Summary attachment for EudraCT 2018-002285-39.

Validating the effect of Ondansetron and Mirtazapine In Treating hyperemesis gravidarum (the VOMIT trial).

The trial was terminated early due to recruiting difficulties.

Results

Participants

A total of 59 participants were randomized from April 2019 through July 2022; 21 participants were randomized to treatment with mirtazapine, 18 to ondansetron and 20 to placebo. Forty participants completed the intervention as planned, 15 (71%) in the mirtazapine group, 14 (78%) in the ondansetron group and 9 (45%) in the placebo group (Figure 1).

Baseline characteristics were similar with mean PUQE-24 scores 13,0 (standard deviation (SD) 2.36), 12,8 (SD 2.17) and 13,1 (SD 1.56) in the mirtazapine, ondansetron and placebo groups, respectively. (Table 1)

Efficacy

Primary outcome

Difference in PUQE-24 score change from baseline to day 2 in the mirtazapine versus placebo group was -1.86 (95% confidence interval (CI) -3.61 to -012, p = 0.04), thus reaching statistical significance and allowing for testing ondansetron versus placebo as a co-primary outcome.

Difference in PUQE-24 score change from baseline to day 2 in the ondansetron versus placebo group was -0.51 (95% CI -2.32 to 1.30, p = 0.59) allowing for no further primary outcomes. Thus,

mirtazapine versus ondansetron was regarded as secondary outcome. Difference in PUQE-24 score change from baseline to day 2 in the mirtazapine versus ondansetron group was -1.35 (95% CI -3,10 to 0.40).

PUQE-24 scores throughout the intervention are showed in Figure 2.

Secondary outcomes

Difference in PUQE-24 score change from baseline to Day-7 was -2.93 (95% CI -4.42 to -1.44) in the mirtazapine versus placebo group, -0.81 (95% CI -2.41 to -0.78) in the ondansetron versus placebo group, and -2.11 (95% CI -3.45 to -0.77) in the mirtazapine versus the ondansetron group.

Difference in PUQE-24 score change from baseline to Day-14 was -2.43 (95% CI -3.94 to -0.92) in the mirtazapine versus placebo group, -0.64 (95% CI -2.26 to 0.99) in the ondansetron versus placebo group, and -1.79 (95% CI -3.19 to -0.39) in the mirtazapine versus ondansetron group.

PUQE-24 score analyses were consistent across analyses with complete cases, imputed data and per protocol as shown in Figure 2.

Analyses for the two additional questionnaires related to symptom severity, the Nausea and Vomiting of Pregnancy Quality of Life Questionnaire (NVPQOL) and the HyperEmesis Level Prediction Score Assessment (HELP), both resulted in higher symptom reduction in the mirtazapine group than the placebo and ondansetron groups on Day-7 and on Day-14.

The analyses for the EuroQol 5-Dimention 5-Level (EQ-5D-5L) questionnaire showed no difference among the groups, and analyses for the modified Pittsburgh Sleep Quality Index (PSQI) showed reduced scores in the mirtazapine group when compared with the placebo and ondansetron groups.

Frequency of discontinuation of trial medication due to treatment failure was lower in the mirtazapine group when compared with both the placebo group (-27.4% (95% CI -51.0% to -3.2%)) and the ondansetron group (-17.5% (95% CI -40.2% to 4.2%)).

Frequency of request for continuation of trial medication after end of intervention was higher in the mirtazapine group than the placebo group (36.7% (95% CI 2.1% to 60.6%)) and ondansetron group (18.7% (95% CI -13.7% to 46.3%)).

Primary and secondary outcomes are shown in Table 2, and Figure 2 shows PUQE-24 score in the different groups.

Safety

Key safety end points are summarized in Table 3. The proportion of participants with any adverse event was highest in the mirtazapine group (86%), as compared with the ondansetron and placebo groups (72% and 40%, respectively). Most were mild or moderate in severity and resolved without apparent sequelae. The most common adverse events in the mirtazapine group were fatigue (48%), dizziness (24%) and headache (24%) and the most common adverse events in the ondansetron group were constipation (44%) and headache (33%).

Three participants (14%), all in the mirtazapine group, discontinued the trial due to adverse events (all fatigue).

No participants died during the trial, and one serious adverse event was reported in each of the mirtazapine (5%) and the ondansetron (6%) groups, and two in the placebo (10%) group. One participant treated with mirtazapine gave birth to a child with congenital malformations. The child was diagnosed with unilateral membranous choanal atresia and stenosis of the pulmonary valve. At two-year follow-up, no pulmonary stenosis was detectable on echocardiography, and the child

had normal development. Since the maternal mirtazapine treatment was initiated at a gestational age 11 weeks and 5 days, after the development of the nasal cavities and the heart, the congenital malformations were considered unrelated to the treatment.

Birth outcome were comparable between the groups and are available in the supplementary material.

Comment

Principal findings

This RCT showed reduced PUQE-24 score in the mirtazapine group compared with the placebo group among people with severe hyperemesis gravidarum. In contrast, the tested ondansetron regimen did not reduce PUQE-24 score significantly, however the study is potentially underpowered for this exposure and the specific dosing and interval between administrations might not be optimal.

The differences in PUQE-24 score between mirtazapine and both ondansetron and placebo are more evident after day 4, and the results are consistent across analyses with complete cases, imputed data and per protocol. Additionally, all analyses regarding symptom severity showed a tendency towards mirtazapine being a more effective treatment then both placebo and ondansetron.

The incidence of mild to moderate adverse events was higher with mirtazapine than with both ondansetron and placebo. Most of these adverse events were tolerable, however few participants in the mirtazapine group discontinued treatment due to side effects. Serious adverse events were evenly distributed across the groups.

Results in the Context of What is known

The present results are highly relevant, as this is the first controlled trial with mirtazapine in hyperemesis gravidarum, and it is the first placebo-controlled trial with ondansetron, which is recommended as a second line treatment despise scarce evidence.

Clinical and Research Implications

Optimally, the present results should be confirmed in larger trials in the future. However, as stated below research in this patient population is challenging, and the present results are likely to be incorporated in future treatment recommendations, despite the limited number of participants in the trial.

Strengths and weaknesses

The compromised power is an obvious limitation of this trial. COVID-19 is partly accountable for this, but other factors also added to the difficulties. The patient population is challenging, as some are too debilitated to engage in clinical trials, and furthermore, many people are reluctant to consent to trial medication in pregnancy. Additionally, trial personnel had difficulties gaining experience with the trial procedures due to the scarcity of eligible participants. Similar challenges have been reported in other clinical trials investigating treatment for hyperemesis gravidarum,(32) and previously conducted RCTs in hyperemesis gravidarum and nausea and vomiting in pregnancy have limited numbers of participants and overall the level of evidence is low.(1)

A recently published systematic review of treatments for hyperemesis gravidarum found low certainty of evidence and need for further studies with emphasis on using validated scoring

systems.(1) Additionally, a James Lind Alliance collaboration stated that investigating effective treatments for hyperemesis gravidarum was a top priority for stakeholders.(33) The present study meets these demands.

Conclusions

Mirtazapine demonstrated a significant reduction in PUQE-24 score among people with severe hyperemesis gravidarum, while the tested ondansetron regimen did not yield a similar effect. This lack of response to ondansetron may be attributed to both compromised power and the tested treatment regimen.

Given these findings, mirtazapine could be considered as an add-on or alternative treatment for people with treatment resistant hyperemesis gravidarum.

Table 1. Characteristics of the Participants at baseline.

	Mirtazapine (n=21)	Ondansetron (n=18)	Placebo (n=20)
Age, median (min, max) years	28.1 [21.5, 35.2]	31.9 [21.7, 41.3]	28.1 [18.9, 36.3]
Inclusion week of gestation, median (min, max)	9.50 [7.00, 15.3]	9.79 [6.86, 19.6]	9.14 [6.71, 17.6]
Weight (kg), median (min, max)	69.4 [46.7, 105]	68.8 [51.6, 97.9]	67.3 [50.1, 114]
BMI (kg/m^2), median (min, max)	23.8 [16.7, 34.8]	24.6 [17.9, 34.3]	22.1 [17.8, 38.4]
Parity, n (%)			
0	7 (33.3)	7 (38.9)	9 (45.0)
1	11 (52.4)	9 (50.0)	10 (50.0)
2	2 (9.5)	2 (11.1)	0 (0.0)
3	1 (4.8)	0 (0.0)	1 (5.0)
PUQE-24 score, mean (SD)	13.0 (2.36)	12.8 (2.17)	13.1 (1.56)
History of pregnancy-related nausea and vomiting, n (%)	13 (61.9)	11 (61.1)	9 (45.0)
NVPQOL, median [min, max]	183 [146, 201]	183 [159, 205]	177 [130, 200]
HELP median [min, max]	34.0 [27.0, 42.0]	33.0 [23.0, 43.0]	34.0 [23.0, 39.0]

EQ-5D-5L, median [min, max]	0.526 [0.073, 0.912]	0.535 [-0.285, 0.778]	0.523 [0.048, 0.785]
Modified PSQI, median [min, max]	7.00 [3.00, 12.0]	10.0 [5.00, 12.0]	5.00 [3.00, 11.0]

Notes: n = number of participants, BMI = Body Mass Index, kg = kilogram, PUQE-24 = Pregnancy-Unique Quantification of Emesis and Nausea over 24 hours, NVPQOL = Nausea and Vomiting in Pregnancy Quality of Life, HELP = Hyperemesis Level Prediction, EQ-5D-5L = EuroQol-5 Dimension-5 Level (a measure of health-related quality of life), PSQI = Pittsburgh Sleep Quality Index.

Table 2. Primary and secondary outcomes.

Intention to Treat

End Points	Mirtazapine (n=21)	Ondansetron (n=18)	Placebo (n=20)	Mirtazapine (n=21)	Ondansetron (n=18)	Placebo (n=20)
Primary		Day 2				
Least-squares mean change in PUQE-24 score, [3 to 15 points]	-4.0 (-5.3 to -2.7)	-2.7 (-4.0 to -1.3)	-2.1 (-3.5 to -0.76)			
Least-squares mean difference vs. placebo (CI)	-1.9 (-3.6 to -0.12), P=0.04	-0.5 (-2.3 to 1.3), P=0.59				
vs. ondansetron (CI)	-1.4 (-3.1 to 0.40)					
Secondary		Day 7			Day 14	
Change in PUQE-24, [3 to 15 points]	-4.6 (-5.6 to -3.5)	-2.4 (-3.54 to -1.33)	-1.6 (-2.93 to -0.32)	-4.9 (-6.0 to -3.7)	-3.1 (-4.3 to -2.0)	-2.5 (-3.8 to -1.2)
Least-squares mean difference vs. placebo (CI)	-2.9 (-4.4 to -1.4)	-0.81 (-2.41 to 0.78)		-2.4 (-3.9 to -0.9)	-0.64 (-2.3 to 0.99)	
vs. ondansetron (CI)	-2.1 (-3.5 to -0.8)			-1.8 (-3.2 to -0.39)		

Change in PUQE-24 well-being score, [0 to 10 points]	2.3 (1.5 to 3.0)	1.2 (0.37 to 1.9)	0.64 (-0.19 to 1.5)	2.5 (1.7 to 3.3)	1.4 (0.6 to 2.3)	1.5 (0.6 to 2.4)
Least-squares mean difference vs. placebo (CI)	1.6 (0.64 to 2.6)	0.51 (-0.50 to 1.5)		0.99 (-0.06 to 2.04)	-0.05 (-1.1 to 1.2)	
vs. ondansetron (CI)	1.1 (0.19 to 2.0)			1.0 (0.01 to 2.08)		
Change in Number of daily vomiting episodes	-6.6 (-8.5 to -4.7)	-4.8 (-6.7 to -2.9)	-4.3 (-6.7 to -2.2)	-7.0 (-8.9 to -5.1)	-6.0 (-8.0 to -4.1)	-4.6 (-6.6 to -2.5)
Least-squares mean difference vs. placebo (CI)	-2.4 (-4.1 to -0.64)	-0.53 (-2.3 to 1.3)		-2.5 (-4.2 to -0.74)	1.5 (-0.33 to 3.3)	
vs. ondansetron (CI)	-1.8 (-3.4 to -0.20)			-0.98 (-2.6 to 0.61)		
Change in Nausea VAS, [0 to 100 points]	-22.5 (-30.4 to -14.6)	-8.0 (-16.6 to 0.55)	-8.6 (-17.9 to 0.60)	-28.9 (-37.3 to -20.6)	-13.3 (-22.4 to -4.3)	-21.8 (-32.3 to -11.4)
Least-squares mean difference vs. placebo (CI)	-13.9 (-34.6 to -3.1)	0.59 (-11.0 to 12.2)		-7.1 (-19.0 to 4.8)	15.6 (4.5 to 26.8)	
vs. ondansetron (CI)	-14.5 (-24.8 to -4.2)			-15.6 (-26.8 to -4.5)		

Change in NVPQOL (health-related quality of life for nausea and vomiting during pregnancy), [30 to 210 points]	-35.4 (-49.3 to 21.7)	-18.4 (-33.9 to -2.9)	-7.73 (-24.4 to 8.9)	-51.7 (-71.8 to -31.6)	-18.61 (-41.0 to 3.8)	-19.86 (-44.5 to 4.7)
Least-squares mean difference vs. placebo (CI)	-27.7 (-48.9 to -6.6)	-10.7 (-33.6 to 12.3)		-31.8 (-62.7 to -0.95)	1.3 (-32.4 to 34.9)	
vs. ondansetron (CI)	-17.1 (-37.7 to 3.5)			-33.1 (-63.0 to -3.1)		
Change in HELP (hyperemesis level prediction), [0-50 points]	-12.9 (-16.6 to -9.17)	-7.0 (-11.14 to -2.90)	-6.1 (-10.58 to -1.55)	-12.9 (-16.6 to -9.17)	-7.02 (-11.14 to -2.90)	-6.1 (-10.6 to -1.6)
Least-squares mean difference vs. placebo (CI)	-6.9 (-12.6 to -1.05)	-0.95 (-7.11 to 5.21)		-6.9 (-12.6 to -1.05)	-0.95 (-7.11 to 5.21)	
vs. ondansetron (CI)	-5.9 (-11.5 to -0.33)			-5.9 (-11.5 to -0.33)		

Change in EQ-5D-5L (health-related quality of life), [-0,757 to 1 index score]	0.19 (0.07 to 0.30)	0.12 (0.00 to 0.25)	0.06 (-0.06 to 0.19)	0.20 (0.06 to 0.35)	0.07 (-0.09 to 0.23)	0.06 (-0.11 to 0.22)
Least-squares mean difference vs. placebo (CI)	0.12 (-0.04 to 0.29)	0.06 (-0.12 to 0.23)		0.14 (-0.07 to 0.36)	0.01 (-0.22 to 0.24)	
vs. ondansetron (CI)	0.06 (-0.10 to 0.23)			0.13 (-0.08 to 0.35)		
Change in Modified PSQI (Pittsburg Sleep Quality Index), [0 to 21 points]	-2.2 (-3.2 to -1.1)	-1.4 (-2.5 to -0.9)	-0.43 (-1.6 to 0.73)	-2.1 (-3.3 to 0.96)	-0.73 (-2.1 to 0.62)	0.54 (-0.98 to 2.1)
Least-squares mean difference vs. placebo (CI)	-1.7 (-3.3 to -0.18)	-0.96 (-2.6 to 0.65)		-2.6 (-4.6 to -0.72)	-1.3 (-3.3 to 0.76)	
vs. ondansetron (CI)	-0.77 (-2.3 to 0.74)			-1.4 (-3.2 to 0.45)		
Change in weight, (kg)	2.0 (1.3 to 2.7)	0.62 (0.10 to 1.3)	0.10 (-0.65 to 0.85)	2.5 (1.6 to 3.3)	0.03 (-0.89 to 0.95)	0.04 (-1.01 to 0.93)

Least-squares mean difference	1.9 (0.91 to 2.9)	0.52 (-0.53 to 1.6)		2.4 (1.2 to 3.7)	-0.01 (-1.4 to 1.3)	
vs. placebo (CI)						
vs. ondansetron (CI)	1.4 (0.40 to 2.4)			2.4 (1.2 to 3.7)		
Area under the curve for PUQE-24 score during the intervention				129.1 (111.8 to 146.5)	153.9 (135.1 to 172.8)	166.6 (146.3 to 187.0)
Least-squares mean difference				-24.8 (-50.3 to 0.68)	-12.7 (-40.6 to 15.2)	
vs. placebo (CI)						
vs. ondansetron (CI)				-37.5 (-63.8 to -11.2)		
Mean patient satisfaction with treatment VAS, [0 to 100 points]	65.9 (53.3 to 78.5)	50.2 (36.6 to 63.9)	34.7 (20.0 to 49.4)	68.7 (54.1 to 83.4)	39.8 (23.7 to 55.9)	35.7 (17.9 to 53.5)
Least-squares mean difference	31.2 (22.2 to 50.1)	15.5 (-4.7 to 35.8)		33.0 (10.2 to 55.9)	4.1 (19.9 to 28.2)	
vs. placebo (CI)						
vs. ondansetron (CI)	15.7 (2.9 to 34.2)			28.9 (7.2 to 50.7)		
Patient consideration of termination of pregnancy, n (%)	1 (4.8)	1 (5.6%)	1 (5.0)	0 (0)	1 (5.6)	0 (0)

Request for dosage increase, percentage points (95% CI)	24.6 (10.3 to 48.0)	57.6 (33.2 to 78.8)	70.20 (43.6 to 87.7)			
Difference vs. placebo	-45.6 (-67.8 to -11.2)	-12.6 (-42.0 to 20.5)				
Difference vs. ondansetron	-33.0 (-58.0 to -0.12)					
Request for continuation of trial medication after end of intervention, percentage points (95% CI)				61.1 (38.5 to 79.8)	42.4 (21.3 to 66.9)	24.4 (8.8 to 51.9)
Difference vs. placebo				36.7 (2.1 to 60.6)	18.0 (-15.7 to 46.3)	
Difference vs. ondansetron				18.7 (-13.7 to 46.3)		
Use of rescue medication (metoclopramid pills during the last week)	5.5 (2.8 to 8.1)	5.3 (2.4 to 8.2)	5.2 (2.4 to 7.9)	7.3 (3.9 to 10.7)	6.0 (2.4 to 9.7)	6.5 (2.8 to 10.2)

Least-squares mean difference	0.32 (-3.5 to 4.1)	0.13 (-3.8 to 4.1)		1.2 (-3.7 to 6.2)	-0.49 (-5.7 to 4.7)	
vs. placebo (CI)						
vs. ondansetron (CI)	0.19 (-3.7 to 4.1)			0.74 (-4.3 to 5.6)		
Days on sick leave (days during the last week)	6.1 (5.2 to 7.1)	6.0 (5.0 to 7.0)	5.7 (4.7 to 6.7)	5.4 (4.3 to 6.5)	5.6 (4.4 to 6.7)	5.7 (4.5 to 6.9)
Least-squares mean difference	0.44 (-0.89 to 1.8)	0.30 (-1.1 to 1.7)		-0.26 (-1.9 to 1.4)	-0.1 (1.8 to 1.6)	
vs. placebo (CI)						
vs. ondansetron (CI)	0.13 (1.2 to 1.5)			-0.14 (-1.7 to 1.4)		
Amount of treatments with i.v.-fluids (liter during last)	3.0 (2.0 to 4.1)	4.5 (3.4 to 5.6)	4.4 (3.3 to 5.5)	2.3 (1.6 to 3.0)	3.0 (2.3 to 3.8)	3.53 (2.78 to 4.28)
Least-squares mean difference	-1.4 (-2.8 to 0.11)	0.11 (-1.4 to 1.7)		-1.2 (-2.2 to -0.29)	-0.51 (-1.5 to 0.51)	
vs. placebo (CI)						
vs. ondansetron (CI)	-1.5 (-3.0 to 0.03)			-0.73 (-1.7 to 0.26)		
Days of hospitalization (days during the last week)	0.53 (-0.06 to 1.1)	0.85 (0.23 to 1.5)	0.89 (0.27 to 1.5)	0.18 (-0.19 to 0.54)	0.50 (0.11 to 0.89)	0.53 (0.02 to 1.0)

Least-squares mean difference vs. placebo (CI)	-0.37 (-1.23 to 0.50)	-0.05 (-0.92 to 0.83)	-0.35 (-0.99 to 0.28)	-0.03 (-0.67 to 0.61)
vs. ondansetron (CI)	-0.32 (-1.18 to 0.54)		-0.32 (-0.86 to 0.21)	
Occurrence of treatment failure, percentage points (95% CI)			4.8 (0.85 to 22.7)	22.2 (9 to 45.2) 32.2 (14.9 to 56.4)
Difference vs. placebo			-27.4 (-51.3 to -3.2)	-10.0 (-36.9 to 18.1)
Difference vs. ondansetron			-17.5 (-40.2 to 4.2)	

Notes: PUQE-24 = Pregnancy-Unique Quantification of Emesis and Nausea over 24 hours, CI = Confidence Interval, VAS = Visual Analogue Scale, NVPQOL = Nausea and Vomiting in Pregnancy Quality of Life, HELP = Hyperemesis Level Prediction, EQ-5D = EuroQol-5 Dimension (a measure of health-related quality of life), PSQI = Pittsburgh Sleep Quality Index, i.v. = intravenous.

Table 3. Adverse events[a].

Event	Mirtazapine (n=21)	Ondansetron (n=18)	Placebo (n=20)
		no. of patients (%)	
Any adverse event	18 (86)	13 (72)	8 (40)
Any adverse event leading to trial discontinuation	3 (14)	0	0
Any adverse event with outcome of death	0	0	0
Serious adverse events	1 (5)	1 (6)	1 (5)
Congenital malformation	1 (5)	0	0
Late miscarriage	0	1 (6)	1 (5)
Induced abortion	0	0	1 (5)
Adverse events occurring in ≥5% of the patients in either group			
Headache	5 (24)	7 (33)	2 (10)
Fatigue	10 (48)	2 (11)	0
Constipation	2 (10)	8 (44)	1 (5)
Dizziness	5 (24)	2 (11)	0
Diarrhea	3 (14)	1 (6)	0
Insomnia	1 (5)	2 (11)	1 (5)
Restlessness	0	1 (6)	2 (10)

Dry mouth	0	2 (11)	0
General discomfort	0	2 (11)	0
Palpitations	2 (10)	0	0
Back pain	0	1 (6)	0
Cough	0	1 (6)	0

[a]The safety population included all the patients who had undergone randomization and received at least one dose of any trial treatment. Adverse events were coded with the use of the preferred terms in the Medical Dictionary for Regulatory Activities, version 27.0.

Figure 1. Flowchart of randomization and follow-up.

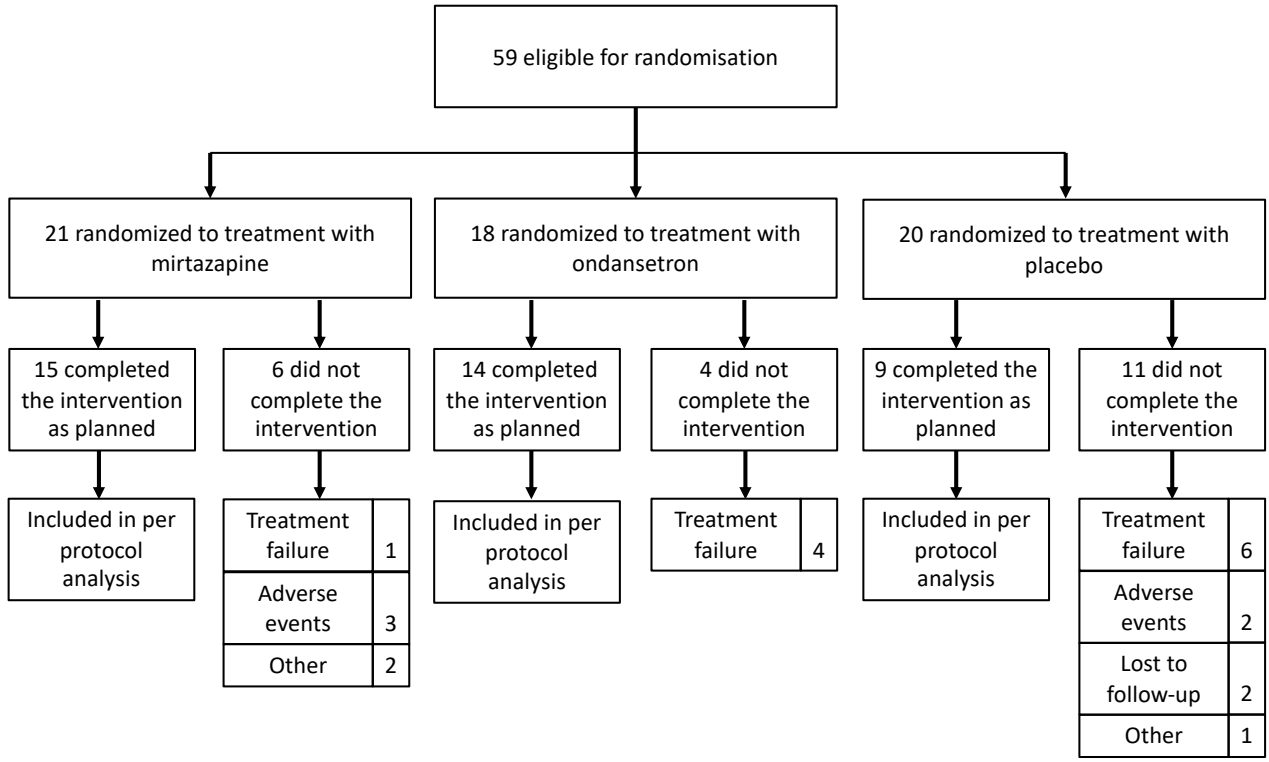

Figure 2. PUQE-24 score during the intervention.