Comparative Short and Long-Term Effectiveness and Safety of Pramipexole and Aripiprazole Augmentation in Treatment Resistant Unipolar Depression. An Observational-Retrospective Study

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Article

Comparative Short and Long-Term Effectiveness and Safety of Pramipexole and Aripiprazole Augmentation in Treatment Resistant Unipolar Depression. An Observational Study

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Abstract: Background. This study compares the short- and long-term effectiveness and safety of pramipexole augmentation (PA) and aripiprazole augmentation (AA) for unipolar treatment-resistant depression (TRD). **Methods**. Patients were recruited in a private out-patients clinic specialized in mood disorders. At intake and at each visit depressive and (hypo)manic symptoms, clinical status, and level of functioning were evaluated with appropriate scales. The trend of outcomes was analyzed using mixed-effect linear regression models. **Results**. The study includes 81 unipolar TRD patients treated with PA and 51 with AA. After 12 and 24 weeks of treatment with PA, the predicted response (64.1% and 76.2%) and remission rates (49.7% and 72.7%) were significantly higher than the predicted response (32.2% and 38.0%) and remission rates (18.9% and 28.1%) for AA. The improvement in psychosocial functioning was significantly greater and faster in PA than in AA. PA showed significant superiority over AA as a maintenance strategy (time spent ill and psychosocial functioning) up to 12 months. No difference in safety was found at each time point. **Conclusions**. PA could be an alternative option for short and long-term treatment of unipolar TRD, more effective and similar in safety with AA. These preliminary results need confirmation from randomized clinical trials.

Keywords: Depressive Disorders; Outpatient Psychiatry; Pharmacotherapy; Dopamine Agonists; Depression Treatment; Treatment Outcome

1. Introduction

Major Depressive Disorder (MDD) is a common [1] and high disabling [2] psychiatric disorder leading to high direct and indirect costs for the society [3]. Although several classes of antidepressants (ADs) of proven efficacy are available for treatment of Major Depressive Episode (MDE), from 15% to 30% of patients do not respond to multiple intervention [4,5].

MDE not responding to two or more different ADs are considered as treatment resistant depression (TRD) [5], a condition associated with suicidal risk, poor prognosis, work impairment, social and family life and physical health decline [6].

Among the different pharmacological strategies proposed for the treatment of TRD, AD augmentation with a second-generation antipsychotic (SGA), mostly aripiprazole, has currently the best evidence of efficacy [7,8] is approved by the FDA, and recommended by international guidelines [9–11]. Regulatory agencies, in consideration of the available evidence [12], recently approved also

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Esketamine nasal spray, an N-methyl-D-aspartate receptor antagonist, in addition to SSRI or SNRI for TRD.

Given the severity of TRD and the uncertain efficacy of available augmentation strategies, new and more effective drugs for AD augmentation are needed.

Some research suggested the possible role of dopamine (DA) dysfunctions in mood disorders: a) levels of DA are decreased, D2 receptor binding in the striatum is increased and striatal DA transporter is increased in depression; b) different DA receptors, mostly D1-D2 heterodimers, and their distribution in different brain region have been supposed to be involved in the etiology of depression, c) mesolimbic DA neurons could be linked to some nuclear symptoms of depression as loss of motivation and motor retardation [13,14].

Pramipexole is a full dopamine agonist with higher affinity for the D3 than for the D1, D2, and D4 receptors and has been approved by the FDA for the treatment of Parkinson's disease and restless legs syndrome [15]. Its marked selectivity for D3 receptors, which have a high concentration in mesolimbic areas and are implicated in mental processes related to emotion and mood [13] and its neuroprotective, antioxidant and anti-inflammatory activity [16–18] provide a rationale for the treatment of depression.

A meta-analysis of 18 randomized controlled trials, showed that pramipexole improve depressive symptoms in patients with Parkinson's disease [19] and another meta-analysis of 5 randomized controlled trials and 8 observational studies, showed its effectiveness and safety for patients with treatment resistant and non-resistant depression, in monotherapy and as augmentation of traditional antidepressant [20].

These preliminary results were confirmed in a later observational study involving only patients with unipolar and bipolar TRD, of which 74.1% achieved response and 66.4% remission after 24 weeks of pramipexole AD-augmentation [21].

Overall, the available preliminary data indicate that pramipexole may be useful as AD-augmentation for TRD but further confirmation is needed.

The aim of this observational, retrospective study is to compare the 12- and 24-week effectiveness and safety and the long-term (12 and 24 months) sustained response and safety of pramipexole and aripiprazole AD augmentation in the treatment of unipolar TRD. We chose aripiprazole as the comparator because it is considered to be the most effective within the antipsychotic class.

2. Methods

2.1. Subjects

Data were extracted from a clinical database of consecutive patients seen from September 2006 to August 2021 at the Institute of Psychopathology in Rome, Italy, a private out-patients clinic specialized in mood and anxiety disorders. Inclusion criteria were: (1) age ≥18 years; (2) meeting DSM-5 diagnostic criteria for major depressive disorder (MDD), single or recurrent (22); (3) meeting DSM-5 criteria for a current MDE; (4) a 21-item Hamilton Depression Rating Scale [$HDRS_{21}$ [23) total score ≥ 14; (5) failure of at least 2 trials with 2 antidepressants of separate classes; (6) augmentation of ongoing antidepressant treatment with pramipexole or aripiprazole.

Patients at least improved at 24 weeks were followed for additional 2 years.

All patients gave their written consent for the use, in anonymous and aggregate form, of clinical records. The content of the consent form as well as the procedures of the study were approved by the local ethical committee (Prot. N. 1521/CE Lazio 1, Roma 30.7.2019) and are in accordance with the Helsinki declaration of 1975, as revised in 2013.

2.2. Assessments

All subjects were evaluated, treated and followed up by the first author (AT), an experienced psychiatrist specialized in anxiety and mood disorders. At intake, the mood and anxiety disorders sections of the SCID-I [24,25] were administered to support the clinical diagnosis and a semi-

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structured interview was used to systematic collect the participants' demographic and clinical retrospective information. Whenever possible, patients' information was supported by secondary clinical data, obtained from other informants or available medical records. During the follow-up visit, which typically occurred each month up to 24 weeks, and subsequently every 2-4 months, information on the course of illness and treatment was systematically collected from patient and caregivers with a semi-structured interview. At intake and at each follow-up visit depressive symptoms were assessed using the $HDRS_{21}$, suicidality using item 3 of $HDRS_{21}$ (score ≤ 1 absent, score ≥ 2 present), (hypo)mania symptoms using Young Mania Rating Scale (YMRS) [26], (clinical status with Clinical Global Impression of Severity (CGI-s) and of Improvement (CGI-i) scales [27], and the overall level of functioning using Global Assessment of Functioning (GAF) [28]. The diagnosis of mixed depression was made using validated Koukopoulos' [29], consisting in the presence of three or more of the following symptoms during a MDD: 1) psychic agitation or inner tension; 2) racing or crowed thoughts; 3) irritability or unprovoked feelings of rage; 4) absence of retardation; 5) talkativeness; 6) dramatic description of suffering or frequent spell of weeping; 7) mood lability and marked emotional reactivity; 8) early insomnia.

Treatment adherence was defined as a $\geq 75\%$ adherence to the prescribed medication regimen according to the patients' and relatives' report.

At each visit the onset of psychotic symptoms (hallucinations and/or delusions), lethargy, gambling, hypersexuality and compulsive shopping were explicitly valued in patients on pramipexole augmentation. Other side effects were assessed through clinical observation and patients' and relative' report. In the medical records we noted all the reported side effects up to 24-week, that needing a dose reduction or the discontinuation of the augmentation during the follow-up.

These assessments are made during routine clinical practice at the Institute and not for research purposes. The rating scales were administered by psychiatrists experienced in mood disorders and not involved in the treatment.

2.3. Treatments

Pramipexole was added to the current AD regimen starting with 0.18 mg/day in the first week and increasing of 0.18 mg/day every week with an initial goal of 0.54 mg/day. If the remission was not achieved, the dose was further increased by 0.18 mg/day every 4 days up to 2.1 mg/day, depending on clinical response and the occurrence of significant side effects. Aripiprazole was added to the current AD regimen starting with 2.5 mg/day and increased up to 10 mg/day if necessary, depending on clinical response and occurrence of significant side effects. A mood stabilizer (lithium carbonate, valproate, carbamazepine, lamotrigine) was added to pramipexole or aripiprazole augmentation in patients with mixed depression or mood instability. Olanzapine was added to pramipexole augmentation in patients with mood congruent psychotic features, when necessary.

All treatments were given as part of routine clinical care and no treatment decision was made with research in mind. Patients and caregivers were informed about the off-label use of pramipexole and its more dangerous side effects, i.e. psychotic symptoms, lethargy, gambling, hypersexuality and compulsive shopping.

2.4. Outcomes

At 12 and 24-week the primary outcome was *remission* defined as a $HDRS_{21}$ total score < 7 after 12 and 24 weeks of treatment and maintained for at least further 4 weeks; secondary outcomes were *response*, defined as a $\geq 50\%$ reduction of baseline $HDRS_{21}$ total score after 12 and 24 weeks of treatment and maintained for at least further 4 weeks, *improvement*, defined as a CGI-i score ≤ 2 ("much improved" or "very much improved") after 12 and 24 weeks of treatment and maintained for at least further 4 weeks, and *improvement of functioning*, defined as increase of GAF score after 12 and 24 weeks of treatment.

During the follow-up the primary outcome was the *absence of recurrences*; secondary outcomes were the percentage of *time spent ill* during the 12 and 24 months of follow-up, *latency of first relapse*

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defined as number of weeks to first recurrence, *and general functioning* defined as median increase of GAF score during the 12 and 24 months of follow-up.

Safety outcomes were *acceptability*, defined as the number of patients who discontinued the study for any reason, *tolerability*, defined as the number of patients who discontinued the study due to any side effect, *suicidality* (defined as $HDRS_{21}$ item 3 $\geq$ 2) (only at 12 and 24-week), *suicide attempt*, *hospitalization*, occurrence of (*hypo)mania* (ruled out clinically and by the increase of YMRS total score). Patients developing (hypo)mania in the 24-week of treatment were considered non responders/remitters.

2.5. Statistical Analysis

Sociodemographic and clinical characteristics of patients with pramipexole augmentation (PA) and with aripiprazole augmentation (AA) were summarized as frequencies and percentages for categorical variables, as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables, as appropriate.

Patients with PA and with AA were compared using Pearson's Chi-square test or Fisher's exact test for categorical variables, t-test for continuous variables with normal distribution, and Mann-Whitney U test for continuous variables with a non-normal distribution. Comparisons of scale scores from baseline to 12-week and to 24-week, stratified by type of augmentation, was performed using Friedman's test in patients with complete data; Bonferroni correction for multiple testing was applied for pairwise comparisons.

To analyse the trend of remission, response, improvement rates and the trend of GAF scale scores between patients with PA and with AA over time (baseline, 12-week, and 24-week), repeated measures linear mixed models were used. The main effects investigated were the mean effect of augmentation (PA vs. AA), the time trend of rates/scores regardless of the type of augmentation and the time trend by group.

To balance the characteristics of patients with PA and with AA, a propensity score was calculated using logistic regression, in which the type of augmentation was regressed on the characteristics that differed significantly between groups at baseline. The predicted probability (i.e., the propensity score) was included as a covariate in the mixed models.

Patients who were at least improved at 24 weeks were followed up for 2 years. The proportion of relapsers at 12-month and 24-months was compared between patients with PA and with AA using Fisher's exact test.

All analyses were carried out by using IBM SPSS, version 25. The significance level was set at 0.05.

3. Results

3.1. Study Sample Characteristics and Treatments

Of the 2938 patients with MDD treated from September 2006 to August 2021 at the Institute, 132 meet the inclusion criteria, 104 (78.8%) with recurrent MDD and 28 (21.2%) with a single episode. Tables 1 and 2 show the demographic and clinical characteristics of the study sample. Briefly, in the overall sample the median (IQR) duration of the disorder was 192 (60; 318) months, the median (IQR) duration of the index episode 63 (48; 162) weeks, the median (IQR) number of AD cycles failed was 4 (3; 6), 90 patients (68.2%) failed also to respond to a *combination strategy* (i.e., to a combination of 2 AD acting on different monoamines) and 34 (25.8%) to an *augmentation strategy* (i.e., to the addiction of a second agent to the antidepressant regimen) and 1 (in AA group) to electroconvulsive therapy.

Table 1. Sociodemographic and clinical features of the study sample at baseline.

	Type of augmentation	**test**

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	Total (n=132)		Pramipexole (n=81)		Aripiprazole (n=51)			p-value
	n	%	n	%	n	%		
Female (n, %)	77	58.3%	49	60.5%	28	54.9%	0.40§	0.526
Age at baseline (yrs), mean (DS)	61.2 (15.1)		65.4 (12.5)		54.6 (16.6)		4.26°	**<0.001**
Employed full time (n, %)	48	36.4%	23	28.4%	25	49.0%	5.75§	**0.016**
Married (n, %)	82	62.1%	55	67.9%	27	52.9%	2.98§	0.084
Diagnosis							0.27§	0.605
Major depressive disorder, recurrent	104	78.8%	65	80.2%	39	76.5%		
Major depressive disorder, single episode	28	21.2%	16	19.8%	12	23.5%		
Any life-time Axis I comorbidity (n, %)	85	64.4%	48	59.3%	37	72.5%	2.41§	0.121
OCD (n, %)	51	38.6%	24	29.6%	27	52.9%	7.17§	**0.007**
PD (n, %)	35	26.5%	21	25.9%	14	27.5%	0.04§	0.847
SP (n, %)	21	15.9%	11	13.6%	10	19.6%	0.85§	0.357
GAD (n, %)	25	18.9%	16	19.8%	9	17.6%	0.09§	0.764
ED (n, %)	9	6.8%	3	3.7%	6	11.8%	3.20§	0.074
Cerebrovascular disease (n, %)	29	22.0%	23	28.4%	6	11.8%	5.05§	**0.025**
Alcohol abuse (n, %)	11	8.3%	7	8.6%	4	7.8%	*	1.000
Substance abuse (n, %)	4	3.0%	3	3.7%	1	2.0%	*	1.000
Suicide attempts (n, %)	18	13.6%	11	13.6%	7	13.7%	0.01§	0.981
Hospitalization (n, %)	30	22.7%	19	23.5%	11	21.6%	0.06§	0.801
Age at first episode (yrs), mean (DS)	42.9 (18.8)		47.1 (18.6)		36.3 (17.3)		3.34°	**0.001**
Duration of disease (months), median (IQR)	192 (60; 318)		168 (60; 348)		204 (60; 288)		2032.5#	0.877

Abbreviations: OCD = Obsessive Compulsive Disorder; PD = Panic Disorder; SP = Social Phobia; GAD = General Anxiety Disorder; ED = Eating Disorder. Data showed in bold are those with statistical p value significance. § Pearson's Chi-square test. *Fisher's exact test ° t-test. # Mann-Whitney U test.

Table 2. Description of the index episode and the AD treatments failed by groups.

	Total (n=132)		Type of augmentation Pramipexole (n=81)		Aripiprazole (n=51)		test	p-value
	n	%	n	%	n	%		
Duration of episode (weeks), median (IQR)	63 (47; 162)		54 (45; 108)		108 (54; 162)		2512.0#	**0.036**
Mixed depression	34	25.8%	13	16.0%	21	41.2%	10.33§	**0.001**
Delusional depression							*	0.280
Yes, congruous delusions	5	3.8%	3	3.7%	2	3.9%		
Yes, incongruous delusions	2	1.5%	0	0.0%	2	3.9%		
AD treatments failed								
N. of AD cycles failed, median (IQR)	4 (3; 6)		4 (3; 5)		4 (3; 6)		2120.0#	0.795
SSRI (n, %)	102	77.3%	61	75.3%	41	80.4%	0.46§	0.497
SNRI (n, %)	96	72.7%	60	74.1%	36	70.6%	0.19§	0.661
TCA (n, %)	86	65.2%	51	63.0%	35	68.6%	0.44§	0.506
MAOI (n, %)	5	3.8%	1	1.2%	4	7.8%	*	0.073
Other (n, %)	67	50.8%	45	55.6%	22	43.1%	1.93§	0.165

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ECT (n, %)	1	.8%	0	0.0%	1	2.0%	*	0.386
Combination (n, %)	90	68.2%	60	74.1%	30	58.8%	3.36§	0.067
Augmentation (n, %)	34	25.8%	30	37.0%	4	7.7%	*	**<0.001**
Baseline scores, median (IQR)								
HDRS	18 (16; 20)		18 (16; 21)		17 (16; 19)		1603.5#	**0.044**
HDRS-3	0 (0; 1)		0 (0; 1)		0 (0; 1)		2034.5#	0.861
YMRS	0 (0; 0)		0 (0; 0)		0 (0; 2)		2584.5#	**0.001**
CGI-s	5 (4; 5)		4 (4; 5)		5 (4; 5)		2353.5#	0.150
GAF	55 (50; 55)		55 (50; 60)		50 (50; 55)		1954.5#	0.587

Abbreviations: SSRI = Selective Serotonin Reuptake Inhibitor; SNRI = Serotonin Noradrenaline Reuptake Inhibitor; TCA = Tricyclic; AD = Antidepressant. Data showed in bold are those with statistical p value significance. § Pearson's Chi-square test. *Fisher's exact test # Mann-Whitney U test.

Eighty-one patients (61.4%) received AD pramipexole augmentation and 51 (38.6%) AD aripiprazole augmentation. Compared with patients with AA, those with PA significantly differ for age (older), full time employment (lower), obsessive compulsive disorder (OCD) (lower) and cerebrovascular disease (higher) comorbidity, age at first episode (higher), duration of the index episode (lower), mixed depression (lower), augmentation strategies previously failed (higher), and for $HDRS_{21}$ total scores (higher) and YMRS total scores (lower) at study entry. These variables were used to calculate the propensity score. The median max dose of pramipexole in patients with PA was 1.05 mg/day (IQR 0.72; 1.08) and of aripiprazole in patients with AA was 3 mg/day (IQR 2.5; 5). As shown in table 3, the two groups did not differ in terms of antidepressant treatment (classes, doses and combination strategies) and additional mood stabilizers (classes and doses) employed for the index episode.

Table 3. Treatment of index episode.

	Total (n=132)		**Type of augmentation**				**test**	**p-value**
			Pramipexole (n=81)		**Aripiprazole (n=51)**			
	n	**%**	**n**	**%**	**n**	**%**		
SSRI (n, %)	**43**	32.6%	23	28.4%	20	39.2%	1.67§	0.196
SSRI dose, median (IQR)	40 (25; 60)		30 (20; 60)		40 (40; 60)		290.5#	0.134
SNRI (n, %)	39	29.5%	26	32.1%	13	25.5%	0.66§	0.418
SNRI dose, median (IQR)	150 (150; 225)		150 (150; 225)		150 (120; 225)		145.0#	0.489
Others (n, %)							5.66§	0.059
Mirtazapina	20	15.2%	17	21.0%	3	5.9%		
Amisulpiride	15	11.4%	8	9.9%	7	13.7%		
TCA (n, %)	70	53.0%	44	54.3%	26	51.0%	0.14§	0.708
TCA dose, median (IQR)	125 (100; 175)		125 (100; 187)		125 (100; 162)		517.0#	0.500
2 AD (n, %)	35	26.5%	24	29.6%	11	21.6%	1.04§	0.307
Mood stabilizer (n, %)							*	0.168
Lithium	9	6.8%	6	7.4%	3	5.9%		
AV/CBZ	15	11.4%	5	6.2%	10	19.6%		
LMT	6	4.5%	4	4.9%	2	3.9%		
OLZ	1	.8%	1	1.2%	0	0.0%		
Mood stabilizer dose, median (IQR)								
Lithium	0.50 (0.40; 0.59)		0.55 (040; 0.59)		0.45 (0.30; 0.56)		5.5#	0.381
AV/CBZ	300 (300; 450)		300 (250; 300)		300 (300; 600)		34.5#	0.254
LMT	200 (200; 200)		200 (175; 225)		200 (200; 200)		4.0#	1.000
OLZ	10 (-)		10 (-)					

Abbreviations: SSRI = Selective Serotonin Reuptake Inhibitor; SNRI = Serotonin Noradrenaline Reuptake Inhibitor; TCA = Tricyclic; AD = Antidepressant. Data showed in bold are those with statistical p value significance. § Pearson's Chi-square test. *Fisher's exact test # Mann-Whitney U test.

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3.2. Twelve and 24-Week Outcomes

Twenty patients (15.2%) dropped out, 8 before 12 weeks (7 with PA, 1 with AA) and 12 before 24 weeks (5 with PA, 7 with AA) without significant differences between the two groups (Exact Fisher's test p=0.117 and p=0.892, respectively). These 20 patients were considered as non-responders/remitters and did not differ in any demographic or clinical characteristics compared to patients followed to 24-week.

The treatment adherence ≥ 75% was found in 67 (82.7%) patients with PA and 47 (92.2%) with AA at 12-week (p=0.124), 57 (70.4%) patients with PA and 41 (80.4%) patients with AA at 24-week (p=0.256).

$HDRS_{21}$ median total score significantly decreased from baseline to 12-week and to 24-week in patients with PA (median [IQR]: 18 [16; 21] vs. 6 [2; 12] vs. 2 [0; 5]; p<0.001) and in patients with AA (median [IQR]: 16.5 [15; 19] vs. 14 [7; 16] vs. 9 [4; 16]; p<0.001).

CGI-s score significantly decreased from baseline to 12-week and to 24-week in patients with PA (median [IQR]: 4 [4; 5] vs. 2 [2; 3] vs. 2 [1; 2]; p<0.001) and in patients with AA (median [IQR]: 5 [4; 5] vs. 4 [3; 5] vs. 3 [2; 4]; p<0.001).

Figure 1 shows the predicted rates of remission, response, improvement and predicted mean GAF score over time and according to type of augmentation, adjusted for the propensity score, resulting from the repeated measures generalized linear mixed models. In the supplementary material are reported the results of the repeated measures generalized linear mixed models (ESM Table 1, A-D), the predicted rates of remission, response, improvement and predicted mean of GAF score according to type of augmentation and time, adjusted for the propensity score (ESM Table 2).

Overall, patients with PA were more likely to remit (OR=4.24; 95%CI: 1.54-11.67) and respond (OR=3.77; 95%CI: 1.48-9.60) than patients with AA, while no difference in improvement rate was observed between the two groups (Figure 1).

No significant effects were observed over time and in the interaction term in any of the three outcomes (ESM Table 1, A-C).

In the overall sample GAF total score significantly increased from baseline to 12-week by 12.2 points (p<0.001) and to 24-week by 14.9 points (p<0.001). In patients with PA the GAF score was on average 10.5 points significantly higher than that of patients with AA (p=0.003). Moreover, patients with PA showed a more rapid increase in GAF scores from baseline to 12-week (b=0.10; p=0.014) and to 24-week (b=0.13; p=0.004) than patients with AA (ESM Table 1, D).

3.3. Twelve and 24-Week Safety

In the PA group 8 patients dropped out due to the side effects, 6 before 12 weeks (3 due to transient visual hallucinations, 1 due to edema of the ankles, drowsiness and increased anxiety, respectively), and 2 before 24 weeks (due to drowsiness); in AA group 4 patients dropped out due to the side effects, 1 before 12 weeks (due to increased irritability) and 3 before 24 weeks (1 due to increased anxiety, buccal dyskinesia, and restlessness/tremor, respectively). No differences in the proportion of drop-outs due to side effects between the two groups were observed (Exact Fisher's test 12-weeks: p=0.282; 24-weeks: p=0.430).

Other reported side effects in PA group during the 12-weeks were 9 spontaneously resolved (drowsiness and nausea 2 cases respectively, fainting/falling, postural instability, agitation, itching and dizziness 1 case respectively) and 2 resolved through pramipexole dose reduction followed by escalation (drowsiness and tremor 1 case respectively); from 12 to 24-weeks other side effects were 4 spontaneously resolved (xerostomia 2 cases, vomit and walking difficulty 1 cases respectively), and 1 resolved through pramipexole dose reduction (fainting/falling).

In AA group 5 side effects were reported during the 12-weeks (restless 2 cases; nausea, somnolence and dizziness 1 case respectively) and 10 from 12 to 24-weeks (weigh increase 5 cases, xerostomia and tremors 2 cases respectively, urinary difficulties 1 case). These side effects required no treatment modification.

The median score of $HDRS_{21}$ suicidality item significantly decreased from baseline to 12-week and to 24-week in patients with PA (baseline: 0 (IQR 0;1) vs. 12-week: 0 (IQR 0;0) vs. 24-week: 0 (IQR

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0;0); p<0.001); in patients with AA the overall significant decrease (p=0.006) was not confirmed in the pairwise comparisons (baseline: 0 (IQR 0;1) vs. 12-week: 0 (IQR 0;0) vs. 24-week: 0 (IQR 0;0)).

YMRS median total score did not change significantly from baseline to 12-week and to 24-week in patients with PA (baseline: 0 (IQR 0;0) vs. 12-week: 0 (IQR 0;0) vs. 24-week: 0 (IQR 0;0) p=0.220), while in patients with AA an overall significant decrease was observed (p=0.002) but none in the pairwise comparisons (baseline: 0 (IQR 0;2) vs. 12-week: 0 (IQR 0;2) vs. 24-week: 0 (IQR 0;0)).

Before 24 weeks 1 patient with PA needed hospitalization due to the severity of depression, no patients committed suicide attempts or developed (hypo)mania.

3.4. Long-Term Outcomes

Sixty patients (43 with PA and 17 with AA) at least improved at 24-weeks were followed for additional 12 months and 39 (30 with PA and 9 with AA) for additional 24 months. The drop-out rate did not differ significantly between PA and AA group before 12 months (4.7% and 17.6%, respectively; p= 0.132) and 24 months (3.3% and 11.1%, respectively; p=0.413). Treatment adherence ≥ 75% was found in 32 (74.4%) patients with PA and 11 (64.7%) with AA at 12 months and 25 (83.3%) patients with PA and 7 (77.8%) with AA at 24 months, without significant difference between the two groups (p= 0.547 and 0.653, respectively).

At 12 months, 34 out of 43 patients with PA (79.1%) and 9 out of 17 patients with AA (52.9%) did not relapse; at 24 months, 24 out of 30 patients with PA (80.0%) and 6 out of 9 patients with AA (67.7%) did not relapse. No difference in the probability of relapse was found between patients with PA and AA at each time point. The polarity of the first relapse was depression in 8 patients with PA and 6 with AA, mixed depression in 1 patient with PA and 1 with AA, hypomania in 1 patient with AA at 12 months: depression in 3 patients with PA and 3 patients with AA, mixed depression in 2 patients with PA, hypomania in 1 patient with PA at 24 months.

No difference in the latency of first relapse was found between PA group and AA group at 12-months (median 40 (IQR 10;60) and 20 (IQR 9;30) weeks, respectively) and at 24 months (median 88 (IQR 76;100) and 52 (IQR 45;88) weeks, respectively).

The number of relapses was 10 in PA group (9 depression, 1 mixed depression) and 13 in AA group (12 depression, 1 mixed depression, 1 hypomania) at 12-month; 7 (3 depression, 3 mixed depression, 1 hypomania) in PA group and 4 (all depression) in AA group at 24-month.

The percentage of time spent on illness was significantly lower in the PA group than in AA group at 12-month (median 0% (IQR 0%;0%) vs. 0% (IQR 0%;22%), respectively; p=0.022), but not at 24-month (median 0% (IQR 0%; 0%) vs. 0% (IQR 0%;14%, respectively; p= 0.566).

The median GAF score was significantly higher in PA group than in AA group at 12 months (77 (IQR 71;91) and 65 (IQR 58;71), respectively; p<0.001) but not at 24 months (81 (IQR 74;84) and 71 (71;(IQR 71; 71), respectively; p=0.072).

3.5. Long-Term Safety

Before 12 months 1 patient with PA dropped-out due to the side effects (increased sexual drive); from 12 to 24 months no patient dropped out due to the side effects.

Moreover, no patient in both needed augmention' dose reduction due the side effects, hospitalization or attempted suicide during the follow up.

As reported in the earlier section, 2 patients developed a hypomania episode during the follow-up, 1 with AA (before 12 month) and 1 with PA (from 12 to 24 months).

4. Discussion

To the best of our knowledge, this is the first study to compare short and long-term outcomes of pramipexole and aripiprazole augmentation in patients with unipolar depression not responding to at least 2 trials with 2 antidepressants of separate classes.

Overall, our findings indicate that both augmentation strategies improved the level of functioning and were safe, but PA had a higher effectiveness. In fact, PA response and remission

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rates were almost twice than those of AA: the predicted response rates were 64.1% and 32.2% at 12-week and 76.2% and 38.0% at 24-week, respectively; the predicted remission rates were 49.7% and 18.9% at 12 weeks and 72.7% and 28.1% at 24 weeks, respectively. Furthermore, patients with PA, compared with those with AA, achieved a greater and faster improvement of psychosocial functioning (measured using the GAF score) from baseline to 12 and 24 weeks.

Notably, the response and remission rates showed in our study for PA are in the range of those reported in previous studies on unipolar patients with TRD (25% to 76% response and 46% to 71% remission) [21,30–33], and for AA at the lower bottom of the range [32.4% to 43.1% response and 25.4% to 44% remission) [34,35]. The difference in depression resistance, to at least 2 ADs of separate classes in our study and to at least 1 AD in the most previous studies, could explains why our response/remission rates to AA are at the lower bottom of the range reported in literature. Although the median max dose of aripiprazole prescribed as augmentation in our study (3 mg/day) is at lower bottom of the dose's range currently recommended in the international guidelines (2-15 mg/day), it corresponds to the maximum target dose-efficacy curve (2-5 mg/day) shown in a recent meta-analysis aims to find the optimal dose of aripiprazole augmentation [36]. So, we can reasonably exclude that AA response/remission rate in our study depends on the aripiprazole' dose employed.

PA and AA did not significantly differ on safety outcomes at 12 and 24 weeks and showed a moderate acceptability and tolerability. Side effects were limited in number and severity and resolved spontaneously or through a dose reduction, no patients committed suicide attempts, developed (hypo)mania symptoms, and one patient, in PA group, needed hospitalization.

Notably, the drop-out rate due to side effects in our study is quite similar to that reported in previous studies for PA in patients with unipolar TRD (7.4% and 6.4%, respectively) [37] and in studies employing an aripiprazole' dosage corresponding to maximum target dose of 4 mg/day for AA in patients with MDD (2% versus 4%, respectively) [36].

Our findings highlight the higher effectiveness of PA over AA as maintenance strategy for TRD, at least up to 12 months. In fact, in the first 12 months of follow-up patients with PA, compared with patients with AA, spent less time ill and achieved a greater improvement of psychosocial functioning. The two augmentations showed a moderate and similar safety during the follow-up: no patients needed hospitalization or attempted suicide, one dropped-out due to side effects (PA group) and two due to the development of a hypomania episode (1 in AA and 1 in PA group).

Notably, our results are consistent with the very limited data available on the topic, showing that PA and AA retain their effectiveness without losing the safety during the follow-up [30,38–40].

The main study limitations are: 1) the flexibility of the add-on schedule, that in some cases implied the partial change of concomitant treatment strategies on the clinical judgement of the treating clinician; and 2) the clinical assessment of side effects that could reduce the number of less severe side effects reported and, in the follow-up, noted in the medical records. Yet, despite these limitations, the results of the present study provide valuable information to improve the treatment strategy for TRD, including the most severe forms.

5. Conclusions

In conclusion, our study shows that PA is a promising strategy for short and long-term treatment of unipolar TRD, more effective and similar in safety with AA, that currently is the augmentation strategy for TRD with the best evidence for efficacy.

Evidence from this study is preliminary and warrants further confirmation. Furthermore, the use of pramipexole as AD-augmentation for TRD is off-label, its prescription should be reserved only to carefully selected patients with severe TRD treated in specialized center and its use need several cautions. Especially, patients and their caregivers must be advised of potentially dangerous side effects as psychotic symptoms, lethargy, gambling, hypersexuality and compulsive shopping and instructed to report it immediately when they occur. Furthermore, the dose of pramipexole must be gradually escalated and its abrupt discontinuation should be avoided to prevent dopamine withdrawal syndrome.

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Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: title; Table S1: title; Video S1: title.

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