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ORIGINAL RESEARCH

Pooled Analysis of Four Non-Interventional Studies: Effectiveness and Tolerability of the Antidepressant Agomelatine in Daily Practice

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ABSTRACT

Introduction: Meta-analyses are useful to increase knowledge and strengthen evidence about antidepressant treatment supplementary to individual studies.

Methods: A pooled analysis of four multicenter, open-label, prospective, non-interventional studies (2009–2013) was performed to provide further evidence about the antidepressant effectiveness and tolerability of agomelatine (25–50 mg/day) in a large number of non-selected German outpatients with major depressive disorder. The main analysis was performed after 12 weeks ($n = 9601$) and in subpopulations after 24 and 52 weeks by descriptive statistical methods.

Results: Overall, 60.1% of patients were pretreated with antidepressants. Concomitant psychiatric diseases (71.9%), co-medication with antidepressants (18.9%) and/or psychotropic medication (31.9%) were observed. Depressive symptoms improved according to the Clinical Global Impression (CGI) in 81% after 12 weeks, a response was observed in 78.7% (CGI-I $\leq$2), and remission in 34.5% of patients (CGI-S = 1 or 2). In subpopulations, response was documented in 79.3% (W24) and 75.9% (W52) and remission in 38.1% (W24) and 47.5% (W52), respectively. Over 12 weeks, adverse drug reactions (ADRs) were reported for 511 patients (5.32%), most frequently headache (0.92%) and nausea (0.75%), and serious adverse drug reactions (sADR) for 18 patients (0.19%). Between W12–W24 and W24–W52, ADRs were reported for 0.49%/0.99% and sADRs for 0.05%/0%, respectively. Overall, 49 patients (0.5%) showed clinically relevant transaminase elevations (AST/ALT >3 times upper normal value), with 19 patients (0.2%) showing preexisting elevations at the study start. One patient (0.03%) developed hepatitis with reversible symptoms after

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treatment discontinuation. ADR predominantly occurred within the first weeks of treatment. Mean weight and body mass index (BMI) remained unchanged over 24 weeks.

Conclusion: In this pooled data analysis, 9601 depressed patients of clinical practice were evaluated over 12 weeks and subpopulations were also analyzed over 24 and 52 weeks. Agomelatine effectively reduced depressive symptoms (CGI-response and remission) with good general tolerability.

Keywords: Agomelatine; BMI; Dosage; Effectiveness; Liver function; Major depression; Pooled analysis; Tolerability

INTRODUCTION

In addition to individual clinical trials, meta-analyses and pooled analyses are used for evidence-based evaluation of therapeutic interventions in depression to extend knowledge about treatment options and analyze specific data based on a larger sample size. In general, efficacy and tolerability of drugs are examined and confirmed by randomized controlled trials (RCTs) with narrowly defined patient collectives, under strict inclusion and exclusion criteria, and with a precisely defined therapeutic regimen. Therefore controlled trials may not fully represent real-world patients in daily practice. In psychiatric care, psychotropic co-medication also represents a risk for comorbid and elderly patients as a result of pharmacological interactions or possible effects on existing somatic diseases. Therefore non-interventional studies can provide relevant information in addition to existing evidence of RCTs, because heterogeneous patient populations are observed in everyday clinical practice.

In order to collect realistic data on agomelatine treatment of comorbid and co-medicated depressed patients, four non-interventional studies were performed in an ambulant setting in Germany between 2009 and 2013.

The antidepressant agomelatine is a melatonergic receptor agonist (MT_1/MT_2) and an antagonist at the postsynaptic serotonin receptor 5-HT_{2c} [1, 2]. Its mode of action may be explained by the synergy of MT_1/MT_2 and 5-HT_{2C} receptors, which increases noradrenergic and dopaminergic neurotransmission, and a specific release of noradrenaline and dopamine has been described in the prefrontal cortex without effect on the extracellular levels of serotonin [3–5]. In addition, an increase of neurotrophic factors (e.g., brain-derived neurotrophic factor, BDNF) and a decrease in stress-related glutamate elevation have also been described [2, 6, 7] as well as resynchronization of circadian rhythms [8–10].

After oral intake, agomelatine is rapidly and well absorbed (≥80%) with low absolute bioavailability (<5%) and substantial interindividual variability. Peak plasma concentration is reached after 1–2 h and mean plasma half-life is between 1 and 2 h. Agomelatine is rapidly metabolized, mainly by hepatic CYP1A2, CYP2C9, and CYP2C19, and inactive metabolites are eliminated in the urine. Agomelatine does not inhibit or induce CYP450 isoenzymes and will not modify exposure of medicinal products metabolized by CYP450. Additionally it is not a substrate, inducer, or inhibitor of P-glycoprotein (P-gp) [11–13]. Antidepressant efficacy and tolerability of agomelatine are confirmed in numerous clinical studies [10, 14–27].

The objective of this pooled analysis was an evaluation of agomelatine therapy in a large number of unselected patients in daily practice in order to gain information about the naturalistic treatment situation of patients with depression. This large sample size enables a valuable assessment of effectiveness, dosage, evolution of body weight, and rare or yet unknown adverse drug reactions (ADRs). Since monitoring of hepatic transaminases is recommended for agomelatine-treated patients, the presented data particularly focus on the analysis of incidence and course of hepatic transaminase elevation under daily treatment conditions.

METHODS

Study Design and Population

The presented analysis was performed by pooling Germany-wide data collected by 1772

psychiatrists or specialized general practitioners (GPs) between 2009 and 2013. Overall 9601 outpatients of four prospective, multicentric, open-label, non-interventional studies with agomelatine were analyzed over a minimum of 12 to a maximum of 52 weeks (follow-up of VIVALDI study): VIVALDI (*V*aldoxan® *I*mproves depressi*V*e symptoms *A*nd norma*L*izes circa-*DI*an rhythms) and VIVALDI follow-up (2009/2010) [28–31] were performed exclusively in patients treated by psychiatrists, VIVALDI Praxis (2010) [32] only in GPs practices, VITAL (*V*aldoxan® *I*mproves *T*reatment of depression and daytime *A*ctivity in real *L*ife; 2011–2012) [33], and VIVRE (*V*aldoxan® *I*mpro*V*es dep*R*ession with anxi*E*ty symptoms; 2012–2013) [34] with psychiatrists and specialized GPs.

Data Collection

The pooled analysis includes all original data that had been collected in each of the individual studies in an identical or comparable way at a corresponding time of investigation. At the baseline visit (week 0), demographic data (age, sex, weight, smoking status), past psychiatric history (number of prior depressive episodes, duration of current episode, psychiatric comorbidities, previous suicide attempts), and form of therapy (pretreatment with antidepressants, psychotropic co-medication) were documented.

The antidepressant effect in all four included studies was assessed using the 7-point clinician rating scale Clinical Global Impression (CGI). Rater training had been offered to doctors in two studies to improve quality of assessment. Physicians evaluated severity of disease (CGI-S = Severity Scale; from 1 = "normal, not at all ill" to 7 = "most extremely ill") and improvement or worsening of disease (CGI-I = Improvement Scale; from 1 = "very much improved" to 7 = "very much worse"); response (CGI-I ≤2) and remission rates (CGI-S = 1 or 2) were analyzed.

Tolerability data including the incidence and type of adverse drug reactions (ADR) were analyzed. Physicians were asked to document emergent ADR at each visit with standardized ADR documentation sheets according to German and European pharmacovigilance requirements. All ADRs were reported to BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte) in accordance with applicable regulations. Hepatic transaminases alanine aminotransferase (ALT = GPT) and aspartate aminotransferase (AST = GOT) were documented, if available, at baseline and in week 6 (W6), 12, 24, and 52, and in accordance with the actual SmPC in 2012 (summary of product characteristics) additionally after 3 weeks in the VIVRE study. Recommended standard values for ALT and AST were used in cases where specified information was not available (50 U/I or 0.83 µmol/L for men; 35 U/I or 0.58 µmol/L for women). Transaminase values ALT and AST were classified as follows (ULN = upper limit of normal range):

Normal, within normal range	≤ULN
Abnormal, above normal range, but not clinically relevant	>ULN and ≤3× ULN
Abnormal, >3 times above normal range, clinically relevant	>3× ULN

The limit for clinical relevance of transaminase elevations (>3× ULN) was defined in accordance with FDA recommendations [35]. Transaminase values as well as ADRs were evaluated overall as well as separately for three treatment phases (W0–12, W12–24, and W24–52), considering acute, continuation, and maintenance treatment.

Data Analysis

Data of all four studies are included in the main analysis over 12 weeks. Patients with data at the inclusion visit and at least one further visit were eligible for statistical analysis of effectiveness ($n = 9283$; 96.2%). All 9601 patients with returned documentation forms were included in the safety analysis (ADR surveillance). Documented hepatic transaminase values (ALT/AST) were available for 9588 patients (at least

one documented value), baseline and at least one follow-up value of ALT/AST for 6443/6282 patients (67%/65%), and values at every visit for 5061/4956 patients (53%/52%). Exclusion criteria for effectivity analysis were patients without intake of agomelatine or retrospective documentation.

Pooled analysis of CGI response and remission rates was performed for patients with valid data at each respective visit, resulting in different numbers of patients at each visit. A second approach of analysis was implemented to validate the results by evaluating only patients with available values at every visit.

Additional analyses of the treatment effect were performed in subpopulations over 24 weeks (VIVALDI follow-up/VITAL; $n = 3610$) and 52 weeks (VIVALDI follow-up; $n = 605$) as a result of the different duration of studies. Long-term tolerability was analyzed accordingly in the safety analysis for week 12–24 (VIVALDI follow-up/VITAL: $n = 3915$) and week 24–52 (VIVALDI follow-up: $n = 605$).

Evaluation of body weight and BMI (body mass index) are based on patients with a valid assessment of height and weight at W0 and weight at the respective follow-up visit (W12 or W24). Therefore body weight and BMI were analyzed over 12 weeks (VIVALDI/VIVALDI Praxis/VIVRE: $n = 5273$ and 5271) and 24 weeks (VITAL: $n = 2687$ and 2686, respectively).

The statistical analysis of pooled data was performed descriptively because of the non-interventional design of the individual studies using SAS® (version 9.2 for Microsoft Windows; SAS Institute Inc., Cary, NC, USA). Quantitative variables were evaluated using the basic statistical parameters (mean value ± standard deviation, median). For qualitative data (e.g., sex) and categorical variables (e.g., scale values), frequency distributions (absolute and relative frequency) were drawn up. Adverse events were coded according to MedDRA® and evaluated on the basis of the coding levels of "system organ class" and "preferred terms".

Data management and statistical analysis were performed by the independent statistical institute GKM Gesellschaft für Therapieforschung mbH.

Compliance with Ethics Guidelines

This current article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

All studies were conducted in accordance with recommendations of the German Medicines Act (AMG), the Federal Institute of Drugs and Medical Devices (BfArM), the Guidelines of the German Working Group for Epidemiology (DAE) ensuring Good Epidemiological Practice as well as recommendations of the Association of Research-Based Pharmaceutical Companies (VfA). All procedures followed were in accordance with ethical standards, all four individual studies were approved by the Free Ethics Committee Freiburg, Germany, submitted to German authorities (BfArM, KBV, GKV-Spitzenverband), included in the international study registry http://www.controlled-trials.com, and published [28–34]. All procedures also followed the ethical standards of the Helsinki Declaration of 1964, as revised in 2000 and 2008. Informed consent form was requested from all patients before being included in the original studies, but not mandatory because of the non-interventional design.

RESULTS

Patient Characteristics

Patient characteristics and demographic data are shown in Table 1. The mean age of the pooled population was 50.5 ± 13.4 years (69% ≥45 years), 65.3% were female, and 60.2% of patients had a recurrent depression. Mean duration of the current episode was almost 11 weeks with the shortest duration reported by GPs (6 weeks) and the longest by psychiatrists (14 weeks). 72% of the pooled population ($n = 6674$) showed psychiatric comorbidities, most frequently sleep disorders (56.6%), anxiety/panic disorder (35.5%), post-traumatic stress disorder (7%), and others (14%), with multiple entries possible. The

Table 1 Demographics of the pooled analysis dataset ($n = 9283$) and individual studies. Modified with permission from [36]

	Pooled analysis ($n = 9283$)	VIVALDI ($n = 3317$)		VIVALDI Praxis ($n = 1070$)	VITAL ($n = 3005$)	VIVRE ($n = 1891$)
		W0–12 ($n = 3317$)	Follow-up ($n = 605$)			
Sex (%)						
Male	34.7	35.5	35.0	34.1	34.0	35.1
Female	65.3	64.5	64.7	65.9	66.0	64.9
Age [years] (mean value ± SD)	50.5 ± 13.4	50.5 ± 13.0	49.3 ± 12.5	52.7 ± 14.2	50.5 ± 13.6	50.3 ± 13.3
Age groups (%)						
<25 years	2.9	3.1	3.2	2.2	3.1	2.8
25 to <45 years	28.2	29.1	31.4	26.8	27.6	28.8
45 to <65 years	54.5	54.4	54.5	50.7	55.3	55.5
65 to <75 years	10.2	11.0	8.8	13.0	9.3	8.4
≥75 years	4.2	2.5	2.2	7.3	4.7	4.4
Duration of observation (weeks)	12 (24/52)	12	52	12	24	12
BMI [kg/m^2] (mean value ± SD)	26.4 ± 4.9	26.4 ± 4.9	26.3 ± 4.8	26.6 ± 4.8	26.4 ± 4.8	26.5 ± 4.9
Smoking status (%)						
Smoker	27.2	28.2	22.6	29.4	25.3	27.6
Non-smoker	58.9	60.2	52.9	55.5	59.7	57.3
Ex-smoker	13.9	11.7	9.1	15.1	14.9	15.0
Diagnosis (%)						
Depressive episode (F32)	39.8	36.4	37.5	40.6	52.9	24.8
Recurrent depression (F33)	60.2	63.6	62.0	59.4	47.1	75.2
Number of depressive episodes in the past history						
Mean value ± SD	3.9 ± 6.1	4.5 ± 7.2	4.7 ± 7.1	4.2 ± 7.2	3.6 ± 5.4	3.2 ± 4.2
Median	2	3	3	2	2	2
Duration of the current depressive episode (weeks)						
Mean value ± SD	10.6 ± 16.4	13.9 ± 21.3	11.8 ± 16.9	6.1 ± 7.4	8.9 ± 11.1	9.8 ± 15.9
Median	6	8	6	4	6	6

Table 1 continued

	Pooled analysis ($n = 9283$)	VIVALDI ($n = 3317$)		VIVALDI Praxis ($n = 1070$)	VITAL ($n = 3005$)	VIVRE ($n = 1891$)
		W0–12 ($n = 3317$)	Follow-up ($n = 605$)			
Suicide attempts (%)						
Yes	5.9	8.0	7.8	2.9	5.1	5.8
No	89.6	87.5	79.8	89.9	91.5	89.8
Unknown	4.4	4.5	3.6	7.2	3.5	4.4
Concomitant psychiatric illnesses (%)						
Yes	71.9	70.4	64.6	8.2	84.4	90.7
No	28.1	29.6	35.4	91.8	15.6	9.3
Pretreatment (%)						
Total	60.1	70.2	67.6	45.0	58.2	54.0
SSRI	31.4	49.1	36.9	19.7	27.1	28.5
TCA	23.2	32.1	31.5	17.0	20.7	15.7
Mirtazapine	15.2	21.0	17.9	9.6	13.2	11.5
SNRI	14.3	24.9	13.1	7.5	10.3	11.7
St. John's wort	8.1	6.5	5.6	11.9	9.6	6.3
MAO inhibitor	1.6	2.9	3.6	0.6	1.4	0.5
Comedication (%)						
Antidepressant	18.9	25.8	26.0	9.1	13.1	19.9
Other psychotropic medication	31.9	30.1	26.8	31.7	4.1	39.1

Calculation based on the patients with data available at start of study
SSRI selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant, *SNRI* serotonin–norepinephrine reuptake inhibitor, *MAO* monoamine oxidase

lowest incidence of psychiatric comorbidities (8.2%) was reported in VIVALDI Praxis (GP study) (see Table 1).

After 12 weeks, 67.8% of patients were treated with agomelatine 25 mg/day (Table 2). In the subpopulation over 24 weeks (VITAL/VIVALDI follow-up) 72.6% of patients ($n = 1914/2637$) were treated with 1 tablet/day (25 mg). A dose increase was documented more frequently by psychiatrists in the VIVALDI study compared to GPs (VIVALDI Praxis) and following studies (VITAL and VIVRE).

Psychotropic Co-medication

Overall, 60.1% of patients ($n = 5581$) were already pretreated with antidepressants, 70.2% in the VIVALDI study and 45.0% in VIVALDI Praxis. SSRI (selective serotonin reuptake inhibitors) were the most common medication in pretreatment (31.4%). In 18.9% of patients, previously prescribed antidepressants were continued in addition to agomelatine.

At baseline, co-medication with other psychotropic drugs was documented for 31.9% of

Table 2 Patients (%) in the pooled dataset and individual studies according to agomelatine dosage over 12 weeks (W12). Modified with permission from [36]

Visit[a]	Pooled analysis (%)	VIVALDI (%)	VIVALDI Praxis (%)	VITAL (%)	VIVRE (%)
25 mg					
W0	98.4	98.9	98.7	97.9	98.0
W2[b]	74.2	68.7	82.4	77.3	73.9
W6	67.7	58.7	79.2	71.0	69.4
W12	67.8	58.3	79.7	70.5	70.6
50 mg					
W0	1.4	1.0	1.1	1.7	1.8
W2[b]	25.4	30.9	17.5	22.2	25.9
W6	31.8	40.1	20.7	28.6	30.4
W12	31.5	40.4	20.0	29.0	29.0

[a] Analysis based on the following number of patients at each respective visit: $n = 9067$, W0; $n = 8654$, W2; $n = 8026$, W6; $n = 7805$, W12

[b] In the VIVRE study dosage was documented after 3 weeks

patients, most frequently zolpidem or zopiclone (13.0%; $n = 1204$), benzodiazepines (10.1%; $n = 933$), antipsychotics/neuroleptics (5.7%; $n = 531$), anticonvulsant drugs (2.2%; $n = 205$), and 6.7% others (multiple entries were possible) (Table 1).

Change in Depressive Symptoms

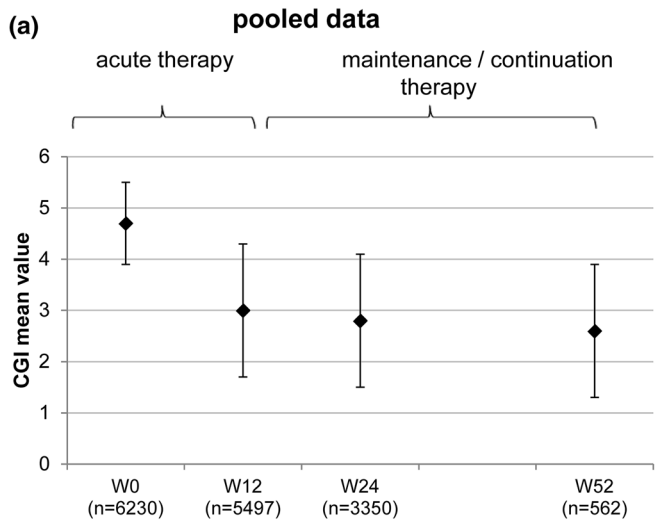
The severity of depression (CGI-S) improved over 12 weeks (VIVALDI, VIVALDI Praxis, and VIVRE) with reduction of CGI-S (mean value) from 4.7 ± 0.8 at baseline (5 = patient is significantly ill) to 3.0 ± 1.3 after 12 weeks (3 = patient is only mildly ill). Overall, there was improvement of CGI-S in 81% of patients. As a result of longer observation periods in the studies VITAL and VIVALDI follow-up, the effect on the severity of depression was also analyzed after 6 months (W24). The pooled data ($n = 3350$) demonstrate a decrease in mean value of CGI-S from 4.7 ± 0.8 (W0) to 2.8 ± 1.3 (W24) (Fig. 1a), corresponding to an improvement of severity of depression (CGI-S) in 82.4% of patients after 24 weeks.

On the basis of the CGI-I score, 78.7% of patients were classified as responders (CGI-I ≤ 2) after 12 weeks and 79.3%/75.9% after 24/52 weeks, respectively; 34.5% of patients met the criteria for remission (CGI-S = 1 or 2) after 12 weeks and 38.1%/47.5% after 24/52 weeks (Fig. 1b).

Tolerability

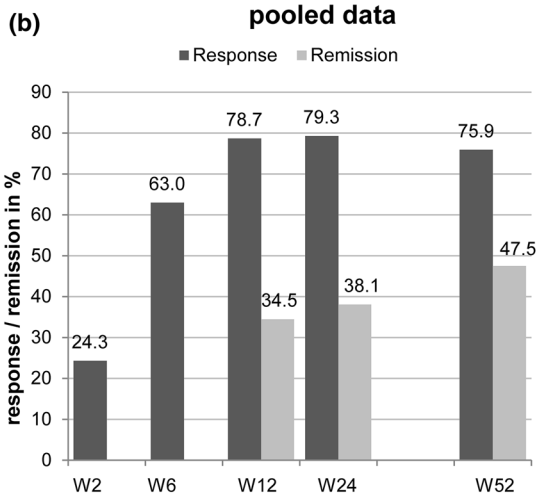
Frequency and type of ADRs, including serious ones (sADRs), were evaluated in the main analysis safety set ($n = 9601$) over 12 weeks: 5.32% of patients (511 of 9601) reported 859 ADRs (8.9%), most frequently headache, nausea, dizziness, and agitation; 0.49% of patients ($n = 19/3915$) reported 28 ADRs between weeks 12 and 24, six patients ($n = 6/605$; 0.99%) with seven ADRs between weeks 24 and 52. Headache, dizziness, and agitation were no longer reported after 24 weeks (Fig. 2a).

Eighteen patients (0.19%) reported 33 sADRs within the first 12 weeks. Three sADRs were documented in two patients (0.05%) between weeks 12 and 24; one of these patients (0.03%) had bradycardia and one patient (0.03%) had symptoms of hepatobiliary disorder starting after 10 weeks of treatment with agomelatine 50 mg/day. The hepatitis symptoms of this



CGI-S* mean (±SD) - pooled data & individual studies				
	Study			
Visit	Pooled data	VIVALDI	VIVALDI-Praxis	VIVRE
W0	**4.7 (±0.8)**	4.7 (±0.8)	4.7 (±0.9)	4.7 (±0.8)
W12	**3.0 (±1.3)**	3.2 (±1.3)	2.8 (±1.1)	2.8 (±1.3)

CGI-S: 7-point scale
1: not ill at all
2: borderline case
3: mildly ill
4: moderately ill
5: ill
6: significantly ill
7: extremely ill



Response / Remission over 12 weeks pooled data & individual studies					
Response					
Visit	Pooled data	VIVALDI	VIVALDI-Praxis	VITAL	VIVRE
W2#	**24.3%**	22.8%	27.6%	20.7%	30.3%
W6	**63.0 %**	55.8%	76.6%	61.1%	69.7%
W12	**78.7%**	72.4%	90.7%	78.0%	82.1%
Remission					
W12	**34.5%**	30.4%	36.3%	-	39.9%

Number of patients per visit (response / remission)				
W2	W6	W12	W24	W52
8996	8501	7932/5497	3322/3350	n=557/562

Fig. 1 Change of depressive symptoms according to CGI in the pooled dataset and individual studies over 12 weeks (W12) and 24/52 weeks (W24/52; subpopulations): **a** improvement of severity (CGI-S; mean value ± standard deviation). *Asterisk* indicates CGI-S values not available in VITAL study after 12 weeks (study duration 24 weeks), **b** response (CGI-I ≤2) and remission (CCI-S = 1 or 2) in %. *CGI* Clinical Global Impression scale, *CGI-S* (severity scale), *CGI-I* (improvement scale); assessment of all patients with available data at each respective visit; # in VIVRE study data were documented after 3 weeks Modified with permission from [36]

patient were completely reversible after discontinuation of treatment and the patient recovered without persisting impairment or sequelae. A detailed description of this patient has already been published [36]. No serious event occurred between weeks 24 and 52 (Table 3).

Regarding psychotropic co-medication, ADRs were documented for 5.28% ($n = 161$) of patients with ($n = 3048$) versus 5.34% ($n = 350$) of patients without co-medication ($n = 6553$) (Fig. 2b), showing no substantial difference in relation to psychotropic co-medication.

sADRs were reported for 0.3% of patients ($n = 9$) with psychotropic co-medication compared to 0.14% of patients ($n = 9$) without co-medication. The difference was mainly due to reports of headache, somnolence,

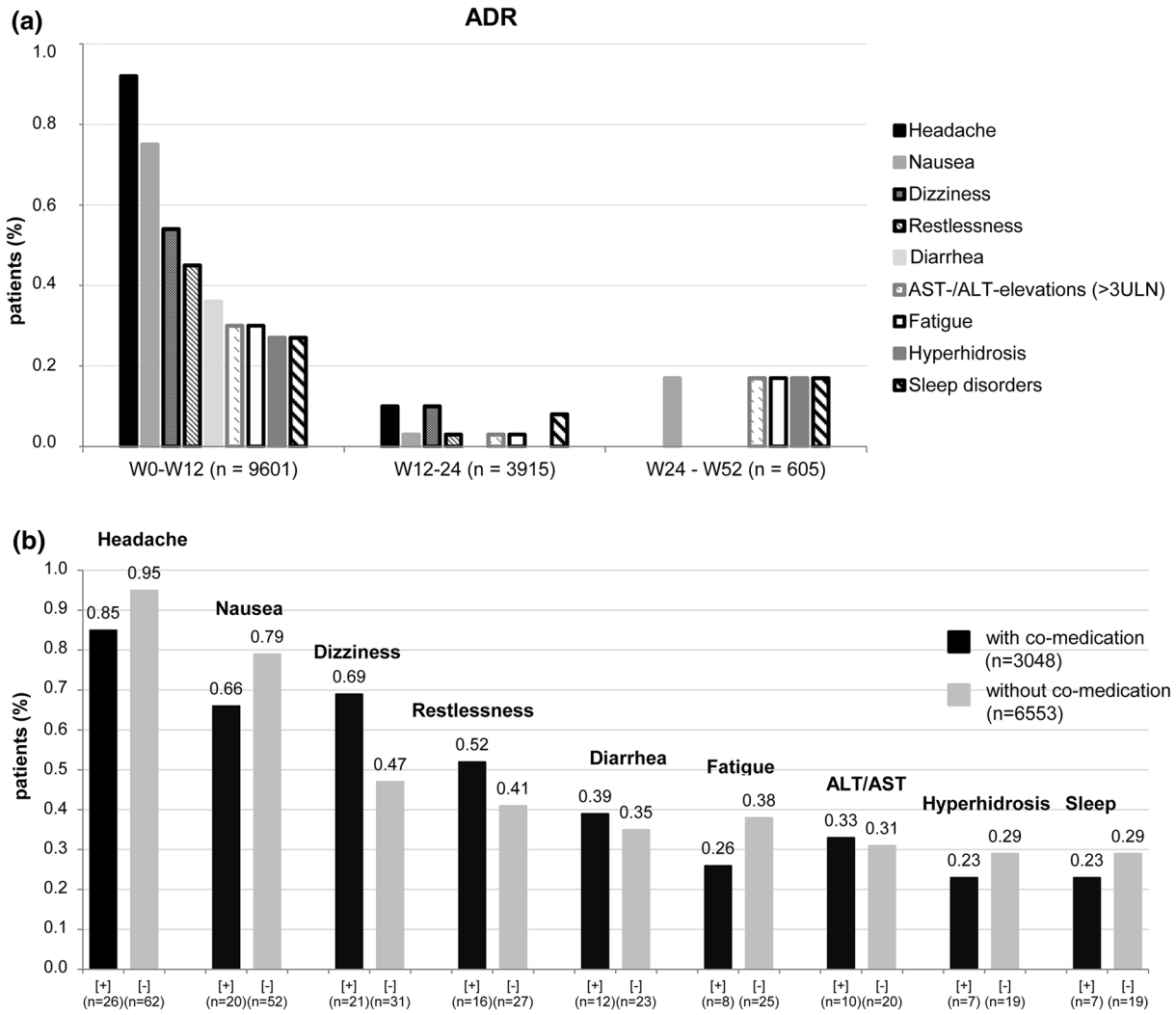


Fig. 2 Tolerability according to most frequent ADRs in the course of treatment: **a** evaluation over 12 weeks, between 12–24 and 24–52 weeks, **b** incidence of ADR regarding psychotropic co-medication over 12 weeks. *ADR* adverse drug reactions, *W* week, *ULN* upper limit of normal range, *>3 ULN* clinically relevant elevation of transaminases; cutoff for incidence over 12 weeks >0.25%; *asterisk* indicates multiple entries were possible

aggression, dissociation, hallucination, insomnia and mania (one report for each symptom), and depression ($n = 2$) in co-medicated patients compared to no reports in patients without co-medication. For one patient of each group (with/without co-medication), transaminase elevations were assessed as sADRs (corresponding to 0.03%/0.02%). No deaths occurred and no long-term impairment was observed in the total population ($n = 9601$).

Change in Hepatic Values

Overall, 9588 patients with liver transaminase values (at least one value available) were included in this analysis. At baseline, hepatic transaminases (ALT and AST) were documented for 78.4% ($n = 7517$) and 76.4% ($n = 7321$) of all patients. Most of these patients showed ALT/AST values within the normal range (≤ULN; 88.4%/90.8%) or a mild increase without clinical relevance (≤3× ULN; 11.4%/9.0%). In 0.2%

Table 3 Number (*n*) and percentage (%) of patients with serious adverse drug reactions (sADR) within different treatment periods (week 0–12/12–24/24–52), based on the safety analysis set (SAS) of each respective period. Modified with permission from [36]

sADR[a]	W0–W12 (*n* = 9601)		W12–W24 (*n* = 3915)		W24–W52 (*n* = 605)	
	Patients		Patients		Patients	
	n	%	*n*	%	*n*	%
Any	18	0.19	2	0.05	–	–
Diarrhea	1	0.01	–	–	–	–
General disorders	2	0.01	–	–	–	–
Hepatic investigations	2	0.01	–	–	–	–
Headache	1	0.01	–	–	–	–
Somnolence	1	0.01	–	–	–	–
Psychiatric disorders	13	0.14	–	–	–	–
Anxiety	2	0.02	–	–	–	–
Depression	2	0.02	–	–	–	–
Restlessness	2	0.02	–	–	–	–
Sleep disorder	2	0.02	–	–	–	–
Suicidal ideation	9	0.09	–	–	–	–
Others	8	0.08	–	–	–	–
Hospitalization	1	0.01	–	–	–	–
Bradycardia	–	–	1	0.03	–	–
Hepatobiliary disorders	–	–	1	0.03	–	–

[a] Multiple responses possible

(ALT) and 0.1% (AST) of patients, a clinically relevant increase (>3× ULN) had already been documented before the start of treatment (Fig. 3).

In comparison of individual studies, values of liver function tests (ALT/AST) were available at every visit in 60.3% (ALT) and 58.9% (AST) of patients treated by GPs and 41.2% and 40.4% of patients treated by psychiatrists. Between 2009 and 2013, the proportion of documented values (ALT/AST) at every visit increased from 41.2%/40.4% up to 54.9%/53.9%. Accordingly, the proportion of documented values at baseline and at least one follow-up visit increased from 54.9%/53.5% to 76.4%/74.6% of patients.

Overall, clinically relevant transaminase elevations (>3× ULN) were documented in 0.5% of patients ($n = 49/9601$), 0.2% ($n = 19$) of whom showed clinically relevant ALT/AST elevations before the treatment with agomelatine at the study start (Table 4) and 30 patients (0.3%) an increase of values (>3× ULN) during treatment. In a calculation according to per protocol analysis (inclusion of patients with available values at every visit), 30 patients with elevations under treatment correspond to 0.6% and 23 patients with at least a possible causal link (ADR) to 0.46%. There was no difference in the incidence of transaminase elevations with respect to psychotropic co-medication (0.33%/0.32% of patients with/without psychotropic co-medication).

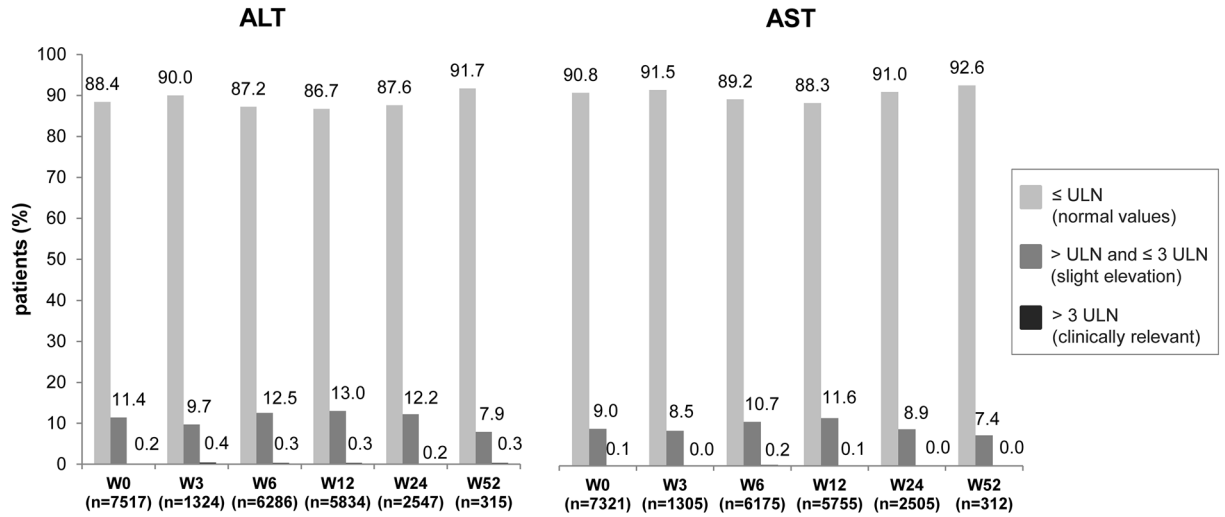


Fig. 3 Patients' hepatic transaminase values (ALT and AST) during the course of treatment over 12 weeks (main analysis) and 24/52 weeks (subpopulations). *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *>3 ULN* >3 times above normal range; transaminase monitoring after 3 weeks was documented in VIVRE study only, according to the actual summary of product characteristics (3/2012) at time of study implementation

Table 4 Clinically relevant transaminase elevations (ALT and/or AST >3ULN) and documentation status of adverse drug reactions (ADR)

ALT ± AST elevations >3 ULN	Patients (W0–W52) (*n*)	Reference population for calculation (%)	
		Total population (*n* = 9588)	Per protocol (ALT = 5061; AST = 4956)
Patients with baseline elevation (i.e., preexisting elevations)	19	0.19	0.38
Elevation during treatment	30	0.31	0.60
ADRs (with at least possible causality)	23	0.24	0.46
No ADR (without causal relationship)	7	0.07	0.14
Total number (including preexisting elevations)	49	0.51	0.98

Calculation of percentage based on total population (with at least one liver function test) or patients with available transaminase values at every visit (corresponding to "per protocol"). Modified with permission from [36]
ALT alanine aminotransferase, *AST* aspartate aminotransferase; *>3 ULN* >3 times above normal range

Transaminase elevations were classified as ADRs in 23 patients (with at least possible causal relationship). Almost 80% of affected patients were between 25 and 65 years of age (4.4% >75 years). Detailed patient characteristics of affected patients are listed in Fig. 4.

Over 12 weeks of treatment, 11 patients (0.2%) with normal baseline values developed ALT elevations and 7 patients (0.1%) AST elevations (>3× ULN). In patients with slight elevations at baseline, 0.1% showed clinically relevant elevations of ALT ($n = 7$) and/or AST ($n = 5$), respectively.

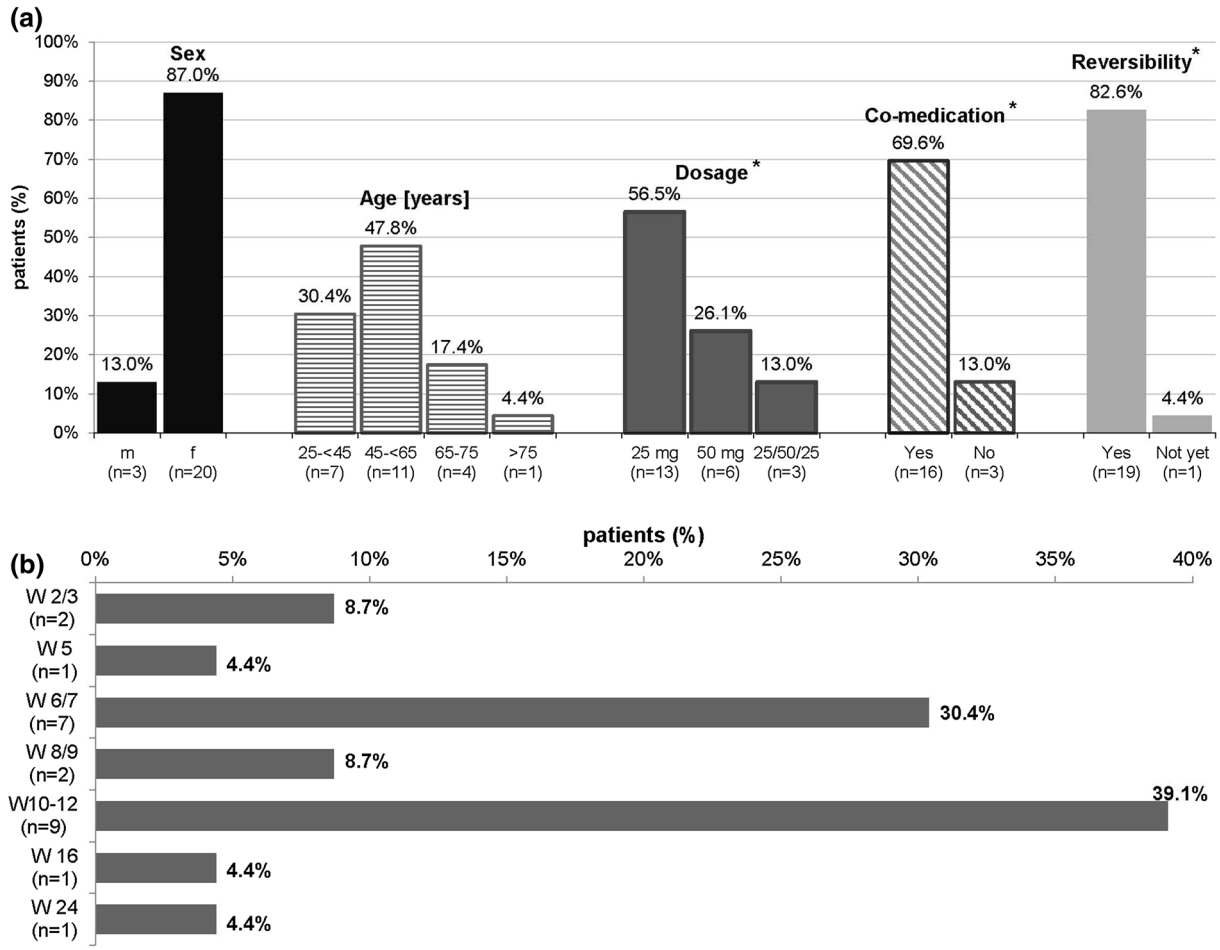


Fig. 4 Patient characteristics of the 23 patients with clinically relevant elevation of hepatic transaminases (ADR): **a** gender, age, used dosage, status of co-medication and reversibility; **b** patients (%) according to their duration of treatment until onset of ALT/AST elevation (>3 ULN). *ADR* adverse drug reaction, *m* male, *f* female, *>3 ULN* >3 times above the normal range; calculation based on pharmacovigilance data of patient reports; *asterisk* indicates no information available for dosage ($n = 1$; 4.4%), co-medication ($n = 4$; 17.4%), reversibility ($n = 3$; 13.0%)

Evaluating liver function in long-term therapy, 0.04% of the patients with normal transaminase values at the beginning of treatment developed a relevant ALT and/or AST elevation (>3× ULN) over 24 weeks ($n = 1/2437$) and 0.3% ($n = 1/288$) over 52 weeks. Two patients with slightly elevated values (≤3× ULN) at the study start showed an ALT elevation (>3× ULN) over 24 weeks (0.1%) and no patient over 52 weeks (available values W0–W24, $n = 2437/2387$; W0–W52, $n = 288/282$). Additionally, no patient with normal or slightly elevated transaminase values at week 12 developed a clinically relevant increase in ALT or AST (>3× ULN) during further treatment.

Body Weight

Mean weight was 76.9 kg (±15.7) at the beginning of the observation period and 77.0 kg (±15.5) after 12 weeks. Corresponding values for the BMI were 26.4 ± 4.9 kg/m^2 (W0) and 26.5 ± 4.8 kg/m^2 (W12). Also after 24 weeks, the evaluated subpopulation (VITAL study) did not show any relevant changes in body weight or BMI (Fig. 5).

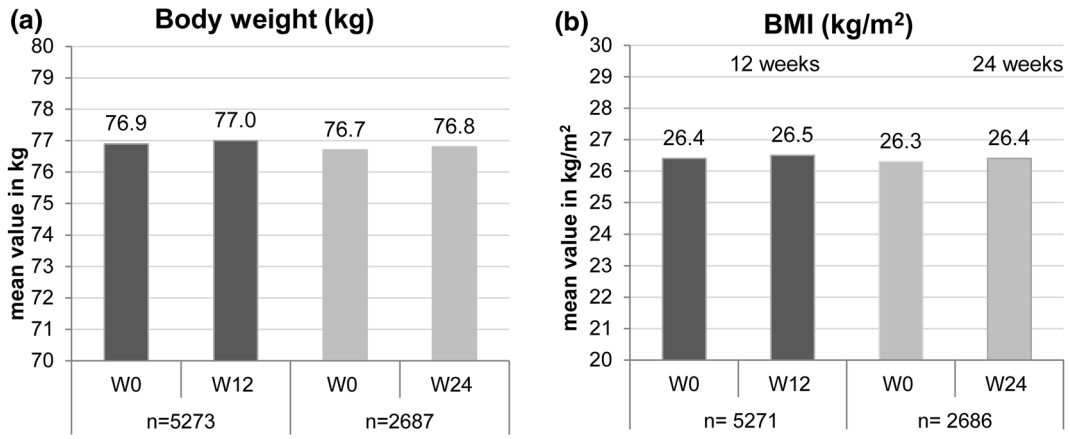


Fig. 5 Evolution of **a** body weight (kg) and **b** BMI (kg/m^2) over 12 weeks (VIVALDI, VIVALDI Praxis, VIVRE) and 24 weeks (subpopulation of VITAL). Evaluation of patients with valid data at baseline and W12 or W24, respectively

DISCUSSION

The presented analysis of naturalistic observational data provides important epidemiological data in a large number of non-selected patients ($n = 9601$). The findings demonstrate the effectiveness and good tolerability profile of agomelatine, which is in line with proven efficacy and tolerability in various RCTs [21, 26]. In the observational VIVALDI study [31] this effect was also demonstrated independent of psychotropic co-medication, which is confirmed in the presented mixed patient cohort.

Demographic data of the evaluated depressed population are representative of daily medical care with a high proportion of pretreated and comorbid patients [37]. Severity of depression was more pronounced in patients treated by specialists, reflected by the proportion of psychiatric comorbidities, co-medication, number and duration of depressive episodes as well as previous suicide attempts.

More than two-thirds of this large sample used agomelatine 25 mg/day (1 tablet) over 12 and 24 weeks, being in line with controlled data where about 75% of patients were medicated with 25 mg/day [38]. A dose increase in the presented patient cohort was documented more frequently by psychiatrists compared to GPs (VIVALDI Praxis), possibly as a result of more pronounced severity of depression and higher incidence of psychiatric comorbidities and co-medication in specialists' practices.

In the present analysis, the CGI scale was used as an indicator for effectiveness, representing a general assessment of severity and improvement of depression by physicians. The CGI usually corresponds well with treatment effects evaluated with more specific scales (MADRS, Montgomery-Asberg Depression Rating Scale; Hamilton Depression Scale, HAM-D) in clinical and observational studies [31, 38, 39]. In the VIVALDI and VIVALDI Praxis trials, the short version MADRS (svMADRS) [40] was used in addition to CGI and confirmed CGI results, also being comparable to RCT data. Improvement according to CGI in our sample can therefore be seen as an indication for effectiveness of agomelatine with response and remission rates supporting the results of controlled data [38, 39]. Moreover, the antidepressant effect in this outpatient setting can also be evaluated in the continuation and maintenance phase of treatment, representing meaningful information in addition to clinical trials over 6–12 weeks, owing to a placebo control arm being included.

The overall incidence of ADRs in our unselected patient population is low with a known profile of adverse events (especially headache, nausea, dizziness). No new information was obtained about previously unknown ADRs compared to the existing database of controlled trials or non-interventional studies. Most ADRs/sADRs were documented within the first weeks of treatment and markedly decreased after

12 weeks. sADRs were no longer reported after week 24. Interestingly, ADRs and sADRs occurred nearly independent of psychotropic co-medication. Taken together, the presented results confirm data of clinical trials considering tolerability without effects on sexual function or cardiovascular parameters and a favorable interaction profile with emergence of ADRs primarily at the beginning of treatment [11].

In our large sample, no relevant changes of body weight occurred during short-term treatment or over 24 weeks. These results are in good agreement with possible positive metabolic effects of agomelatine described in several studies [41, 42]. A specific receptor profile without affinity to other receptors (especially no anti-histaminergic effect), normalization of circadian rhythms by melatonergic effects, and a positive influence on cortisol levels could serve as an explanation. These characteristics of the substance seem relevant, since weight gain is a frequently observed undesired effect with psychotropic medication [43].

In order to investigate the influence of agomelatine treatment on liver function, transaminase values were documented in all four studies. For the present pooled analysis, transaminase values (ALT/AST) were available for about half of the patients at every visit and for about two-thirds of all patients at baseline and at least one further follow-up visit. Comparison of the included individual studies confirms the assumption that transaminase monitoring is performed more often by GPs compared to psychiatrists. Besides, the increasing proportion of documented transaminase values over time between 2009 and 2013 is shown, presumably correlating with increasing awareness of physicians concerning transaminase monitoring in agomelatine-treated patients. Overall, clinically relevant elevations of ALT and/or AST (>3× ULN) were documented for 49 patients (0.5%), 19 (0.2%) of whom already showed elevations before the beginning of medication, hence not being classified as ADR. Transaminase values generally normalized after discontinuation of agomelatine, in some cases even during continuation of treatment, which is in line with RCT data [22, 23, 44]. One patient with symptoms of hepatitis and icterus recovered without any further impairment after discontinuation of treatment. A detailed case description has previously been published [36]. Before treatment initiation, only incomplete laboratory values were available for this patient, further supporting the importance of transaminase monitoring before medication, and thereby improving risk detection of preexisting impaired liver function. It is worth mentioning that no case of acute liver failure occurred under controlled conditions with strictly requested blood tests in RCTs in nearly 8000 patients [44].

Presented pooled data show a lower incidence rate of clinically relevant elevations compared to numerous controlled trials [11, 22, 23, 44]. Recruitment practice could possibly account for a higher incidence in RCTs, especially compared to American studies with more patients having preexisting risk factors (e.g., hepatobiliary disorder) [23, 45]. Strict clinical monitoring under controlled conditions could also explain higher reporting rates in RCTs compared to this naturalistic design. The demonstrated lower incidence in this pooled data set, however, is verified by an additional analysis based on patients with available values at every visit (ALT, $n = 5061$; AST, $n = 4956$). This additional calculation (comparable to "per protocol" analysis) confirms lower incidence rates of transaminase elevations (ADRs) in 23 patients corresponding to 0.46% and of all documented cases including preexisting baseline elevations with 0.98% ($n = 49$).

Various database analyses have been published so far, investigating spontaneous reports of adverse hepatic effects during agomelatine treatment [46–48], to explore quantitative signals about reporting frequencies without causality assessments, since reports listed in safety databases are "raw data" [49]. Gahr and colleagues describe that hepatic effects in agomelatine-treated patients (mostly asymptomatic transaminase increase) occur primarily in the initial phase of treatment. Polypharmacy, female gender, and age over 50 years were described as possible risk factors [46].

Our results confirm the emergence of transaminase elevations within the first weeks of treatment, reversibility, and increased

occurrence in women and patients with co-medication. Older age, however, did not correlate with higher risk of transaminase abnormalities in our population with two-thirds of the patients being younger than 55 years.

This result is confirmed by RCT data, demonstrating good tolerability in older patients up to 6 months of treatment [50, 51] without the necessity for dose adjustment in elderly patients [11]. Higher incidence of transaminase elevations in women within this sample could possibly be explained by the high proportion of women in the depressed population in general. Nevertheless, even taking baseline data into account with a ratio of 2:1 (female/male), the presented results still show a trend for a higher frequency in women.

With the objective of ensuring therapeutic safety, the European Medicines Agency (EMA) has developed increasingly rigorous criteria regarding quality of studies and especially pharmacovigilance procedures. Regular monitoring of various blood tests, ECG (electrocardiogram), EEG (electroencephalography), or other controls are required or recommended for many antidepressants or psychotropic drugs in guidelines, standard references, and textbooks [37, 47, 52, 53].

In this context, monitoring of hepatic transaminases is listed in the SmPC of agomelatine and should be performed before the initiation of treatment, after approximately 3, 6, 12, and 24 weeks, after emergence of clinical symptoms of hepatic dysfunction, and after a dose increase [11].

Considering the general risk of possible drug-related liver damage during treatment with psychotropic drugs, monitoring of liver function tests is recommended in general [11, 37, 47, 52, 54, 55]. Thereby therapeutic safety as well as early detection of patients at risk with preexisting relevant diseases can be improved, especially in case of polypharmacy [37, 52, 54–57].

Limitations

An important limitation to be mentioned is the non-interventional, open-label, observational design of the four individual studies included in the present pooled analysis, with lack of randomization, blinding, and placebo control group. Therefore the observational design might lead to an overestimation of therapeutic effects compared to RCTs. Controlled studies with strict inclusion/exclusion criteria, however, do not represent naturalistic patient populations with comorbidities and co-medication, which underlines the relevance of non-interventional studies. Even though observational trials are not able to provide proof of efficacy because of methodological reasons, they nonetheless provide important information of everyday clinical practice. The notable strength of the presented pooled analysis is the large number of non-selected patients.

Potential underestimation of adverse drug reactions due to possible underreporting can not be completely ruled out. As a result of the non-interventional design, ADRs were not assessed systematically but were documented in the form of open questions at each visit. Considering data of controlled studies, however, type, severity, and time of emerging ADRs within our presented pooled data are in line with the tolerability profile demonstrated in RCTs.

Short duration of individual studies over 3 months is a further limitation worth being discussed. The main analysis of pooled data was performed after 12 weeks, thereby representing short-term treatment. However, this correlates well with the duration of RCTs between 6 and 12 weeks. Besides, a subgroup over 24 weeks with more than 3000 patients was additionally analyzed in this pooled dataset, providing relevant data for continuation treatment in unselected patients.

Another limitation to be mentioned is the mixed nature of data due to significant differences in investigators. In the presented pooled analysis the treatment effect of agomelatine has been evaluated rather generally by means of the CGI as a less specific scale compared to more detailed scales used in psychiatry. Besides, GPs in VIVALDI Praxis were offered a rater training (like psychiatrists in the VIVALDI study) via a video test version of the more complex svMADRS questionnaire to ensure a high

quality of collected data. Concerning the analysis of tolerability, the specialization of doctors should probably generate only minor differences. According to the objective of gaining information about psychiatric care in daily routine, the strength of the actual pooled analysis is the large sample of comorbid and co-medicated patients of daily practice, as in German psychiatric care the intersectoral treatment situation between hospital care and outpatient treatment (by specialists and/or GPs) is an actual and important issue.

As a result of possible differences in the point of view on psychiatric disorders between the two groups of physicians, separate results for psychiatrists and GPs would have been informative. In conformity with the statistical analysis plan (SAP) and the stated objective of analyzing a large sample of naturalistic psychiatric patients as an overall group, stratified data analysis according to doctors' specialization has not yet been performed. However, baseline data, dosage, and evolution of depressive symptoms by means of CGI are presented in the total population and on the basis of individual studies, thereby allowing a first insight into this interesting question. Further evaluation of this large database with a focus on stratification could offer an additional objective for a prospective data analysis.

CONCLUSION

In the presented pooled analysis of four prospective open-label studies, agomelatine demonstrated good clinical effectiveness and tolerability in a heterogeneous patient cohort ($n = 9601$) over 12 weeks and over 24/52 weeks (subpopulations). Overall improvement of depressive symptoms is demonstrated in CGI response and remission rates. The incidence of adverse drug reactions is low (5.3%), irrespective of psychotropic co-medication, and no new information about previously unknown or very rare ADR is obtained. Additionally, the results provide naturalistic information about potential effects of agomelatine on liver function, mainly observed in the form of reversible transaminase elevations and primarily observed within the first 12 weeks. Presented data confirm current recommendations for transaminase monitoring, especially during the first months of treatment.

In summary, the pooled data analysis reflects effectiveness and tolerability of agomelatine, supplementary to clinical trials, and independent of psychotropic co-medication in non-selected patients of daily clinical practice.

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Disclosures. Gerd Laux received honoraria from Servier as scientific coordinator for two included studies and of presented pooled

analysis, also honoraria for expert board lectures, position papers or articles, and congress. Bettina Barthel is an employee of Servier Deutschland GmbH, Munich (Medical Affairs Department). Göran Hajak received honoraria for scientific support for one of the included studies, expert board, lectures, position papers or articles, and congress. Matthias Lemke received honoraria for scientific support for one included study, lectures, position papers, and congress. Hans-Peter Volz received honoraria for scientific support for one included study, honoraria for expert boards, lectures, articles, and congress.

Compliance with Ethics Guidelines. This current article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors. The original studies were conducted in accordance with recommendations of the German Medicines Act (AMG), the Federal Institute of Drugs and Medical Devices (BfArM), the Guidelines of the German Working Group for Epidemiology (DAE) ensuring Good Epidemiological Practice as well as recommendations of the Association of Research-Based Pharmaceutical Companies (VfA). All procedures followed were in accordance with ethical standards and all four individual studies were approved by the Free Ethics Committee Freiburg, Germany, submitted to German authorities (BfArM, KBV, GKV-Spitzenverband), included in the international study registry http://www.controlled-trials.com, and published [28–34]. All procedures also followed the ethical standards of the Helsinki Declaration of 1964, as revised in 2000 and 2008. Informed consent form was requested from all patients before being included in the original studies, but not mandatory because of the non-interventional design.

Data Availability. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. De Bodinat C, Guardiola-Lemaitre B, Mocaer E, Renard P, Munoz C, Millan MJ. Agomelatine, the first melatonergic antidepressant: discovery, characterization and development. Nat Rev Drug Discov. 2010;9(8):628–42.

2. Racagni G, Riva MA, Molteni R, et al. Mode of action of agomelatine: synergy between melatonergic and 5-HT(2C) receptors. World J Biol Psychiatry. 2011;12(8):574–87.

3. Millan MJ, Gobert A, Lejeune F, et al. The novel melatonin agonist agomelatine (S20098) is an antagonist at 5-hydroxytryptamine2C receptors, blockade of which enhances the activity of frontocortical dopaminergic and adrenergic pathways. J Pharmacol Exp Ther. 2003;306(3):954–64.

4. Millan MJ, Brocco M, Gobert A, Dekeyne A. Anxiolytic properties of agomelatine, an antidepressant with melatoninergic and serotonergic properties: role of 5-HT2C receptor blockade. Psychopharmacology. 2005;177(4):448–58.

5. Chenu F, El Mansari M, Blier P. Electrophysiological effects of repeated administration of agomelatine on the dopamine, norepinephrine, and serotonin systems in the rat brain. Neuropsychopharmacology. 2013;38(2):275–84.

6. Molteni R, Calabrese F, Pisoni S, et al. Synergistic mechanisms in the modulation of the neurotrophin BDNF in the rat prefrontal cortex following acute agomelatine administration. World J Biol Psychiatry. 2010;11:148–53.

7. Paizanis E, Renoir T, Lelievre V, et al. Behavioural and neuroplastic effects of the new-generation antidepressant agomelatine compared to fluoxetine in glucocorticoid receptor-impaired mice. Int J Neuropsychopharmacol. 2010;13(6):759–74.

8. Schmelting B, Corbach-Söhle S, Kohlhause S, Christina S, Flügge G, Fuchs E. Agomelatine in the tree shrew model of depression: effects on stress-induced nocturnal hypertehrmia and hormonal status. Eur Neuropsychopharmacol.

2013;24(3):437–47. doi:10.1016/j.euroneuro.2013.07.010.

9. Hickie IB, Rogers NL. Novel melatonin-based therapies: potential advances in the treatment of major depression. Lancet. 2011;378:621–31.

10. Kasper S, Hajak G, Wulff K, et al. Efficacy of the novel antidepressant agomelatine on the circadian rest-activity cycle and depressive and anxiety symptoms in patients with major depressive disorder: a randomized, double-blind comparison with sertraline. J Clin Psychiatry. 2010;71(2):109–20.

11. Fachinformation. Valdoxan 25 mg. 2016.

12. Buoli M, Mauri MC, Altamura AC. Pharmacokinetic evaluation of agomelatine for the treatment of generalised anxiety disorder. Expert Opin Drug Metab Toxicol. 2014;10(6):885–92.

13. Genève HU. Interactions Medicamenteuses, Cytochromes P450 et P-Glykoproteine (Pgp): Centre d'informations thérapeutique et de pharmacovigilance; 2014. http://www.pharmacoclin.ch. Accessed 17 Nov 2016.

14. Loo H, Hale A, D'Haenen H. Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT(2C) antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. Int Clin Psychopharmacol. 2002;17(5):239–47.

15. Olie JP, Kasper S. Efficacy of agomelatine, a MT1/MT2 receptor agonist with 5-HT2C antagonistic properties in major depressive disorder. Int J Neuropsychopharmacol. 2007;10(5):661–73.

16. Kennedy SH, Rizvi S, Fulton K, Rasmussen J. A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. J Clin Psychopharmacol. 2008;28(3):329–33.

17. Lemoine P, Guilleminault C, Alvarez E. Improvement in subjective sleep in major depressive disorder with a novel antidepressant, agomelatine: randomized, double-blind comparison with venlafaxine. J Clin Psychiatry. 2007;68(11):1723–32.

18. Hale A, Corral RM, Mencacci C, Ruiz JS, Severo CA, Gentil V. Superior antidepressant efficacy results of agomelatine versus fluoxetine in severe MDD patients: a randomized, double-blind study. Int Clin Psychopharmacol. 2010;25(6):305–14.

19. Quera Salva MA, Hajak G, Philip P, et al. Comparison of agomelatine and escitalopram on nighttime sleep and daytime condition and efficacy in major depressive disorder patients. Int Clin Psychopharmacol. 2011;26:252–62.

20. Corruble E, de Bodinat C, Belaidi C, Goodwin GM. Efficacy of agomelatine and escitalopram on depression, subjective sleep and emotional experiences in patients with major depressive disorder: a 24-wk randomized, controlled, double-blind trial. Int J Neuropsychopharmacol. 2013;16(10):2219–34.

21. Taylor D, Sparshatt A, Varma S, Olofinjana O. Antidepressant efficacy of agomelatine: meta-analysis of published and unpublished studies. BMJ. 2014;348:g1888.

22. Stahl SM, Fava M, Trivedi MH, Caputo A, Shah A, Post A. Agomelatine in the treatment of major depressive disorder: an 8-week, multicenter, randomized, placebo-controlled trial. J Clin Psychiatry. 2010;71(5):616–26.

23. Zajecka J, Schatzberg A, Stahl S, Shah A, Caputo A, Post A. Efficacy and safety of agomelatine in the treatment of major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled trial. J Clin Psychopharmacol. 2010;30(2):135–44.

24. Goodwin GM, Boyer P, Emsley R, Rouillon F, de Bodinat C. Is it time to shift to better characterization of patients in trials assessing novel antidepressants? An example of two relapse prevention studies with agomelatine. Int Clin Psychopharmacol. 2013;28(1):20–8.

25. Goodwin GM, Emsley R, Rembry S, Rouillon F. Agomelatine prevents relapse in patients with major depressive disorder without evidence of a discontinuation syndrome: a 24-week randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2009;70(8):1128–37.

26. Guaiana G, Gupta S, Chiodo D, Davies SJ, Haederle K, Koesters M. Agomelatine versus other antidepressive agents for major depression. Cochrane Database Syst Rev. 2013;12:CD008851.

27. Khoo A, Zhou H, Teng M, et al. Network meta-analysis and cost-effectiveness analysis of new generation antidepressants. CNS Drugs. 2015;29(8):695–712. doi:10.1007/s40263-015-0267-6.

28. Laux G, VIVALDI-Studiengruppe. Antidepressive Therapie mit Agomelatin in der Facharztpraxis. Ergebnisse der VIVALDI-Studie. Psychopharmakotherapie. 2011;18(1):18–26.

29. Laux G. The antidepressant agomelatine in daily practice: results of the non-interventional study VIVALDI. Pharmacopsychiatry. 2012;45(7):284–91.

30. Laux G, Huttner N. Agomelatin in der Depressionsbehandlung über 12 Monate—follow-up der

VIVALDI-Studie. Psychopharmakotherapie. 2013;20(3):119–27.

31. Laux G, Huttner N. Subgroup analysis of the non-interventional study VIVALDI: agomelatine in treatment-naive patients, in combination therapy and after treatment switch. Int J Psychiatry Clin Pract. 2014;18(2):86–96.

32. Laux G, Steinmann C. Antidepressive Behandlung mit Agomelatin in der Hausarztpraxis: Ergebnisse der Studie VIVALDI-Praxis DGPPN 2011;P-011 008.

33. Lemke M, Barthel B, Hajak G. Antidepressiver Therapieeffekt unter Agomelatin über 6 Monate und prädiktiver Wert einer frühen Verbesserung. Psychopharmakotherapie. 2016;23(4):151–61.

34. Volz HP, Escafit-Schülke ML. Effekte von Agomelatin bei depressiven Patienten im Praxisalltag—Ergebnisse der nicht-interventionellen Studie VIVRE. Nervenheilkunde. 2015;34:809–17.

35. FDA. Clinical White Paper. CDER-PHRMA-AASLD Conference. 2000. http://www.fda.gov/downloads/drugs/scienceresearch/researchareas/ucm091457.pdf. Accessed 12 Dec 2016.

36. Laux G, Barthel B, Hajak G, Lemke M, Volz HP. Wirk- und Verträglichkeitsprofil des Antidepressivums Agomelatin in der täglichen Praxis: Gepoolte Analyse von vier nicht-interventionellen Studien. Psychopharmakotherapie. 2015;22(3):136–47.

37. S3-NVL. S3-Leitlinie/Nationale VersorgungsLeitlinie Unipolare Depression—Langfassung, 2. Auflage. 2015. Version 3: DGPPN, BÄK, KBV, AWMF, AkdÄ, BPtK, BApK, DAGSHG, DEGAM, DGPM, DGPs, DGRW (Hrsg.) für die Leitliniengruppe Unipolare Depression; 2015. http://www.depression.versorgungsleitlinien.de. Accessed 23 May 2016.

38. Kennedy SH, Rizvi SJ. Agomelatine in the treatment of major depressive disorder—review article. CNS Drugs. 2010;24:479–99.

39. Landgrebe M, Hajak G. Agomelatin—von der Forschung zur klinischen Praxis: Thieme Verlag; 2011.

40. Möller HJ, Schnitker J. Einsatz einer modifizierten MADRS bei depressiven Patienten in einer prospektiven Kohortenstudie. Nervenarzt. 2007;78(6):685–90.

41. Karaiskos D, Tzavellas E, Ilias I, Liappas I, Paparrigopoulos T. Agomelatine and sertraline for the treatment of depression in type 2 diabetes. Int J Clin Pract. 2013;67:257–60.

42. Kang R, He Y, Yan Y, Li Z, et al. Comparison of paroxetine and agomelatine in depressed type 2 diabetes mellitus patients: a double-blind, randomized, clinical trial. Neuropsychiatric Dis Treat. 2015;11:1307–11.

43. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. J Clin Psychiatry. 2010;71(10):1259–72.

44. Perlemuter G, Cacoub P, Valla D, et al. Characterisation of agomelatine-induced increase in liver enzymes: frequency and risk factors determined from a pooled analysis of 7605 treated patients. CNS Drugs. 2016;30(9):877–88.

45. Möller HJ. Das Problem der Heterogenität zwischen in den USA und nicht in den USA durchgeführten Antidepressiva Studien. Psychopharmakotherapie. 2014;21(5):211–8.

46. Gahr M, Freudenmann R, Connemann B, et al. Agomelatine and hepatotoxicity: implications of cumulated data derived from spontaneous reports of adverse drug reactions. Pharmacopsychiatry. 2013;46(6):214–20.

47. Gahr M, Zeiss R, Lang D, Connemann BJ, Hiemke C, Schonfeldt-Lecuona C. Drug-induced liver injury associated with antidepressive psychopharmacotherapy: an explorative assessment based on quantitative signal detection using different MedDRA terms. J Clin Pharmacol. 2016;56(6):769–78.

48. Friedrich ME, Akimova E, Huf W, et al. Drug-induced liver injury during antidepressant treatment: results of AMSP, a drug surveillance program. Int J Neuropsychopharmacol. 2016;19(4). doi:10.1093/ijnp/pyv126.

49. BfArM. Pharmakovigilanz—Datenbank unerwünschter Arzneimittelwirkungen. 2013. http://www.bfarm.de/DE/Arzneimittel/Pharmakovigilanz/Risikoinformationen/uawDB/node.html. Accessed 12 Dec 2016.

50. Heun R, Ahokas A, Boyer P, Gimenez-Montesinos N, Pontes-Soares F, Olivier V. The efficacy of agomelatine in elderly patients with recurrent major depressive disorder: a placebo-controlled study. J Clin Psychiatry. 2013;74(6):587–94.

51. Heun R, Corral R, Ahokas A, et al. Sustained efficacy and safety of agomelatine versus placebo over 24 weeks in elderly out-patients suffering from major depressive disorder. Eur Neuropsychopharmacol. 2014;24(Suppl 2):S403 P.2.b.042.

52. Benkert O, Hippius H, editors. Kompendium der psychiatrischen Pharmakotherapie: 11. Heidelberg: Auflage, Springer; 2015.

53. Gründer G, Benkert O, editors. Handbuch der Psychopharmakotherapie: 2. Heidelberg: Aufl. Springer; 2012.

54. Park SH, Ishino R. Liver injury associated with antidepressants. Curr Drug Saf. 2013;8(3):207–23.

55. Voican C, Corruble E, Naveau S, Perlemuter G. Antidepressant-induced liver injury: a review for clinicans. Am J Psychiatry. 2014;171:404–15.

56. Tajiri K, Shimizu Y. Practical guidelines for diagnosis and early management of drug-induced liver injury. World J Gastroenterol. 2008;14:6774–85.

57. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for industry drug-induced liver injury. Silver Spring: FDA; 2009. Accessed 12 Dec 2016.