0.001$) in the unanchored MADRS score to a mean (SD) value of 13.0 (9.1) at visit 4 (approximately 8 weeks). In terms of the individual unanchored MADRS items, statistically significant decreases in the mean score from baseline to visit 4 were documented for all ten items (all $p < 0.001$, LOCF) (Fig. 3b). At visit 4 (approximately 8 weeks), 72.3% (95% CI 66.0, 78.1; $n = 162$, LOCF) of patients were MADRS responders and 42.4% (95% CI 35.9, 49.2; $n = 95$, LOCF) were MADRS remitters (Fig. 3c).

Severity of illness, measured using the CGI-S scale, decreased significantly from marked illness at baseline

(mean 4.9) to each of the study visits (all $p < 0.001$, LOCF) and, ultimately, to mild illness (mean 2.9) at visit 4 (Fig. 4). The overall mean (SD) reduction in the CGI-S score from baseline to visit 4 was 2.0 (1.2) points, indicating a clinically relevant improvement.

According to the CGI-I, the state of illness was considered very much or much improved for 84.3% ($n = 172/204$) of patients at visit 4. The mean (SD) CGI-I score at visit 4 was 1.9 (0.9) (i.e. illness was much improved).

The severity of impairment of aspects of everyday functioning decreased from baseline to visit 4 across all six domains assessed (Fig. 5). At baseline, most patients experienced moderate or severe impairment of functioning (72.6–92.4%, depending on the domain), with 22.9–38.1% of patients experiencing severe impairment. At visit 4, the majority of patients had mild or no impairment (78.0–87.0%, depending on domain), with 22.8–42.6% experiencing no impairment.

Based on clinician and patient evaluations, 90.6% ($n = 202$) of clinicians and 88.8% ($n = 198$) of patients rated the efficacy of vortioxetine treatment as good or very good (Fig. 6). Efficacy after 8 weeks of vortioxetine treatment was comparable in patients with or without a comedication at visit 2, according to the change in sum of unanchored MADRS items from baseline to visit 4 (23.3 and 21.2, respectively, $p = 0.76$) and mean sum of unanchored MADRS items at visit 4 (12.6 and 12.0, respectively, $p = 0.59$). A comparable proportion of patients with or without a comedication achieved a response (76.3% and 69.3%, respectively, $p = 0.29$) and remission (41.2% and 43.3%, respectively, $p = 0.79$) at visit 4. All other measures of efficacy were comparable between the groups.

3.3 Safety and Tolerability

Adverse drug reactions (all ADRs and adverse events for which a causal connection with the study drug could not be ruled out) and special notifiable cases are summarised in Table 2. A total of 40 ADR events were reported in 7.5% ($n = 17$) of patients treated with vortioxetine, the most common being nausea, headache and dizziness. Most ADR events were not serious (36/40 events; 16/17 patients) and most had resolved or were resolving (34/40 events) at the time of reporting. The outcome was unknown for two events. Withdrawal from the study because of ADRs occurred in 2.7% of patients ($n = 6$).

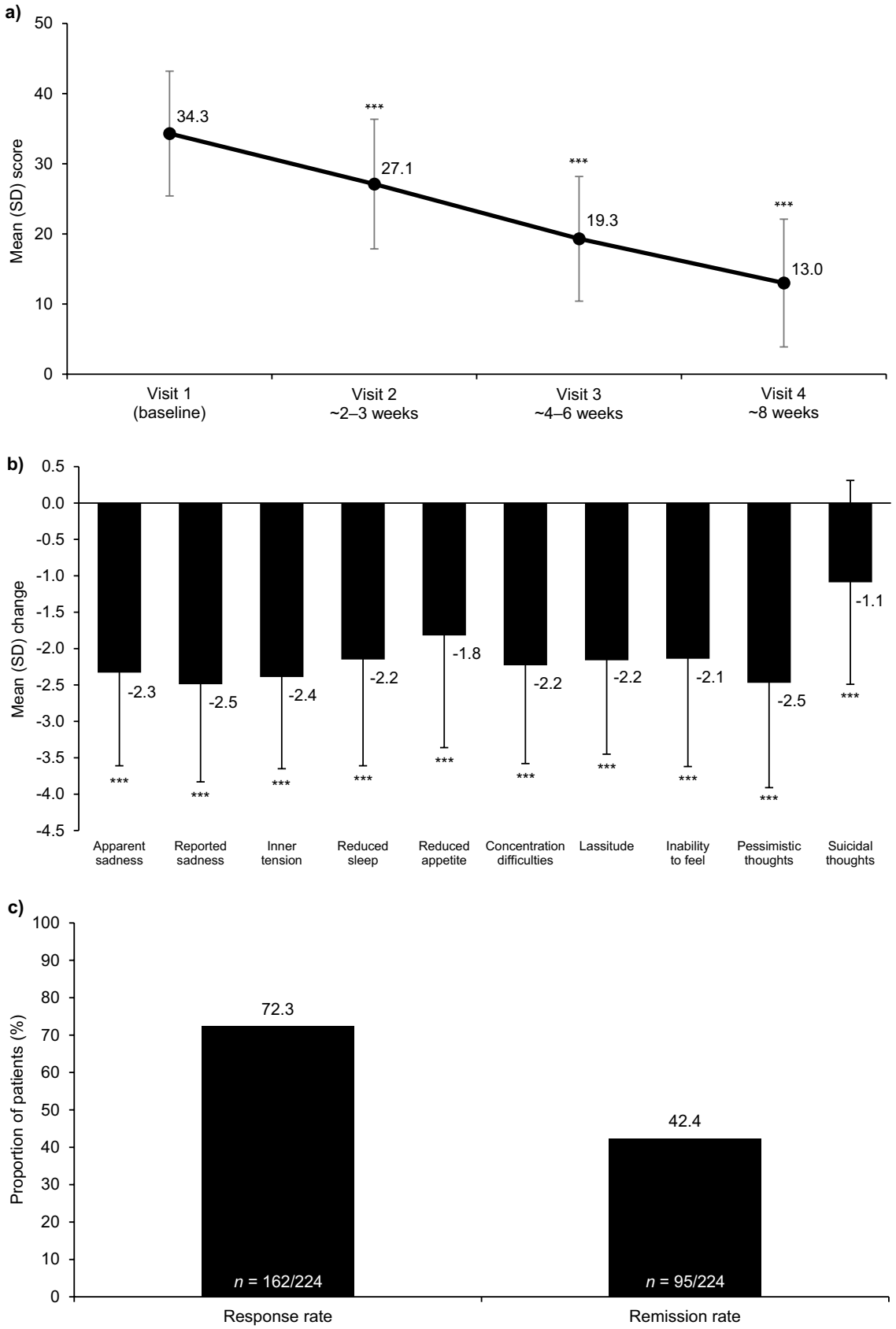
Of the special notifiable cases reported by 19.5% ($n = 44$) of patients at any time during the treatment period, including during titration, 'no or little effect' was the most frequent, documented in 18.6% ($n = 42$) of patients. Tolerability was comparable in patients with or without a comedication at visit 2. When evaluated by clinicians and patients, 92.0% ($n = 206$) of clinicians and 91.5% ($n = 205$) of patients rated the tolerability of vortioxetine as good or very good (Fig. 7).

4 Discussion

In this study, to our knowledge the first real-world study of vortioxetine in Switzerland, outpatients experiencing a major depressive episode were treated with vortioxetine based on the decision of their treating psychiatrist, independent of the study. At baseline, patients tended to be severely depressed, as indicated by the sum of the unanchored MADRS items, CGI-S and impairment of functioning. When assessed by the sum of the unanchored MADRS items, the mean severity of the current depressive episode at baseline was severe (sum of the unanchored MADRS score of ≥30). When assessed by CGI-S, most patients were rated as clearly ill (5) or above. However, when estimating severity without any scale, clinicians tended to underestimate the severity of the depressive episode, rating most episodes as moderate (which would approximate a sum of the unanchored MADRS score of ≥20–29 and a CGI-S score of 4). This illustrates that utilising a measurement-based assessment of severity in clinical practice, even if simplified, is a useful tool to ensure that patients receive adequate and appropriate treatment.

Over approximately 8 weeks of observation following vortioxetine initiation (a median observation time of 9 weeks), the severity of depressive symptoms decreased, as shown by the significant reductions from baseline to visit 4 in the sum of the unanchored MADRS items ($p < 0.001$) and the CGI-S score ($p < 0.001$). The observed 2-point reduction in the CGI-S score indicates a clinically meaningful improvement. Moreover, significant reductions from baseline to visit 4 were observed for all ten unanchored MADRS items (all $p < 0.001$), showing improvements across the spectrum of depressive symptoms.

The observed overall reduction in the sum of the unanchored MADRS items (−21.3 points) is consistent with reductions in the MADRS of −13 to −20 points in 6- to 8-week RCTs of vortioxetine in MDD [15, 16, 18–22, 34–36]. This suggests that the effects observed with vortioxetine in controlled research environments may be transferrable to real-life clinical practice. The data observed corroborate prior findings for vortioxetine in the real-world setting [37–39]. For example, compared with the present study, patients in a non-interventional, prospective, multicentre study in Greece showed similar baseline depression characteristics and improvements according to the MADRS total score and individual MADRS items [38]. The overall reduction in the MADRS total score was 23 points after 12 weeks of vortioxetine treatment [38]. Other real-world studies in different countries also indicated a significant


a)
Mean (SD) score
50
40
30
20
10
0
34.3
27.1
19.3
13.0
***
Visit 1 (baseline)
Visit 2 ~2–3 weeks
Visit 3 ~4–6 weeks
Visit 4 ~8 weeks
b)
Mean (SD) change
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-4.5
-2.3
-2.5
-2.4
-2.2
-1.8
-2.2
-2.2
-2.1
-2.5
-1.1
Apparent sadness
Reported sadness
Inner tension
Reduced sleep
Reduced appetite
Concentration difficulties
Lassitude
Inability to feel
Pessimistic thoughts
Suicidal thoughts
c)
Proportion of patients (%)
100
90
80
70
60
50
40
30
20
10
0
72.3
42.4
n = 162/224
n = 95/224
Response rate
Remission rate

◂**Fig. 3** Severity of depression as indicated by the sum of unanchored MADRS item assessments over the study duration ($N = 224$). **a** Mean (SD) sum of the unanchored MADRS item scores during the observation period. **b** Mean (SD) change from baseline to visit 4 (approximately 8 weeks) in individual unanchored MADRS item scores. **c** MADRS response and remission rates according to the sum of the unanchored MADRS items at visit 4 (approximately 8 weeks). ***$p < 0.001$ versus baseline; last observation carried forward. Mean (SD) unanchored MADRS item scores at visit 1 (baseline): apparent sadness, 3.9 (1.1); reported sadness, 4.2 (1.1); inner tension, 4.0 (1.1); reduced sleep, 3.5 (1.4); reduced appetite, 2.8 (1.6); concentration difficulties, 4.0 (1.1); lassitude, 3.6 (1.3); inability to feel, 3.4 (1.4); pessimistic thoughts, 3.7 (1.4); suicidal thoughts, 1.3 (1.5). Response was defined as a ≥50% reduction in the sum of the unanchored MADRS items from baseline to visit 4 (approximately 8 weeks). Remission was defined as the sum of the unanchored MADRS items ≤10 at visit 4 (approximately 8 weeks). *MADRS* Montgomery–Åsberg Depression Rating Scale, *SD* standard deviation

alleviation of depressive symptoms with vortioxetine treatment [37]. It is important to note that 51.3% ($n = 116$) of patients in the present study were experiencing their first depressive episode, which is similar to the proportion of first-episode patients (48.5%) in the aforementioned real-world study in Greece [38]. Conversely, controlled clinical trials of vortioxetine tended to focus on patients with a diagnosis of recurrent depression or included a lower proportion of patients with a first depressive episode [15, 16, 18–20, 22, 35, 36]. These population differences demonstrate that vortioxetine is considered a suitable option for the treatment of a first depressive episode by psychiatrists. The findings also reinforce the importance of collecting real-world data, which provide an insight into the use of a medication in routine clinical practice.

Of all patients enrolled in the study, 43.8% ($n = 99$) received vortioxetine as first-line treatment for the current depressive episode, irrespective of recurrence status. Similar use of vortioxetine was observed in real-world studies in Canada, China, France, Italy, South Korea and the USA, with 43.6–55.2% of patients receiving vortioxetine as first-line treatment [39–41]. This suggests that vortioxetine is often used for first-line treatment, as recommended by the 2023 Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of adults with major depressive disorder [42], as well as for patients who require a switch from a prior antidepressant. Prior to initiation of vortioxetine, 56.2% ($n = 127$) of all patients had received treatment for the current depressive episode and/or accompanying symptoms, such as insomnia. Escitalopram was the most common prior treatment, used in 9.7% of all patients. In 72.7% of patients who had received escitalopram, efficacy was considered insufficient, which may have prompted the change to vortioxetine. These findings are in line with a real-world study in Canada, France, Italy and the USA, which reported that escitalopram was the most common prior treatment (26.7% of patients), and inefficacy of prior treatment was the most frequent reason for switching to vortioxetine [39].

In the present study, 5.8% of patients received concomitant treatment with escitalopram at any time during the observation period, including during possible cross-titration. However, no patients receiving vortioxetine for maintenance treatment after the observation period received concomitant escitalopram. This observation suggests that patients previously treated with escitalopram completely switched to vortioxetine. This approach is consistent with current guidelines, which propose a switch to another class of antidepressant as a strategy if efficacy is insufficient [42–45]. Through its multimodal mechanism of action [10], vortioxetine acts beyond the serotonin reuptake inhibition of selective serotonin reuptake inhibitors such as escitalopram and, therefore, might provide benefits for patients with an inadequate response to selective serotonin reuptake inhibitors. Such potential benefits have been previously documented in randomised, double-blind, active-controlled trials, and in an open-label study of vortioxetine in patients with inadequate response to selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors [46–48].

Quetiapine extended release is approved for the adjunctive treatment of depressive episodes in patients who have responded inadequately to monotherapy with at least one antidepressant, in the sense of an augmentation strategy following antidepressant therapy carried out in accordance with current clinical guidelines [49]. The antidepressive properties of quetiapine were investigated in studies with 300 mg and 600 mg daily doses [49]. In the present study, quetiapine was used in 8.9% of patients prior to vortioxetine initiation (mean dose 48 mg), in 9.7% of patients during vortioxetine treatment (mean dose 45 mg), and was generally considered efficacious. In clinical practice, the sedative properties of low-dose quetiapine are often utilised to treat sleeping problems [50], which are very common in depressed patients [51]. Similarly, trazodone, which is approved for the treatment of depressive episodes with or without sleep disturbances in standard doses of 200–600 mg/day [44, 52], is frequently utilised in clinical practice in sub-therapeutic doses to promote sleep [53]. In the present study, trazodone treatment was reported in 8.9% of patients prior to and concomitantly with vortioxetine treatment in mean doses of 84 mg and 74 mg, respectively, and was generally considered efficacious. Together, these data suggest that quetiapine and trazodone were used as sleep-promoting agents rather than for their antidepressant effects. Moreover, the concomitant use of quetiapine and trazodone was reduced to 3.5% and 4.0%, respectively, in the maintenance phase. This might indicate that, with the improvement of depressive symptomatology observed with vortioxetine treatment, there was a reduced need for sleep-promoting agents.

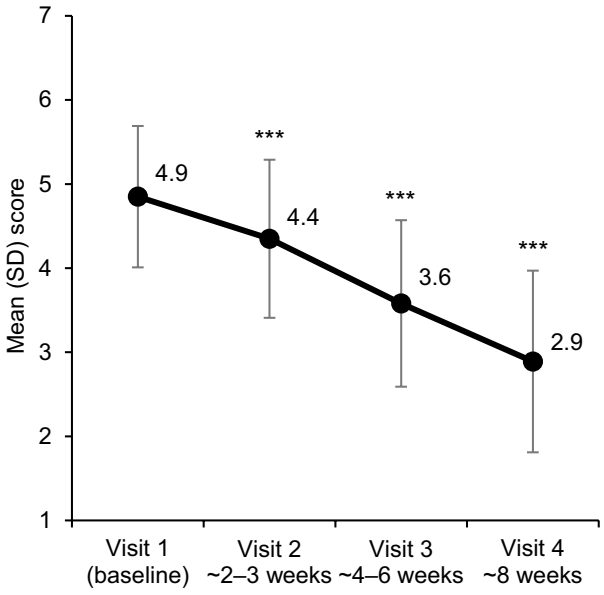


Fig. 4 Severity of illness as assessed by the clinician-rated Clinical Global Impression-Severity scale during the observation period ($N = 224$). ***$p < 0.001$ versus baseline; last observation carried forward. *SD* standard deviation

To account for concomitant medication during a possible cross-titration to vortioxetine, a sub-analysis of patients with versus without concomitant treatment at visit 2 (2–3 weeks after baseline) was conducted. Despite patients with a comedication being more severely depressed at baseline, efficacy was comparable between the groups, with similar response and remission rates after 8 weeks of treatment. Most concomitantly used agents not discontinued during the observation period had sedative characteristics. Vortioxetine does not have sedative properties. It seems that, if a sedative effect is required, vortioxetine is combined with the above-mentioned substances in clinical practice. Tolerability was comparable between the groups, indicating that vortioxetine was well tolerated also when concomitant medication was considered necessary.

Impaired psychosocial functioning due to depression is a major concern for patients [54]. The International Classification of Diseases, Eleventh Revision recognises significant impairment in personal, family, social, educational, occupational or other important domains of functioning as a common feature of depressive disorders [55] and the restoration of pre-morbid functioning is included as a relevant treatment goal in current clinical guidelines [43, 45]. As improvement in depressive symptoms correlates only partially with functional outcomes [56], it is relevant to include assessments of functioning in clinical trials [54].

In this real-world population, the proportion of patients with functional impairment at baseline was >95% for all measured domains, except for professional activities (89.7%) — a finding that may be owing to the fact that not all patients were employed before the current depressive episode. Severe impairment was reported for >25% of patients in each domain at baseline, except for family functioning (22.9%). After approximately 8 weeks of treatment with vortioxetine, improvements in the domains of everyday functioning — cognition, professional activities, family, social and leisure activities, physical well-being and quality of life — were observed, which is consistent with findings from previous clinical trials and real-world studies for vortioxetine [14, 16, 17, 35, 38, 39, 57]. In each functional domain, more than 80% of patients experienced no or mild functional impairment at the last visit, except for professional activities (78.0%). Furthermore, in each domain, a maximum of 3.1% of patients experienced severe impairment at the last visit, except for professional activities (6.3%). In an open-label study in working patients with MDD, Chokka et al. observed significant improvements in workplace productivity after 12 weeks of vortioxetine treatment [57]. In light of these findings, it is possible that the ability to fulfil the complex requirements of professional activities may require longer to recover than the 8-week observation period in the present study. Additionally, across all functional domains assessed in this study, the proportion of patients with severe impairment was highest for professional activities (38.1% at baseline). It may be relevant to conduct a detailed evaluation of functioning and employment status during the observation period specifically in the working population.

Overall, a relatively low proportion of patients (7.5%) experienced ADRs during the study, and few withdrew from the study because of ADRs (2.7%). A meta-analysis of RCTs has shown that during treatment of acute depressive episodes vortioxetine was not significantly different from placebo in terms of the dropout rate, indicating a high rate of acceptability [58], and separately, in the maintenance phase of treatment was superior to placebo with respect to discontinuation because of any cause [59]. The tolerability profile observed is also in line with observations from previous clinical studies for short-term and maintenance treatment and with the established tolerability profile of vortioxetine [18–20, 25, 37, 46, 59] with nausea, headache and dizziness being the most frequently observed side effects. While previous placebo-controlled RCTs of vortioxetine with fixed dosing schedules showed an incidence of nausea of 20.9–31.2% [25], nausea was observed with a lower incidence of 3.5% here. However, this is in line with several previous non-interventional real-world studies reporting a low incidence of nausea (<4%) [37]. Flexibility of dosing according to individual patient needs, which is particularly practicable with an oral drop formulation, and open communication about possible side effects at treatment initiation might contribute to better tolerability of vortioxetine in the real-world setting compared

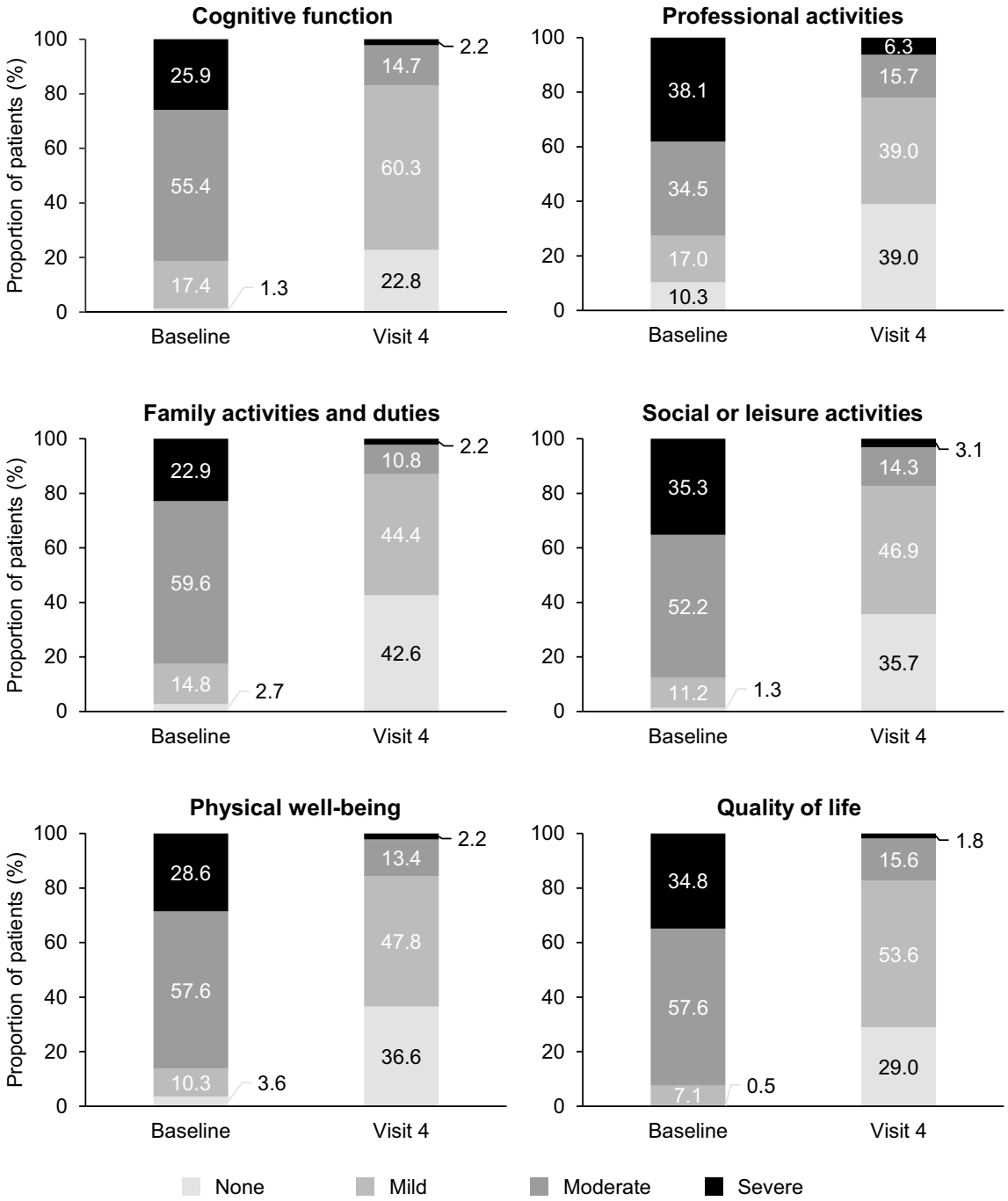


Fig. 5 Clinician-rated severity of impairment of everyday functioning on a 4-point scale at baseline and at visit 4 (approximately 8 weeks). *N*-values (last observation carried forward) were the same at baseline and visit 4: cognitive function ($N = 224$), professional activities ($N = 223$), family activities and duties ($N = 223$), social or leisure activities ($N = 224$), physical well-being ($N = 224$) and quality of life ($N = 224$)

with RCTs. Here, >60% of patients initiated treatment with a dose ≤5 mg. This may have influenced the low rate of nausea observed, which is known to be a dose-dependent side effect of vortioxetine [25].

Many patients in the present study reported comorbid conditions (31.9%), primarily overweight (6.2%), hypertension (5.8%), diabetes mellitus (3.1%), and attention-deficit hyperactivity disorder (2.2%). Considering that comorbidities are common in patients with MDD [60], the low incidence of ADRs with vortioxetine in a real-world patient population is a reassuring observation. This is also corroborated by a previous meta-analysis of clinical trials,

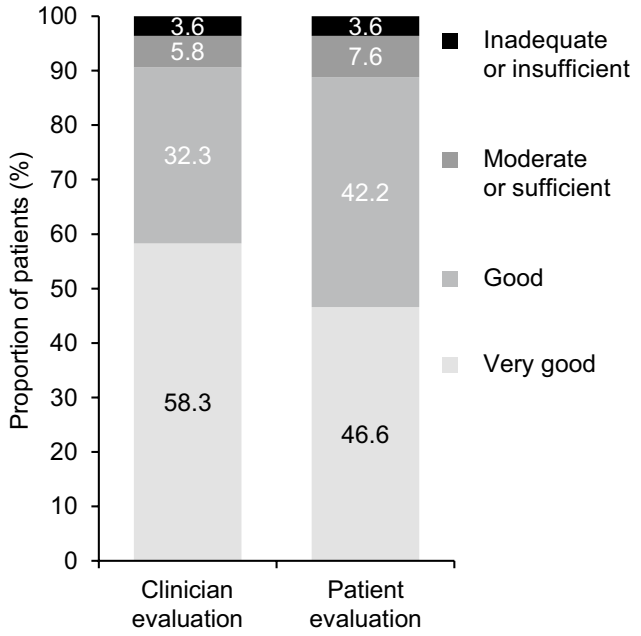


Fig. 6 Clinician- and patient-rated assessment of efficacy of vortioxetine on a 4-point scale at the end of observation ($N = 223$)

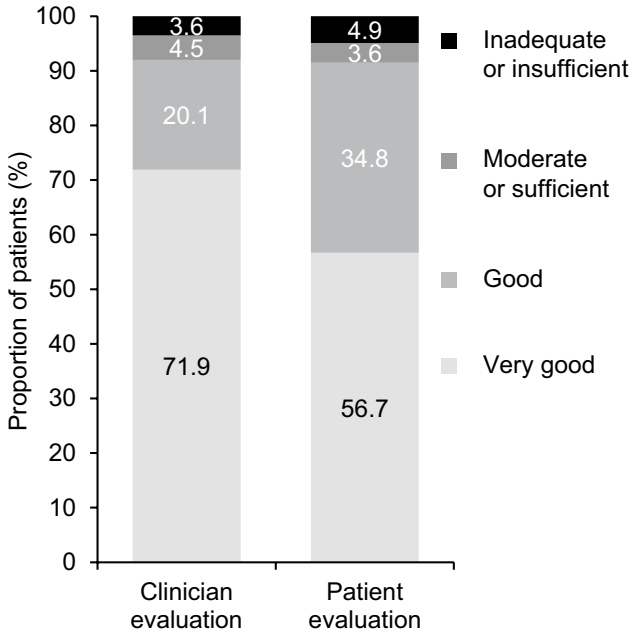


Fig. 7 Clinician- and patient-rated assessment of the tolerability of vortioxetine on a 4-point scale at the end of observation ($N = 224$)

Table 2 Safety and tolerability of vortioxetine as assessed by the incidence of ADRs and special notifiable cases over the study period

n (%)	Patients ($N = 226$)
Incidence of ADRs	17 (7.5)
ADRs occurring in ≥1% of patients	
Nausea	8 (3.5)
Headache	4 (1.8)
Dizziness	3 (1.3)
Incidence of special notifiable cases[a]	44 (19.5)
Special notifiable cases occurring in ≥1% of patients	
No or little effect	42 (18.6)

ADR adverse drug reaction

[a]Pre-defined special notifiable cases to be reported comprised: no or little effect; use in an unapproved indication (off-label use); overdose, misuse or abuse; drug interactions; use in paediatric patients; use during pregnancy/breastfeeding; incorrect use; occupational or accidental exposure; withdrawal symptoms; transmission of infectious diseases; unexpected positive effect; and transfer of the medicinal product via semen

which concluded that vortioxetine was efficacious and well tolerated, irrespective of stable key comorbidities [61].

In the present study, a high proportion of patients (86.3%) continued treatment with vortioxetine beyond the 8 weeks of observation, which may reflect its effectiveness together with its favourable tolerability profile. This finding is in line with a meta-analysis of RCTs for antidepressant maintenance treatment where the authors conclude that vortioxetine had reasonable efficacy, acceptability and tolerability in the treatment of adults with stable MDD [59]. These findings were complemented by subjective assessments of efficacy and tolerability by clinicians and patients. Efficacy and tolerability of vortioxetine was rated as good or very good by >90% of psychiatrists and >88% of patients.

Taken together, the observations in the real-world clinical setting, where patients were treated with vortioxetine for a current depressive episode according to the judgement of their treating psychiatrist, indicate that vortioxetine might be a suitable treatment option for different patient populations. These populations may include patients experiencing their first major depressive episode, patients with comorbidities, patients initiating an antidepressant for their current episode (i.e. first-line treatment), or patients requiring a switch from their prior antidepressant.

4.1 Limitations

Limitations of this study include those inherent to the observational nature of the study design such as selection and observer bias. The observational uncontrolled design of the study limits the ability to determine how much of the improvement in depressive symptoms and functioning is related to treatment with vortioxetine as no control group was included. It should be remembered that symptom trajectories may fluctuate naturally over the course of depressive disorders, including remissions and relapses, which may not be associated with specific treatment [62, 63]. Furthermore,

according to the non-interventional nature of the study, no systematic reporting of all adverse medical events during the observation period irrespective of possible causality with the study medication as obligatory in interventional trials was done. Under-reporting of adverse events remains an imminent risk for real-world observations; however, the treating psychiatrists were obliged to report all ADRs and all adverse events for which a causal relationship with the study medication could not be ruled out. Despite these limitations, the findings of such an observational study may provide valuable insight into the use of vortioxetine in real-life clinical practice, which is difficult to achieve in a controlled clinical trial. Second, the short observation period of approximately 8 weeks limits the ability to explore the course of depressive symptoms, durability of response and tolerability of vortioxetine over a longer period of time. The short study duration is, however, equivalent to the treatment periods used in controlled clinical trials of vortioxetine, which were sufficient for assessing the efficacy of vortioxetine when initiated for the treatment of an acute depressive episode. The study is also the first to be conducted in a Swiss patient population, which builds upon research conducted in other countries. Prescribing guidelines for vortioxetine can vary between countries, with vortioxetine considered an appropriate choice of first-line therapy in Switzerland and Canada [9, 42], and a later-line treatment option in other countries such as the UK [64]. Accordingly, many patients in this study received vortioxetine as first-line treatment in clinical practice, which might be different elsewhere. Additionally, differences in healthcare systems between countries could influence the generalisability of our study finding to other countries. Third, a simplified version of the MADRS, the unanchored MADRS, was used, which is unvalidated and may limit the ability to compare the findings of this study with those of previous trials as it may be prone to variability in clinician interpretation. It is important to note that this simplified scale was chosen to reflect daily clinical practice and to minimise the possibility of any intervention, as the conventional MADRS is not commonly used in Swiss clinical practice and therefore not permitted because of country-specific regulations. A secondary analysis of the current study describing the effectiveness and tolerability of vortioxetine oral drops versus oral tablets, which also employed the unanchored MADRS as an outcome measure, has recently been published [65] and additionally, the CGI-I and CGI-S tools were used as validated measures that have been widely used in RCTs. Notably, the findings according to the unanchored MADRS are consistent with those obtained for the CGI-I and CGI-S. The six-item clinician-rated functional assessment used in this study is an unvalidated ad-hoc tool and may therefore have limited clinical comparability, reliability and interpretability. Clinician- and patient-rated assessment of overall efficacy and tolerability utilised non-standardised tools that may be subject to bias.

5 Conclusions

During treatment with vortioxetine in routine clinical practice for a major depressive episode, patients experienced clinically relevant improvements in depressive symptoms and everyday functionality over approximately 8 weeks. Vortioxetine was also well tolerated, with a low incidence of ADRs reported. The underestimation of depressive episode severity by clinicians when relying on clinical estimation without any scale reinforces the importance of using rating scales in clinical practice, even if simplified, such as the unanchored MADRS items or the well-established CGI-severity scale.

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Declarations

Funding The study was funded by Lundbeck (Schweiz) AG and coordinated by the contract research organisation, ANFOMED GmbH. The sponsor distributed study documentation to clinicians participating in the study in accordance with the Pharma Code (Pharmakodex, 2015). The sponsor also reviewed the manuscript for scientific accuracy. All clinicians received an expense allowance for their involvement in the study, which was based on the time required to complete the relevant tasks (communicate information and complete study documentation) at each study visit.

Conflicts of Interest/Competing Interests Martin Kammerer holds shares in Roche Pharma AG and Alpine Health AG, and reports speaker honoraria from Lundbeck and Servier. Gregor Hasler reports speaker/consultant fees from Janssen, Lundbeck, OM Pharma, Salon Pharma, Sanofi, Schwabe, Servier, Sunovion and Takeda. Barbara Hochstrasser is a member of the Advisory Board for vortioxetine of Lundbeck Pharma Switzerland, and a speaker at Lundbeck-sponsored symposia and teaching events for physicians. Axel Baumann is a member of the Swiss Advisory Board on Brintellix and Lundbeck and a speaker in Lundbeck-sponsored symposia. Alexandra Sousek is a full-time employee of Lundbeck (Schweiz) AG.

Ethics Approval On the 2 April 2017, the Ethics Committee of the Canton of Zurich confirmed that the study protocol did not require specific ethics approval because of its purely observational nature. The study complied with the Declaration of Helsinki.

Consent to Participate Written informed consent was obtained from all participants included in the study.

Consent for Publication Not applicable.

Availability of Data and Material The data that support the findings of this study are not openly available because of reasons of sensitivity and are available from the corresponding author upon reasonable request.

Code Availability Not applicable.

Authors' Contributions Conceptualisation: MK. Methodology: MK. Formal analysis and investigation: MK, AB and AS. Writing (review and editing): MK, GH, BH, AB and AS. Supervision: AS. All authors have read and approved the published version of the manuscript and agreed to be accountable for all aspects of the work.

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